‘Fit for surgery’; retrospective analysis of the relationship between cardiorespiratory fitness and postoperative outcome

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Abstract

Introduction: The aging population is a major concern for healthcare providers and the number of surgical procedures performed is increasing each year. The ‘high-risk’ patient accounts for 13% of surgical cases but contributes to over 80% of postoperative deaths. Evidence suggests that cardiorespiratory fitness (CRF) may be an independent predictor of postoperative outcome. However, this relationship requires further understanding and optimisation to better inform patient care.

Aims: The overarching objective was to explore the ‘potential’ relationship between CRF and postoperative outcome (morbidity and survival) in patients undergoing major intra-abdominal surgery. Three aims were established to: 1) Improve the detection and interpretation of CRF, 2) Explore novel thresholds of CRF predictive of postoperative outcome, and 3) Enhance patient management using exercise.

Hypotheses: It was hypothesised that: 1) Natural variation (biological and analytical noise) is present in markers of CRF and thus impacts upon patient fitness stratification, 2) CRF is impaired in diseased patients and can predict postoperative outcomes, 3) Preoperative CRF is lower in females which may translate into inferior postoperative outcomes over males, 4) Preoperative exercise training is well tolerated and associated with objective cardiopulmonary improvement.

Methodology: *Study 1* – In a two-armed experiment, natural variation was calculated for CRF in a young, healthy population. Subsequent values of natural variation were retrospectively applied to an anonymised database of patients who underwent preoperative cardiopulmonary exercise testing (PCPET) before colorectal surgery, to re-appraise fitness stratification. *Study 2* – A retrospective cross-sectional analysis of patients (n=124) with abdominal aortic aneurysm (AAA) was conducted to compare CRF with that of a matched apparently healthy cohort, and to examine the association between impaired CRF and postoperative outcome. *Study 3* – In a large cohort of patients (n=640) who underwent PCPET prior to colorectal surgery, firstly, the association between impaired CRF and postoperative outcome was investigated and compared with traditional cardiovascular disease (CVD) risk factors. A subsequent comparative analysis was conducted to investigate sex-differences in preoperative CRF and postoperative outcomes to re-appraise risk stratification. *Study 4* – A case-report was conducted describing a 70-year-old high-risk female patient with a complicated medical history, who required major thoraco-abdominal surgery. A preoperative supervised 10-week high intensity interval training (HIIT) exercise intervention was conducted, and its ability to improve perioperative risk stratification evaluated.

Results: *Study 1* – Natural variation was present in measures of CRF and accounted for up to ± 19%, 13%, and 10% for oxygen consumption at anaerobic threshold ($\dot{V}O_2$-AT), peak oxygen consumption ($\dot{V}O_2$ peak), and ventilatory equivalent of carbon dioxide at anaerobic threshold ($\dot{V}_E/\dot{V}CO_2$-AT) respectively. A theoretical potential for up to 60% of patients to have indeterminate fitness existed if natural variation was not considered. *Study 2* – Patients with AAA undergoing PCPET highlighted impaired CRF compared to age adjusted/sex-matched sedentary controls. Values of <13.1 mL $O_2.min^{-1}.kg^{-1}$ for $\dot{V}O_2$ peak and ≥34 for $\dot{V}_E/\dot{V}CO_2$-AT were independent predictors of postoperative mortality at 2-years. *Study 3* – Being ‘unfit’ defined by preoperative CRF ($\dot{V}O_2$ peak <14.3 mL kg^{-1} min^{-1} and > 34 for $\dot{V}_E/\dot{V}CO_2$-AT) identified a five-fold greater 1-year mortality rate and was a stronger predictor than traditional CVD risk factors in a large cohort of patients undergoing colorectal surgery. Female patients exhibited lower preoperative CRF, and more were stratified ‘high risk’, however postoperative outcomes were equivalent to males. Consequently, females demonstrated lower threshold values of CRF than male counterparts and the application of sex-specific thresholds improved the prediction of postoperative mortality. *Study 4* – 10 weeks of HIIT proved well tolerated and

conferred impressive gain in CRF (27 and 36% for $\dot{V}O_2$-AT and $\dot{V}O_2$ peak respectively) which exceeded sources of variation and positively changed perioperative risk stratification in a high-risk patient prior to major thoraco-abdominal surgery.

Discussion: The overarching premise that CRF is related to postoperative outcome in patients undergoing intra-abdominal surgery is strongly supported. CRF was impaired relative to similarly aged apparently healthy people prior to major surgery and being unfit was a stronger predictor of mortality than traditional CVD risk factors. Furthermore, a 3 to 5-fold greater risk of postoperative mortality occurred in patients undergoing vascular and colorectal surgery if stratified unfit. This work has demonstrated: 1) Improved detection and interpretation of CRF, however unlike previous work the use of $\dot{V}O_2$-AT is not supported, the consequence of experimental 'noise' (mostly biological variation) that requires consideration when interpreting PCPET results. 2). Novel threshold values of CRF in specific patient cohorts undergoing surgery improved mortality prediction, and importantly, patients should be stratified by sex as females are more sensitive to CRF, with lower values yet equivalent postoperative outcomes. 3) Preoperative CRF was objectively improved using a short duration HIIT intervention that was well tolerated in the high-risk patient and enabled fitness to transcend stratification boundaries.

