THE EFFECTS OF NEOADJUVANT CHEMORADIOTHERAPY AND A STRUCTURED EXERCISE TRAINING PROGRAMME ON PHYSICAL FITNESS AND *IN VIVO* MITOCHONDRIAL FUNCTION IN ADVANCED RECTAL CANCER PATIENTS

Faculty of Health and Life Sciences
Institute of Ageing and Chronic Disease

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By

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DECLARATION IN HIGHER DEGREE THESIS

This thesis is the result of my own work. The material contained in this thesis has not been presented, not is currently being presented, either wholly or in part for any other degree or other qualification.

The research was carried out at Aintree University Hospital NHS Foundation Trust, Liverpool, United Kingdom, at the Department of Musculoskeletal Biology II, Institute of Ageing and Chronic Disease and the Magnetic Resonance and Image Analysis Research Centre (MARIARC), Faculty of Health and Life Sciences, University of Liverpool, Liverpool, United Kingdom.

Technical / clinical procedures undertaken in collaboration with other colleagues:

Nil

ABSTRACT

Outcomes after major surgery depend partly on patients' physiological tolerance to iatrogenic trauma. Objectively measured fitness assessments (cardiopulmonary exercise testing; CPET) show a link between poor fitness and poor surgical outcome, especially in major colorectal surgery. However evidence on fitness of surgical patients undergoing neoadjuvant chemoradiotherapy (NACRT) and/or preoperative exercise training is lacking. This thesis focuses on the physiological effects of NACRT and a preoperative structured responsive exercise training programme (SRETP) on objectively measured physical fitness using cardiopulmonary exercise testing, and the related effects on mitochondrial function using 31-phosphorus magnetic resonance spectroscopy (^{31}P MRS) in operable advanced rectal cancer patients.

First, CPET variables (oxygen uptake ($\dot{V}o_2$) at estimated lactate threshold ($\hat{\theta}_L$) and at peak exercise) were measured in advanced rectal cancer patients pre and post-NACRT and were followed up to 1 year postoperatively. A reduction in $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak exercise was observed (-1.5 and -1.4 ml.kg^{-1}.min^{-1} respectively; $p<0.0001$), both significantly associated with in-hospital complications. This is the first direct evidence that the benefits of NACRT in tumour downsizing may be partly offset by increased perioperative risk due to a reduction in physical fitness.

A SRETP was then constructed, and a feasibility and tolerability study carried out. The SRETP improved physical fitness within 6 weeks following NACRT ($\dot{V}o_2$ at $\hat{\theta}_L$ +3.3 ml.kg^{-1}.min^{-1} and $\dot{V}o_2$ Peak by +5.8 ml.kg^{-1}.min^{-1}), enough to reverse the deleterious effects of NACRT. A 98% adherence proves the SRETP both feasible and tolerable, with no adverse events encountered.

Next, locally advanced rectal cancer patients were recruited to an interventional pilot study scheduled to undergo standardised NACRT and a 6-week SRETP (exercise group n=22) or a control period (n=13). A significant benefit in $\dot{V}o_2$ at $\hat{\theta}_L$ of +2.12 ml.kg^{-1}.min^{-1} ($p<0.0001$) in the exercise group was observed. This study reinforces the benefits of prehabilitation with exercise training to improve physical fitness after the deleterious effects of NACRT prior to the added insult of major surgery.

Lastly, patients were randomized to the SRETP or to negative control after undergoing standardized NACRT, serial measures of whole body fitness and *in vivo* mitochondrial function by ^{31}P MRS (measuring the rate constant of phosphocreatine recovery, k_{PCr}). Significant reductions in $\dot{V}o_2$ at $\hat{\theta}_L$ (-2.36 $ml.kg^{-1}.min^{-1}$) were observed with NACRT, after which the SRETP improved fitness ($\dot{V}o_2$ at $\hat{\theta}_L$ +3.85 $ml.kg^{-1}.min^{-1}$). A significant reduction in k_{PCr} of -0.34 was found with NACRT, improved by +0.66 after SRETP.

These novel, clinically relevant findings show a significant decline in fitness with NACRT in an advanced rectal cancer cohort, reversible by a tailored exercise intervention post-NACRT. Concomitant changes in muscle mitochondrial function may account for this acute loss in fitness. The improvement in mitochondrial function observed with exercise, might indicate that a structured intervention immediately after NACRT is necessary to rescue and reverse NACRT's deleterious effect on mitochondrial function and fitness in this patient cohort.

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LIST OF SYMBOLS AND ABBREVIATIONS

NACRT – Neoadjuvant Chemoradiotherapy

SRETP – Structured, Responsive, Exercise, Training, Programme

MR – Magnetic Resonance

ASA – American Society of Anesthesiologists

CPET – Cardiopulmonary Exercise Testing

MDT – Multi-Disciplinary Team

IQR – Inter-Quartile Range

WHO – World Health Organisation

TNM – Tumour, Node, Metastasis

^{31}P MRS – 31-Phosphorous Magnetic Resonance Spectroscopy

$\dot{V}o_2$ – Oxygen Uptake

$\hat{\theta}_L$ – Estimated Lactate Threshold

$\dot{V}o_2$ Peak – Oxygen Uptake at Peak Exercise

NHS – National Health Service

AUH – Aintree University Teaching Hospitals NHS Foundation Trust, Liverpool, UK

PFTs – Pulmonary Function Tests

CT – Computer Tomography Scan

MRI – Magnetic Resonance Imaging

LAR – Low Anterior Resection

TME – Total Mesorectal Excision

APE – Abdomino-Perineal Excision

SCPRT – Short Course Preoperative Radiotherapy

RT – Radiotherapy

HR – Hazard Ratio

RR – Relative Risk

QoL – Quality of Life

5-FU – 5-Fluorouracil

DNA – Deoxyribonucleic Acid

mRNA – messenger Ribonucleic Acid

OR – Odds Ratio

POSSUM - Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

DASI – Duke Activity Status Index

METs – Metabolic Equivalents

$\dot{V}o_2$ Max – Oxygen Uptake at Maximal Exercise

ECG – Electrocardiography

DTS – Dipyridamole-Thallium Scintigraphy

$\dot{V}_E/\dot{V}CO_2$ – Ventilatory Equivalent for Carbon Dioxide

$\dot{V}_E/\dot{V}O_2$ – Ventilatory Equivalent for Oxygen

AAA – Abdominal Aortic Aneurysm

RCRI – Revised Cardiac Risk Index

SAPS – Simplified Acute Physiology Score

APACHE – Acute Physiology and Chronic Health Evaluation

ROC – Receiver Operator Characteristic Curve

AUC – Area Under the Receiver Operator Characteristic Curve

GI – Gastrointestinal

LOS – Length of Stay

POMS – Post Operative Morbidity Survey

6MWD – 6-Minute Walking Distance

HR max – Maximum Heart Rate

HRR – Heart Rate Reserve

AEs – Adverse Events

ADP – Adenosine Diphosphate

ATP – Adenosine Triphosphate

TCA – Tricarboxylic Acid

ETC – Electron Transport Chain

PaO_2 – Partial Pressure of Oxygen

Pi – Inorganic Phosphate

FiO_2 – Inspired Oxygen Levels

PCr – Phosphocreatine

MRS – Magnetic Resonance Spectroscopy

$\dot{V}$ – Respiration Rate

$\dot{V}\,o_{2\ muscle}$ – Muscle Oxygen Consumption

NIRS – Near Infra-Red Spectroscopy

NMR – Nuclear Magnetic Resonance

^{31}P – 31-Phosphorus

^{13}C – 13-Carbon

^{1}H – 1-Hydrogen

rf – Radio Frequency

FID – Free-Induction Decay

CK – Creatine Kinase

Mg^{2+} – Magnesium Ion

PME – Mono-Phosphoesters

PDE – Di-Phosphoesters

BMI – Body Mass Index

BSA – Body Surface Area

ECG – Electrocardiography

BP – Blood Pressure

WR – Work Rate

SaO_2 – Oxygen Saturation

O_2 – Oxygen

CO_2 – Carbon Dioxide

V_E – Minute Ventilation

FEV1– Forced Expiratory Volume in One Second

FVC – Forced Vital Capacity

PET_{CO2} – End Tidal Partial Pressure of Carbon Dioxide

PET_{O2} – End Tidal Partial Pressure of Oxygen

RPM – Revolutions per Minute

Q – Cardiac Output

SV – Stroke Volume

$[C(a–v)O_2]$ – Arteriovenous O_2 Content Difference

CR- POSSUM – Colorectal - Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

RER – Respiratory Exchange Ratio

RQ – Respiratory Quotient

LED – Light Emitting Diode

MVC – Maximum Voluntary Contraction

k_{PCr} – Phosphocreatine Recovery Rate Constant

ACSM – American College of Sports Medicine

MET – Metabolic Equivalent

COPD – Chronic Obstructive Pulmonary Disease

F&T – Feasibility and Tolerability

ACPGBI – Association of Coloproctology Great Britain and Ireland

τ – Tau, the time constant it takes to reach 63% of steady state

[PCr] – Phosphocreatine Concentration

ROS – Reactive Oxygen Species

mtDNA – Mitochondrial DNA

Chapter 1

Introduction and Thesis Overview

CHAPTER 1 – Introduction and Thesis Overview

1.1 INTRODUCTION

This thesis reports the results of investigations into the effects of preoperative (neoadjuvant) chemoradiotherapy (NACRT) and an exercise training programme (SRETP) on objectively measured physical fitness (fitness and physical fitness are used interchangeably throughout this thesis) in patients with locally advanced rectal cancer who are about to undergo major elective oncological resection. It describes the impact of NACRT and SRETP on *in vivo* mitochondrial function in human skeletal muscle using a non-invasive magnetic resonance (MR) based approach.

Major abdominal surgery is associated with a substantial burden of postoperative morbidity and mortality particularly in the elderly or those with significant co-morbidity. Large audits in the United Kingdom reveal 30-day mortality rates of 5.6% for elective colorectal cancer surgery (1). A recent study estimated that in the United Kingdom more than 4 million surgical procedures are performed annually, 12.3% of which are performed on patients classified as "high-risk" (expected mortality >5%) (2). These "high risk" patients can be clearly identified by utilizing subjective (e.g. American Society of Anesthesiologists Scores - ASA) or objective measures of physical fitness (e.g. cardiopulmonary exercise testing – CPET). Patients deemed unfit on preoperative CPET are reliably linked to a higher proportion of adverse postoperative surgical outcomes i.e. morbidity or mortality (3–5). This group accounts for the large majority of the observed postoperative mortality (83.4%), and also has a significantly longer hospital stay which is a surrogate marker of in-hospital morbidity. Outcome after major surgery is dependent on both controllable factors, such as the medical care received before, during and after surgery, as well as fixed factors, such as the patient's physiological ability to tolerate surgical trauma. Accurate perioperative risk assessments allows the multidisciplinary team (MDT) to ensure appropriate modification of patients' preoperative status as well as optimising intra and postoperative management for these high risk surgical patients. Therefore, the preoperative identification of patients unable to withstand physiological trauma from neoadjuvant cancer treatments or major surgery should be a priority.

In the United Kingdom colorectal cancer is the third commonest cause of cancer death (6,7). In 2010, 33,218 new cases were registered (58 new cases per 100,000 men and 37 new cases per 100,000 women), with 15,776 deaths (6,7). In 2012, of ~9000 patients diagnosed with

rectal cancer (35% above age of 75 years), 75% underwent major resection (8). Twenty-five per cent of cases are locally advanced (TNM stage - T3/T4) cancers considered for NACRT to control local disease, improve operability, achieve tumour downsizing and negative resection margins (9–13). Only two trials suggest that rectal cancer patients with a lower subjective performance status (WHO Score >1) have a worse postoperative outcome after combined chemotherapy or chemo-radiation and surgery (14,15). It is therefore important to understand quantitatively the impact of NACRT on general physical fitness and also its clinical implications on surgical outcome. The mechanism of changing fitness with cancer therapies is currently unknown and needs to be explored. Impairment of skeletal muscle mitochondrial function will greatly affect muscle bioenergetics, decreasing the efficiency of whole body exercise performance and potentially affecting overall patients' capability in dealing with surgical stress. Furthermore, other mechanisms e.g. cancer-induced cachexia, cancer related fatigue, oxidative stress (16–18) (which causes muscle weakness and fatigue), chemotherapy induced loss of muscle mass (19,20), reactive oxygen species (ROS) (21), reduced antioxidant levels (22) and mitochondrial death (23) may be the cause of reduced fitness.

Knowledge of the effects of cancer and cancer therapies on physical fitness and mitochondrial function is critical in developing interventions to promote recovery of physical fitness, especially as these effects may impair fitness for surgical intervention. These issues will be addressed in subsequent chapters. To date there is no evidence linking the deleterious effects of cancer therapies on physical fitness and surgical outcome, and there is only some evidence showing that preoperative exercise training improves surgical morbidity and mortality after major surgery. This present thesis originates from a study that I led in 2009 whilst undergoing my surgical training in University Hospitals Aintree. This consisted of a cohort of colonic surgical patients about to undergo major surgery. CPET was in its infancy and I wanted to undertake a study which aimed to investigate any relationship between short term in hospital surgical outcomes and objectively measured CPET variables in these high risk patients. One hundred and ninety eight patients were recruited in this trial. Selected CPET variables were found to be associated with postoperative morbidity and a risk stratification model was developed. This trial led to further hypothesis generation around the effects of neoadjuvant cancer therapies in colorectal cancer patients and novel ways to counteract its effects. Hence this thesis consists of independent studies in which objective measures of physical fitness (assessed by means of CPET) and *in vivo* mitochondrial energetics (assessed by means of 31-Phosphorus Magnetic Resonance Spectroscopy – ^{31}P MRS) are utilised to derive quantitative measures of the impact of NACRT and a preoperative exercise training programme on inter-related global physical

fitness and mitochondrial muscle function. These studies will attempt to elucidate the complex links between observed changes in whole body cardiopulmonary physiology and muscle mitochondrial energetics in rectal cancer patients during NACRT and exercise (Figure 1.1).

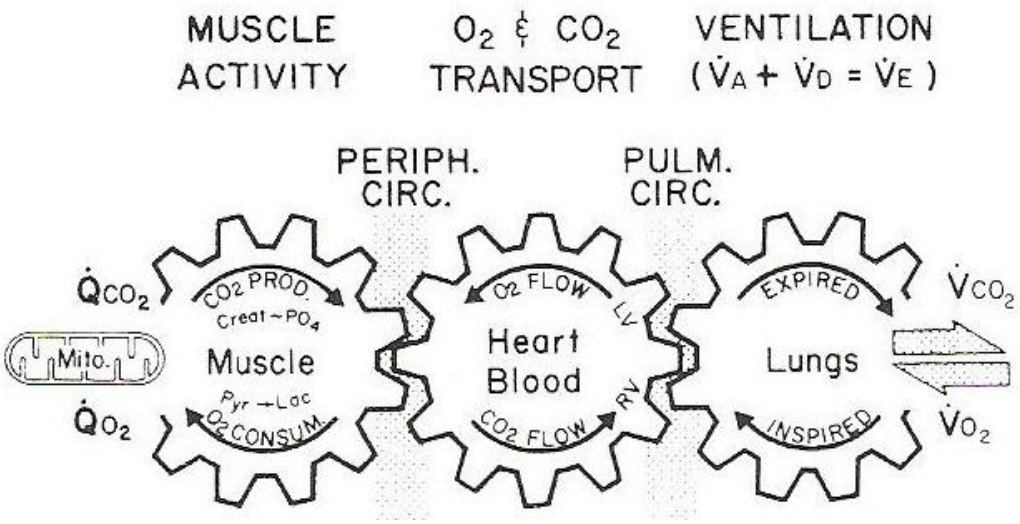


Figure 1.1 – Gears represent the complex functional interdependence of physiological components (musculoskeletal, cardiovascular and respiratory systems) resulting in physical fitness assessment (Wasserman and colleagues).

Each study addresses important clinical issues which are largely unexplored in the literature. Detailed physiological and pathophysiological background will be presented in Chapter 2, whilst the rationale of each study will be presented in the individual chapters. An outline is provided here to orientate the reader.

There are 4 major components presented in this thesis:

- The first study objectively defines changes in physical fitness after NACRT prior to elective surgery for locally advanced rectal cancer. The study hypothesises that long-course NACRT prior to elective surgery would impair physical fitness as objectively assessed by CPET. Secondary aims include determining the relationship of CPET variables (Oxygen uptake ($\dot{V}o_2$) at estimated lactate threshold ($\hat{\theta}_L$) and $\dot{V}o_2$ at Peak exercise) to Day 5 postoperative in-hospital morbidity, 180-day morbidity and 1 year mortality.
- The second study outlines the development of the iterative process around the structured, responsive, exercise training programme (SRETP). It also reports the

evaluation of its feasibility, tolerability, safety and adherence amongst patients' immediate post-NACRT and for the subsequent 6 weeks.

- The SRETP was then applied to a cohort of rectal cancer patients in the third study. This is a consecutive, non-randomised, parallel group study to investigate the effects of NACRT and a 6-week training programme or standard care (negative control) on objectively measured physical fitness and surgical outcomes. Here the aim of this pre-pilot study was to observe changes in physical fitness and their relationship to postoperative outcome after a period of standard care (no intervention) or a 6-week SRETP (structured intervention).
- In the fourth study, physiological methods of measuring physical fitness and assessments of *in vivo* mitochondrial function were applied together in the same cohort of patients. Here I describe the relationship between changes in physical fitness and changes in mitochondrial function pre- and post-NACRT, as well as, after randomization to standard care (no intervention) or a 6-week SRETP (structured intervention). The main aim of this study is to identify the biochemical mechanism for the observed changes in physical fitness.

1.2 GENERAL AIMS OF THIS RESEARCH

The aims of this current research work are:

1. To explore changes in physical fitness after NACRT prior to elective surgery for locally advanced rectal cancer using objective CPET methodology, and to subsequently attempt to establish a preliminary relationship between change in fitness and postoperative morbidity and mortality (Day 5 postoperative in-hospital morbidity, 180-day morbidity and 1 year mortality).
2. To develop a novel post-NACRT training protocol (SRETP) which is feasible, safe and tolerable in the pre-operative period of this surgical population.
3. To explore the changes in physical fitness and surgical outcomes after a period of SRETP or routine care (negative control) in a pre-pilot parallel group non-randomized setting.
4. Finally, to apply ^{31}P MRS and CPET methods to study *in vivo* skeletal muscle mitochondrial function and whole body physical fitness assessments in an attempt to identify a biochemical mechanism for these changes in physical fitness using a randomized controlled design (negative control vs. structured intervention).

1.3 ORGANIZATION OF THESIS CHAPTERS

This thesis is presented in 8 chapters.

- ***Chapter 1: The present chapter*** - this briefly outlines the introduction, general aims of this research, organisation of the chapters presented in this thesis, the setting of the study and how these integrate into the National Health Service (NHS) colorectal cancer care pathway.
- ***Chapter 2: Background – Physiology and Pathophysiology*** – this chapter provides a background of the appropriate theory and reviews the literature around all methods and techniques used in this thesis.
- ***Chapter 3: General Methods and Experimental Setup*** - this chapter provides a description of the general experimental protocols, equipment set-up, as well as data acquisition, interpretation and analysis of methods used i.e. Cardiopulmonary exercise testing, the exercise training programme and ^{31}P MRS.
- ***Chapter 4: The Effect of NACRT on Physical Fitness and Morbidity in Rectal Cancer Patients*** – this study explores the changes in objectively measured physical fitness using CPET after NACRT in a cohort of locally advanced rectal cancer patients. This study also explores the relationship between changes in physical fitness and surgical outcome at 5, 180 and 365 days postoperatively. This addresses the novel way of observing changes in physical fitness in this homogenous group of patients. The physiological and clinical relevance of these observations are further discussed in this chapter.
- ***Chapter 5: Development of a Structured Responsive Exercise Training Programme (SRETP) and Feasibility Study*** – this study details the iterative processes that led to the development of the exercise training programme. Additionally, the feasibility and tolerability of the SRETP is explored.
- ***Chapter 6: Prehabilitation – A Pre-Pilot Parallel Group Controlled Study*** – this study is designed to further define the effects of neoadjuvant chemoradiotherapy (NACRT) and to pilot the SRETP derived in Chapter 5. This chapter specifically focuses on a pre-pilot, non-randomised, parallel group controlled study investigating the changes in objectively measured CPET derived variables and their relationship to in-hospital morbidity.
- ***Chapter 7: Effects of Neoadjuvant Chemoradiotherapy and a 6-Week Structured Exercise Programme on In Vivo Mitochondrial Function – A Randomised Controlled Study*** – this chapter specifically focuses on a randomised controlled study

investigating the effects of NACRT and SRETP on *in vivo* mitochondrial muscle function and objectively measured physical fitness.

- ***Chapter 8: Summary, Conclusion and Future Work*** – this concluding chapter presents a summary of results from each individual study and their implications to clinical practice. The strengths and potential methodological limitations are also addressed. The conclusions from the research work as well as future studies are presented.

1.4 STUDY SETTING AND INTEGRATION INTO NHS CANCER PATHWAYS

This thesis deals with rectal cancer patients who are recruited from within NHS cancer care pathways. This section is aimed to firstly acquaint the reader with both the previous (Figure 1.2) and current rectal cancer pathway (Figure 1.3) used at Aintree University Hospitals NHS Foundation Trust (AUH is the hospital where these patients are recruited from), and secondly, to illustrate the integration of the research investigations/interventions (presented in Chapters 4 to 7) into the aforementioned NHS rectal cancer pathway (Figure 1.2 and 1.3).

During the course of my PhD work the standard cancer care pathway for locally advanced rectal cancer was changed. Two main changes involved the re-staging scans which were moved from week 7 to week 9 post-NACRT, and the surgery which was also moved from week 9 to week 15 post-NACRT. These changes were undertaken to be in line with recently published evidence illustrating the effects of delaying time of surgery for locally advanced rectal cancer patients after neoadjuvant chemoradiotherapy (24–26). The rationale for the timing for surgical intervention post-NACRT, as well as the radiobiological sense for using NACRT will be discussed in Sections 2.3 and 2.4.

Figures 1.2 and 1.3 show the integration of research investigations and interventions presented in Chapters 4-7. These do not alter the standard NHS cancer pathways. All research investigations and interventions were specifically designed to fit around the standard cancer pathway used at AUH, mainly utilizing the waiting times between standard care investigations and the hiatus between end of NACRT and surgery. Ethical approval for this project was granted by the Northwest Regional Ethics Committee on the 18th March 2011(REC Reference Number 11/H1002/12), and further favourable ethical approval was given for two amendments on the 20th June 2011 and 30th January 2012 (REC Reference Number 11/H1002/12a and 11/H1002/12b).

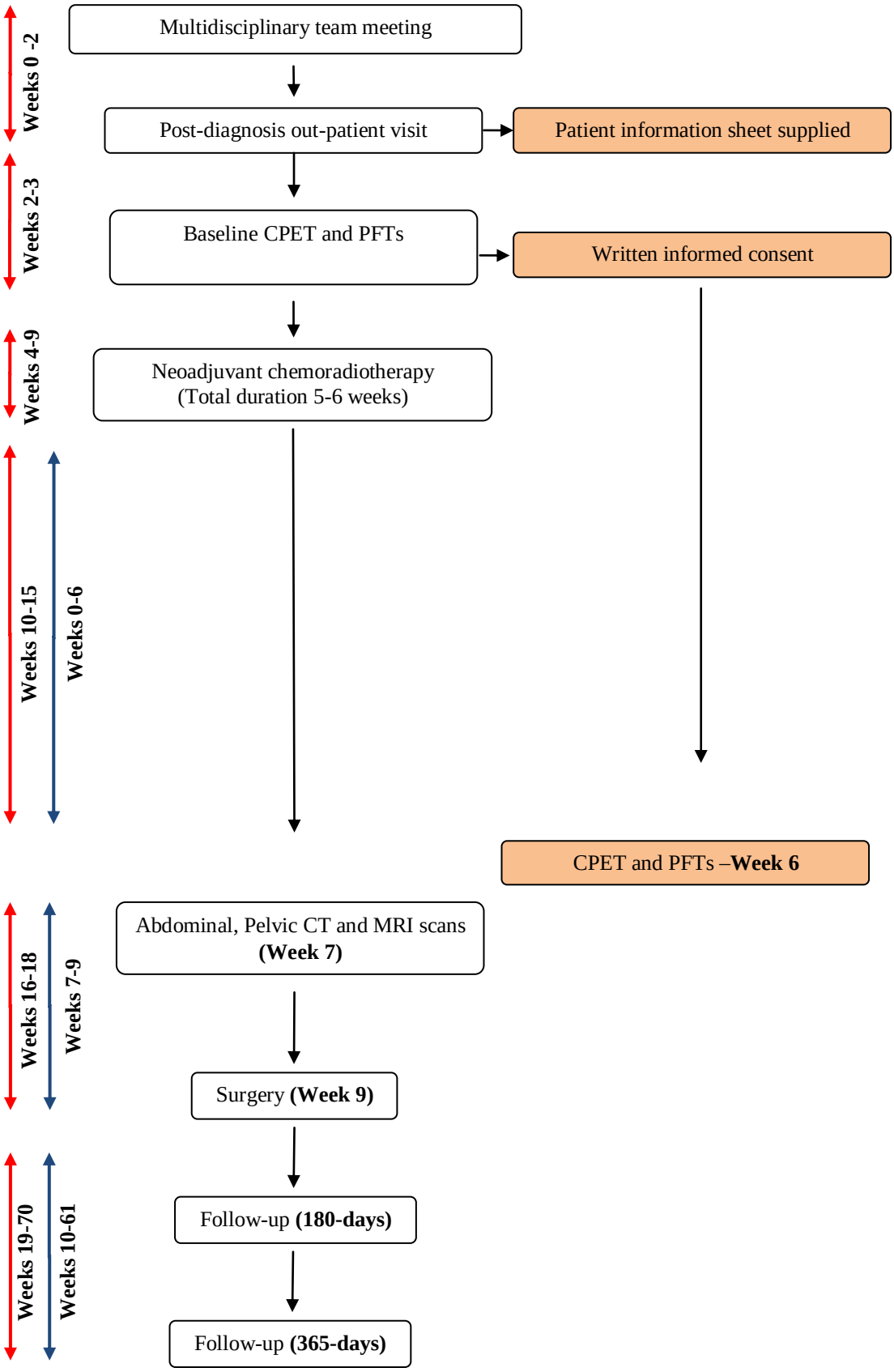


Figure 1.2 – Previous standard rectal cancer pathway at AUH (until October 2011), with the addition of research investigations (highlighted in orange) as described in Chapter 4.

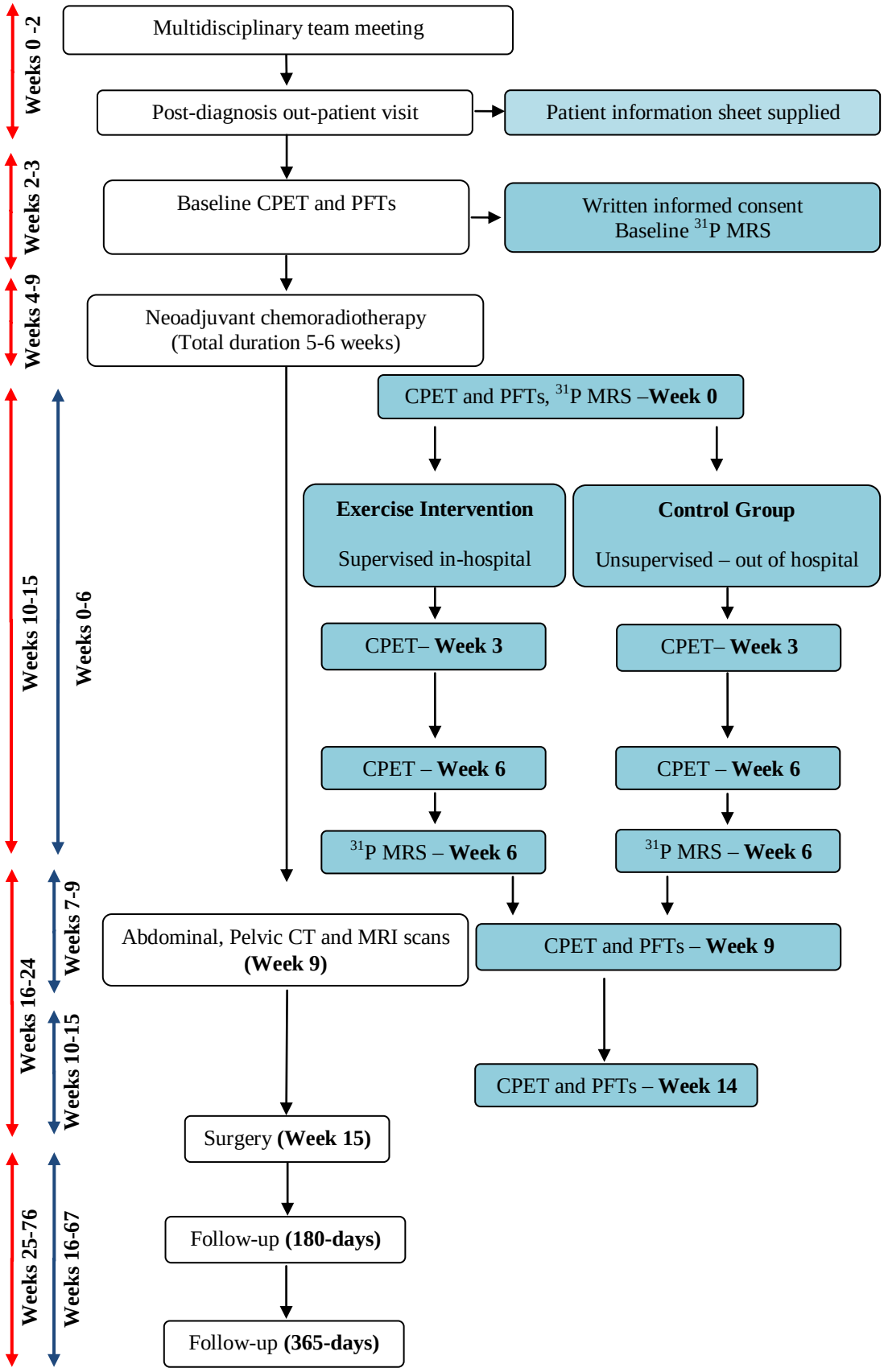


Figure 1.3 – Current standard rectal cancer pathway at AUH (from October 2011 to date), with the addition of research investigations/interventions (highlighted in blue) as described in Chapters 5 to 7.

Chapter 2

Background – Physiology and Pathophysiology

CHAPTER 2 – Background – Physiology and Pathophysiology

2.1 ANATOMY OF THE RECTUM

The rectum is continuous with the sigmoid colon at the level of the third sacral vertebra, the junction being at the lower end of the sigmoid mesocolon. It descends along the sacrococcygeal concavity, with an anteroposterior curve, then curves down and backwards, and finally down and forwards to join the anal canal by passing through the pelvic diaphragm. The adult rectum is 18-20cm in length and is divided into three equal parts: the upper third, which is mobile and has a peritoneal covering; the middle third, which is the widest part and is confined within the bony pelvis, covered by peritoneum only on the anterior and part of the lateral surfaces; and the lowest third, which lies within the muscular floor of the pelvis and has important relations to fascial layers (Figure 2.1).

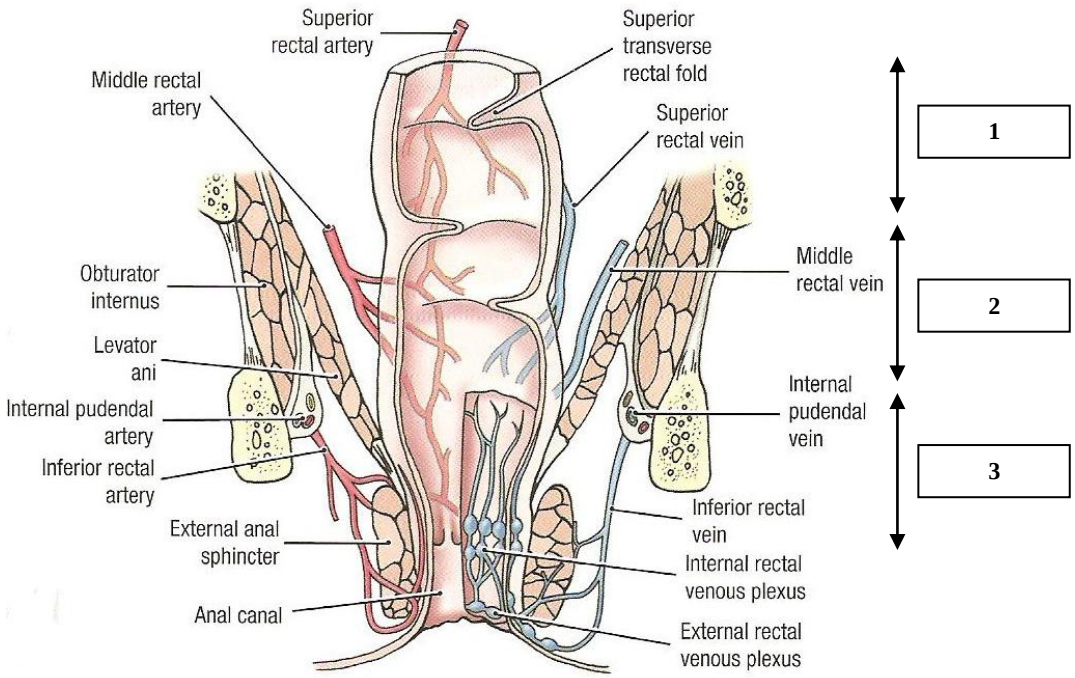


Figure 2.1 – Anatomy of the rectum; 1 – upper rectum, 2 – middle rectum; 3 – lower rectum

The lowest part of the rectum is separated from the prostate in front by a fascial condensation called Denonvilliers' fascia and from the coccyx and last two sacral vertebrae behind by another fascial layer called Waldeyer's fascia. These layers are surgically important as they are a barrier to malignant penetration and are valuable guides at operation. Blood supply of the rectum is mainly from the superior rectal artery which is a continuation of the inferior mesenteric artery. This divides into anterior and posterior branches and is

accompanied by lymphatics which are all kept applied to the back of the rectum by dense mesorectal connective tissue. The lymphatic drainage of the mucosal lining of the rectum interchanges freely with those of the muscular layers. They flow upwards (only to a limited extent laterally and downwards). This is important in surgical excision of malignant disease as the surgeon aims to achieve wide clearance of proximal lymph nodes.

2.2 ORIGIN OF CARCINOMA

Colorectal cancer is now thought to originate through a multistep process called the adenoma-carcinoma sequence, a term that describes the stepwise progression from normal to dysplastic epithelium to carcinoma associated with the accumulation of multiple clonally selected genetic alterations (27). This concept provides an excellent model to study precursor lesions and their transition into invasive cancer. 40% of the western population will develop adenomatous polyps, but only 3% will go on to suffer from colorectal cancer. The evidence supporting the adenoma-carcinoma sequence can be classified as epidemiological, clinicopathological and genetic, with the most recent body of evidence relating to molecular genetic events i.e. oncogenes, tumour suppressor genes and DNA repair genes and their cellular effects i.e. methylation status and microsatellite instability (27), however the origins and precursors of colorectal cancer are beyond the scope of this thesis.

2.2.1 RECTAL CANCER

In the United Kingdom colorectal cancer is the third commonest cause of cancer death (6,7). In 2010, 33,218 new cases were registered (58 new cases per 100,000 men and 37 new cases per 100,000 women), with 15,776 deaths (6,7). In 2013, of ~9000 diagnosed with rectal cancer (35% above age of 75 years), 75% underwent major resection (28). Twenty-five per cent of cases are locally advanced (TNM stage - T3/4 N+) cancers considered for long-course neoadjuvant chemoradiotherapy as these cancers are considered to threaten the circumferential resection margins, which is associated with a poor prognosis (9–13,29). Different types of histopathological variations exist with the most common being; well-differentiated adenocarcinomas, moderately differentiated adenocarcinomas and poorly differentiated adenocarcinomas. Rectal cancer can spread in 4 ways; local spread, lymphatic spread, venous spread and peritoneal dissemination (30).

- Local spread: This occurs circumferentially rather than longitudinally. After the muscular coat has been penetrated, the growth spreads into the surrounding mesorectum, but is still limited by the perirectal fascia. If penetration occurs anteriorly, the prostate, seminal vesicles or the bladder may become involved in the male, whilst in a female, the vagina or the uterus may become invaded. In either sex, with lateral extension, a ureter may become invaded, whilst posterior extension may involve the sacrum or the sacral plexus.
- Lymphatic spread: Rectal cancer above the peritoneal reflection spreads almost exclusively upwards, whilst below that level to within 1-2cm of the anal orifice lymphatic spread is still upwards, however pararectal lymph nodes of Gerota might become involved. The exception to this rule is when the neoplasm lies within the field of the middle rectal artery, i.e. between 4 and 8 cm from the anus, in which case primary lateral spread along the lymphatics that accompany the middle rectal vein might ensue. Metastasis at a higher level than the main trunk of the superior rectal artery occurs late in the disease. A radical operation should ensure that the highest lying lymph nodes are removed by ligation of the inferior mesenteric artery and vein as close to their aortic origin as possible. Surgical technique is discussed in Section 2.3.2.
- Venous spread: Cancer spread via the venous system is a late phenomenon. The principal sites for blood-borne metastasis are liver (34%), lungs (22%) and adrenals (11%). The remainder is divided among remaining sites.
- Peritoneal dissemination: This occurs following penetration of the peritoneal coat by a high lying rectal cancer.

In 1932, the Dukes classification (Figure 2.2) was introduced to stage colorectal cancers (31). This has been subsequently modified by Astler in 1954 (32). Dukes classified carcinoma of the rectum into three stages, with the fourth added by Astler:

A The growth is limited to the rectal wall. Prognosis is excellent.

B The growth is extended to the extrarectal tissues, but no metastasis to the regional lymph nodes. Prognosis is reasonable.

C There are secondary deposits in the regional lymph nodes. These are subdivided into C1, in which the local pararectal lymph nodes alone are involved, and C2, in which the nodes accompanying the supplying blood vessels are implicated up to the point of division. Prognosis is poor.

D Widespread metastases.

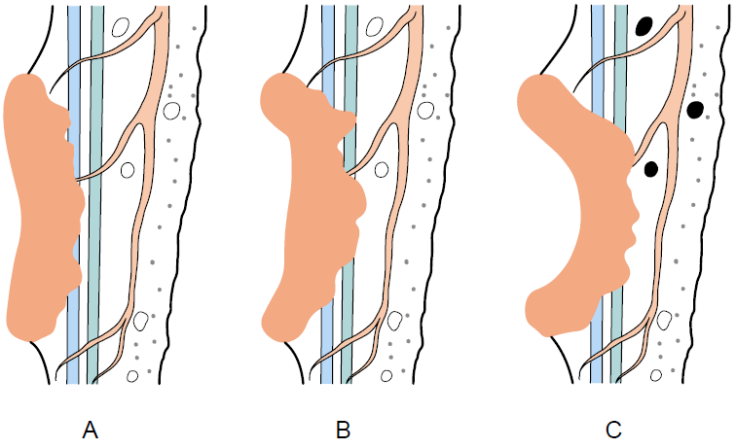


Figure 2.2 – Duke's Classification of the three cardinal stages of colorectal cancer progression

The TNM (Tumour, Node, Metastasis) classification is now the gold standard staging tool used by the Royal College of Pathologists (33); T-stage represents the extent of local spread and there are four grades – T1 – 4, depending on whether the tumour is confined to the mucosa or has penetrated the rectal wall. N-stage describes nodal involvement and M-stage describes the presence of distant disease.

2.2.2 CLINICAL FEATURES

Signs and symptoms from rectal cancer are often considered insignificant and so patients might not seek medical advice for some time. Bleeding is the earliest and most common symptom. Tenesmus (a feeling of incomplete emptying) is a very important early symptom which is almost invariably present in tumours of the lower half of the rectum. Alteration in bowel habit is also a frequent symptom, with patients having a change in stool consistency or habit of defecation. Pain is a late symptom, but pain of a colicky character may accompany some degree of intestinal obstruction. Infiltration into prostate or bladder may cause severe pain, as well as back pain or sciatica if sacral plexus infiltration occurs. Weight loss and reduced appetite is suggestive of systemic disease.

2.3 MANAGEMENT OF LOCALLY ADVANCED RECTAL CANCER

Locally advanced rectal cancer is defined as tumours which are operable, non-metastatic, T3/4 N+ rectal adenocarcinomas and threaten the circumferential resection margins (34). The gold standard of treatment for this cancer type is neoadjuvant chemoradiotherapy followed by definitive total mesorectal excision surgery (35,36).

2.3.1 INVESTIGATIONS

Abdominal examination is negative in early cases, whilst the liver may become palpable when metastases occur. In approximately 90% of cases, the tumour may be felt digitally. Ulceration, raised and everted edges, together with induration is a frequent and unmistakable finding.

A colonoscopy is required in all patients to exclude synchronous tumour and to obtain a biopsy of the tumour for pathological assessment. Local and distant assessment of the tumour is performed by computed tomography (CT) of the chest, abdomen and pelvis. This is usually coupled with MRI of the pelvis. In recent years magnetic resonance imaging (MRI) has emerged as the dominant method of pelvic imaging in rectal cancer (37,38). The MDT is using MRI to better plan surgical resection and neoadjuvant treatments. With better availability of neoadjuvant options, preoperative staging used to differentiate between good- versus poor-prognosis tumours is very useful, as this translates into optimized outcomes (39). The relationship between the tumour and the sphincter complex and the ability to achieve clear radial and distal margins is key to success of rectal cancer surgery (37). MRI offers superb soft tissue contrast between tumour and other soft tissues on T2-weighted MRI (Figure 2.3) (40–44), while CT has difficulties in this regard (38,44).

Figure 2.3 – A T2-weighted sagital MR image of a male with rectal cancer. The image shows a typical appearance of the tumour with raised rolled edges (white arrowheads). The lower black arrowhead is the point at which the lower most edge of tumour can be measured to the anal verge and the height measured (white dotted line)

2.3.2 SURGICAL TREATMENT

Radical excision of the rectum, together with the mesorectum and associated lymph nodes is the mainstay of rectal cancer surgery (30). When the tumour appears to be locally advanced, the administration of a course of preoperative radiotherapy or combination chemoradiotherapy may reduce its size and make it more amenable to radical excision. This will be reviewed in more detail in Section 2.4.

Patients who are unfit for radical surgery or have wide-spread metastases may still benefit from a local procedure such as transanal excision, laser destruction or local radiation to control symptoms; however this is outside the scope of this thesis and will not be discussed. The main focus of this section is to discuss surgery for locally advanced rectal cancer patients.

When a tumour appears to be locally advanced, the administration of neoadjuvant (preoperative) radiotherapy or combined chemoradiotherapy has been shown to be beneficial in preventing local recurrence. This will be discussed further in Section 2.4. When rectal excision is possible, whenever feasible, the aim should be to restore gastrointestinal continuity and continence by preserving the anal sphincter. A sphincter-saving operation (anterior resection) is usually possible for tumours of the upper two-thirds of the rectum, although removal of the rectum with a permanent colostomy (abdominoperineal excision) is often required for tumours of the lower third of the rectum. The introduction of the stapling gun has enabled many more of these patients to be treated by a sphincter-saving procedure. Provided a minimum distal margin of clearance of 2 cm can be secured, it is safe to restore gastrointestinal continuity. Because of the much wider degree of local spread by anaplastic tumours and the high risk of local recurrence, it has been customary not to perform restorative operations when these carcinomas are in the lower third of the rectum. However, with the realisation that a preoperative biopsy is often inaccurate with respect to the degree of histological differentiation, coupled with the more widespread use of preoperative and postoperative radiotherapy, many more anaplastic lesions are being treated by sphincter-saving procedures.

Low anterior resection (LAR) is now performed in least two-thirds of patients presenting with carcinoma of the rectum. The principles of the operation involve radical excision of the neoplasm, with at least a 2-cm margin of normal bowel below the lower edge of the tumour, removal of all the mesorectum, i.e. total mesorectal excision (TME) (45) and high proximal ligation of the inferior mesenteric lymphovascular pedicle. The plane of dissection follows

the relatively avascular areolar plane, between the mesorectal fascia surrounding the mesorectum and parietal tissues (Figure 2.4). This plane is usually terminated at the pelvic floor, having dissected the mesorectum off the levator muscles. However, this plane of dissection can be continued into the intersphincteric plane, with low anastomosis to restore intestinal continuity. To produce uninvolved margins, the tumour must not extend to ≥1 mm of the mesorectal fascia. If the tumour extends into the sphincter complex, then the intersphincteric plane should be tumour-free and the tumour should not extend to within 1 mm of the outer border of the internal sphincter. This plane can be further extended distally to perform an intersphincteric abdomino-perineal excision (APE) —essentially the same plane as low AR, but intestinal continuity is not maintained. Once the rectum has been mobilised adequately, it is removed, and the remaining bowel and rectal stump are washed out proximally and distally. Restoration of continuity by direct end-to-end anastomosis (manually or by stapling) must be carried out by a meticulous technique to reduce risks of suture line breakdown.

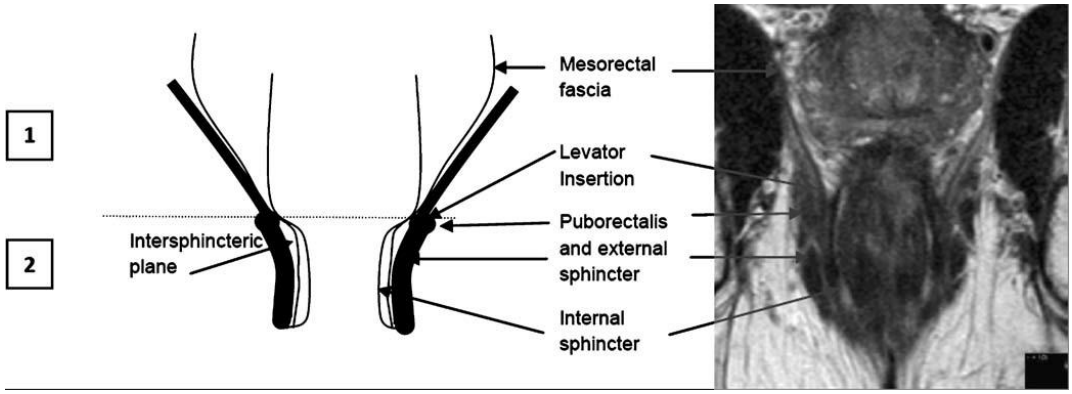


Figure 2.4 – A coronal diagram depicting the two anatomical levels (Level 1 and 2) of the distal rectum to help define the surgical approach

The main indications for an extra-levator APE procedure are extension of tumour into or beyond the levator muscles and/or tumour involving the intersphincteric plane plus or minus the external anal sphincter. This operation is typically carried out in two phases and has been well described by Holm and colleagues (46).

Finally a pelvic exenteration can be performed when extensive local invasion by a T4 tumour is found; however this is beyond the purpose of this thesis as all of the patients recruited in Chapters 4 to 7 underwent LAR or APE procedures.

2.4 EVIDENCE FOR UTILISING CANCER THERAPIES PRIOR TO LOCALLY ADVANCED RECTAL CANCER SURGERY

In this next section I will attempt a summary of the evidence for utilizing neoadjuvant cancer treatment prior to major rectal cancer surgery. In the 2012 National Bowel Cancer Audit (8), 4684 patients were diagnosed with rectal cancer and had major surgery, of which 24.2% had neoadjuvant long-course radiotherapy and 14.8% had neoadjuvant short-course radiotherapy. 7.9% had a positive circumferential resection margin (assuming all missing values were negative). The effectiveness of any form of preoperative therapy is dependent on the subsequent quality of surgery. As described in 2.3.2, TME is now the accepted standard resection for most rectal cancers, whilst an APE may be required for lower rectal tumours. The value of neoadjuvant therapy for low rectal tumours is debatable at present and requires further evaluation.

The gains in local control from preoperative radiotherapy are well established (47,48) but this needs to be balanced against the significant late effects in terms of sexual, urinary and bowel dysfunction and also the potential risk of second malignancies. Although preoperative chemoradiotherapy and Short-Course Preoperative Radiotherapy (SCPRT) are widely used to reduce the risks of local recurrence over surgery alone, and have similar biological equivalent radiation doses, there is uncertainty over which schedule to use in which particular clinical setting. SCPRT is a brief (typically 5 days) treatment with high dose radiotherapy. Short term side effects are minimal though there is some risk from long-term morbidity. Chemoradiotherapy involves a protracted (minimum of 5 weeks) course of radiotherapy with concomitant chemotherapy. Short term side effects are more marked and although long term effects do occur, there are less published data to establish their extent. Since this section only addresses preoperative and not postoperative therapy, the results of the large MRC CR07/NCIC-CTG C016 trial (49) of preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer are not considered in this evidence review.

Three systematic literature searches were conducted to look for available evidence. These are presented in Appendix 1 and 2. The literature search found in Appendix 1 relate to Sections 2.4.1 and 2.4.2, whereas the literature search found in Appendix 2 relate to Section 2.4.3.

2.4.1 PREOPERATIVE RADIOTHERAPY VERSUS SURGERY ALONE FOR OPERABLE RECTAL CANCER

The evidence for this comparison comprised a systematic review (47) and data from long term follow-up of randomised trials (48,50,51). In addition there was a systematic review (52) which addressed the late adverse effects of preoperative (and postoperative) radiotherapy (RT) in patients treated for rectal cancer.

Wong et al. (47) calculated pooled hazards ratios (HR) for overall survival from fourteen studies (HR: 0.93 [95%CI: 0.87-1.0] (p=0.04)). They conclude that short-course preoperative RT was superior to surgery alone; however this could not be replicated using individual patient data. Long term data from the Dutch TME trial also found no significant difference in the rate of overall survival between patients who had SCPRT compared with those patients who had surgery alone (64.2% versus 63.5%) (51).

Pooled data for disease-specific survival indicated an advantage of SCPRT in improving disease-free survival (HR: 0.87 [95%CI: 0.78-0.98] (p=0.02)) but there was high heterogeneity between studies so the results may not be reliable. The data for local recurrence were highly heterogeneous and were not appropriate for pooling. However, an overall reduction in the rate of second malignancies was in favour of SCPRT (HR: 0.89 [95%CI: 0.82-0.97] (p<0.001). The most common side effect of preoperative RT is diarrhoea (20%) (47) and patients in the surgery only group experienced more post-surgical toxicity.

Peeters et al. (51) analysed long term data from the Dutch TME trial and found no significant difference in the rate of overall survival between patients who had preoperative RT compared with those patients who had surgery only (64.2% versus 63.5%). They also found no significant difference in 5 year cancer specific survival in irradiated versus non-irradiated patients (75.4% versus 72.4%). However, there was a 49% reduction in local disease recurrence (p<0.001) for irradiated patients but no significant difference in the rate of distant recurrence after 5 years of follow-up. Quality of life comparisons showed a non-significant trend towards worse outcomes in irradiated patients. There was more scarring of the anal sphincters in this group (33%) when compared with the non-irradiated group (13%) and most also suffered some a degree of incontinence. The maximum resting and squeezing pressures were significantly lower in the irradiated group (47). Birgisson et al. (50) observed an increased risk of infections among irradiated patients during the first 6 months after treatment (RR: 7.67 (95%CI: 1.76-33.39)) and similarly in gastrointestinal diagnoses (RR:

2.57 (95%CI: 1.55-4.26)). There was an increase in the risk of non-specific infections (n=10; RR: 8.06 (95%CI: 1.02-63.69) in the irradiated group although the risk of cardiac arrhythmia was reduced (RR: 0.57 (95%CI: 0.36-0.91). In relation to gastrointestinal diagnoses, increased relative risk was observed in irradiated patients for bowel obstruction, nausea and non-specific abdominal pain whereas the risk for inguinal hernia was lower. This systematic review was the first to collate outcomes post-radiotherapy and rectal cancer surgery.

2.4.2 PREOPERATIVE CHEMORADIOTHERAPY VERSUS PREOPERATIVE RADIOTHERAPY FOR OPERABLE RECTAL CANCER

Evidence for this comparison arises from four papers (53–56) which report different outcomes from the same trial comparing conventionally fractionated neoadjuvant chemoradiotherapy (NACRT) with SCPRT. Patients were randomised to receive either preoperative 5.5 Gy irradiation with subsequent TME performed within 7 days or NACRT (50.4 Gy, 1.8 Gy per fraction plus bolus 5-fluorouracil and leucovorin) followed by TME after 4– 6 weeks.

Bujko et al. (53) reported no significant difference in the rate of 4 year survival (HR: 1.01 (95%CI: 0.69- 1.48) or 4 year disease free survival (HR: 0.96 (95%CI: 0.69-1.35) between patients having received NACRT compared with RT. There was also no significant difference in the 4 year incidence of local recurrence (HR: 0.65 (95%CI: 0.32-1.28), the crude incidence of distant metastases, late toxicity (RR: 1.05 (95%CI: 0.72-1.53) or late severe toxicity (RR: 1.43 (95%CI: 0.67-3.07). The same authors in 2004 (54) found no significant difference in the rate of sphincter preservation between patients having had RT and those having NACRT (61% versus 58%), whilst in 2005 (55) they found no significant difference in the rate of postoperative complications or severe complications, including death. Unfortunately, as this was not the primary outcome of the trial, the study was underpowered to have detected a difference between the interventions had one existed.

Pietrzak et al. (56) specifically addressed quality of life (QoL) and observed no significant difference in the mean scores for the global health/quality of life status (p=0.22) or for anorectal and sexual function in patients having had NACRT or RT. Approximately two-thirds of patients complained of faecal and gas incontinence, urgency and inability to differentiate between stool and gas. Approximately two-thirds of respondents stated that the disturbances in anorectal function had a negative impact on their QoL, with approximately 20% stating the impact was considerable. There was no significant difference between the

two groups in relation to the impact on sexual function (p=0.56 for males; p=0.10 for females).

Fiorica et al. (57) presented a systematic review and meta-analysis of long term follow-up data from seven trials, including one abstract, comparing NACRT and preoperative RT in patients with resectable rectal cancer. The conclusions of the study were that the addition of chemotherapy to preoperative radiotherapy reduced the risk of local recurrence (RR: 1.05; 95%CI: 1.01- 1.10; p=0.02) but did not improve overall survival (RR: 1.02; 95%CI: 0.94-1.09; p=0.68) or the risk of distant metastases (RR: 0.97; 95%CI: 0.93-1.02; p=0.21). Treatment-associated toxicity was also higher with NACRT.

2.4.3 PREOPERATIVE RADIOTHERAPY OR PREOPERATIVE CHEMORADIOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER VERSUS IMMEDIATE SURGERY

This section deals with a large volume of evidence which addresses the issue of preoperative treatment (radiotherapy or chemoradiotherapy) versus immediate surgery in locally advanced, high risk rectal cancer patients. In relation to preoperative NACRT versus preoperative RT alone, two Cochrane reviews (58,59) were available along with a number of randomised trials. In relation to preoperative chemoradiotherapy versus surgery alone there were a number of case series studies available. One Cochrane review (47) was available to provide evidence for preoperative radiotherapy versus surgery alone, which was already discussed in Section 2.4.1.

There was no evidence available to address the issue of preoperative chemotherapy versus surgery alone, nor were there any studies comparing preoperative chemotherapy with preoperative radiotherapy for patients with locally advanced rectal cancer.

2.4.3.1 PREOPERATIVE CHEMORADIOTHERAPY VERSUS PREOPERATIVE RADIOTHERAPY ALONE

Two Cochrane reviews specifically reviewing this topic found no significant differences between the two treatment groups in terms of overall survival (pooled odds ratio, 1.01; 95% CI, 0.85-1.20, p=0.88 (59) and odds ratio, 0.79-1.14, p=0.58 (58)) at five years. However, a more clinically relevant and significant difference in the rates of local recurrence at 5 years

was observed for patients in the RT group compared to patients in the NACRT group (OR 0.39-0.72, p<0.00001 (58) and OR 0.56, 95% CI 0.42-0.75, p<0.0001 (59)). Using data from 2 randomised controlled studies, De Caluwe et al. (58) reported no significant difference in 5-year disease free survival between the radiotherapy and chemoradiotherapy groups (OR 0.92-1.34, p=0.27). Pooled analysis from the same Cochrane review showed a significant difference in pathological complete response in favour of NACRT with an OR of 2.12-5.84, p<0.00001. Pooled analysis by McCarthy et al (59) showed significantly higher rates of grade III/IV toxicity in the NACRT group (OR 3.96, 95%CI 3.03-5.17, p<0.000001). This was confirmed by the updated review by De Caluwe et al. (58) (OR 1.68-10, p=0.002); although a limitation of this review is the significant heterogeneity found on data pooling from the two reviews. The increased toxicity reported marginally affected postoperative overall morbidity (OR 0.67-1.00, p=0.05), whilst it did not affect postoperative mortality and anastomotic leak rates.

2.4.3.2 PREOPERATIVE CHEMORADIOTHERAPY VERSUS IMMEDIATE SURGERY

For this comparison, there was little evidence available. Evidence was drawn from a small number of case series, both prospective and retrospective. Patient numbers in these studies were relatively small and this was considered to be a major limitation. Chessin et al. (60) showed no significant difference in either overall survival (p=0.09) or relapse free survival (p=0.10) between patients experiencing major complications and those with no complications. From a second case series, Coco et al. (61) observed that the actuarial overall survival at 5 years was 75.5%, 7 year survival was 67.8% and 10 year survival was 60.4%; actuarial cancer-related survival at 5 years was 77.9%, at 7 years was 70% and at 10 years was 65.8%. Mermershtain et al. (62) reported a 5-year overall survival of 70% and 8-year overall survival of 58% in a retrospective case series of 30 people. In a retrospective case series of 43 patients, Twu et al. (63) compared patients that responded to chemoradiotherapy with patients that did not respond and found no significant difference between the two groups in relation to overall survival, though a significant difference in local recurrence rate was observed in favour of the patients responding to NACRT (p=0.002). They also observed that disease-free survival was higher in the group of patients responding to NACRT compared with those patients not responding to NACRT (p=0.06).

The largest retrospective review of 390 patients treated for rectal cancer presenting with T3 or T4 disease and/or involved lymph nodes receiving neoadjuvant chemoradiotherapy (5'-

FU) before TME compared patients with T1 and T2 disease with no suspicion of involved nodes received TME directly. Time to death, local or distant recurrence was not significantly different between groups but the prognosis was more unfavourable for those patients who had positive nodes regardless of group (64).

Most retrospective case-series (62,63,65) observed pathological complete response rates of 12-13% in patients treated with NACRT.

2.4.3.3 CHEMORADIOTHERAPY UTILISING CAPECITABINE

5-Fluorouracil (5-FU) is a fluorinated analogue of uracil that has been commercially available since 1957. 5-FU's molecular activity is quite complex, showing interference with DNA synthesis and mRNA translation. 5-FU is transformed to 5-fluorodeoxyuridine by the action of thymidine phosphorylase. This then binds to thymidylate synthetase and to tetrahydrofolate, forming a stable complex which prevents the formation of thymidine from thymine. Finally DNA synthesis is blocked leading to cell death (66). Because of its unpredictable gastrointestinal absorption and degradation 5-FU must be administered intravenously. The drawbacks of continuous infusions are hospital and/or home health costs, infection risk, and patient burden. To overcome these disadvantages whilst preserving the benefits of continuous-infusion doses, and oral pro-drug was developed. Capecitabine is a carbonated derivative of doxifluoridine (5'-DFUR) that is absorbed via the intestine in pro-drug form. This is then activated both in the tumour and in normal tissues, however the converting enzyme thymidine phosphorylase is found in higher concentrations in most tumour tissues than in normal tissues, hence allows for the theoretical advantage of Capecitabine to have a selective activation within the tumour with a lower systemic toxicity.

Numerous phase II trials with a total of 953 patients, all with similar inclusion/exclusion criteria, were found (14,67–83). All studies reported grade III/IV toxicity. This was observed in 27% (260/953) of patients (range 0-34.5%). The most commonly reported toxicity was diarrhoea; other reported toxicities included anaemia, radiation dermatitis and leucocytopenia. Sphincter preservation rate was reported in all studies and ranged from 33% to 84% (mean 62%). Pathological complete response rate was 17.1% (range 9.1-26%), whilst tumour and node down staging was 59.2% (range 32-84%). All studies conclude that neoadjuvant Capecitabine and radiation therapy is better tolerated than bolus 5-FU and is more effective in the promotion of both down-staging and sphincter preservation in patients

with locally advanced rectal cancer. Capecitabine was also shown to be more cost-effective than other standard intra-venous treatments.

I conducted a literature search (Appendix 3) looking specifically for an association between preoperative markers of physical fitness and surgical outcome in gastrointestinal cancer patients treated with RT or NACRT undergoing surgical interventions. Interestingly, only Swellengrebel et al. (14) and Cunningham et al. (84) comment on the association of poor preoperative World Health Organisation (WHO) performance status and surgical complications. Swellengrebel et al. observed that a poor WHO performance status (≥2 at diagnosis) and the extent of surgery in locally advanced rectal cancer patients were associated with postoperative complications. They make inferences to the role of baseline physical fitness on surgical outcome and wound healing. Cunningham et al. also observed an association between WHO performance status and death following neoadjuvant chemotherapy in operable gastro-oesophageal cancer patients. Although this did not reach statistical significance, they demonstrate that less fit patients (WHO PS ≥1) may receive less benefit from NAC than fitter patients.

2.4.4 CHEMORADIOTHERAPY REGIME USED LOCALLY

All patients recruited to the studies presented in this thesis were recruited from Aintree University Hospitals NHS Foundation Trust, via the colorectal MDT. All patients received their neoadjuvant chemoradiotherapy at the Clatterbridge Cancer Centre, Wirral, UK, under the supervision of one medical oncologist (RS – acknowledged). All recruited patients received a standardised NACRT regime. This was kept constant for all recruited patients, in an attempt to obtain a homogenous patient sample and to remove any potential treatment bias. Patients receiving non-standard NACRT were excluded from the results presented in this thesis.

Preoperative radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a three-dimensional conformal technique with CT guidance. Patients were treated prone (on a belly-board) to spare small bowel, with a comfortably full bladder. The clinical target volume included the primary tumour, the mesorectum and mesorectal lymph nodes, including the perirectal, presacral and internal iliac nodes. The upper radiation extent was 3 cm above the tumour but no further than the sacral promontory. The perineum was included if an APE was planned, while for LAR the lower radiation border was 3 cm below the tumour. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. 825 $mg.m^{-2}$ oral

capecitabine was given twice daily on radiotherapy days. No patients received brachytherapy. Patients recruited in Chapter 4 had their surgery planned on the 9th week post-NACRT, whilst patients recruited in Chapters 5-7 had their surgery planned on the 15th week post-NACRT.

2.5 MEASURES OF SURGICAL RISK AND PREOPERATIVE FITNESS FOR SURGERY

Major abdominal surgery is associated with a substantial burden of postoperative morbidity and mortality particularly in elderly patients and those with co-morbidities. The 2012 the UK National Bowel Cancer audit documented 90-day mortality rates of 3.8% for elective colon cancer surgery, 4% for recto-sigmoid cancer and 2.5% for elective rectal cancer surgery (8). When considering emergency surgery this increased to 13.4% for colonic cancer patients and 13.9% for rectal cancer patients. Approximately 4 million surgical procedures are performed annually in the UK, 12.3% of which are performed on patients classified as "high-risk" (expected mortality >5%) (2,85). In this analysis, the "high-risk" group accounted for the majority of postoperative mortality (83.4%), and had a significantly longer hospital stay and therefore increased resource usage. These high risk individuals need to be risk-assessed preoperatively and have their perioperative management tailored so as to reduce avoidable surgical morbidity and mortality.

Outcomes after major surgery are dependent on modifiable factors, such as the medical care received before, during and after surgery, as well as more fixed factors, such as the patient's physiological tolerance of surgical trauma. Accurate risk prediction allows the multidisciplinary team to ensure appropriate modification of patients' preoperative status as well as optimising intra- and postoperative management for high-risk surgical patients. Such risk prediction also facilitates the most efficient use of scarce resources (e.g. intensive care beds). Importantly, better risk prediction also provides a higher quality of data to physicians and patients thereby enhancing the process of shared decision making before surgery (86). So the preoperative identification of patients at high risk of adverse outcome following the trauma of major surgery should be a priority.

2.5.1 CARDIOPULMONARY EXERCISE TESTING VERSUS OTHER METHODS OF ESTIMATING PHYSICAL FITNESS

The advantage of CPET over other methods of preoperative assessment is that it provides an integrated assessment of oxygen utilisation under conditions of dynamic exercise stress. It is recognised that dynamic tests, in comparison with static tests, are a more effective means of evaluating whole-body human physiology. Moreover, patients have an intuitive understanding of the concept of being "Fit for Surgery" and therefore the test has good face validity. The concept underlying CPET is that the physiological reserve defined by an exercise challenge, reflects, at least in part, the reserve available of the patient to meet the physiological challenges of the surgical trauma and the perioperative period. These challenges include major fluid shifts, acute inflammation and acute catabolism to name a few. CPET is also an objective, repeatable, non-invasive, quick, specific and sensitive means to detect cardiac failure and myocardial ischaemia at subclinical levels. CPET methodology and equipment setup will be discussed in more detail in Section 3.2.

CPET variables can be compared with others methods of assessing exercise tolerance, overall fitness and physiological reserve. These range from simple assessments including clinical acumen, clinical prediction scores e.g. ASA, Duke's Activity Scores, Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM), colorectal specific POSSUM (CR-POSSUM) (87–89), and assessment of metabolic equivalents (METs) to more complex assessments including walk tests (90), plasma biomarkers (91) and various measures of cardiac function (92–94).

Simple direct questioning to assess a patient's cardiorespiratory fitness has long been part of the preoperative assessment by the anaesthetist and has been shown to correlate with postoperative outcome (95). The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), both highlight the importance of estimating exercise capacity in assessing perioperative risk (96,97). Both guidelines recommend estimating functional capacity in METs, using questions derived from the DASI. This questionnaire relies on the patient answering 12 questions from which an estimated $\dot{V}o_2$ at Peak exercise can be obtained (98). However, it is patient reported and subjective, which may therefore not always correlate with an individual's true function. Predicting risk as a measure of exercise tolerance can also be done by using various risk stratification scores, namely the American Society of Anesthesiologists physical status (ASA-PS) score (87), the Charleston Age-Comorbidity Index and the Physiological and

Operative Severity Score for the nUmeration of Mortality and morbidity (POSSUM) (88,89,99). A recent systematic review identified all risk stratification tools which have been validated in heterogeneous patient cohorts, however this concludes that more research is needed in the form of impact studies measuring the effect of using risk stratification on clinician behavior, patient outcomes and resource utilization (100).

Serological markers of inflammation, such as the high-sensitivity C-reactive protein (hsCRP) and plasma N-terminal Pro-Brain Natriuretic Peptide, have also been shown to predict cardiovascular complications in elderly patients undergoing non-cardiac and non-vascular operations however the evidence is not strong (101).

In clinical practice, $\dot{V}o_2$ Max and the ratio between $\dot{V}o_2$ Max and resting $\dot{V}o_2$, named METs, is used as an indirect measure of physical and functional performance. The METs reached under maximal effort indicate the number of times a subject can increase their resting energy expenditure and are considered as an indicator of health and an independent predictor of coronary events and mortality (102,103). Adults usually have METs in the range of 10–12, while the few studies investigating MET levels during effort in elderly people have shown that this number drops to around 6–8 (104,105). This decline in $\dot{V}o_2$ Max and METs with advancing age is due to loss of skeletal muscle mass (106), deterioration in muscle oxidation capacity (107) and a reduced cardiovascular efficiency (108). Reilly et al. (95) showed the association between perioperative complications and asking if the patient would be able to climb two flights of stairs unaided (equivalent to eight METs). This posed uncertainty, as patients have different perceptions of work, number of steps and speed at which they climbed them.

Incremental shuttle walk tests also offer a mean of estimating fitness. This test involves walking incremental ‘shuttles’ of 10m between auditory markers. As the test progresses, the markers get closer to each other; thus the time to walk 10m gets shorter. The test continues until the patient cannot complete one shuttle between the given markers. Murray et al. (109) showed its usefulness to assess perioperative fitness in surgical patients undergoing upper gastrointestinal resection. Together with CPET, the shuttle walk test has also been included as part of the preoperative work-up of patients undergoing lung cancer surgery, as part of the British Thoracic Society algorithm (110). According to Win et al. (111) a distance of 400 m on the shuttle walk test would correlate with a peak oxygen consumption of 15 $ml.kg^{-1}min^{-1}$ on a formal exercise test. However, a recent study by Struthers et al. (90) comparing the

shuttle walk test, the DASI Questionnaire and CPET shows that the first two discriminate poorly between high-risk and low-risk patients in the surgical population.