Conclusion: Preoperative CRF better predicted postoperative outcome than traditional CVD risk factors, and PCPET should be considered a principal component of surgical risk assessment. This work advances the potential to use CRF to predict postoperative outcome to help clinicians better direct care provision and advance patient outcomes following major surgery.

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Thank you!

Abbreviations

AAA – Abdominal Aortic Aneurysm

AHA – American Heart Association

ANOVA – Analysis of Variance

ASA – American Society of Anesthesiologists

AT – Anaerobic Threshold

ATP – Adenosine Triphosphate

AUROC – Area Under Receiver Operating Characteristic

BMI – Body Mass Index

CaO_2 – Arterial oxygen content

CvO_2 – Venous oxygen content

CD – Critical Difference

CO_2 – Carbon Dioxide

COPD – Chronic Obstructive Pulmonary Disease

CPET – Cardiopulmonary Exercise Test

CRF – Cardiorespiratory Fitness

CVA - Cerebrovascular Accident

$CV_{\mathbf{A}}$ – Coefficient of Analytical Variation

$CV_{\mathbf{B}}$ – Coefficient of Biological Variation

CVD – Cardiovascular Disease

$CV_{\mathbf{w}}$ – Coefficient of Within Participant Variation

DASI – Duke Activity Status Index

DO_2 – Oxygen Delivery

EACPR – European Association for Cardiovascular Prevention and Rehabilitation

ECG – Electrocardiogram

ETO_2 – End Tidal Oxygen Tension

ERAS – Enhanced Recovery After Surgery

EVAR – Endovascular Aneurysm Repair

FEV_1 – Forced Expired Volume in 1 Second

FVC – Forced Vital Capacity

Hb – Haemoglobin

HDU – High Dependency Unit

HITT – High Intensity Interval Training

HQIP - Healthcare Quality Improvement Partnership

HR – Hazard Ratio

ICC – Intra-class correlation coefficient

ICU – Intensive care unit

IHD – Ischaemic Heart Disease

MCID – Minimal Clinically Important Difference

MISS – Moderate Intensity Steady State

MVV – Maximal Voluntary Ventilation

NHS – National Health Service

NO – Nitric Oxide

NSQIP – National Surgical Quality Improvement Program

O_2 – Oxygen

ONS – Office for National Statistics

O_2 Pulse – Peak Oxygen Pulse

OUES – Oxygen Uptake Efficiency Slope

OXINOS - Oxidative-Inflammatory-Nitrosative Stress

PACU – Post-Anaesthesia Care Unit

PCPET – Preoperative Cardiopulmonary Exercise Test

PH – Proportional Hazards

POSSUM – Physiological and Operative Score for Enumeration of Mortality and Morbidity

$\dot{Q}$ – Cardiac Output

RCRI – Revised Cardiac Risk Index

RER – Respiratory Exchange Ratio

RNS – Reactive Nitrogen Species

ROC – Receiver Operating Characteristic

ROS – Reactive Oxygen Species

RPM – Revolutions Per Minute

RR – Relative Risk

SORT – Surgical Outcome Risk Tool

UK – United Kingdom

$\dot{V}CO_2$ – Volume of Carbon Dioxide Produced

$\dot{V}_E$ – Minute Ventilation

$\dot{V}_E/\dot{V}CO_2$-AT - Ventilatory Equivalent of the Volume of Carbon Dioxide Produced at Anaerobic Threshold

$\dot{V}_E/\dot{V}O_2$-AT - Ventilatory Equivalent of the Volume of Oxygen Consumed at Anaerobic Threshold

$\dot{V}O_2$ – Volume of Oxygen Consumed

$\dot{V}O_2$-AT – Volume of Oxygen Consumed at Anaerobic Threshold

$\dot{V}O_2$ peak – Peak Oxygen Consumption

W – Watts

Table of Contents

Chapter 1

Thesis Overview

1.1. General Introduction

"*It is more important to know what sort of person has a disease than to know what sort of disease a person has*" (Hippocrates, 460 to 370 BC).

Between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22% (World Health Organisation, 2018). In the United Kingdom (UK) alone, by mid-2017, people aged 65 years or over accounted for 18.2% of the population and this age-group is projected to grow to 20.7% by 2027 (Office for National Statistics, 2018). The prevalence of disease is higher in the geriatric population and the requirement treat this growing burden is a major concern for healthcare providers. Indeed, a key priority area of the World Health Organisation's Consultation on Global Strategy and Action Plan on Ageing and Health (World Health Organistaion, 2017) is "Improving measurement, monitoring and understanding" whereby "focused research, new metrics and analytical methods are needed for a wide range of ageing issues". More than 5.1 million surgical procedures take place each year in the UK National Health Service (NHS) alone; a rate that is growing by 1 per cent per annum (Abbott et al., 2017) and by 2030, it is estimated that one-fifth of the 75 years and older age-category will undergo surgery each year (Fowler et al., 2019).

Longevity has a proven association with cardiorespiratory fitness (CRF); moreover, this modifiable risk factor is inversely associated with long-term all-cause mortality (Mandsager et al., 2018, Kokkinos et al., 2010). Additionally, and importantly given the ageing population and greater burden of disease carried by the elder age groups, a growing body of evidence has emerged demonstrating that impaired CRF is also associated with poor patient outcomes following major surgery.

The seminal work of Older et al. (1993) established that patients stratified ‘unfit’ (with impaired CRF) prior to major surgery demonstrated markedly higher mortality rates than those classified as ‘fit’ (18% *vs*. 0.8% respectively), and many studies have since supported this association in patients undergoing a variety of intra-abdominal surgeries (Moran et al., 2016). Current practice in the UK suggests that approximately 68% of NHS centres now offer a preoperative cardiopulmonary exercise testing (PCPET) service to determine CRF and plan perioperative care, with approximately 30,000 PCPET conducted per year (Reeves et al., 2018). Despite the growing adoption of PCPET as standard of practice, the supporting evidence is predominantly based around association, with few interventional studies conducted, and to a lesser degree, a detailed mechanistic understanding of the protection that improved oxygen (O_2) transport may provide, is not clearly established.

A review of current knowledge, limitations of current practice, and a theoretical framework describing the protective effects of improved O_2 transport emphasise the requirement to optimise the interpretation of preoperative CRF in *Chapter 2*. Here, the development of the hypotheses will also be described. Subsequently, *Chapter 3* provides a description of the general methodologies used to measure CRF and postoperative outcome in clinical practice that is common to all experimental investigations.

Four studies are presented in *Chapter 4* in response to the hypotheses stated, three of which are based on a retrospective evaluation of a clinical database, and the fourth a clinical case report of a preoperative exercise intervention. *Study 1* establishes a quality control standard for the scientific measurement and clinical interpretation of CRF. This study investigates the potential for incorrect stratification of patient fitness if natural variation (biological and analytical noise) associated with the measurement of CRF is not accounted for, thus optimising clinical interpretation of CRF when planning the perioperative care of patients. *Study 2* focuses on a patient cohort with vascular disease, to investigate firstly if CRF is impaired, and subsequently the relationship between CRF and postoperative mortality. *Study 3* focuses on a cohort of patients undergoing major colorectal surgery, predominantly to treat cancer. This allowed both the opportunity to examine a different population (with cellular disease in contrast to vascular disease), and to also compare the prognostic utility of CPET as a function of sex, hitherto unexplored. *Study 4* has taken an interventional approach employing exercise in a patient with a very challenging medical history. The study examined efficacy and feasibility of high intensity interval training (HIIT) to improve patient fitness, thus reducing risk and enabling surgery.

Finally, *Chapter 5* discusses the general findings of each study, their limitations and future research plans, which collectively demonstrates the impact of this work and potential for optimising future clinical practice. Prior to completion of this thesis, *Studies 1, 2, 4,* and the Literature Review have been published in peer reviewed biomedical journals and *Study 3* is currently under peer review. Publications arising from this thesis can be found in the appendices.

This work arose from a collaboration between the Neurovascular Research Laboratory, University of South Wales, and Consultant Anaesthetists (Drs Richard Davies and Ian Appadurai) delivering the Preoperative Assessment Clinic at University Hospital of Wales, Cardiff. Given the impact of integrated research with potential to inform policy and optimise patient care, the findings are tempered with appreciation of the importance of precise clinical interpretation since this may govern surgical selection, notwithstanding the clinical/economic benefits of exercise as an intervention, and by mechanisms that remain to be fully elucidated.

Chapter 2

Literature Review

Surgery is the third largest cause of death after ischaemic heart disease and stroke, and accounts for 7.7% of all deaths globally (Nepogodiev et al., 2019). By 2030, it is estimated that one-fifth of people aged 75 years and older will undergo surgery each year (Fowler et al., 2019). Therefore, to better understand and mitigate this risk, we need to consider not just the sort of disease or surgical procedure a person has, but also what sort of person is about to undergo the physiological insult of major surgery, and how they may cope to prolong survival. This review explores our relationship with O_2, the elixir of life, and investigates to what extent our ability to transport and use O_2 is associated with 'fitness for surgery'.

2.1. Evolution of oxygen and our dependency on oxidative metabolism

When the solar system emerged 4.6 billion years ago (Dickerson, 1978), Earth's atmosphere was devoid of O_2, a vast difference compared with today's atmospheric inspired fraction of 20.93%. The emergence of life, likely originating in alkaline thermal vents at the bottom of the oceans, gave rise to the orders of archaea and bacteria (Miller and Bada, 1988). Approximately 1.5 billion years ago, cyanobacteria began to release O_2, breathing life into the atmosphere (Nisbet and Sleep, 2001). These organic compounds that emerged from the 'primordial soup' were able to photosynthesise by capturing solar radiation and creating the organic molecule glucose. In turn, the O_2 released into the atmosphere signalled a major evolutionary event; arguably described by two oxidation 'pulses', the Great Oxidation Event and the Neoproterozoic Event, or as a progressive evolution, the Great Oxidation Transition (Lyons et al., 2014). This gave rise to atmospheric O_2, and the evolution of O_2 dependent organisms from primitive eukaryotic unicellular structures performing metabolism, locomotion, and reproduction, to present day homo sapiens.