The current conviction that investigations, such as exercise ECG, Dipyridamole-thallium scintigraphy (DTS), dobutamine stress echocardiography and transthoracic echocardiography, have a good predictive power to assess fitness prior to major surgery has been questioned by various authors (92–94,112). When considering the latter three tests, these investigations were considered to be subjective, operator dependent, and costly, requiring radioactive substances, patient fasting and highly specialised exercise transthoracic echogenicity, which makes them less suitable for the elderly patient as a risk-stratification tool when compared to a cardiopulmonary exercise test. Evaluating physical fitness using cardiopulmonary exercise testing (CPET) has been used extensively for risk prediction prior to thoracic or abdominal surgery. The use of CPET as a risk predictor and its relationship to surgical outcome will be discussed in Section 2.5.2.

2.5.2 CARDIOPULMONARY EXERCISE TESTING - THE RELATIONSHIP BETWEEN PHYSICAL FITNESS AND SURGICAL OUTCOME

Almost two decades ago, Older and colleagues identified an association between low physical fitness as determined by CPET, and poor patient outcome following non-cardiopulmonary surgery (113). Based on this and subsequent published literature, CPET-derived variables have been increasingly adopted as the objective measure of fitness prior to surgery, particularly within the National Health Service in the UK (114). Information derived from CPET is now used to inform operative decisions, choice of peri- and intraoperative management, as well as to inform discussions of operative risk with patients. This section aims to provide the reader with a review of the current literature pertaining to the value of CPET as a perioperative risk assessment tool and the relationship between CPET variables and surgical outcome in the management of patients undergoing major abdominal surgery.

Cardiopulmonary exercise testing is a well tolerated, non-invasive, cost-effective way of performing perioperative risk assessment in patients who are scheduled to undergo high-risk procedures. It is also useful for those who are at high risk of postoperative complications due to advanced age or poor nutritional status, and for those with a history of cardiopulmonary morbidity. It provides a global assessment of the integrated response to increasing aerobic work involving the cardiovascular, respiratory, neuropsychological and skeletal muscle

systems, all of which are activated during the metabolic stress response to surgery (115). It allows evaluation of the integrated oxygen delivery system when the demand for oxygen is high and the system is required to function near to its maximum capacity. Despite requiring a moderate to high level of exertion, CPET is well tolerated by patients and is safe to conduct on most patient cohorts (116). Variables derived from CPET, along with the physiological basis of those variables, the derivation of the lactate threshold and also the methodology of conducting a CPET will be further described in Section 3.2.

Older et al. (117) showed that cardiovascular mortality was virtually restricted to patients with a $\dot{V}o_2$ at estimated lactate threshold ($\hat{\theta}_L$) of less than 11 $ml.kg^{-1}min^{-1}$. Since this publication in the early 1990s, a large number of studies have addressed the association between CPET-derived variables and perioperative outcome in a variety of clinical contexts. Several of these have also evaluated the predictive utility of CPET-derived variables as a means of describing perioperative risk in clinical practice. This next section reviews this literature to evaluate the utility of CPET as a risk stratification tool prior to major abdominal surgery. Section 2.5.2.1 is an updated version of a literature review I have published in 2011 (LL– acknowledged) (4).

2.5.2.1 MAJOR INTRA-ABDOMINAL SURGERY

Older et al. (117) recorded the presurgical $\dot{V}o_2$ at $\hat{\theta}_L$ of 187 elderly patients undergoing major intra-abdominal surgery. They found that an $\dot{V}o_2$ at $\hat{\theta}_L$ <11 $ml.kg^{-1}min^{-1}$ was associated with increased cardiovascular mortality. In patients with a low $\dot{V}o_2$ at $\hat{\theta}_L$ and preoperative ischaemia, the mortality rate was 42%, in comparison with 4% in patients not meeting these criteria. This established the idea of preoperative risk stratification and provision of increased postoperative care for high-risk patients. In a latter study and clinical review (113,104) Older investigated the impact of triaging patients on the basis of such data. If a patient had an $\dot{V}o_2$ at $\hat{\theta}_L$ of less than 11 $ml.kg^{-1}min^{-1}$, they were assigned to ICU preoperatively. This accounted for 28% of the patients. Of the 9 patients who died postoperatively from cardiopulmonary complications, 7 had an $\hat{\theta}_L$ <11 $ml.kg^{-1}min^{-1}$, and the other two were in the high dependency unit (HDU) category. No deaths were recorded in the patients admitted to the ward.

Assessing 843 patients undergoing major colorectal, radical nephrectomy and cystectomy surgery, Wilson et al. (120) concluded that a $\dot{V}o_2$ at $\hat{\theta}_L$ of 10.9 $ml.kg^{-1}min^{-1}$ or less and a

ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) of 34 or more had a sensitivity of 88% and a specificity of 47% for hospital mortality. Survival at 90 days was significantly greater in patients with an $\hat{\theta}_L$ of greater than 11 (p=0.034), $\dot{V}_E/\dot{V}CO_2$ less than 34 (p=0.021) and in patients without ischaemic heart disease (p=0.02).

Snowden et al. (121) also evaluated the use of CPET in preoperative risk assessment in a surgical population (age mean 70 years). They reported the relationship between CPET derived variables and morbidity after major intra-abdominal surgery and showed that an $\hat{\theta}_L$ of 10.1 $ml.kg^{-1}min^{-1}$ had a sensitivity (88%) and specificity (79%) for the prediction of postoperative complications. In a follow up study Snowden et al. (122) studied the relationship between cardiorespiratory fitness and age in the context of postoperative mortality and morbidity in older people undergoing hepatobiliary surgery. 389 adults with a mean age of 66 years (range 26–86 years) were included. They conclude that the anaerobic threshold was the most significant independent predictor for postoperative mortality (p=0.003 and odds ratio=0.52) in 18 of 389 (4.6%) patients who died during their in-hospital stay, and that age was not a significant predictor. Older people with normal cardiorespiratory fitness spent the same number of days in the hospital or critical care unit as younger people with similar cardiorespiratory fitness (13 vs. 12; p=0.08 and 1 vs. 1; p=0.103 respectively). Patients older than 75 years with low cardiorespiratory fitness spent a median of 11 days longer in hospital (23 vs. 12; p<0.0001) and 2 days longer in critical care (2.9 vs. 0.9; p<0.0001) when compared with patients with adequate cardiorespiratory fitness.

In a smaller study of 32 patients undergoing major intra-abdominal surgery, Hightower et al. (87) reported that an $\hat{\theta}_L$ less than 75% of the predicted value identified those at increased risk of complications [area under curve (AUC) 0.72; sensitivity 88%; specificity 79%; p=0.016]. A particular strength of the studies by Snowden and Hightower is that clinicians were blinded to the CPET results, ensuring that these did not influence patient care or data collection based on the CPET results. This should give a more accurate reflection of the true magnitude of association between CPET variables and outcome by removing the effect of confounding due to clinicians acting on CPET variables, which could influence outcome (e.g. choice of level of postoperative care or type of surgery received by the patient) (123).

Junejo et al. (124) evaluated the use of preoperative CPET in predicting outcome following major hepatic resection. Two hundred and four patients were assessed for hepatic resection, of whom 108 had preoperative CPET. An $\hat{\theta}_L$ of 9.9 $ml.kg^{-1}min^{-1}$ predicted in-hospital death and subsequent survival. Below this value, $\hat{\theta}_L$ was 100% sensitive and 76% specific for in-

hospital mortality. Age and $\dot{V}_E/\dot{V}CO_2$ at $\hat{\theta}_L$ (34.6 = 84% specificity and 47% sensitivity) were also significantly related to postoperative complications. Long-term survival of those with an $\hat{\theta}_L$ of less than 9·9 $ml.kg^{-1}min^{-1}$ was significantly worse (Hazard ratio for mortality 1.81, 95% confidence interval (CI), 1.04–3·17; p = 0.036).

Otto et al. (125) evaluated patients awaiting abdominal and pelvic surgery. Four hundred and fourteen patients were studied. They found that $\dot{V}o_2$ at $\hat{\theta}_L$ values in Crohn's disease were lower than colorectal cancer (11.4±3.4 vs. 13.2± 3.5 $ml.kg^{-1}.min^{-1}$, p=0.03) and for all other colorectal disease groups combined (12.6±3.5 $ml.kg^{-1}.min^{-1}$, p=0.03). $\dot{V}o_2$ at $\hat{\theta}_L$ of Ulcerative colitis and Crohn's disease patients together were reduced compared to population reference values ($p<0.05$). This cohort of patients may impact CPET variables differently than standard benign or malignant preoperative patients. The reason for low $\dot{V}o_2$ at $\hat{\theta}_L$ remains to be defined.

Ausania et al. (126) undertook a prospective review of 124 patients who underwent pancreaticoduodenectomy and CPET. They found that a low $\dot{V}o_2$ at $\hat{\theta}_L$ was significantly associated with pancreatic anastomotic leaks, postoperative complications and prolonged hospital stay. On multivariable analysis, an $\dot{V}o_2$ at $\hat{\theta}_L$ of 10·1 $ml.kg^{-1}min^{-1}$ or less was the only independent factor associated with pancreatic anastomotic leaks. Chandrabalan et al. (127) undertook a similar retrospective review of a hundred patients who underwent pancreaticoduodenectomy or total pancreatecomy for pancreatic head lesions. They found that an $\dot{V}o_2$ at $\hat{\theta}_L$ of <10 $ml.kg^{-1}.min^{-1}$ had a significantly greater incidence of postoperative pancreatic fistula and major intra-abdominal abscesses (Clavien-Dindo Grade III-IV 22.4% vs. 7.8%). These patients were subsequently less likely to undergo adjuvant therapy. Also a low $\dot{V}o_2$ at $\hat{\theta}_L$ was associated with a prolonged length of hospital stay. Junejo et al. (128) conducted a prospective cohort study of patients undergoing pancreaticoduodenectomy. Neither $\dot{V}o_2$ at $\hat{\theta}_L$ nor $\dot{V}o_2$ Max predicted morbidity or mortality; however $\dot{V}_E/\dot{V}CO_2$ at $\hat{\theta}_L$ with a threshold of 41 was predictive for postoperative mortality (75% sensitive and 95% specific).

Colson et al. (129) undertook a review of 1725 patients referred for CPET that subsequently underwent major surgery. Thirty-six percent died within 5 years. Death was associated with gender, type of surgery (worst for upper gastrointestinal and best for vascular surgery) and forced vital capacity.

In summary, the above studies agree that selected CPET variables have a predicative value in determining postoperative complications and length of hospital stay across a range of intra-abdominal surgical procedures.

2.5.2.2 VASCULAR SURGERY

A recently published systematic review by Young et al. (130) was performed to assess the role of CPET in the preoperative evaluation of patients with abdominal aortic aneurysms or peripheral vascular disease requiring surgery. They concluded that there are major limitations including small sample sizes, lack of blinding, and an absence of reporting standards. They also say that the paucity of robust data precludes routine adoption of CPET in risk stratifying patients undergoing major vascular surgery and that the use of CPET should be restricted to clinical trials and experimental registries. However, I believe that the evidence to date suggests CPET is of valuable prognostic assessment prior to abdominal aortic aneurysm surgery and as such merits consideration as a preoperative investigation. Young et al. review six studies (90,131–135), with the largest three all reporting that CPET was a useful predictor of outcome in patients undergoing abdominal aortic aneurysm repair. One of the included studies, by McEnroe and Wilson (135) was actually a retrospective audit of 119 patients, published only in abstract form. The other three peer-reviewed studies mentioned in the review were all of 30 or fewer patients and were therefore likely to lack the power to detect the influence of CPET results on patient outcome. One of the studies, Kothmann et al. (132), did not even report outcome data and was designed as a test of inter-individual (test–retest) variability; it is difficult to understand why such a study was included in a systematic review of this nature. Furthermore, all of the 'grey literature' articles listed in the article (eight studies) supported the use of CPET in the setting of AAA repair.

Carlisle et al. (133) retrospectively studied the association between four CPET markers ($\dot{V}o_2$ at peak, $\dot{V}o_2$ at $\hat{\theta}_L$, $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$), four other risk stratification methods (revised cardiac risk index (RCRI), POSSUM, simplified acute physiology score (SAPS) II and the acute physiology and chronic health evaluation (APACHE) II) and all-cause mortality following abdominal aortic aneurysm (AAA) repair. The study differs from other CPET articles in non-cardiopulmonary surgery, in that the mortality was not only measured in the initial postoperative period, but also up to a median of 35 months. Of the 130 patients studied, a total of 29 (22.3%) died by the time of their last follow-up, 14 (10.8%) doing so in hospital within 30 days of surgery. All CPET variables correlated with mid-term survival, as

did the other four risk stratification methods, although to a lesser degree. The $\dot{V}_E/\dot{V}CO_2$ had the strongest association with mortality rate at 30 days and at mid-term (hazard ratio for mortality was 1.14 (95% CI, 1.08–1.20; p<0.001)). A $\dot{V}_E/\dot{V}CO_2$ value of ≥42 and RCRI >1 were found to be the optimal thresholds to distinguish patients at increased risk of death. Very recent publications by Hartley (136), Prentis (137) and Thompson (134) et al. agree that a low $\dot{V}o_2$ at $\hat{\theta}_L$ is associated with postoperative complications, prolonged length of hospital stay, prolonged length of critical care stay, and early death following abdominal aortic aneurysm surgery. They conclude that CPET has become increasingly important in determining the optimum management for these patients and that clinical management, patient decision making and risk stratification can be reliably informed by CPET.

2.5.2.3 UPPER GASTOINTESTINAL AND BARIATRIC SURGERY

In 1994, Nagamatsu et al. investigated the association between CPET derived variables and outcome following upper gastrointestinal (GI) surgery. They analysed data from 52 patients who had a right thoracolaparotomy for thoracic oesophageal cancer, and observed significant differences in $\dot{V}o_2$ Max and $\dot{V}o_2$ at $\hat{\theta}_L$ (both normalised to body surface area) between patients with and without postoperative cardiopulmonary complications. In a follow-up study (138), they retrospectively analysed data from 91 patients (mean age 59 years) who had undergone an oesophagectomy with three-field lymphadenectomy for squamous cell carcinoma and preoperative CPET. Consistent with their original study, $\dot{V}o_2$ Max values (normalised to body surface area) were significantly lower in the cohort of patients that experienced cardiopulmonary complications than in those without complications (p<0.001). However, no association was observed between complications and $\dot{V}o_2$ at $\hat{\theta}_L$. In a later study, Forshaw (139) investigated the capacity of CPET markers to predict patients at increased risk of postoperative complications following oesophagectomy. Consistent with previous CPET studies in patients undergoing upper GI surgery, $\hat{\theta}_L$ did not differ between those with and without cardiopulmonary complications.

The association between CPET variables and outcome following bariatric surgery was also investigated in 109 obese patients (mean body mass index (BMI) 48.1 kg/m^2) undergoing laparoscopic Roux-en-Y gastric bypass surgery (140). Primary outcome variables assessed were death, unstable angina, myocardial infarction, deep vein thrombosis, pulmonary embolus, renal failure and stroke; secondary outcomes were hospital length of stay (LOS)

and readmission. The population was divided into tertiles according to $\dot{V}o_2$ at peak values achieved during treadmill exercise. The rate of complications and length of hospital stay was significantly higher for the first tertile. The $\dot{V}o_2$ at peak threshold value of 15.8 $ml.kg^{-1}min^{-1}$, (which was the upper boundary of the lowest tertile), had a sensitivity of 75% and a specificity of 73% to predict the occurrence of postoperative complications. These results indicate that for a morbidly obese population having bariatric surgery, an $\dot{V}o_2$ at peak less than or equal to 15.8 $ml.kg^{-1}min^{-1}$ has a reasonable capacity to predict those at increased risk of postoperative complications and longer hospital stay.

In a recent paper published by Hennis et al. (141) $\dot{V}o_2$ at $\hat{\theta}_L$ was lower in patients with postoperative complications than in those without (9.9 (1.5) vs. 11.1 (1.7) $ml.kg^{-1}min^{-1}$, p=0.049) and in patients with a LOS >3 days compared with LOS ≤3 days (10.4 (1.4) vs. 11.3 (1.8) $ml.kg^{-1}min^{-1}$, p=0.023). Receiver operator characteristic curve (ROC) analysis identified $\dot{V}o_2$ at $\hat{\theta}_L$ as a significant predictor of LOS >3 days (AUC 0.640, p=0.030). They conclude that $\dot{V}o_2$ at $\hat{\theta}_L$, predicts LOS after gastric bypass surgery.

2.5.2.4 TRANSPLANT SURGERY

In a study performed by Epstein et al (142) in 2004, symptom-limited CPET conducted at an average of 15 months before surgery, was found to be associated with short-term outcome after hepatic transplantation. Specifically, they found that reduced aerobic capacity as defined by a reduced peak $\dot{V}o_2$ (% predicted) and reduced $\dot{V}o_2$ at $\hat{\theta}_L$ was associated with increased mortality during the first 100 days after hepatic transplantation. Non-survivors were more likely to have a peak $\dot{V}o_2$ of less than 60% predicted (p=0.04) and an $\dot{V}o_2$ at $\hat{\theta}_L$ of less than 50% predicted (p=0.03).

Very recently, Snowden and colleagues (143) assessed the feasibility of preoperative submaximal CPET in determining the cardiopulmonary reserve in patients being assessed for liver transplantation and its potential for predicting 90-day post-transplant survival. Sixty of the 182 patients (33%) underwent liver transplantation, and the mortality rate was 10% (6/60). The mean $\dot{V}o_2$ at $\hat{\theta}_L$ value was significantly higher for survivors versus non-survivors (12.0 ± 2.4 versus 8.4 ± 1.3 $ml.kg.^{-1}min^{-1}$, p<0.001). Logistic regression revealed that $\dot{V}o_2$ at $\hat{\theta}_L$, donor age, blood transfusions and fresh frozen plasma transfusions were significant univariate predictors of outcomes. In a multivariate analysis, only $\dot{V}o_2$ at $\hat{\theta}_L$ was

retained as a significant predictor of mortality. A ROC curve analysis demonstrated sensitivity and specificity of 90.7% and 83.3%, respectively, with good model accuracy (CI 0.82–0.97, p=0.001). The optimal $\dot{V}o_2$ at $\hat{\theta}_L$ level for survival was defined as >9 ml.kg^{-1}min^{-1}.

2.5.3 THE ASSOCIATION OF PHYSICAL FITNESS AND POSTOPERATIVE MORBIDITY AFTER MAJOR RECTAL CANCER SURGERY – THE AINTREE EXPERIENCE

Between January 2010 and December 2011, I recruited patients as part of a single-centre, prospective, observation cohort study to test the hypothesis that CPET variables are related to in-hospital morbidity in patients undergoing major rectal cancer surgery (144). This follows on a previous study which I initiated in 2009 studying the same hypothesis in patients undergoing colonic surgery (145). All patients underwent a CPET at 2 weeks prior to starting NACRT or 2 weeks prior to undergoing major surgery. All patients were followed prospectively during their postoperative period. Short-term surgical outcome was assessed by medical and nursing staff blind to any CPET data using the 9 domains listed in the Post-Operative Morbidity Survey (POMS) (146) on day 5, Clavien-Dindo Classification (highest grade for the most serious sustained in-hospital complication) and in-hospital mortality. In the present study, I chose to use a simple score of postoperative morbidity as a primary outcome measure, due to the considerable importance this has to early recovery and length of stay. The POMS has previously been used in a clinical setting in both the United Kingdom and United States and will also be used as the main morbidity measure in subsequent chapters of this thesis (Chapters 4 to 7). Length of hospital stay (days) was recorded prospectively, and patients were followed up to 1 year for mortality. The colorectal MDT (including anaesthetists) and the medical staff collecting the outcome data were blind to all CPET data. In this study our primary variable of interest was $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg^{-1}.min^{-1}). Exploratory variables included $\dot{V}o_2$ at Peak exercise (ml.kg^{-1}.min^{-1}). Here the primary aim was to establish the relationship between postoperative complications (assessed by POMS present or absent on day 5) and $\dot{V}o_2$ at $\hat{\theta}_L$. I also aimed to explore the multivariable relationship between CPET variables and postoperative in-hospital complications.

One hundred and five patients were recruited, of whom 10 had no surgery (3 due to patient choice, 7 due to irresectable metastasis). All 95 patients (72 male and 23 female) who had adequate CPET and underwent major elective surgery had complete outcome data. 68

patients (72%) underwent NACRT. 66 patients (70%) underwent an anterior resection, 22 (23%) an abdominoperineal resection, 4 (4%) a Hartman's procedure and 3 (3%) other major rectal resections. Patient demographics differed significantly in BMI (p=0.003) and preoperative heart failure (p=0.008). There was no difference in cancer therapy, clinical or pathological staging between patients with and without postoperative morbidity. Patients with a complication had significantly lower $\dot{V}o_2$ at $\hat{\theta}_L$ (12.7 vs. 9.4 ml.kg^{-1}.min ^{1}; p<0.0005), $\dot{V}o_2$ at Peak (21.8 vs. 15.8 ml.kg^{-1}.min ^{1}; p<0.0005), Workload at $\hat{\theta}_L$ (65 vs. 45.5W; p<0.0001) and Oxygen pulse at $\hat{\theta}_L$ (9.4 vs. 8.0 ml.beat^{-1}; p=0.004).

Forty-six patients (48%) sustained an in-hospital complication. No 30-day mortality was registered. The median number of complications on day 5 (POMS day 5) was 1 (IQ range, 0–2). Pulmonary, infective, gastrointestinal, cardiovascular and wound complications differed between groups (p=0.001, p<0.0005, p=0.014, p=0.019, p=0.01 respectively).

Independently $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak were significantly associated with in-hospital morbidity (p<0.0001). For $\dot{V}o_2$ at $\hat{\theta}_L$, AUC was 0.87 (CI 0.78-0.95), whilst the optimal cut-point was 10.6 ml.kg^{-1}.min^{-1}, giving a sensitivity of 84% and a specificity of 92%. For $\dot{V}o_2$ at Peak AUC was 0.85 (CI 0.77-0.93), whilst the optimal cut-point was 18.6 ml.kg^{-1}.min^{-1}, giving a sensitivity of 82% and a specificity of 80%.

For multivariable logistic regression, from the 5 candidate variables, $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak were retained in the final model. However, since neither variable meaningfully contributed to the other (they are highly correlated), univariate models were used instead. Due to the dichotomisation this resulted in two identical models. As a result, the odds of POMS day 5 surgical morbidity were reduced by 93% for patients above the median compared with those below the median (OR 0.07, CI 0.03-0.19, p<0.0001). The medians were 11.2 ml.kg^{-1}.min^{-1} and 18.8 ml.kg^{-1}.min^{-1} for $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak respectively. Additionally a sensitivity analysis was conducted whereby the same multivariable selection procedure was used with NACRT (yes/no) as an additional covariate. NACRT was not retained in the final model which was unsurprising given a univariate logistic regression p-value of 0.963.

Overall median length of stay was 9 days (IQ range 6–16 days). Patients with no POMS defined morbidity on Day 5 had a median length of stay of 7 days (IQ range 6–9) compared with 15 days (IQ range 7–24) in patients with POMS-defined morbidity on Day 5

($p<0.0001$). All patients were followed up to 1 year postoperatively for mortality. 7 patients died within 1 year of their operation; all had an $\dot{V}o_2$ at $\hat{\theta}_L$ of <10.6 $ml.kg^{-1}.min^{-1}$ and suffered from postoperative in-hospital morbidity.

This study further supports the literature presented in Section 2.5.2.1. Here, I have shown that CPET variables namely $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak are the best prognostic markers of postoperative complications for this cohort, with a high sensitivity and specificity when compared to other studies (113,121,124). The identification of $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak as a predictor for short term outcome in rectal cancer surgery is novel. This study inspired future work which is presented in Chapter 4 where the effect of NACRT on physical fitness and postoperative morbidity will be explored in the same patient cohort. Furthermore, in Chapter 5 and 6, I endeavour to study the effects of NACRT and a novel prehabilitation exercise programme on objectively measured physical fitness and postoperative outcome in locally advanced rectal cancer patients.

2.6 IMPROVING PHYSICAL FITNESS WITH PREOPERATIVE EXERCISE IN ABDOMINAL CAVITY CANCER PATIENTS

Traditionally, efforts have been made to improve the postoperative recovery process by intervening after major surgery. The preoperative period may be a more emotionally salient time to intervene with regard to the factors that contribute to recovery as, beyond the physical benefits, active engagement of the individual in the preparation process is likely to alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process.

We now know that aerobic exercise training is beneficial in improving physical fitness in a variety of patient populations (147–150), even over a short time period. Aerobic training augments cardiac, respiratory and musculoskeletal functions, therefore implementing a preoperative training intervention to improve physical fitness prior to major cancer surgery would appear plausible. Preoperative conditioning before a stressful event (i.e. surgical trauma) is termed prehabilitation (151). The goal of prehabilitation is to improve preoperative physical fitness through an exercise intervention programme in an attempt to accelerate postoperative recovery.

There is nascent literature in this area suggesting that, notwithstanding the time constraints imposed by the surgical timetable, exercise training may provide benefit in this patient group. In this systematic review of the literature I concentrated on attempting to answer several key questions, namely: Can pre- and postoperative exercise training improve fitness? Does any improvement in fitness translate into an improvement in outcome? Do patients benefit from this approach? What are the key elements of perioperative training interventions – modality, frequency, duration, intensity and pattern?

Whilst I have already discussed the predictive utility of CPET derived variables in Section 2.5, there is now convincing evidence that physical fitness is associated with outcome following major surgery; i.e. less fit patients having a greater risk of complications and death postoperatively. This has led to the hypothesis that prehabilitation would improve physical fitness and thereby reduce the incidence of adverse surgical outcomes. There is emerging evidence that such 'prehabilitation' may also improve HRQL and fitness levels, however, there have been few adequately powered randomised trials in this field and there is little current evidence to support the benefits of prehabilitation in terms of improving surgical outcome. On the other hand, rehabilitation following other acute stressors has been extensively used and is now common NHS practice e.g. following cardiac events (cardiac rehabilitation) (150) and also following chronic obstructive pulmonary disease exacerbations (pulmonary rehabilitation) (152).

2.6.1 PREOPERATIVE AEROBIC EXERCISE TRAINING IN ELECTIVE INTRA-CAVITY SURGERY: A SYSTEMATC REVIEW

I recently published a literature review (153) on perioperative exercise training in elderly subjects, this was then followed up by a systematic review of preoperative aerobic exercise training in elective intra-cavity surgery (154) which I co-authored. In this section I will provide an overview of this systematic review. Appendix 4 provides full details about methodology, search strategy, inclusion and exclusion criteria, data extraction and analysis details, details regarding the quality assessment tool used, as well as a list of excluded studies. Ten studies were included in this review. Table 2.1 includes characteristics of these included studies. The search identified studies using preoperative aerobic exercise training interventions with reported measures of physical fitness having been performed in patients undergoing gastrointestinal (5 studies, 219 patients),(155–159) thoracic (4 studies, 59 patients),(160–163) and cardiac (1 study, 246 patients) (164) surgery. All studies were single-centre and the median number of patients recruited was 20.5; only 2 studies recruited

more than 100 patients. Two studies employed a control group (158,164) and two employed a sham intervention (156,157). Seven of the 10 studies were published within the last 5 years. Mean patient age ranged from 55-71 years across the studies.

Patient outcome measures following surgery were reported in 7 studies and are presented in Table 2.2. Arthur et al. reported a significantly shorter hospital and intensive care unit length of stay in the intervention group (164). Asoh et al. reported that of the 4 patients deemed "unfit" at surgery, despite aerobic exercise training, all developed postoperative complications and 2 died of heart failure within 30 days of their operation. In the group deemed to be "fit", 12% developed postoperative complications and one died within one year of the operation due to inoperable gastric cancer (155). Two studies found no differences between the intervention and sham intervention group in postoperative clinical outcome measures (156,157).

The measures of physical fitness before and after the exercise intervention are presented in Table 2.3. Eight studies reported a significant improvement in at least one measure of physical fitness. Four studies showed significant improvement in $\dot{V}o_2$ at Peak with aerobic exercise training. In the next sections I will review the characteristics of the exercise interventions adopted in various trials included in this review (Section 2.6.1.1), the feasibility and safety of such interventions (Section 2.6.1.2) and I shall also give a brief summary of each of the included trials (Section 2.6.1.3).

Study	Country	Journal	Study design	Number of Centres	N	Mean Age (Years)	Patient Surgery Group	Exercise Intervention
Arthur et al. (164)	Canada	Annals of Internal Medicine	RCT with concealed randomisation	Single	246 (37F)	I: 62 C: 64	Coronary Artery Bypass Graft	Aerobic Interval
Asoh et al. (155)	Japan	The Japanese Journal of Surgery	Observational	Single	29 (NR)	68	GI	Aerobic Continuous
Bobbio et al. (161)	Italy	European Journal of Cardio-Thoracic Surgery	Observational pilot	Single	12 (2F)	71	Lung Cancer ($\dot{V}o_2$ at Peak <15ml/kg/min)	Aerobic Continuous, Strength, Breathing Exercises
Carli et al. (156)	Canada	British Journal of Surgery	RIT	Single	112 (47F)	I: 61 SI: 60	Colorectal	Aerobic Continuous, Strength
Cesario et al. (162)	Italy	Lung Cancer	Observational pilot	Single	8 (NR)	NR	Lung Cancer (deemed unfit for surgery)	High Intensity Continuous, Breathing & Abdominal Exercise
Debigaré et al. (163)	Canada	Journal of Cardiopulmonary Rehabilitation	Observational	Single	19 (7F)	61	Lung Volume Reduction (emphysema)	Aerobic Continuous, Strength
Dronkers et al. (157)	Holland	Clinical Rehabilitation	Single blind RIT	Single	42 (11F)	I: 71 SI: 69	GI Cancer	Aerobic Continuous, Strength, Breathing Exercises
Jones et al. (160)	Canada	Cancer	Observational	Single	20 (14F)	65	Lung Cancer (NSCLC)	Aerobic Continuous and Interval
Kim et al. (158)	Canada	The Tohoku Journal of Experimental Medicine	RCT (2:1, I:C)	Single	21 (8F)	I: 55 C: 65	Colorectal	Aerobic Continuous
Timmerman et al. (159)	Holland	Physiotherapy Theory and Practice	Observational	Single	15 (3F)	59	GI	Aerobic Continuous

Table 2.1 – Preoperative Aerobic Exercise Training Study Characteristics. RCT, randomised controlled trial; RIT, randomised intervention trial comparing intervention with sham intervention; F, female; I, intervention; C, control; SI, sham intervention; NR, no record; NSCLC, non-small cell lung cancer; GI, Gastrointestinal.

Study	Postoperative complications (patients)	Length of hospital stay (Days (SD))	In-hospital mortality (patients)	Long-term mortality (patients)
Arthur et al. (164)	NR	I: 5 * C:6	NR	1 (within 6 months)[1]
Asoh et al. (155)	"Fit"- 3/25, "Unfit" - 4/4	NR NR	"Fit" - 0/25, "Unfit" - 2/4	"Fit"- 1/25 (Within 3 months) "Unfit" – 3/4 (within 3 months)
Bobbio et al. (161)	8 of 11	17.5 ±14.8	NR	0 (follow up period not stated)
Carli et al. (156)	NR	I: 11.9 ±34.6 SI: 6.6 ±3.6	NR	NR
Cesario et al. (162)	2/8	NR	NR	0 (follow up period not stated)
Dronkers et al. (157)	I: 9 SI:8	I: 16.2 ±11.5 SI: 21.6 ±23.7	NR NR	NR NR
Jones et al. (160)	7 of 20	NR	NR	NR

Table 2.2 – Preoperative Aerobic Exercise Training Clinical Outcomes. * denotes a statistically significant difference ($P<0.05$); [1] group allocation not reported; NR, No record; Fit, achieved plateau in HR during a constant load exercise test; Unfit, did not achieve plateau in HR during a constant load exercise test; I, Intervention; C, Control; SI, Sham intervention.

Study	N	Measure	Group	Baseline (mean ±SD)	Post Intervention (mean ±SD)	Improvement
Arthur et al. (164)	246 (37F)	$\dot{V}o_2$ at Peak ($ml.min^{-1}$)	I	1327.6 ±320	NR	N
			C	1201.2 ±288	NR	N
Asoh et al. (155)	11 (NR)	Achieved steady state HR	I	11 of 29 "unfit"	4 of 29 "unfit"	7 of 11
Bobbio et al. (161)	12 (2F)	$\dot{V}o_2$ at Peak ($ml.kg.^{-1}min^{-1}$)	I	13.5 ±1.3	16.3 ±1.9	Y (P<0.001)
		$\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg.^{-1}min^{-1}$)	I	10.1 ±1.9	13.4 ±3.3	Y (P<0.02)
		WR peak (W)	I	65 ±14	79 ±19	Y (P<0.001)
Carli et al. (156)	112 (47F)	6 MWD (m)	I	474.3 ±15.1	463.6 ±18.5	N
			SI	494.1 ±15.5	502.8 ±15.8	N
		$\dot{V}o_2$ at Peak ($ml.min^{-1}$)	I	1395 ±76	1529 ±88	Y (P=0.003)
			SI	1400 ±71	1511 ±84	Y (P=0.007)
Cesario et al. (162)	8 (NR)	6MWD (m)	I	261 ±97	340 ±66	Y (P<0.05)
Debigaré et al. (163)	19 (7F)	$\dot{V}o_2$ at Peak ($ml.min^{-1}$)	I	630 ±172	698 ±207	Y (P<0.05)
		WR peak (W)	I	37.6 ±12.1	44.7 ±16.2	Y (P<0.05)
		6MWD (m)	I	354 ±116	425 ±110	Y (P<0.01)
		TTE (s)	I	201 ±162	710 ±668	Y (P<0.01)
Dronkers et al. (157)	42 (11F)	Predicted $\dot{V}o_2$ at Peak ($ml.kg.^{-1}min^{-1}$)	I	29.4 ±9.5	27.6 ±6.5	N
			SI	31.6 ±6.5	32.9 ±6.9	N
Jones et al. (160)	20 (14F)	$\dot{V}o_2$ at Peak ($ml.kg.^{-1}min^{-1}$)	I	15.7 ±3.7	18.0 ±3.4	Y (P=0.002)
		6MWD (m)	I	438 ±77	478 ±75	Y (P=0.03)
		WR peak (W)	I	82 ±24	91 ±30	N (P=0.055)
Kim et al. (158)	21 (8F)	$\dot{V}o_2$ at Peak ($ml.kg.^{-1}min^{-1}$)	I	21.5 ±10.1	20.9 ±8.7	N
			C	20.3 ±4.6	19.9 ±5.6	N
		WR peak (W)	I	103 ±57	117 ±57	Y (P<0.05)
			C	109 ±39	109 ±39	N
		$\dot{V}o_2$ Submax ($ml.kg.^{-1}min^{-1}$)	I	18.9 ±8.5	16.9 ±7.4	Y (P<0.05)
			C	17.5 ±4.7	17.0 ±4.7	N
		6MWD (m)	I	436 ±64	467 ±80	N
			C	478 ±99	504 ±103	N
Timmerman et al. (159)	15 (3F)	Predicted $\dot{V}o_2$ at Peak ($ml.kg.^{-1}min^{-1}$)	I	25 ±0.5	33 ±0.9	Y (P=0.002)

Table 2.3 - Changes in objective measures of fitness; I, Intervention; C, Control; SI, Sham Intervention; N, no; Y, yes; HR, heart rate; Unfit, unable to achieve a plateau in HR during a constant load exercise test; TTE, time to exhaustion during a constant load exercise test; $\dot{V}o_2$ Submax, oxygen consumption during a constant load sub maximal exercise test

2.6.1.1 CHARACTERISTICS OF EXERCISE INTERVENTIONS

Characteristics of the interventions (frequency, intensity and duration) are reported in Table 2.4. The frequency of the exercise sessions ranged from 2 to 14 sessions per week and lasted between 20 and 180 minutes per session. The duration of the interventions ranged from 1 to 12 weeks. Nine of the aerobic exercise training studies utilised continuous aerobic exercise for part or all of the exercise session, one study used only interval aerobic exercise (164). Strength training, involving weight lifting, was incorporated into 4 of the training interventions (156,157,161,163). Breathing exercises were incorporated into three of the training interventions (157,161,162).

The intensity of the aerobic exercise training component of the interventions varied across studies. One study required patients to exercise continuously, keeping heart rate below 130bpm (155). Seven studies used intensities based on an initial exercise test (156,160–164). Intensities between 40% and 85% of maximum heart rate (HRmax), heart rate reserve (HRR); HRmax minus resting heart rate, Work load at peak, functional capacity and $\dot{V}o_2$ at Peak were used. Two studies used a combination of the Borg score (between 11-16) and 40-65% HRR or 55-75% HRmax (157,158). One study included one interval exercise session per week in addition to 4 continuous exercise sessions per week. The interval exercise session involved exercise at 100% $\dot{V}o_2$ at Peak for 30 seconds followed by a 60 second rest, repeated 10-15 times (160).

The aerobic exercise training sessions were performed in-hospital for six of the studies, at home for three of the studies and a combination of hospital and home aerobic exercise training for one of the studies.

2.6.1.2 FEASIBILITY AND SAFETY OF EXERCISE INTERVENTIONS

The dropout rate for the primary aerobic exercise training intervention, excluding control arms, ranged from 0-17%. Reasons for drop out included; fatigue, sickness, no longer having surgery, having surgery at another institution, myocardial infarction, undergoing a surgical procedure not related to the study, COPD exacerbation, death of spouse, unable to participate due to work commitments. Adherence was reported in six of the studies. In five of the studies, adherence was reported as a percentage of the total number of exercise sessions completed and ranged from 72 to 97%. One study reported a 16% adherence rate,

this was calculated by the number of patients that completed the proposed 3.5 hours per week of physical activity for every week of their training program.

There were 2 exercise related adverse events (AEs); drop in systolic blood pressure >20mmHg. There were 15 AEs reported that occurred outside of aerobic exercise training. Twelve were in patients awaiting CABG surgery; eight AEs were in the control group and 4 AEs were in the intervention group. The AEs were; unstable angina (5 control, 1 intervention), myocardial infarction (2 control, 1 intervention), undiagnosed worsening status (1 control, 2 intervention). Three AEs were in patients awaiting lung volume reduction surgery and were due to exacerbation of COPD.

Study	Intervention (N)	Intervention Duration (weeks)	Frequency (per week)	Duration (min per session)	Hospital / Home intervention	Intensity	Exercise adverse Events	Non-exercise Adverse Events	Adherence	Dropout
Arthur et al. (164)	123 (16F)	8	2	90	Hospital	30 mins: 40-70% functional capacity	NR	12	NR	10
Asoh et al. (155)	11 (NR)	1-3	14	20	Hospital	20 mins: HR<130bpm	0	NR	NR	0
Bobbio et al. (161)	12 (2F)	4	5	90	Hospital	30mins:50-80% WRpeak	NR	NR	NR	0
Carli et al. (156)	58 (24F)*	7.7 ±7.6	7	20-45	Home	20-30mins: >50% HRpeak	NR	NR	16% fully adhered	9
Cesario et al. (162)	8 (NR)	4	5	180	Hospital	80% WRpeak	NR	NR	NR	0
Debigaré et al. (163)	19 (7F)	10-12	5	36 ±8	Home	15-45 mins: ≥50% $\dot{V}o_2$ at Peak	0	3	97%	4
Dronkers et al. (157)	22 (7F)	2-4	7	60	Hospital (2 sessions) and Home (5 sessions)	20-30mins: 55-75% HRmax / Borg 11-13	0	NR	In hospital was 97%	3
Jones et al. (160)	20 (14F)	4-6	5	30-40	Hospital	Continuous 20-30mins: 60-65% $\dot{V}o_2$ at Peak; Interval 15 x 30:60s 100% $\dot{V}o_2$ at Peak	2	NR	72%	2
Kim et al. (158)	14 (5F)	3.8 ±1.2	7	20-30	Home	20-30mins: 40-65% HRR / Borg 11-16	0	NR	74%	2
Timmerman et al. (159)	15 (3F)	5	2	120	Hospital	30-50mins: 65-85%HRR	0	NR	84%	0

Table 2.4 - Frequency, duration, intensity, adverse events and adherence of the exercise intervention

2.6.1.3 SUMMARY OF INCLUDED TRIALS

Arthur et al. (164)

A single centre randomised controlled trial (RCT) (n=246) investigating the effects of an 8 week individualised preoperative aerobic exercise training intervention compared with usual care in patients awaiting coronary artery bypass graft surgery (CABG). The intervention involved aerobic interval exercise training on a cycle ergometer, treadmill or cross trainer (Table 2.4). Physical fitness ($\dot{V}o_2$ at Peak) was not different between groups after 8 weeks of training. Functional status, measured by questionnaire, was higher in the intervention group at the time of surgery. Hospital length of stay and Intensive Care Unit (ICU) length of stay were 1 day fewer in the intervention group.

Asoh and Tsuji (155)

A single centre observational study (n=29) in patients with cardiovascular disease awaiting major intra-abdominal surgery. Fitness levels were identified through a constant load treadmill test. Those who reached a plateau in heart rate were considered to have adequate fitness (n=18) and those who did not were considered to have inadequate fitness (n=11). The inadequate fitness group were exercise trained in-hospital (Table 2.4) and then reassessed for fitness. Seven of 11 patients gained adequate fitness following aerobic exercise training. There was one death due to unresectable cancer and 3 postoperative complications in the adequate fitness group (n=25). All patients with inadequate fitness (n=4) had postoperative complications and 3 patients died. Two deaths were within 30 days of surgery due to cardiac failure, the third was due to metastatic cancer 3 months following surgery.

Bobbio et al. (161)

A single centre observational study (n=12) investigating the effects of preoperative pulmonary rehabilitation in patients awaiting lung resection surgery for stage 1 or 2 non-small cell lung cancer with $\dot{V}o_2$ at Peak <15 ml kg^{-1} min^{-1}. The intervention involved five 90 minute in-hospital sessions of pulmonary rehabilitation per week for 4 weeks and twice-daily breathing exercises at home. The in-hospital pulmonary rehabilitation involved aerobic exercise training (Table 2.4), muscle stretching exercises and free weight exercise training. There were improvements in $\dot{V}O_2$ peak, AT, maximum work rate (WR peak) and oxygen pulse ($\dot{V}O_2$/heart rate). Eight of 11 patients had postoperative pulmonary complications following surgery and one patient did not have surgery.

Cesario et al. (162)

A single centre prospective observational study (n=8) investigating the effects of preoperative pulmonary rehabilitation in patients with operable lung cancer who were denied surgery due to poor pulmonary function. The intervention involved five 3 hour rehabilitation sessions per week for 4 weeks. Each session included incremental cycling or treadmill exercise at 80% of maximum workload, abdominal muscle activities, breathing exercises, and educational sessions. Lung function and 6MWD significantly improved and all patients became eligible for surgery following preoperative pulmonary rehabilitation. There were no deaths and two patients had complications in the immediate postoperative period.

Carli et al. (156)

A single centre randomised intervention trial (n=112) investigating the effects of a preoperative bike and strengthening exercise intervention (intervention) compared with a walking and breathing exercise intervention (sham intervention) in patients awaiting colorectal surgery. The intervention involved daily cycling exercise (Table 2.4), and strength training 3 times per week with upper and lower body exercises using free weights and own body weight exercises. The sham intervention group was encouraged to walk for 30 minutes per day, and perform breathing exercises and leg exercises. Adherence to the exercise interventions was low, particularly in the bike and strengthening exercise group. 6MWD, the primary outcome measure, did not change after exercise training. $\dot{V}o_2$ at Peak improved significantly in both groups. Outcome was measured by assessing 6MWD at approximately 10 weeks post-surgery. A greater number of patients showed an improvement in 6MWD post-surgery in the Control group.

Debigaré et al. (163)

A single centre observational study (n=23) investigating the effects of a preoperative exercise intervention in patients with severe emphysema awaiting lung volume reduction surgery. Patients were tested for aerobic exercise capacity, aerobic endurance, 6MWD, muscle strength, and quality of life before and after an exercise training intervention. The exercise intervention involved 5 sessions per week for 10-12 weeks with a strength and aerobic component to every session. Strength training involved leg, arm and abdominal exercises using resistance bands, with between 10 and 30 reps per exercise. Aerobic exercise training is described in Table 2.4. $\dot{V}o_2$ at Peak, WR peak, peak lactate, peak time to exhaustion, 6MWD, muscle strength and quality of life were significantly improved following preoperative exercise training.

Dronkers et al. (157)

A single centre RIT (n=42) investigating the effects of a preoperative exercise intervention in patients aged ≥60 years awaiting elective colon surgery. The intervention involved a warm-up, strength exercises, breathing exercises, aerobic exercise (Table 2.4), training in functional activities and a cool down. The sham intervention group were encouraged to walk or cycle for >30minutes per day and were given a pedometer and weekly feedback on number of steps achieved. Inspiratory muscle endurance improved significantly in the intervention group. There were no changes in fitness measures between groups and postoperative lengths of stay were similar. Number of steps travelled in the preoperative period was similar between groups. Patients in either group who travelled fewer steps had an increased incidence of postoperative complications following surgery.

Jones et al. (160)

A single centre observational study (n=20) investigating the effects of preoperative aerobic exercise training in patients awaiting lung resection surgery for malignant lung lesions. The intervention is described in Table 2.4. There were two adverse events during aerobic exercise training. $\dot{V}o_2$ at Peak and 6MWD increased significantly after aerobic exercise training, however pulmonary function did not. Adherence was good, those with >80% adherence had significantly greater improvements than those with <80% adherence. Seven patients had postoperative complications.

Kim et al.(158)

A single centre randomized controlled trial (n=21), randomised 2:1 (intervention : control), investigating the effects of a preoperative aerobic exercise training intervention in patients awaiting colorectal surgery. The intervention is described in Table 2.4. The control group were given no formal exercise prescription but were encouraged to perform breathing and circulatory exercises. WR peak improved significantly in the intervention group. $\dot{V}o_2$ at Peak did not change in either group. $\dot{V}o_2$, heart rate and minute ventilation were lower at the same submaximal intensity following the aerobic exercise training program in the intervention group. There were small improvements for 6MWD in both groups.

Timmerman et al. (159)

A single centre observational study (n=39) investigating the effects of preoperative exercise training in patients with intra-abdominal or thoracic cancer awaiting resection surgery. Exercise training involved cycling exercise (Table 2.4), and resistance training of large muscle groups with 3 sets of 12-20 repetitions per muscle exercise at 60-80% of their 1

repetition maximum. Intensity of the resistance training was increased throughout. Predicted $\dot{V}o_2$ at Peak and muscle strength significantly improved following exercise training.

2.6.1.4 DISCUSSION

The principle finding of this review was that preoperative aerobic exercise training was associated with reduced postoperative length of stay in one study of patients undergoing cardiac surgery. However, it remains uncertain whether this intervention is effective in improving postoperative clinical outcome for other intra-thoracic or intra-abdominal surgeries. The secondary findings identified that preoperative aerobic exercise training improved at least one measure of physical fitness in the majority of studies and improved or maintained preoperative HRQL. Moreover, preoperative aerobic exercise training appeared to be a feasible and safe intervention.

The largest (n>100) randomized controlled trial included in this review reported clinical outcome measures and found a reduced hospital and a reduced intensive care length of stay in the intervention group. As such, no conclusions regarding the primary objective of this review could be made, other than in cardiac surgery where preoperative aerobic exercise training was associated with a reduced length of hospital stay. Moreover, eight of 10 studies reported improvement in at least one reported measure of physical fitness following aerobic exercise intervention. These data are promising; however, control groups were employed in only 2 studies, thus limiting the strength of the findings. Several CPET variables were used to quantify improvement in physical fitness. $\dot{V}o_2$ at Peak and $\dot{V}o_2$ at $\hat{\theta}_L$ are probably the most widely accepted measures of fitness used for physical fitness assessment and preoperative risk assessment. However, only 6 studies reported $\dot{V}o_2$ at Peak and 4 used $\dot{V}o_2$ at Peak for primary assessment of change in physical fitness, no studies reported $\dot{V}o_2$ at $\hat{\theta}_L$.

The frequency, duration and intensity of preoperative aerobic exercise training programs varied significantly between studies; however, the majority of studies showed an improvement in physical fitness. Furthermore, aerobic exercise training was feasible, well tolerated and showed an acceptable adherence with only few dropouts from the intervention groups. In one study, greater adherence was associated with larger improvements in physical fitness (160).

Carli and Zavorsky (151) first reviewed the concept of prehabilitation for intra-abdominal and orthopaedic surgery. Only two preoperative aerobic exercise training studies were identified (155,164). The authors acknowledged the limited number of studies and concluded that preoperative aerobic exercise training appeared beneficial in patients awaiting cardiac and abdominal surgery. More recently, Valkenet et al. and Singh et al. (165,166) reviewed the effects of preoperative interventions on surgical outcome. These reviews included a broader range of preoperative interventions including aerobic exercise, breathing exercise and limb strength training, and also included urological and pelvic floor continence surgery. The author's drew similar conclusion in recommending further research into prehabilitation as exercise interventions seemed to improve surgical outcomes. Prehabilitation for joint replacement and for urological/pelvic floor continence surgery was excluded in my present review because prehabilitation, in this context, is predominantly focused on strength, mobility, pelvic floor and biofeedback exercises which is conceptually different to that of aerobic exercise training to improve whole-body physical fitness during the perioperative period.

This section provides an up-to-date review of the current prehabilitation literature incorporating aerobic exercise training in patients awaiting major intra-abdominal and intra-thoracic surgery. The systematic review I carried out was conducted in a rigorous manner using specific search terms to identify relevant articles (seen in Appendix 4). Bias was minimized by having two investigators independently screening candidate articles using predefined criteria. Prehabilitation is a broad term encompassing various interventions with different theoretical underlying mechanisms but have a common goal to improve postoperative clinical outcome. Narrowing the focus to a specific area of prehabilitation, aerobic exercise training, provided meaningful analysis of the practicalities of the intervention and a clearer understanding of its effectiveness.

In conclusion, preoperative aerobic exercise training appears to be beneficial in patients awaiting cardiac surgery; however the effect in patients prior to major intra-thoracic and intra-abdominal surgeries is uncertain. In general, most studies showed the intervention to be effective in improving physical fitness. Preoperative aerobic exercise training was safe, feasible and well tolerated. The optimal design of a preoperative exercise training program however remains unclear. Future studies should report appropriate measures of clinical outcome, physical fitness and cost effectiveness and be adequately powered to determine the effects of aerobic exercise training on postoperative clinical outcome. In a very recently published paper Li et al. (167) show improved postoperative function capacity after 1-month

of trimodal prehabilitation, however this is only pilot data and their randomised controlled trial is still ongoing (NCT01356264).

In an attempt to introduce prehabilitation to rectal cancer patients post-NACRT, I will endeavour to illustrate the methodology behind my structured, responsive, exercise, training programme in Chapter 3 (Section 3.3). In Chapter 5, I will explain the iterative process around the SREPT and will also apply it to an unselected cohort of patients as a feasibility and tolerability trial, with an adequately powered non-randomised pre-pilot parallel group study to follow in Chapter 6.

2.7 MECHANISMS OF EXERCISE TOLERANCE OR INTOLERANCE IN HEALTH AND DISEASE

This next section provides an overview of the potential mechanisms of exercise tolerance and potential limitation in health and cancer states.

The mechanisms of exercise intolerance in individuals who are healthy, ageing, athletic, or who have a chronic disease like cancer have been studied (116). A sound scientific knowledge of the underlying limitations of exercise tolerance exists. This information should be used to guide effective exercise training and rehabilitation programmes to improve clinical outcomes. Exercise intolerance has received comparably little attention in individuals diagnosed with cancer. The prevailing dogma was that unlike other chronic diseases, the pathophysiology of most cancer diagnoses, other than lung cancer, does not directly impact on the functional or structural integrity of the systems associated with oxygen transport and utilisation. Given the recent increased interest in exercise therapy as a component of cancer management, it has become apparent that cancer patients have markedly reduced cardiorespiratory fitness (168) which might have implications for acute and late-occurring cancer-related toxic effects and for clinical outcome especially in the postoperative period.

An individual's cardiorespiratory fitness is the efficiency with which oxygen is transported from the atmosphere into mitochondria in muscle cells. Maximum, or peak, oxygen consumption is the gold standard measurement of cardiorespiratory fitness and is strongly and inversely related to risk of death (102,169). Cardiorespiratory fitness is determined by the transport of oxygen from the environment to the skeletal muscle mitochondria via a series of convective and diffusive steps involving a sequential reduction in the partial

pressure of oxygen commonly termed the oxygen cascade. This involves several components of the pulmonary and cardiovascular systems, including the blood, blood vessels, and skeletal muscles all of which might be implicated in the process of exercise intolerance. During inspiration, oxygen from the environment, at a partial pressure of about 160 mm Hg, is delivered to the alveoli where partial pressure of oxygen is around 105 mm Hg. Oxygen diffuses across the blood–gas barrier, at an arterial partial pressure of about 100 mm Hg, into the blood in the pulmonary capillaries and binds to haemoglobin. Through the cardiovascular system acting as a pump, oxygen is convectively transported throughout the arterial system to the capillaries. In the capillaries, partial pressure of oxygen drops as oxygen diffuses out of the capillaries and moves into the intracellular space; this forces haemoglobin to off-load oxygen. Diffusion occurs throughout the length of the capillary with mean capillary partial pressure of oxygen estimated to be about 40 mm Hg (170). Inside the muscle cell, oxygen is transported to the mitochondria via myoglobin but this may also occur independent of myoglobin through a mechanism that may be dependent on a partial pressure gradient between cytosolic partial pressure of oxygen (estimated at about 3 mm Hg) and mitochondrial partial pressure of oxygen (commonly assumed to be close to 0 mm Hg).

During intense exercise, ATP requirements of metabolically active skeletal muscle increase substantially from resting values. This increase in ATP requirement is accompanied by comparative responses in cardiac output (to increase convective oxygen delivery) and pulmonary oxygen diffusion capacity. In humans, aerobic metabolism is the most efficient method for ATP resynthesis and oxygen consumption in the muscles is closely matched by oxygen supply by the heart, lungs, and vasculature. In healthy individuals (at sea level), the ability of the lungs to increase diffusion capacity far exceeds that of the other components of the oxygen cascade in all but the fittest individuals. Thus, lung diffusion capacity continually increases up to maximal oxygen consumption without reaching an upper limit. Similarly, mitochondria appear to maintain a relatively large reserve for increasing oxidative phosphorylation, as physiological manipulations that increase convective oxygen delivery or intracellular partial pressure of oxygen have been shown to augment mitochondrial maximal oxygen consumption. As such, convective oxygen delivery to the muscle capillary and diffusive oxygen delivery into the muscle cell have been identified as primary sites of limitation to maximal oxygen consumption peak in healthy individuals although all steps within the oxygen cascade integratively determine cardiorespiratory fitness.

As seen in Figure 2.5, multiple causes of exercise limitation exist. A summary of these causes are detailed hereunder.

- Age-related exercise limitation - more than 50% of all cancer diagnoses and 71% of cancer deaths are in individuals older than 65 years.
- Cardio-respiratory fitness is reduced in both women and men by around 10% per decade of life (171). This decrease in fitness is caused by unfavourable changes in diastolic filling and in ventricular compliance and relaxation, and losses in systolic function, lung elastic recoil, mechanical ventilation, vascular conductance, and oxidative capacity (Figure 2.5) (172).
- Co-morbid disease adversely affects the oxygen cascade and contributes to ageing effects.
- Physical inactivity (often neglected as a cause of exercise intolerance). Inactivity as a result of pain, weakness, locoregional or systemic therapy might exacerbate the loss of cardiorespiratory fitness in patients with cancer (173–175). In the seminal Dallas Bed Rest study, 3 weeks of inactivity led to a substantial reduction in cardiac output, oxidative capacity, and muscle cross-sectional area. An update of this study found that 30 years of ageing led to a reduction in peak oxygen uptake of about 20%, with physical inactivity thought to account for as much as 40% of the decline. In fact, peak oxygen uptake was lower after 30 days of bed rest than after 30 years of ageing, showing the devastating effect of inactivity on exercise tolerance (172). Dozens of interventional studies have tested the feasibility and potential benefits of exercise in cancer survivors. Recent meta-analyses of randomised trials involving exercise interventions after cancer, encouragingly demonstrate that the benefits of exercise spanned across several common cancer types and following a range of treatments including surgery, radiotherapy, chemotherapy, hormones and even the newer biological therapies. The most recent meta-analysis of 34 randomised trials published in the BMJ in 2012 involving patients exercising after cancer, demonstrated a benefit for a number of troublesome symptoms particularly fatigue, mood, anxiety and depression; muscle power, hand grip, exercise capacity and quality of life (148). The American College of Sports Medicine also published a comprehensive review of exercise intervention studies in cancer populations which included data from 85 RCT's of exercise in cancer survivors. Evidence consistently demonstrated that exercise could be performed safely in adjuvant and post-treatment settings. Exercise led to significant improvements in aerobic fitness; increased flexibility and strength; quality of life; anxiety and depression; fatigue, body image, size and composition. Interestingly the concept that exercise counteracts fatigue has been around for a long while, however the concept of deconditioning after a cancer diagnosis or the recognition that cancer patients get deconditioned as a results of

their cancer treatment is novel. Deconditioning is frequently seen in ill patients, elderly, and the obese. Fatigue has many factors including chemical reactions, such as that of tumor necrosis factor, Interleukin-1, -6, and others, as well as cognitive, emotional and physiological components. It has been estimated to be present in 40% of cancer patients. When a person becomes partially or fully incapacitated with a loss of independence it can be looked upon as a *rapid aging process*, leading to frailty, which also goes along with the loss of vital capacity. It becomes harder to maintain daily functions, such as ambulation, with an altered oxygen capacity and increased lactic acid production affecting muscle strength and function. Normal activities of daily living, such as walking, increase the demands of oxygen consumption, leading to fatigue through deconditioning. In the specific rectal cancer cohort described in this thesis, it is hypothesised that physical inactivity might lead to acute deconditioning with neoadjuvant cancer treatment. This might be a substantial contributor to a declining physical fitness, however the biological mechanisms of increased tumour burden, acute deconditioning and other whole body effects i.e. reduction in mitochondrial efficiency etc. resulting in a decline in physical fitness need disentangling.

- The pathophysiology of certain cancers might also directly affect the functional or structural integrity of components of the oxygen cascade. Tumours in the lungs, from either primary or metastatic lung cancer, are thought to disrupt pulmonary mechanics and gas exchange, however most cancers are typically accompanied by weight loss, anorexia, anaemia, protein catabolism, and muscle wasting; however in the specific rectal cancer cohort described in this thesis these factors were not thought to be the main factors for a reduction in physical fitness.
- Cancer treatments – chemotherapy, radiotherapy or both are considered highly toxic and exert massive physiological stresses on cancer patients especially in the preoperative setting prior to the further physiological stressor of elective surgical trauma. These cancer treatments are discussed in Section 7.6.2, with specific relation to their effects on mitochondrial function.

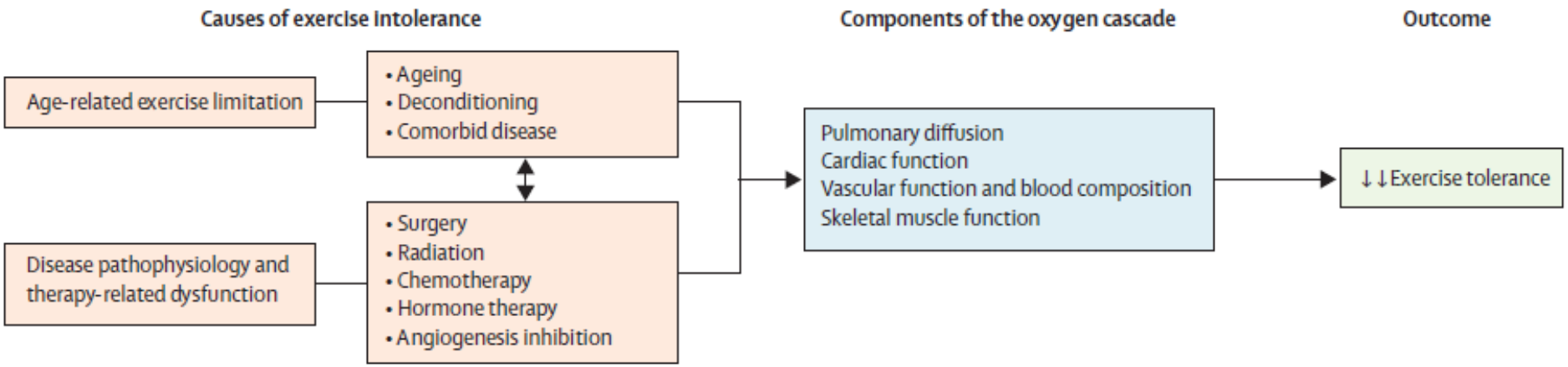


Figure 2.5 – Proposed causes of reduced exercise tolerance in patients with cancer that are mediated by adverse changes in the components of the oxygen cascade (176).

Within this thesis, different approaches were adopted to probe different parts of the whole lungs-heart-muscle system to investigate changes in physical fitness and the causes of exercise intolerance. Whole body function/capacity during exercise was tested by using cardiopulmonary exercise testing. As reviewed previously (Sections 2.5.1 and 2.5.2 and data presented in Chapters 4 to 7) this allows in depth objective testing of the cardiopulmonary system at rest and under stress and is now widely used to measure preoperative physical fitness. CPET can be usefully combined with ^{31}P MRS (177,178) to probe *in vivo* mitochondrial metabolism and skeletal muscle function during rest and exercise in selected peripheral muscle groups (Section 2.9). With this two pronged approach most of the components of the oxygen cascade illustrated above will be investigated with rigorous and robust methodology using validated techniques.

2.8 THE ASSESSMENT OF MITOCHONDRIAL FUNCTION

The next section will provide a review of the functional aspects of mitochondria in relation to muscle energy production, mitochondrial ATP synthesis and the assessment of mitochondrial function as a measure of physical fitness. The principles behind 31-phosphrous magnetic resonance spectroscopy (^{31}P MRS) for studying skeletal muscle mitochondrial energetics are also reviewed.

2.8.1 ROLE OF MITOCHONDRIA IN SKELETAL MUSCLE ENERGETICS

Mitochondria are cellular organelles which have a primary role of high energy production of adenosine triphosphate (ATP) through aerobic metabolism. The efficiency of mitochondria is particularly important in skeletal muscle, as muscle is metabolically very active and requires high rates of ATP turnover during exercise states. ATP is crucial in the contractile process as it is directly involved in ion transportation, action potential propagation and myofilament sliding. Reduction in ATP generation may contribute to premature muscle fatigue and a reduction in physical fitness.

Energy metabolism by the mitochondria involve several pathways of energy transfer which may be summarised as: 1) reactions generating Acetyl-co-enzyme A from oxidation of the pyruvate dehydrogenase reaction (glucose substrate) and the β-oxidation system (fatty acid substrate); 2) the reactions of the tricarboxylic acid (TCA) or the Krebs cycle; 3) the oxidation of electron carriers (NADH and $FADH_2$) generated from the TCA cycles in the

electron transport chain, and finally; 4) ATP synthesis from ADP and phosphate (processes summarised in figure 2.6) (179). The coupling of electron transport and ATP synthesis is called oxidative phosphorylation. This is a critical function of mitochondria and is represented by the following equation:

$$NADH + ½O_2 + H^+ + 3ADP + 3Pi \rightarrow 3ATP + NAD^+ + H_2O$$

Hence, ATP production is regulated by any of the 4 aforementioned substrates. These could act as a primary regulator for oxidative phosphorylation during muscle rest-to-work transitions; however this remains controversial despite extensive research.

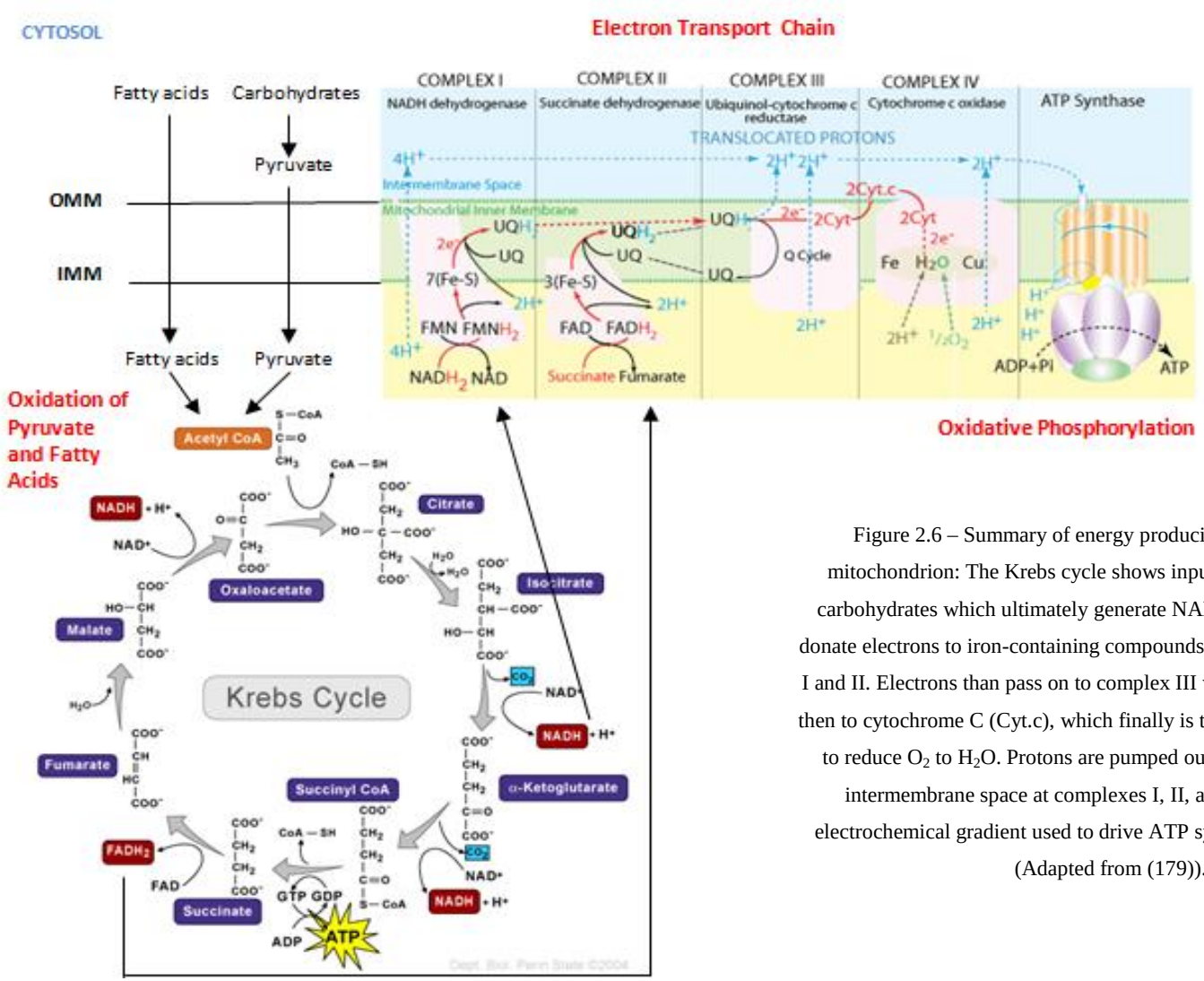


Figure 2.6 – Summary of energy producing pathways in the mitochondrion: The Krebs cycle shows input from fatty acids and carbohydrates which ultimately generate NADH and $FADH_2$. These donate electrons to iron-containing compounds (Fe-S) within complexes I and II. Electrons than pass on to complex III via ubiquinone (UQ) and then to cytochrome C (Cyt.c), which finally is transferred to complex IV to reduce O_2 to H_2O. Protons are pumped out of the matrix into the intermembrane space at complexes I, II, and IV generating an electrochemical gradient used to drive ATP synthesis by complex V. (Adapted from (179)).

2.8.2 REGULATION AND MODULATION OF MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION

Computational models of oxidative phosphorylation in intact skeletal and heart muscle have led to the concept of 'parallel activation' or 'step-activation' mechanisms for tighter control of ATP supply and demand (180). This model advances the idea that there is no single primary regulator for controlling the rate of ATP synthesis, but instead, all components of ATP synthesis reactions are directly activated by some cytosolic factor (still unknown) in parallel with the activation of ATP consumption during muscle work. Mitochondrial capacity for oxidative ATP synthesis is a function of both the structural and functional aspects of the organelle. The structural aspect of mitochondria is determined by the mitochondrial content of the cells (i.e. volume and density of mitochondrial proteins and enzymes) and their morphological profiles, while mitochondrial functional integrity is reflected in the capacity for ATP production per unit of mitochondria (181). The functional properties of mitochondria may be affected by various factors including enzyme and structural functionality, availability of substrates driving the metabolic reactions (e.g. ADP) and other factors, in particular oxygen availability.