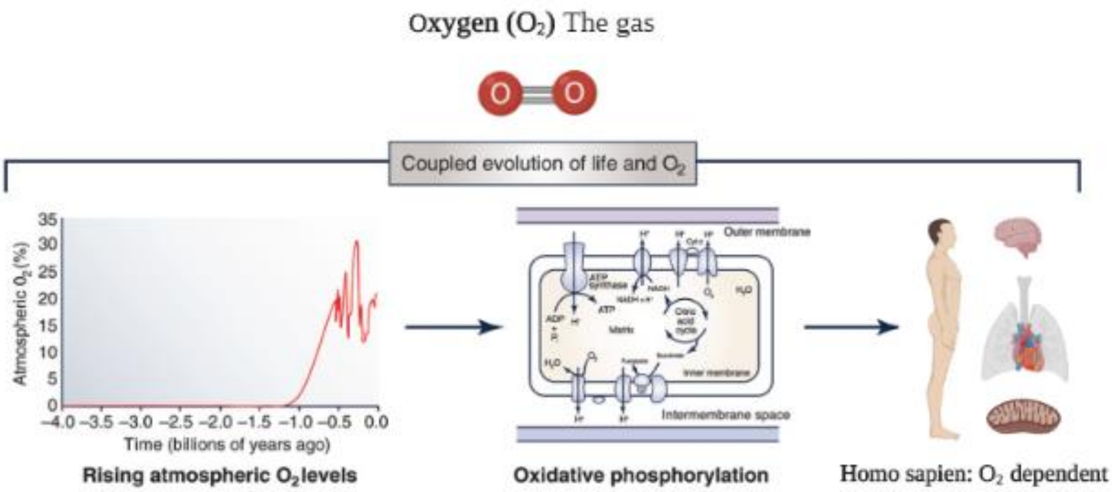


Figure 1. The evolution of oxygen (O_2), dependency of mitochondrial oxidative phosphorylation upon O_2, and the evolution of homo sapiens to support oxygen delivery. Adapted from Bailey (2019).

Figure 1. adapted from Bailey (2019) describes the evolution of O_2, and the entire dependency of the respiring mammalian cell for the constancy of electron flow, with molecular O_2 serving as the terminal electron acceptor in mitochondrial oxidative phosphorylation. Homo sapiens, like all mammals, have a remarkable ability (or dependency), to harness O_2 allowing a rapid turnover of adenosine triphosphate (ATP) enabling cells, tissue, and organs to sustain life. Human evolution has thus taken a structure, function and physiological organisation that efficiently coordinates the convective delivery and diffusive uptake of O_2, to support life.

2.2. Mouth to mitochondria; convective and diffusive determinants of O_2 transport

The first measurements describing O_2 uptake ($\dot{V}O_2$) in humans at the onset of intense movement were conducted by Hill and Lupton (1923) and demonstrated a rapid and exponential response as skeletal muscle has the capacity to increase metabolism by an astounding 50 to 100-fold rate above resting requirements. This challenges a rapid delivery of O_2 to the mitochondrial inner membrane for use as the terminal electron acceptor, whereby oxidative phosphorylation generates ATP. O_2 is transported either by convection, which describes movement within the circulation driven by the heart as a pump, or by diffusion, the passive movement down a concentration gradient such as from the microcirculation into tissue.

Figure 2. illustrates the major organs and processes, both convective and diffusive that describe the 'oxygen cascade'. Following inspiration of air into the lungs, O_2 diffuses down a concentration gradient at the alveolar-capillary membrane and binds with haemoglobin (Hb, the Haldane transformation), an allosteric protein with affinity for four molecules of O_2. In addition to binding with Hb, O_2 also dissolves in plasma. Deoxygenated venous blood is therefore saturated in the pulmonary capillaries, the concentration of which is proportional to the partial pressure exerted by O_2 on the plasma at a given temperature (Henry's Law). Oxygenated blood then travels the vascular system driven by the heart. This convective component is referred to as 'oxygen delivery' (DO_2), the product of cardiac output ($\dot{Q}$) and arterial O_2 content ($\dot{Q}$ x CaO_2). Finally, transport is complete when O_2 diffuses across the microcirculatory capillary beds and reaches the mitochondrial matrix where it is used as the terminal electron carrier. $\dot{V}O_2$ as described by the Fick Principle is equal to the product of $\dot{Q}$ and the difference between arterial and venous oxygen content ($CaO_2 - CvO_2$). Notably, the 'rate limiting' step for O_2 uptake is attributed to the diffusive components of the cascade (Wagner, 2000).