Much interest has been raised over the years on the relationship between oxygen availability, ATP demand and ATP production in view of the potential role of oxygen as an important modulator of muscle metabolism (179–181). Oxygen is an indispensible substrate of mitochondrial oxidative ATP synthesis with a primary function as the terminal electron acceptor within the electron transport chain (ETC). Therefore, reduced availability of oxygen conceptually attenuates maximal rate of oxidative ATP synthesis in mitochondria. Mitochondrial oxygenation is determined by the capillary O_2 driving pressure (convective oxygen transport) and the local diffusion capacity (diffusive oxygen transport), interacting with the rate of O_2 utilization (182). Both muscle blood flow and O_2 dissociation from haemoglobin determine convective O_2 delivery, and improvement in one or both would, therefore, be expected to elevate intracellular PaO_2. The change in diffusion capacity for O_2 from the red blood cell into the myocyte is a function of diffusion distances and surface area, both of which are dependent on capillary recruitment. The key question is whether oxygen has a role in limiting the rate of mitochondrial respiration (i.e. a potential controller of mitochondrial ATP synthesis), or, whether it is a substrate which merely modulates rather than controls mitochondrial ATP synthesis rate. Historical work done on isolated mitochondrial preparation suggested that the maximal rates of mitochondrial respiration could be maintained at a very low levels of oxygen, as intracellular oxygenation level must be reduced to a very low level compared to the arterial or venous PaO_2 to have an effect on

mitochondrial respiration (183). The available oxygen in the tissues even in hypoxic conditions is thought to still remain in excess of that required to limit mitochondrial respiration.

In intact tissues however, there has been a suggestion that the affinity of cytochrome *c* oxidase for oxygen molecules may be much lower compared to *in vitro* conditions, implying that even normoxic oxygen tension could potentially be rate limiting for mitochondrial oxidative phosphorylation (184). However, more recent *in vivo* studies support the concept that oxygen is not a direct controller of oxidative phosphorylation, but rather has an indirect regulator of signals such as ADP, Pi, phosphorylation potential (i.e. [ATP]/[ADP][Pi]) and PCr (185–187). The *in vivo* effect of oxygen availability on muscle bioenergetics has been studied by several investigators, mainly by ^{31}P MRS methods, through observation of the changes in the muscle metabolites considered as surrogate markers of mitochondrial oxidative capacity in conditions during which manipulations of inspired oxygen levels (FiO2) were implemented. For instance, presuming that phosphocreatine (PCr) hydrolysis is one of the signals for mitochondrial respiration, as proposed by Haseler and colleagues (185), after a random switching of the FiO_2 in 3 different conditions (normoxia, hypoxia and hyperoxia), the PCr levels were raised or declined in accordance to the increased or decreased FiO_2, suggesting a role of oxygen is modulating one of the proposed regulators of tissue respiration (i.e. PCr) during steady state exercise. This observation has been supported by an animal study showing that when oxygen delivery to working muscle was reduced by either ischaemia or hypoxaemia, the relationship between the rates of tissue respiration (as reflected by measurement of muscle oxygen consumption i.e. $\dot{V}o_2$) and the measured variables believed to regulate respiration (i.e. ADP, Pi and PCr) was altered such that a greater regulatory signal was required to drive mitochondrial respiration to elicit a given $\dot{V}o_2$ (187). These findings are however, not universal. A recent study combining a novel optical spectroscopic method to measure intracellular PaO_2 with ^{31}P MRS technique yielding PCr and pH measurement (used to calculate phosphorylation state i.e. [ATP]/[ADP][Pi]) in mouse skeletal muscle seems to indicate a constant phosphorylation state despite the decline in intracellular PaO_2 to a low level thought to affect the regulation of mitochondrial respiration. Based on the dissociation between intracellular PaO_2 and the observed level of the regulatory signal ([ATP]/[ADP][Pi]), the authors rejected the hypothesis that oxygen has a regulatory role in cellular respiration through direct coupling with metabolic signals driving mitochondrial respiration (188). Thus, the role of oxygen in modulating mitochondrial function remains to be further elucidated. The hypothesis of a potential reduction in mitochondrial energetics due to an alteration of intracellular PaO_2 or a reduction

in mitochondrial function post-NACRT in this rectal cancer patient cohort is an interesting one. This however, has never been illustrated in any patient population and might be novel findings relating preoperative changes in mitochondrial function to whole body physical fitness. This is further discussed in Chapter 7.

2.8.3 METHODS OF ASSESSMENT OF MITOCHONDRIAL FUNCTION

The assessment of mitochondrial function can be performed by using a variety of techniques, each with its distinct advantages and limitations. Functional characterisation of mitochondria using *ex vivo* approach has the advantage of permitting detailed assessment of specific components of the ATP-synthesis pathways in addition to allowing enormous complementary data to be obtained from the same sample of biopsied tissue (e.g. morphometric and histological analysis, quantification of mitochondrial DNA copy number, mRNA and protein expressions and activities of various mitochondrial enzymes). However, it has the inherent limitation of being invasive and thus impractical for multiple sampling particularly during study protocols such as the study presented in Chapter 7. In addition, it allows a very limited sampling volume which may not be a representative portion of the whole muscle considering the heterogeneity of muscle tissue. Lastly, the *ex vivo* experimental conditions may not reflect normal physiological conditions. In contrast, an *in vivo* method such as magnetic resonance spectroscopy (MRS) is able to investigate mitochondrial functional properties from a large tissue sample in normal physiological conditions (i.e. intact circulatory and regulatory systems), and allows frequent sampling intervals due to its completely non invasive nature. These advantages, together with the readily available expertise and technology available at the University of Liverpool were the reasons why MRS was utilized in this thesis. MRS however also has limitations, these include the inability of distinguishing the functional status of specific enzyme complexes, thus only reflecting the overall oxidative capacity of the mitochondria or mitochondrial energetics. In addition, due to its inherent relatively low sensitivity, this method does not provide information at the level of a single fibre, but instead records metabolic changes from a mixture of fibres with different metabolic characteristics. The basic principles and relevance of tissue biopsy, whole body oxygen consumption and MRS for the assessment of skeletal muscle mitochondrial function is further described below.

2.8.3.1 EX-VIVO MITOCHONDRIAL ANALYSIS BY TISSUE EXCISION BIOPSY

Analysis of mitochondrial properties *ex vivo* could be performed either on isolated mitochondria or permeabilized fibres preparation from biopsied tissue samples. The general approach is to obtain muscle tissue sample via a biopsy technique (e.g. Bergström procedure or open biopsy). Following adequate sample preparation, materials are then subjected to further analysis for quantitative assessment of mitochondrial oxidative capacity. Various approaches have been taken to provide quantitative information of mitochondrial energetic function. The conventional *ex vivo* approach involves measurements of maximal activities of key mitochondrial enzymes such as citrate synthase (which is a common enzyme marker of mitochondrial matrix) as well as succinate dehydrogenase and/or cytochrome *c* oxidase (both of which are the representative enzymes from inner mitochondrial membrane) via spectrophotometric based enzyme activity assays (189).

Two other approaches which have been widely utilised for a more comprehensive *ex vivo* analysis of mitochondrial oxidative capacity include polarographic measurement of mitochondrial oxygen consumption (183) and direct measurement of ATP production rates using a bioluminescence approach (190). Both quantitative and qualitative aspects of mitochondrial respiration could be assessed by this method.

2.8.3.2 MITOCHONDRIAL FUNCTION DERIVED FROM OXYGEN CONSUMPTION DURING EXERCISE

The oxidative phosphorylation reaction for ATP synthesis is heavily dependent on the availability of oxygen to mitochondria as previously discussed in Section 2.8.2. This in turn, relies on the efficiency of muscle oxygen consumption. Thus, measurement of muscle oxygen consumption ($\dot{V}o_{2\ muscle}$) could be used to reflect the extent of mitochondrial oxygen utilisation for ATP synthesis i.e. a marker of mitochondrial function. Muscle oxygen consumption could either be indirectly ascertained from measurement of pulmonary oxygen consumption at maximal or peak exercise (reflecting whole body oxygen consumption) measured from expired gas concentration at the mouth using CPET, or, inferred from measurement of local oxygen consumption using near infrared spectroscopy (NIRS). A more direct measurement of $\dot{V}o_{2\ muscle}$ could be obtained from a relatively invasive procedure such as thermodilution method with subsequent arterial-venous blood sampling which provides measurement of the difference in oxygen content between the arterial and venous

compartment, reflecting the extent of oxygen extraction by the muscle. In this section I shall concentrate on the derivation of mitochondrial function from oxygen consumption measured by CPET as this technique is utilized extensively in the assessment of physical fitness in this thesis (Chapters 4 to 7). This technique and its methodology are discussed in more detail in Chapter 3, Section 3.2.

Measurement of maximal oxygen consumption ($\dot{V}o_2$ Max or $\dot{V}o_2$ Peak) during maximal or peak exercise is an indicator of an individual's ability to sustain muscular activities, and represents a marker of physical fitness which is closely related to surgical risk stratification and surgical outcome as described in Section 2.5. $\dot{V}o_2$ Max can be defined as the failure of the $\dot{V}o_2$ to increase despite an increase in work rate (191). It is physiologically governed by the capacity of the cardiovascular system to provide adequate oxygen supply to the skeletal muscle (i.e. cardiac output), as well as the capacity of the muscle to extract and utilize the supplied oxygen (represented by arteriovenous difference in O_2 content) which is largely determined by muscle metabolic factors. $\dot{V}o_2$ Max is thus universally represented by the following Fick equation:

$$\dot{V}o_2 \text{ Max} = \text{Cardiac Output} \times \text{Arteriovenous } O_2 \text{ difference.}$$

Although the absolute value of this measurement is not conventionally used to specifically reflect mitochondrial oxidative capacity, it could be used to infer measurement of $\dot{V}o_2$ in the exercising legs, which could in turn be converted into measurement of maximal ATP synthesis rate. This is based on the assumption that as work increases, the principal site of greater oxygen utilization is presumed to be the working muscle, and therefore, the changes in whole body $\dot{V}o_2$ are expected to be a reflection of the increasing muscle $\dot{V}o_2$.

Another method of studying mitochondrial function is by magnetic resonance spectroscopy. This is a non-invasive technique which allows *in vivo* detection of various biologically relevant metabolites within a tissue of interest. Amongst the various MR visible nuclei, the 31-phosphorus (^{31}P) nucleus is the principle metabolite involved in energy transduction. Its detection is therefore very useful for studying skeletal muscle energetics. The two MR-spectroscopic approaches involving ^{31}P nuclei detection which can be used to study muscle energy metabolism and mitochondrial function are ^{31}P magnetic resonance saturation transfer technique, and ^{31}P magnetic resonance spectroscopy (^{31}P MRS). The latter has been extensively used for non- invasive measurement of mitochondrial energy metabolism. This

technique is utilised in this current thesis (Chapter 7) to study mitochondrial function *in vivo* and will therefore be described in a greater detail in the next section (Section 2.9). To permit further understanding of this MR approach, a review of the physical basis of the MR method is necessary. The next section provides the introductory background to the general principles of the MR method, and outlines the basis of the ^{31}P MRS technique for studying skeletal muscle bioenergetics *in vivo*.

2.9 31-PHOSPHORUS MAGNETIC RESONANCE SPECTROSCOPY (^{31}P MRS)

Nuclear magnetic resonance (NMR) is a phenomenon initially described independently by Bloch and Purcell (192,193), in which particular atomic nuclei with nuclear spin respond to the application of magnetic fields by absorbing energy in the radiofrequency range of the electromagnetic spectrum, and re-emit this energy in the form of radio signals when the nuclei transfer to their original state. MRI and MRS are the two major clinical applications of NMR techniques. The MRS technique has been adapted for acquiring biochemical information *in vivo* from a defined volume of tissue. It complements MRI as a non-invasive means for tissue characterization. The two techniques are fundamentally similar, with the exception of the originating atomic nucleus generating the signals and the manner in which the data is displayed. MRS obtains resonance signals from specific metabolites (e.g. ^{13}C, ^{31}P, ^{1}H) within tissues, which are subsequently displayed as a function of frequency (a spectrum). These signals are normally obtained in the absence of a magnetic field gradient. On the other hand, MR imaging obtains resonance signals originating from ^{1}H nuclei in the intra- and extracellular water and some lipids in the presence of a field gradient, which in turn, are presented as anatomical images. MRS techniques have evolved from a simple application for studying the chemical properties of solids and solutions, to the studies of biochemical and metabolism properties of isolated tissue *in vivo.*

^{31}P MRS has been extensively used for evaluating muscle bioenergetics in healthy and pathological conditions (194–198). This method allows for detection of changes in ^{31}P nuclei within various energy-related compounds such as PCr, ATP and Pi during exercise and recovery. ^{31}P MRS measurements can be made to yield quantitative estimates of ATP turnover, mitochondrial oxidative capacity, and proton handling in skeletal muscle (199,200).

2.9.1 GENERAL PRINCIPLES OF MAGNETIC RESONANCE

The phenomenon of nuclear magnetic resonance can be induced in atomic nuclei that contain either an odd number of protons or neutrons. The odd particle imparts a net angular momentum or 'spin' to the nucleus, creating a magnetic moment for that nucleus. Such nuclei may therefore be considered as small magnets spinning on their axes (Figure 2.7 i). When placed in a homogenous magnetic field of high intensity, these nuclei precess (circle in an orbit) about the field and tend to align in specific ways depending on their spin states (Figure 2.7 ii). Nuclei lining up against the external magnetic field (anti-parallel) are considered to have relatively higher energy state compared to those in parallel alignment with the external magnetic field lines (Figure 2.7 iii). In a typical NMR experiment, resonance (i.e. transitions between the nuclear orientations, thus energy states), can be induced repeatedly in a controlled manner by irradiation with radiofrequency (rf) energy, which is typically applied as a short pulse at a specific resonance frequency. At a given magnetic field, each of these various magnetically active nuclei (e.g. ^{1}H, ^{31}P,^{13}C) will absorb the radiation and precess at very different frequencies (Larmor frequency), the relationship of which being expressed by the following equation:

$$\nu = \gamma B0/2\pi$$

where ν , the absorbed frequency (hertz), depends on the strength of the external magnetic field, B0 (Tesla unit) and γ (the gyromagnetic ratio) which is a constant of proportionality reflecting the characteristic property of the specific nucleus. This relationship allows a spectrometer and coil probe to be tuned onto the frequency of a selected nucleus (e.g. 63.5 MHz for hydrogen at 1.5 Tesla, and 25.8 for phosphorus at 1.5 Tesla). Although the nuclei can assume only two orientations with respect to the static/external magnetic field, *B0* (i.e. along *Z*-axis), they are free to rotate around *B0*, and thus, their projections may occupy any position in a circle on the *X*-*Y* plane (Figure 2.7 iv). Therefore, in the presence of *B0*, the typical slight excess of nuclei in the lower energy level (but random in *X*-*Y* plane) results in a net magnetization vector, ***M***, parallel to *B0* (Figure 2.7 iii).

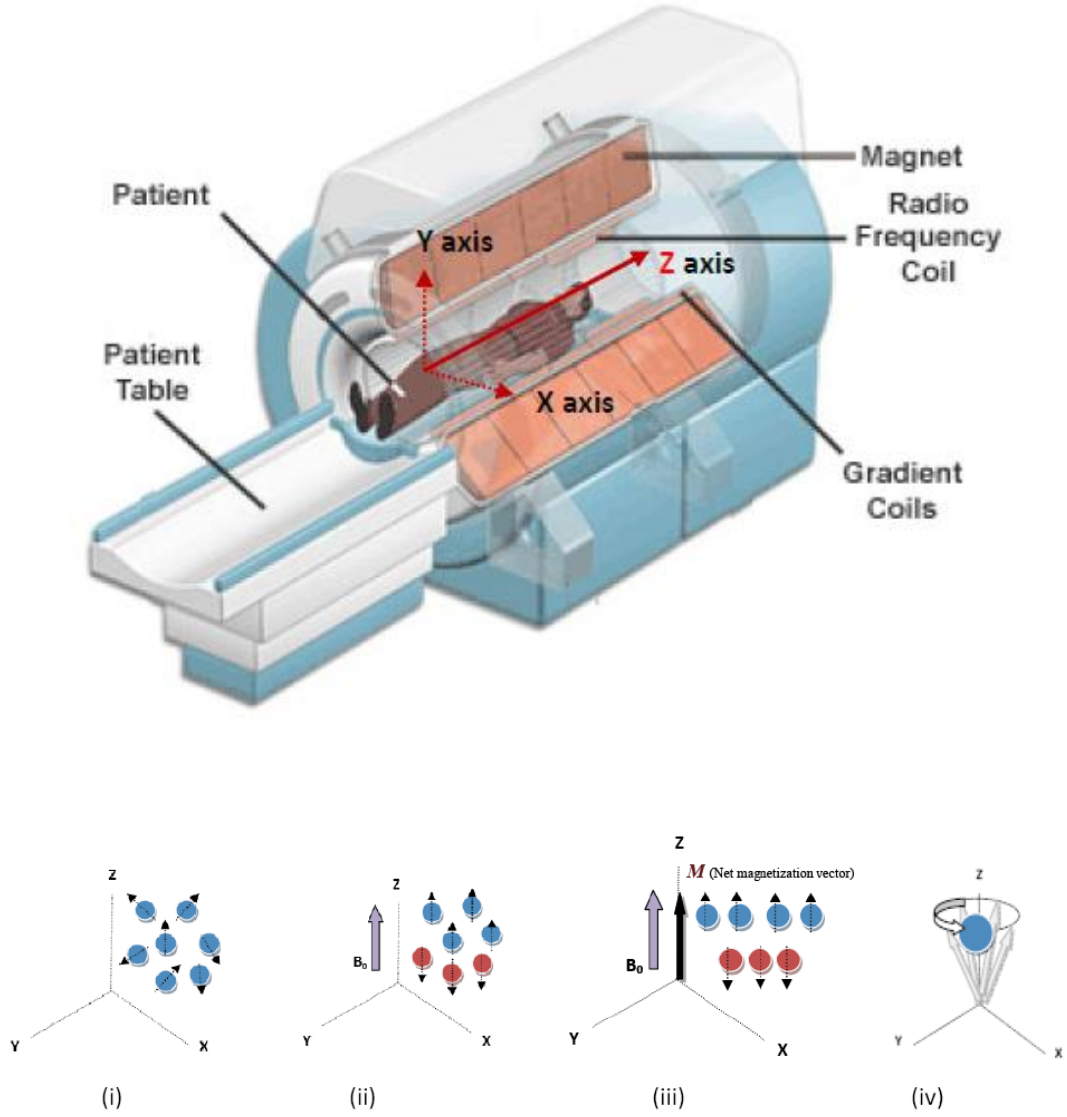


Figure 2.7 – Diagram of a magnetic resonance imaging scanner showing the NMR phenomenon (i): random alignment of the nuclei spin in the absence of external magnetic field, (ii): In the presence of external magnetic field (*B0*), nuclei spin precess and tend to align themselves either parallel or anti-parallel to *B0* (Note that nuclei in anti-parallel position have relatively higher energy state). (iii): The relative balance between 'spin-up' and 'spin-down' nuclei reflects the magnetization in longitudinal plane (iv): The nuclei are also free to rotate around *B*0 occupying any position in the *X*-*Y* plane. The combination of (iii) and (iv) will result in the net magnetization vector of the nuclei, ***M***.

Application of a short, broad bandwidth pulse of radiofrequency energy tuned to the nucleus precession frequency causes the specific nucleus to absorb this energy (i.e. more nuclei will be in the anti-parallel/ high energy state), and change its angle of precession (i.e. rotation of ***M*** away from the *Z* axis). The angle to which ***M*** moves out of alignment is referred to as the flip angle (Figure 2.8 v). The largest signals are obtained after a 900 pulse, because in that

phase, ***M****xy* is at its maximum. In addition to movement of the nuclei's net magnetization in the transverse plane, excitation of nuclei induced by the RF pulse also results in individual nuclear magnetic moment to move in phase with each other (coherent) i.e. nuclei are in the same place on the precession path around B0 at any given time (Figure 2.8 vi).

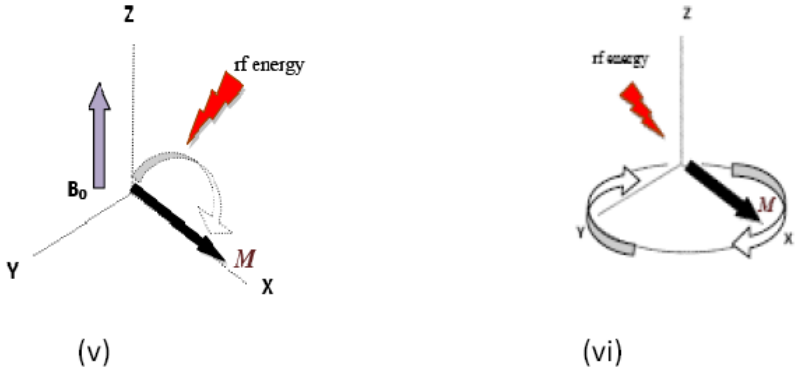


Figure 2.8 - Application of radiofrequency (rf) energy in the presence of external magnetic field leads to 2 main effects: (v) – rotation of ***M*** away from Z-axis towards the XY plane (caused by more nuclei being transferred into a higher energy state position following absorption of energy induced by the rf pulse); and (vi) – nuclei move around B0 in a coherent pattern / in phase with each other (i.e. nuclei are in the same place on the precession path at any given time).

During the interval between the excitation waves, the nucleus reverts back into its original alignment and emits energy, which is detected by a receiver coil (Figure 2.9 vii). The return of ***M*** to its original state with concurrent release of energy is called relaxation. The resonance signal generated by transverse relaxation of nuclei following RF pulse is captured by the receiver coil in the form of sinusoidal wave, termed free-induction decay (FID) (Figure 2.9 viii). This represents an exponential decrease of resonance signal from the nucleus over time. The initial intensity of the signal is proportional to the number of the nuclei it originates from (Figure 2.9 ix).

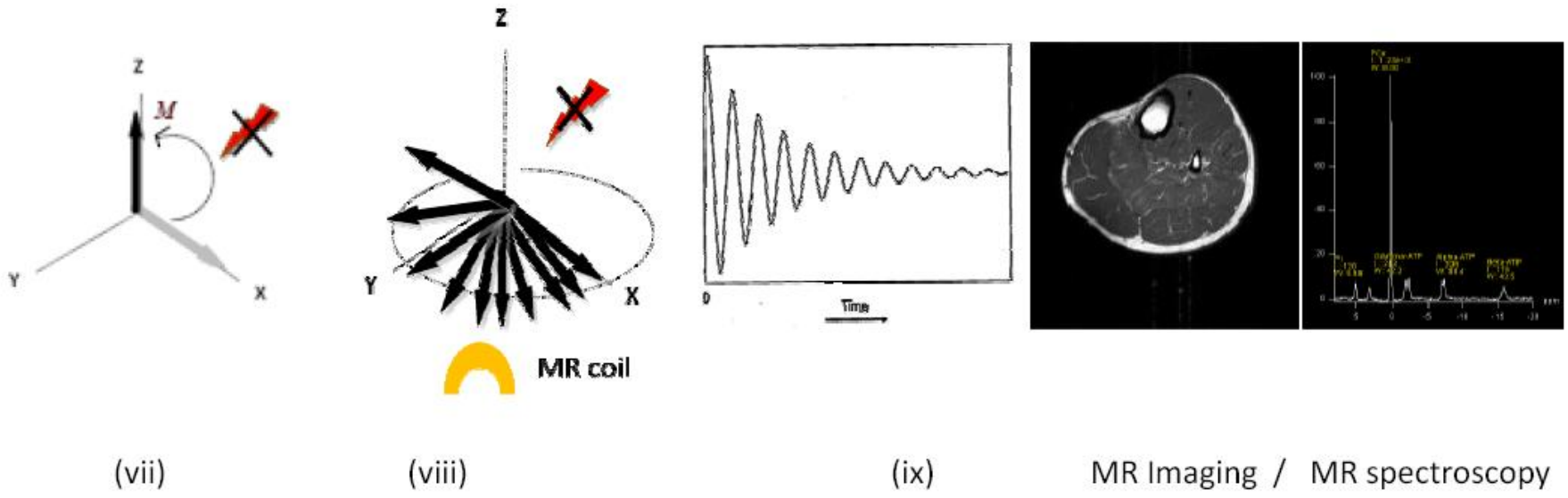


Figure 2.9: When the RF pulse is turned off, the nuclei spin give up the absorbed energy into their surrounding and ***M*** reverts back to its original position (vii). The rate at which ***M*** recovers to its original position represents T1 relaxation. At the same time, the nuclei also experience loss of coherent transverse magnetization (de-phasing) resulting from the loss of energy into the neighbouring nuclei (viii). MR raw signal (in the form of free induction decay/ FID) is produced when coherent magnetization cuts across the coil producing magnetic field fluctuations inside the coil which induce an electrical voltage in the coil (ix); The FID signal could then be mathematically transformed to produce either an MR image or MR spectra.

In MR imaging, the free-induction delay (FID) signal is mathematically transformed into a two- or three-dimensional image (Figure 2.9ix MR imaging/spectroscopy). The relaxation properties of hydrogen atom in different tissues determine the image contrast in MR Imaging. In MR spectroscopy, the recording of FID from various nuclei/compounds can be translated into a display of peak intensities versus frequencies (spectra) by using the Fourier transformation. Since MRS is a relatively insensitive technique, many radiofrequency impulses have to be applied and the resulting FID have to be signal-averaged in order to obtain MR spectra with sufficient "signal-to-noise-ratio'. In a MR spectrum, the relative frequency position of the metabolite signal, known as the 'chemical shift', is influenced by the local magnetic environment of the nucleus, which in turn, is dependent on the chemical properties of the nucleus. Therefore, different nuclei have different signature peaks at a specific chemical shift, which is useful for their identification. Signals from different chemicals containing the same nuclei are also separated by the nuclei chemical shift. The chemical shift is measured using the dimensionless units, parts per million (ppm), i.e. ppm = (observed frequency – reference frequency)/Larmor frequency x 106. The positions of resonance peaks are measured relative to a standard/reference material, i.e., *in vivo* reference (internal standard) includes water at 4.7 ppm for ^{1}H spectroscopy or creatine phosphate at 0 ppm for ^{31}P spectroscopy.

2.9.2 ^{31}P MRS – IN-VIVO BIOENERGETICS AND ASSESSMENT OF MITOCHONDRIAL FUNCTION IN HUMAN SKELETAL MUSCLE

^{31}P MRS is an increasingly recognized non-invasive technique mainly used for evaluating skeletal muscle metabolism *in vivo* (196,201). Unlike direct biochemical and histochemical analyses which are generally designed to show the activity of a single enzyme or complex under conditions of maximal activity, ^{31}P MRS provides information about the entire enzymatic pathway such as glycolysis in the cytoplasm and/or oxidative metabolism within the skeletal muscle mitochondria. This method offers the opportunity of continuously measuring the phosphorylated compounds involved in muscle bioenergetics in real time and in a totally non-invasive manner. However, only metabolites in human muscle which are unbound and present at concentration of at least 1 mM result in the ^{31}P MRS spectral peaks that are sufficiently narrow and have adequate signal-to-noise ratio to be 'visible'. It is a fortunate property of ^{31}P MRS that this includes some metabolites of key bioenergetic significance. ^{31}P MRS probes *in vivo* mitochondrial metabolism during rest and exercise in selected muscle groups. These findings in skeletal muscle can be usefully combined with CPET (177,178) corroborating whole body measurements. Furthermore, good correlations

have been shown to exist between *in vivo and in vitro* measurement of mitochondrial function in health and chronic conditions (e.g. type-2 diabetes). This makes the estimation of mitochondrial function by ^{31}P MRS an attractive and reliable modality when repeated measurements need to be undertaken (178,202,203), which is why this modality has been chosen to assess mitochondrial function in this cohort of patients (Chapter 7).

2.9.3 ^{31}P MRS SPECTRUM

An example of a ^{31}P MRS spectrum can be seen in Figure 2.10. This spectrum obtained from muscle is characterized by peaks due to PCr, the three (α, β and γ) phosphate moieties of ATP, unbound inorganic phosphate, and mono- and di-phosphoesters (PME, PDE). With the exception of ADP, which is present in too low a concentration to be observed in resting muscle, the principal metabolites involved in energy transduction can be observed, which makes in vivo ^{31}P MRS particularly useful for studying muscle energetics. Phosphodiesters such as glycerophosphocholine and glycerophosphoethanolamine, which is also detected as a small peak in normal muscle spectra, are indicative of membrane breakdown and has been shown be elevated in disorders of muscle necrosis and atrophy such as muscle dystrophy, but it also increases as a result of normal aging (197).

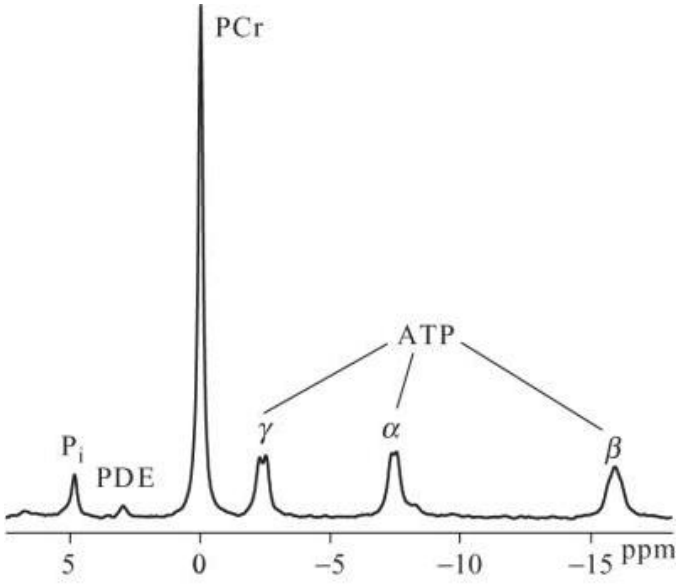


Figure 2.10- An example of a ^{31}P magnetic resonance spectrum of human calf muscle *in vivo*. Resonances are visible for adenosine triphosphate (ATP), phosphocreatine (PCr), phosphodiesters (PDE), and inorganic phosphate (Pi). Adapted from Befroy et al. (197)

In addition, three more pieces of information that are of functional relevance can be retrieved from the ^{31}P spectra, albeit indirectly, i.e. the intracellular pH, the free concentration of ADP and Magnesium (Mg^{2+}) ions. Tissue pH can be deduced from the chemical shift of Pi. The ^{31}P MRS pH measurement makes use of the fact that the basic and acidic species of Pi that coexist at physiological pH have different chemical shifts and are in rapid chemical exchange (204). The relative proportion of the two species and the actual resonance position is determined by pH. Following proper calibration, the measured Pi resonance frequency can thus be used to estimate the intracellular pH. Secondly, the CK equilibrium can be used to calculate the free levels of ADP in the cell. The concentration of ADP in resting and moderately active muscle is typically in the tens of micromoles range, which is too low to allow direct detection by ^{31}P MRS. Knowledge of ADP levels is highly relevant, since ADP is an important regulator of the mitochondrial ATP synthesis. This use of the CK reaction is based on the fact that total CK activity exceeds the ATP utilizing and delivering fluxes several fold, implying that dynamic changes in PCr levels can be used indirectly to quantify changes in the ADP (and ATP) levels (205). Therefore, quantitative analysis of the changes in the concentration of phosphorylated compound and intracellular pH derived from the ^{31}P MR spectra obtained during transition from rest-exercise-recovery period have been applied to characterise skeletal muscle energy metabolism and mitochondrial function *in vivo* (206).

2.9.4 ^{31}P MRS METABOLIC CHANGES DURING EXERCISE AND RECOVERY

^{31}P MRS has opened a window on bioenergetics during skeletal muscle exercise and recovery in a non-invasive manner and with a time resolution typically of the order of seconds. This has made a major contribution to the understanding of mammalian cell energy metabolism, its control and the way in which it can be affected in disease. This is of particular interest as this approach will be implemented in this thesis. I will attempt to show changes in mitochondrial function *in vivo* at three different time points in rectal cancer patients: at diagnosis, after standardised NACRT treatment and also after a period of structured exercise or control (no intervention) (Chapter 7). This is novel as an interventional ^{31}P MRS randomized controlled study in a cancer patient cohort has never been attempted.

Figure 2.11 shows a typical dynamic time series of ^{31}P MR spectra of human muscle acquired serially at rest, during exercise and subsequent recovery. At rest the intramuscular concentration of ATP is relatively low (averaging 6-8 mmol.kg^{-1} wet weight) compared to its

turnover rate during exercise. In a recent ^{31}P MRS investigation on human medial gastrocnemius, the maximal total ATP flux was found to be approximately 217 mmol.ATP^{-1}.min^{-1} during high intensity exercise (207). Despite large increase in ATP demand during muscular activity, it has been widely demonstrated that ATP concentration remains constant throughout the transition from rest to exercise (208). The continuous re-synthesizing of ATP to closely match its utilization rate during exercise is being provided by activation of three major metabolic pathways in the skeletal muscle: 1) the net hydrolysis of muscle's PCr stores through the creatine kinase reaction; 2) breakdown of glycogen to lactate in anaerobic glycolysis; and 3) oxidative metabolism of carbohydrates and lipids in mitochondria.

At the start of the energy challenge, hydrolysed ATP is resynthesized from PCr breakdown and depending on conditions, from anaerobic glycogenolysis. Thus, PCr levels decrease and Pi levels increase, while ATP levels remain constant. PCr hydrolysis consumes protons and generally results in a small rise in cellular pH (alkalinization) at the start of exercise. During aerobic exercise, most of the energy is subsequently provided by oxidative metabolism. Anaerobic glycogenolysis produces protons via lactate production and typically results in cellular acidification. After the energy challenge, the PCr buffer is restored and Pi levels normalize. The ATP used for resynthesis of PCr is mostly derived from oxidative phosphorylation. The relative contribution of these ATP-producing pathways is dependent on the intensity of the exercise, such that oxidative ATP synthesis dominates during low- and moderate-intensity exercise. During exercise, the ^{31}P MRS spectrum shows declining levels of PCr with stoichiometric increase in Pi level, while ATP level remains unchanged (Figure 2.11). The total PCr change over the entire duration of exercise (i.e. $-\Delta[PCr]/\Delta t$) is a measure of average failure of oxidative ATP synthesis to meet the ATP demand in purely aerobic exercise. An increase in this parameter (either due to increased PCr depletion, reduced exercise duration, or both) may reflect either increased ATP demand or impaired oxidative ATP supply (209). The initial rate of PCr depletion at the onset of exercise ($-\Delta [PCr]/ \Delta t$) is a measure of the ATP turnover rate (i.e. rate of ATP hydrolysis), reflecting the ATP demand during exercise. This measurement divided by force output per unit cross-sectional area reflects the contractile efficiency, which measures how well ATP is used to generate force (209).

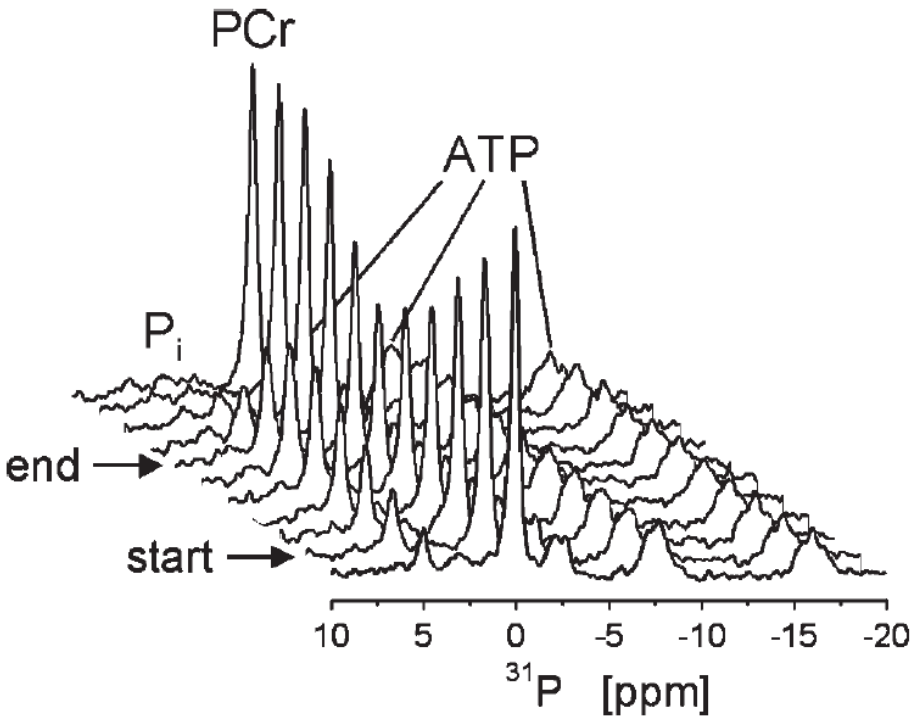


Figure 2.11 – Dynamic ^{31}P MRS time series of human quadriceps muscle at rest, during knee flexion exercise and subsequent recovery. The subject performed 2.5 min of single-legged knee flexion exercise at 70% maximal voluntary contraction. Note that PCr levels decline during exercise with a corresponding increase in Pi. PCr then returns to baseline during recovery. ATP remains constant throughout the workload transition.

With the cessation of exercise, the anaerobic metabolic pathways are immediately deactivated, but mitochondrial oxidative phosphorylation continues at an accelerated rate to replenish high-energy phosphate stores utilized during exercise. PCr re-synthesis is carried out by the reversed creatine kinase reaction, which transfers a high energy phosphate group from ATP (produced entirely from oxidative phosphorylation in mitochondria) to creatine. In a concurrent event, the ADP levels that had increased during exercise (via ATP hydrolysis) recovers to their low resting level, as oxidative phosphorylation converts ADP to ATP. Since oxidative phosphorylation reaction occurs exclusively in the mitochondria, the post-exercise PCr and ADP recovery rates are valuable indices of mitochondrial function. Therefore, aspects of mitochondrial function obtained from ^{31}P MRS can be expressed in various ways:

PCr recovery kinetics: i) the half-time of PCr recovery (**PCr t½**), denoting the time it takes for the depleted amount of PCr to recover to half of its pre-exercise level, or, ii) PCr recovery rate constant (**k_{PCr}**), i.e. 0.693/t½ PCr assuming monoexponential kinetics (as in the present experiments – Chapter 7).

ADP recovery kinetics: i) the half-time of ADP recovery (**ADP t½**), denoting the time for half of ADP concentration to be depleted, being utilized in mitochondrial oxidative phosphorylation reaction to re-synthesize ATP), or ii) rate constant of ADP recovery (***k*ADP**), i.e. 0.693/t½ADP. These variables are not going to be utilized in this thesis.

The initial rate of PCr re-synthesis, V (i.e. **d[PCr]/dt**) calculated from [PCr] at the end of exercise and the initial data point in recovery. This represents a direct estimate of the end exercise rate of ATP synthesis that is purely oxidative. This variable is not going to be utilized in this thesis.

The simplest analysis is by using pure aerobic exercise (that is exercise below the $\dot{V}o_2$ at $\hat{\theta}_L$, where glycolytic ATP synthesis can be neglected) and recovery. During this type of exercise PCr kinetics are monoexponential, and at least in the early stages, so are pulmonary $\dot{V}o_2$ kinetics (210). Since PCr recovery has been shown to follow a monoexponential time course, the parameters related to the recovery kinetics of PCr are derived from a typical least square regression fit, based on the following equation:

$$[PCr]t = [PCr]0 + (\Delta[PCr] (1 - e(-t/\tau))$$

where [PCr]t is the PCr concentration at a given time point during recovery, [PCr]0 is the PCr level at the onset of recovery, Δ[PCr] is the change in PCr concentration from rest to the onset of recovery, t = time, and τ is a time constant. So the monoexponential PCr kinetics imply a linear steady-state relationship of oxidative ATP synthesis to the fall in PCr, and vice versa (211). A similar relationship is seen between oxidative ATP synthesis rates and ATP hydrolysis rate. This predicts that post-exercise PCr resynthesis will be exponential, and that the absolute PCr resynthesis rate measures suprabasal oxidative ATP synthesis rate. Therefore k_{PCr} is taken to be a surrogate marker of *in vivo* mitochondrial function (212).

Figure 2.12 shows an example of oxidative exercise described above. Mitochondrial function can thus be derived using PCr recovery kinetics. Figure 2.13 plots PCr synthesis against the relative fall in [PCr] (Δ[PCr]). The slope from the origin to the end-exercise point is an apparent rate constant; if PCr kinetics are monoexponential the data will lie on a straight line whose slope is the exponential rate constant k_{PCr}.

All of the ^{31}P MRS- derived parameters above provide essentially the same information and are rooted from the concept that PCr is recovered solely through mitochondrial oxidative

phosphorylation, therefore k_{PCr} or τ_{PCr} can be used as a relative for mitochondrial function. Good correlations between the above mentioned MRS measurements and biochemical markers of mitochondrial function (citrate synthase activity) have been previously demonstrated, validating the use of this method for non-invasive assessment of mitochondrial function *in vivo* (178,202).

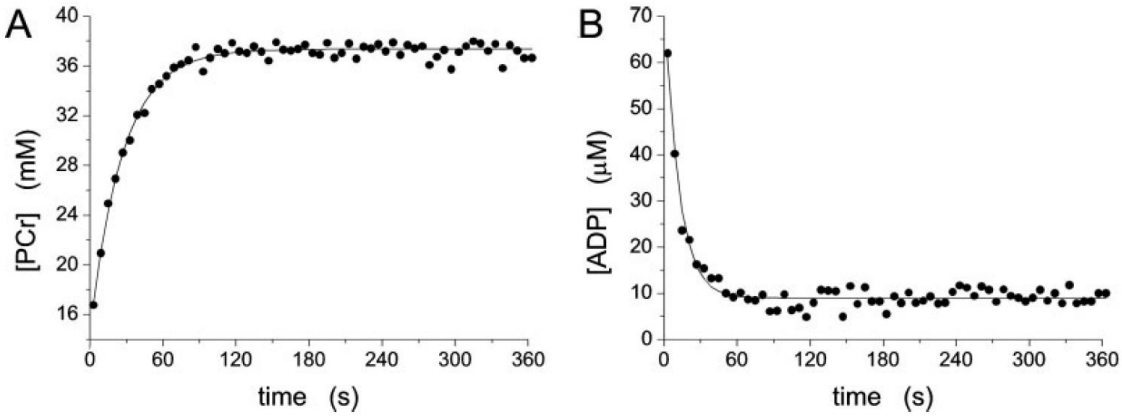


Figure 2.12 – PCr (a) and ADP (b) recovery curves for an individual subject deduced from dynamic ^{31}P MRS.

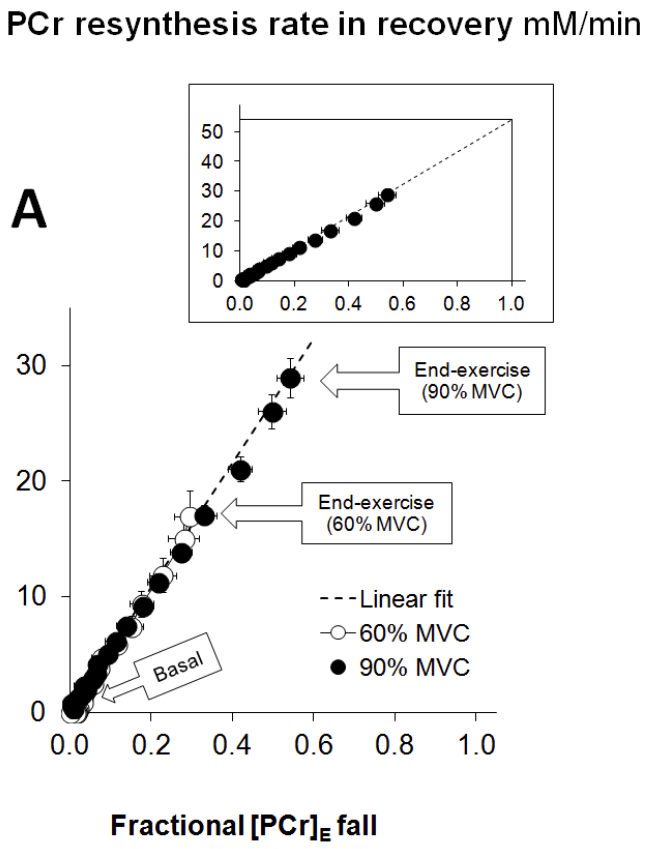


Figure 2.13 – Derivation of the monoexponential rate constant k_{PCr} by linear fit.

Chapter 3

General Methods and Experimental Setup

CHAPTER 3 – General Methods and Experimental Setup

3.1 INTRODUCTION

The studies described in this thesis demonstrate a combination of non-invasive methods utilised to study whole body physical fitness and mitochondrial function. These methods were used to assess changes in fitness and mitochondrial function in locally advanced rectal cancer patients who were recruited from within NHS cancer care pathways. In Chapter 1 the reader was acquainted with both the previous (Figure 1.2) and current colorectal cancer pathways (Figure 1.3) used at Aintree University Teaching Hospitals NHS Foundation Trust. In Figures 3.1 and 3.2, I attempt to illustrate the integration of the research investigations/interventions (presented in Chapters 4 to 7) into the aforementioned NHS rectal cancer pathways (Figure 1.2 and 1.3).

As one can observe in Figures 3.1 and 3.2 the integration of research investigations and interventions presented in Chapters 4-7 does not alter the standard NHS cancer pathways. All research investigations and interventions were specifically designed to fit around the standard cancer pathway used at AUH, utilizing the waiting times between standard care investigations and the hiatus between the end of NACRT and surgery. Ethical approval for this project was granted by the Northwest Regional Ethics Committee on the 18th March 2011 (REC Reference Number 11/H1002/12), and further favourable ethical approval was given for two amendments on the 20th June 2011 and 30th January 2012 (REC Reference Number 11/H1002/12a and 11/H1002/12b). All studies presented in this thesis were registered with the clinicaltrials.gov website (Chapter 4 – NCT 01334593, Chapter 6 – NCT01325909 and Chapter 7 – NCT01859442).

Methodological approaches described in this chapter include the cardiopulmonary exercise testing protocol, the structured responsive exercise training programme protocol and the 31-Phosphorus Magnetic Resonance Spectroscopy (^{31}P MRS) methodology. This chapter describes the general experimental protocols and set up for the methods detailed above, all of which have been implemented in Chapters 4 to7.

Figure 3.1 – Previous standard rectal cancer pathway at AUH (until October 2011), with the addition of research investigations (highlighted in orange) as described in Chapter 4.

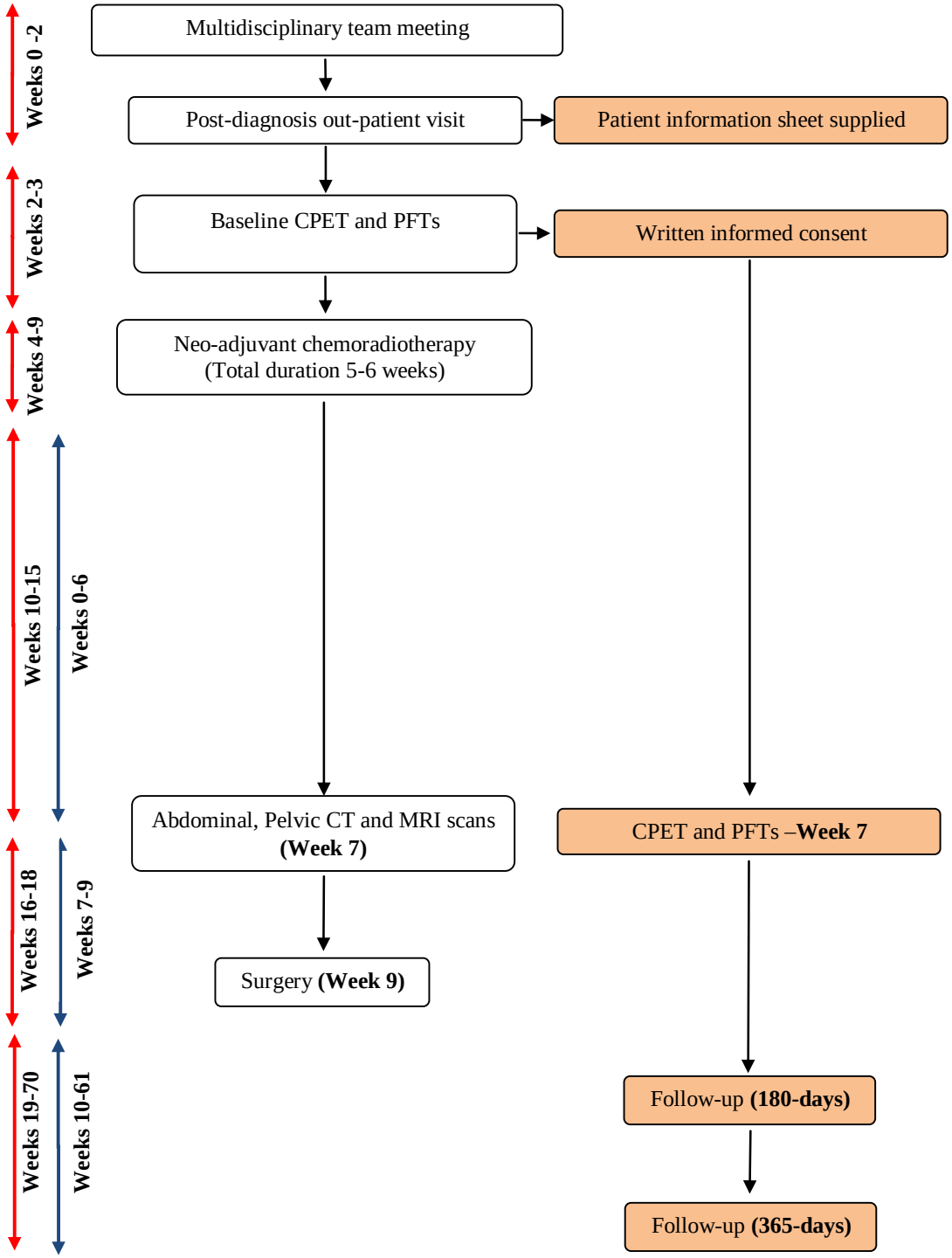
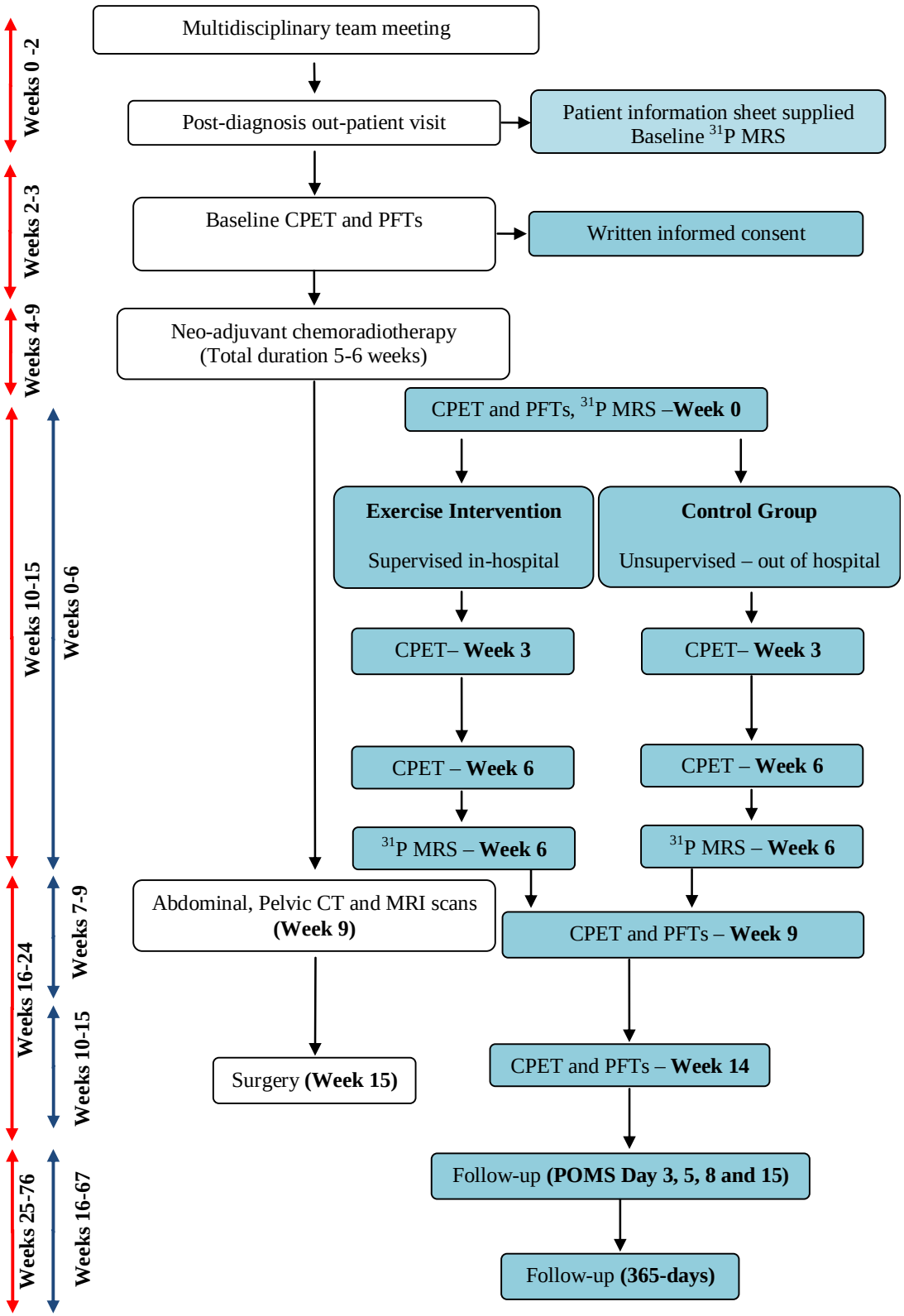


Figure 3.2 – Current standard rectal cancer pathway at AUH (from October 2011 to date), with the addition of research investigations/interventions (highlighted in blue) as described in Chapters 5 to 7.



3.2 CARDIOPULMONARY EXERCISE TESTING

As described in Section 2.5.1, the advantage of CPET over other methods of preoperative assessment is that it provides an integrated assessment of oxygen utilisation under conditions of dynamic exercise stress. CPET has already been validated for the assessment of advanced cancer patients (168,173). CPET is an objective, repeatable, non-invasive, quick, specific and sensitive means of assessing physical fitness in the preoperative setting. The relationship between fitness variables derived from CPET and surgical outcome is described in Section 2.5.2. The equipment and test setup (Section 3.2.1), exercise protocol (Section 3.2.2), derived variables, their physiological basis and definitions (Section 3.2.3) and the determination of the estimated lactate threshold by the V-slope method (Section 3.2.3.4) are all discussed hereunder in more detail.

3.2.1 EQUIPMENT AND SETUP

CPET followed the American Thoracic Society/ American College of Chest Physicians recommendations (116) and the CPET in clinical oncology practice recommendations by Jones and colleagues (168) . All patients were assessed for CPET contraindications (Table 3.1) by accessing their electronic health care records at AUH (116).

Absolute Contraindications	**Relative Contraindications**
Acute myocardial infarction	Left main coronary stenosis
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	Severe untreated arterial hypertension at rest (systolic > 200mmHg, 120mm Hg diastolic)
Syncope	Tachyarrhythmia or bradyarrhythmia
Active endocarditis	Hypertrophic cardiomyopathy
Acute myocarditis or pericarditis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Thrombosis of lower extremity	Electrolyte abnormalities
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest <85% if no known lung pathologies	

Respiratory failure	
Acute non-cardiopulmonary disorder that may affect exercise performance	
Mental impairment leading to inability to co-operate	

Table 3.1 – Absolute and relative contraindications to CPET

CPET was conducted on an electromagnetically braked cycle ergometer (Ergoline 2000) with the patient breathing through a facemask. Attached to the facemask is a flow sensor (Geratherm Respiratory GmbH), which is a device that measures differences in flow stream pressures across a variable orifice membrane. The flow sensor is connected to a gas analyzer via a 2 meter gas-sampling tube. The gas analyzer measures concentrations of O_2 and CO_2 separately. Gas transport delay (time required for gas to traverse the distance from the sampling site to the analyser) and analyzer response (the kinetics of response to a change in gas composition introduced into the analyzer) generally of the order of 0.2 to 0.4 seconds was compensated for by the computer software used (Blue Cherry version 1.1.4.0 – Geratherm Respiratory GmbH). Part of the gas-sampling tube is made of a Nafion polymer which reduces the water vapour content in the analysed gas, in order to reduce the partial pressure of water vapour in the sampled gas which may introduce substantial errors in the metabolic rate calculations if left uncorrected (213). Ambient temperature, pressure and humidity were recorded in real time (Ambi Stick - Geratherm Respiratory GmbH). The flow sensor was calibrated for flow (L/s) prior to each test with a standard 3L syringe. A range of flow rates were performed to simulate the wide range of flow rates that occur in going from rest to heavy exercise. Agreement in calculated volumes to within ±3% signified adequate calibration. Gas calibrations for O_2 and CO_2, together with their respective delays was also performed prior to each test. Gas calibrations were performed (two point calibration) with ambient O_2 and CO_2 with standard, gravimetrically weighed, bottled calibration gas of know concentrations (BOC gases, accurate to ±1%). A typical CPET setup is shown in Figure 3.3.

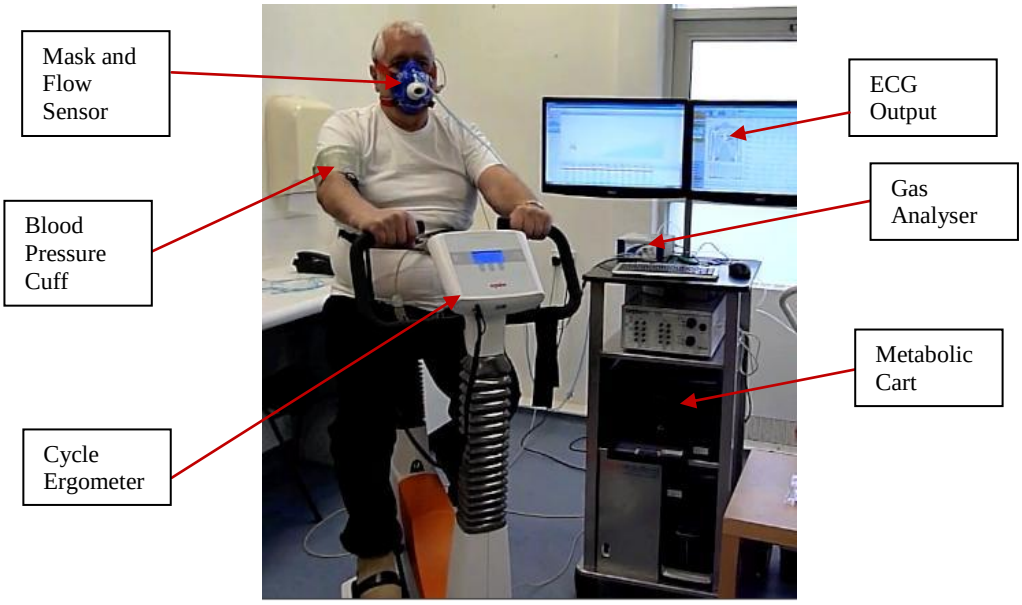


Figure 3.3 – CPET set-up showing a metabolic cart with two video monitors showing real time respiratory variables and full 12-lead ECG, a study patient who is fitted with a flowsensor and mask and an electromagnetically braked cycle ergometer

Prior to testing a cardiac arrest trolley was checked and available. The patient's demographics were entered into the software. This included date of birth, hospital identification, trial anonymization code, gender, height (cms), and weight (kg). Calculations for body mass index (BMI – $kg.m^{-2}$) and body surface area (BSA – m^2) were performed. Electrocardiography electrodes were placed in the usual 12-lead positions. Skin preparation and sweat-resistant adhesives were used to reduce noise on the ECG tracing. The leads were attached to the electrodes and to the ECG analyzer (AMEDTEC). Heart rate was measured from the R-R interval of the ECG. Electrodes and ECG detection software were configured to reject movement artifact. Baseline spirometry was then performed by utilizing the flow-volume loop icon on the Blue Cherry software (Figure 3.4). The mouthpiece and flow-sensor was placed in the patients' mouth with a good air tight seal and a nose-peg was placed appropriately. A face mask was used if the mouthpiece was poorly tolerated by the patient. The patient was then asked to breathe in as deeply as possible (full inspiration). The patient held their breath long enough to seal their lips with the mouthpiece, and then was instructed to blow out forcibly as hard and as fast as possible, until their lungs were empty. All patients were given consistent encouragement to keep blowing out (end expiration). Three attempts which were within 100ml or 5% of each other were performed and saved (Figure 3.4).

A ramp exercise protocol was then calculated and selected (more details on protocol in Section 3.2.2). The correct size facemask was selected for the patient. The facemask was

placed on the patients face ascertaining a good seal around the mask cushion, with no leaks on air tightness testing. The patient was then coached to give their "best effort", however they were also told to stop if any adverse events were encountered (described in Section 3.2.2). The patient was then asked to climb onto the stationary cycle ergometer. The height of the seat was assessed, adjusted and recorded with the patient not overextending at the knee joint on the descending pedal stroke. Patients were instructed to pedal between 55 and 65 rpm for the duration of the test until volitional termination.

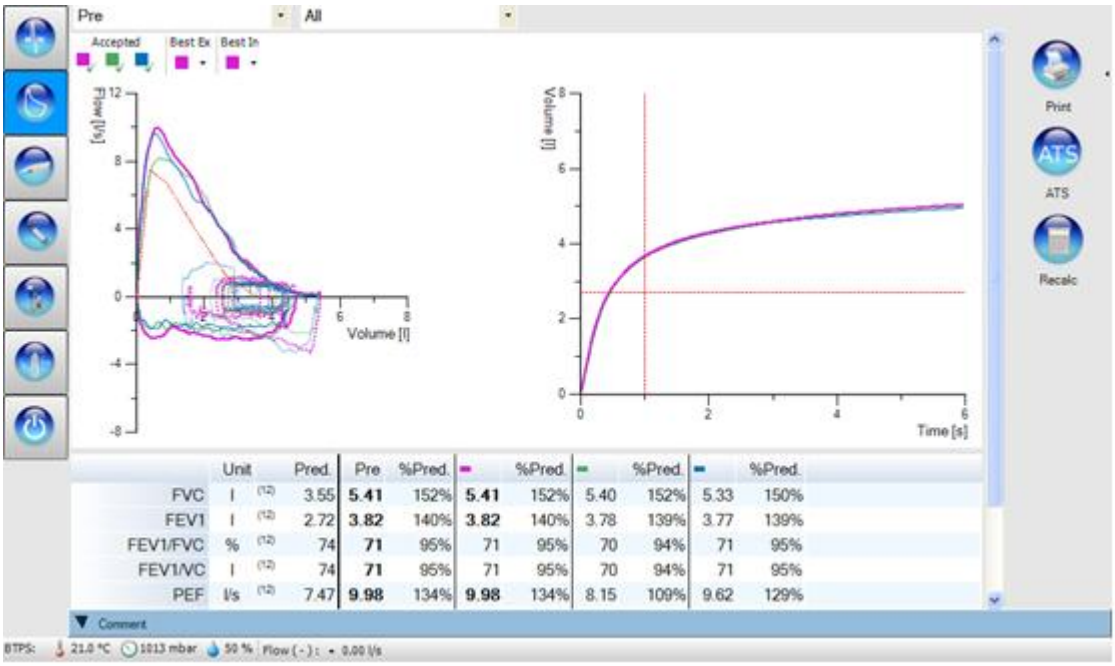


Figure 3.4 – Three consistent flow volume curves

A non-invasive blood pressure (BP) cuff was fitted to the patients' right arm, and an automated BP was measured at rest, and every 2 minutes during exercise and recovery. Patients were also monitored with continuous pulse oximetry via an ear probe.

3.2.2 RAMP EXERCISE PROTOCOL

All patients were tested at the same time of day and time to ensure consistency and eliminate bias. Baseline measurements included resting heart rate, blood pressure, SpO_2, and ECG were undertaken. The test protocol included four phases; an initial rest phase (three minutes) is employed to establish baseline values. Baseline CPET measurements of VE, $\dot{V}o_2$, end-tidal PO_2 and PCO_2 were noted and allowed to stabilise. This was followed by three minutes of unloaded cycling (zero watts) to allow the patient to become familiar with the cycling

motion and to reduce the influence of the lag present between increased work rate (WR) and the $\dot{V}o_2$ response. Following this, the incremental exercise phase begins. A ramp incremental protocol was used, during which the set work rate was increased linearly with time, with a corresponding increase in the intensity of the exercise. The ramp incremental protocol was determined for each patient by using a formula by Wasserman et al. (214):

$$\dot{V}o_2 \text{ unloaded pedaling } (mls.min^{-1}) = 150 + (6 \times \text{Weight in kg})$$

$$\text{Peak } \dot{V}o_2 \, (mls.min^{-1}) = \text{Height (cms)} - \text{Age (years)} \times 20 \text{ (sedentary males)}$$

$$\text{Peak } \dot{V}o_2 \, (mls.min^{-1}) = \text{Height (cms)} - \text{Age (years)} \times 14 \text{ (sedentary females)}$$

$$\text{Work rate increment/min} = \text{Peak } \dot{V}o_2 - \dot{V}o_2 \text{ unloaded pedaling} / 100$$

The patient was given verbal feedback and encouragement throughout the test; this was kept as constant as possible with a lot of encouragement given towards the end of the test. The test was terminated by the patient at volitional exhaustion or symptoms (e.g. shortness of breath, chest pain etc.). Specific criteria for stopping were:

- The patient stops pedalling due to leg fatigue, dyspnoea, pain or light headedness, and,
- The patient fails to maintain an RPM of greater than 40 RPM for more than 1 minute and does not respond to encouragement.

An exercise period of between 8 to 12 minutes was ideal. All patients were coached to give their "best effort" all throughout the test. Following test completion, a recovery period (five minutes) of low intensity exercise was performed to maintain venous return, thereby reducing the risk of pooling of blood in the leg veins which can be associated with symptomatic hypotension (e.g. light-headedness, faint). The patient was observed throughout recovery until physiological variables including heart rate, blood pressure, ventilation, and oxygen saturation, returned close to baseline levels and any exercise induced ECG changes had resolved. The test was stopped if the patient experienced any adverse symptoms namely (96,116,215);

- Angina
  - 2mm ST depression if symptomatic or 4mm if asymptomatic or > 1mm ST elevation
- Significant arrhythmias
- Fall in systolic pressure > 20mmHg from the highest value during the test

- Hypertension > 250mm Hg systolic; > 120 mm Hg diastolic
- Severe desaturation: SpO_2 < 80% accompanied by limiting hypoxaemia
- Sudden pallor
- Loss of coordination
- Mental confusion
- Signs of respiratory failure

Test data was displayed in both numerical and graphical formats by the software. $\hat{\theta}_L$ derivations were done using the V-slope methods described in Section 3.2.3.5. CPETs were reported by myself and LL (Clinical Exercise Physiologist - acknowledged) in an unblinded fashion; however these were then dually reported by an experienced consultant clinical scientist (SJ - acknowledged) who was blinded to all CPET data points, clinical data and patient allocation. All reported CPET data is defined in Section 3.2.3.

3.2.3 VARIABLES AND DEFINITIONS

A number of important physiological variables are recorded during CPET. These are briefly defined in Table 3.2, however a more detailed description of the physiological basis of these variables will be provided in Section 3.2.3.1. Some of these variables, as described in Section 2.5, have been used to identify patients at high risk of perioperative morbidity and mortality: Estimated Lactate Threshold ($\hat{\theta}_L$) (113,117,120,121), $\dot{V}o_2$ Peak (140), and $\dot{V}_E/\dot{V}_{CO2}$ (120,133). These three variables are most commonly used to stratify risk for non-cardiopulmonary surgery (3–5,114,119).

Estimated Lactate Threshold ($\hat{\theta}_L$)	The exercise $\dot{V}o_2$ above which anaerobic high-energy phosphate production supplements aerobic high-energy phosphate production, with consequential lowering of the cellular redox state, increase in lactate/pyruvate ratio, and net increase in lactate production at the site of anaerobiosis. Exercise above the $\hat{\theta}_L$ is reflected in the muscle effluent and central blood by an increase in lactate concentration, lactate/pyruvate ratio and metabolic acidosis.