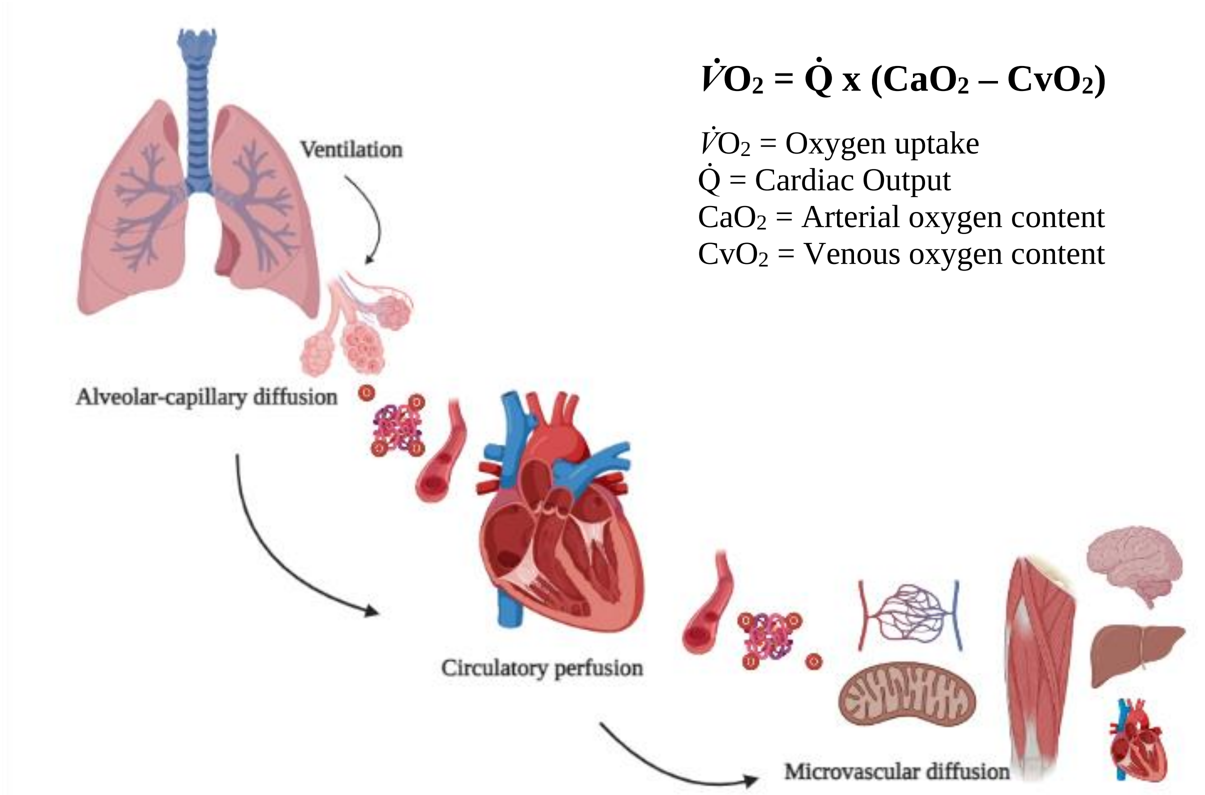


Figure 2. The O_2 transport system characterised by pulmonary ventilation, alveolar-capillary diffusion, circulatory perfusion driven by the cardiovascular system, and diffusion at the microvasculature. The volume of O_2 transport, described by the Fick Principle, is determined by the product of convective (cardiac output) and diffusive (the difference between the O_2 content of arterial and venous blood) terms.

2.3. Metrics and meaning; assessment of CRF

The advent of breath-by-breath measurement technology has allowed us to measure the capacity of the O_2 transport system and determine metrics describing the magnitude of CRF, which not only describes an individual's ability to perform physical activity, but is linked to cardiovascular health (Ross et al., 2016) and longevity (Blair et al., 1989). CPET is used to objectively measure the ability of a patient to uptake O_2 and typically involves an incremental exercise test to symptom limited exhaustion (Figure 5). CPET can also identify emerging pathology and evaluate the impact of chronic comorbidities on O_2 uptake. Recently, the use of

CPET has been widely adopted in patients prior to major surgery and approximately 30,000 tests are conducted each year in the UK alone (Reeves et al., 2018). These data are used to support patient care decisions, to plan appropriate postoperative critical care, and to direct prehabilitation programs aimed at improving CRF (Levett et al., 2018).

Three primary metrics describing CRF are typically reported when conducting CPET:

1. ***Peak oxygen consumption ($\dot{V}O_2$ peak),*** defined as the $\dot{V}O_2$ attained during an incremental test to exhaustion, expressed in absolute terms ($mL.min^{-1}$) or relative to body mass ($mL.kg^{-1}.min^{-1}$) which can be subject to allometric scaling, and measured as the highest value recorded.