Oxygen Uptake ($\dot{V}o_2$)	The amount of oxygen extracted from the inspired gas in a given period of time ($ml/L.min^{-1}$).
Oxygen Pulse (0_2 pulse)	The $\dot{V}o_2$ divided by the heart rate. This represents the amount of oxygen (O_2) extracted by the tissues from the O_2 carried in each stroke volume. This variable can be calculated at $\hat{\theta}_L$ and at peak exercise ($ml.beat^{-1}$).
Heart Rate Reserve (HRR)	The difference between the predicted highest heart rate attainable during maximum exercise and the actual highest heart rate.
Peak Oxygen Uptake ($\dot{V}o_2$ Peak)	The highest oxygen uptake achieved during a maximum work rate test, calculated as the average $\dot{V}o_2$ in the last 30 seconds of exercise.
Work rate	The rate at which work is performed in Watts.
Ventilatory Equivalents for CO_2 and O_2 ($\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$)	The ventilatory equivalents for CO_2 and O_2 are measurements of the ventilatory requirement for a given metabolic rate. Both variables can be calculated at $\hat{\theta}_L$ and at peak exercise.
Minute Ventilation (V_E)	The volume of gas exhaled divided by the time of collection in minutes.
Forced Expiratory Volume in 1 Second (FEV1)	Volume that has been exhaled at the end of the first second of forced expiration
Forced Vital Capacity (FVC)	The determination of the vital capacity from a maximally forced expiratory effort
FEV1/FVC	A calculated proportion of a person's vital capacity that they are able to expire over one second
End tidal P_{CO2} (PET_{CO2})	Partial pressure of CO_2 (P_{CO2}) of respired gas, determined at the end of an exhalation. This is commonly the highest P_{CO2} measured during the alveolar phase of the exhalation. It is expressed in mmHg.
End tidal P_{O2} (PET_{O2})	Partial pressure of O_2 (P_{O2}) of respired gas, determined at the end of an exhalation. This is commonly the highest P_{O2} measured during the alveolar phase of the exhalation. It is expressed in mmHg.

Table 3.2: Cardiopulmonary Exercise testing variable definitions

Other variables recorded during a CPET include: heart rate (HR), blood pressure (BP), oxygen saturation (SaO_2).

3.2.3.1 PHYSIOLOGICAL BASIS OF CPET VARIABLES AND TEST INTERPRETATION

This section will review the physiological basis of important CPET derived variables, noting there normal response to exercise. Although the meaning and limitations of each variable will be considered individually, for the purposes of optimal test interpretation, the greatest diagnostic potential and impact on clinical decision-making does not rest on the utility of one variable alone, but rather on their integrated use. Their integrated use has been used in risk stratification and fitness assessment in this thesis.

3.2.3.2 OXYGEN UPTAKE

Oxygen uptake ($\dot{V}o_2$) is determined by cellular O_2 demand up to the point where it equates to the maximal rate of O_2 transport. $\dot{V}o_2$ can be computed from blood flow and O_2 extraction by the tissues expressed in the Fick equation:

$$Q = (SV \times HR) = \dot{V}o_2 / [C(a–v)O_2]$$

Where Q indicates cardiac output, SV indicates stroke volume, and $[C(a–v)O_2]$ indicates the arteriovenous O_2 content difference, which is related to the O_2 extraction. Factors that can influence O_2 availability are oxygen carrying capacity of the blood, dissociation curve shift (with temperature, CO_2 and pH), cardiac function, redistribution of peripheral blood flow, and extraction by the tissues (influenced by capillary density, mitochondrial function/density, adequacy of perfusion and tissue diffusion).

$\dot{V}o_2$ normally increases nearly linearly as external work increases. The slope of $\dot{V}o_2$ vs. external work rate reflects the efficiency of the metabolic conversion of chemical potential energy to mechanical work and the mechanical efficiency of the musculoskeletal system. Change in $\dot{V}o_2$ divided by change in work rate is normally about 8.5-11 ml/min/watt and is independent of gender, age or height (214). Obese individuals may show an increased in $\dot{V}$

o_2 for a given external work rate, but the rate of rise in $\dot{V}o_2$ with increasing external work should be normal. A reduction in this often indicates inadequacies of O_2 transport or abnormal O_2 utilization.

With increasing $\dot{V}o_2$ and work rates, patients begin to approach volitional termination of exercise, or a clear plateau in $\dot{V}o_2$, which is described as the $\dot{V}o_2$ Max. $\dot{V}o_2$ Max is the best index of aerobic capacity and the gold standard of cardiorespiratory fitness. It represents the maximal achievable level of oxidative metabolism involving large muscle groups. However, in clinical practice, this is very hard to achieve before symptom limitation. Consequently $\dot{V}o_2$ Peak is often used as an estimate for $\dot{V}o_2$ Max. $\dot{V}o_2$ Peak is dependent on the quantity of exercising muscle, age, sex and body size an can be affected by training. $\dot{V}o_2$ is usually reported as absolute or adjusted for body weight. $\dot{V}o_2$ can also be referenced to lean body mass (fat free mass), however its routine measurement is difficult. A reduced $\dot{V}o_2$ Peak may reflect problems with oxygen transport i.e. cardiac or pulmonary limitations, tissue oxygen extraction, neuromuscular or musculoskeletal limitations and of course is effort dependent. $\dot{V}o_2$ Peak is always reported as the highest $\dot{V}o_2$ achieved during CPET averaged over last 30 seconds of loaded exercise data. A formula for estimating $\dot{V}o_2$ Peak reported by Wasserman and Whipp (214) is as follows :

Predicted $\dot{V}o_2$ during unloaded pedalling ($ml.min^{-1}$) = (5.8 x weight in kg) + 151

$\dot{V}o_2$ Peak ($ml.min^{-1}$) = Height (cm) – age (years) x 20 (sedentary males) <u>or</u> x 14 (sedentary females)

3.2.3.3 CARBON DIOXIDE OUTPUT

Carbon dioxide output ($\dot{V}co_2$) during exercise is determined by factors similar to those that govern $\dot{V}o_2$, i.e. cardiac output, CO_2 – carrying capacity of the blood, and tissue exchange. However, because CO_2 is much more soluble in tissues and blood, CO_2 output measured at the mouth is more strongly dependent on ventilation than $\dot{V}o_2$. In addition because CO_2 is a weak acid, the body uses CO_2 regulation to compensate for acute metabolic acidosis, which affects the pattern of $\dot{V}co_2$ as work increases above anaerobic metabolism. During short duration exercise, glycogen is used primarily by muscle for energy, and the relation between O_2 consumption and CO_2 production is almost equimolar. As such, during progressive exercise, $\dot{V}co_2$ increases nearly as much as $\dot{V}o_2$ over low work rates, with an average

relationship of slightly less than 1 (Figure 3.5, slope S_1). There is then a relatively sharp change in slope toward the midrange of the $\dot{V}o_2$ response (Figure 3.5, AT (anaerobic threshold) or $\dot{V}o_2$ at $\hat{\theta}_L$ – red line). This results in a steeper, but linear profile over the upper work rate range (Figure 3.5, slope S_2). The steeper slope reflects the CO_2 generated in excess of that produced by aerobic metabolism due to bicarbonate buffering of increased lactic acid production. With anaerobic metabolism, $\dot{V}co_2$ increases as a result of the chemical reaction between hydrogen ions (from lactate) and dissolved CO_2:

$$[H^+] + [HCO_3^-] \leftrightarrow [H_2CO_3] \leftrightarrow [CO_2] + [H_2O]$$

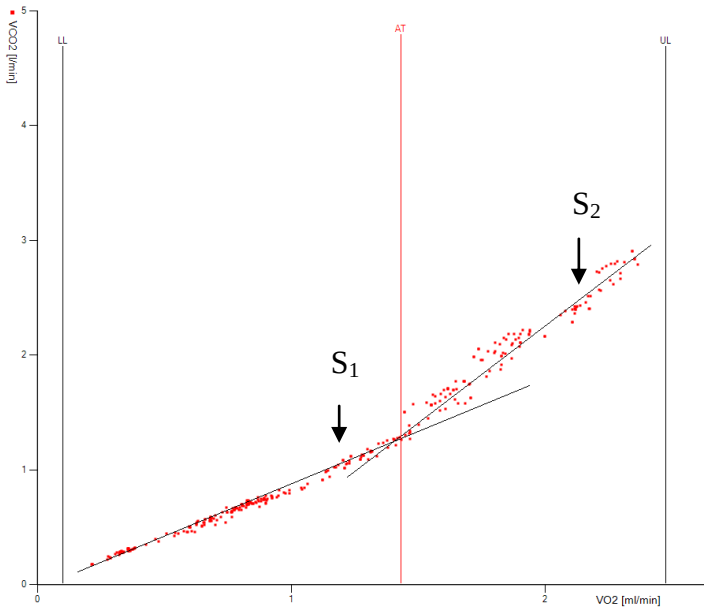


Figure 3.5 – Graph depicting $\dot{V}co_2$ vs. $\dot{V}o_2$ increasing with a ramp incremental protocol (actual patient data)

As tissue lactate production increases $[H^+]$, the reaction is driven to the right, producing extra CO_2 above that produced aerobically. The excess CO_2 may also come from reduction in the body CO_2 stores as a result of hyperventilation (manifested as arterial hypocapnia). CO_2 output needs to be measured accurately as it is the basis for the calculation of several derived variables, including, the respiratory exchange ratio, the respiratory quotient, alveolar ventilation etc.

The ratio of $\dot{V}co_2 / \dot{V}o_2$ is called the respiratory exchange ratio (RER). Under steady state conditions, the RER equals the respiratory quotient (RQ), whose value is determined by the fuels used for the metabolic processes. An RQ of 1.0 indicates a mixture of carbohydrates, whereas an RQ of less than 1.0 indicates a mixture of carbohydrate with fat (about 0.7) or

protein (about 0.8). If true steady state exists, the blood and gas transport systems are keeping pace with tissue metabolism; thus the RER can replace the RQ. An RER of greater than 1.0 could be caused by CO_2 derived from lactic acid or hyperventilation because of the 20-fold or higher tissue solubility of CO_2 compared with O_2, therefore when testing both these sources of CO_2 must be considered when the RER is above 1.0.

3.2.3.4 LACTATE THRESHOLD

The lactate threshold ($\hat{\theta}_L$) is considered an estimator of the onset of metabolic acidosis caused predominantly by the increased rate of rise of arterial lactate during exercise. After 30 years the physiological mechanism underlying the increase in muscle and blood lactate that occurs at the $\hat{\theta}_L$ still remain controversial (216).

Energy for muscle contraction is provided by high-energy phosphate groups supplied in the form of adenosine triphosphate (ATP). ATP is supplied by the breakdown of glycogen to pyruvate, which enters the tricarboxylic acid (TCA) cycle via acetyl-coA, and breakdown of fats to produce acetyl-coA. Further processing of acetyl-coA in the TCA cycle and electron transport chain produces ATP needed for muscle contraction. If processing occurs only in the glycolytic pathway, a smaller amount of ATP is formed along with lactic acid (described in Section 2.7.1). The extra acid produced causes an increase in $\dot{V}co_2$ by buffering of CO_2 in the blood. Controversy persists as to whether a deficiency of oxygen delivery versus oxidative capacity also contributes to the onset of lactic acid production, hence the term "anaerobic threshold." It is possible that both processes, that is, the pattern of muscle fibre recruitment and a potential imbalance between oxygen supply and oxidative metabolism, contribute to the increase in lactic acid as exercise intensity increases.

In normal individuals, the $\hat{\theta}_L$ occurs at about 50–60% $\dot{V}o_2$ Max predicted in sedentary individuals, with a wide range of normal values. The $\hat{\theta}_L$ determination is age, modality and protocol specific. The $\hat{\theta}_L$ derived from arm exercise is lower than that derived from leg exercise, and that derived from cycle ergometry is lower than that derived from treadmill. This reflects differences in exercising muscle mass and possibly differences in the dominant fibre type of exercising muscle. The $\hat{\theta}_L$ demarcates the upper limit of a range of exercise intensities that can be accomplished almost entirely aerobically. Whereas work rates below the $\hat{\theta}_L$ can be sustained essentially indefinitely until fatigue, a progressive increase in work rate above $\hat{\theta}_L$ is associated with a progressive decrease in exercise tolerance. So in patients

who become symptom limited with premature cessation of exercise, the $\hat{\theta}_L$ is an effort-independent measurement may represent a sub-maximal variable that may assist in clinical decision making (3–5).

3.2.3.5 V-SLOPE METHOD OF LACTATE THRESHOLD DERIVATION AND TEST INTERPRETATION

Several methods are available for the determination of $\hat{\theta}_L$. These include invasive methods (arterial lactate, bicarbonate) or non-invasive methods (ventilatory equivalents, V-slope or modified V-slope). All $\hat{\theta}_L$ derivations and their corresponding CPET variables reported in this thesis were performed using the modified V-slope method described hereunder.

As work rate increases, $\dot{V}o_2$ and $\dot{V}co_2$ increase linearly until exercise lactic acidosis develops. This changing relationship was used to identify the lactate threshold using a technique known as the "V-slope" method. $\dot{V}co_2$ is plotted against $\dot{V}o_2$ with the former on the y-axis and the latter on the x-axis (Figure 3.5). To confirm that this change of slope is not occasioned by hyperventilation, monitoring ventilatory equivalents and end-tidal Pco_2 is necessary. Consequently, the ventilatory equivalents for O_2 and end-tidal O_2 reach their nadir and begin to rise in concert with the S_1–S_2 transition, without an increase in the ventilatory equivalent for CO_2 and/or decrease in end-tidal Pco_2. The intercept of these two slopes is the $\hat{\theta}_L$ as measured by gas exchange (Figure 3.6). The technique of derivation of the $\hat{\theta}_L$ is referred to as the V-Slope method (214,217). The modified V-Slope method identifies the $\hat{\theta}_L$ as the tangential breakpoint in the $\dot{V}co_2$- $\dot{V}o_2$ relationship from the line of unity ('line of one') during the incremental stage of the exercise test (Figure 3.7). Because inappropriate increases in $\dot{V}co_2$ disproportionate to increases in metabolic rate $\dot{V}o_2$ due to acute hyperventilation invalidate the non-invasive determination of the $\hat{\theta}_L$, the V-slope and ventilatory equivalents were used together with the RER (approaching 1.0) to more accurately identify the $\hat{\theta}_L$.

The V-slope methods depend solely on the physicochemical reaction of lactate with bicarbonate and thus the occurrence of the breakpoint is independent of chemoreceptor sensitivity and the ventilatory response to exercise - although the magnitude of the response is (217,218). However, the physiological basis for this variable remains controversial (216), but the inter-observer variability for experienced clinicians is very acceptable (219).

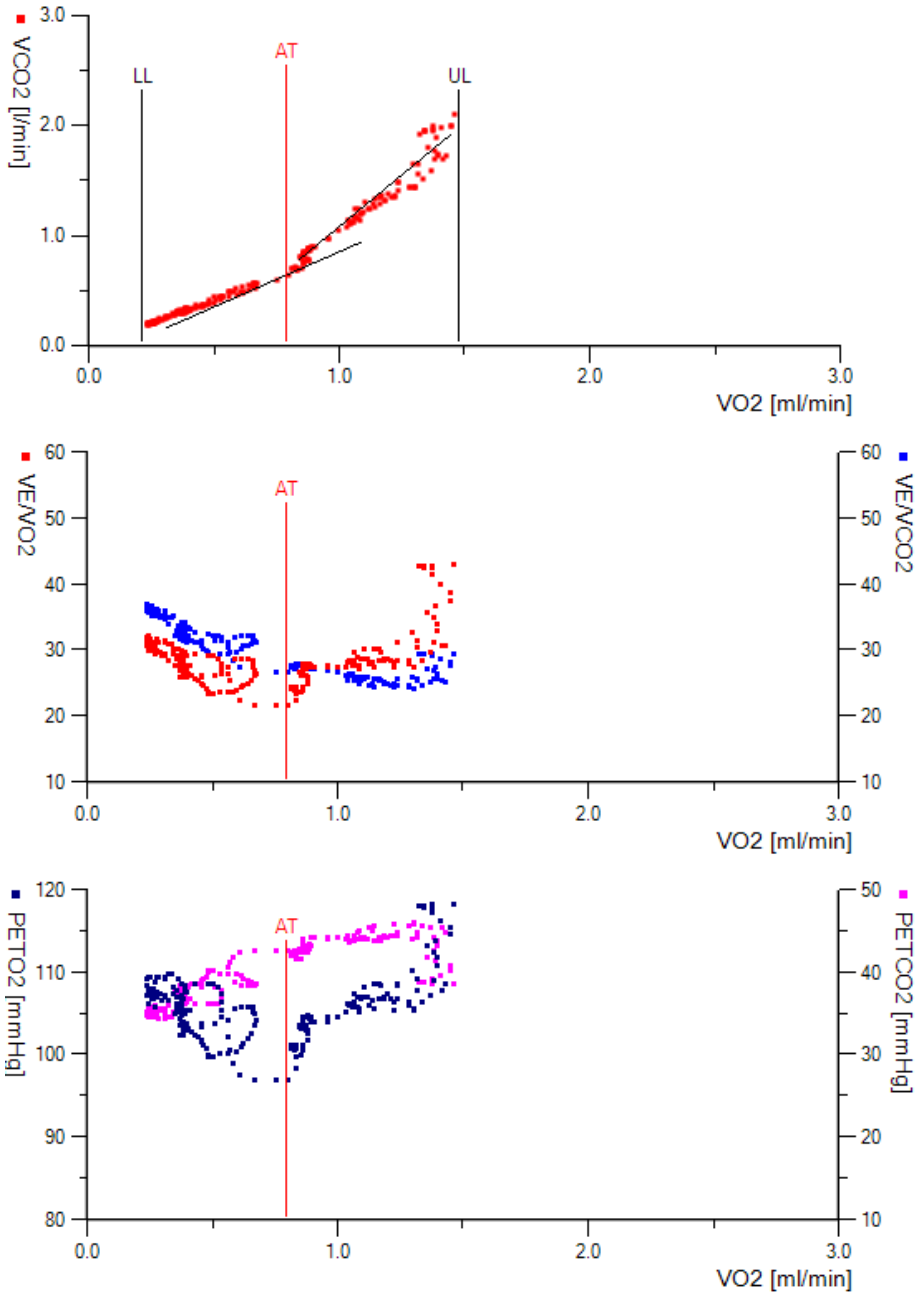


Figure 3.6 - An example trace showing $\dot{V}o_2$ at $\hat{\theta}_L$ determination (actual patient data) as described in the section above. A mixture of the tangential breakpoint seen in the $\dot{V}co_2$- $\dot{V}o_2$ relationship (first panel), together with the ventilatory equivalents (second panel) and the end tidal graph (third panel) is used in the modified V-slope technique.

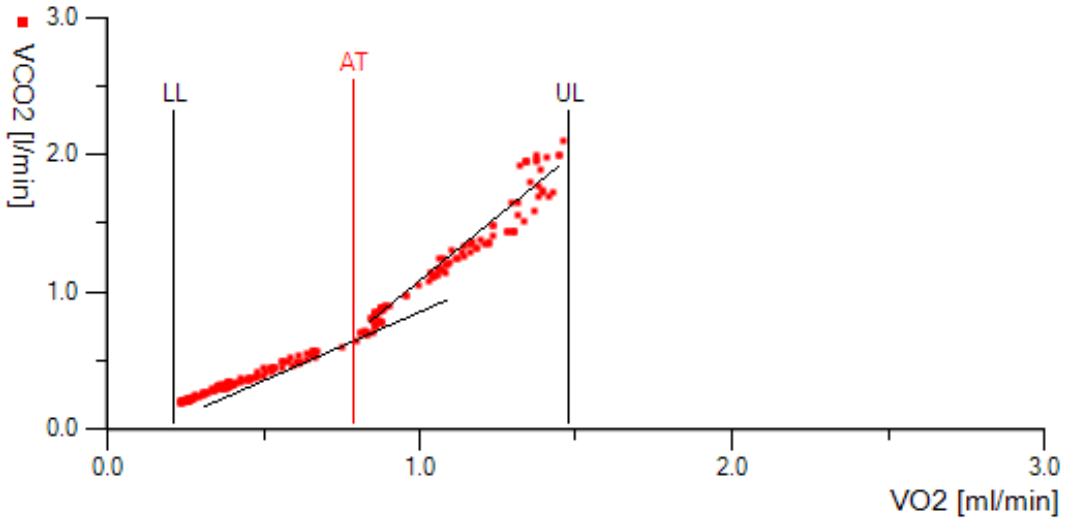


Figure 3.7 - The modified V- Slope method of $\hat{\theta}_L$ determination. At the $\hat{\theta}_L$ the gradient of the $\dot{V}o_2$ - $\dot{V}co_2$ relationship will increase above 1. The breakpoint - marked by the red vertical line is the $\hat{\theta}_L$ (actual patient data)

3.3 STRUCTURED RESPONSIVE EXERCISE TRAINING PROGRAMME

Between Week 0 and 6 post-NACRT, patients in the exercise group underwent a structured, responsive, exercise training programme (SRETP). An iterative process was undertaken prior to implementation of this exercise programme based on the systematic review outlined in Section 2.6. This iterative process led to the development of the final training programme which will be summarised in Chapter 5.

3.3.1 SETUP AND TRAINING PROGRAMME CALCULATION

The SRETP encompassed a:

- **Structured**: 3 times a week for a duration of 6 weeks (18 sessions in total – including 3 CPETs).
- **Responsive**: Informed by a CPET at week 3 (mid-exercise programme).
- **Exercise**: Interval training including moderate and severe intensity aerobic exercise.
- **Training**: Undertaking a course of exercise in preparation for a major stressor.
- **Programme**: A series of goals to be accomplished.

Patients participated in a 6 week in-hospital, supervised exercise training program on a computer controlled, electromagnetically braked, cycle ergometer (Ergoline 200, Germany) (Figure 3.8). Severe and moderated intensity interval training, consisting of repeated short periods of severe and moderate intensity work and recovery which was directed by changes in work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak was undertaken.

Figure 3.8 – A computer controlled electromagnetically braked exercise training bike (Courtesy of Love Medical Ltd, Manchester, UK)

The training program was individually set/ tailored to be responsive to each patients' changing fitness. This was set following the initial CPET test post-NACRT (Week 0). Each session was 4 to 5 repeats of: a) 3 minutes severe intensity cycling immediately followed by, b) 2 minutes of moderate intensity (20 minutes total in total for the first 3 sessions, then 30 minutes for the following sessions). 5 minutes of unloaded cycling was performed at the start and end of all training sessions for a warm-up and cool down. Moderate intensity exercise (80% $\hat{\theta}_L$) was set at a power output equivalent to 80% of the work rate at $\dot{V}o_2$ at $\hat{\theta}_L$ and severe intensity was set at a power output that is half-way between work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak (termed 50%Δ). This is illustrated by the formula below:

Moderate intensity exercise – (Work load at $\dot{V}o_2$ at $\hat{\theta}_L$ – ⅔ of work ramp) x 80%

Severe intensity exercise – ((Work load at $\dot{V}o_2$ Peak - Work load at $\dot{V}o_2$ at $\hat{\theta}_L$ - ⅔ of work ramp) x 50%) + Work load at $\dot{V}o_2$ at $\hat{\theta}_L$

Patients attend 3 exercise sessions per week for 6 weeks. Each exercise session lasted 30 minutes in total for the first 3 sessions and then the duration was increased to 40 minutes in total for the next 12 sessions. Patients were screened prior to each session to ensure that it was safe to perform exercise. Blood pressure was monitored throughout the exercise and heart rate was recorded continuously from the R-R interval (Polar FT7, Warwick, UK). Sessions 0, 7 and 18 (Weeks 0, 3, and 6) were standard CPETs (protocol as per Section 3.2.2) included to make the exercise programme responsive to the patients individual needs and monitor the progression of training-induced changes in physical fitness. The absolute power output for subsequent training sessions was adjusted according to the outcome of the CPET test.

Exercise and CPET sessions could be terminated by the patient or the exercise supervisor at any time if any of the criteria to stop the session are met. This was based on the ATS CPET safety guidelines as per Section 3.2.2. A schematic of the training programme is illustrated in Figure 3.9 hereunder. A screen shot of the graphical result which is visible to the patient on the exercise bike at the end of each training session is illustrated in Figure 3.10. This is considered to be a valuable help for both the patient and the exercise supervisor and aids monitoring of the session's progress. Variables recorded during the exercise training programme included:

- Blood pressure
- Heart Rate
- Power output (Watts)

Week 1 (sessions 1-3)							
3 min **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**

Week 2-6 (sessions 4-17, excluding 7 and 18)									
3 min **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**	**3 min** **80% $\hat{\theta}_L$**	**2 min** **50%Δ**

Figure 3.9 – Schematic of exercise training programme

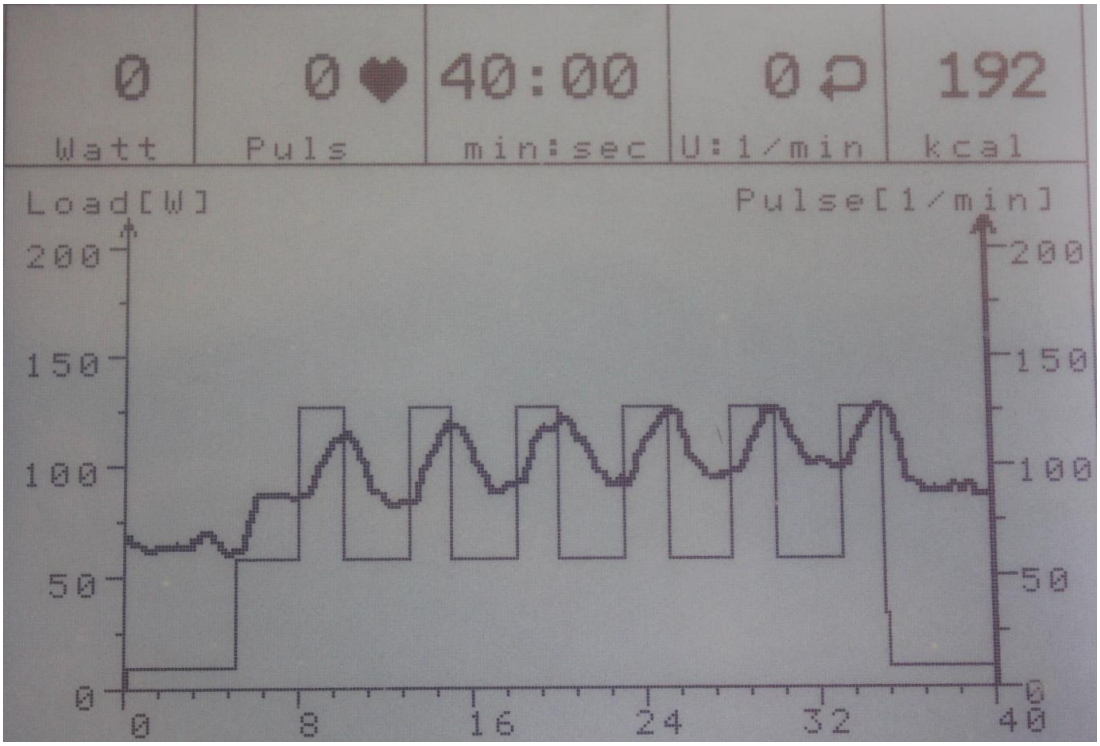


Figure 3.10 – Screen shot of the display on exercise ergometer at the end of a 40 minute exercise session. This shows workload (W) and heart rate (beats.min^{-1}) on the y-axis vs. time (min) on the x-axis. The square wave pattern on the background is the preloaded exercise training programme. The sinusoidal pattern on the foreground is the variation in heart rate with the different training intensities recorded over time.

3.4 31-PHOSPHORUS MAGNETIC RESONANCE SPECTROSCOPY (^{31}P MRS)

This section describes the general experimental protocol and set up for the ^{31}P MRS implemented in chapter 7 of this thesis. All experiments were conducted in a whole-body 3.0 Tesla MR scanner (Magnetom TRIO, Siemens, Erlangen, Germany) at the Magnetic Resonance and Image Analysis Research Centre (MARIARC), University of Liverpool. All patients were screened using standard pre-experimental questionnaires to ensure no contraindications to exercising inside the MR scanner were found. All subjects were requested to abstain from heavy exercise at least 24 hours prior to the experiment. Subjects were also advised not to consume any caffeinated beverages and to refrain from smoking at least 6 hours prior to testing.

3.4.1 SETUP AND EXERCISE EQUIPMENT

^{31}P MRS assessments of peripheral muscle mitochondrial function in quadriceps muscle was carried out using an isometric knee extension exercise protocol similar to a study published by Kemp et al. using a plantar flexion exercise protocol (209). All patients had repeat tests on the same day and time as their previous tests to avoid bias. Subjects lay supine (secured with a Velcro strap across the hips) with the right knee flexed over a rigid foam support in a custom-built rig permitting isometric knee extension exercise against a strap across the anterior lower shin/ankle connected to an aluminum bar fitted with a strain gauge (Figure 3.11). The quadriceps exercise rig is composed of a knee support system which is attached to a flattened sturdy hardwood base and an ankle brace which is secured to the hardwood base via the aluminum bar. The knee support system is constructed from two pieces of medium density fibre board screwed on to two other pieces of triangular chip boards, forming a triangular wedge which supports the knee in a flexed position at an angle of ~130 degrees at rest (~ 50 degrees from terminal extension). Construction of a more acute angle of flexion was not possible due to height restriction in the magnet bore. The force produced during muscle contraction is detected by a strain gauge attached to the exercise rig, and is fed back to the light emitting diode (LED) display unit placed above the patient's head. To allow viewing of the LED, a flexibly adjusted mirror-mounted head-gear is strapped to the patient's head. Patients used real-time visual and auditory feedback from the LED display and from an audible metronome to achieve their target workloads during the exercise protocol.

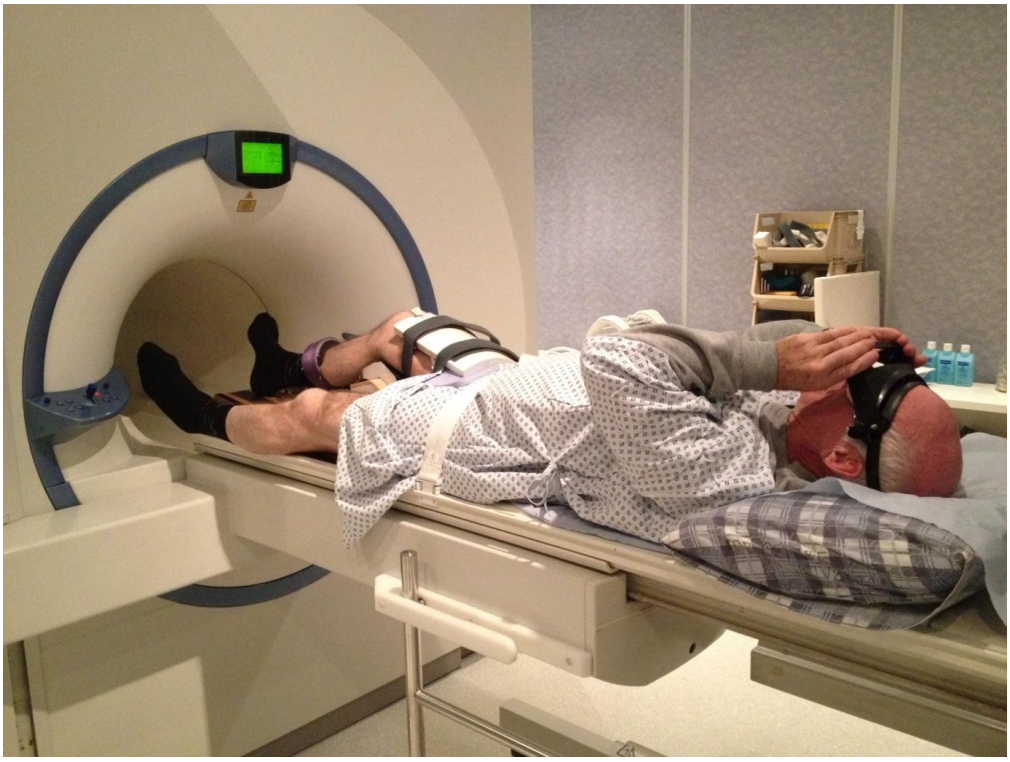


Figure 3.11 – A patient on the MR table attached to the quadriceps exercise rig in the scanner room. The right leg is mounted on the scanner bed. The coil is attached on the right thigh with Velcro straps. The patient is fitted with a head gear which has a mirror mounted on the inner surface so as to be able to look at an LED display unit placed at the top of the scanner table. A non-extensible strap is placed over the patient's lower abdomen to minimise the back muscles contributing to the exercise

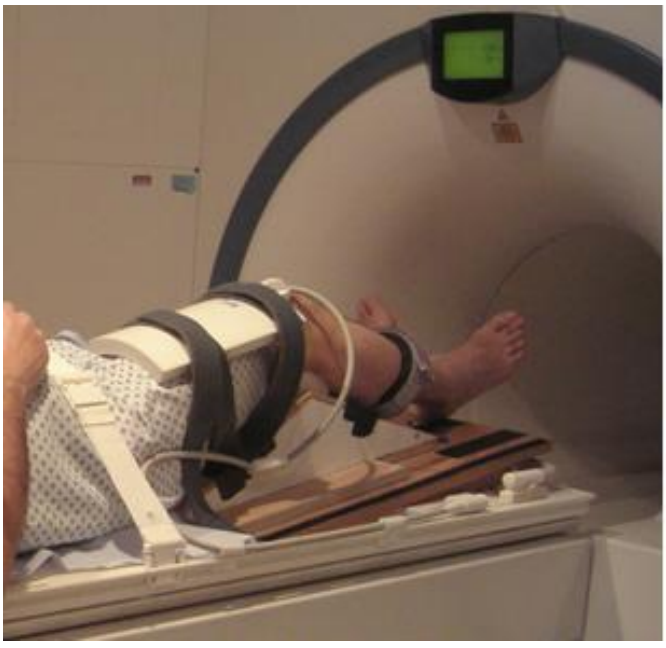


Figure 3.12 - A close up of the exercise rig setup on the scanner table with the patient's leg strapped in the exercising position

^{31}P MRS data were acquired from right quadriceps muscle (vastus lateralis) using a dual-tuned 18cm/15cm diameter ^{31}P/^{1}H surface coil (RAPID Biomedical, Rimpar, Germany), Velcro-strapped to the anterior thigh (midway between anterior superior iliac spine and patella) as shown in Figure 3.12. The level of maximum voluntary contraction (MVC) in this rig was used as a functional measure of maximal power output during exercise. In isometric exercise, power output (i.e. work rate = force x distance x rate) is formally zero (since there is no change in muscle length during contraction), but the force-time integral can be used as an analogue of work. The patient's MVC was determined prior to initiation of every exercise session. The patient was instructed to extend their knee and attempt to 'snap' the Velcro strap at their ankle with maximum effort. The sensitivity of the force transducer was manually adjusted until the subject's MVC levelled at number 10 in the LED display scale, and the patient was able to sustain his/her MVC at that level for at least 1 second. Three consecutive MVCs were performed separated by at least 15 seconds of rest. The highest value of the 3 maximum forces was used as 100% MVC for the individual. Force output data during exercise was recorded on a personal computer running Chart software (version 5) via the PowerLab data acquisition system (AD Instruments, Hastings, UK). Force was measured in voltage units after multiplication with the instrument's sensitivity level (Figure 3.13). A 5cm wide non-distensible strap was placed over the patients lower abdomen and secured the patient to the scanner table to minimise the contribution of the back muscles throughout the exercise. To ensure accuracy and consistency in both the timing and duration of contractions, an audible cue was provided to the subject by means of an electronic metronome set at the same contraction frequency. The patient was instructed to contract at the start of the tone, maintain contraction during the tone and release the contraction upon the disappearance of the audible cue, such that a square-wave pattern of exercise was achieved (i.e. constant workload) (Figure 3.13).

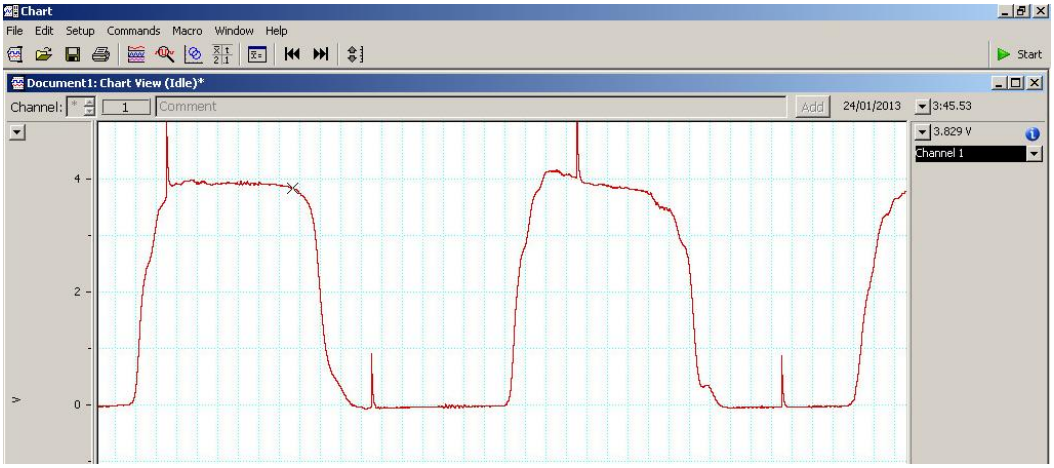


Figure 3.13 – Chart software tracing with patient performing the exercise protocol (Voltage on y-axis and time on x-axis)

3.4.2 EXERCISE PROTOCOL, DATA PROCESSING AND INITIAL ANALYSIS

After an automated set-up and manual shimming using tissue water, a 4-scan fully relaxed (TR=10s) spectrum and a 32-scan partially saturated (TR=2s) resting spectrum were collected (Figure 3.14).

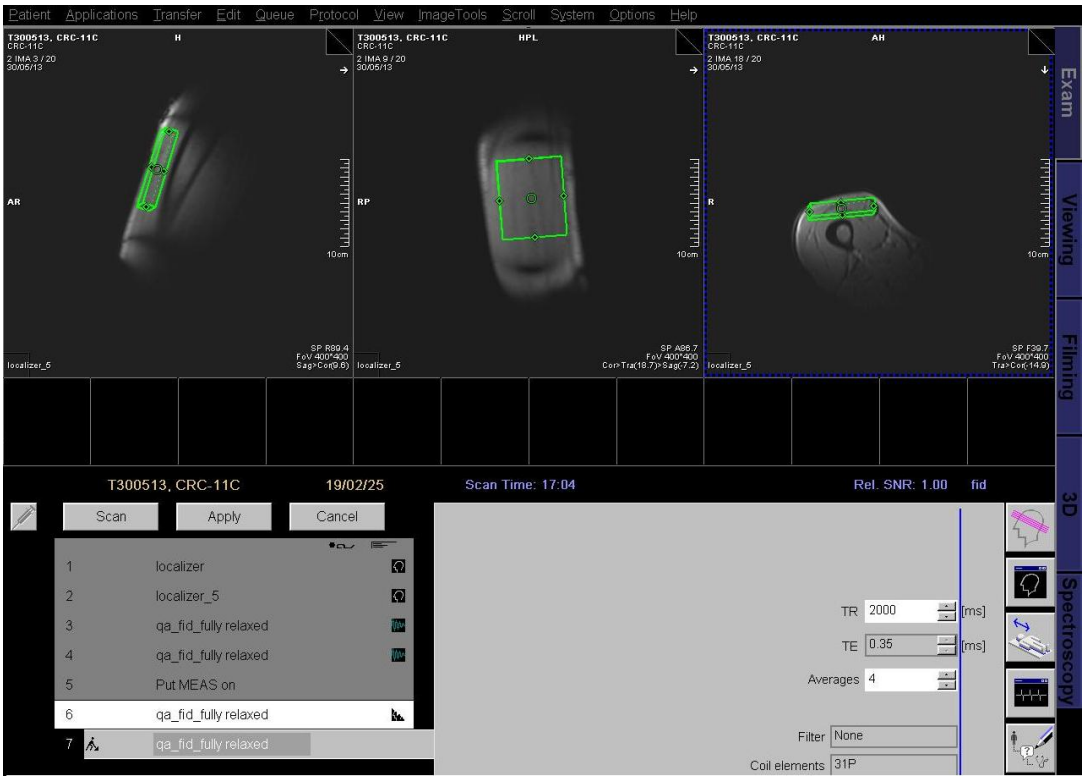
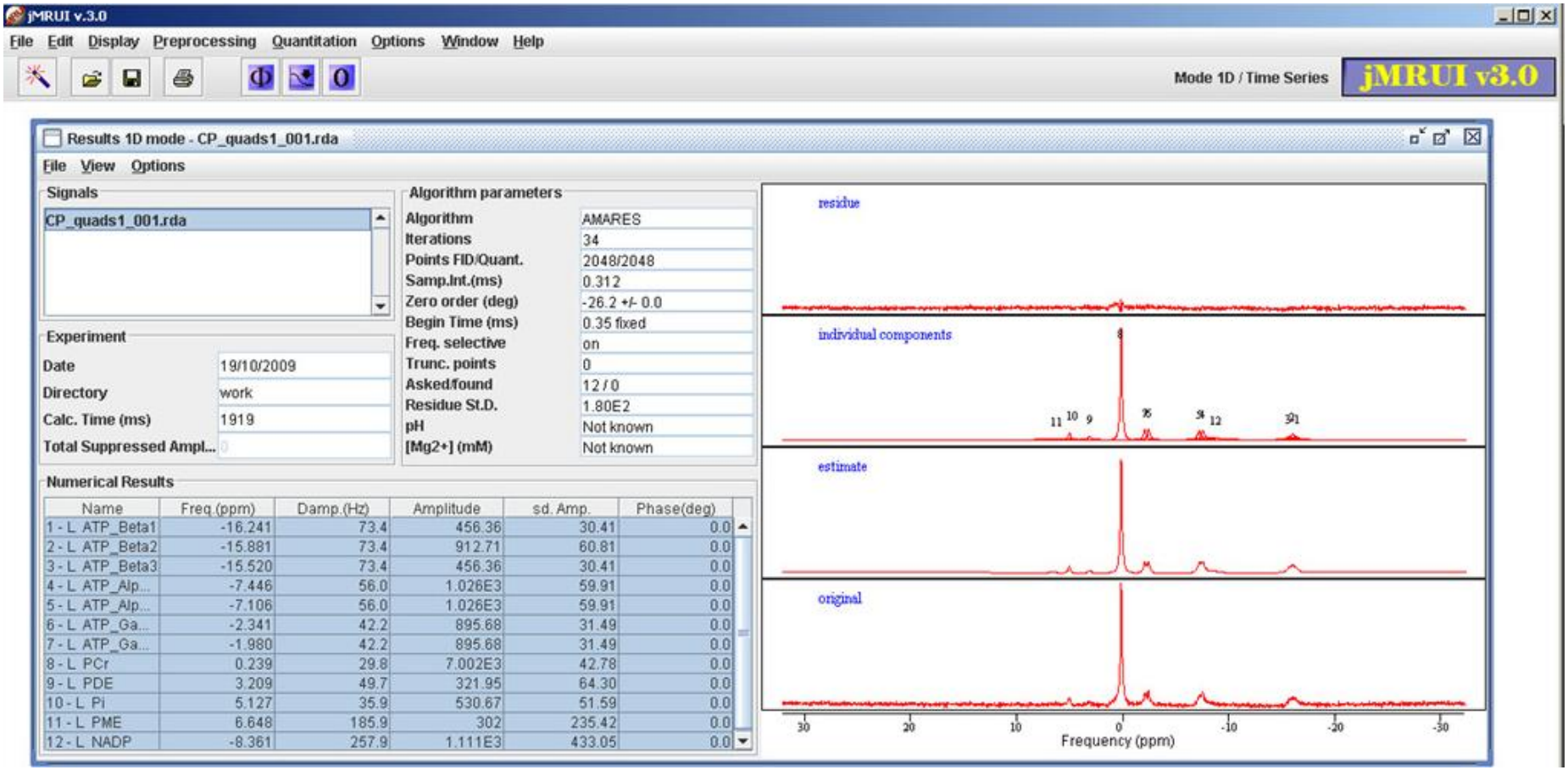
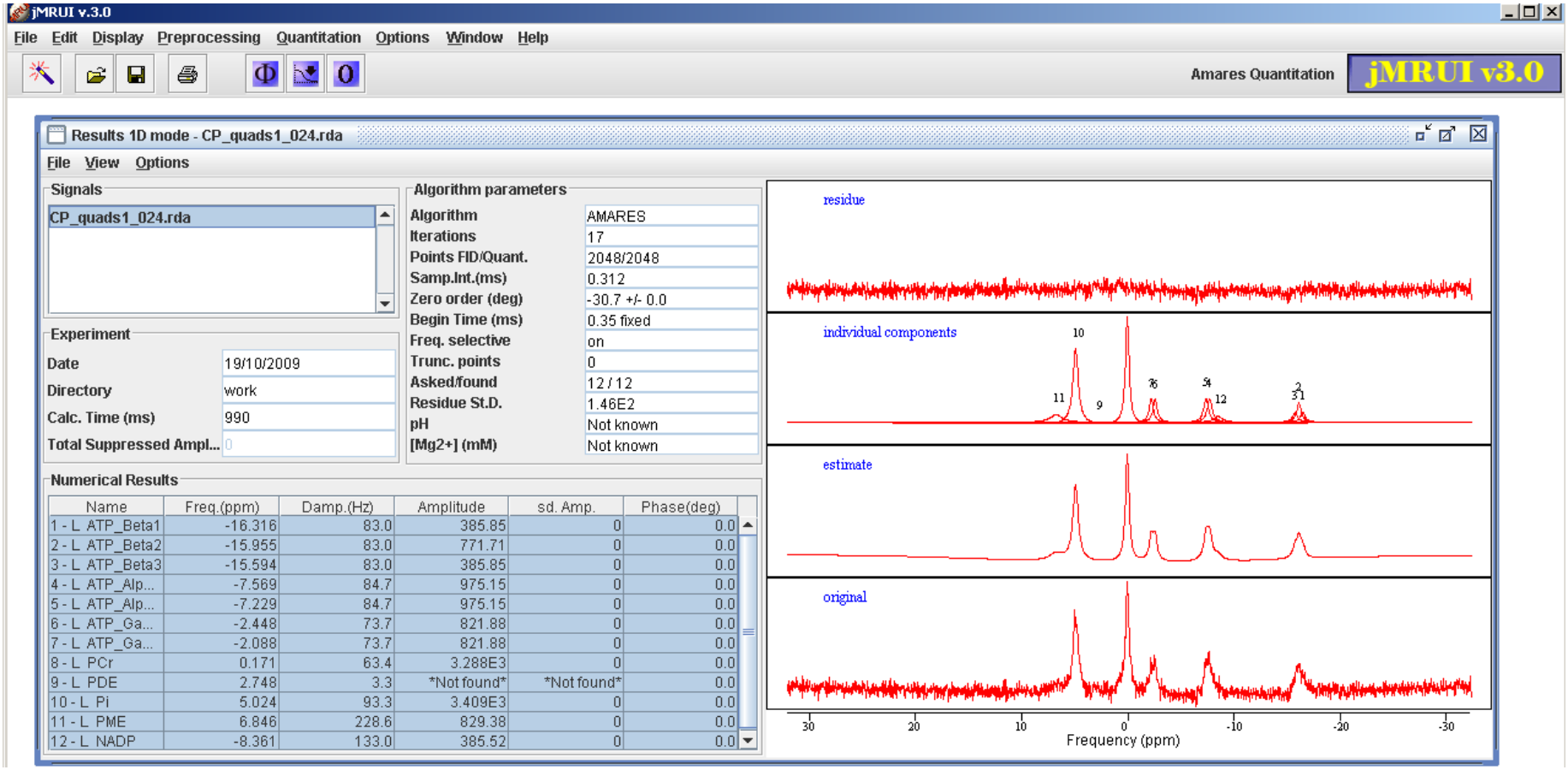


Figure 3.14 – Manual shimming with anatomical localization done in multiple planes (axial, coronal and sagital)

The exercise protocol consisted of 5 min rest followed by 2 bouts of isometric exercise each followed by 7 min recovery periods, while spectra were collected (TR=2s) every 8 s paced at 0.25 Hz (2 seconds on, 2 seconds off) by an audible cue. Two exercise intensities were used, corresponding to 70% and 90% of MVC established in 3 brief trials prior to MRS acquisition (in pilot experiments these intensities were found to give acceptable PCr depletion with minimal acidification in typical subjects). Block MRS data output files from exercise-recovery acquisitions were converted to text using a specially-written MATLAB routine. All ^{31}P MRS data were processed using the java-based Magnetic Resonance User Interface (jMRUI v.3.0), using the AMARES (Advanced Method for Accurate, Robust and Efficient Spectral fitting) time-domain fitting algorithm (Figure 3.15). Data were fitted assuming Lorentzian lineshapes for PCr, Pi, PDE, PME, NADP and ATP (β-ATP a 1:2:1 triplet, α-ATP and γ-ATP both 1:1 doublets) based on prior knowledge of the metabolite peaks (prior knowledge file kindly provided by Dr Damian Tyler, University of Oxford). The chemical shift of the inorganic phosphate (Pi) peak relative to PCr (σ parts per million) was used by standard means to determine intracellular pH. PCr recovery time courses were fitted to a monoexponential function to estimate the recovery rate constant (k min^{-1}). In the absence of appreciable changes in pH, this is accepted as a measure of effective muscle mitochondrial function, the latter being a system property which reflects cardiovascular oxygen supply and mitochondrial oxygen usage (220). As the PCr recovery rate constant did not differ significantly between the two exercise intensities, and as pH changes were small throughout, values of k are presented as mean of the two intensities to reduce variability (209).


jMRUI v.3.0
File Edit Display Preprocessing Quantitation Options Window Help
Mode 1D / Time Series
jMRUI v3.0
Results 1D mode - CP_quads1_001.rda
File View Options
Signals
CP_quads1_001.rda
Experiment
Date 19/10/2009
Directory work
Calc. Time (ms) 1919
Total Suppressed Ampl... 0
Algorithm parameters
Algorithm AMARES
Iterations 34
Points FID/Quant. 2048/2048
Samp.Int.(ms) 0.312
Zero order (deg) -26.2 +/- 0.0
Begin Time (ms) 0.35 fixed
Freq. selective on
Trunc. points 0
Asked/found 12 / 0
Residue St.D. 1.80E2
pH Not known
[Mg2+] (mM) Not known
Numerical Results
Name Freq.(ppm) Damp.(Hz) Amplitude sd. Amp. Phase(deg)
1 - L ATP_Beta1 -16.241 73.4 456.36 30.41 0.0
2 - L ATP_Beta2 -15.881 73.4 912.71 60.81 0.0
3 - L ATP_Beta3 -15.520 73.4 456.36 30.41 0.0
4 - L ATP_Alp... -7.446 56.0 1.026E3 59.91 0.0
5 - L ATP_Alp... -7.106 56.0 1.026E3 59.91 0.0
6 - L ATP_Ga... -2.341 42.2 895.68 31.49 0.0
7 - L ATP_Ga... -1.980 42.2 895.68 31.49 0.0
8 - L PCr 0.239 29.8 7.002E3 42.78 0.0
9 - L PDE 3.209 49.7 321.95 64.30 0.0
10 - L Pi 5.127 35.9 530.67 51.59 0.0
11 - L PME 6.648 185.9 302 235.42 0.0
12 - L NADP -8.361 257.9 1.111E3 433.05 0.0
residue
individual components
estimate
original
30 20 10 0 -10 -20 -30
Frequency (ppm)


jMRUI v.3.0
File Edit Display Preprocessing Quantitation Options Window Help
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jMRUI v3.0
Results 1D mode - CP_quads1_024.rda
File View Options
Signals
CP_quads1_024.rda
Experiment
Date 19/10/2009
Directory work
Calc. Time (ms) 990
Total Suppressed Ampl... 0
Algorithm parameters
Algorithm AMARES
Iterations 17
Points FID/Quant. 2048/2048
Samp.Int.(ms) 0.312
Zero order (deg) -30.7 +/- 0.0
Begin Time (ms) 0.35 fixed
Freq. selective on
Trunc. points 0
Asked/found 12 / 12
Residue St.D. 1.46E2
pH Not known
[Mg2+] (mM) Not known
Numerical Results
Name Freq.(ppm) Damp.(Hz) Amplitude sd. Amp. Phase(deg)
1 - L ATP_Beta1 -16.316 83.0 385.85 0 0.0
2 - L ATP_Beta2 -15.955 83.0 771.71 0 0.0
3 - L ATP_Beta3 -15.594 83.0 385.85 0 0.0
4 - L ATP_Alp... -7.569 84.7 975.15 0 0.0
5 - L ATP_Alp... -7.229 84.7 975.15 0 0.0
6 - L ATP_Ga... -2.448 73.7 821.88 0 0.0
7 - L ATP_Ga... -2.088 73.7 821.88 0 0.0
8 - L PCr 0.171 63.4 3.288E3 0 0.0
9 - L PDE 2.748 3.3 *Not found* *Not found* 0.0
10 - L Pi 5.024 93.3 3.409E3 0 0.0
11 - L PME 6.846 228.6 829.38 0 0.0
12 - L NADP -8.361 133.0 385.52 0 0.0
residue
individual components
10
11
9
8
5
12
2
3
1
estimate
original
30
20
10
0
-10
-20
-30
Frequency (ppm)

Figure 3.15 - Examples of MRUI output from the AMARES fitting of: (top panel) resting ^{31}P MR spectra and (bottom panel) exercise spectra (at 60% MVC) obtained from the right quadriceps muscle of a young healthy male volunteer. Four sections were generated from the output: 1) the 'original' section displayed the original spectra transformed from the raw FID data; 2) the 'estimate' section displayed the pre-specified peaks (i.e. prior knowledge), 3) the integration of the 2 previous sections (i.e. fitting of the peaks) resulted in the fitted peak metabolites which were displayed in the 'individual component' section, and lastly, 4) any residual unfitted peaks were displayed in the 'residue' section. Note that the amplitude of Pi peak has increased considerably by this point of the exercise. A good fit is generally indicated by the absence of any residual amplitude in the 'residue' column, as shown above. As expected, the signal-to-noise ratio was relatively poorer in the exercise compared to resting spectra due to leg movement during exercise

Time course data were edited for occasional outliers by replacing the amplitude under question with the average value of amplitude before and after the suspected data point: these can include spurious transient large fluctuations in metabolite amplitudes unrelated to the underlying physiological observation (probably arising due to the alteration in signal-to-noise properties of the ^{31}P MRS technique), and spurious unphysiological pH values due to failure of fit to small Pi peaks.

The ^{31}P MRS data processing and analysis steps are briefly summarized as follows:

- Raw data from the scanner were processed by MRUI software (AMARES fitting procedure) to generate measurements of metabolites peak amplitudes.

- The 3 separate MRUI outputs (i.e. fully relaxed, partially saturated and saturated spectra) from each individual subject were exported and combined into a single data output Excel spreadsheet for the respective subject.

- An analysis workbook was constructed to automate the data analysis procedure in order to save labour and minimise human error in manual input of the data (courtesy of Prof. Graham Kemp). The analysis workbook was linked to the individual subject's data output spreadsheet to enable direct extraction of the MRUI-processed data. Various additional data processing steps were taken including expressing the metabolite amplitudes in relative terms (i.e. relative to resting baseline), calculation of pH and calculation of ADP concentration.

- Various parameters were calculated from analysis of the recovery data related to PCr and ADP recovery time courses. In the initial analysis of the recovery data, PCr and ADP recovery time courses were fitted to a monoexponential function to determine their respective recovery kinetics i.e. rate constant values (k_{PCr}).

- All curve fitting was performed using Microsoft Excel solver function to execute least squares regression.

- Analysis was performed in a blinded fashion, with the assessor blind to individual patients' clinical details, CPET variables, group allocation (i.e. exercise or control) and MR time points (i.e. baseline (pre-NACRT), Week 0 and Week 6 (post-NACRT)).

Analysis of the post-exercise k_{PCr} in the vastus lateralis muscle quantified the *in vivo* mitochondrial oxidative capacity of skeletal muscle because, during recovery from exercise, PCr is resynthesized purely as a consequence of oxidative ATP synthesis. These measures correlate with *ex vivo* measurements of muscle mitochondrial function and whole-body measures of aerobic fitness in healthy controls (178) and were taken as surrogate markers of mitochondrial function *in vivo*.

Chapter 4

The Effect of Neoadjuvant Chemoradiotherapy on Physical Fitness and Morbidity in Rectal Cancer Patients

CHAPTER 4 – The Effect of Neoadjuvant Chemoradiotherapy on Physical Fitness and Morbidity in Rectal Cancer Patients

4.1 INTRODUCTION

This chapter defines the effects of neoadjuvant chemoradiotherapy on objectively measured physical fitness determined by CPET with specific focus on (1) the changes in objectively measured $\dot{V}o_2$ at $\hat{\theta}_L$ pre- and post-NACRT, (2) changes in other CPET-derived variables measured pre- and post-NACRT, and (3) the relationship of CPET variables to in-hospital morbidity and medium term follow-up.

In 2012, the UK National Bowel Cancer Audit reported that the ASA score (a categorical descriptor of fitness for surgery) was the strongest predictor of death within 30 days of surgery (8). Twenty-five per cent of audited cases in 2013 were locally advanced (T3/T4 N+) cancers considered for long-course neoadjuvant chemoradiotherapy (NACRT) to control local disease, improve operability, and achieve tumour downsizing and negative resection margins (9,10,12,13,28) (Section 2.4). However, standard NACRT based on external beam radiation and oral or intravenous fluoropyrimidines causes dose-limiting toxicity (most commonly diarrhoea, hand-foot syndrome, cardiotoxicity and haematological toxicity) reaching Grade 3–5 in ~20% (Common Terminology Criteria for Adverse Events, Version 3.0) (14). It is less clear whether there are further metabolic adverse effects from cancer therapies which could impact outcome after surgery.

As described in previous sections (2.5.2) cardiorespiratory fitness, assessed by cardiopulmonary exercise testing (CPET), correlates well with outcome following major surgery. Knowledge of the effects of cancer and cancer therapies on physical fitness is critical in developing interventions targeted at improving preoperative fitness and promoting recovery of muscle mass. Subjective assessment tools have been used to predict surgical outcomes, however there is little evidence linking objectively-measured physical fitness and surgical outcome in this group. Meta-analyses of randomized trials along with few published randomized controlled trials suggest that neoadjuvant chemotherapy and/or radiation therapy slightly increase the risk of morbidity and mortality (221,222), however these meta-analyses deal with oesophageal cancer patients. Nordlinger et al. (223) evaluated the effect of preoperative chemotherapy on hepatic metastasis and showed a 36% increase in complications with chemotherapy. Other studies though, failed to show any association between neoadjuvant chemotherapy and increased postoperative morbidity and mortality

(224–226). In a very large recently published patient dataset the use of neoadjuvant chemotherapy in cancer patients undergoing resection surgery was not associated with a higher rate of early postoperative morbidity and mortality (227).

In rectal cancer only a few trials suggest that patients with a lower subjective performance status (WHO Score >1) have worse postoperative outcome after combined chemotherapy or chemo-radiation and surgery (14,15,228,229). To my knowledge the assessment of changes in objectively measured physical fitness and its relation to postoperative outcome in this cohort of patients has never been attempted before.

4.2 STUDY OBJECTIVES

In this chapter I set out to test the hypothesis that NACRT prior to elective locally advanced rectal cancer surgery would impair objectively measured physical fitness ($\dot{V}o_2$ at $\hat{\theta}_L$). Secondary aims include: (1) studying the change of other CPET derived variables post-NACRT, (2) determining the relationship of CPET variables to Day 5 postoperative in-hospital morbidity, (3) and to report 180-day morbidity and 1 year mortality.

4.3 PATIENTS AND STUDY METHODS

This single-centre, prospective, observational cohort study was based at Aintree University Teaching Hospitals, Liverpool, UK. Ethics approval was sought from the Northwest Research Ethics Committee (11/H1002/12) and the study was registered with ClinicalTrials.gov (NCT01334593). Written informed consent was obtained from all patients. From July 2011 to end of October 2011, I recruited consecutive patients referred to the Colorectal Multi-Disciplinary Team (MDT), age ≥18 years, with locally advanced (circumferential resection margin threatened) electively resectable rectal cancer, who were scheduled for standardized NACRT on the basis of Tumour, Node, Metastasis (TNM) classification >T2/N+ with no distant metastasis (230) and a WHO Performance Status <2 (231). Patients were excluded if they were diagnosed with non-resectable disease, were unable to perform CPET (due to mechanical reasons e.g. unable to pedal), declined surgery or NACRT, received non-standard NACRT or were unable to give informed consent. CPET was performed 2 weeks before and 7 weeks post-NACRT (prior to surgery at 9 weeks post-NACRT). TNM staging investigations involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen and pelvis computer-aided tomography (CT) and a

1.5 Tesla (Magnetom Aera, Siemens, Erlangen, Germany) pelvis magnetic resonance imaging (MRI).

Eligible patients then underwent NACRT for 5 weeks. Preoperative radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a three-dimensional conformal technique with CT guidance. Patients were treated prone (on a belly-board) to spare small bowel, with a comfortably full bladder. The clinical target volume included the primary tumour, the mesorectum and mesorectal lymph nodes, including the perirectal, presacral and internal iliac nodes. The upper radiation extent was 3 cm above the tumour but no further than the sacral promontory. The perineum was included if an abdomino-perineal resection (APR) was planned, while for low anterior resection (LAR) the lower radiation border was 3 cm below the tumour. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. 825 $mg.m^{-2}$ oral capecitabine was given twice daily on radiotherapy days (Section 2.4.4). No patients received brachytherapy.

Acute toxicity and adverse events were discussed at the weekly colorectal multidisciplinary meeting (MDT). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (version 3.0), and the acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system.

Patients completing NACRT went on to have CPET (for protocol refer to Section 3.2), spirometry and a re-staging chest, abdomen and pelvic CT and pelvic MRI at 7 weeks post-NACRT. All patients underwent total mesorectal excision (TME) surgery (232,233) after completing NACRT. A defunctioning stoma was constructed at the discretion of the surgeon. The colorectal MDT, anaesthetists and medical staff collecting outcome data were blind to CPET results.

Patients were assessed pre- and postoperatively by the Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) (234), and postoperatively by the Post-Operative Morbidity Survey (POMS) (146) and the Clavien-Dindo Classification of Surgical Complications (235) by staff blind to CPET data at day 5 postoperatively. Patients were followed up by telephone consultation at 180-days postoperatively for morbidity and up to 1 year for mortality using hospital records.

4.4 STATISTICAL ANALYSIS

Continuous variables are presented as mean and standard deviation (SD) or as medians and interquartile range (IQR), depending on their distribution. Categorical variables are presented as frequency and/or proportion. Pre- and post-NACRT data were compared using paired t-tests. Relationships between the change in haemoglobin concentration and the change in $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak ($ml.kg^{-1}min^{-1}$) were assessed using the Pearson correlation coefficient. Statistical significance was accepted at $p<0.05$; no corrections were made for multiple comparisons. Descriptive analysis was used to compare baseline characteristics of patients pre- and post-NACRT (Table 4.1), to document in-hospital complications using POMS day 5 and Clavien-Dindo classification, together with 180-day morbidity using Clavien-Dindo classification, loco-regional recurrence rates (Table 4.4) and 1 year mortality.

The primary outcome variable was $\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg.^{-1}min^{-1}$). Secondary outcome variables included $\dot{V}o_2$ Peak ($ml.kg.^{-1}min^{-1}$), oxygen pulse ($ml.beat^{-1}$), $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$ and Peak exercise and the relationship of $\dot{V}o_2$ at $\hat{\theta}_L$ to postoperative in-hospital morbidity.

Logistic regression models were used to assess in-hospital complications, converting the continuous CPET variable of $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak into a categorical one (coded as 0 if below median and 1 if equal to or greater than the median value). Receiver operator characteristic (ROC) curves were constructed for $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak. From these the optimal cut-point was identified by minimising the distance to the top-left corner.

I aimed to recruit 22 patients who would undergo NACRT and elective rectal surgery as an intention to treat for rectal cancer. This estimate was based on a two-sample t-test with 90% power to detect an estimated mean (SD) minimum clinically relevant difference in $\dot{V}o_2$ at $\hat{\theta}_L$ of 1.5 (1.0) $ml.kg.^{-1}min^{-1}$). A drop-out rate of 10% was assumed (based on a previous pilot study).

4.5 RESULTS

Thirty-five patients were eligible for surgery, of whom 5 did not consent and 3 were recruited into a different trial; 27 patients were recruited and underwent CPET prior to

NACRT; 2 withdrew their consent before undergoing the post-NACRT CPET, the remaining 25 (17 males and 8 females, mean age 68 years) completed NACRT and underwent elective rectal cancer surgery (Figure 4.1 illustrates a CONSORT diagram depicting patient flow for this study).

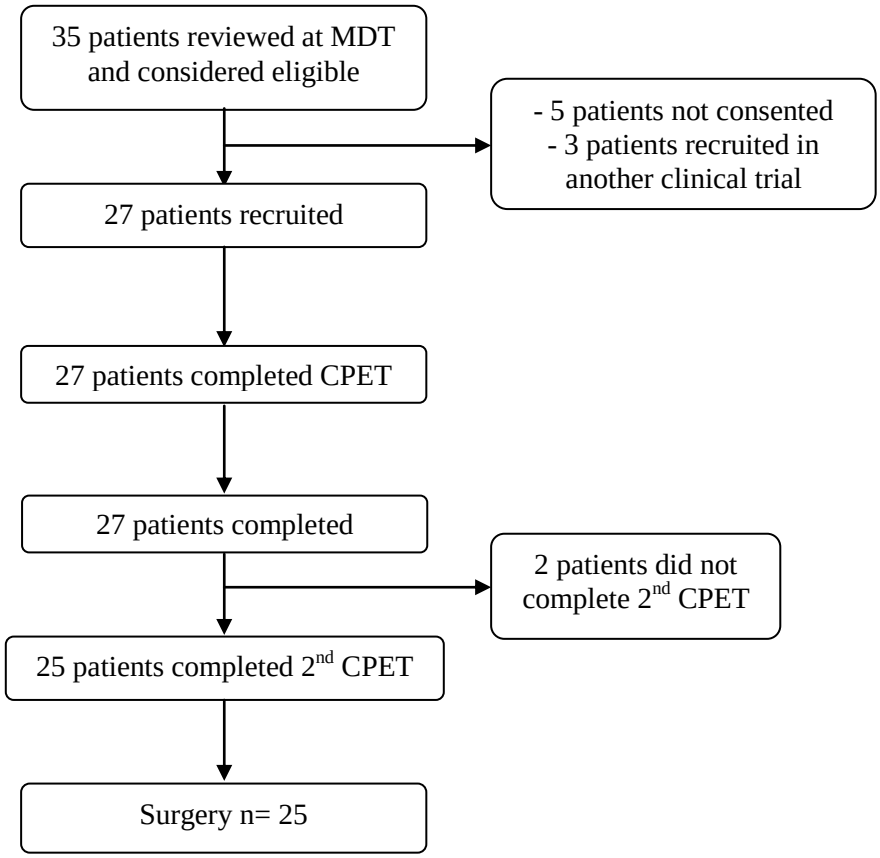

Figure 4.1 – Consort diagram

Table 4.1 describes patient characteristics and Table 4.2 describes tumour and treatment characteristics. There were no significant changes in WHO performance status, haemoglobin or lung function following NACRT. CPET was performed at 2.0 ± 0.8 weeks pre-NACRT and at 7.0 ± 1.0 weeks post-NACRT. Eighty-four per cent of diagnosed rectal cancers were T3, with 52% having a good response to NACRT determined by MRI. All patients underwent CT and MR-directed staging, then total mesorectal excision (TME) surgery (complete resection (R0)) at median of 63 (range 51-78) days post-NACRT. The circumferential resection margin (CRM) was >5mm in all cases. No patients had complete pathological response.