Whilst $\dot{V}O_2$ peak is reflective of a patient's 'best effort', it may not necessarily reflect a true highest value, defined as maximal oxygen uptake ($\dot{V}O_2$ max) with an observed plateau present in the O_2 uptake work-rate slope (Hill and Lupton, 1923). Controversy exists here, and evidence suggests only a minority of tests, even in young healthy people, yield a measurable plateau (Day et al., 2003). Nevertheless, an exercise test to exhaustion is important since it allows for the site of transport limitation across the O_2 cascade to be identified (Wagner, 2000).

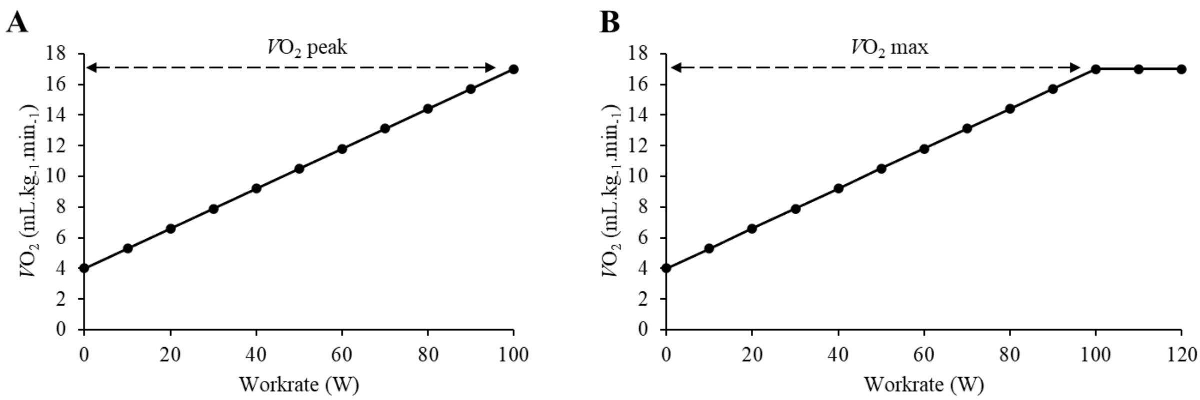


Figure 3. Schematic representation of O_2 consumption at the limit of exercise tolerance during CPET. **A**. $\dot{V}O_2$ peak reported as the highest value recorded, **B**. $\dot{V}O_2$ max idealised as a true

highest value with observed plateau present. $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}O_2$ max, maximal oxygen uptake.

2. ***Anaerobic threshold (AT),*** a submaximal index of CRF defined as the $\dot{V}O_2$ above which anaerobic metabolism supplements oxidative phosphorylation with additional carbon dioxide (CO_2) production, creating a deflection point on a plot of pulmonary CO_2 excretion *vs*. O_2 uptake. AT is expressed in $mL.kg^{-1}.min^{-1}$ or $mL.min^{-1}$.

Whilst the AT signifies a transition to increased glycolysis with associated metabolic acidosis, a multitude of definitions and controversy exist. Thus in the context of preoperative CPET, AT refers to the respiratory gas threshold typically measured using the 'Gold Standard' V-slope (Beaver et al., 1986) method of determination (further explained in *Chapter 3* and Figure 15).

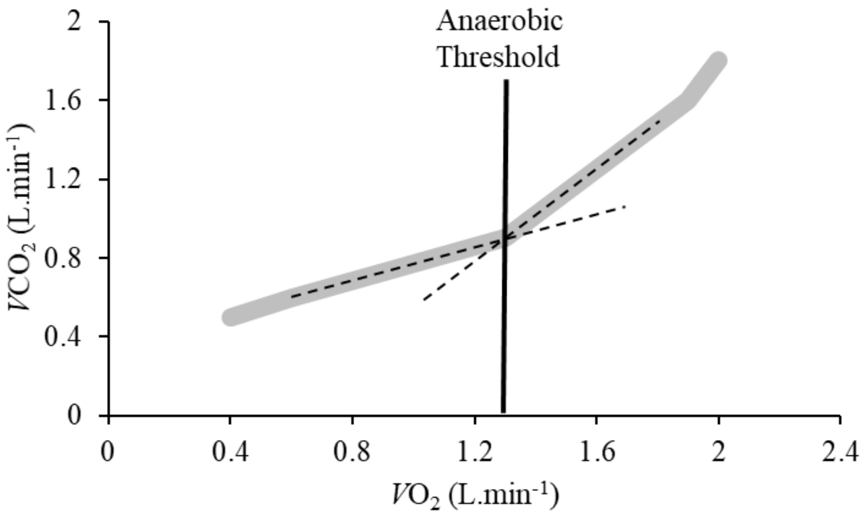


Figure 4. Schematic representation of the V-slope method (Beaver et al., 1986) for estimation of the AT during CPET. AT is identified at the intersection of two linear sections of the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship, represented by the solid black line. A further deflection point in the relationship may be observed during the latter stages of CPET and represents respiratory compensation.

3. ***The ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$),*** defined as a ratio (thus unitless) of minute ventilation to CO_2 production and is usually reported at the AT.