	Total	Pre-NACRT	Post-NACRT	Mean Difference (95% CI)	p-value
Age (years)[1]	67.7(9.2)				
Gender M:F (%)[1]	17(68) : 8(32)				
CR-POSSUM- Operative Severity Score*	11.2(1.2)				
CR-POSSUM- Physiological Score*	9(1.8)				
CR-POSSUM- Predicted Mortality (%)*	7.8(4.5)				
Weight (kg)[1]		75 (16.9)	75.3 (17.4)	0.30 (-1.2, 0.6)	0.54
Height (m)[1]		166.4 (8)	166.6 (8.1)	0.20 (-0.6, 0.1)	0.16
BMI ($kg.m^{-2}$)[1]		27.0 (5.5)	27.0 (5.6)	0.01 (-0.3, 0.4)	0.94
WHO Performance Status[3]		1 (0-2)	1 (0-2)		
FEV1 (L) [1]		2.5 (0.8)	2.5 (0.7)	0 (-1.2,1.2)	0.92
FVC (L) [4]		3.7 (2.9-4.4)	3.7 (3.0-4.5)	0.04 (-0.1, 0.1)	0.36
FEV1/FVC (%)[1]		67.2 (10.5)	67.0 (11.5)	-0.02 (-2.0, 1.6)	0.79
Haemoglobin ($g.dl^{-1}$)[1]		13.6 (1.5)	13.5 (1.6)	-0.03 (-0.5, 0.4)	0.87
Clinical TNM classification[2#]					
cT2		1(4)	3(12)		
cT3		21(84)	19(76)		
cT4		3(12)	3(12)		
cN0		7(28)	13(52)		
cN1		13(52)	9(36)		
cN2		5(20)	3(12)		
cM0		25	25		

Table 4.1 – Patient characteristics; * Mean (SD) CR-POSSUM components [#] with percentages in parentheses; [1] Values presented as mean (SD); [2] International Union against Cancer tumour node metastasis (TNM); [3] Median (range) World Health Organisation (WHO) Performance Status; [4] Values presented as median (IQR)

	Number of Patients (n=25)[#]
Tumour distance from anal verge	
<5 cm	6(24)
6-10cm	14(56)
>10cm	5(20)
Operation Type	
Open	14 (56)
Laparoscopic	11(44)
Surgery	
Low Anterior Resection and diverting stoma	15 (60)
Abdomino-perineal resection and end stoma	7 (28)
Hartmann procedure	3 (12)
Pathological TNM	
pT1	4 (16)
pT2	5 (20)
pT3	11 (44)
pT4	5 (20)
pN0	15 (60)
pN1	6 (24)
pN2	4 (16)
Dukes Staging	
A	8 (32)
B	7 (28)
C 0/1	10 (40)
Resection margins	
R0	25 (100)

Table 4.2 – Patient tumour and treatment demographics; [#] With percentages in parentheses

4.5.1 CHEMORADIOTHERAPY AND ACUTE TOXICITY

The mean cumulative dose of capecitabine was 96% (range 84-100%); 3 patients needed dose reduction. 96% of patients (all but 1) received at least 45Gy radiotherapy, and all completed the full 25 fractions. Seven patients (28%) (including 3 patients receiving a diverting stoma because of obstructive symptoms prior to NACRT) experienced grade 3 toxicity, notably diarrhoea and radiation dermatitis, but no grade 4 toxicity.

4.5.2 THE EFFECT OF NACRT ON PHYSICAL FITNESS

Table 4.3 shows CPET-derived variables pre- and post-NACRT. Post-NACRT, both absolute ($ml.min^{-1}$) and relative ($ml.kg.^{-1}min^{-1}$) $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak exercise were reduced ($p<0.0001$). Figure 4.2 and 4.3 show a pair-plot of individual patients' $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak pre- and post-NACRT.

	Pre-NACRT	Post-NACRT	Mean Difference (95% CI)	P-value
$\dot{V}o_2$ at $\hat{\theta}_L$ $(ml.kg^{-1}.min^{-1})^2$	12.1 (9.4-13.0)	10.6 (8.2-12.0)	-1.5 (-1.7, -1.2)	**<0.0001**
$\dot{V}o_2$ at $\hat{\theta}_L$ $(ml.min^{-1})^1$	905.2 (343.4)	803.0 (323.5)	-102.2 (-75.7,-128.7)	**<0.0001**
$\dot{V}o_2$ Peak $(ml.kg^{-1}.min^{-1})^2$	18.1 (15.7-20.4)	16.7 (12.1-19.2)	-1.4 (-3.1, -1.0)	**<0.0001**
$\dot{V}o_2$ Peak $(ml.min^{-1})^1$	1370 (710)	1180 (690)	-190 (-86.7, -252.1)	**<0.0001**
O_2 pulse at $\hat{\theta}_L$ $(ml.beat^{-1})^1$	8.7 (2.9)	8.0 (2.7)	-0.7 (-1.2, -0.2)	**0.005**
O_2 pulse at Peak $(ml.beat^{-1})^1$	11.2 (3.6)	10.1 (3.0)	-1.1 (-1.8, -0.4)	**0.002**
$\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$ [1]	33.5 (5.1)	33.1 (5.1)	-0.4 (-1.7, 0.9)	0.54
$\dot{V}_E/\dot{V}co_2$ at Peak[1]	35.8 (5.5)	35.8 (6.1)	0 (-1.2, 1.2)	0.99
Baseline heart rate $(beats.min^{-1})^2$	85 (68-91)	83 (70-88)	-2 (-4.7, 2.1)	0.43
Peak heart Rate $(beats.min^{-1})^2$	124 (103-144)	122 (110-139)	2 (-6.4, 10.5)	0.62
Work load at $\hat{\theta}_L$ $(W)^2$	46 (35-56)	41 (24-55)	-5 (-10.0, 0.1)	0.06
Work load at Peak $(W)^2$	104 (66-122)	96 (60-116)	-8 (-13.4, -2.7)	**0.005**

Table 4.3 – CPET variables pre- and post-NACRT. [1] Values presented as mean (SD); [2] Values presented as median (IQR)

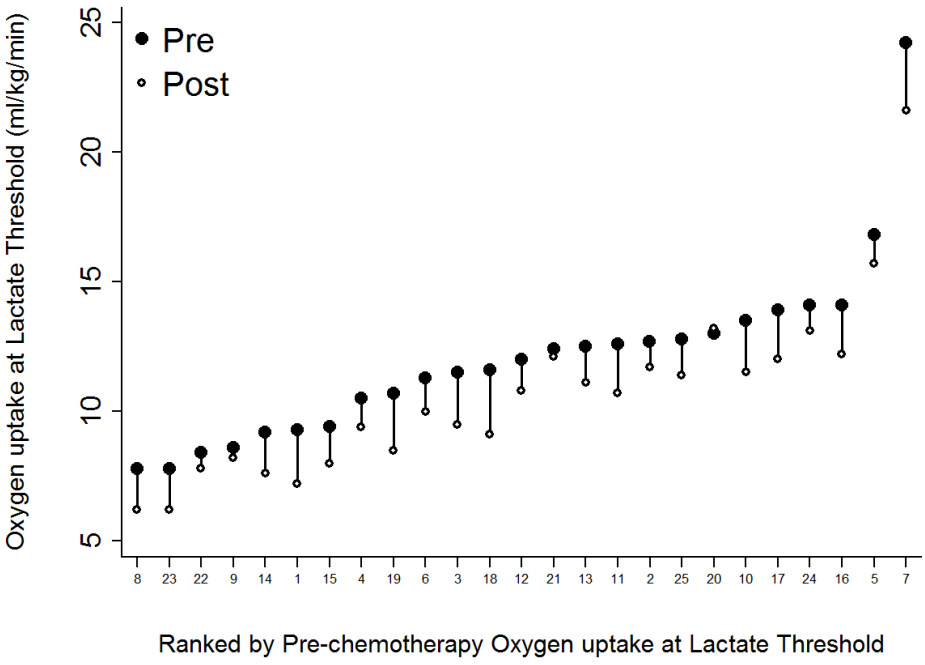

Figure 4.2 – Pair-plot of $\dot{V}_{O_2}$ at $\hat{\theta}_L$ (ml.kg.$^{-1}$min^{-1}) pre and post-NACRT

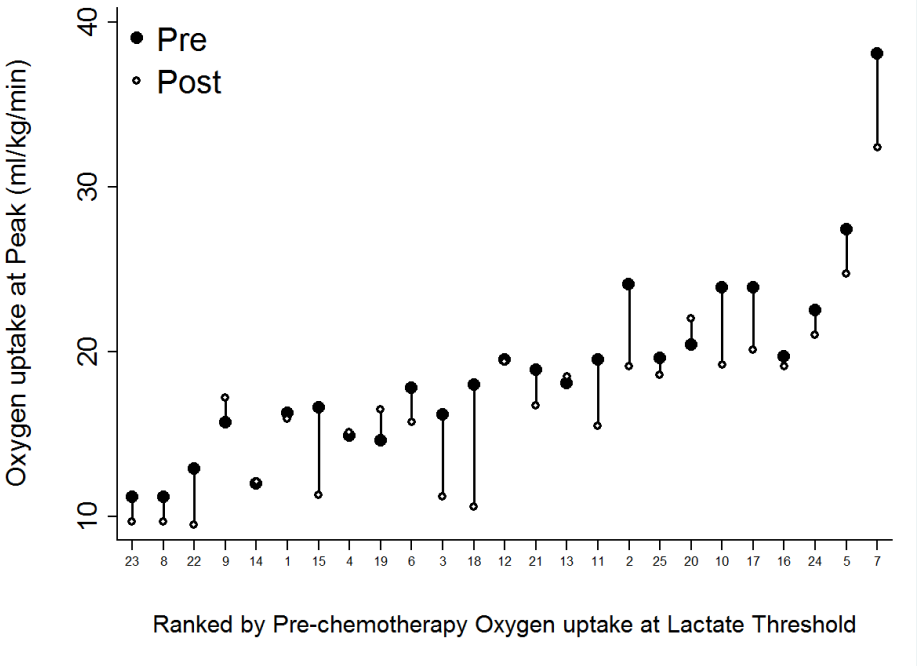

Figure 4.3 - Pair-plot of $\dot{V}_{O_2}$ at Peak (ml.kg.$^{-1}$min^{-1}) pre- and post-NACRT

Oxygen pulse (ml.beat^{-1}) decreased at both $\hat{\theta}_L$ (p=0.005) and Peak (p=0.002). $\dot{V}_E/\dot{V}co_2$ did not change. There was a trend towards (however statistically non-significant) a change in median workload at $\hat{\theta}_L$ (p=0.06), but a significant reduction in maximum power (p=0.005) was found. There was no change in resting or peak heart rate, spirometry and haemoglobin, and no relationship was found between changes in $\dot{V}o_2$ at $\hat{\theta}_L$ and change in haemoglobin with NACRT (r=0.18; p>0.05).

4.5.3 RELATIONSHIP BETWEEN PHYSICAL FITNESS AND SURGICAL OUTCOME

The median WHO performance status of 1 (0-2) pre-NACRT did not change post-NACRT. CR-POSSUM was calculated using variables collected immediately pre- and postoperatively, with patients having a mean operative severity score of 11.2 (1.2), physiological score of 9 (1.8) and predicted mortality of 7.8% (4.5). No in-hospital mortality was observed. Two patients (8%) were dead at 1 year follow up due to radiologically documented liver and brain metastasis; both had an $\dot{V}o_2$ at $\hat{\theta}_L$ of $\leq$10.7ml.kg.$^{-1}$min^{-1} post-NACRT, and suffered from postoperative anastomotic leaks (Grade IIIa). 15 of 25 patients (60%) experienced $\geq$1 postoperative complications (Grade $\geq$1). 10 of 15 patients with an in-hospital complication (67%) had a $\dot{V}o_2$ at $\hat{\theta}_L$ less than 10.7ml.kg.$^{-1}$min^{-1}. The mean (SD) $\dot{V}o_2$ at $\hat{\theta}_L$ pre- vs. post-NACRT in patients with POMS 0 at day 5 was 13.1±4.1 vs. 10.8±1.9 ml.kg.$^{-1}$min^{-1} respectively, compared with 11.8±3.9 vs. 9.3±2.0 ml.kg.$^{-1}$min^{-1} in patients with POMS $\geq$1. Table 4.4 shows complication grade as described by Clavien-Dindo classification, as well as POMS at day 5 and at 180-days.

Complication Type	In-Hospital Morbidity			180-day Morbidity		
	CD	POMS at Day 5		CD	Observed Episodes	
		LT ≤10.7 * (n=13)	LT >10.7 * (n=12)		LT ≤10.7 * (n=13)	LT >10.7 * (n=12)
Pulmonary						
Pneumonia	II	2	0	II	0	2
Infection						
Febrile requiring Antibiotics	II	3	1	II	1	3
Anastomotic Leak requiring re operation	IIIb	2	1	0	0	0
Renal						
Acute Kidney Injury	I	1	0	0	0	0
Gastrointestinal						
Ileus	I	4	0	0	0	0
Total Parenteral Nutrition	II	5	1	II	1	0
High Output stoma	0	0	0	II	1	0
Abdominal Collection	0	0	0	IIIa	0	2
Bowel Obstruction	0	0	0	IIIb	1	0
Cardiovascular						
Arrhythmias	II	1	0	0	0	0
Neurological	0	0	0	0	0	0
Haematological	II	1	0	II	1	0
New Postoperative Pain	I	0	1	0	0	0
Wound Dehiscence						
Abdominal	II	1	0	0	0	0
Perineal	II	3	2	I	1	2

Table 4.4 – Total postoperative in-hospital morbidity assessed by Clavien-Dindo Classification (CD) and POMS at Day 5 dichotomized at the ROC cut-off for $\dot{V}o_2$ at $\hat{\theta}_L$ post-NACRT (10.7 ml.kg.$^{-1}$min^{-1}). 180-day morbidity assessed by Clavien-Dindo Classification and number of observed POMS morbidity episodes dichotomized at the ROC cut-off $\dot{V}o_2$ at $\hat{\theta}_L$ post-NACRT.

ROC curves were constructed to discriminate between patients with and without postoperative in-hospital complications based on their pre- and post-NACRT $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak. An optimal $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak of 12.0 and 18.1 ml.kg.$^{-1}$min^{-1} respectively (Figure 4.4A and B) predicted those at risk of increased postoperative complications; this was 77% sensitive and 75% specific ($\dot{V}o_2$ at $\hat{\theta}_L$ - Area under curve (AUC) = 0.71, 95% CI 0.50-0.93; $\dot{V}o_2$ at Peak – AUC = 0.75, 95% CI 0.55-0.95) for both $\hat{\theta}_L$ and Peak variables. Repeating the ROC analysis with the post-NACRT variables (Figure 4.5A and B), optimal cut-off points were 10.7 and 16.7 ml.kg.$^{-1}$min^{-1} respectively; this was 77% sensitive and 83%

specific for $\dot{V}o_2$ at $\hat{\theta}_L$ (AUC = 0.72, 95%CI 0.50-0.94) and 85% sensitive and 83% specific for $\dot{V}o_2$ at Peak (AUC = 0.80, 95% CI 0.60-1.00).

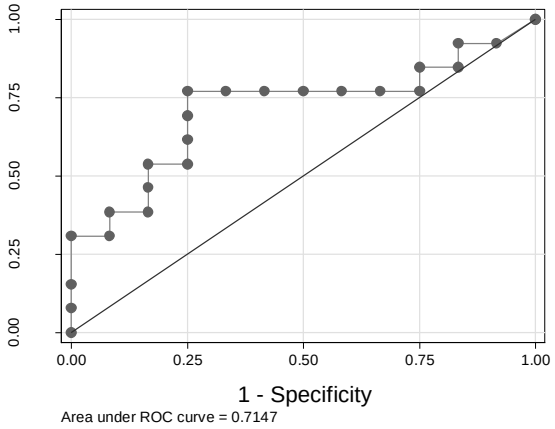

Figure 4.4A – ROC curve for $\dot{V}o_2$ at $\hat{\theta}_L$ pre-NACRT

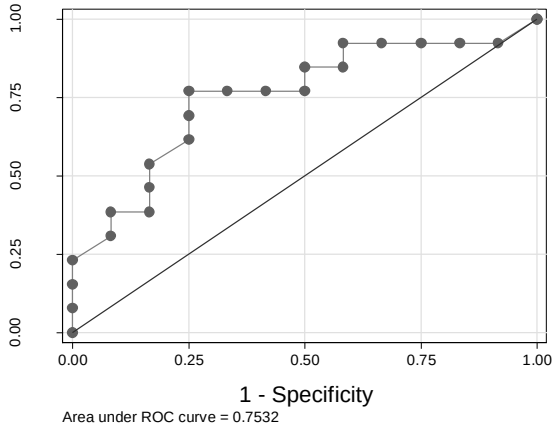

Figure 4.4B – ROC curve for $\dot{V}o_2$ Peak pre-NACRT

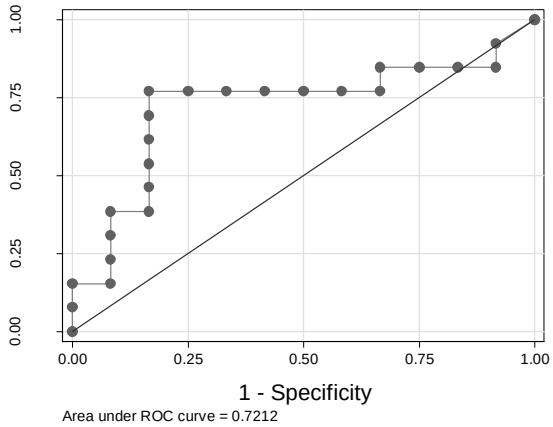

Figure 4.5A – ROC curve for $\dot{V}o_2$ at $\hat{\theta}_L$ post-NACRT

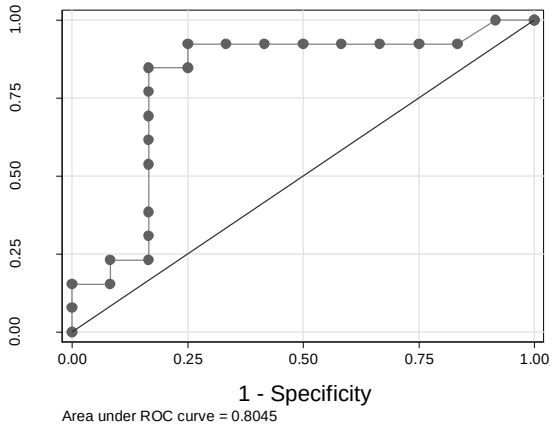

Figure 4.5B – ROC curve for $\dot{V}$o2 Peak post-NACRT

A logistic regression model was used to investigate the association of CPET variables with in-hospital complications. Complication episodes were dichotomized around the ROC cut-off values of 12.0 ml.kg.$^{-1}$min^{-1} for pre-NACRT and 10.7 ml.kg.$^{-1}$min^{-1} for post-NACRT $\dot{V}o_2$ at $\hat{\theta}_L$. A 90% reduction in the odds of complications was observed respectively (pre-NACRT – OR 0.10, 95% CI 0.16-0.63; p=0.01, post-NACRT – OR 0.09, 95% CI 0.01-0.61; p=0.01). Fitting the same model for pre- and post- $\dot{V}o_2$ Peak (Cut-off 18.1 ml.kg.$^{-1}$min^{-1} pre-NACRT and 16.7 ml.kg.$^{-1}$min^{-1} post-NACRT), the odds of complications reduced by 85% and 94% respectively (pre-NACRT – OR 0.15, 95% CI 0.03-0.87; p=0.04; post-NACRT – OR 0.06, 95% CI 0-0.44; p=0.006).

4.6 DISCUSSION

This work reports three important novel findings. Firstly, in patients with resectable locally advanced rectal cancer, NACRT prior to surgery impairs objectively measured physical fitness (significant reduction in $\dot{V}o_2$ and oxygen pulse both at $\hat{\theta}_L$ and Peak exercise and significant reduction in peak work rate). This reduction in fitness following NACRT is consistent across a broad range of levels of baseline fitness (Figures 4.2 and 4.3). Secondly, reduced physical fitness ($\dot{V}o_2$ at $\hat{\theta}_L$ and Peak) is associated with an unfavourable postoperative in-hospital outcome. Lastly, using cut-off values derived from the ROC analysis for $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak exercise, postoperative in-hospital morbidity can be predicted with a good accuracy. Taken together these findings suggest that physiological reserve (the ability to increase $\dot{V}o_2$ in response to a stressor) is important for rectal cancer patients exposed to the dual challenges of NACRT and major surgery. Furthermore, the decline in physical fitness objectively determined by CPET in this cohort is associated with postoperative outcome. This has obvious clinical implications.

The main motive for this present work is that the effects of cancer therapies on objectively measured physical fitness have not previously been explored in any patient cohort. The benefits of NACRT in rectal cancer are improved local disease control (12) and possibly overall and cancer-specific survival (236). Although it may seem unsurprising that NACRT impairs physical fitness, only Swellengrebel and colleagues (14) clearly link poor performance status at diagnosis (a subjective measure of fitness assessment) and the extent of surgery to postoperative morbidity.

The mechanism of this decline in fitness has not been explored in this cohort. However, it is know that cancer-induced cachexia may cause loss of up to 75% of skeletal muscle (237), resulting in fatigue and higher mortality (238). In this cohort, cancer progression is not a contributing factor as tumours on average were downstaged (Table 4.2). Equally haemoglobin, BMI, and weight remained stable during NACRT which makes cachexia or anemia an unlikely cause for this acute reduction in fitness. Chemotherapy, particularly capecitabine may also directly contribute (239–241), by mechanisms which are not fully understood. It is known that oxidative damage (16–18) (which causes muscle weakness and fatigue) caused by doxorubicin-based chemotherapy causes loss of muscle mass (19,20), up-regulation of E3 ubiquitin-ligase/MAFbx (242) and causes mitochondrial death (23). Moreover, drugs with a quinone moiety can directly interact with oxygen to generate reactive oxygen species (ROS) (21), while other chemotherapeutic agents decrease

antioxidant levels. The effects of capecitabine in relation to oxidative damage and mitochondrial damage are currently unknown. However, it is known that chemotherapy affects cardiorespiratory and microcirculatory function (243), physical activity (240,244), and mitochondrial and other cellular metabolism (245), but cellular/physiological mechanisms of this type of chemoradiotherapy used in this population remain elusive. The link between neoadjuvant cancer therapies and postoperative outcome is not clear. A large retrospective study in a diverse cancer populations has shown that the odds of mortality or composite 30-day postoperative morbidity appears not to differ in patients who were or were not given chemotherapy within 30 days before surgery (227).

The mechanism of reduced fitness due to NACRT is currently unknown. This appears to be the first study in which a reduction in objectively measured physical fitness and its link to short and medium term postoperative outcome has been explored using validated and robust methodology. A recent study has explored the impact of neoadjuvant chemotherapy (NAC) on physical fitness in upper gastrointestinal cancer patients prior to elective surgery. This used self-paced exercise tests in resectable oesophageal squamous cell cancer and found that NAC had no impact on physical fitness and activity (defined by 6-minute walking distance and the International Physical Activity Questionnaire); however objective measures such as CPET or activity monitoring were not used (246). A recently published observational study has observed the same decline in fitness with NAC in upper gastrointestinal cancer patients with a significant association between objectively measured fitness (using CPET) and 1-year survival (43).

Apart from the novelty of the observation, the strengths of this study include the low risk of confounding by indication (44), the consistently blinded objective physiological evaluation, the standardization of the NACRT regime, the homogenous cancer cohort and a comprehensive short- and medium-term follow up. Limitations lie in the observational design, the small sample size and the recall bias introduced by the telephone 180-day follow-up. Whilst this study was adequately powered (90%) to detect a 1.5 $ml.kg.^{-1}min^{-1}$ difference in $\dot{V}o_2$ at $\hat{\theta}_L$, it was not 'powered' (i.e. designed to have a sufficient sample size) to detect a link between change in physical fitness and postoperative outcome: a larger, adequately powered, prospective studies will be required to achieve this goal.

A reduction in CPET variables observed could be a consequence of factors including anaemia, progression of disease, inactivity or poor nutritional intake: however, haemoglobin, weight and BMI were unchanged and tumours were on average downstaged in our cohort (Table 4.1 and 4.2).

The findings presented in this chapter have potentially important clinical implications. A seen in Section 2.5.2, reduced physical fitness is associated with increased perioperative morbidity and mortality. These data presented here provide the first direct evidence that the benefits of NACRT in tumour downsizing may be at least partly offset by increased perioperative risk due to reduced physical fitness. Further, these data show that standardised and objective measurements of fitness allow an accurate preoperative assessment with some predictive power for short term postoperative morbidity; however a more definitive study is needed to validate these findings. A detailed understanding of the pre-treatment state is particularly important in patients with borderline baseline fitness, where a further fitness decline may be linked to adverse postoperative outcomes. This relationship merits further investigation, as does the possibility of intervention by exercise training during NACRT or in the preoperative period to attenuate these deleterious effects of NACRT on physical fitness. This will be investigated in my feasibility and tolerability pilot study (Chapter 5) and in the ensuing prehabilitation parallel group, non-randomized controlled trial (Chapter 6) investigating the improvements in physical fitness resulting from a 6-week structured responsive exercise training programme.

In conclusion, NACRT before major rectal cancer surgery significantly reduces physical fitness objectively assessed by CPET. Furthermore, the observed association between reduced physical fitness and unfavourable postoperative outcome relating to both in-hospital and 180-day morbidity merits further study. These effects should influence the perioperative management of locally advanced rectal cancer patients, with special emphasis on an intervention to improve physical fitness using a preoperative tailored exercise training programme as will be illustrated in Chapter 5 and 6.

Chapter 5

Development of the Structured Responsive Exercise Training Programme and a Feasibility Study

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5.1 INTRODUCTION

Aerobic exercise training is known to be beneficial in improving physical fitness in a variety of clinical populations (147–150,247). Exercise training has been shown to improve objectively measured physical fitness over a short time period, with significant augmentation of cardiac (248), respiratory (249) and musculoskeletal function (250). The decrease in physical fitness post-NACRT described in the previous chapter (Section 4.5.2), together with the unfavourable postoperative outcome (Section 4.5.3) highlights the need for an intervention, in the form of an exercise programme, to improve physical fitness prior to major surgery and potentially improve postoperative surgical outcome.

The implementation of an aerobic exercise training intervention between diagnosis and surgery already appears to be feasible in the preoperative period, however the evidence to support this and the possibility of improving postoperative outcome is currently very limited (151,153,154). As seen in Section 2.6, systematic reviews of the literature on preoperative exercise interventions are limited by the number of available studies and the large heterogeneity of the exercise techniques and surgical patient cohorts.

In this next chapter I will detail the iterative processes that led to the development of the proposed exercise training programme presented in Section 3.3. Additionally, this intervention will then be tested for its feasibility and tolerability in Section 5.3 of this chapter.

5.2 DEVELOPMENT OF THE EXERCISE TRAINING PROGRAMME

Recent guidance published by the American Heart Association and the American College of Sports Medicine (ACSM) (118,251) have helped clarify public health recommendations for physical activity in adults and the elderly with chronic conditions. These have been subsequently incorporated into the recently published position statement published by the ACSM (252). They conclude that the benefits of exercise outweigh the risks in most adults. A programme of regular exercise that includes cardiorespiratory, resistance, flexibility, and neuromotor exercise training in addition to activities of daily living is essential for most

adults to improve and maintain physical fitness and health. The ACSM also recommends that most adults engage in moderate-intensity cardiorespiratory exercise training for more than 30 minutes per day on an average of 5 days per week for a total of approximately 150 minutes per week, or vigorous-intensity cardiorespiratory exercise training for more than 20 minutes per day for 3 days per week. A combination of moderate- and vigorous-intensity exercise should aim to achieve a total energy expenditure of approximately 500–1000 METs/min/week. Bearing all these recommendations in mind, I set out to review the literature around preoperative exercise training (discussed in Section 2.6 and published in the British Journal of Anaesthesia 2013 (154)). Due to the rigorous nature of the quality tools applied when conducting the systematic review, some important studies reporting exercise programmes in different settings may have not been included. I now revisit this literature in Section 5.2.1 and detail how these studies also contributed to the iterative process and design of the final exercise training programme.

My aim was to set up an exercise training programme which was achievable, tolerable and feasible for locally advanced rectal cancer patients immediately after NACRT. An obvious challenge was the time constraint of undertaking this exercise programme in an NHS target-driven rectal cancer pathway. The exercise programme was designed to improve physical fitness (meeting patients' needs, goals and initial abilities) in the time period following NACRT and prior to surgery. The intensity of the exercise training programme was designed to be tailored and responsive to each patient's initial and evolving abilities by using CPET as an objective measure of physical fitness. All exercise training programmes in cancer patients have been undertaken either during or following adjuvant cancer therapies, designing such a new programme required focus and emphasis placed on individual patient abilities post-NACRT. This proved challenging as patients following such treatment often present with treatment-related side effects and are by default high-risk due to the nature of the tumour and cancer therapies they receive. Furthermore, to my knowledge this was never attempted before in this cohort of patients.

5.2.1 REVIEW OF EXERCISE TRAINING INTERVENTIONS

The role of exercise in cardiac (253) and pulmonary rehabilitation (152) is well established. A recent meta-analysis investigated the effects of different levels of training intensity (high vs. low) and type (continuous vs. interval) on exercise capacity and health-related quality of life for chronic obstructive pulmonary disease (COPD) patients (254). They concluded that comparisons between the higher and lower training intensities were limited due to the small

number of included studies and participants. Furthermore, comparisons between continuous and interval training, appear to be equally effective in improving exercise capacity. Intensity, duration and exercise modality are important determinants of the physiological adaptations that occur in response to training. In COPD, these have not been explored in great detail; however there seems to be greater physiological benefits obtained through high-intensity compared to moderate-intensity training programmes (255,256). However, high-intensity exercise training in a continuous fashion may not be applicable to certain types of patient cohorts. Implementation of exercise type is also crucial; interval training in pulmonary rehabilitation has been advocated as an alternative to continuous exercise. Interval and continuous training can both be applied safely and effectively within the context of pulmonary rehabilitation (152), however the choice of interval or continuous training will be a matter of patient and/or therapist preference. Interval training may require a higher therapist to patient ratio to ensure adequate work rate and rest intervals are achieved compared with continuous training; however interval training has been found to be more acceptable to patients (257,258) and can also be used to deliver higher intensity training which is easily tolerable (254).

Section 2.6 answered several related questions using a systematic review of preoperative exercise programmes; however this review excluded (see Appendix 4 for exclusion criteria) several studies which were nevertheless considered important and were utilised in the derivation of the exercise programme detailed in Section 3.3. This literature will be presented briefly in Table 5.1.

Study	Population	Exercise Intervention	Frequency	Intensity	Duration
Myers et al. (259)	Abdominal Aortic Aneurysm	Resistance	3/week	60% HRR up to 80%	10 min
Kothmann et al. (260)	Abdominal Aortic Aneurysm	Continuous	2/week	12-14 BORG RPE	30 min
Adamsen et al. (261)	Cancer patients undergoing chemotherapy	High intensity resistance and interval	3/week	85-95% Max HR	90 min
Courneya et al. (262)*	Colorectal cancer	Walking	3-5/week	65-75% Max HR	20-30 min
Courneya et al. (263)*	Lymphoma	Aerobic training	3/week	60-75% $\dot{V}o_2$ Peak and 1 session interval training at 100% $\dot{V}o_2$ Peak	15-45 min
Segal et al. (264)*	Prostate cancer	Aerobic vs. resistance training	3/week	50-75% $\dot{V}o_2$ Peak	15-45 min
Courneya et al. (265)	Breast cancer	Aerobic vs. resistance training	3/week	60-80% $\dot{V}o_2$ Peak	15-45 min
Herrero et al. (266)*	Breast cancer	Combined aerobic and resistance	3/week	70-80% Max HR	20-30 min
Courneya et al. (267)*	Breast cancer	Aerobic training	3/week	70-75% $\dot{V}o_2$ Peak	15-35 min
Burnham et al. (268)*	Cancer patients	High vs. low intensity aerobic training	3/week	HIT – 40-60% HRR LIT – 25-40% HRR	14-32 min
Jones et al. (269)	Breast cancer	Moderate vs. moderate-high intensity aerobic	150min/ week	Moderate – 60-75% $\dot{V}o_2$ Peak High – 60-100% $\dot{V}o_2$ Peak	20-45 min
Dimeo et al (270)*	Cancer patients	Interval training	5/week	Week 1 5x3 min Week 2 4x5 min Week 3 3x8 min 80% Max HR	30 min

*- cancer survivors

Table 5.1 – Training programme characteristics of studies exclude by the systematic review presented in Section 3.3. HRR – Heart Rate Response, min – minutes, RPE – rating of perceived exertion scale, Max HR –maximum heart rate, HIT – high intensity training, LIT – low intensity training.

Various exercise training programmes have been used in a variety of pre- or post- operative settings as seen in the table above and in Section 2.6. Most of these training programmes have been associated with improvement in exercise variables with minimal adverse effects.

The literature presented above as well as that presented in Section 2.6 was carefully presented to a Steering Group of exercise training experts (acknowledged). Taking everything I have discussed into consideration, this led to the development of an iterative process, which resulted in the final training programme presented in Section 3.3. In the next section (Section 5.2.2) I will attempt to deconstruct the training programme, justify the rationale behind the individual components and detail how these come together to make up the final exercise intervention.

5.2.2 EXERCISE PRESCRIPTION

During the iterative process that led to the final design of the exercise training protocol, myself and the Steering Group considered:

- Planning and integration into a standard NHS cancer pathway
- Training setting (home based, hospital based or a combination)
- Programme duration
- Session duration
- Session frequency
- Programme modality (bike vs. treadmill)
- Training modality (continuous, interval, resistance, etc.)
- Exercise intensity (high, moderate, low etc.)
- Monitoring response (session and whole programme)
- Tailoring training intensity to individual ability
- Primary and secondary exercise variables to serve as endpoints

Planning and Integration into a Standard NHS Cancer Pathway

The training programme was planned to take place in the hiatus between the end of NACRT (i.e. Week 0) and the re-staging scans at Week 9 (Figure 3.2; Chapter 3). Due to the rigor and time constrains of the standard NHS cancer pathway, the patients only had a maximum of 14 weeks to train prior to surgery. A decision was taken to start the training immediately after NACRT (usually the following Monday after completion of NACRT) as it was agreed that the patients would anecdotally be at their weakest physical fitness immediate after NACRT, and exercise could potentially halt the deleterious effects of NACRT on their fitness (based on the findings presented in Section 4.5). The Steering Committee

immediately identified the need for a feasibility and tolerability (F&T) study, as this would test two important aspects of the training protocol i.e. that patients immediately post-NACRT are able to sit on a static ergometer and cycle effectively, and also that patients could complete an exercise training programme.

Training Setting

Due to the novelty of the training programme, the specialised equipment needed and the unknown risk to the population pertaining to exercise training immediately after NACRT, the Steering Group decided to offer a supervised, in-hospital training programme, which would be delivered by me with the help of an exercise physiologist, with full resuscitation equipment immediately available.

Programme Duration

As discussed in the integration section above, the maximum length of the training programme (until the date of surgery) could have been up to 14 weeks, however the time to rectal cancer surgery post-NACRT is quite long at AUH and is not common practice in other NHS hospitals. The usual time to surgery post-NACRT is approximately 6-8 weeks, therefore the steering committee decided to implement a 6 week programme of exercise, as this is the absolute minimum time window that any NHS hospital would wait post-NACRT prior to surgery, thus the exercise programme can be easy implemented in other NHS trusts without the need to change their standard cancer care pathway.

Session Duration

ACSM guidance was used to decide the duration of the exercise sessions (252). A 30 minute exercise session for the first 3 sessions, increasing to 40 minutes for the next 12 sessions was deemed to be appropriate. This was also based on the level of exercise intensity that the patients will be doing, as well as the average age of the population and concomitant medical co-morbidities. The F&T study was to investigate whether this was appropriate.

Session Frequency

Again, the ACSM guidelines were used to arrive to the conclusion that 3 sessions per week (usually Monday, Wednesday and Friday), preferably at the same time of day was optimal. The F&T study was to investigate whether this was appropriate (252).

Programme Modality

A cycle ergometer was chosen by the Steering Group as the modality for exercise delivery. The stationary ergometer has the advantage of providing weight-supported exercise to the

patients, albeit with the discomfort of having to sit down on a seat. The seat tolerability was a source of concern for the steering committee particularly in this patient cohort, however as these patients would be monitored by CPET using a cycle ergometer it was felt that cycle training would provide the safest and most accurate way of quantifying work rates prescribed (214). Moreover, the exercise training ergometers purchased had the function of a fully programmable chip and pin card which drove the exercise training programme and a screen (Figure 3.9) which guided the patient through the programme. This provides help, guidance and self-monitoring for the patient as they progress through the exercise sessions.

Training Modality

Various training modalities have been employed in both preoperative and postoperative exercise training programmes as well as in cardiac or pulmonary rehabilitation. The largest body of evidence is around interval and continuous training within the context of pulmonary rehabilitation (152).

Interval exercise was chosen for this cohort of patients as it has been found to be more acceptable to high risk patients (257,258) and to deliver higher intensity training which was easily tolerable (254). Moreover, interval exercise training has been successfully used in colorectal cancer patients (270) and in various other high risk groups. Meyer et al. (271) used interval training (80% max heart rate) in patients post-coronary bypass surgery, which increased fitness and lowered baseline heart rates. Moholdt et al. (272) randomized patients post-coronary bypass surgery to an interval (4 min at 90% max heart rate and 3 min 70% max heart rate) or continuous exercise (70% max heart rate for 46 min). They showed significant improvements in $\dot{V}o_2$ Peak in both groups within 4 weeks, however at 6 months the interval group shows a better long-term effect. Freyssin et al. (273) randomized chronic heart failure patients to high-intensity interval (12 repetitions of 30 seconds at 50% and 80% max workloads during the first 4 weeks and the last 4 weeks respectively and 60 seconds of complete rest) vs. continuous training (45 min of heart rate at $\dot{V}o_2$ at $\hat{\theta}_L$). Both types of exercise were deemed safe and tolerable for this population. The interval group significantly increased their $\dot{V}o_2$ Peak and 6-min waking time when compared to the continuous group. Wisloff et al. (274) randomized post-infarction heart failure patients to moderate continuous training (70% of peak heart rate) or aerobic interval training (95% of peak heart rate) 3 times per week for 12 weeks. $\dot{V}o_2$ Peak increased more with aerobic interval training than moderate continuous training (46% vs. 14%, $p<0.001$). Left ventricular end-diastolic and end-systolic volumes declined with aerobic interval training only, by 18% and 25%, respectively; left ventricular ejection fraction increased 35%, and pro-brain natriuretic

peptide decreased 40%. Of interest, mitochondrial function in lateral vastus muscle increased with aerobic interval training only. No changes occurred in the control group (38).

Gloeckl et al. (275) randomized lung transplant candidates to interval (100% $\dot{V}o_2$ Peak work rate for 30 seconds alternating with 30 seconds rest) vs. continuous training (60% $\dot{V}o_2$ Peak work rate) during a 3-week inpatient rehabilitation program. This was well tolerated and both groups achieved similar clinically relevant improvements in 6-minute walking distance; however patients in the interval group had lower dyspnoea and had fewer unintended breaks. In a mechanistic study, Daussin et al. (276) studied the effects of continuous vs. interval training (4 min work load at $\dot{V}o_2$ at $\hat{\theta}_L$ followed by 1 min at 90% work load at $\dot{V}o_2$ Max) on skeletal muscle and cardiorespiratory adaptations in sedentary subjects. An 8-week training program in a cross-over design, separated by 12 weeks of detraining, was conducted. Maximal oxygen uptake ($\dot{V}o_2$ Max) increased after both trainings, whereas only the interval group was associated with faster $\dot{V}o_2$ kinetics (τ: 68.0 ± 1.6 vs. 54.9 ±0.7 s, P <0.05) measured during a test to exhaustion. Skeletal muscle mitochondrial oxidative capacities (V max) were only increased after interval training (3.3 ±0.4 before and 4.5 ±0.6 μmol O_2.min^{-1}.g dw^{-1} after training; P <0.05). The gain of V max was correlated with the gain of $\dot{V}o_2$ Max with interval training. These results suggest that fluctuations of workload and oxygen uptake during training sessions, rather than exercise duration or global energy expenditure, are key factors in improving muscle oxidative capacities. In this study, interval training seems to be optimal in maximizing both peripheral muscle and central cardiorespiratory adaptations, permitting significant physical fitness improvement.

As seen above both modalities can be applied safely and effectively, however the choice of interval or continuous training will usually be down to the patient and/or therapist preference. Both interval and continuous training require patient supervision, however as the equipment used in this study enabled the training programme to be fully automated, the level of input from the person supervising the exercise programme was minimal. The tolerability of the derived interval training programme will be assessed in the F&T study.

Exercise intensity

Historically, the rationale for interval exercise training has been the ability to impose very high power outputs from peripheral muscles without overloading the cardiorespiratory capacity. In healthy young people, high-intensity interval training induces greater improvement in oxygen consumption (277), work rate, ventilatory and lactate thresholds (278) compared to continuous training. Studies on muscle fibre metabolism during interval

exercise in healthy subjects have shown that glycogen depletion is similar between type I and II fibres, suggesting that both fibre types are recruited to a similar degree. Although, heavy intensity continuous exercise induces high blood lactate levels (due to the depletion of phosphocreatine and the use of myoglobin-bound oxygen reserves), interspersed periods of sub-lactate threshold work rates may facilitate lactate removal and partially restore the phosphocreatine levels (279).

Compared with the same total amount of work performed continuously, interval exercise imposes maximal loads on both peripheral muscles and oxygen-transporting organs without significant engagement of anaerobic processes. In moderate exercise with short exercise periods (< 30 sec) healthy young subjects can endure very high rates of aerobic exercise thereby yielding very little lactate production. This type of high intensity periodic activity is shown to be effective not only in athletic training but also in COPD (257,280) and chronic heart failure (274,281).

A moderate alternating with high intensity exercise programme was chosen (3 min moderate intensity alternating within 2 min severe intensity exercise) for this study. The literature is equivocal when considering the intensity of exercise training programmes; however, levels of intensity were used which coincided to the work rate at $\dot{V}o_2$ at $\hat{\theta}_L$ (282,283) and $\dot{V}o_2$ Peak (284) as this has been shown to be an adequate training stimulus for sedentary adults (118,251) and in a preoperative setting (154,260). Moderate intensity exercise will be defined as an intensity equivalent to 80% of the work rate at $\dot{V}o_2$ at $\hat{\theta}_L$. This will ensure that during this bout the patient is exercising in the moderate intensity domain. Severe intensity exercise will be defined as a work rate intensity equivalent to 50% of the difference between the $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak. This severe exercise intensity was selected to approximate intensities used in studies that utilize maximal heart rate or maximal workload intensities approaching 70-80% (156,159,162,259,261,263–266,270,285). Defining exercise training intensities using the workloads derived by CPET is reliable, accurate and objective. The tolerability of the interval training programme intensity and intervals will be assessed in the F&T study.

Monitoring Training Response

The patients' training response will be monitored by CPET, so the steering committee decided to include a further CPET at session 7 (mid-exercise). This allows monitoring and tailoring individual patient's training programme in response to their mid-exercise CPET.

Intensity Tailoring

Work rates at moderate and severe intensity will be tailored to the patients' individual needs as assessed by CPET. At session 7 (mid-exercise), the work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak are re-derived and the moderate and severe intensity domains are changed accordingly (see formula Section 3.3.1). If no change or a decline in workloads is found, the same workloads as the first 5 training sessions will be maintained. The tolerability of changes in intensity will be assessed in the F&T study.

Primary and Secondary Exercise Variable Endpoints

The Steering Committee decided that the primary end point was to study the changes in $\dot{V}o_2$ at $\hat{\theta}_L$ as this was felt to be a clinically relevant outcome variable which is non-volition dependant and reliably identified by CPET. The steering committee was guided by the results from Section 4.5 which show a -1.5 $ml.kg^{-1}.min^{-1}$ significant change between $\dot{V}o_2$ at $\hat{\theta}_L$ pre- and post NACRT. This was felt to be clinically relevant and important. Kothmann and colleagues (286) established a minimum clinically significant difference of 2.0 $ml.kg^{-1}.min^{-1}$ in $\dot{V}o_2$ at $\hat{\theta}_L$ in patients undergoing major intra-abdominal surgery, hence an improvement of this magnitude was considered clinically relevant and significant in this population. If the F&T proves successful (i.e. attaining a clinically significant change in $\dot{V}o_2$ at $\hat{\theta}_L$), a change of 2.0 $ml.kg^{-1}.min^{-1}$ in $\dot{V}o_2$ at $\hat{\theta}_L$ will be used to provide a sample size calculation for the prehabilitation study (detailed in Chapter 6). Secondary outcome variables which the F&T study, together with the definitive prehabilitation study will investigate include changes in: $\dot{V}o_2$ Peak, work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak, O_2 pulse at $\hat{\theta}_L$ and Peak, $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$ and Peak, and baseline and peak heart rates.

5.3 FEASIBILITY AND TOLERABILITY STUDY

This section is aimed to study the effects of the structured, responsive, exercise training programme (SRETP) detailed in Section 5.2.2 in patients immediately after a standardized period of neoadjuvant chemoradiotherapy. This study is designed to test the feasibility and tolerability of a 6-week SRETP with specific focus on; (1) the changes in the primary outcome variable ($\dot{V}o_2$ at $\hat{\theta}_L$), (2) the changes in the secondary outcome variables (as above), (3) the feasibility of a 6 week SRETP, (4) the patient's ability to tolerate the SRETP immediately after standardized NACRT, (5) the tolerability of the exercise session duration, (6) the tolerability of the exercise session frequency, (7) the tolerability of performing

exercise on a cycle ergometer immediately post-NACRT, (8) the tolerability of the interval training schedule, (9) the tolerability of the exercise intensity and, (10) the tolerability of the change in exercise intensity at session 8.

5.3.1 PATIENTS AND STUDY METHODS

This single-centre, prospective, interventional feasibility and tolerability study was based at Aintree University Teaching Hospitals, Liverpool, UK. Written informed consent was obtained from all patients. From October to November 2011, I recruited consecutive patients referred to the Colorectal Multi-Disciplinary Team (MDT), age ≥18 years, with locally advanced electively resectable rectal cancer, who were scheduled for standardized NACRT on the basis of Tumour, Node, Metastasis (TNM) classification >T2/N+ with no distant metastasis (230) and WHO Performance Status < 2 (231). Patients were excluded if they were diagnosed with non-resectable disease, were unable to perform CPET (due to mechanical reasons e.g. unable to pedal), declined surgery or NACRT, underwent a non-standardized NACRT regime or were unable to give informed consent.

CPET was performed 2 weeks before, immediately post-NACRT (week 0), at week 3 and 6 weeks post-NACRT (prior to surgery at 15 weeks post-NACRT) (see Figure 3.2; Chapter 3). TNM staging investigations involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen and pelvis computer-aided tomography (CT) and a 1.5 Tesla (Magnetom Area, Siemens, Erlangen, Germany) magnetic resonance imaging (MRI) of the pelvis. Eligible patients then underwent a standardized NACRT regime for 5 weeks. The standardized neoadjuvant radiotherapy regime consisted of 45 Gy in 25 fractions on weekdays using a three-dimensional conformal technique with CT guidance. Patients were treated prone (on a belly-board) to spare small bowel, with a comfortably full bladder. The clinical target volume included the primary tumour, the mesorectum and mesorectal lymph nodes, including the perirectal, presacral and internal iliac nodes. The upper radiation extent was 3 cm above the tumour but no further than the sacral promontory. The perineum was included if an abdominoperineal excision (APE) was planned, while for low anterior resection (LAR) the lower radiation border was 3 cm below the tumour. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. 825 $mg.m^{-2}$ oral capecitabine was given twice daily on radiotherapy days (Section 2.4.4). No patients received brachytherapy. Acute toxicity and adverse events were discussed at the weekly colorectal multidisciplinary meeting (MDT). Adverse events were graded according to the National Cancer Institute

Common Terminology Criteria (version 3.0), and the acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system.

All patients went on to have CPET (for protocol refer to Section 3.2), spirometry and re-staging chest, abdomen and pelvic CT and pelvic MRI at 9 weeks post-NACRT. The Colorectal MDT, anaesthetists and medical staff collecting outcome data were blind to all CPET results. All patients underwent the SRETP immediately after finishing NACRT (see Figure 3.2; Chapter 3). This was undertaken as a feasibility and tolerability trial, in an attempt to study the effect of the SRETP in this patient population. Details of the SRETP protocol are given in Section 3.3. All patients underwent rectal cancer surgery with a total mesorectal excision (TME) (232,233) at week 15. A defunctioning stoma was constructed at the discretion of the surgeon.

Continuous variables are presented as mean and standard deviation (SD) or as medians and interquartile range (IQR), depending on their distribution. Categorical variables are presented as a frequency and/or proportion. The primary outcome variable was $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg.$^{-1}$min^{-1}). Secondary outcome variables included $\dot{V}o_2$ Peak (ml.kg.$^{-1}$min^{-1}), work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak, oxygen pulse at $\hat{\theta}_L$ and Peak (ml.beat^{-1}), $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$ and Peak and baseline and peak heart rates. Although no formal statistical analysis is performed in this feasibility and tolerability study, a change in $\dot{V}o_2$ at $\hat{\theta}_L$ of +2.0 ml.kg^{-1}.min^{-1} was considered clinically significant (286). Furthermore, this study is only aimed at answering specific questions addressed in the aims section above; hence no statistical testing is undertaken.

For this study I aimed to recruit 5 patients who completed a course of standardised NACRT and were listed to have elective surgery as an intention to treat for rectal cancer.

5.3.2 RESULTS

Five consecutive patients were recruited. Table 5.2 describes the patient characteristics and Table 5.3 describes tumour characteristics. CPET was performed at 2.0 ± 0.5 weeks pre-NACRT (Baseline), then immediately post-NACRT (week 0 ± 0.5 weeks), at session 7 (week 3 ± 0.5 weeks) and at session 18, the end of the exercise programme (week 6 ± 0.5 weeks). All patients underwent CT and MR-directed staging, then TME surgery at a median of 105 (range 100-111) days post-NACRT.

Patient Characteristics	Total
Age (years)[1]	74.6 (4.2)
Gender M:F (%)[1]	5 (100) : 0 (0)
Past Medical History[#]	
Heart Failure	1 (20%)
Diabetes	1 (20%)
Ischaemic heart Disease	1 (20%)
Cerebrovascular Disease	0
ASA[2]	2 (2-2)
WHO Performance Status[2]	0 (0-0)
Clinical MRI TNM classification[3#]	
cT3	4 (80%)
cT4	1 (20%)
cN1	3 (60%)
cN2	2 (40%)
cM0	5 (100%)

Table 5.2 – Patient characteristics; [#] with percentages in parentheses, [1] Values presented as mean (SD); [2] Median (range) World Health Organisation (WHO) Performance Status and American Society of Anaesthesiologists Score (ASA); [3] International Union against Cancer tumour node metastasis (TNM) MRI pre-NACRT staging

Tumour Characteristics	Total [#]
Tumour distance from anal verge	
<5 cm	1(20)
6-10cm	0
>10cm	4(80)
Pathological TNM	
pT1	1 (20)
pT2	0
pT3	3 (60)
pT4	1 (20)
pN0	4 (80)
pN1	1 (20)
pN2	0
Dukes Staging	
A	1 (20)
B	2 (40)
C 0/1	2 (40)
Resection margins	
R0	4 (80)

Table 5.3 – Patient tumour and treatment characteritcs; [#] with percentages in parentheses

The mean cumulative dose of capecitabine was 100%; none of the patients needed dose reduction. 100% of patients received at least 45Gy radiotherapy, and all completed the full 25 fractions. None of the patients experienced grade 3 or 4 toxicity. All patients successfully underwent 18 sessions of the SRETP set out in Section 3.3, with no adverse events. The adherence to the full 18 sessions (3 sessions per week) was 98%, with only 2 patients not attending 1 session each. On questioning about the length and tolerability of the training programme immediate after completing NACRT, all patients thought this was achievable. All patients completed the full exercise sessions (30 or 40 minute sessions) in the pre-determined order (3 sessions per week for 6 weeks, usually on Monday's, Wednesday's and Friday's) and none of the patients had to stop due to adverse events. When asked about the tolerability of the length and frequency of the individual sessions all the patients agreed that this was achievable. Three out of 5 patients complained of saddle soreness after completing the exercise sessions, especially at the end of the week or when the exercise intensity was increased. This did not impede the patients from completing any individual session. The patients preferred the seat to be more comfortable, so gel cushions were fitted to the training bikes. All patients completed an interval training schedule and found this acceptable, although one patient found the change in intensities difficult at first. All the patients commented on the advantage of tailored, supervised exercise, and found it re-assuring that the exercise was undertaken in a hospital setting. All patients found the training intensity challenging during the first 3 sessions (rating the first 3 sessions as very hard on the rating of perceived exertion (RPE) scale), however this got better as the sessions progressed (with the RPE's decreasing to somewhat hard). Only 2 out of 5 patients noticed a change in work rate intensity at session 8.

Table 5.4 shows CPET-derived variables (primary and secondary outcome variables) pre-NACRT, and at week 0, 3 and 6 post-NACRT. Figures 5.1 and 5.2 show the changes over time for all 5 patients (plotted in grey) and median changes (plotted in red) for $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ peak respectively.

	Baseline	Week 0	Week 3	Week 6
BMI ($kg.m^{-2}$)[1]	29 (4.3)	28.6 (4.8)	30.1 (5.3)	29.3 (5.0)
FEV1 (L) [1]	2.9 (1.0)	2.9 (1.0)	3.3 (0.7)	2.9 (1.0)
FVC (L) [1]	4.2 (1.0)	4.3 (0.9)	4.6 (0.8)	4.3 (0.9)
FEV1/FVC (%)[1]	66.1 (13.9)	66.0 (12.6)	71.5 (6.1)	66.4 (12.2)
Haemoglobin ($g.dl^{-1}$)[1]	13.7 (1.5)	13.6 (1.2)	n/a	13.5 (1.0)
$\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$)[2]	10.3 (9.5-12.4)	9.2 (7.7-10.6)	10.8 (10.0-12.0)	12.5 (12.1-12.5)
$\dot{V}o_2$ at $\hat{\theta}_L$ ($L.min^{-1}$)[2]	1.0 (0.9-1.0)	0.9 (0.7-1.0)	1.1 (1.0-1.1)	1.2 (1.2-1.2)
$\dot{V}o_2$ Peak ($ml.kg^{-1}.min^{-1}$)[2]	17.2 (15.6-19.9)	14.3 (10.8-15.5)	19.0 (18.4-19.7)	20.1 (19.0-21.1)
$\dot{V}o_2$ Peak ($L.min^{-1}$)[2]	1.6 (1.6-1.7)	1.3 (1.0-1.4)	1.8 (1.7-1.9)	1.9 (1.7-2.1)
O_2 pulse at $\hat{\theta}_L$ ($ml.beat^{-1}$)[2]	8.6 (8.5-10.1)	8.2 (6.3-8.6)	10.4 (9.3-11.4)	10.8 (10.7-11.2)
O_2 pulse at Peak ($ml.beat^{-1}$)[2]	11.1 (11.1-13.9)	9.9 (7.1-10.7)	13.4 (12.1-13.5)	13.9 (12.9-14.2)
$\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$ [2]	29.6 (28.9-35.5)	31.6 (31.4-32.4)	33.2 (31.0-37.0)	32.9 (29.0-34.4)
$\dot{V}_E/\dot{V}co_2$ at Peak[2]	30.6 (30.1-35.9)	34.4 (31.3-35.1)	32.7 (32.0-36.6)	34.2 (28.8-37.5)
Baseline heart rate ($beats.min^{-1}$)[2]	89 (88-92)	82 (79-84)	80 (76-80)	80 (75-84)
Peak heart Rate ($beats.min^{-1}$)[2]	139 (119-146)	123 (114-137)	132 (121-142)	132 (132-135)
Work rate at $\hat{\theta}_L$ (W)[2]	58 (44-62)	56 (56-58)	60 (56-62)	70 (68-72)
Work rate at Peak (W)[2]	120 (116-120)	118 (112-120)	136 (116-138)	138 (138-140)

Table 5.4 – CPET variables at all four study time points. Values presented as [1]mean (SD) and [2]median (IQR)

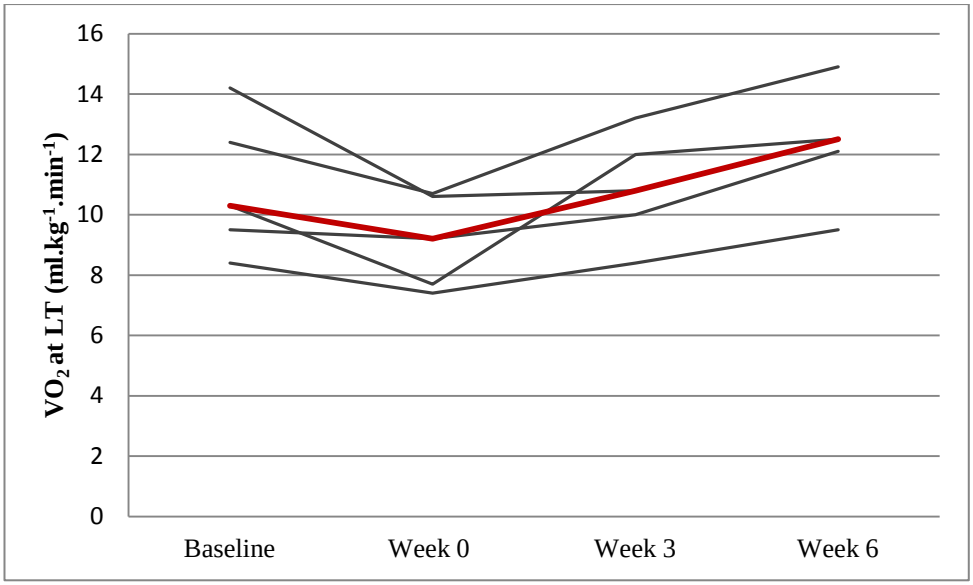


Figure 5.1 – Line graph of $\dot{V}_{O_2}$ at $\hat{\theta}_L$ (ml.kg.$^{-1}$min^{-1}) showing changes over time. Individual patients plotted in grey and median change plotted in red.

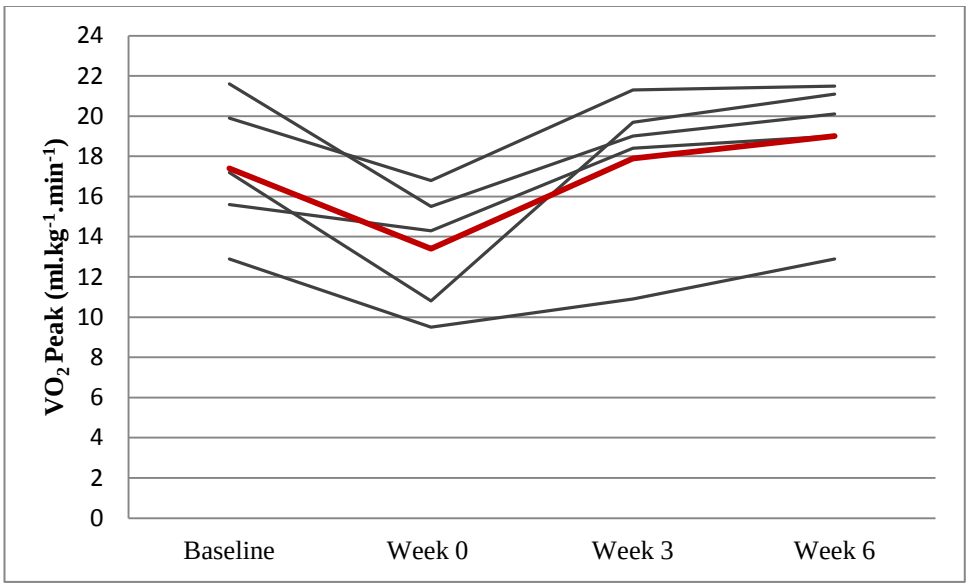


Figure 5.2 – Line graph of $\dot{V}_{O_2}$ Peak (ml.kg.$^{-1}$min^{-1}) showing changes over time. Individual patients plotted in grey and median change plotted in red.

5.3.3 DISCUSSION

This feasibility and tolerability study yielded important novel findings. Firstly and most importantly, that the exercise programme can improve objectively measured physical fitness in this cohort of patients' between week 0 and week 6. A similar decline in physical fitness post-NACRT (baseline vs. week 0) is observed in the results above (Figure 5.1 and 5.2) as seen in Section 4.5.2. Here $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak declined by -1.1 and -2.9 $ml.kg^{-1}.min^{-1}$ respectively after standardised NACRT (baseline vs. week 0), however the SRETP (week 0 vs. week 6) improved both $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak by +3.3 and +5.8 $ml.kg^{-1}.min^{-1}$ respectively. Although no formal statistical analysis was applied, the +3.3 $ml.kg^{-1}.min^{-1}$ improvement in $\dot{V}o_2$ at $\hat{\theta}_L$ is considered to be a clinically relevant finding. As seen in Figures 5.1 and 5.2 all patients sustained a reduction in physical fitness variables post-NACRT and an improvement in these variables after a structured exercise programme. The benefit of the intervention was sufficient to reverse the deleterious effects of NACRT. This change in objectively measured physical fitness will be further studied with the addition of a parallel control group in Chapter 6, so as to validate these changes in physical fitness and compare them to a control group assigned to standard care (negative control, no exercise). The volume of exercise prescribed to these individuals, (i.e. frequency x duration x intensity) together with the length of the training programme produced a large improvement in physical fitness. Moreover, the 98% adherence rate to the exercise programme provides initial proof of concept that the SRETP is feasible and tolerable in its duration, setting, frequency, intensity and schedule in this cohort of patients. Of note, no problems or adverse events were encountered by starting the exercise programme immediately after finishing NACRT, even though one of the patients tumours was <5cm from the anal verge (these patients in particular tend to suffer from perineal burns post-NACRT). To my knowledge no other study reports an exercise training programme that starts immediately after neoadjuvant cancer treatment in any preoperative cancer population. The intensity of the training programme was chosen because it best approximates the published literature that uses maximal heart rate or maximal work rate intensities approaching 70-80%. Furthermore, this interval intensity was already shown to be safe in other patient cohorts (156,159,162,259,261,263–266,270,285). Work rate at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak were utilised because they were felt to be reliably identified by CPET, and most importantly because they can be reliably implemented using the exercise training bikes. I believe that these points remain valid, especially in the light of the results of this F&T study. With regards to appropriate primary outcome measures to gauge physical fitness improvement, $\dot{V}o_2$ Max or $\dot{V}o_2$ Peak may prove to be more valid. These measurements, however, depend on

pushing patients to volitional exhaustion and consequently raise safety concerns in these high-risk individuals. $\dot{V}o_2$ Peak measurements also depends on an individual's motivation during exercise testing, raising some concerns in relation to repeatability in other patient groups. In contrast, $\dot{V}o_2$ at $\hat{\theta}_L$ measurement can be safely achieved during sub-maximal exercise and is independent of subject motivation. These considerations, and the fact that the evidence base for improved surgical outcome is founded on this measurement make the combination of $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak appropriate outcome measures of physical fitness as tested above.

From a clinical stand-point, the patients who achieved the largest improvement in $\dot{V}o_2$ at $\hat{\theta}_L$ could change their perioperative risk classification from high risk to intermediate or else from intermediate to low risk, therefore it would be reasonable to assume (based on the current evidence base presented in Section 2.5.2) that such a shift might equate to improved surgical outcome in this high-risk population. This however, needs to be tested in a larger cohort of patients in a randomized controlled fashion.

The steering committee felt that if such an improvement in physical fitness using a SRETP is attained in 6 weeks after NACRT in a feasibility setting, this would merit further investigation in a pre-pilot setting to inform a larger, definitive randomized controlled trial.

Chapter 6

Prehabilitation – A Pre-Pilot Parallel Group Controlled Study

CHAPTER 6 – Prehabilitation – A Pre-Pilot Parallel Group Controlled Study

6.1 INTRODUCTION

This chapter aims to further define the effects of neoadjuvant chemoradiotherapy (NACRT) and to pilot the structured, responsive exercise training programme (SRETP) developed in Chapter 5. This chapter specifically focuses on a pre-pilot, non-randomised, parallel group controlled study investigating; (1) the changes in objectively measured $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak over the study period (Figure 3.2, Chapter 3), (2) changes in other CPET derived variables over the study period, (3) the relationship of CPET variables to in-hospital morbidity in the exercise and control groups, and (4) the extended safety and tolerability of the exercise programme.

Traditionally, efforts to improve recovery and outcome from surgery have used interventions in the intra-operative and the postoperative periods (287,288), mainly with the adoption of enhanced recovery programmes in major colorectal surgery. However, this might be too late in high risk populations like locally advanced cancer patients following neoadjuvant cancer therapies. With poor objectively measured physical fitness being clearly linked to poor postoperative outcomes (4,120,122,133,289), the preoperative period is thought to offer a more emotionally salient and opportune time to intervene and actively engage patients in preparation for major surgery and postoperative recovery. The process of enhancing physical fitness to enable individuals to withstand the stress of a major traumatic event has been termed as prehabilitation (156,290). There is however a paucity of literature around pre-surgical exercise interventions (154) especially in cancer patients (166,291). This has already been discussed in Section 2.6 of this thesis (154). Preoperative aerobic exercise training appears to be beneficial in patients awaiting cardiac surgery, but the effect in patients prior to major intra-thoracic and intra-abdominal surgeries still remained uncertain. The reviewed literature however shows that an intervention prior to surgery is safe, feasible, well tolerated and appears to improve objectively measured physical fitness. In Section 5.2, the iterative process around the structured, responsive, exercise training programme demonstrated a reassuring feasibility and tolerability profile in this patient cohort.

The concept of preoperative intervention with exercise training is a new one in this cohort of patients; therefore, there is a need to identify prehabilitation programmes that can be used to optimise patients' fitness following the insult of NACRT prior to major surgical trauma. Due to the improvements in patients' objective physical fitness in the feasibility study (Section

5.3), a larger, adequately powered pre-pilot study investigating the improvements in physical fitness with the exercise training programme derived in Chapter 5 was performed. This will be the main focus of the chapter hereunder.

6.2 STUDY OBJECTIVES

The objective of this pre-pilot non-randomised, parallel group interventional study is to evaluate, in patients scheduled for rectal cancer surgery following NACRT, the extent to which a 6-week structured exercise programme carried out preoperative may be used to improve objectively measured physical fitness.

The primary end point was to investigate changes in $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak between week 0 and week 6 in both the exercise and control groups to assess the impact of the exercise intervention on physical fitness. Further exploratory end points were to investigate the:

- changes in $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak with NACRT (between baseline and week 0),
- changes in other selected CPET variables with the exercise intervention (between week 0 and week 6),
- continued safety, tolerability and patient adherence to the exercise intervention (number of adverse events and adherence recorded with CPET or exercise training sessions),
- relationship of selected CPET variables to in-hospital morbidity, and
- differences in length of hospital stay, 1 year mortality and 1 year disease free survival in between groups.

6.3 PATIENTS AND STUDY METHODS

Approval by the North West – Liverpool East Research and Ethics Committee (11/H1002/12) was sought and the trial was registered with clinicaltrials.gov (NCT01325909). Written informed consent was obtained from all patients. We recruited consecutive patients between October 2011 and February 2013 who were referred to the Colorectal Multi-Disciplinary Team (MDT), age ≥18 years, with locally advanced (circumferential resection margin threatened) resectable rectal cancer, scheduled for standardized NACRT on the basis of Tumour, Node, Metastasis (TNM) classification

>T2/N+ with no distant metastasis (230) and WHO Performance Status < 2 (231). Predefined exclusion criteria were: inability to give informed consent, non-resectable disease, inability to perform CPET or bicycle exercise due to leg dysfunction, patients who declined surgery or NACRT, or who received non-standard NACRT.

TNM staging involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen and pelvis computer-aided tomography (CT) and a 1.5 Tesla (Magnetom Area, Siemens, Erlangen, Germany) pelvic magnetic resonance imaging (MRI). All patients then underwent NACRT for 5 weeks. Standardized radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a 3-dimensional conformal technique with CT guidance. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. Oral capecitabine (825 $mg.m^{-2}$) was given twice daily on radiotherapy days. No patients received brachytherapy. When patients completed NACRT they were restaged using chest, abdomen and pelvic CT and pelvic MRI at 9 weeks post-NACRT. The colorectal multidisciplinary team (MDT) was blind to the CPET results and patient allocation, which therefore did not influence perioperative management. All patients underwent total mesorectal excision (TME) surgery (232). A defunctioning stoma was constructed at the discretion of the surgeon.

Any acute toxicity whilst undergoing NACRT was discussed at the weekly colorectal MDT meeting. Toxicity events were graded according to the National Cancer Institute Common Terminology Criteria (version 3.0), and the acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system.

CPET followed our standard protocol described in Section 3.2. Recorded patient characteristics included age, gender, height, weight, cancer staging, surgical procedure planned, WHO classification and ASA-PS, as well as established diagnosis of diabetes, ischaemic heart disease, cerebrovascular disease, or heart failure. Resting flow-volume loops were used to derive Forced Expiratory Volume over 1 second (FEV1) and Forced Vital Capacity (FVC). All patients underwent CPET 2 weeks before NACRT (baseline) and immediately post-NACRT (Week 0). Patients in both groups then underwent CPET at Weeks 3, 6, 9 and 14 before surgery at Week 15. Patients in the exercise group undertook the intervention continuously between Week 0 and Week 6. The study schedule is summarised in Chapter 3, Figure 3.2 and in more detail in Figure 6.1. CPET data were reported by two experienced assessors blind to patient characteristics, group allocation and outcome data. Any CPET-related adverse events were discussed at the weekly colorectal MDT meeting.

After completing NACRT, all patients were allocated to the exercise training group by default. If patients were unable to commit to the predefined exercise schedule for any reason (residing >20 miles from hospital or have carer responsibilities), they were asked to act as contemporaneously recruited controls (no exercise intervention) with the same CPET follow-up as the exercise group. Patients in the exercise group attended an in-hospital exercise training programme which was supervised (by a team member trained in advanced life support), structured (3 sessions/week for 6 weeks) and responsive (informed by measured work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak at Week 3). The exercise schedule is described in Section 3.3. Patients exercised in groups of two (for camaraderie), each patient being prescribed a programme tailored to individual fitness (based initially on CPET results at Week 0). After session 7 (Week 3), work rates were individually adjusted in line with mid-programme CPET results.

Patients were assessed pre- and postoperatively using the Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) (234). Patients were assessed postoperatively on days 3,5,8 and 15 using the Post-Operative Morbidity Survey (POMS) (146) and the Clavien-Dindo Classification of Surgical Complications (235) by members of the research team blind to CPET data and group allocation. Patients were followed up for local/distant radiologically documented metastasis and mortality at 1 year postoperatively.

6.4 STATISTICAL ANALYSIS

Our aim was to recruit 30 patients (15 patients in the exercise group and 15 in the control group) who would undergo standardised NACRT and surgery as an intention to treat for rectal cancer. This sample size was based on an unpaired t-test with 90% power to detect an estimated minimum difference in $\dot{V}o_2$ at $\hat{\theta}_L$ of 1.5 $ml.kg^{-1}.min^{-1}$ and an SD of 1.1 $ml.kg^{-1}.min^{-1}$, and allowed for 20% patient drop-out (based on a previous pilot study (292)). Descriptive statistics are reported as mean (SD) or median and inter-quartile range (IQR) and categorical statistics as frequency (percentage). A statistical comparison of patient characteristics between groups was undertaken. A two-sample t-test was used for continuous variables when relevant distributional assumptions were met, and the Mann-Whitney U test otherwise. Categorical variables were compared using Chi-Square tests or, when cell counts were insufficient, Fishers Exact test. $p < 0.05$ was taken as indicating a statistically significant difference.

For the primary analysis, compound symmetry covariance pattern linear mixed models were used to model $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak exercise over the 3 time-points: baseline (pre-NACRT), Week 0, and Week 6 post-NACRT. Both group (exercise/control) and visit (baseline, Week 0 and Week 6) were included as main effects in addition to the interaction between them i.e. there was sufficient statistical evidence to suggest that the effect of visit differed between the two groups. Formal comparisons were considered to be statistically significant at a Bonferroni-corrected significance level of $p<0.008$. Model selection was based on Akaike's Information Criterion (AIC) and residuals and model fit were assessed using QQ plots and residual versus predicted mean plots. The impact of potential confounders on between-group comparisons was assessed by incorporating variables listed in Table 6.0 into the final models as sensitivity analyses. All mixed model statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary NC). Length of stay for the exercise and control groups were estimated using the Kaplan-Meier method and compared using the Log rank Test. The univariate association between in-hospital complications (yes/no) with other variables was assessed using logistic regression. These analyses were conducted using Stata version 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.)

6.5 RESULTS

A total of 39 patients were recruited, of whom 22/22 and 13/17 completed the study in the exercise and control groups respectively (4 patients having dropped out before baseline CPET after allocation to the control group). Figure 6.1 illustrates a CONSORT diagram depicting detailed patient flow for this study.

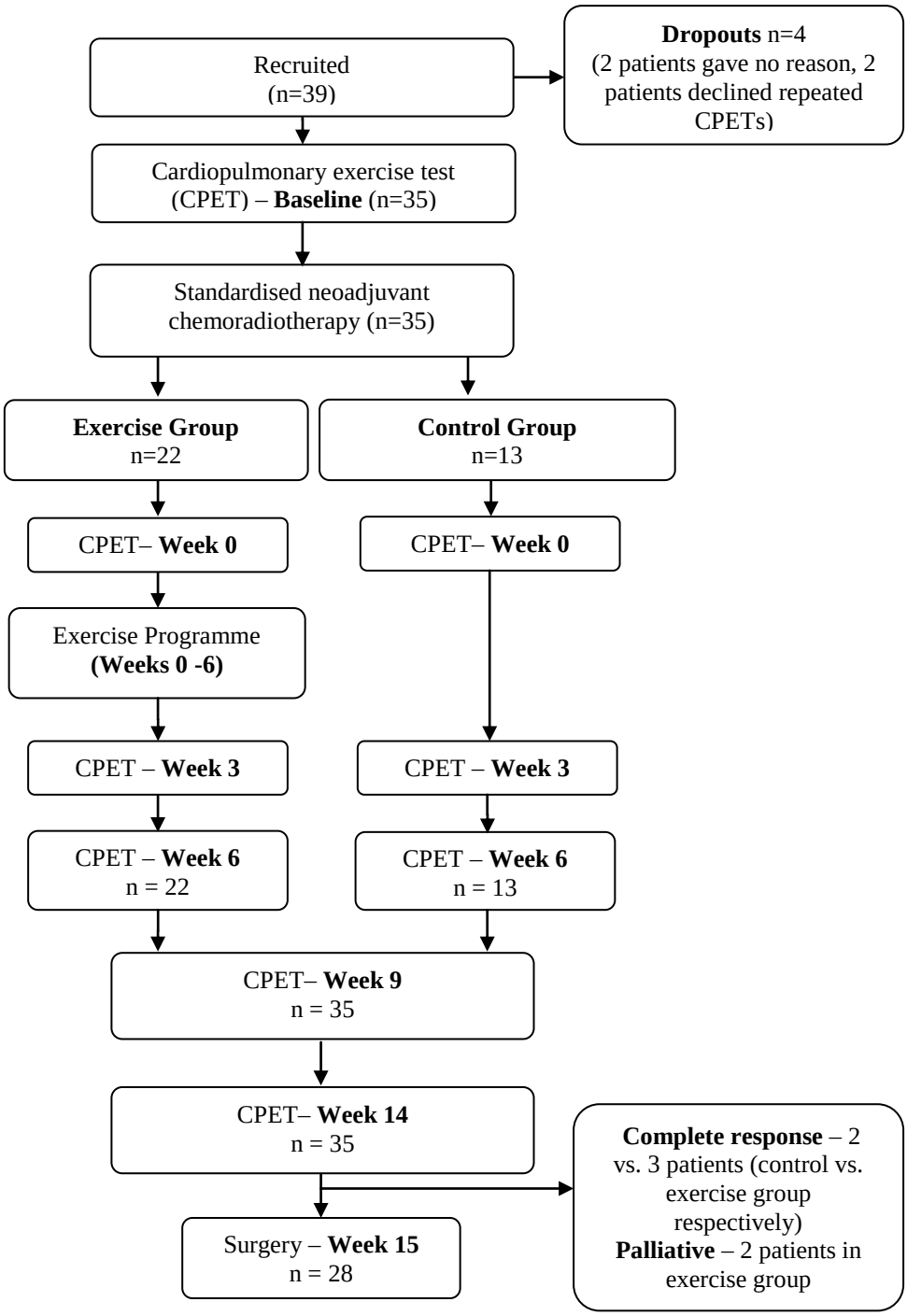


Figure 6.1 – Consort diagram

Patient characteristics are shown in Table 6.1. There were significant baseline differences between the groups in age, ASA, WHO performance status and CR-POSSUM predicted morbidity scores, with the control group being older and having poorer subjective performance.

	Exercise (n=22)	**Control (n=13)**	***p*-value**
Age (years)[1]	64 (9.6)	72 (7.3)	**0.015**
Gender M:F (%)	14 (64) :8 (36)	9 (69) : 4 (31)	1
Smoking (%)	10 (45)	4 (31)	0.617
Past Medical History[2]			
Heart Failure	3 (14)	1 (8)	1
Diabetes	2 (9)	1 (8)	1
Ischaemic heart Disease	5 (23)	5 (38)	0.444
Cerebrovascular Disease	0	0	1
ASA[2]			
1	11 (50)	0	
2	9 (41)	11 (85)	
3	2 (9)	2 (15)	**0.003**
WHO Performance Status[2]			
0	18 (82)	8 (62)	
1	4 (18)	3 (23)	
2	0	2 (15)	**0.035**
CR-POSSUM- Physiological Score*	8.0 (1.8)	9.3 (2.3)	0.162
CR-POSSUM- Predicted Mortality (%)*	3.2 (1.1)	9.4 (8.9)	**0.003**
CR-POSSUM- Operative Severity Score*	9.8 (2.0)	11.4 (0.5)	0.236

Table 6.1 - Patient characteristics; Smoking status assessed as currently smoking - yes (1) vs. no (0) [1]Values presented as mean (SD); [2]Number of patients (%). World Health Organisation (WHO) Performance Status and American Society of Anaesthesiologists Score (ASA); *Values are mean (SD) for CR-POSSUM components – Exercise n=17 and Control n=11. Four patient drop outs immediately before 1st CPET (dropouts not included).

Table 6.2 shows changes in BMI, spirometry variables (FEV1, FVC, FEV1/FVC) and haemoglobin over the whole study period in the exercise and the control groups, along with MRI tumour staging and re-staging post-NACRT (Week 9). There were no significant baseline differences in these variables between the two groups.

		Exercise (n=22)	Control (n=13)	*p*-value
BMI ($kg.m^{-2}$)[1]				
Baseline		27.4 (5.1)	24.9 (3.9)	0.121
Week 0		27.3 (5.0)	25.1 (3.9)	
Week 3		27.6 (5.2)	29.0 (3.1)	
Week 6		27.8 (5.6)	25.1 (3.4)	
Week 9		27.0 (5.6)	27.0 (4.6)	
Week 14		27.7 (6.0)	26.5 (5.3)	
FEV1 (L) [1]				
Baseline		2.8 (0.8)	2.5 (0.6)	0.232
Week 0		2.7 (0.8)	2.5 (0.6)	
Week 3		2.9 (0.7)	3.0 (0.4)	
Week 6		2.8 (0.8)	2.6 (0.6)	
Week 9		2.8 (0.8)	3.1 (0.3)	
Week 14		2.8 (0.8)	3.0 (0.4)	
FVC (L) [1]				
Baseline		3.8 (1.0)	3.8 (0.7)	0.898
Week 0		3.8 (1.0)	3.9 (0.7)	
Week 3		3.8 (1.0)	4.3 (0.6)	
Week 6		3.8 (0.9)	3.9 (0.7)	
Week 9		3.5 (0.9)	4.3 (0.6)	
Week 14		3.6 (1.0)	4.5 (0.7)	
FEV1/FVC (%)[1]				
Baseline		72.6 (12.1)	66.6 (8.1)	0.051
Week 0		72 (11.7)	66.2 (9.7)	
Week 3		73.3 (9.8)	71.3 (9.0)	
Week 6		73.0 (11.6)	66.7 (9.8)	
Week 9		74.4 (10.7)	71.7 (5.2)	
Week 14		74.5 (11.4)	67.3 (5.0)	
Haemoglobin ($g.dl^{-1}$)[1]				
Baseline		13.7 (1.4)	13.2 (1.2)	0.303
Week 0		13.4 (1.4)	13.0 (1.4)	
Week 6		13.6 (1.5)	13.3 (1.3)	
Clinical MRI TNM classification[2#]	cTx	0	0	1
	cT2	2 (9)	1 (8)	
	cT3	17 (77)	10 (77)	
	cT4	3 (14)	2 (15)	
Baseline	cN0	2 (9)	2 (15)	0.892
	cN1	12 (55)	7 (54)	
	cN2	8 (36)	4 (31)	
	cM0	22 (100)	13 (100)	1
Clinical MRI TNM classification[2#]	cTx	2 (9)	2 (15)	0.321
	cT2	3 (14)	4 (31)	
	cT3	15 (68)	5(38)	
	cT4	2 (9)	2 (15)	
Week 9	cN0	14 (64)	3 (23)	0.100
	cN1	6 (27)	9 (69)	
	cN2	2 (9)	1 (8)	
	cM0	20 (91)	13 (100)	0.519

Table 6.2 - Patient characteristics; [#] with percentages in parentheses; [1] Values presented as mean (SD); [2] International Union against Cancer tumour node metastasis (TNM) MRI staging. 4 patient drop outs immediately after 1st CPET (dropouts not included in demographics).

Table 6.3 shows tumour and cancer treatment characteristics for both groups. A significant, large difference was found between the groups in the response to NACRT (defined as mrTRG response with standardised NACRT). All patients completed NACRT. One patient needed capecitabine dose reduction, while 4 patients (3 in the exercise group and 1 control) sustained perineal radiation skin changes (maximum score 2 out of 4).

	Exercise (n=22)	**Control (n=13)**	***p*-value**
Tumour distance from anal verge			
<5.0 cm	10 (45)	9 (69)	0.395
5.1-10.0cm	10 (45)	3 (23)	
>10.1cm	2 (9)	1 (8)	
Response to NACRT (mrTRG)			
Favourable	19 (86)	6 (46)	**0.006**
Not Favourable	0	5 (38)	
Complete Clinical Response	3 (14)	2 (15)	
Operation Type [#]			
Open	11 (65)	8 (73)	1
Laparoscopic	6 (35)	3 (27)	
Surgery Type [#]			
Low anterior resection	12 (71)	5 (45)	0.299
Abdomino-perineal excision	5 (29)	5 (45)	
Hartmann procedure	0	1 (9)	
Pathological TNM [#]			
pT1	1 (6)	1 (9)	1
pT2	3 (18)	2 (18)	
pT3	10 (59)	7 (64)	
pT4	3 (18)	1 (9)	
pN0	9 (53)	7 (64)	0.651
pN1	6 (35)	2 (18)	
pN2	2 (12)	2 (18)	
Dukes Staging [#]			
A	4 (24)	3 (27)	0.701
B	4 (24)	4 (36)	
C	9 (53)	4 (36)	

Table 6.3 - All values are presented as number of patients (frequency). MRI Tumour Regression Grading (mrTRG) – Favourable = T0-3a, Not Favourable T3b>. [#]28 out of 35 patients had surgery (exercise n=17 and control n=11).

6.5.1 CHANGES IN PHYSICAL FITNESS WITH NACRT AND EXERCISE

The median time to starting the exercise programme after completion of NACRT was 2 working days (IQR 1-7 days). The mean (SD) % adherence to the exercise programme (defined as % of the total of 18 sessions completed) was 96 (5) %. The mean (SD) % adherence to CPETs (defined as % of the total of 6 CPETs attended) was 92 (14) % in the exercise group vs. 60 (5) % in the control group. There were no adverse events recorded following CPET or exercise. Table 6.4 shows changes in all CPET-related variables at the different time points.

	Exercise (n=22)	**Control (n=13)**
Adherence to exercise programme (%)[1]	96 (5.3)	n/a
Adherence to CPETs (%)[1]	92 (14.2)	60 (5.1)
$\dot{V}$ **o_2 at** $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$)[1]		
Baseline	12.0 (2.5)	12.2 (2.3)
Week 0	10.3 (2.6)	10.1 (3.4)
Week 3	11.3 (2.5)	10.5 (0.6)
Week 6	12.4 (2.7)	9.5 (2.9)
Week 9	12.1 (3.6)	10.7 (3.4)
Week 14	11.7 (3.0)	8.1 (2.1)
$\dot{V}$ **o_2 at** $\hat{\theta}_L$ ($L.min^{-1}$)[1]		
Baseline	0.9 (0.3)	0.8 (0.2)
Week 0	0.8 (0.2)	0.7 (0.2)
Week 3	0.9 (0.2)	0.8 (0.1)
Week 6	1.0 (0.2)	0.7 (0.2)
Week 9	1.0 (0.4)	0.8 (0.1)
Week 14	0.9 (0.2)	0.7 (0.1)
$\dot{V}$ **o_2 Peak** ($ml.kg^{-1}.min^{-1}$)[1]		
Baseline	18.9 (5.1)	17.9 (3.1)
Week 0	16.0 (4.3)	15.7 (5.0)
Week 3	18.0 (3.8)	14.1 (1.6)
Week 6	18.7 (4.3)	14.4 (4.5)
Week 9	18.0 (5.3)	14.4 (5.4)
Week 14	18.1 (4.7)	12.4 (5.0)
$\dot{V}$ **o_2 Peak** ($L.min^{-1}$)[1]		
Baseline	1.4 (0.4)	1.2 (0.3)
Week 0	1.2 (0.4)	1.1 (0.3)
Week 3	1.4 (0.4)	1.2 (0.1)
Week 6	1.5 (0.4)	1.1 (0.2)
Week 9	1.4 (0.4)	1.2 (0.3)
Week 14	1.4 (0.4)	1.1 (0.2)

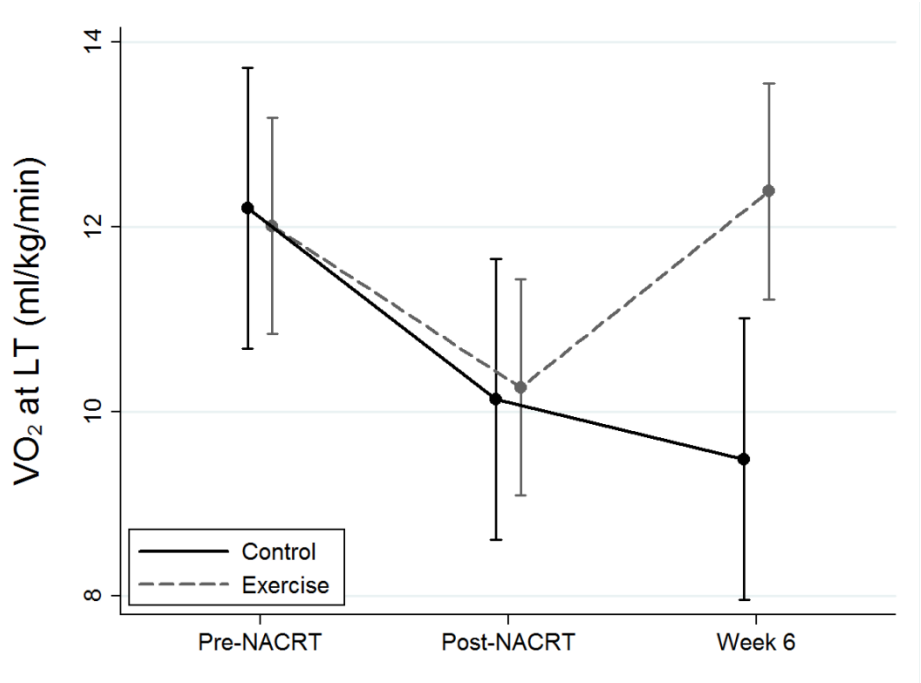
O_2 pulse at $\hat{\theta}_L$ ($ml.beat^{-1}$)[1]		
Baseline	8.7 (2.4)	8.5 (2.1)
Week 0	7.6 (2.1)	7.0 (1.7)
Week 3	8.6 (2.3)	8.7 (1.7)
Week 6	8.9 (2.3)	7.4 (1.7)
Week 9	8.4 (2.8)	8.7 (1.0)
Week 14	8.3 (2.1)	7.8 (1.0)
O_2 pulse at Peak ($ml.beat^{-1}$)[1]		
Baseline	10.5 (2.9)	10.3 (2.6)
Week 0	9.4 (2.7)	8.9 (1.9)
Week 3	10.9 (2.8)	9.4 (1.3)
Week 6	10.7 (2.9)	9.3 (2.1)
Week 9	9.8 (3.7)	9.9 (1.3)
Week 14	10.0 (2.7)	9.3 (1.5)
$\dot{V}_E/\dot{V}co_2$ **at $\hat{\theta}_L$** [1]		
Baseline	30.5 (4.7)	34.6 (4.2)
Week 0	31.8 (4.4)	33.8 (5.1)
Week 3	31.9 (5.0)	35.9 (4.0)
Week 6	31.0 (5.0)	34.1 (4.1)
Week 9	30.2 (4.4)	35.0 (3.4)
Week 14	30.4 (4.5)	34.8 (4.0)
$\dot{V}_E/\dot{V}co_2$ **at Peak**[1]		
Baseline	31.9 (4.3)	36.7 (4.5)
Week 0	33.6 (4.8)	37.0 (6.7)
Week 3	33.0 (4.6)	38.0 (4.8)
Week 6	34.1 (4.4)	37.9 (6.0)
Week 9	33.4 (4.8)	37.7 (5.7)
Week 14	33.1 (4.3)	34.8 (2.7)
Baseline heart rate ($beats.min^{-1}$)[3]		
Baseline	84.0 (71.3, 91.0)	83.0 (74.0, 88.0)
Week 0	82.5 (71.3, 89.0)	83.0 (70.0, 93.0)
Week 3	77.0 (70.0, 86.0)	81.0 (77.0, 87.5)
Week 6	77.5 (70.3, 84.8)	87.0 (81.0, 93.0)
Week 9	78.0 (71.3, 84.3)	88.5 (82.8, 90.3)
Week 14	86.0 (69.0, 89.0)	72.0 (62.0, 77.5)
Peak heart Rate ($beats.min^{-1}$)[3]		
Baseline	139.0 (124.0, 145.0)	136.0 (113.0, 142.0)
Week 0	134.0 (122.0, 145.0)	122.0 (110.0, 142.0)
Week 3	139.0 (125.0, 145.0)	114.0 (108.0, 114.0)
Week 6	138.0 (132.0, 147.0)	121.0 (115.0, 142.0)
Week 9	142.0 (132.0, 159.0)	119.0 (112.0, 128.0)
Week 14	145.0 (136., 156.0)	112.0 (112.0, 129.0)
Work rate at $\hat{\theta}_L$ (W)[3]		
Baseline	58.0 (44.5, 70.0)	46.0 (42.0, 50.0)
Week 0	53.0 (34.8, 63.0)	35.0 (25.0, 50.0)
Week 3	60.0 (47.0, 80.0)	42.0 (36.0, 53.0)
Week 6	72.0 (48.5, 80.0)	34.0 (30.0, 42.0)
Week 9	69.0 (45.3, 79.0)	48.0 (42.0, 58.5)
Week 14	68.0 (44.0, 76.0)	52.0 (47.5, 71.0)

Work rate at Peak (W)[3]		
Baseline	118.0 (92.5, 130.0)	104.0 (74.0, 112.0)
Week 0	109.0 (82.5, 124.0)	80.0 (62.0, 102.0)
Week 3	122.0 (96.0, 136.0)	112.0 (102.5, 113.0)
Week 6	131.0 (95.5, 143.0)	85.0 (70.0, 95.0)
Week 9	123.0 (88.0, 146.0)	109.0 (95.3, 124.5)
Week 14	116.0 (85.0, 146.0)	112.0 (93.5, 129.0)

Table 6.4 – CPET variables reported at each study time point. [1] Values presented as mean (SD). [2] Values presented as mean (CI). [3]Values presented as median (IQR). $\dot{V}o_2$ at $\hat{\theta}_L$, Oxygen uptake at estimated lactate threshold; $\dot{V}o_2$ Peak, Oxygen uptake at peak exercise; O_2 pulse at $\hat{\theta}_L$, Oxygen pulse at estimated lactate threshold; O_2 pulse at Peak, Oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at peak exercise; Work rate at $\hat{\theta}_L$, Work rate at estimated lactate threshold; Work rate at Peak, Work rate at peak exercise.

$\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak were the primary outcome variables. There was a significant reduction in $\dot{V}o_2$ at $\hat{\theta}_L$ (-1.91 ml.kg^{-1}.min^{-1}; 95%CI -1.27 to -2.55; p<0.0001) and $\dot{V}o_2$ at Peak (-2.52 ml.kg^{-1}.min^{-1}; 95%CI -1.33 to -3.71; p<0.0001) post-NACRT (Week 0). The exercise group showed a significant improvement in both primary endpoints during the intervention period (Week 0 to Week 6), in contrast to the worsening physical fitness in the control group (Figure 6.2 A and B). The exercise group improved $\dot{V}o_2$ at $\hat{\theta}_L$ by +2.12 ml.kg^{-1}.min^{-1} (95%CI +1.34 to +2.90; p<0.0001), while the control group showed a non-significant decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.65 ml.kg^{-1}.min^{-1} (95% CI: -1.66 to +0.37; p=0.204). A direct comparison of $\dot{V}o_2$ at $\hat{\theta}_L$ between groups at week 6, correcting for differences in $\dot{V}o_2$ at $\hat{\theta}_L$ between the groups at Week 0, shows a difference of +2.77 ml.kg^{-1}.min^{-1} (95%CI +1.49 to +4.05; p<0.0001). $\dot{V}o_2$ Peak shows similar changes in the exercise group: +2.65 ml.kg^{-1}.min^{-1} (95%CI +1.19 to +4.10; p=0.0005), while the control group worsened by -1.25 ml.kg^{-1}.min^{-1} (95% CI: -3.14 to +0.64; p=0.19). A similar direct comparison of $\dot{V}o_2$ Peak between groups at Week 6, correcting for differences in $\dot{V}o_2$ Peak at Week 0, shows a change of +3.90 ml.kg^{-1}.min^{-1} (95%CI +1.52 to +6.28; p=0.0017). Adjusting for potential confounders had negligible effect on these analyses (not shown). A secondary analysis of $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak, including all time-points, was conducted and the results are shown in Figure 6.3 A and B.

(A)



(B)

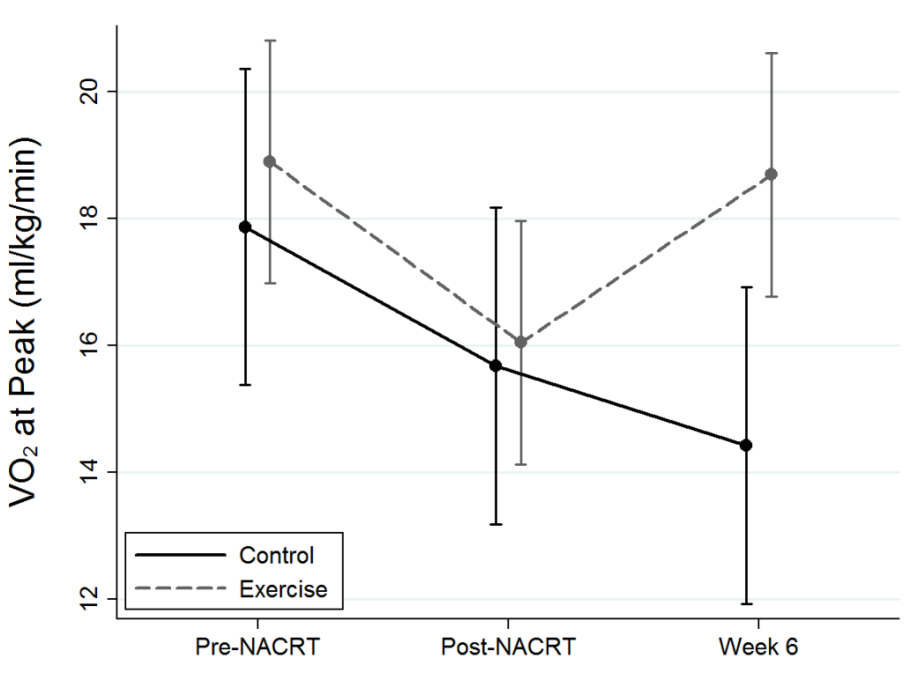
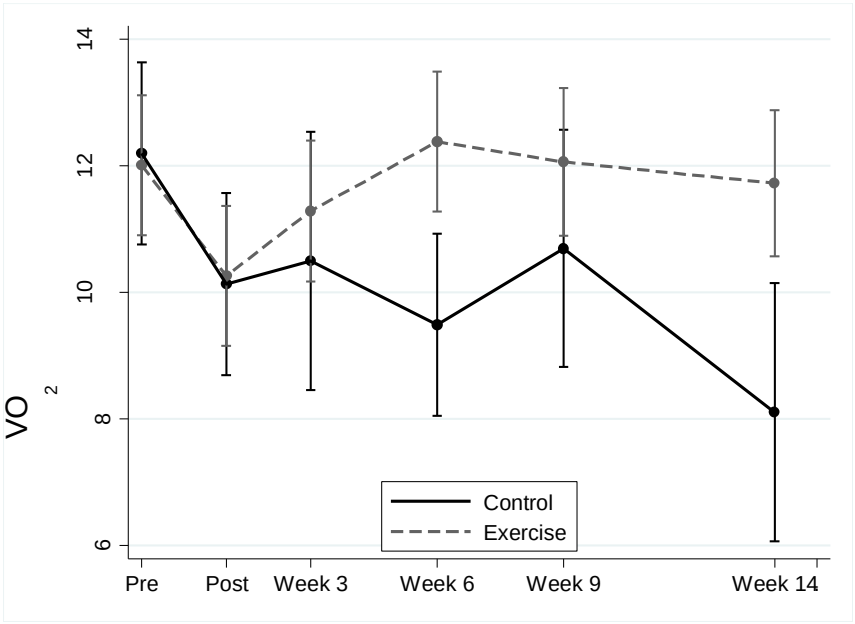


Figure 6.2A and B – Line diagram showing fitted means and 95%CI for $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg^{-1}.min^{-1}) (A) and $\dot{V}o_2$ Peak (ml.kg^{-1}.min^{-1}) (B) at baseline (pre-NACRT), week 0 (post-NACRT) and Week 6 for the exercise (dashed line) and control groups (solid line)

(A)



(B)

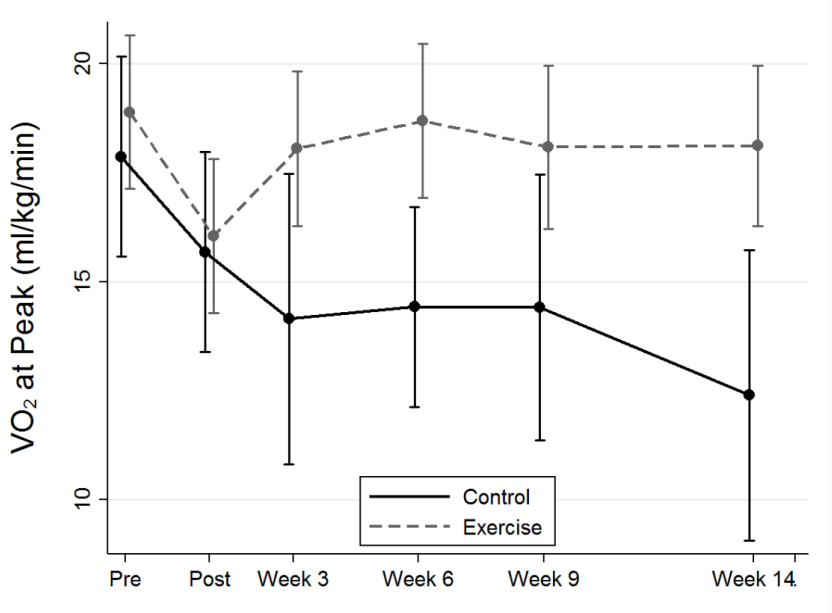
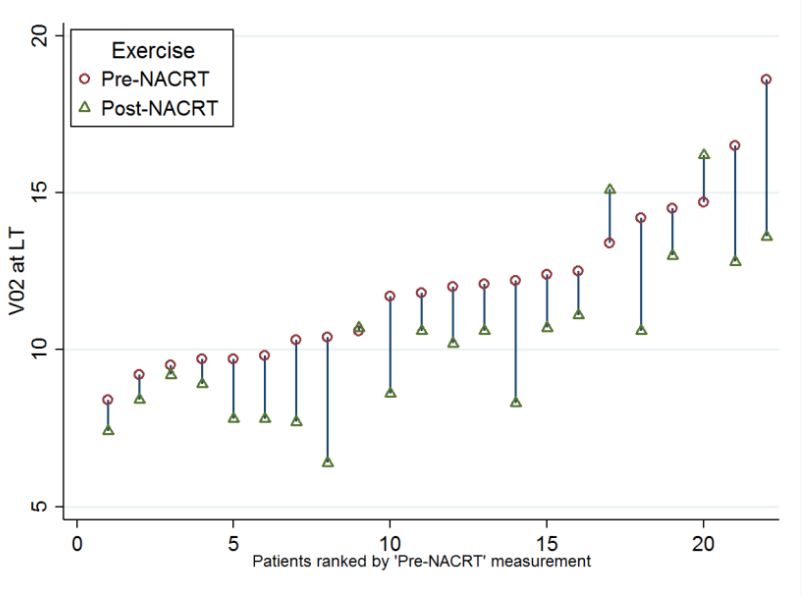


Figure 6.3A and B – Line diagram showing fitted means and 95%CI for $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg^{-1}.min^{-1}) (A) and $\dot{V}o_2$ Peak (ml.kg^{-1}.min^{-1}) (B) for the exercise group and the control group over the whole study period (baseline pre-NACRT to week 14 pre-surgery – secondary analysis)

Changes in individual patients' $\dot{V}o_2$ at $\hat{\theta}_L$ (Figures 6.4 and 6.5) and $\dot{V}o_2$ Peak (Figures 6.6 and 6.7) were plotted on point-to-point graphs as seen on Figures 6.4A (baseline to Week 0) and B (Week 0 to Week 6) for the exercise group and Figures 6.5A (baseline to Week 0) and B (Week 0 to Week 6) for the control group. $\dot{V}o_2$ Peak data were plotted on Figures 6.6A

(baseline to Week 0) and B (Week 0 to Week 6) for the exercise group and Figures 6.7A (baseline to Week 0) and B (Week 0 to Week 6) for the control group.

(A)



(B)

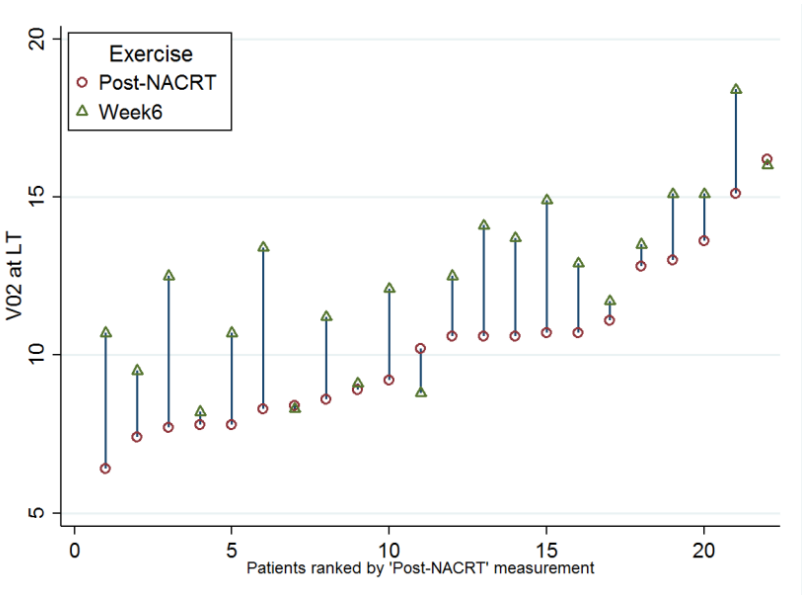
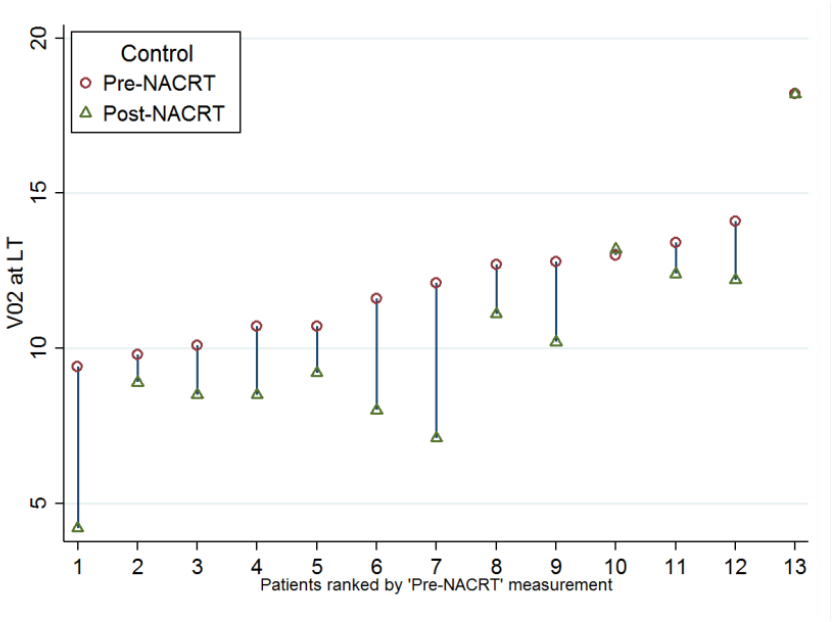


Figure 6.4 – (A) Point-to-point graphs of $\dot{V}_{O_2}$ at $\hat{\theta}_L$ for patients between pre-NACRT (baseline) and post-NACRT (Week0); and (B) between post-NACRT and Week 6 in the exercise group

(A)



(B)

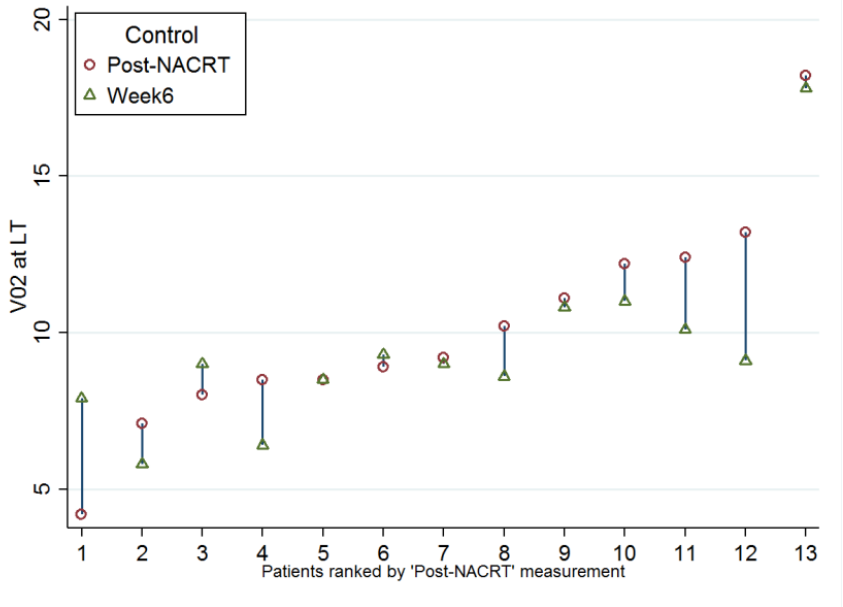
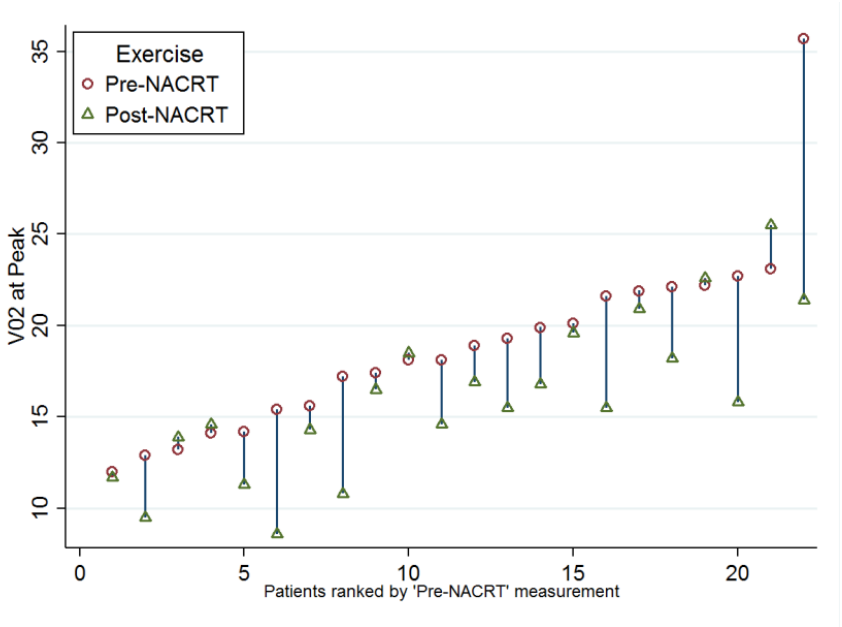


Figure 6.5 – (A) Point-to-point graphs of $\dot{V}_{O_2}$ at $\hat{\theta}_L$ for patients between pre-NACRT (baseline) and post-NACRT (Week0); and (B) between post-NACRT and Week 6 in the control group

(A)



(B)

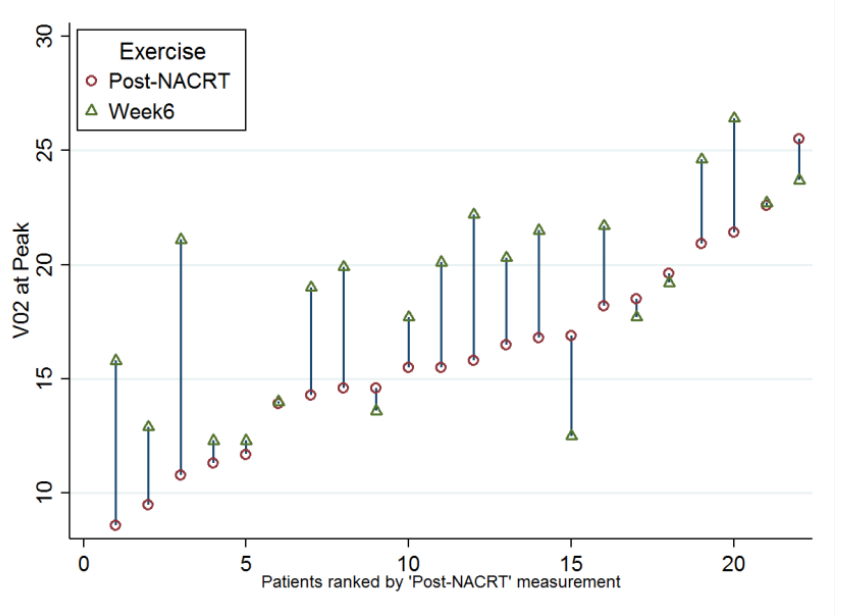
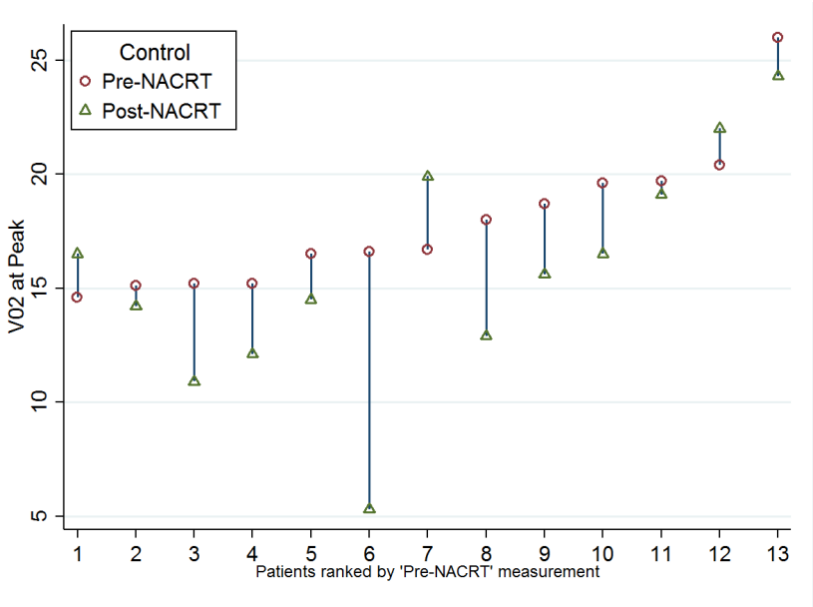


Figure 6.6 – (A) Point-to-point graphs of $\dot{V}o_2$ at Peak for patients between pre-NACRT (baseline) and post-NACRT (Week0); and (B) between post-NACRT and Week 6 in the exercise group

(A)



(B)

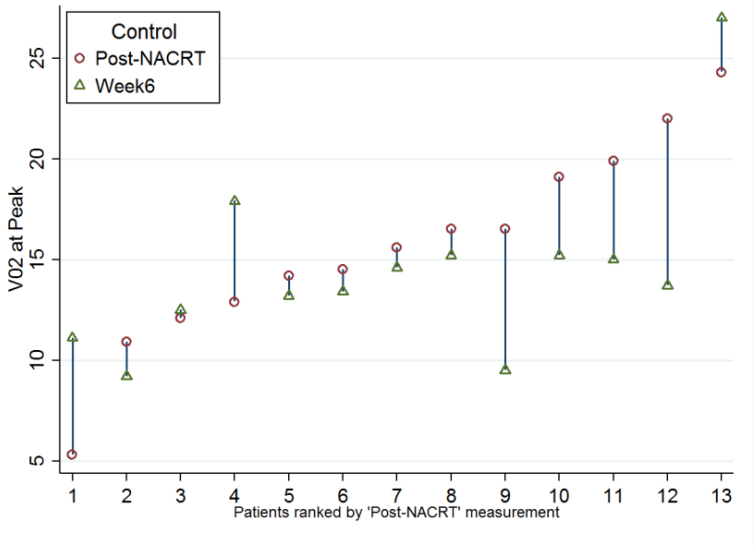


Figure 6.7 – (A) Point-to-point graphs of $\dot{V}o_2$ at Peak for patients between pre-NACRT (baseline) and post-NACRT (Week0); and (B) between post-NACRT and Week 6 in the control group

6.5.2 OUTCOMES FROM PREOPERATIVE RE-STAGING INVESTIGATIONS

Five patients (14%) from the total cohort had a complete clinical response on re-staging investigations at Week 9 (2 in the control group (15%) vs. 3 in the exercise group (14%)). These patients did not undergo surgery and were allocated to a watch and wait follow-up program. The control group had a significantly poorer tumour response to NACRT on re-staging MRI (mrTRG) (p=0.006), however there was no evidence of a statistical difference in TNM re-staging between the two groups (p=0.822). 11 patients (85%) in the control group and 17 patients (77%) in the exercise group underwent surgery. Unfortunately 2 patients (9%) in the exercise group were deemed palliative on re-staging investigations (one patient developed liver metastasis, while another developed local tumour progression). Both patients completed the exercise programme however both patients were unable to improve their fitness post-NACRT.

6.5.3 RELATIONSHIP BETWEEN PHYSICAL FITNESS AND SURGICAL OUTCOME

Surgical outcome and post-operative follow up until 1 year is shown in Table 6.5. Figure 6.8 shows that there was no significant differences in the median length of hospital stay between the groups (p=0.848).

	Exercise (n=17)				Control (n=11)			
Length of Stay (days) [1]	9 (6-16)				9 (8-15)			
Total Parenteral Nutrition (days) [1]	0 (0-0)				0 (0-0)			
Level 2/3 Care (days) [1]	0 (0-0)				0 (0-2)			
	POMS Day				**POMS Day**			
	3	**5**	**8**	**15**	**3**	**5**	**8**	**15**
Discharge rate (%)[#]	0	2 (12)	7 (41)	12(71)	0	0	4(36)	8 (73)
In Hospital Morbidity positive[#]	5 (29)	7 (41)	7 (41)	5 (29)	6 (55)	6 (55)	5 (45)	3 (27)
In Hospital Morbidity negative[#]	12(71)	8 (47)	3 (18)	0	5 (45)	5 (45)	2 (19)	0
POMS[#]								
Pulmonary	0	2 (12)	2 (12)	0	0	2 (18)	2 (18)	0
Infectious	2 (12)	4 (24)	3 (18)	2 (12)	1 (9)	2 (18)	3 (27)	2 (18)
Renal	2 (12)	0	1 (6)	1 (6)	1 (9)	1 (9)	1 (9)	0
Gastrointestinal	4 (24)	5 (29)	4 (24)	4 (4)	3 (27)	4 (36)	5 (45)	3 (27)
Cardiovascular	1 (6)	0	0	0	1 (9)	1 (9)	0	0
Neurological	0	0	0	0	1 (9)	0	0	0
Haematological	0	0	0	1 (6)	0	0	0	0
Wound	0	0	0	1 (6)	0	0	2 (18)	2 (18)
Pain	1 (6)	1 (6)	0	0	1 (9)	1 (9)	1 (9)	1 (9)

	Exercise (n=17)	Control (n=11)
Clavine-Dindo Score[#]		
Grade I	3 (18)	2 (18)
Grade II	2 (12)	2 (18)
Grade IIIa	0	0
Grade IIIb	2 (12)	3 (27)
Grade IVa	1 (6)	1 (9)
Grade IVb	0	0
30-day Mortality (%)[#]	0	0
30-day Readmission (%)[#]	2 (12)	8 (73)
1 year mortality (%)[#]	4 (24)	2 (18)
1 year recurrence rates (%)[#]	7 (41)	2 (20)

Table 6.5 – Tables showing postoperative outcome until 1year follow up. Post-operative follow up at day 3,5,8 and 15 was undertaken using the post-operative morbidity survey. Further follow up was then undertaken at 30-days for mortality, morbidity (Clavine-Dindo score) and hospital readmission and at 1 year for radiologically documented recurrence or distant metastasis, and mortality. [1] Values presented as median (interquartile range). [#] Values are presented as number of patients (frequency).

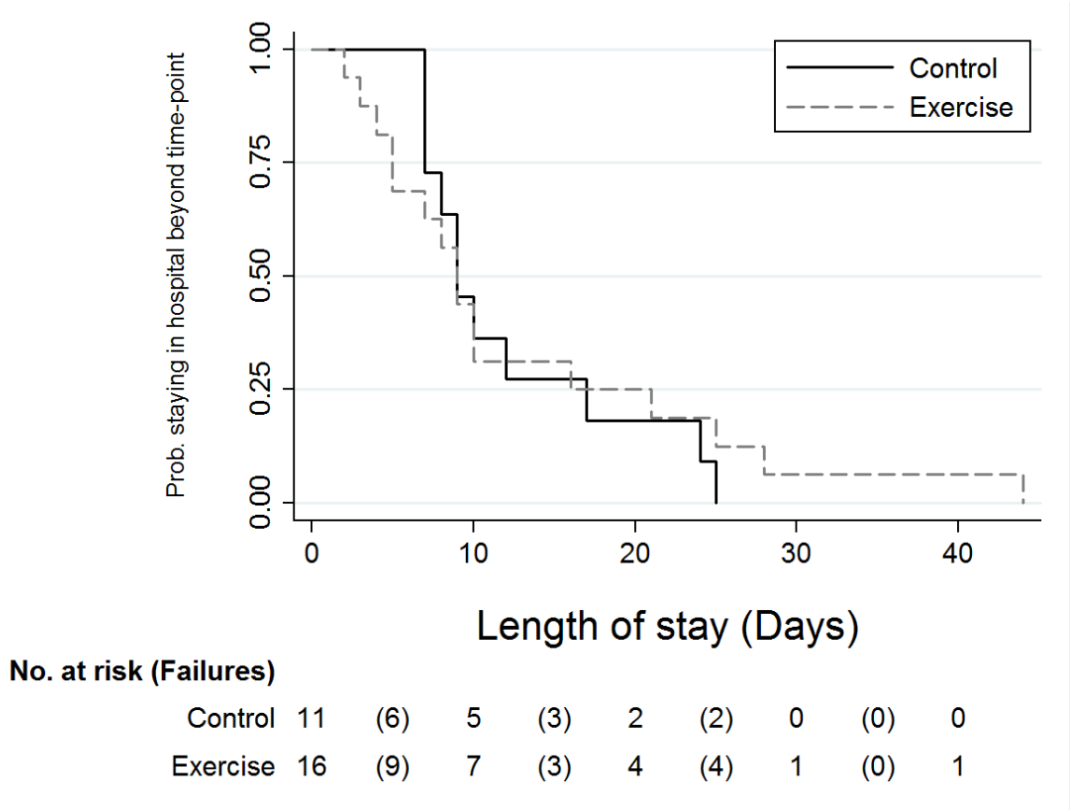


Figure 6.8 – Kaplan-Meier curve comparing length of hospital stay in days between the exercise and control groups

73% of the control group developed in hospital complications vs. 53% of the exercise group. On univariate logistic regression age, group allocation, operation method (Laparoscopic vs. Open), gender, $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak were tested (Table 6.6). None of the selected variables were found to be significantly associated with postoperative complications.

	OR (95% CI)	***p*-value**
Age	1.04 (0.95, 1.12)	0.388
Exercise/Control	0.42 (0.08, 2.16)	0.300
Laparoscopic/Open	1.37 (0.27, 6.87)	0.701
Gender	1.11 (0.21, 6.01)	0.903
$\dot{V}o_2$ at $\hat{\theta}_L$ (Week 14)	0.87 (0.63, 1.21)	0.413
$\dot{V}o_2$ at Peak (Week 14)	0.83 (0.66, 1.05)	0.128

Table 6.6 – Univariate associations between in-hospital complications (yes/no) and selected variables. OR – Odds Ratio; CI – Confidence Interval

None of the patients died within 30-days of surgery. 73% of the patients in the control group were readmitted to hospital within 30-days of being discharged. 24% of patients in the exercise group vs. 18% in the control group died within 1 year of their surgery. 41% of patients in the exercise group vs. 20% in the control group developed radiological documented distant or local metastasis within 1 year of their surgery. No statistical analysis was undertaken for 30-day or 1-year outcomes.

6.6 DISCUSSION

This interventional pilot study shows that a 6-week structured exercise programme improves objectively measured physical fitness ($\dot{V}o_2$ at $\hat{\theta}_L$ as determined by CPET) in patients scheduled for rectal cancer surgery following standardised NACRT. There was a significant mean benefit in $\dot{V}o_2$ at $\hat{\theta}_L$ of +2.12 ml.kg^{-1}.min^{-1} (95%CI +1.34 to +2.90; p<0.0001) in the exercise group at the end of the intervention period. $\dot{V}o_2$ Peak showed similar changes in the exercise group: +2.65 ml.kg^{-1}.min^{-1} (95%CI +1.19 to +4.10; p=0.0005). These changes are similar to those found in the feasibility and tolerability study (Section 5.3.2) where patients improved both $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak by +3.3 and +5.8 ml.kg^{-1}.min^{-1} respectively. The control group showed a non-significant decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.65 ml.kg^{-1}.min^{-1} (95% CI: -1.66 to +0.37; p=0.204). $\dot{V}o_2$ Peak shows similar changes in the control group worsening by -1.25 ml.kg^{-1}.min^{-1} (95% CI: -3.14 to +0.64; p=0.19). A direct comparison of $\dot{V}o_2$ at $\hat{\theta}_L$ between groups at week 6, correcting for differences in $\dot{V}o_2$ at $\hat{\theta}_L$ between the groups at Week 0, shows a difference of +2.77 ml.kg^{-1}.min^{-1} (95%CI +1.49 to +4.05; p<0.0001).

In this study the training programme was still deemed safe and feasible (96% adherence to the intervention) in this group of patients immediately post-NACRT, with no recorded adverse events after CPET or exercise sessions.

A similar deleterious effect of NACRT on physical fitness was observed, with all patients showing a significant decline in $\dot{V}o_2$ at $\hat{\theta}_L$ between baseline and Week 0 of -1.91 ml.kg^{-1}.min^{-1} (95%CI -1.27 to -2.55; p<0.0001) consistent with results in Sections 4.5.2 (-1.5 ml.kg^{-1}.min^{-1} (95%CI -1.7 to -1.2); p<0.0001) and 5.3.2 (-1.1 ml.kg^{-1}.min^{-1}), which reinforces results seen in previous pilot work (292) and with recently published data from Chapter 4 (293).

This study reinforces the concept of successful prehabilitation with exercise training to improve physical fitness after the deleterious effects of NACRT and prior to an added physiological insult of major cancer surgery. We know that poor preoperative physical fitness, reflecting poor physiological reserves, is associated with postoperative morbidity (3–5), and that rehabilitation following acute or chronic stressors (chronic obstructive pulmonary disease, chronic heart failure or myocardial infarction) (147,149,150) can improve fitness and quality of life. It therefore seems reasonable that an exercise intervention (prehabilitation) should be aimed at restoring physical fitness back to baseline levels (pre-NACRT) prior to another acute stressor (major cancer surgery). Section 2.6 of this thesis (154) concludes that preoperative aerobic exercise training is feasible, safe and tolerable in several surgical patient groups, and improves at least one measure of physical fitness. However, because of the small number of published studies, limitations in study design (few randomised controlled trials or interventional trials without a control group) and the heterogeneous reporting of interventions and outcomes, evidence is lacking on the benefits of prehabilitation on physical fitness and surgical outcome. This study strengthens this evidence with an adequately powered, controlled, blinded study which shows a clinically significant improvement in physical fitness in a high risk homogenous group of preoperative patients. This study also reports on in-hospital postoperative surgical outcomes, and length of hospital stay in both the exercise and the control groups (no significant differences found). Furthermore, none of the variables selected for univariate logistic regression (Table 6.6) were found to be significantly associated with postoperative complications. Patients in the exercise group had a better response to NACRT as opposed to the control group on re-staging mrTRG. Also, interestingly when looking at the 30-day readmission rates, 73% of the control group was readmitted to hospital (median length of readmission stay 10 days). Only 12% of the exercise group were readmitted (National Bowel Cancer Audit 2013 data for 30-day readmission rates = 24% (28)). Furthermore, long term data from this study shows an average 1 year survival (76% in the exercise group vs. 82% in the control group) (National Bowel Cancer Audit 2013 data 2 year survival rate = 86% (28)), however 1 year radiologically documented local/distant recurrence rates (41% in the exercise group vs. 20% in the control group) especially in the exercise group were deemed to be high. No statistical analysis was carried out on the out of hospital outcome measures, as this was outside the scope of this study and is only reported for completeness.

To my knowledge, this study is the first to show a significant decline in objectively measured physical fitness post-NACRT and a clinically meaningful improvement in physical fitness by using a structured, responsive, exercise training programme in patients following NACRT prior to rectal cancer surgery. Comparison of this study to similar

prehabilitation studies found in the literature is difficult, however in a randomized controlled trial of colorectal cancer patients, Carli and colleagues (156) found no differences between a structured bike and strengthening regime vs. simple walking and breathing exercises. In a subsequent observational study of a trimodal prehabilitation programme they demonstrated better postoperative walking capacity (6 min walking distance) in the intervention group (167). Other randomised studies on aerobic training in patients undergoing colonic resection showed improvement in subjectively measured oxygen uptake, peak power output and heart rate (157,158). Kothmann and colleagues (286) undertook an interventional training study in abdominal aortic aneurysm patients under surveillance. They define a minimum clinically important difference (MCID) in $\dot{V}o_2$ at $\hat{\theta}_L$ of +2.0 ml.kg^{-1}.min^{-1}. Although Kothmann significantly improved objectively measured physical fitness ($\dot{V}o_2$ at $\hat{\theta}_L$) of this high risk cohort using a moderate intensity continuous exercise training programme, they were unable to attain MCID, possibly because of too low an exercise duration and intensity (286). My aim was to return patients fitness back to pre- NACRT levels, therefore the sample size estimate was based on the changes in fitness between baseline and week 0 ($\dot{V}o_2$ at $\hat{\theta}_L$ of -1.5 ml.kg^{-1}.min^{-1} observed in my previous pilot work and in Chapter 4 of this thesis (292,293)) using an unpaired comparison with 90% power to detect a mean minimum relevant difference in $\dot{V}o_2$ at $\hat{\theta}_L$ of 1.5 ml.kg^{-1}.min^{-1}. Using a MCID of $\dot{V}o_2$ at $\hat{\theta}_L$ of 2.0 ml.kg^{-1}.min^{-1} as per Kothmann at el. the sample size was estimated at 9 patients in each group, which was deemed to be a small patient cohort. However, using a higher intensity, interval training regime of longer duration, as suggested by Kothmann and colleagues (286) a between group difference in $\dot{V}o_2$ at $\hat{\theta}_L$ at week 6 of +2.77 ml.kg^{-1}.min^{-1} (95%CI +1.49 to +4.05; $p<0.0001$) was attained which is considered to be a substantial clinically significant difference.

Another interesting finding is the clear difference between individual patient response to the exercise training programme. By examining figures 6.4B and 6.6B, we can observe a clear responder vs. non-responder difference. The mechanism of this is yet unknown. This is not to say that if a patient is a non-responder he/she is unable to improve oxygen uptake variables irrespective of the intervention. A non-responder to interval training may be a responder to continuous or resistance training with a different stimulus, however this needs to be ascertained using a multimodal exercise RCT. This observation is not novel. Carli (156) and Kothmann (286) and colleagues have described this phenomenon in their prehabilitation papers, however to date no biological mechanism has been put forward. Moreover, if the exercise group is split into responders ($\dot{V}o_2$ at $\hat{\theta}_L$ at week 6 of $\geq$2.0 ml.kg^{-1}.min^{-1}) and non-responders ($\dot{V}o_2$ at $\hat{\theta}_L$ at week 6 of <2.0 ml.kg^{-1}.min^{-1}) and then compared

to their respective mrTRG outcomes a trend towards better oncological response when patients are exercise responders is noted. This phenomenon needs further evaluation due to its potential clinical significance as this study was not powered to investigate this.

These findings have important clinically significant implications. Over time (Figure 6.2) a sharp change in fitness was observed in the first 6 weeks in the exercise group, whilst the control group was unable to recover from the physiological insult of NACRT, showing a sustained decline from Week 3 to Week 14. Moreover, the exercise group overshoots their baseline fitness ($\dot{V}o_2$ at $\hat{\theta}_L$ pre-NACRT) at Week 6, with their fitness thereafter slowly declining to baseline (pre-NACRT) levels. Thus, by Week 6 patients in the exercise group have completely recovered from the effects of NACRT on fitness, while those in the control group are now at a higher risk of adverse surgical outcome on the basis of conventional risk stratification cut-off points for $\dot{V}o_2$ at $\hat{\theta}_L$ of around 10.1 $ml.kg^{-1}.min^{-1}$ to 10.9 $ml.kg^{-1}.min^{-1}$ (120,121,144,145). Moreover, this illustrates an important point; in surgical units where CPET is part of the routine perioperative cancer pathway, rectal cancer patients usually undergo CPET prior to NACRT and not upon re-staging. Thus, fitness for surgery assessments made using pre-NACRT $\dot{V}o_2$ at $\hat{\theta}_L$ and other CPET variables might be incorrect as changes in fitness post-NACRT are not accounted for.

Strengths of this study include the homogenous nature of the study population (only operable locally advanced rectal cancer patients were included), the blinded reporting of objectively measured CPET outcome variables (blind to patient characteristics, group allocation and timeline), the blinded collection of postoperative outcomes, the prospective nature of the study, the rigorous conduct of the exercise intervention, the standardization of the NACRT regime and the statistical modeling undertaken.

Potential weaknesses include the single-centre design, the baseline differences between the exercise and the control groups in age and performance status, CR-POSSUM predicted mortality, response to NACRT, and lower peak work rates and less efficient ventilatory equivalents. Another weakness is the non-randomized design of the study. Due to the lack of randomization, the observed changes in physical fitness between the groups may be due to other group differences. Although a sensitivity analyses was performed here, this is no substitute for randomization, however, the main objective of this study was to satisfy study objectives listed in 6.2 and provide initial pilot evidence to further investigate the safety and feasibility of the exercise intervention which is useful to inform a larger multicentre randomized controlled study in the same patient cohort.

In conclusion, this study reinforces findings described elsewhere in this thesis (Sections 4.5.2 and 5.3.2, and previous published work (19,20)) showing that there is an acute significant reduction in physical fitness with NACRT. Furthermore, this study also shows that an objective improvement in physical fitness, with a clinically significant difference in $\dot{V}o_2$ at $\hat{\theta}_L$ in the exercise group at week 6 of +2.12 $ml.kg^{-1}.min^{-1}$ (95%CI +1.34 to +2.90; $p<0.0001$) can be attained with a structured exercise programme immediately post-NACRT prior to surgery. Moreover, this continues to be safe and feasible in this high risk cancer patient cohort. The exercise intervention was aimed at returning patients to a pre-NACRT level of fitness; however at week 6 baseline fitness was improved. Unfortunately, the control group, sustained the same deleterious insult of NACRT as seen in previous Sections (4.5.2 and 5.3.2), but these patients continued to register a decline in physical fitness that remained uncorrected due to the lack of a preoperative intervention. This is a novel finding in a high risk surgical cohort; however the need for a randomised controlled trial to validate these findings is now apparent. Furthermore, a larger randomised controlled trial is also necessary to investigate the role of prehabilitation on postoperative surgical and tumour outcomes.

Chapter 7

Effects of Neoadjuvant Chemoradiotherapy and a 6-week Structured Exercise Programme on *In Vivo* Mitochondrial Function – A Randomised Controlled Study

CHAPTER 7 – Effects of Neoadjuvant Chemoradiotherapy and a 6-Week Structured Exercise Programme on *In Vivo* Mitochondrial Function – A Randomised Controlled Trial

7.1 INTRODUCTION

Given the reduction in objectively measured physical fitness found in locally advanced rectal cancer patients following a period of standardized neoadjuvant chemoradiotherapy (Section 4.5 and 6.5) and the clinically significant improvement with a SRETP (as opposed to a period of no intervention in the contemporaneously recruited control group (Section 6.5)), the logical next step was to explore potential mechanisms that might account for these changes in physical fitness. Mitochondrial function as an aspect of *in vivo* skeletal muscle function was an obvious starting point (see Section 2.7 and 2.8 for background) , as no change in CPET markers of cardiac, respiratory or circulatory function were observed in this patient cohort in prior experiments presented in this thesis (Section 4.5, 5.3, 6.5) which would account for the exercise intolerance observed. Skeletal muscle function and mitochondrial energetics have been explored in chronically ill patient groups (e.g. chronic obstructive pulmonary disease (COPD), heart failure and type-2 diabetes) but not in cancer patients especially following neoadjuvant cancer treatments. Thus using similar validated, non-invasive techniques to assess *in vivo* mitochondrial function would be an acceptable and interesting pilot study in these cancer patients.

Magnetic resonance spectroscopy (MRS) methods can give information about cellular metabolism *in vivo* which is difficult to obtain by other ways. Section 2.8 of this thesis reviews the role of mitochondria in skeletal muscle energetics, while Sections 2.8.3 and 2.9 review the *ex vivo* and *in vivo* assessment methods of measuring mitochondrial function. ^{31}P MRS measurements of the post-exercise recovery kinetics of cytosolic pH and the cytosolic concentrations of phosphocreatine (PCr), orthophosphate (Pi) and ADP contain much information about muscle mitochondrial function (ATP synthesis, its regulation and abnormalities) and what might be called cellular pH homeostasis *in vivo*; however, quantitative interpretation depends on understanding the physiological basis of these measurements (196,199,212,294). ^{31}P MRS probes *in vivo* mitochondrial metabolism during rest and exercise in selected muscle groups, where the PCr recovery time constant (k_{PCr}) is taken to be a marker of *in vivo* mitochondrial function.

A different approach to probe whole body function/capacity during exercise is the use of cardiopulmonary exercise testing (reviewed in Sections 2.5.1 and 2.5.2 and data presented in

Chapters 4,5 and 6) which can be usefully combined with ^{31}P MRS (177,178) to probe different parts of the whole lungs-heart-muscle system. Furthermore, good correlations exist between *in vivo and* in *vitro* measures of mitochondrial function in health and in many chronic conditions (e.g. type-2 diabetes). This makes the estimation of mitochondrial function by ^{31}P MRS an attractive, non-invasive and reliable modality when repeated measurements need to be undertaken (178,202,203).

The pathogenesis of cancer related fatigue and reduction in fitness is complex (295,296), and the actual muscle metabolism mechanism of subjective weakness, reduced physical fitness and lack of energy remains elusive. The mechanism of the reduction in objectively measured physical fitness with NACRT (Section 4.5.2 and 6.5.1) and its improvement with structured exercise (Section 5.3.2 and 6.5.1) in this cohort of patients has never been explored prior to these experiments presented in this thesis. The work described in this chapter is designed to characterise the dynamic interrelationships between changes in whole body physical fitness (due to neoadjuvant chemoradiotherapy, structured exercise training or control periods i.e. no intervention) and *in vivo* mitochondrial function. This chapter specifically focuses on a randomised controlled study investigating; (1) the effects of NACRT on *in vivo* mitochondrial muscle function and physical fitness, and (2) the effects of a 6-week structured responsive exercise training programme or a control period (no intervention) on *in vivo* mitochondrial muscle function and physical fitness.

7.2 STUDY OBJECTIVES

The aims of this randomised controlled pilot study are to evaluate:

- the effects of NACRT on *in vivo* mitochondrial muscle function (k_{PCr}) and selected CPET variables ($\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak exercise) between baseline and Week 0; and
- the effects of a 6-week structured responsive exercise training programme or a control (no intervention) on *in vivo* mitochondrial muscle function (k_{PCr}) and selected CPET variables ($\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak) (between Week 0 and Week 6).

Primary variables of interest are $\dot{V}o_2$ at $\hat{\theta}_L$, $\dot{V}o_2$ Peak ($ml.kg^{-1}.min^{-1}$), and mean PCr recovery rate constant (k_{PCr} min^{-1}).