The $\dot{V}_E/\dot{V}CO_2$ signifies ventilatory (in)efficiency and may be used to identify a mismatch in ventilation perfusion, typical of 'dead spot' areas of the lung which receive oxygen but no blood flow, thus ventilated but not perfused. Elevated values for $\dot{V}_E/\dot{V}CO_2$ occur in heart failure, respiratory disease, and pulmonary hypertension (ATS/ACCP, 2003, Snowden et al., 2010, Sun et al., 2001).

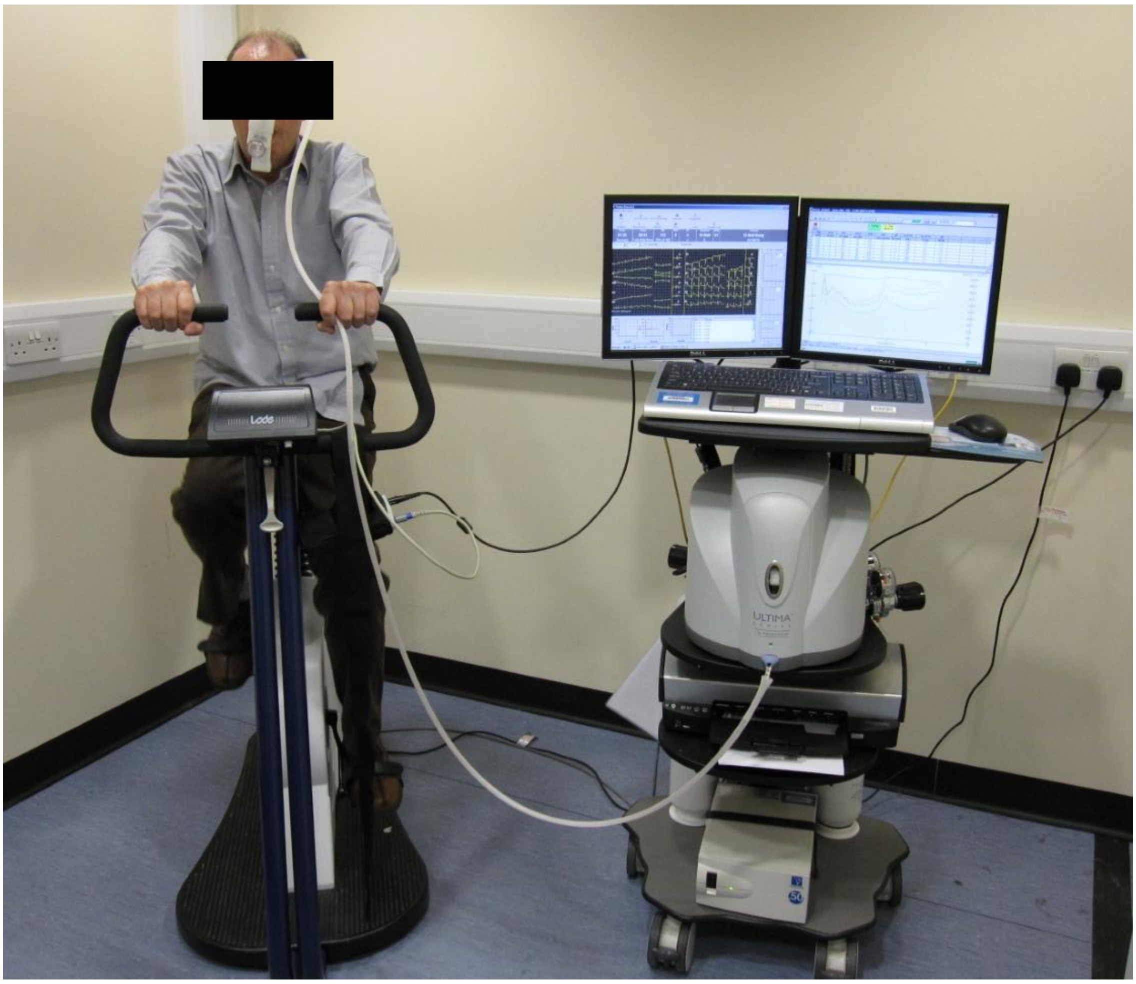


Figure 5. A patient undergoing CPET to determine both the ability to transport O_2, thus objectively measuring CRF, and to identify the causes of limitations.

2.4. CRF and surgery; link to survival

Mortality following major surgery is a significant risk despite progress being made in surgical technologies, anaesthesia, and peri-operative care. In colorectal surgery, mortality is reported at 3.2% within 90-days (NBOCA, 2017) with complication rates above 30% (Lucas and Pawlik, 2014). Similarly, in-hospital mortality for elective abdominal aortic aneurysm (AAA) repair is 2.9% for open repair and 0.4% for endovascular repair (VSQI, 2017). Furthermore, the insult of major surgery is estimated to reduce the CRF by ~40%, with hospital stay of 7 to 9 days, and only 50% of patients regain preoperative levels of CRF, measured by submaximal cycle ergometry heart rate after 6 months (Jensen et al., 2011).