7.3 PATIENTS AND STUDY METHODS

Approval by the North West – Liverpool East Research and Ethics Committee (11/H1002/12b) was sought and the trial was registered with clinicaltrials.gov (NCT01859442). Written informed consent was obtained from all patients. We recruited consecutive patients between January 2013 and October 2013 who were referred to the Colorectal Multi-Disciplinary Team (MDT), age ≥18 years, with locally advanced resectable rectal cancer (circumferential resection margin threatened), scheduled for standardized NACRT on the basis of Tumour, Node, Metastasis (TNM) classification >T2/N+ with no distant metastasis (230) and WHO Performance Status < 2 (231). Predefined exclusion criteria were: inability to give informed consent, non-resectable disease, inability to perform CPET or bicycle exercise due to leg dysfunction, patients who declined surgery or NACRT, patients who received non-standard NACRT and patients who failed the MR safety screening.

TNM staging involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen and pelvis computer-aided tomography (CT) and a 1.5 Tesla pelvic MRI (Magnetom Aera, Siemens, Erlangen, Germany). All patients then underwent standardised NACRT for 5 weeks. Standardized radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a 3-dimensional conformal technique with CT guidance. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. Oral capecitabine (825 $mg.m^{-2}$) was given twice daily on radiotherapy days. No patients received brachytherapy. The colorectal multidisciplinary team (MDT) was blind to CPET results and patient allocation, which therefore did not influence perioperative management. All patients underwent total mesorectal excision (TME) surgery (232). A defunctioning stoma was constructed at the discretion of the surgeon.

Any acute toxicity whilst undergoing NACRT was discussed at the weekly colorectal MDT meeting. Toxicity events were graded according to the National Cancer Institute Common Terminology Criteria (version 3.0), and the acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system.

CPET followed a standard protocol described in Section 3.2. ^{31}P MRS scanning followed a standard protocol described in Section 3.4. Recorded patient characteristics included age, gender, height, weight, diagnosis, TNM staging, surgical procedure planned, WHO classification and ASA-PS, as well as established diagnosis of diabetes, ischaemic heart disease, cerebrovascular disease, or heart failure. Resting flow-volume loops were used to

derive Forced Expiratory Volume over 1 second (FEV1) and Forced Vital Capacity (FVC). All patients underwent CPET and a ^{31}P MRS scan at 2 weeks before NACRT (baseline) and immediately post-NACRT (Week 0). Patients were randomised 1:1 to an exercise group or control group using a random number generating software. Patients in both groups then underwent CPET at Weeks 3, and 6. Patients underwent a final ^{31}P MRS scan at Week 6. Patients in the exercise group undertook the exercise intervention continuously between Week 0 and Week 6. The study schedule is summarised in Chapter 3; Figure 3.2 and in more detail in Figure 7.1 below. CPET data were reported by two experienced assessors blind to patient characteristics and group allocation. Any CPET or exercise-related adverse events were discussed at the weekly colorectal MDT meeting. ^{31}P MRS scan analysis was performed in a blinded fashion, with the assessor blind to individual patients' clinical details, CPET variables, group allocation and MR time points (i.e. baseline (pre-NACRT), Week 0 and Week 6 (post-NACRT)).

Patients in the exercise group attended an in-hospital exercise training programme which was supervised (by a team member trained in advanced life support), structured (3 sessions/week for 6 weeks) and responsive (informed by measured work rates at $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak at Week 3). The exercise schedule is described in Section 3.3. Patients exercised in groups of two (for camaraderie), each patient being prescribed a programme tailored to individual fitness (based initially on CPET results at Week 0). After session 7 (Week 3), work rates were individually adjusted in line with mid-programme CPET results.

7.4 STATISTICAL ANALYSIS

Our aim was to recruit 12 patients (6 patients in the exercise group and 6 in the control group) who would undergo standardised NACRT, CPET and ^{31}P MRS scans at baseline (pre-NACRT), at Week 0 (immediately post-NACRT) and Week 6. Descriptive statistics are reported as mean (SD) or median and inter-quartile range (IQR) and categorical statistics as frequency (percentage). No statistical comparisons of patient characteristics between groups were undertaken. Randomization was performed by randomly assigning patients to one of the two groups (exercise vs. control) in a 1:1 fashion, using a computer-based random number generator. Randomization was done on completion of NACRT. The central investigator performed the randomization; however personnel who reported CPET and ^{31}P MRS tests were blind to the randomization sequence.

For the primary analysis, baseline and Week 0 measurements for $\dot{V}o_2$ at $\hat{\theta}_L$, $\dot{V}o_2$ Peak and k_{PCr} were compared using a paired t-test. Week 6 variables were compared between exercise and control groups using ANCOVA. Correction for Week 0 variables was done. Spearman correlations were performed between changes in haemoglobin and $\dot{V}o_2$ at $\hat{\theta}_L$ (baseline vs. Week 0). Spearman correlations were also performed between $\dot{V}o_2$ at $\hat{\theta}_L$, $\dot{V}o_2$ Peak and k_{PCr} at each time point. Formal comparisons were considered to be statistically significant at $p<0.05$. These analyses were conducted using Stata version 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.)

7.5 RESULTS

A total of 12 patients were recruited, all of whom completed the study period. Figure 7.1 illustrates a diagram depicting detailed patient flow for this study.

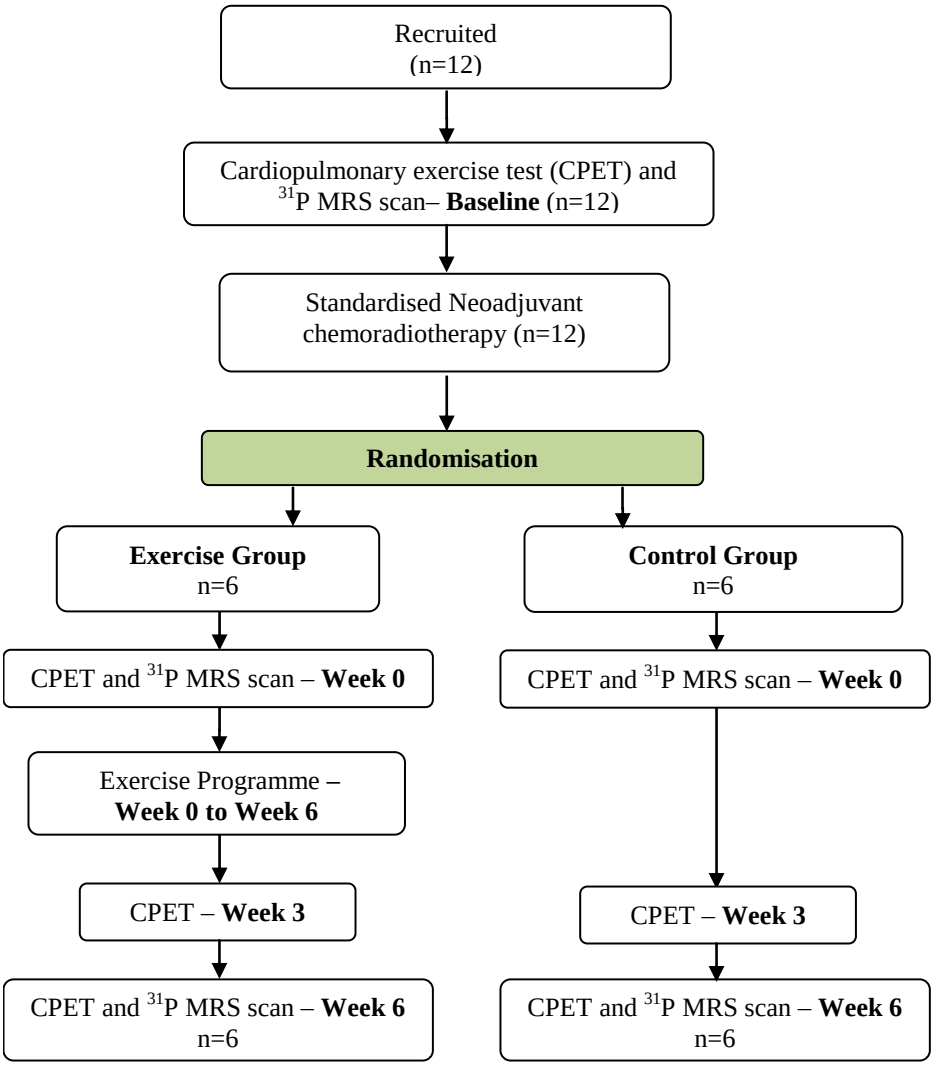


Figure 7.1 – Consort diagram

Patient characteristics are reported in Table 7.1.

	Exercise (n=6)	Control (n=6)
Age (years)[1]	67 (12.2)	70 (7.8)
Gender M:F (%)[2]	4 (67) : 2 (33)	6 (100) : 0
Smoking (%)[2]	0	2 (33)
Past Medical History[2]		
Heart Failure	0	0
Diabetes	0	1 (17)
Ischaemic heart Disease	0	2 (33)
Cerebrovascular Disease	0	0
ASA[2]		
1	3 (50)	3(50)
2	3 (50)	3(50)
WHO Performance Status[2]		
0	4 (67)	5 (83)
1	2 (33)	1 (17)

Table 7.1 – Patient characteristics; Smoking status assessed as currently smoking - yes (1) vs. no (0). [1]Values presented as mean (SD); [2] Number of patients (%). World Health Organization (WHO) Performance Status and American Society of Anaesthesiologists Score (ASA).

Table 7.2 shows changes in BMI, spirometry variables (FEV1, FVC, FEV1/FVC) and haemoglobin over the whole study period in the exercise and the control groups, along with MRI tumour staging at baseline.

	Exercise (n=6)	Control (n=6)
BMI ($kg.m^{-2}$)[1]		
Baseline	27.5 (3.6)	26.2 (4.3)
Week 0	27.1 (3.3)	25.5 (3.2)
Week 3	27.2 (3.1)	26.4 (4.2)
Week 6	27.7 (3.7)	26.6 (4.4)
FEV1 (L)[1]		
Baseline	3.0 (0.8)	3.1 (0.6)
Week 0	2.9 (1.0)	2.9 (0.8)
Week 3	3.3 (0.6)	3.1 (0.6)
Week 6	2.9 (0.8)	2.8 (0.6)
FVC (L)[1]		
Baseline	4.6 (0.9)	4.2 (0.7)
Week 0	4.6 (0.9)	3.9 (0.9)
Week 3	4.3 (0.9)	3.8 (0.7)
Week 6	4.3 (0.8)	3.8 (0.6)
FEV1/FVC (%)[1]		
Baseline	71 (8.2)	73 (6.9)
Week 0	73 (8.5)	73 (6.7)
Week 3	77 (6.2)	74 (6.4)
Week 6	71 (14.4)	73 (7.6)

Haemoglobin ($g.dl^{-1}$)[1]			
Baseline		12.8 (1.5)	13.7 (1.4)
Week 0		12.6 (1.6)	13.1 (1.5)
Week 6		12.8 (1.2)	13.1 (1.6)
Tumour distance from anal verge [1]			
<5.0 cm		4 (67)	2 (33)
5.1-10.0cm		2 (33)	3 (50)
>10.1cm		0	1 (17)
Clinical MRI TNM classification[2#]	cTx	0	0
	cT2	0	0
	cT3	5 (83)	5 (83)
	cT4	1 (17)	1 (17)
Baseline	cN0	2 (33)	1 (17)
	cN1	1 (17)	3 (50)
	cN2	3 (50)	2 (33)
	cM0	6 (100)	6 (100)

Table 7.2 – Patient and tumour characteristics; [#] with percentages in parentheses; [1] Values presented as mean (SD); [2] International Union against Cancer Tumour Node Metastasis (TNM) MRI staging.

7.5.1 CHANGES IN PHYSICAL FITNESS WITH NACRT AND EXERCISE

The median time to starting the exercise programme after completion of NACRT was 2 working days (IQR 1-6 days). The mean (SD) % adherence to the exercise programme (defined as % of the total of 18 sessions completed) was 89 (5) %. The mean % adherence to CPETs (defined as % of the total of 6 CPETs attended) was 97% in the exercise group vs. 100 % in the control group. There were no adverse events recorded following CPET or any of the exercise sessions. One patient in the exercise group only completed 5 of 18 exercise sessions. This patient sustained severe (grade 3 of 4) perineal burns and was unable to sit for prolonged periods of time, therefore was unable to adhere with the exercise programme. Table 7.3 shows changes in all CPET related variables that were measured.

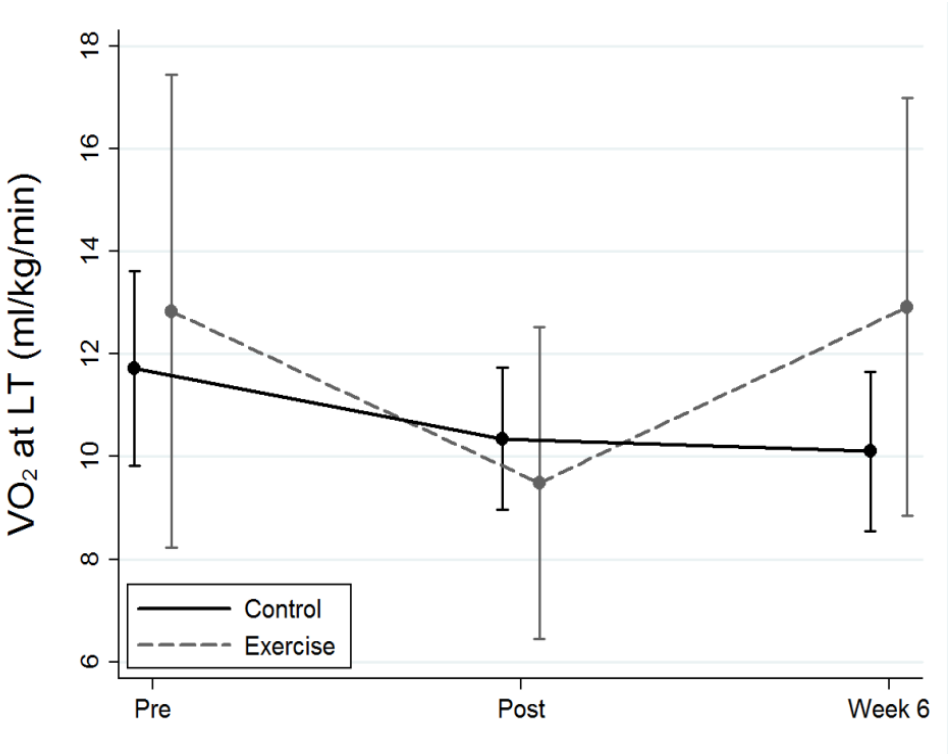
	Exercise (n=6)	Control (n=6)
k_{PCr} (min^{-1})		
Baseline	1.47 (0.5)	1.45 (0.5)
Week 0	1.05 (0.4)	1.18 (0.3)
Week 6	1.83 (0.6)	1.33 (0.7)
$\dot{V}$ **o_2 at** $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$)[1]		
Baseline	12.8 (4.6)	11.7 (1.9)
Week 0	9.5 (3.0)	10.4 (1.9)
Week 3	12.9 (3.0)	9.4 (0.8)
Week 6	12.9 (4.1)	10.1 (1.5)
$\dot{V}$ **o_2 at** $\hat{\theta}_L$ ($L.min^{-1}$)[1]		
Baseline	1.0 (0.4)	0.9 (0.2)
Week 0	0.7 (0.3)	0.8 (0.2)
Week 3	1.0 (0.3)	0.7 (0.1)
Week 6	1.0 (0.3)	0.7 (0.1)
$\dot{V}$ **o_2 Peak** ($ml.kg^{-1}.min^{-1}$)[1]		
Baseline	19.3 (8.4)	18.1 (3.4)
Week 0	14.2 (4.9)	15.3 (3.1)
Week 3	19.2 (4.7)	14.3 (2.7)
Week 6	18.8 (6.7)	15.3 (1.9)
$\dot{V}$ **o_2 Peak** ($L.min^{-1}$)[1]		
Baseline	1.5 (0.7)	1.3 (0.3)
Week 0	1.1 (0.4)	1.1 (0.3)
Week 3	1.5 (0.5)	1.0 (0.3)
Week 6	1.5 (0.5)	1.1 (0.2)
O_2 pulse at $\hat{\theta}_L$ ($ml.beat^{-1}$)[1]		
Baseline	9.0 (3.8)	8.8 (2.2)
Week 0	7.1 (2.9)	8.4 (1.1)
Week 3	9.4 (2.6)	8.1 (1.2)
Week 6	9.3 (3.2)	8.3 (1.2)
O_2 pulse at Peak ($ml.beat^{-1}$)[1]		
Baseline	10.5 (4.9)	10.5 (2.0)
Week 0	7.8 (2.8)	9.6 (0.8)
Week 3	10.7 (3.2)	9.3 (1.6)
Week 6	10.7 (4.3)	9.9 (0.9)
$\dot{V}_E/\dot{V}$ **co_2 at** $\hat{\theta}_L$ [1]		
Baseline	35.7 (7.8)	33.3 (5.0)
Week 0	34.4 (5.7)	33.9 (2.7)
Week 3	33.7 (2.3)	35.0 (3.7)
Week 6	33.8 (5.5)	34.2 (4.2)
$\dot{V}_E/\dot{V}$ **co_2 at Peak**[1]		
Baseline	36.2 (5.9)	35.7 (3.2)
Week 0	38.3 (6.1)	35.9 (3.3)
Week 3	37.0 (2.8)	35.3 (2.7)
Week 6	38.5 (5.6)	35.3 (4.0)

Baseline heart rate (beats.min^{-1})[2]		
Baseline	84 (77,92)	71 (64,75)
Week 0	77 (71,87)	61 (60,64)
Week 3	76 (71,93)	61 (60,64)
Week 6	84 (76,88)	63 (60,70)
Peak heart Rate (beats.min^{-1})[2]		
Baseline	142 (136,145)	126 (121, 133)
Week 0	141 (134,151)	113 (106, 125)
Week 3	140 (133,144)	109 (101, 127)
Week 6	135 (130,146)	108 (99,126)
Work rate at $\hat{\theta}_L$ (W)[2]		
Baseline	54 (36,82)	55 (43,71)
Week 0	56 (43,72)	52 (37,70)
Week 3	74 (70,94)	57 (39,67)
Week 6	75 (62,88)	58 (51,60)
Work rate at Peak (W)[2]		
Baseline	109 (70,156)	109 (80,123)
Week 0	113 (87, 135)	99 (70,123)
Week 3	126 (116, 172)	99 (69,124)
Week 6	126 (108, 161)	110 (91,128)

Table 7.3 – Exercise and ^{31}P MRS variables presented at all study time points. [1] Values presented as mean (SD). [2]Values presented as median (IQR). k_{PCr}, Phosphocreatine recovery time constant; $\dot{V}o_2$ at $\hat{\theta}_L$, Oxygen uptake at estimated lactate threshold; $\dot{V}o_2$ Peak, Oxygen uptake at peak exercise; O_2 pulse at $\hat{\theta}_L$, Oxygen pulse at estimated lactate threshold; O_2 pulse at Peak, Oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; $\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at peak exercise; Work rate at $\hat{\theta}_L$, Work rate at estimated lactate threshold; Work rate at Peak, Work rate at peak exercise.

$\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak were the primary outcome CPET variables. There was a significant reduction in $\dot{V}o_2$ at $\hat{\theta}_L$ (-2.36 ml.kg^{-1}.min^{-1}; 95%CI -3.78 to -0.93; p<0.0039) and $\dot{V}o_2$ at Peak (-3.95 ml.kg^{-1}.min^{-1}; 95%CI -6.79 to -1.11; p<0.0108) post-NACRT (Week 0). The exercise group showed a significant improvement in both primary endpoints during the intervention period (Week 0 to Week 6), in contrast to the worsening physical fitness in the control group (Figure 7.2 A and B).

(A)



(B)

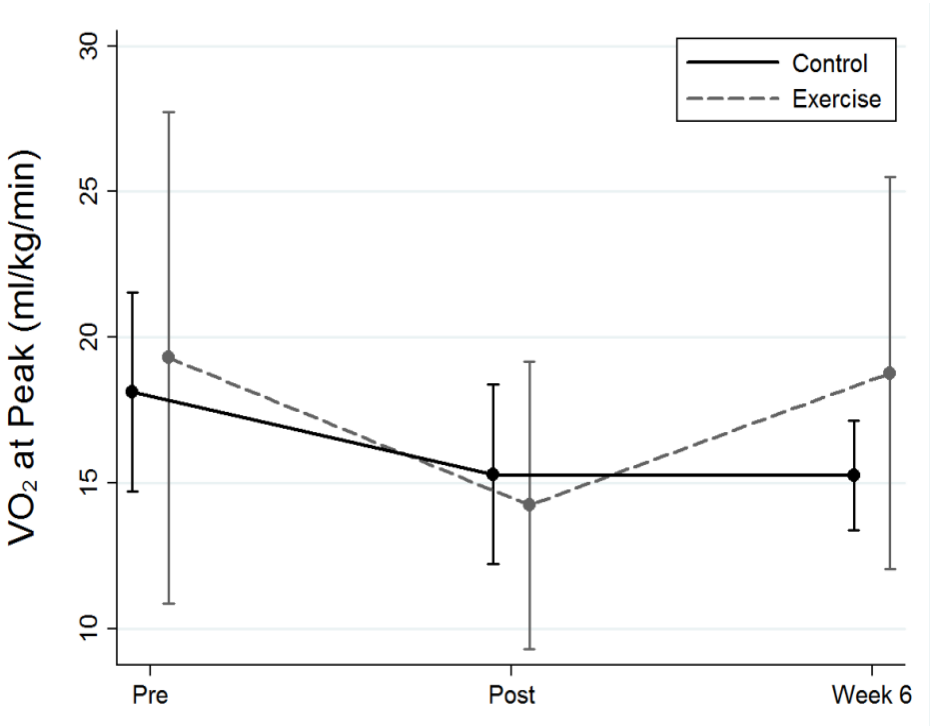


Figure 7.2A and B – Line diagram showing fitted means and SD for $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg^{-1}.min^{-1}) (A) and $\dot{V}o_2$ Peak (ml.kg^{-1}.min^{-1}) (B) at baseline (pre-NACRT), week 0 (post-NACRT) and Week 6 for the exercise (dashed line) and control groups (solid line)

During the intervention period, the exercise group improved $\dot{V}o_2$ at $\hat{\theta}_L$ by +3.43 ml.kg^{-1}.min^{-1} (95%CI +1.96 to +4.91), while the control group showed a further decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.25 ml.kg^{-1}.min^{-1} (95%CI: -1.53 to +1.03). A direct comparison of $\dot{V}o_2$ at $\hat{\theta}_L$ between groups at week 6, correcting for differences in $\dot{V}o_2$ at $\hat{\theta}_L$ between the groups at Week 0, shows a clinically significant difference of +3.85 ml.kg^{-1}.min^{-1} (95%CI +2.12 to +5.59; p=0.001). $\dot{V}o_2$ Peak shows similar changes in the exercise group: +4.53 ml.kg^{-1}.min^{-1} (95%CI +0.31 to +8.76), while the control group worsened by -0.03 ml.kg^{-1}.min^{-1} (95%CI: -2.00 to +1.93). A similar direct comparison of $\dot{V}o_2$ Peak between groups at Week 6, correcting for differences in $\dot{V}o_2$ Peak at Week 0, shows a change of +4.49 ml.kg^{-1}.min^{-1} (95%CI +0.14 to +8.84; p=0.044). Figure 7.3 displays individual patient data between baseline and week 0 for $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak, while data for individual patient data in the exercise and control groups between week 0 and week 6 for $\dot{V}o_2$ Peak and $\dot{V}o_2$ at $\hat{\theta}_L$ is displayed in Figure 7.4 and Figure 7.5 respectively.

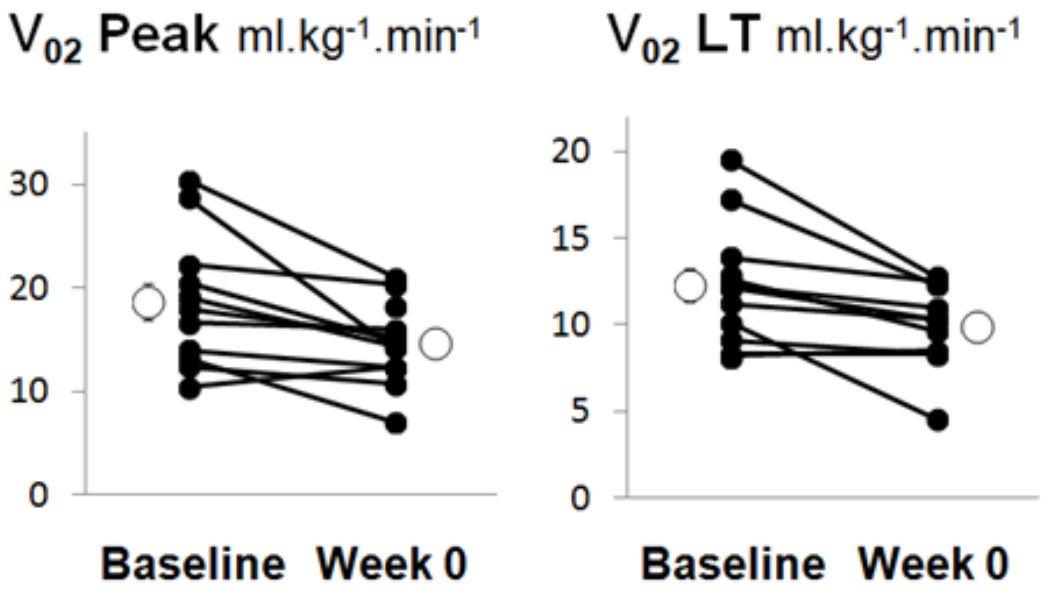


Figure 7.3: CPET variables ($\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak) Baseline (before NACRT)) and at Week 0 (post-NACRT): lines link data-points (closed circles) for individual patients, and open circles show overall mean±SEM

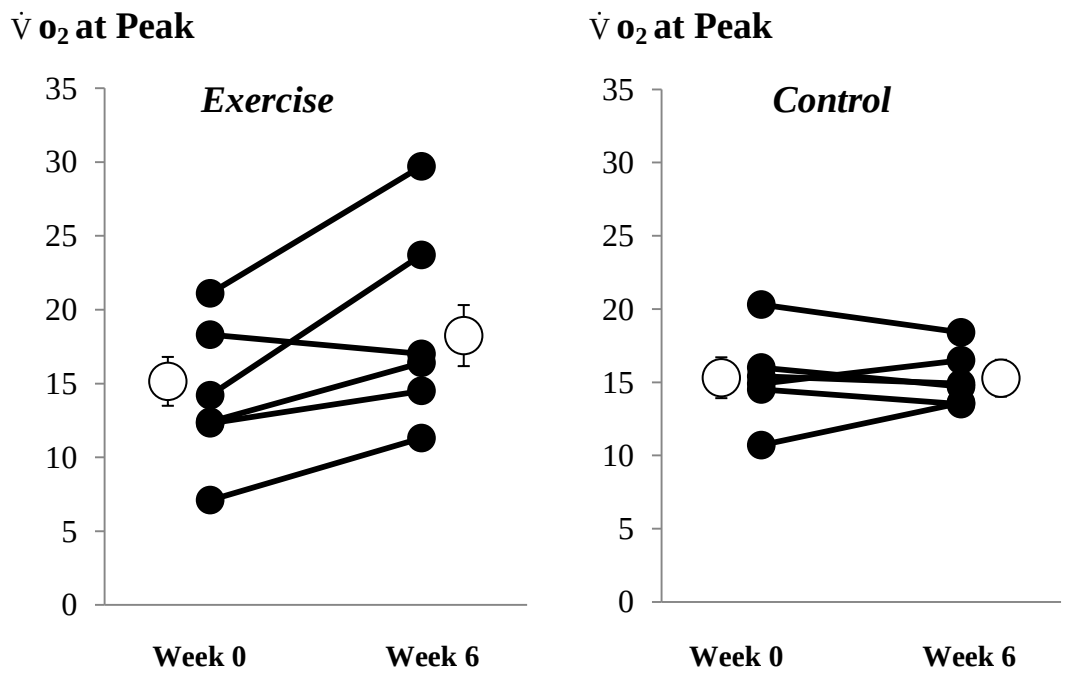


Figure 7.4: Changes in individual patient data for $\dot{V}_{O_2}$ at Peak between Week 0 (post-NACRT) and Week 6 (after 6 weeks of structured exercise or control): lines link data-points (closed circles) for individual patients, and open circles show overall mean±SEM

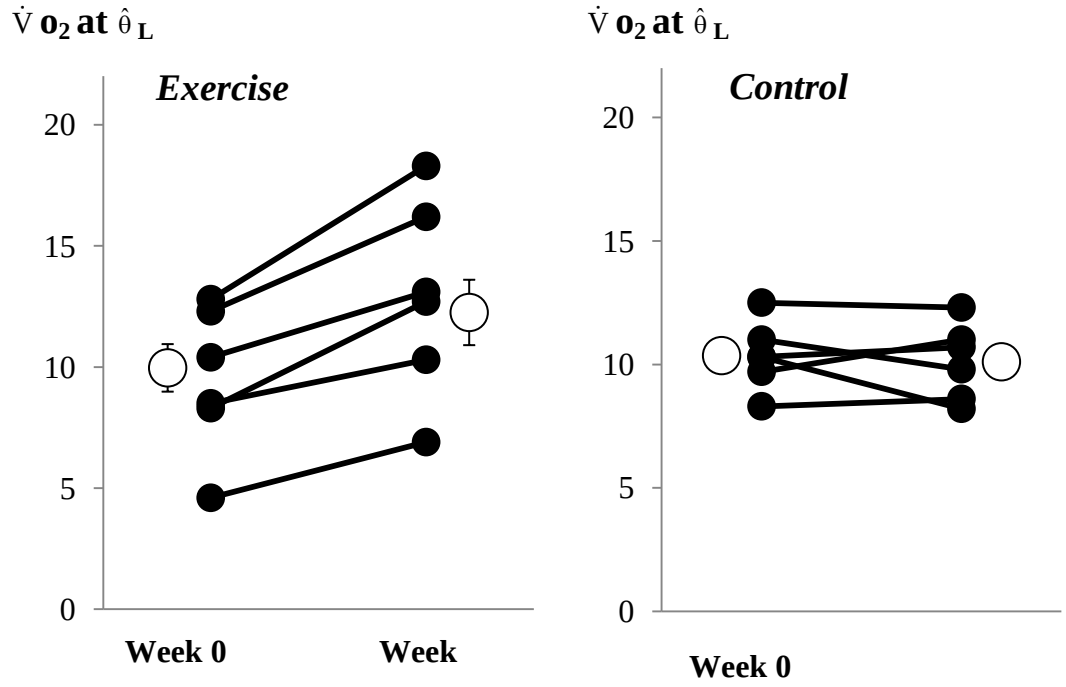


Figure 7.5: Changes in individual patient data for $\dot{V}_{O_2}$ at $\hat{\theta}_L$ between Week 0 (post-NACRT) and Week 6 (after 6 weeks of structured exercise or control): lines link data-points (closed circles) for individual patients, and open circles show overall mean±SEM

7.5.2 CHANGES IN MITOCHONDRIAL FUNCTION WITH NACRT AND EXERCISE

All ^{31}P MRS scans were undertaken at a minimum of 48 hours following the CPET (median time following CPET is 2+0.5 days). All 12 patients were adherent to all three ^{31}P MRS scans. There were no adverse events recorded following any of the scans. Figure 7.6 shows a complete time course of pH and k_{PCr} at baseline and during the whole of the exercise and recovery periods. Figures 7.7A and B show the mean fractional PCr recovery at baseline (A - pre-NACRT) and at Week 0 (B - post-NACRT) with exponential fitting. The mean fractional PCr recovery with exponential fitting has been repeated for Week 6 data however this is not shown.

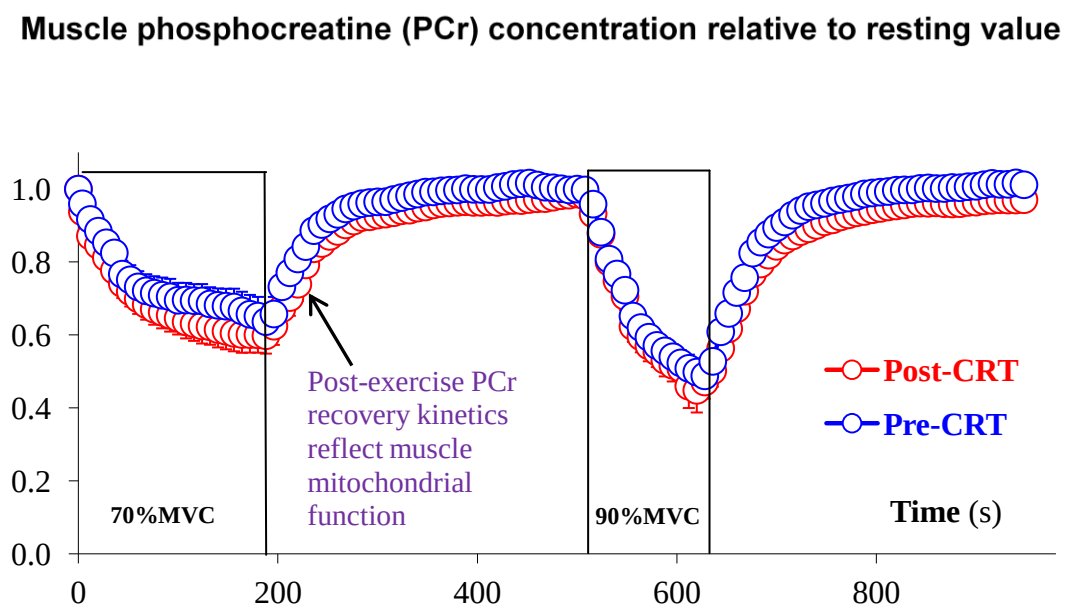


Figure 7.6 – Line graph showing time course of changes in the group mean data of k_{PCr} and pH (relative to baseline) during the experimental protocol (exercise and recovery) in response to the 2 workloads with associated kinetic fits. MVC – Maximal Voluntary Contraction

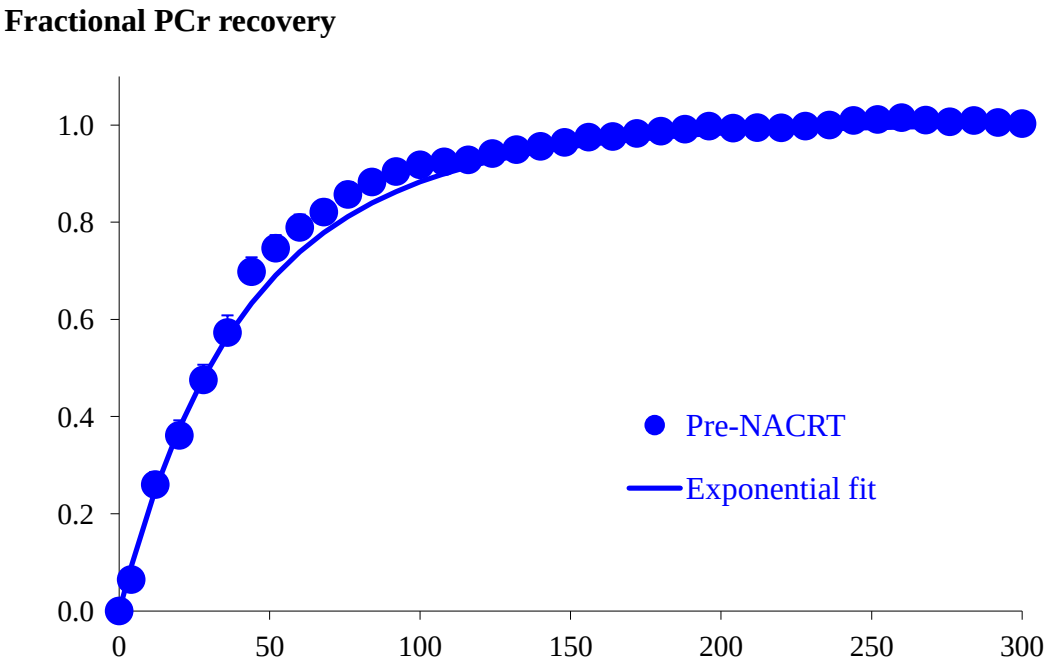


Figure 7.7A shows the mean fractional PCr recovery (min^{-1}) at baseline (pre-NACRT) showing exponential fit against time

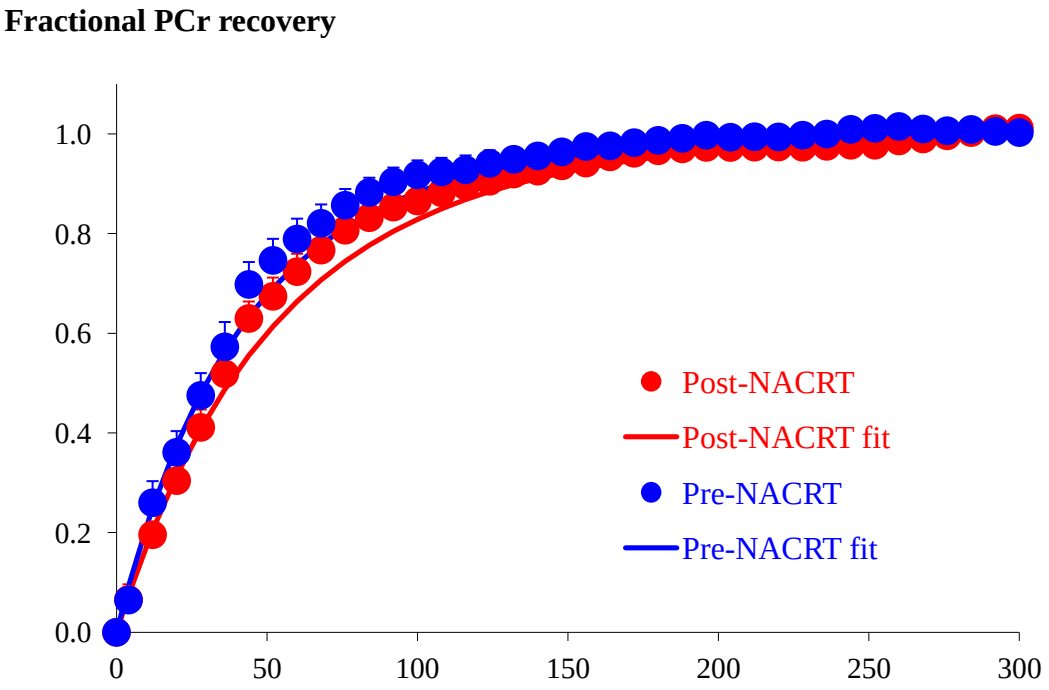


Figure 7.7B shows the mean fractional PCr recovery (min^{-1}) at Week 0 (post-NACRT) showing exponential fit against time

A statistically significant decline in k_{PCr} of -0.34 (95%CI -0.51, -0.17; p=0.0009) was found in all patients post-NACRT (between baseline and Week 0) (Figure 7.8). During the intervention period, the exercise group improved k_{PCr} by +0.78 (95%CI +0.26 to +1.31), while the control group also showed a small improvement in k_{PCr} of +0.15 (95%CI: -0.32 to +0.62). A direct comparison of k_{PCr} between groups at week 6, correcting for differences in k_{PCr} between the groups at Week 0, shows a significant difference of +0.66 (95%CI 0 to +1.31; p=0.049) (Figure 7.9A (exercise group) and Figure 7.9B (control group). A line diagram showing changes in k_{PCr} over the whole study period is shown in Figure 7.10.

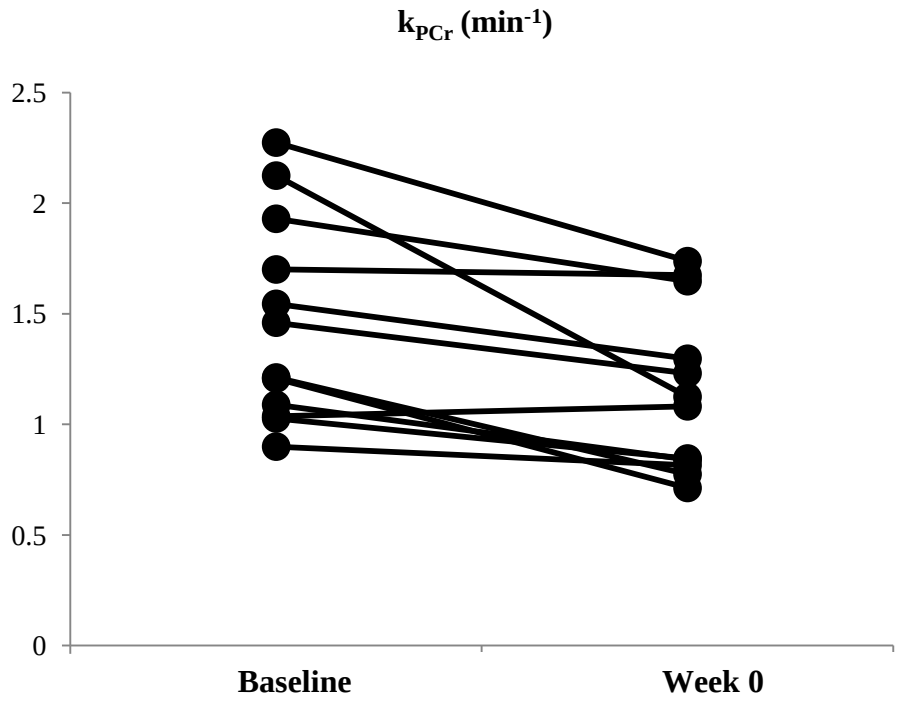


Figure 7.8: Line diagram linking data-points (closed circles) for individual patients, and overall mean±SEM (open circles) showing changes in k_{PCr} between baseline (before NACRT) and Week 0 (post-NACRT)

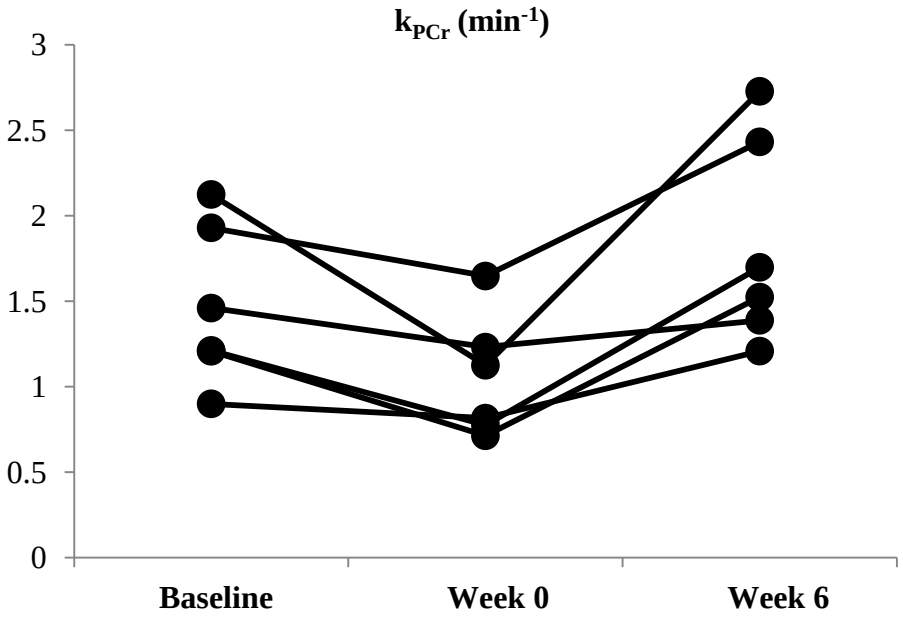


Figure 7.9A: Line diagram linking data-points (closed circles) for individual patients, and overall mean±SEM (open circles) showing changes in k_{PCr} between Week 0 (post-NACRT) and Week 6 in the exercise group

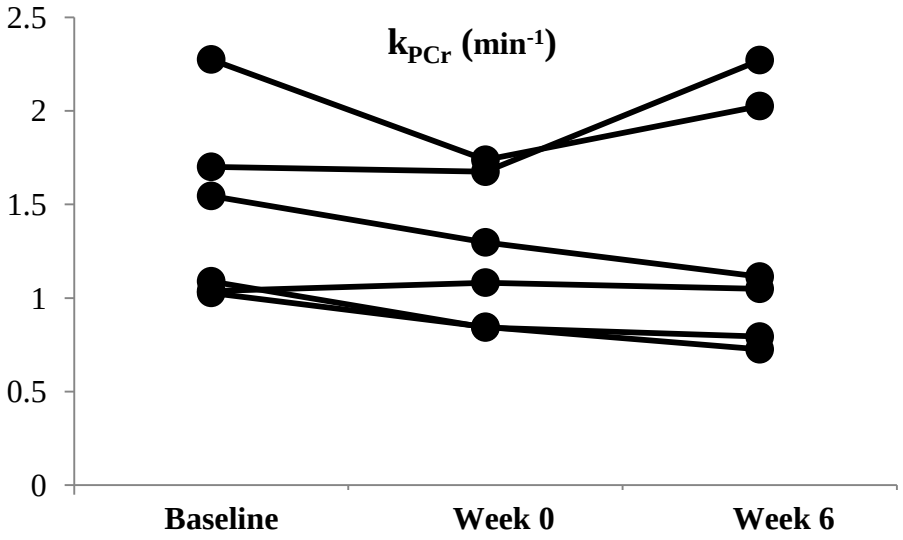


Figure 7.9B: Line diagram linking data-points (closed circles) for individual patients, and overall mean±SEM (open circles) showing changes in k_{PCr} between Week 0 (post-NACRT) and Week 6 in the control group

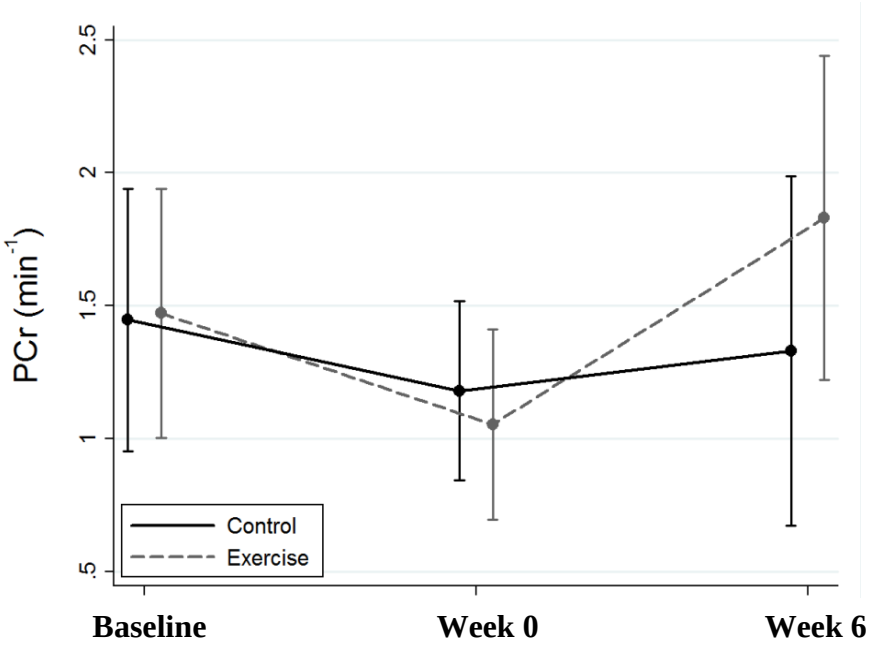


Figure 7.10 – Line diagram showing fitted means and SD for k_{PCr} at baseline (pre-NACRT), week 0 (post-NACRT) and Week 6 for the exercise (dashed line) and control groups (solid line)

No significant relationship was found between the change in $\dot{V}o_2$ at $\hat{\theta}_L$ and change in haemoglobin between baseline and Week 0 (Figure 7.11); r=0.27; p=0.396.

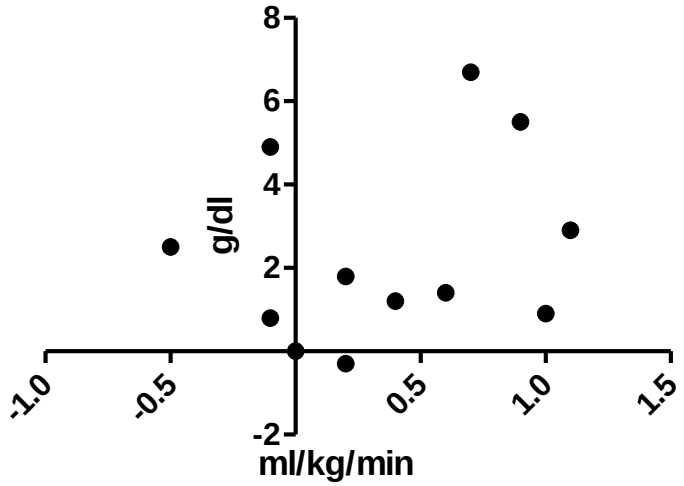
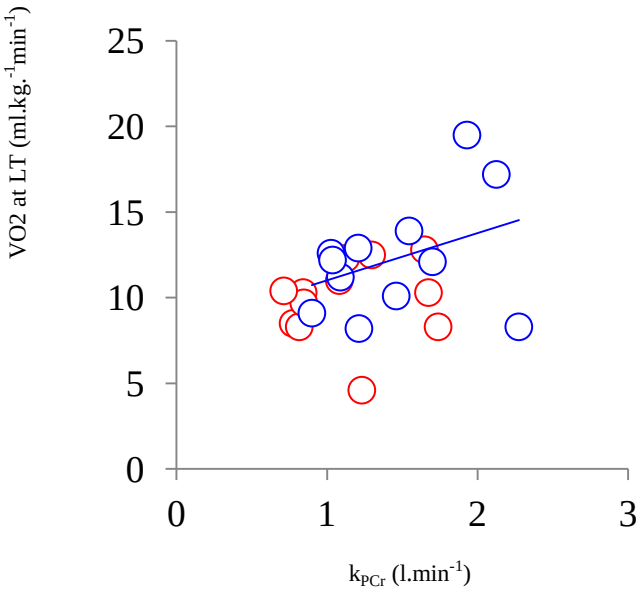


Figure 7.11 – Correlation plot showing changes in $\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$) vs. changes in haemoglobin ($g.dl^{-1}$) between baseline (pre-NACRT) and week 0 (post-NACRT)

No significant relationship was found for the whole group (SRETP plus control) between $\dot{V}o_2$ at $\hat{\theta}_L$ and k_{PCr} at the two time points before and after NACRT (Baseline - r=0.37, p=0.23; Week 0 – r=0.13, p=0.67), and between $\dot{V}o_2$ at Peak and k_{PCr} (Baseline - r=0.37, p=0.24; Week 0 – r=0.06, p=0.84) between baseline and Week 0 (Figure 7.12A and B).

(A)



(B)

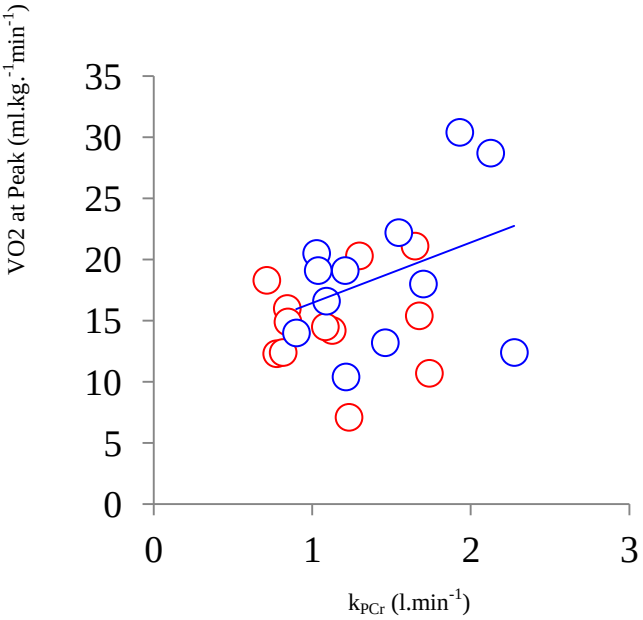
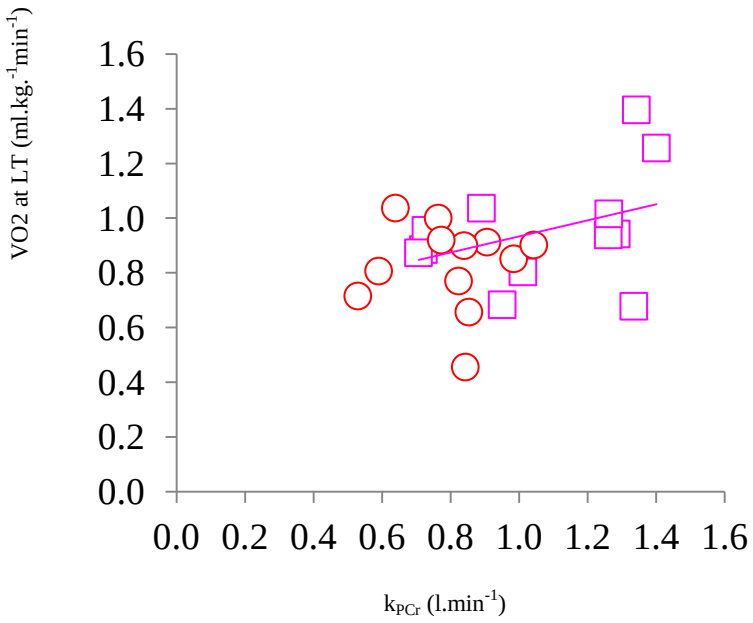


Figure 7.12A and B - Correlation plots showing changes in $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg.$^{-1}$min^{-1}) (A) and $\dot{V}o_2$ Peak (ml.kg.$^{-1}$min^{-1}) (B) vs. changes in k_{PCr} (l.min^{-1}) between baseline (Pre) and Week 0 (Post). Blue circles represent baseline whilst red circles represent Week 0 measurements.

Furthermore, no significant relationship was found for the whole group at the two later time points between the change in $\dot{V}o_2$ at $\hat{\theta}_L$ and change in k_{PCr} (Post - r=0.001, p=1.00; Week 6 – r=0.38, p=0.23), and between the change in $\dot{V}o_2$ at Peak and change in k_{PCr} (Post - r=-0.07, p=0.82; Week 6 – r=0.45, p=0.14) between Week 0 and Week 6 relative to baseline (Figure 7.13A and B).

(A)



(B)

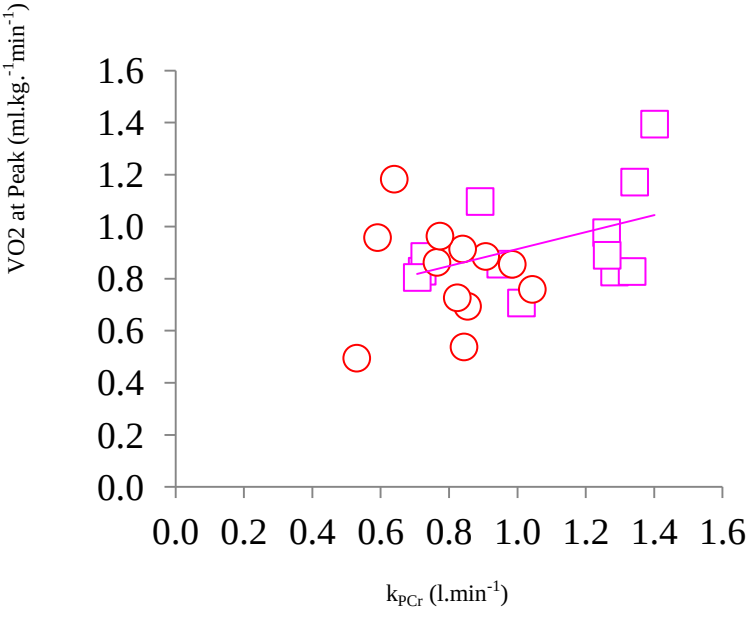
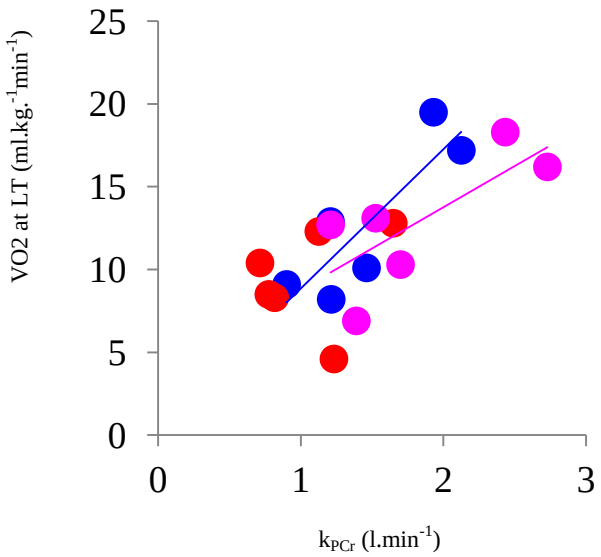


Figure 7.13A and B - Correlation plots showing relative (i.e. no change = 1.0) changes in $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg.$^{-1}$min^{-1}) (A) and $\dot{V}o_2$ Peak (ml.kg.$^{-1}$min^{-1}) (B) vs. changes in k_{PCr} (l.min^{-1}) between Week 0 (Post) and Week 6. Red circles represent Week 0 whilst pink squares represent Week 6 measurements.

When assessing the relationship between the changes in $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak and the changes in k_{PCr} across the 3 time points in the exercise group alone, a strong relationship was found for baseline ($\dot{V}o_2$ at $\hat{\theta}_L$ r=0.84, p=0.04 and $\dot{V}o_2$ at Peak r=0.86, p=0.03) and Week 6 ($\dot{V}o_2$ at $\hat{\theta}_L$ r=0.82, p=0.04 and $\dot{V}o_2$ at Peak r=0.74, p=0.08) measurements (Figure 7.14A and B). No relationship was found for Week 0 measurements.

(A)



(B)

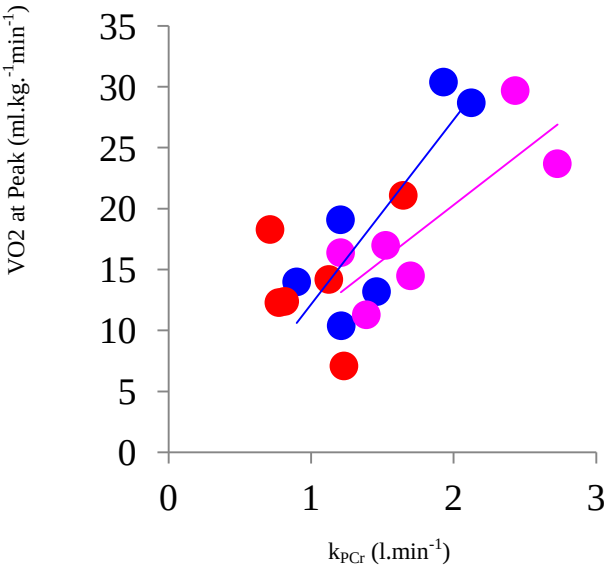


Figure 7.14A and B - Correlation plots showing changes in $\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg.$^{-1}$min^{-1}) (A) and $\dot{V}o_2$ Peak (ml.kg.$^{-1}$min^{-1}) (B) vs. changes in k_{PCr} (l.min^{-1}) between all 3 time points for the exercise group alone. Blue circles represent baseline, red circles represent Week 0, whilst pink circles represent Week 6 measurements.

7.6 DISCUSSION

This randomized controlled pilot study shows significant reductions in $\dot{V}o_2$ at $\hat{\theta}_L$ (-2.36 $ml.kg^{-1}.min^{-1}$) and $\dot{V}o_2$ at Peak (-3.95 $ml.kg^{-1}.min^{-1}$) between baseline and Week 0 (post-NACRT) in locally advanced rectal cancer patients consistent with findings observed in Section 6.5. Furthermore, also consistent with results from the study in Chapter 6, a 6-week structured exercise intervention period is shown to improve objectively measured physical fitness in patients scheduled for rectal cancer surgery following standardised NACRT. A clinically significant mean improvement in $\dot{V}o_2$ at $\hat{\theta}_L$ of +3.85 $ml.kg^{-1}.min^{-1}$ was seen in the exercise group, as opposed to the control group who showed a decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.25 $ml.kg^{-1}.min^{-1}$. Similar changes were found in $\dot{V}o_2$ at Peak.

The main objective of this chapter was to attempt to define changes in *in vivo* mitochondrial function measured by ^{31}P MRS which might underlie changes in physical fitness measured objectively by whole body measurements (using CPET). This was done in an attempt to elucidate a potential mechanistic link driving the changes in objectively measured whole body physical fitness with NACRT and the structured exercise programme. Between baseline and Week 0, a significant reduction in k_{PCr} of -0.34 was found in all patients (Figure 7.8). Between Week 0 and Week 6, the exercise group showed a significant improvement in k_{PCr} as opposed to the control group of +0.66 (Figure 7.9 A and B). These are important, novel, potentially clinically relevant findings which show changes in whole body measures of physical fitness (CPET variables) consistent with previous results in Section 4.5 (decline in fitness with NACRT), Section 5.3 (improvement in fitness with SRETP) and Section 6.5 (decline in fitness with NACRT, with an improvement in fitness in the exercise group compared with the control group). These changes in whole body measures of fitness are now seen to be consistent with changes in mitochondrial function seen in peripheral muscle. Therefore, the acute decline in mitochondrial function with NACRT (-34%) may account for the acute loss in fitness over the neoadjuvant treatment period. Moreover, over the next 6 weeks, the acute improvement in mitochondrial function observed with exercise (+71%) as opposed to no intervention (+21%), might indicate that a structured intervention immediately after NACRT arrests and ameliorates the deleterious effect of NACRT on mitochondrial function.

This pilot study was not powered to detect between-individual correlations between ^{31}P MRS and CPET measurements either at baseline, after NACRT or after SRETP (Figure 7.12 for the whole group, and Figure 7.14 for the exercise group only), or between changes in

these measurements from baseline at the latter two time points (Figure 7.13 for the whole group, and Figure 7.14 for the exercise group only). There is perhaps a suggestion of such relationships in the whole-group (Figures 7.12 and 7.13), but this fails to reach statistical significance. In the exercise group alone, however, the baseline and post-exercise data do show a significant correlation, which is not seen post-NACRT, when both variables shows a notably reduced range. The mechanism proposed here would predict such correlations in all groups, but clearly a larger study would be required to define these precisely.

7.6.1 MITOCHONDRIAL FUNCTION ALTERATION IN CHRONIC DISEASE

^{31}P MRS studies of this kind have never been attempted in cancer patients. Mitochondrial function has been shown to be impaired in patients with exercise intolerance (cramping, fatigue, muscle pain, stiffness or burning) during mild muscular exertion (297) and in chronic disease states such as cardiac failure (298) and peripheral arterial occlusive disease (209,299). ^{31}P MRS findings from chronic disease states reveal abnormalities in skeletal metabolism during exercise, more specifically in heart failure patients k_{PCr} concentrations were lower with respect to matched controls, which would indicate reduced ATP and k_{PCr} resynthesis despite a lower ATP utilization rate due to substantial lower work rates carried out by the patients. Furthermore, a lower k_{PCr} suggested impaired oxidative phosphorylation, which is hypothesised to be due to an acidic change in pH or an intrinsic change in skeletal muscle fibre type. When considering other chronic disease states such as patients with arterial insufficiency or claudication similar trends emerge; slower k_{PCr} at the end of the exercise protocol in the claudication group with respect to healthy controls, and no changes in pH indicating altered mitochondrial function (299). This was further elucidated by Kemp and colleagues (209) who found that peripheral vascular disease patients have normal muscle cross-sectional area, maximal voluntary contraction, ATP turnover and contractile efficiency (ATP turnover per force/area), larger PCr changes during exercise (i.e. increased shortfall of oxidative ATP synthesis) and slower k_{PCr} recovery (47% ± 7% [mean ± SEM] decrease in functional capacity for oxidative ATP synthesis, p=0.001), faster deoxygenation during exercise and slower post-exercise reoxygenation (59% ± 7% decrease in rate constant, p=0.0009). Results from this cohort of patients have been consistent however; arguments for the reduction in k_{PCr} have been inconsistent with interpretations ranging from a simple direct impairment of oxygen supply to exercising muscle to a more complex multifactorial interplay of intrinsic mitochondrial defects; such as change in fibre type, change in oxidative enzymes and mitochondrial damage due to oxidative stress.

Mitochondrial dysfunction has also been described in patients with COPD (300,301). These patients exhibit decrease in oxidative capacity and an excessive production of reactive oxygen species (ROS). Oxidative capacity can be directly assessed by measuring the activity of key enzymes, such as those of the citric acid cycle (Krebs cycle) (i.e., citrate synthase and succinate dehydrogenase) and β-hydroxyacyl-CoA dehydrogenase (an enzyme involved in β-oxidation of fatty acids), the concentrations of which are typically lower in patients with COPD than in healthy controls (302). Consistent with these results, the recovery time for k_{PCr} after exercise, measured by ^{31}P-MRS, is significantly prolonged (i.e., reduced oxidative capacity) in these patients (303). Reasons for this are still unclear, however causes for the overall decreased oxidative capacity and mitochondrial respiration might be due to reduced mitochondrial density (found to be lower in COPD patients than in age-matched, healthy controls (304)). The reduced mitochondrial density and oxidative capacity found in COPD patients are likely a consequence of the shift from type I fibers (slow, oxidative) to type IIx fibers (fast twitch, glycolytic) that is consistently observed in the peripheral skeletal muscle of COPD patients (304). While such muscle atrophy and loss of oxidative capacity is the typical physiological response to muscle disuse/deconditioning (305) and can be corrected with training (302,306), mechanisms for skeletal muscle dysfunction other than inactivity (i.e., inflammation, hypoxia, oxidative stress, nutrition) have been postulated and are still under debate (307,308). Similar mechanisms as the ones described above might mediate the decline in physical fitness with cancer therapies in cancer patients.

7.6.2 MITOCHONDRIAL FUNCTION ALTERATION WITH CANCER AND CANCER THERAPIES

Cancer and cancer treatments can potentially induce lean tissue degradation and abnormalities in the metabolic system in cardiac and skeletal muscle, resulting in loss of muscular weakness in cancer survivors which may resemble the muscle dysfunction discussed above. Multiple factors appear to contribute to muscle wasting and cellular dysfunction, such as generation of cytokines (tumor necrosis factor-a, interleukin 1, interleukin 6, interferon-c), fatty acid-derived eicosanoids and reactive oxygen (ROS) and nitrogen species (RNS). When generation of ROS/RNS exceeds cellular adaptive and repair capacities – a condition of oxidative stress is known to exert damaging effects to biological molecules such as nucleic acids, proteins, membrane phsopholipds etc. which may lead to deregulation of cell function or of sub cellular structures e.g. mitochondria or even whole cell death. Many cancer therapies exert an oxidative stress effect on non-targeted tissues leading to “normal tissue injury” (21). This collateral damage from cancer therapies leads to

impairment of normal tissue function, which is hypothesised to account for a reduction in fitness in our cancer cohort due to a deregulation of normal mitochondrial function. A review by Chen et al (21) suggests that a better understanding of the mechanisms involved in oxidative injury to normal tissues is essential to design intervention strategies that will attenuate the toxicity of chemotherapeutic agents without compromising their anticancer effects. This was the aim of the structured exercise training programme (SRETP) which was implemented in this chapter as well as in Chapters 5 and 6, in an attempt to attenuate the deleterious effects of NACRT on physical fitness seen consistently throughout this thesis (Chapters 4 to 7).

Another potential factor involved in cellular harm is proteolysis-inducing factor (PIF). PIF activates the ubiquitin–proteasome proteolytic pathway, which may be the proteolytic pathway for muscle breakdown in cancer patients. The interaction of tumour products, hormones and inflammatory mediators promotes gluconeogenesis, limits anabolism and increases catabolism, which contributes to the poor performance status (closely associated with fitness) of cancer survivors and threatens cancer survival (309). The loss of lean muscle mass occurs due to a decline in protein synthesis in conjunction with enhanced protein catabolism. Cancer survivors experience the decline in protein synthesis due to physical inactivity (deconditioning) coupled with a possible reduction in the supply of amino acids in protein production, while protein degradation appears to be due to an increased expression of components in the ubiquitin–proteasome proteolytic pathway. The major adaptations that occur as a result of a decline in protein synthesis and protein degradation include (a) a reduction in muscle and muscle fibre cross-sectional area as a result of a loss of myofibrils and myofilaments; (b) a loss of muscle extensibility; and (c) a decrease in proteins necessary for metabolism, especially the oxidative enzymes in the Krebs cycle and electron transport chain, leading to a reduction in the muscles' oxidative potential (309,310).

In this cohort of patients receiving both neoadjuvant chemotherapy and radiotherapy, mechanisms for the reduction in fitness might be multifactorial. It is known that in patients receiving ionising radiation as a means of thoracic cancer treatment causes excessive fibrosis, or non-healing wound responses, characterised by upregulation of a proinflammatory cascade in local tissue (311). Together with the perturbation of homoeostatic control of reactive oxygen species, this cascade of events leads to excessive deposition of extracellular matrix and collagen, vascular damage, and ischaemia. Incidental radiation damage to the heart and lungs is especially relevant to exercise tolerance; however this is not immediately evident in this cohort of locally advanced rectal cancer patients. In a prospective study of patients who received radiotherapy for left-sided breast cancer between

1998 and 2005, subclinical abnormalities in myocardial perfusion were noted in more than 50% of patients (312). Radiation can also cause pulmonary damage. Symptomatic shortness of breath following radiation occurs in about 1% of patients treated with tangents alone, but can occur in up to 5% of patients who receive local and regional (i.e. nodal) irradiation along with systemic chemotherapy (313). These adverse effects of radiation on the heart and lungs might contribute to exercise intolerance by reducing pulmonary diffusion capacity and convective oxygen delivery. No study has addressed whether radiation directly reduces cardiorespiratory fitness in patients with cancer. Miller and colleagues (314) found that 6 min walk distance, a measure of functional capacity and a common surrogate of cardiorespiratory fitness in patients with respiratory disease, was associated with pulmonary toxicity in 31 patients who received radiation treatment for inoperable lung cancer. Higher walking distance was associated with lower radiation-induced lung injury. In the patient cohort studied in this thesis, NACRT has not been shown to affect lung function as measured by spirometry or CPET ($\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$ or $\dot{V}_E/\dot{V}co_2$ at Peak) or cardiac function (O_2 Pulse at $\hat{\theta}_L$ or O_2 Pulse at Peak).

Haemoglobin concentration is another component of oxygen delivery known to be affected by chemotherapy. Anaemia can affect 30–100% of patients as a result of bone-marrow damage and lowered production of red blood cells (315). Lower haemoglobin concentrations were found to be independently associated with a lower oxygen uptake during the preoperative CPET (316). Haemoglobin was measured at baseline, Week 0 and Week 6 before CPET. None of the patients in this cohort was found to be anaemic at any time point and there were no significant differences between time points, so a reduction in oxygen delivery/uptake due to anaemia was deemed to be unlikely in this patient cohort.

Breast cancer patients receiving chemotherapy are known to suffer from acute or long-term cardiovascular complications (317). Although many of the complications do not persist after completing chemotherapy, cardiac toxicity is considered permanent and leads to reduced systolic function and diastolic filling, leaving patients at a high risk of age-related cardiac disorders in the future (318). The generation of reactive oxygen species and induction of cardiac myocyte apoptosis are thought to have a central role in this process (319). Mercuro and colleagues (320) prospectively examined early myocardial dysfunction among 16 patients undergoing anthracycline (epirubicin)-containing chemotherapy using conventional echocardiography with tissue doppler imaging integrated with biochemical markers of myocardial damage and inflammation/reactive oxygen species. Levels of inflammation and reactive oxygen species increased significantly during chemotherapy and were correlated

with change in myocardial strain. Unfavorable alterations in myocardial tissue result in impaired left ventricular ejection fraction (LVEF) and cardiac output, which in turn would reduce convective oxygen delivery. Molecular and cellular mechanism affecting cardiac muscle have been postulated to be as a result of myocyte death, myocyte injury due to reactive oxygen species, sarcomere "sarcopenia", sarcomere structure disruption, myofilament degradation due to degradation of Titin (an entopic spring element in the sarcomere that regulates length-dependent calcium sensitivity), suppression of transcription sarcomere proteins, and most importantly disruption of specific growth factors e.g. neuregulin which regulates cardiac muscle myocyte sarcomere turnover (319).

Similarly, oxidative stress produced by other chemotherapies (e.g. anthracyclines – cysplatin and epirubicin used commonly in clinical oncology practices) (21) show similar oxidative stress-mediated injury to cardiac muscle, kidneys and brain tissue. At subcellular levels, mitochondria are the main targets of chemotherapy induced oxidative stress. Electron micrographs clearly demonstrate profound damage is caused to the organelle, including mitochondrial vacuolization, mitochondrial degeneration, and disruption of the mitochondrial membrane. Mitochondrial DNA (mtDNA) is an important target for oxidative stress. Compared with nuclear DNA, mtDNA is more susceptible to oxidative damage, owing to its proximity to the site of ROS generation, its lack of introns and histones, and the limited DNA repair capacities in mitochondria (321). The heightened, oxidation sensitive mutability of mtDNA has obvious implications for cellular energy production.

The chemotherapy component of the NACRT is oral capecitabine which is known as a cytotoxic antimetabolite, which is converted into 5-fluorouracil (5-FU) and highly expressed in cancer cells, thus giving less toxicity than intravenous 5-FU, however oral Capecitabine is still known to cause hand-foot syndrome, diarrhoea, nausea, vomiting, and muscle fatigue (322). Similar mechanisms as the ones described above might be implicated in the deregulation of mitochondrial function in this cohort of patients. The only study that investigates the role of chemoradiotherapy bystander effects in tissue explants models from colorectal cancer patients is by Gorman and colleagues (323). In this study, bystander cells were exposed to media from radiation (2Gy and 5Gy) and FOLFOX (Folinic acid, fluorouracil and oxaliplatin) treated tumour and matching normal tissue. Gorman showed a significant reduction in telomere lengths and an increase in bridge formations compared to bystander cells treated with media from un-irradiated tissue (0 Gy) at 24 h. Bystander cells exposed to media from 2Gy irradiated tumour tissue showed significant depolarisation of the mitochondrial membrane potential and an increase in reactive oxygen species levels. In this study bystander cells overexpressing a mitochondrial antioxidant manganese superoxide

dismutase (MnSOD) was examined. The hypothesis being that this antioxidant could rescue the mitochondrial changes and subsequently influence nuclear instability events. Gorman found that in MnSOD treated cells, ROS levels were significantly reduced and mitochondrial membrane potential significantly increased. These events were coupled with a significant reduction in percentage of cells with anaphase bridges and also a reduction in the number of cells undergoing telomere length shortening. Using a human colorectal cancer explant tissue model, this study has demonstrated that radiation and chemotherapy bystander responses induce early genomic instability events such as telomere shortening and bridge formations coupled with mitochondrial dysfunction. These results support results found in Section 7.5.2 of this chapter, where mitochondrial function was seen to decline with NACRT and was found to improve in the exercise group as opposed to the control group. Similar cellular bystander harm may be operating in this patient cohort leading to a reduction in fitness. For our purposes exercise is likened to the antioxidant effects of MnSOD. In a review by Clarkson and colleagues (324) physical training was thought to enhance the antioxidant defense system to offset ROS induced damage by severe exercise or in this case cancer treatments which mimic these ROS.

7.6.3 EXERCISE AND MITOCHONDRIAL FUNCTION

More than 70 studies have investigated the effects of structured exercise training with a wide range of psychosocial and physiological outcomes among individuals diagnosed with cancer (325–327). The association between exercise training and improvement in quality of life, exercise capacity, physical functioning and fatigue has already been reviewed by Doherty and West, Burke and West (154,328) and in Section 2.6 of this thesis.

The effects of exercise on sequential steps within the oxygen cascade (Figure 7.15) and the molecular mechanisms that regulate exercise adaptations within each step have not yet been investigated. Cardiorespiratory fitness in oncology patients is determined by the integrative responses of all components of the oxygen cascade. Nevertheless, the relative importance of each component governing exercise tolerance may differ considerably across cancer populations according to primary site, stage, current cancer therapies, and co-morbid disease. In the largest study so far, about 17 weeks of aerobic training did not improve peak oxygen consumption among women receiving anthracycline-containing chemotherapy for early breast cancer, although peak oxygen consumption did decline by about 5% among women randomly assigned to the sedentary control group (265).

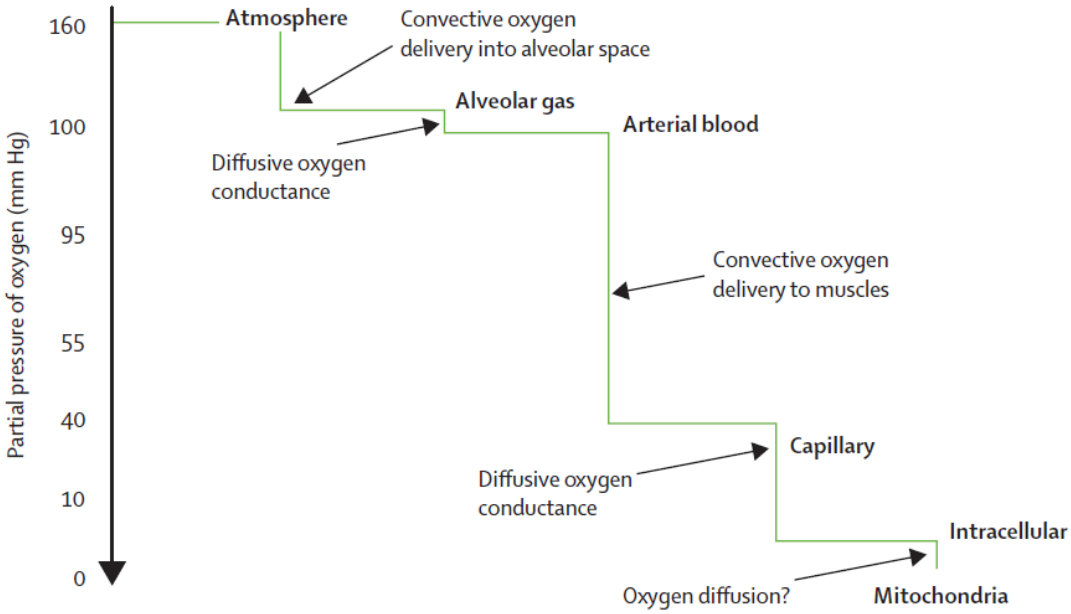


Figure 7.15 – Illustration showing sequential reduction in the partial pressure of oxygen throughout the oxygen cascade, from the air to mitochondria in muscle cells.

Similarly, Jones and colleagues found that aerobic training was associated with substantial improvements in peak oxygen consumption among postsurgical patients with non-small-cell lung cancer, but these effects were confined to those not receiving cisplatin-based adjuvant chemotherapy (329). These results suggest that either the direct or secondary effects of chemotherapy might suppress exercise-induced adaptations in components of the oxygen cascade.

Aerobic training is known to lead to improvements in cardiac morphology, including increases in ventricular mass and volume, and diastolic relaxation and filling, which increase the stroke volume and maximum cardiac output (330). Aerobic training also increases blood volume; an initial increase in plasma volume is followed by a delayed increase in red-blood-cell mass to normalise the haematocrit. The subsequent increase in haemoglobin concentration, combined with an enhanced cardiac output, will increase convective oxygen delivery independent of a change in lung diffusion capacity - assuming no diffusion limitation exists. In skeletal muscle, aerobic exercise leads to substantial augmentation of mitochondrial size and number, activity and number of aerobic enzymes, and capillary surface area. Exercise also induces a change in muscle morphology towards a more oxidative phenotype. These changes vastly improve the oxidative capacity of skeletal muscle and its ability to resynthesise ATP (176,331,332).

Cancer cells have dramatically altered cellular metabolism and have increased rates of glycolysis relative to normal cells (333). Both insulin and IGF-1 are cellular survival factors. Exercise is considered a cornerstone intervention for metabolic control. Skeletal muscle is the major tissue responsible for insulin-stimulated glucose uptake and fat oxidation and accounts for about 80% of glucose disposal under insulin-stimulated conditions. Exercise can increase glucose uptake by 20–100 times in the muscle via insulin-independent mechanisms (334). Central to this response are activation of hypoxia inducible factor-1 (HIF-1), peroxisome proliferator-activated receptor co-activator (PGC)-1a, and AMP-activated protein kinase (AMPK) which likely act in concert to stimulate mitochondrial biogenesis, oxidative phosphorylation, and cellular respiration (335). Because altered tumour-cell metabolism is strongly linked with cancer, (333) the modifying effects of exercise on metabolic control in patients with cancer, either alone or in conjunction with drugs, is an exciting avenue for future investigation.

7.6.4 STRENGHTS, WEAKNESSES AND CONCLUSION

Particular strengths of this study are the low risk of confounding by indication (123), the blinded physiological evaluations (both CPET and ^{31}P MRS reporters were blind to group allocation, timeline and data resulting from both tests), the standardization of the NACRT and the homogenous cancer cohort. Limitations lie in the small sample size (albeit only pilot in nature) and the inherent limitations in the MRS measurement. These include low signal sensitivity, limited spatial localisation, and less accurate determination of tissue metabolite concentrations in absolute terms. The 'pulse-and-acquire' (non-localised) sequence which has been used in this study offers very good temporal resolution (i.e. 8 seconds), but at the expense of limited spatial resolution. The surface coil only enables spectral collection within ~ 8 mm depth of muscle from the surface. There is no means of distinguishing between the different muscle fibre types or variations in fibre recruitment. Thus, the acquired spectra are representative of a heterogeneous pool of fibres within a sampled area which vary in their oxidative capacities and ability to produce maximal tension. Another limitation of MRS is the difficulty of determining absolute concentrations of phosphorus metabolites. There are several methods which have been used to quantify phosphorus-containing metabolites by ^{31}P MRS, briefly summarized in a recent review by Kemp and colleagues (200). In essence, k_{PCr} could be estimated by any of the following approaches: 1) from the signal ratio of PCr/ATP (making appropriate correction for saturation effect), using [ATP] (assumed from literature value) as an internal standard; 2) to use water as an internal standard, measured by ^{1}H MRS; and 3) to use external standards (phantom) in a defined sample of volume either measured in

the same experiment, or in a separate experiment but with the same volume of interest after correction for coil loading and sensitivity. In the present thesis, the first approach was adopted for the ease of implementation.

In conclusion, this randomized controlled pilot study shows a significant reduction in $\dot{V}o_2$ at $\hat{\theta}_L$ (-2.36 ml.kg^{-1}.min^{-1}) and $\dot{V}o_2$ at Peak (-3.95 ml.kg^{-1}.min^{-1}) between baseline and Week 0). Furthermore, a clinically significant mean improvement in $\dot{V}o_2$ at $\hat{\theta}_L$ of +3.85 ml.kg^{-1}.min^{-1} was seen in the exercise group, as opposed to the control group who showed a decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.25 ml.kg^{-1}.min^{-1}. Moreover, a significant, novel reduction in mitochondrial function (k_{PCr}) with NACRT (between baseline and Week 0) was found in the vast majority of patients. Mitochondrial function was significantly improved with a period of structured interval exercise training as opposed to the control group where no intervention was carried out between Week 0 and 6 post-NACRT. These important, novel, clinically relevant findings closely mirror changes in whole body measures of physical fitness objectively derived by CPET, which may account for the acute loss in fitness with NACRT and improvement in fitness with the SRETP. In conjunction these two novel findings, together with the potential mechanistic links explored above, make a rational case for a tentative link between changes found in mitochondrial function and physical fitness observed with cancer therapies and exercise in this thesis. Finally, the changes in mitochondrial function observed in this study need to be correlated with potential clinical patient benefit and surgical outcome so as to determine whether the change in mitochondrial function with exercise is associated with improved surgical outcomes.

Chapter 8

Summary, Future Work and Conclusion

CHAPTER 8 – Summary, Future Work and Conclusion

8.1 INTRODUCTION

Major surgery carries substantial morbidity and mortality, particularly in advanced cancer patients with co-morbidities (28,336–338). Outcomes after major surgery are a significant public health issue and depend on modifiable factors such as perioperative medical care, as well as fixed factors like the patients' physiological tolerance to iatrogenically induced trauma; in the form of neoadjuvant cancer treatments or major surgery. The study of physical fitness and mitochondrial function in cancer patients is novel. With recent advances in objectively measured fitness assessments (i.e. CPET), a link between poor fitness and poor surgical outcome is now clear especially in major surgical patients (3,4,144,145). Accurate perioperative fitness assessments and risk prediction allows the multidisciplinary team to ensure appropriate modification of patients' preoperative status as well as optimising intra- and postoperative management for high-risk surgical candidates. Such risk prediction also facilitates the most efficient use of scarce hospital resources, enhances the process of shared decision making before surgery (86), permits personalised (or at least stratified) patient care, and most importantly ensures the best outcome to avoid unnecessary postoperative morbidity and mortality. The assessment of patients' fitness in the perioperative setting has never been more topical, however this has never been objectively undertaken in patients undergoing neoadjuvant cancer therapies i.e. a high risk surgical cohort. Therefore, the individual needs of these patients in terms of fitness and physiological preparation for surgery has never been addressed. This thesis specifically attempts to identify and address these important fitness changes in advanced rectal cancer patients undergoing NACRT. The novel observations found in the experiments summarised below show clinically important changes in objectively measured physical fitness with neoadjuvant cancer treatment and an exercise programme. Furthermore, an interesting link between physical fitness (measured by whole body measurements) and *in vivo* mitochondrial function (measured by ^{31}P MRS) is also explored. All the experiments carried out in this thesis highlight the urgent need for accurate preoperative risk assessment as well as a tailored intervention in patients at high risk of adverse outcome following the physiological trauma of neoadjuvant cancer therapies prior to major cancer surgery.

8.1 SUMMARY AND IMPLICATIONS

In Chapter 4, 27 locally advanced rectal cancer patients were recruited. 25 patients completed CPET evaluation at baseline and post-NACRT as well as a 180-day morbidity and 1 year mortality follow up. $\dot{V}o_2$ at $\hat{\theta}_L$ (Figure 4.2) and Peak exercise (Figure 4.3) were reduced (-1.5 and -1.4 $ml.kg^{-1}.min^{-1}$ respectively; $p<0.0001$). Oxygen pulse decreased at both $\hat{\theta}_L$ (-0.7 $ml.beat^{-1}$; $p=0.005$) and Peak (-1.1 $ml.beat^{-1}$; $p=0.002$). $\dot{V}_E/\dot{V}co_2$ did not change. There was no change in median workload at $\hat{\theta}_L$ ($p=0.06$), however a reduction in maximum power (-8W; $p=0.005$) was observed. There was no change in resting or peak heart rate, spirometry and haemoglobin, and no relationship was found between changes in $\dot{V}o_2$ at $\hat{\theta}_L$ and changes in haemoglobin with NACRT ($r=0.18$; $p>0.05$). Optimal ROC cut-off values for $\dot{V}o_2$ at $\hat{\theta}_L$ and Peak of 12.0 and 18.1 $ml.kg.^{-1}min^{-1}$ respectively (Figure 4.4A and B) predicted those at risk of increased postoperative complications; this was 77% sensitive and 75% specific ($\dot{V}o_2$ at $\hat{\theta}_L$ - Area under curve (AUC) = 0.71, 95% CI 0.50-0.93; $\dot{V}o_2$ Peak – AUC = 0.75, 95% CI 0.55-0.95) for both variables. Repeating the ROC analysis with the post-NACRT variables (Figure 4.5A and B), optimal cut-off points were 10.7 and 16.7 $ml.kg.^{-1}min^{-1}$ respectively; this was 77% sensitive and 83% specific for $\dot{V}o_2$ at $\hat{\theta}_L$ (AUC = 0.72, 95% CI 0.50-0.94) and 85% sensitive and 83% specific for $\dot{V}o_2$ at Peak (AUC = 0.80, 95% CI 0.60-1.00). A logistic regression model was used to investigate the association of CPET variables with in-hospital complications. A 90% reduction in the odds of complications was observed respectively (pre-NACRT – OR 0.10, 95% CI 0.16-0.63; $p=0.01$, post-NACRT – OR 0.09, 95% CI 0.01-0.61; $p=0.01$). Fitting the same model for pre- and post- $\dot{V}o_2$ Peak (Cut-off 18.1 $ml.kg.^{-1}min^{-1}$ pre-NACRT and 16.7 $ml.kg.^{-1}min^{-1}$ post-NACRT), the odds of complications reduced by 85% and 94% respectively (pre-NACRT – OR 0.15, 95% CI 0.03-0.87; $p=0.04$; post-NACRT – OR 0.06, 95% CI 0-0.44; $p=0.006$). These data provide the first direct evidence that the benefits of NACRT in tumour downsizing may be at least partly offset by increased perioperative risk due to a reduction in physical fitness. Further, these data show that standardized and objective measurements of fitness allow an accurate preoperative assessment with high predictive power for postoperative morbidity. This chapter concludes that NACRT before rectal cancer surgery significantly reduces physical fitness (293). The observed association between reduced physical fitness and unfavourable postoperative outcome relating to both in-hospital and 180-day morbidity as well as 1-year mortality merits further study. Taken together these findings suggest that physiological reserve (the ability to increase $\dot{V}o_2$ in response to a stressor) is important for rectal cancer patients exposed to the dual challenges of NACRT

and major surgery. In addition it is recommended that the perioperative management of this cancer cohort should be altered, with emphasis placed on fitness assessment post-NACRT and on the implementation of an intervention to improve preoperative fitness.

Chapter 5 illustrates the iterative derivation process of the exercise intervention (Section 5.2). A five patient feasibility and tolerability study was also conducted (Section 5.3). This chapter shows important novel findings. Firstly and most importantly, the exercise programme was shown to improve objectively measured physical fitness in this cohort of patients' within a 6 week period following NACRT. Secondly, a similar decline in physical fitness post-NACRT (baseline vs. week 0) was observed (Figure 5.1 and 5.2). $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak declined by -1.1 and -2.9 $ml.kg^{-1}.min^{-1}$ respectively between baseline and week 0. With the SRETP (week 0 vs. week 6) an improvement in both $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ Peak by +3.3 and +5.8 $ml.kg^{-1}.min^{-1}$ was observed. Although no formal statistical analysis was undertaken, the +3.3 $ml.kg^{-1}.min^{-1}$ improvement in $\dot{V}o_2$ at $\hat{\theta}_L$ was considered to be a clinically relevant finding. The benefit of the intervention was considered of large enough magnitude to reverse the deleterious effects of NACRT. The frequency, intensity, timing and length of the exercise training programme prescribed were well tolerated. Moreover, the 98% adherence rate to the exercise programme provides initial proof of concept that the SRETP is feasible and tolerable in its duration, setting, frequency, intensity and schedule in this cohort of patients. No adverse events were encountered by starting the exercise programme immediately after finishing NACRT. Taken together these findings show that a SRETP immediately post-NACRT is feasible, tolerable and able to acutely improve physical fitness in this patient cohort.

In Chapter 6, 39 locally advanced rectal cancer patients were recruited to an interventional pilot study scheduled to undergo a standardised NACRT regime and a 6-week structured exercise programme (exercise group n=22) or a control period (n=13). A significant mean benefit in $\dot{V}o_2$ at $\hat{\theta}_L$ of +2.12 $ml.kg^{-1}.min^{-1}$ ($p<0.0001$) (Figure 6.2A) in the exercise group at the end of the intervention period was observed. $\dot{V}o_2$ Peak showed similar changes in the exercise group: +2.65 $ml.kg^{-1}.min^{-1}$ ($p=0.0005$) (Figure 6.2B). These changes are similar to those found in the feasibility and tolerability study (Section 5.3.2). The control group showed a non-significant decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.65 $ml.kg^{-1}.min^{-1}$ ($p=0.204$) (Figure 6.2A). $\dot{V}o_2$ Peak shows similar changes in the control group worsening by -1.25 $ml.kg^{-1}.min^{-1}$ ($p=0.19$) (Figure 6.2B). A direct comparison of $\dot{V}o_2$ at $\hat{\theta}_L$ between groups at week 6, correcting for differences in $\dot{V}o_2$ at $\hat{\theta}_L$ between the groups at Week 0, shows a difference

of +2.77 ml.kg^{-1}.min^{-1} (95%CI +1.49 to +4.05; p<0.0001). Changes in other CPET variables were reported (Table 6.4). In this study the training programme was still deemed safe and feasible (96% adherence to the intervention) immediately post-NACRT, with no recorded adverse events after CPET or any of the exercise sessions. Moreover, a similar deleterious effect of NACRT on physical fitness was observed, with all patients showing a significant decline in $\dot{V}o_2$ at $\hat{\theta}_L$ between baseline and Week 0 of -1.91 ml.kg^{-1}.min^{-1} (p<0.0001) consistent with results in Sections 4.5.2 and 5.3.2. When considering other exploratory outcomes, the control group had a significantly poorer tumour response to NACRT on re-staging MRI (mrTRG) (p=0.006), however there was no evidence of a statistical difference in TNM on re-staging between the two groups (p=0.822). 85% of the control group and 77% of the exercise group underwent elective surgery. This study also reports on in-hospital postoperative surgical outcomes, and length of hospital stay in both the exercise and the control groups, however no significant differences were found. Furthermore, none of the variables selected for univariate logistic regression (Table 6.6) were found to be significantly associated with postoperative complications. This was expected as the study is not powered to detect differences in such variables. However, interestingly when looking at the 30-day readmission rates, 73% of the control group was readmitted to hospital. These findings have important clinically significant implications. Over time (Figure 6.3) an acute change in fitness was observed in the first 6 weeks in the exercise group, whilst the control group was seen to be unable to recover from the physiological insult of NACRT, showing a sustained decline from Week 3 to Week 14. Moreover, the exercise group is seen to overshoot their baseline fitness ($\dot{V}o_2$ at $\hat{\theta}_L$ pre-NACRT) at Week 6, with their fitness thereafter slowly declining to baseline (pre-NACRT) levels. Thus, by Week 6 patients in the exercise group have completely recovered from the effects of NACRT on fitness, while those in the control group, are now at a higher risk of adverse surgical outcome on the basis of conventional risk stratification cut-off points. Moreover, where CPET is part of the routine perioperative cancer pathway, rectal cancer patients should undergo CPET after neoadjuvant cancer treatment as part of standard re-staging investigations so correct risk stratification is performed based upon their current preoperative fitness levels taking into account any changes with neoadjuvant cancer therapy. Furthermore this study reinforces the benefits of prehabilitation with exercise training to improve physical fitness after the deleterious effects of neoadjuvant cancer treatment prior to the added physiological insult of major cancer surgery.

In Chapter 7, 12 patients were randomized to a SRETP or to negative control (i.e. no exercise intervention) after undergoing standardized NACRT and serial measures of whole

body fitness and *in vivo* mitochondrial function. This study was specifically designed to characterise the dynamic interrelationships between changes in whole body physical fitness (due to neoadjuvant chemoradiotherapy, structured exercise training or control periods) and *in vivo* mitochondrial function in an attempt to explore potential mechanisms that accounted for the observed changes in physical fitness. This study shows significant reductions in $\dot{V}o_2$ at $\hat{\theta}_L$ (-2.36 ml.kg^{-1}.min^{-1}) and $\dot{V}o_2$ at Peak (-3.95 ml.kg^{-1}.min^{-1}) between baseline and Week 0 (post-NACRT) (Figure 7.2) consistent with findings observed in Section 6.5. Furthermore, in keeping with results from previous chapters, the 6-week structured exercise intervention period was shown to improve objectively measured physical fitness following standardised NACRT. A clinically significant mean improvement in $\dot{V}o_2$ at $\hat{\theta}_L$ of +3.85 ml.kg^{-1}.min^{-1} was seen in the exercise group, as opposed to the control group who showed a decline in $\dot{V}o_2$ at $\hat{\theta}_L$ by -0.25 ml.kg^{-1}.min^{-1}. Similar changes were found in $\dot{V}o_2$ at Peak. Between baseline and Week 0, a significant reduction in k_{PCr} of -0.34 was found (Figure 7.8). Between Week 0 and Week 6, the exercise group showed a significant improvement in k_{PCr} as opposed to the control group of +0.66 (Figure 7.9 A and B). These are important, novel, clinically relevant findings which re-confirm the changes seen in whole body measures of physical fitness (CPET variables) consistent with previous results seen in Sections 4.5 (decline in fitness with NACRT), 5.3 (improvement in fitness with SRETP) and 6.5 (decline in fitness with NACRT and an improvement in fitness in the exercise group compared with the control group). The changes in whole body measures of fitness are also consistent with changes in mitochondrial function seen in peripheral muscle. Therefore, the acute decline in mitochondrial function with NACRT may account for the acute loss in fitness over the neoadjuvant treatment period. Moreover, the dramatic improvement in mitochondrial function observed with exercise as opposed to no intervention, might indicate that a structured intervention immediately after NACRT is necessary to rescue and reverse NACRT's deleterious effect on mitochondrial function and fitness in this patient cohort.

8.2 STRENGTHS AND LIMITATIONS OF THIS PRESENTED WORK

Several strengths and novel aspects of the present work are worth highlighting.

1. Firstly, the major strength of this work lies in the consistently blinded objective physiological evaluation used to measure physical fitness by CPET. All of the CPET reporting was done by an experienced clinician scientist blind to group allocation (i.e. exercise vs. control) and timeline (i.e. baseline, Week 0,3,6,9 or 14).

2. The colorectal MDT, anaesthetists and medical staff collecting outcome data were blind to CPET results and patient group allocation, this ensured a low risk of confounding by indication (123).

3. All studies presented in this thesis consist of prospectively recruited consecutive patients who underwent a standardized NACRT regime and were of a homogenous rectal cancer staging (only operable locally advanced >T2N+ with threatened circumferential resection margins with no distant radiologically evident metastasis were included).

4. All patients in Chapters 4 and 6 underwent a comprehensive short- and medium-term follow up.

5. The novelty of the structured exercise programme is also worth highlighting. To my knowledge no other study reports an exercise training programme that starts immediately after neoadjuvant cancer therapy in an operable cancer population. The exercise programme underwent a rigorous iterative development and was tested for its feasibility and tolerability study tailoring it to the rectal cancer patient cohort described above (Chapter 5). Following the F&T study a formal prehabilitation pre-pilot study was undertaken. This also benefits from the strengths of the studies described above; however it is also worth noting the rigorous conduct of the exercise intervention and also the statistical modeling undertaken.

6. The final study (Chapter 7) also has several strengths including the detailed quantitative analysis of the ^{31}P MRS mitochondrial function data, the utilization of validated and robust MRS methodology, blinding of ^{31}P MRS reporting (to patient group allocation, CPET variables and timeline), as well as utilizing of the MRS measurement in a cancer patient cohort which has never been done before.

7. Apart from the novelty and clinical importance of the studies performed in this thesis efforts have been made to standardise and control for many variables. I believe that the robust serial analyses of physical fitness using a consistent CPET protocol, consistent delivery of the exercise intervention, consecutive recruitment of a homogenous patient cohort, controlling for neoadjuvant cancer therapies, consistent blinding and the evaluating of mitochondrial function using a standard quantitative approach are key to the high quality experiments that were undertaken

and are well reflected in the consistency of the results from the two different techniques.

The limitations of each part of this project have been acknowledged and discussed in the individual chapters however a summary of the main limitations are discussed hereunder.

1. Firstly, the single-centre design of all studies presented in this thesis might limit generalisability, as there may be specific characteristics of the study population that are not typical of other populations.

2. The baseline differences between the exercise and the control groups in Chapter 6 is a potential source of location bias.

3. The non-randomized design of the study presented in Chapter 6.

4. The observational design of studies in Chapters 4 to 6 limits generalisability.

5. The relatively small number of subjects – although adequately powered – the small sample size may increase the likelihood of non-generalisable findings. Moreover, studies presented in Chapter 4 and 6 were adequately powered to detect differences in $\dot{V}o_2$ at $\hat{\theta}_L$, however these were not designed to have a sufficient sample size to detect a link between changes in physical fitness and postoperative outcome.

6. The single type of surgery and homogenous patient cohort maybe considered as a strength for exploring potential mechanisms, however, this limits generalizability to other types of surgeries or patient cohorts.

7. The inherent limitations of ^{31}P MRS (which were discussed in Chapter 7) as opposed to *ex vivo* muscle mitochondrial respirometry should be acknowledged.

8. The randomized controlled study presented in Chapter 7 was able to demonstrate significant changes in muscle mitochondrial function *in vivo* likely to represent the major contribution to changes in whole-body aerobic fitness, however this was a pilot study, and was not powered to detect the between-individual correlations which the proposed mechanism would predict.

9. Finally, the ^{31}P MRS work presented in Chapter 7 should ideally have been corroborated with peripheral muscle biopsy tissue based mitochondrial function.

8.3 FUTURE WORK

The work described in this thesis has provided a platform for several potential future studies which may include the following areas:

Studies to clarify the deleterious effect of neoadjuvant cancer therapies – In Chapter 4 an observational study was undertaken to study the effects of NACRT on objectively measured physical fitness. This study is the first of its kind. Translating these novel findings to other cancer cohorts and other neoadjuvant cancer treatments is therefore a priority. A study by the Fit-4-Surgery Consortium, of which I am part, has undertaken a similar study in an upper gastrointestinal cancer cohort receiving neoadjuvant platinum based chemotherapy (339). Using similar methodology we have shown a similar significant decline in $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at Peak. In this group of patients this decline in fitness was significantly related to one-year mortality in patients who completed a full course of chemotherapy and surgery, suggesting that in some patients the harm of neoadjuvant cancer treatments can be sometimes outweighed by its benefits.

Studies to clarify the role of prehabilitation on surgical outcome – In Chapter 6 an interventional pre-pilot study was conducted to study the effects of a standardised NACRT regime and a 6-week structured exercise programme or a control period on physical fitness in locally advanced rectal cancer patients. Results from this chapter where used to inform a successful National Institute for Health Research, Research for Patient Benefit grant application (PB-PG-0711-25093). This larger, randomized controlled study (currently recruiting) will assess changes in physical fitness and quality of life following a 9-week exercise intervention in this patient group. Furthermore, a larger trial is also needed to investigate the effects of prehabilitation on postoperative surgical morbidity, mortality and tumour outcomes. Prehabilitation trials studying different exercise regimes with different exercise intensities and durations are also needed.

Studies to clarify the changes in health related quality of life – findings from Chapters 4 to 7 have shown changes in physical fitness with NACRT and an exercise programme. In addition all patients recruited also underwent quality of life assessments either by qualitative or quantitative measurements. This has already lead to a publication entitled “Patients’

perceptions of quality of life during active treatment for locally advanced rectal cancer: the importance of preoperative exercise" (328). A further publication amalgamating quality of life questionnaires and results from semi-structured quality of life interviews undertaken with the patients recruited for the work described in this thesis is currently in preparation. Further work to clarify the deleterious effects of NACRT, as well as the improvements in quality of life following the SRETP needs to be validated by undertaking a larger, randomized controlled trial.

Studies to clarify the changes in physical activity - changes in physical fitness might be linked to changes seen in physical fitness. Some of the patients recruited in Chapters 4, 6 and 7 underwent a period of activity monitoring as a pilot study to investigate the changes in physical activity in relation to changes in fitness with NACRT and also with exercise vs. standard care (control period) (174,175). Changes in physical activity in a colorectal cancer population have never been documented, especially when exploring the effects of neoadjuvant cancer therapies or an exercise intervention on physical activity. Further work to clarify this important clinically relevant issue needs to be done to validate these preliminary findings.

Studies to clarify the effects of exercise response on tumour volume, tumour regression and mitochondrial function – the improvement in physical fitness seen with the exercise programme might translate into a further benefit in tumour response (i.e. larger decrease in tumour volume, improved tumour regression and improved post-NACRT MRI staging) owing to potentially more favourable oxidative conditions. Further work to clarify the mechanisms of the effects of exercise in addition to neoadjuvant therapies on tumour stage and volume needs to be investigated. Furthermore, future animal and cellular work could prove invaluable in conducting chemotherapy and/or chemoradiotherapy dose intervention studies and other exercise intervention studies exploring the role of genetics, epigenetics, tumour and fitness phenotyping in various cancer orthotopic animal models.

Studies to clarify the impacts of neoadjuvant cancer therapies and exercise on mitochondrial function – the mechanistic relationship of NACRT and exercise on mitochondrial function explored in Chapter 7 should be validated in a larger randomized controlled trial. The *in vivo* measurements should be validated by using *ex vivo* techniques (e.g. muscle biopsies) in an attempt to identify a mechanism of harm caused by NACRT and the benefit caused by an exercise intervention in a cancer population. If a mechanistic link is identified, cancer therapy modulation as well as preventative protective therapies can be instigated, instead of ameliorating the deleterious effects post-hoc. This has potential clinical

implications as the harm done to patients by specific neoadjuvant cancer therapies might be avoided.

8.4 CONCLUSION

In conclusion, the work described in this thesis has studied the effects of neoadjuvant chemoradiotherapy and a structured responsive exercise training programme on physical fitness and *in vivo* mitochondrial function in resectable locally advanced rectal cancer patients. Changes in physical fitness with NACRT and a prehabilitation programme have been studied using cardiopulmonary exercise testing. The relationship between mitochondrial function and fitness has been studied using 31P MRS. The present work is the first to identify a decline in fitness with NACRT and a improvement in fitness using a novel patient tailored prehabilitation programme (as opposed to a decline in fitness with no intervention). Furthermore, the present work is also the first to successfully identify a decline of *in vivo* mitochondrial function with NACRT and an improvement using a tailored exercise programme (as opposed to a small change with no intervention). Taken together these are important, novel, clinically relevant findings. These findings suggest that physiological reserve i.e. the ability to increase oxygen uptake/utilization in response to a major stressor (NACRT) is important in this patient cohort prior to major surgery. The possibility of an exercise intervention following the insult of NACRT prior to major cancer surgery is feasible, tolerable and achievable. If there is no intervention following NACRT, a steady decline in fitness is seen, which remains uncorrected prior to a further physiological insult from major surgery. *In vivo* assessments of mitochondrial function in this patient group corroborate the results of whole body physical fitness assessments and illustrate a possible mechanism underlying changes in fitness with NACRT and tailored exercise. In this cancer cohort, the changes in fitness and mitochondrial function with NACRT will have an impact on patients' perioperative cancer pathways, timing for surgery and timing of fitness assessment prior to major surgery. Furthermore, tailored interventions to improve preoperative fitness after neoadjuvant cancer treatments should be offered to patients as part of their routine cancer treatment.

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Publications Related To This Thesis

PUBLICATIONS RELATED TO THIS THESIS

ABSTRACTS

M. West, L. Loughney, C. Barben, M. Grocott, S. Jack. *A pilot study to investigate improvements in physical fitness resulting from a 6-week structured, responsive, endurance, training programme following neoadjuvant chemoradiotherapy prior to elective rectal cancer surgery.* British Journal of Surgery 2012; 99 (Suppl. 6):83-222

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Appendices

APPENDICES

APPENDIX I: SYSTEMATIC REVIEW SEARCH STRATEGY FOR SECTION 2.4.1 AND 2.4.2

Search Strategy for Sections 2.4.1 and 2.4.2

Question title – For patients with operable rectal cancer, what is the effectiveness of preoperative short course radiotherapy or chemoradiotherapy versus surgery alone?

Review protocol (using the PICO methodology)

Population – Patients with operable rectal cancer
Intervention – Preoperative RT or NACRT
Comparison – Surgery alone with RT or NACRT
Outcomes – Survival, local control, morbidity, Quality of life, second malignancies

All titles and abstracts were reviewed by 2 reviewers (MW and LL), full articles were reviewed by the same two reviewers and any discrepancies were resolved before the final articles were included. The date limit was set (after consultation with Steven Kerr - Senior Librarian at the Royal College of Surgeons, Edinburgh) from 1990 onwards as it was considered that this was when relevant data for current practices became available. All searches were done with the help of Steven Kerr.

Exclusion criteria:

Comparisons in studies not relevant to PICO
Population not relevant to PICO
Outcomes not relevant to PICO
Foreign language studies not in English
Expert reviews

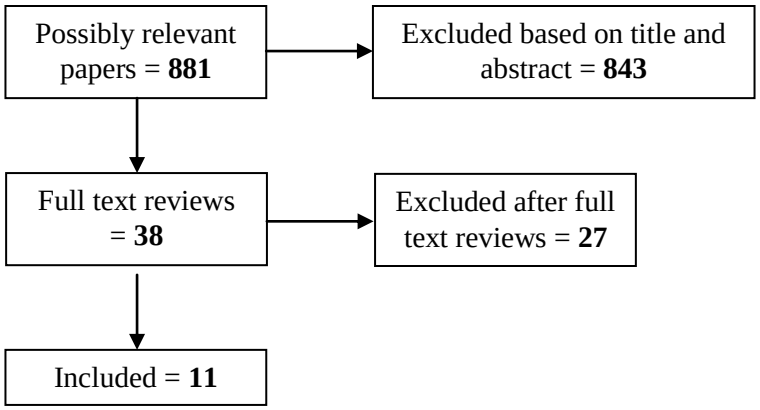
Medline search strategy *(This search strategy is adapted to each database.)*
Rectal Cancer AND Preoperative Therapy
1. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
2. exp Rectal Neoplasms/
3. operable rectal cancer*.tw.
4. 1 or 2 or 3
5. exp Drug Therapy/
6. exp Antineoplastic Agents/
7. exp Neoadjuvant Therapy/

8. exp Antineoplastic Combined Chemotherapy Protocols/
9. neoadjuvant chemotherapy*.tw.
10. exp Radiotherapy/
11. (radiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
12. neoadjuvant radiotherap*.tw.
13. chemoradiotherapy.mp.
14. (chemoradiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
15. neoadjuvant chemoradiotherap*.tw.
16. (short course radiotherap* or short term radiotherap*).tw.
17. hyperfraction* radiotherap*.tw.
18. exp Combined Modality Therapy/
19. exp Dose Fractionation/
20. exp Radiotherapy Dosage/
21. exp Preoperative Care/
22. (care adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
23. exp Treatment Outcome/
24. exp Comparative Effectiveness Research/
25. exp Postoperative Complications/
26. exp Risk Factors/
27. exp Prospective Studies/
28. exp Follow-Up Studies/
29. Or/5-28
30. 4 and 29
RCT and SR filters were applied to the search strategy.

Search Outputs

Database	Dates Covered	Number of references found	Number of references retrieved
Medline	1990- 12/2012	2680	456
Embase	1990- 12/2012	2572	327
Cochrane	1990- 12/2012	101	29
Cinahl	1990- 12/2012	93	50
Web of Science (SCI and SSCI) and ISI Proceedings	1990- 12/2012	1241	281

Total references retrieved (after removal of duplicated articles) – <u>881</u>



Quality of included studies:

Cochrane reviews = 1
Systematic review of randomised controlled trials = 3
Randomised controlled trials = 7

APPENDIX II: SYSTEMAIC REVIEW SEARCH STRATEGY FOR SECTION 2.4.3

Search Strategy for Section 2.4.3

Question title – For patients with locally advanced rectal cancer is preoperative radiotherapy or preoperative chemoradiotherapy more effective than immediate surgery alone?

Review protocol (using the PICO methodology)

Population – Patients with locally advanced operable rectal cancer
Intervention - Preoperative RT or NACRT
Comparison – Surgery alone with RT or NACRT
Outcomes – Quality of surgery, Safety, Risk, Survival, Local control, Morbidity, Quality of life, Local recurrence, Toxicity

All titles and abstracts were reviewed by 2 reviewers (MW and LL), full articles were reviewed by the same two reviewers and any discrepancies were resolved before the final articles were included. The date limit was set (after consultation with Steven Kerr - Senior Librarian at the Royal College of Surgeons, Edinburgh) from 1997 onwards as it was considered that this was when relevant data for current practices became available. All searches were done with the help of Steven Kerr.

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Population not relevant to PICO
Outcomes not relevant to PICO
Foreign language studies not in English
Expert reviews
Abstract only

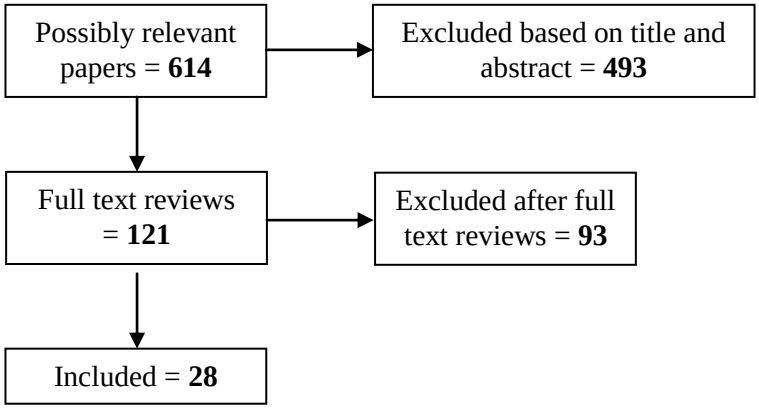
Medline search strategy *(This search strategy is adapted to each database.)*
Locally advanced Rectal Cancer AND (Preoperative Radiotherapy OR Preoperative Chemotherapy OR Preoperative Chemoradiotherapy)
1. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
2. exp Rectal Neoplasms/
3. 1 or 2
4. locally advanced.mp.
5. non metastatic.mp.
6. 5 or 4
7. exp Drug Therapy/
8. exp Antineoplastic Agents/
9. exp Angiogenesis Inhibitors/

10. exp Neoadjuvant Therapy/
11. exp Antineoplastic Combined Chemotherapy Protocols/
12. neoadjuvant chemotherapy*.tw.
13. exp Leucovorin/
14. leucovorin*.tw.
15. Bevacizumab*.tw.
16. oxaliplatin*.tw.
17. exp Fluorouracil/
18. (Fluorouracil* or 5-FU*).tw.
19. folinic acid*.tw.
20. 10 or 8 or 16 or 11 or 19 or 14 or 13 or 7 or 17 or 18 or 15 or 9 or 12
21. exp Radiotherapy/
22. (radiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
23. neoadjuvant radiotherap*.tw.
24. chemoradiotherapy.mp.
25. (chemoradiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
26. neoadjuvant chemoradiotherap*.tw.
27. 25 or 22 or 21 or 24 or 26 or 23
28. 27 or 20
29. 6 and 3
30. 28 and 29
31. limit 30 to yr="1997 - 2011"
RCT, SR and OS filters were applied to this search strategy.

Search Outputs

Database	Dates Covered	Number of references found	Number of references retrieved
Medline	1997 - 12/2012	929	261
Embase	1997 - 12/2012	772	218
Cochrane	1997 - 05/2013	176	90
Cinahl	1997 - 12/2012	388	90
Web of Science (SCI and SSCI) and ISI Proceedings	1997 - 12/2012	979	256

Total references retrieved (after removal of duplicated articles) – <u>614</u>



Quality of included studies:

Cochrane reviews = 3
Case Series/Phase II trials = 24
Review articles = 1

APPENDIX III: SYSTEMAIC REVIEW SEARCH STRATEGY FOR SECTION 2.4.3.3

Search Strategy for Section 2.4.3.3

Question title – Preoperative patient fitness relates to surgical outcome in gastrointestinal cancer patients who underwent neoadjuvant chemotherapy, radiotherapy or both.

Review protocol (using the PICO methodology)

Population – Patients with gastrointestinal cancer
Intervention - Preoperative RT or NACRT
Comparison – Surgery alone with RT or NACRT
Outcomes – Quality of surgery, Safety, Risk, Survival, Local control, Morbidity, Quality of life, Local recurrence, Toxicity, Surgical Outcomes, Fitness

All titles and abstracts were reviewed by 2 reviewers (MW and LL), full articles were reviewed by the same two reviewers and any discrepancies were resolved before the final articles were included. No date limit was set (after consultation with Steven Kerr - Senior Librarian at the Royal College of Surgeons, Edinburgh). All searches were done with the help of Steven Kerr. Due to the high number of hits produced by the first search (n=1513), we added a second search tier looking specifically for MESH terms relating to the 1st search and markers of physical fitness (lactate threshold, cardiopulmonary exercise testing, Duke's score, shuttle walk, metabolic equivalents, exercise, anaerobic, aerobic, WHO performance status). This brought the hits down to 524.

Exclusion criteria:

Comparisons in studies not relevant to PICO
Population not relevant to PICO
Outcomes not relevant to PICO
Foreign language studies not in English
Expert reviews
Abstract only

Medline search strategy *(This search strategy is adapted to each database.)*

Full-Text Search Terms

- Neoplasm* OR malignan* OR cancer* OR carcino*
- Chemother* OR Adjuvan* OR "Radiother* OR chemoradiotherap*
- Surger* OR surgical* OR surgeon* OR *operat* OR procedur*

- Outcom* OR Assess* OR complication* OR Mortalit* OR Morbidit*OR Postop*
- (lactat* AND threshold*) OR (cardiopul* AND exercis*) OR (duke* AND activit*) OR (shuttl* AND walk*) OR (6 AND walk*) OR (six AND walk*) OR ("Metabol* AND Equivalen*) OR Fitness OR Athlet* OR Exercis* OR Anaerobic* OR aerobic*)

Title/Mesh Terms – 1st Search

- (Neoplasm* [ti] OR malignan* [ti] OR cancer* [ti] OR carcino* [ti]) OR (Neoplasm* [mesh] OR malignan* [mesh] OR cancer* [mesh] OR carcino* [mesh])
- (Chemother* [ti] OR Adjuvan* [ti] OR "Radiother* [ti] OR chemoradiotherap* [ti]) OR (Chemother* [mesh] OR Adjuvan* [mesh] OR "Radiother* [mesh] OR chemoradiotherap* [mesh])
- (Surger* [ti] OR surgical* [ti] OR surgeon* [ti] OR * operat* [ti] OR procedur* [ti]) OR (Surger* [mesh] OR surgical* [mesh] OR surgeon* [mesh] OR * [mesh]operat* [mesh] OR procedur* [mesh])
- (Outcom* [ti] OR Assess* [ti] OR complication* [ti] OR Mortalit* [ti] OR Morbidit* [ti] OR Postop* [ti]) OR (Outcom* [mesh] OR Assess* [mesh] OR complication* [mesh] OR Mortalit* [mesh] OR Morbidit* [mesh] OR Postop* [mesh])

Title/Mesh Terms – 2nd Search

- (lactat* [ti] AND threshold* [ti]) OR (cardiopul* [ti] AND exercis* [ti]) OR (duke* [ti] AND activit* [ti]) OR (shuttl* [ti] AND walk* [ti]) OR (6 AND walk* [ti]) OR (six AND walk* [ti]) OR ("Metabol* [ti] AND Equivalen* [ti]) OR Fitness OR Athlet* [ti] OR Exercis* [ti] OR Anaerobic* [ti] OR aerobic* [ti])
- (lactat* [mesh] AND threshold* [mesh]) OR (cardiopul* [mesh] AND exercis* [mesh]) OR (duke* [mesh] AND activit* [mesh]) OR (shuttl* [mesh] AND walk* [mesh]) OR (6 AND walk* [mesh]) OR (six AND walk* [mesh]) OR ("Metabol* [mesh] AND Equivalen* [mesh]) OR Fitness OR Athlet* [mesh] OR Exercis* [mesh] OR Anaerobic* [mesh] OR aerobic* [mesh])
- (lactat* AND threshold*) OR (cardiopul* AND exercis*) OR (duke* AND activit*) OR (shuttl* AND walk*) OR (6 AND walk*) OR (six AND walk*) OR ("Metabol* AND Equivalen*) OR Fitness OR Athlet* OR Exercis* OR Anaerobic* OR aerobic*)

Search History

#64 Search Outcom* OR Assess* OR complication* OR Mortalit* OR Morbidit* OR Postop* Limits: English 11:07:45 3631591

#63 Search Outcom* OR Assess* OR complication* OR Mortalit* OR Morbidit*OR Postop* Limits: English 11:07:26 3602711

#62 Search (lactat* AND threshold*) OR (cardiopul* AND exercis*) OR (duke* AND activit*) OR (shuttl* AND walk*) OR (6 AND walk*) OR (six AND walk*) OR ("Metabol* AND Equivalen*) OR Fitness OR Athlet* OR Exercis* OR Anaerobic* OR aerobic*) Limits: English 11:06:35 373975

#61 Search Surger* OR surgical* OR surgeon* OR operat* OR procedur* Limits: English 11:05:02 2307338

#60 Search Chemother* OR Adjuvan* OR "Radiother* OR chemoradiotherap* Limits: English 11:04:50 410411

#59 Search Neoplasm* OR malignan* OR cancer* OR carcino* Limits: English 11:04:21 1906608

#58 Search Neoplasm* [ti] OR malignan* [ti] OR cancer* [ti] OR carcino* [ti] Limits: English 11:01:48 714998

#57 Search #55 OR #39 Limits: English 10:58:13 24

#56 Search #55 OR #39 10:57:38 28

#55 Search (#20 OR #46) AND (#38 OR #50) 10:54:39 28

#50 Search (lactat* [ti] AND threshold* [ti]) OR (cardiopul* [ti] AND exercis* [ti]) OR (duke* [ti] AND activit* [ti]) OR (shuttl* [ti] AND walk* [ti]) OR (6 [ti] OR (six [ti]) AND walk* [ti]) OR ("Metabol* [ti] AND Equivalen* [ti]) OR Fitness[ti] OR Athlet* [ti] OR Exercis* [ti] OR Anaerobic* [ti] OR aerobic* [ti]) 10:50:36 113502

#54 Related Citations for PubMed (Select 16822992) 10:40:18 180

#52 Search Perioperative Chemotherapy versus Surgery Alone 10:39:12 60

#46 Search #44 AND #45 10:38:24 498

#51 Search #46 AND #50 10:32:05 0

#49 Search #46 AND #38 10:26:38 0

#48 Search #44 AND #45 AND 2006 AND Perioperative [ti] 10:25:22 3

#47 Search #44 AND #45 AND 2006 10:24:45 173

#45 Search Outcom* [ti] OR Assess* [ti] OR complication* [ti] OR Mortalit* [ti] OR Morbidit* [ti] OR Postop* [ti] 10:23:43 529772

#44 Search #40 AND #41 AND #42 10:21:22 4391

#43 Search #40 AND #41 OR #42 10:20:54 628985

#42 Search Surger* [ti] OR surgical [ti] OR surgeon* [ti] OR operat* [ti] OR procedur* [ti] 10:20:17 564332

#41 Search Chemother* [ti] OR Adjuvan* [ti] OR "Radiother* [ti] OR chemoradiotherap* [ti] 10:20:04 125076

#40 Search Neoplasm* [ti] OR malignan* [ti] OR cancer* [to] OR carcino* [ti] 10:19:48 1334276

#39 Search #20 AND #38 09:51:18 11

#38 Search #32 OR #33 OR #34 OR #35 OR #36 OR #37 09:50:27 71217

#37 Search lactat* [ti] AND threshold* [ti] 09:46:57 285

#36 Search cardiopul* [ti] AND exercis* [ti] 09:46:24 623

#35 Search duke* [ti] AND activit* [ti] 09:45:57 13

#34 Search shuttl* [ti] AND walk* [ti] 09:45:33 62

#33 Search (6 [ti] OR six [ti]) AND walk* [ti] 09:45:09 511

#32 Search "Metabolic Equivalent"[Mesh] OR "Physical Fitness"[Mesh] OR "Athletic Performance"[Mesh] OR "Exercise Test"[Mesh] OR "Anaerobic Threshold"[Mesh] 09:44:16 70793

#20 Search #4 AND #9 AND #12 AND #19 09:31:16 42974

#19 Search "Outcome Assessment (Health Care)"[Mesh] OR "Outcome and Process Assessment Health Care"[Mesh] OR "complications" [Subheading] OR "Mortality"[Mesh] OR "mortality" [Subheading] OR "Hospital Mortality"[Mesh]OR "Morbidity"[Mesh] OR "Postoperative Complications"[Mesh] 09:25:38 2736081

#18 Search "Outcome Assessment (Health Care"[Mesh] OR "Outcome and Process Assessment Health Care"[Mesh] OR "complications" [Subheading]) OR "Mortality"[Mesh] OR "mortality" [Subheading] OR "Hospital Mortality"[Mesh] OR "Morbidity"[Mesh] OR "Postoperative Complications"[Mesh] 09:24:10 2736081

#12 Search "Surgical Procedures, Operative"[Mesh] OR "Specialties, Surgical"[Mesh] OR "surgery" [Subheading] OR "General Surgery"[Mesh] 08:00:10 2678044

#9 Search "Chemotherapy, Adjuvant"[Mesh] OR "Drug Therapy"[Mesh] OR "Radiotherapy"[Mesh] OR "Neoadjuvant Therapy"[Mesh] OR chemoradiotherap* [ti] 07:42:20 1005581

#8 Search "Chemotherapy, Adjuvant"[Mesh] OR "Drug Therapy"[Mesh] OR "Radiotherapy"[Mesh] OR "Neoadjuvant Therapy"[Mesh] 07:41:46 1004968

#4 Search "Neoplasms"[Mesh] OR (intracavit* [ti] AND malignan* [ti]) 07:27:46 2237272

#3 Search "Neoplasms"[Mesh] 07:27:06 2237264

#1 Search Neoplasms

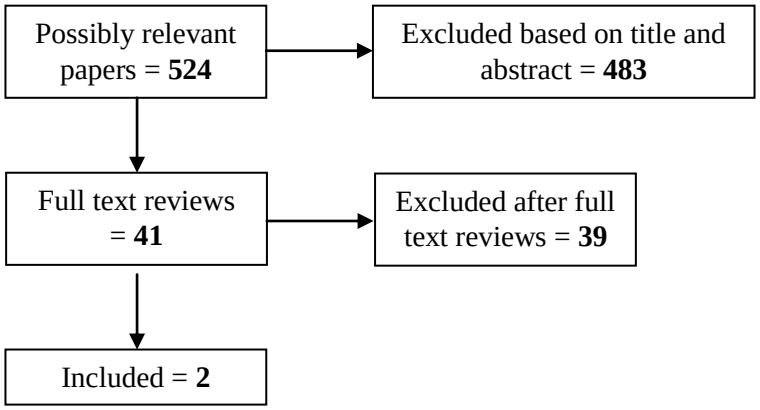
Search Outputs – 1st Search

Database	Dates Covered	Number of references found	Number of references retrieved
Medline	1997 - 12/2012	1456	1456
Embase	1997 - 12/2012	57	57
Cochrane	1997 - 05/2013	0	0

Search Outputs – 2nd Search

Database	Dates Covered	Number of references found	Number of references retrieved
Medline	1997 - 12/2012	524	524
Embase	1997 - 12/2012	35	35
Cochrane	1997 - 05/2013	0	0

Total references retrieved (after removal of duplicated articles) – 524



Quality of included studies:

Cochrane reviews = 0
Case Series = 1
Randomised controlled trials = 1

APPENDIX IV: SYSTEMATIC REVIEW SEARCH STRATEGY FOR SECTION 2.6.1

Search Strategy Section 2.6.1 (Literature review search conducted on 19.09.2011)

Question title – Evaluation of outcomes, methods, feasibility, safety and cost-effectiveness in studies utilising preoperative aerobic exercise training intervention in patients awaiting intra-thoracic and intra-abdominal surgery.

Review protocol (using the PICO methodology and Down's Quality assessment)

Population – Patients awaiting thoracic and abdominal surgery
Intervention – Preoperative aerobic exercise training
Comparison – Exercise group versus control group
Outcomes – Exercise outcomes, intervention methodology, feasibility, safety and cost-effectiveness

MW and AFO conducted a systematic search (PubMed and EMBASE) of clinical trials of preoperative aerobic exercise training in patients awaiting intra-cavity surgery. Abstracts were independently screened by same two investigators and reviewed against inclusion and exclusion criteria. Data were extracted by AFO in accordance with predefined criteria. The *primary hypothesis* was; aerobic exercise training prior to elective intra-cavity surgery improves postoperative clinical outcome. The *secondary hypotheses* were; aerobic exercise training prior to major surgery improves physical fitness and HRQL and is feasible, safe and cost effective.

Aerobic exercise training was defined as a prescribed period of aerobic physical activity, involving large muscle groups with a minimum of 3 planned exercise sessions and each session lasting greater than 10 minutes, during the time period leading to surgery. *Intra-cavity surgery* was defined as elective intra-abdominal and intra-thoracic surgery. The *primary outcome* was death following surgery. *Secondary outcome* measures included; any other measure relating to patient clinical outcome following surgery (e.g. postoperative morbidity, length of hospital stay), change in physical fitness following aerobic exercise training, HRQL, feasibility (adherence, compliance), safety (reported training related adverse events) and cost effectiveness.

Search strategy
Searches were performed on PubMed and EMBASE using search terms defined by the reviewers (see below). Two investigators (MW, AFO) independently reviewed the abstracts and titles of the studies found in the initial search. After agreement on the primary selection of papers, full text versions were accessed and reviewed against the following predefined inclusion and exclusion criteria.

Inclusion criteria
Studies recruiting human adult participants awaiting major cardiac, respiratory or gastrointestinal surgery were included in the present review. Studies were eligible for inclusion if the intervention was a preoperative aerobic exercise training program evaluated using measures of physical fitness. Measures of physical fitness included, but were not restricted to:

peak oxygen uptake ($\dot{V}o_2$ at Peak), estimated lactate threshold ($\dot{V}o_2$ at $\hat{\theta}_L$) or 6 minute walk distance (6MWD).

Exclusion criteria

Studies which solely investigated the effects of strength training or respiratory muscle training were excluded. Studies investigating the effects of postoperative aerobic exercise training, aerobic exercise training in patients <18 years and animal studies were excluded. Studies which duplicated data that had been reported in an earlier publication and studies that did not report measures of physical fitness were also excluded, as were papers not written in the English language.

Data extraction

Data were extracted by MW and AFO using a predefined pro-forma. The *study characteristics* data included; the journal and country of publication, the number of centres involved in the study, the study design and a quality measure. The *patient characteristics* data extracted were; age, gender and surgical type. The *primary outcome* variable was mortality following surgery (longest follow-up). *Secondary outcomes* included mortality (all other timeframes), morbidity, physical fitness, HRQL, adherence, safety, resource utilisation, and cost effectiveness. The *exercise outcomes* data extracted were; objective and subjective measures of physical fitness. The *aerobic exercise training characteristics* data extracted were; the frequency, intensity, mode and duration of the exercise intervention.

Quality assessment

The quality of the included studies was evaluated by using a checklist designed to assess the methodological quality of randomised and non-randomised studies. The checklist comprised of 27 questions under the headings; reporting, external validity, internal validity, and power. Each question was scored out of 1, except question 5 which was scored out of 2 and question 27 which was scored out of 5, giving a total score of 33. High scores reflect high quality studies. The studies were scored independently by MW and AFO and discrepancies were resolved by discussion.

PubMed search strategy

Full-Text Search Terms

(Surgery OR "General Surgery"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR “pre-operative” OR “preoperative” OR “preoperative care” OR “pre-assessment”) AND (“Prehabilitation” OR “Exercise training” OR “physical training” OR “Pre-conditioning” OR “preconditioning” OR “exercise intervention” OR “exercise program” OR “exercise”[Mesh] OR “exercise therapy”[Mesh]) AND (“Aerobic capacity” OR “VO2 peak” OR “Functional capacity” OR “Anaerobic threshold” OR “VO2 max” OR “exercise tolerance” OR “fitness” OR “VO2” OR “oxygen uptake” OR “aerobic fitness” OR “VO2max” OR “VO2peak” OR “AT” OR “cardiorespiratory reserve” OR “physical capacity”) NOT animals

EMBASE search strategy

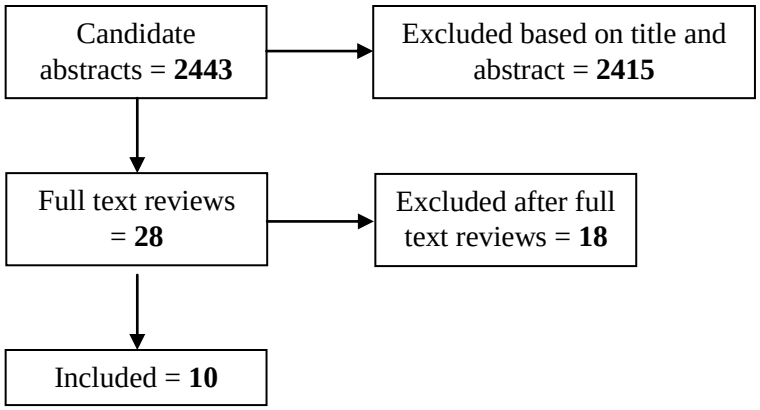
Full-Text Search Terms

1. Surgery : Explode
2. General Surgery : Explode
3. Surgical Procedures, Operative
4. pre-operative
5. preoperative evaluation
6. preoperative period
7. preoperative treatment
8. preoperative care
9. pre-assessment
10. preassessment
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. Prehabilitation
13. Exercise training
14. physical training
15. Pre-conditioning
16. preconditioning
17. exercise intervention
18. exercise program
19. exercise : explode
20. exercise therapy / kinesiotherapy
21. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. Aerobic capacity : explode
23. VO2 peak
24. Functional capacity
25. Anaerobic threshold : explode
26. VO2 max
27. exercise tolerance
28. fitness
29. VO2
30. oxygen uptake
31. oxygen consumption
32. aerobic fitness
33. VO2max
34. VO2peak
35. cardiorespiratory reserve
36. physical capacity
37. 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36
38. 11 AND 21 AND 37
39. limit 37 to huma

Search Outputs

Database	Dates Covered	Number of references found	Number of references retrieved
Medline	1950 - 09/2011	873	26
Embase	1950 - 09/2011	1564	2

Total references retrieved (after removal of duplicated articles) – 28



Quality of included studies:

Cochrane reviews = 0
Observational Studies = 6
Randomised controlled trials = 2
Randomised interventional trials = 2

Excluded studies

Methods papers

Cho H, Tsuburaya A, Sakamoto J. A Randomized Phase II Trial of Preoperative Exercise to Reduce Operative Risk in Gastric Cancer Patients with Metabolic Syndrome: Adjuvant Exercise for General Elective Surgery (AEGES) Study Group. *Jpn J Clin Oncol*. 2008; 38:71-3.

Jones LW, Douglas PS, Eves ND, et al. Rationale and design of the Exercise Intensity Trial (EXCITE): A randomized trial comparing the effects of moderate versus moderate to high-intensity aerobic training in women with operable breast cancer. *BMC Cancer*. 2010; 10:531.

Appropriate measures of physical fitness not reported

Furze G, Dumville JC, Miles JN, Irvine K, Thompson DR, Lewin RJ. "Prehabilitation" prior to CABG surgery improves physical functioning and depression. *Int J Cardiol*. 2009; 132:51-8.

Herdy AH, Marcchi PL, Vila A, et al. Pre- and postoperative cardiopulmonary rehabilitation in hospitalized patients undergoing coronary artery bypass surgery: a randomized controlled trial. *Am J Phys Med Rehabil*. 2008; 87:714-9.

Mooney M, Fitzsimons D, Richardson G. "No more couch-potato!" Patients' experiences of a pre-operative programme of cardiac rehabilitation for those awaiting coronary artery bypass surgery. *Eur J Cardiovasc Nurs*. 2007; 6:77-83

Rosenfeldt F, Braun L, Spitzer O, et al. Physical conditioning and mental stress reduction - a randomised trial in patients undergoing cardiac surgery. *BMC Complement Altern Med*. 2011; 11:20.

Sekine Y, Chiyo M, Iwata T, et al. Perioperative Rehabilitation and Physiotherapy for Lung Cancer Patients with Chronic Obstructive Pulmonary Disease. *Jpn J Thorac Cardiovasc Surg*. 2005; 53:237-43.

Not exclusively surgical patients or had not undergone surgery at time of follow-up

Adamsen L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ*. 2009; 13;339:b3410.

Kothmann E, Batterham AM, Owen SJ, et al. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study. *Br J Anaesth*. 2009; 103:505-10.

Myers JN, White JJ, Narasimhan B, Dalman RL. Effects of exercise training in patients with abdominal aortic aneurysm: preliminary results from a randomized trial. *J Cardiopulm Rehabil Prev*. 2010; 30:374-83

Duplicate publication of data

Jones LW, Eves ND, Peddle CJ, et al. Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. *Appl Physiol Nutr Metab*. 2008; 34:197-202.

Peddle CJ, Jones LW, Eves ND. Effects of Presurgical Exercise Training on Quality of Life in Patients Undergoing Lung Resection for Suspected Malignancy. *Cancer Nurs*. 2009; 32:158-65.

Peddle C.J., Jones L.W., Eves N.D. Correlates of adherence to supervised exercise in patients awaiting surgical removal of malignant lung lesions: results of a pilot study. *Oncology nursing forum*. 2009; 36:287-95.

Postoperative rehabilitation

Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A. Randomized trial of exercise therapy in women treated for breast cancer. *J Clin Oncol*. 2007; 25:1713-21.

Schneider CM, Hsieh CC, Sprod LK, Carter SD, Hayward R. Exercise training manages cardiopulmonary function and fatigue during and following cancer treatment in male cancer survivors. *Integr Cancer Ther*. 2007; 6: 235-41.

Non-surgical procedure

Bäck M, Wennerblom B, Wittboldt S, Cider A. Effects of high frequency exercise in patients before and after elective percutaneous coronary intervention. *Eur J Cardiovasc Nurs*. 2008; 7:307-13

Abdominal exercises

Futter CM, Weiler-Mithoff E, Hagen S. et al. Do pre-operative abdominal exercises prevent post-operative donor site complications for women undergoing DIEP flap breast reconstruction? A two-centre, prospective randomised controlled trial. *Br J Plast Surg*. 2003; 56:674-83.

Letter to the authors that did not present original data

Honnesh S, Goosen L, Adams N, Forni L, Lavies N, Venn R. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms. *Br J Anaesth*. 2010; 104:265-6