Accurate prediction of surgical risk is required to improve patient outcomes and plan perioperative care. Traditionally, subjective clinical acumen alone was used however objective scoring systems are now available such as the Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM; Whiteley et al., 1996), American Society of Anesthesiologists (ASA) physical status, Charleston Comorbidity Index, and measures of cardiac function (Moyes et al., 2013). These systems are generally weak and complimentary 'biomarkers' are needed. CRF, a modifiable risk factor, has long been (inversely) associated with all-cause mortality (Mandsager et al., 2018, Kokkinos et al., 2010), and evidence also suggests that impaired CRF (see Older et al., 1993 below) is associated with reduced survival and increased morbidity following major surgery (Moran et al., 2016).

The seminal work of Older et al. (1993) first described an association between preoperative CRF and postoperative outcome. They studied 184 elderly patients undergoing elective major intra-abdominal surgery and established that patients classified as 'unfit' exhibited markedly higher mortality rates than those deemed 'fit' (18% *vs*. 0.8%, $P < 0.001$). Patients were considered unfit by preoperative CPET if O_2 uptake at AT was < 11 ml O_2. $kg^{-1}.min^{-1}$, a value originally described by Weber and Janicki (1985) that characterised the AT in patients with moderate to severe heart failure. Many studies have since used the AT as a measure of CRF, and further supported the inverse association between CRF and postoperative mortality and morbidity in patients undergoing a variety of intra-abdominal surgeries, as indicated in Table 1 adapted from Moran et al. (2016).

Table 1. Prominent studies demonstrating an association between CRF and postoperative outcome following non-cardiac intra-abdominal surgery, adapted from (Moran et al., 2016). Risk thresholds relate to a level of CRF below which an inferior postoperative outcome has been observed and are either defined from the respective study data or have been adopted from other studies and applied to the study data.

Author	Patients (n)	AT risk threshold (mL.O_2 $kg^{-1}.min^{-1}$)	$\dot{V}O_2$ peak risk threshold (mL. $kg^{-1}.min^{-1}$)	$\dot{V}_E/\dot{V}CO_2$ risk threshold	Risk thresholds Defined/Adopted	Postoperative outcome
Intra-abdominal surgery						
Older et al. (1993)	187	Yes < 11.0	Not measured	Not measured	Adopted	Hospital Mortality
Older et al. (1999)	548	Yes < 11.0	Not measured	No	Adopted	Hospital Mortality
Wilson et al. (2010)	847	Yes < 10.9	Not measured	Yes > 34	Adopted	Mortality 90d
Snowden et al. (2010)	116	Yes < 10.1	No	No	Defined	Morbidity: Comp
Vascular AAA surgery						
Carlisle and Swart (2007)	130	Yes	Yes	Yes > 42	Defined	Mortality: 2yrs
Hartley et al. (2012)	415	Yes < 10.2	Yes < 15.0	Yes > 42	Adopted	Mortality: 30d, 90d
Prentis et al. (2012)	185	Yes < 10.0	No	No	Defined	Morbidity: LoS
Goodyear et al. (2013)	188	Yes < 11.0	Not measured	Not measured	Adopted	Mortality: 30d Morbidity: LoS
Grant et al. (2015)	506	Yes < 10.2	Yes < 15.0	Yes > 42	Adopted	Mortality: 3 yrs
Rose et al. (2018a)	124	No	Yes < 13.1	Yes ≥ 34	Defined	Mortality: 2 yrs
Colorectal surgery						
Lai et al. (2013)	269	Yes < 11.0	Not measured	Not measured	Adopted	Mortality: 2 yrs Morbidity: LoS
West et al. (2014b)	136	Yes < 10.1	Yes < 16.7	Yes > 32	Defined	Morbidity: Comp
West et al. (2014a)	105	Yes <10.6	Yes < 18.6	No	Defined	Morbidity: Comp
Wilson et al. (2019)	1375	No	Not measured	Yes >39	Defined	Mortality: 90d
Upper gastrointestinal surgery						
McCullough et al. (2006)	109	No	Yes < 15.8	No	Defined	Morbidity: Comp
Nagamatsu et al. (2001)	91	Yes	Yes < 800mL	Not measured	Defined	Morbidity: Comp
Moyes et al. (2013)	108	Yes < 9.0	No	No	Defined	Morbidity: Comp
Patel et al. (2019)	120	No	Yes < 17.0	No	Defined	Morbidity: Comp

AAA, (open) abdominal aortic aneurysm; AT, anaerobic threshold; Comp, complications; LoS, hospital length of stay; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide.

A theoretical model (Figure 6) originally developed by Clegg et al. (2013) helps visualise why (elevated) CRF is associated with improved postoperative outcome. The model describes potential differences in surgical outcome between a hypothetical patient who is unfit for surgery (for example with an AT < 11 ml O_2. $kg^{-1}.min^{-1}$) vs. one who is fit (AT ≥ 11 ml O_2. $kg^{-1}.min^{-1}$). The unfit patient is more likely to require care in a High Dependency Unit (HDU) or Intensive Care Unit (ICU) with a greater likelihood of complications and risk of mortality, whereas the fit patient may experience a normal and faster recovery on the Ward.

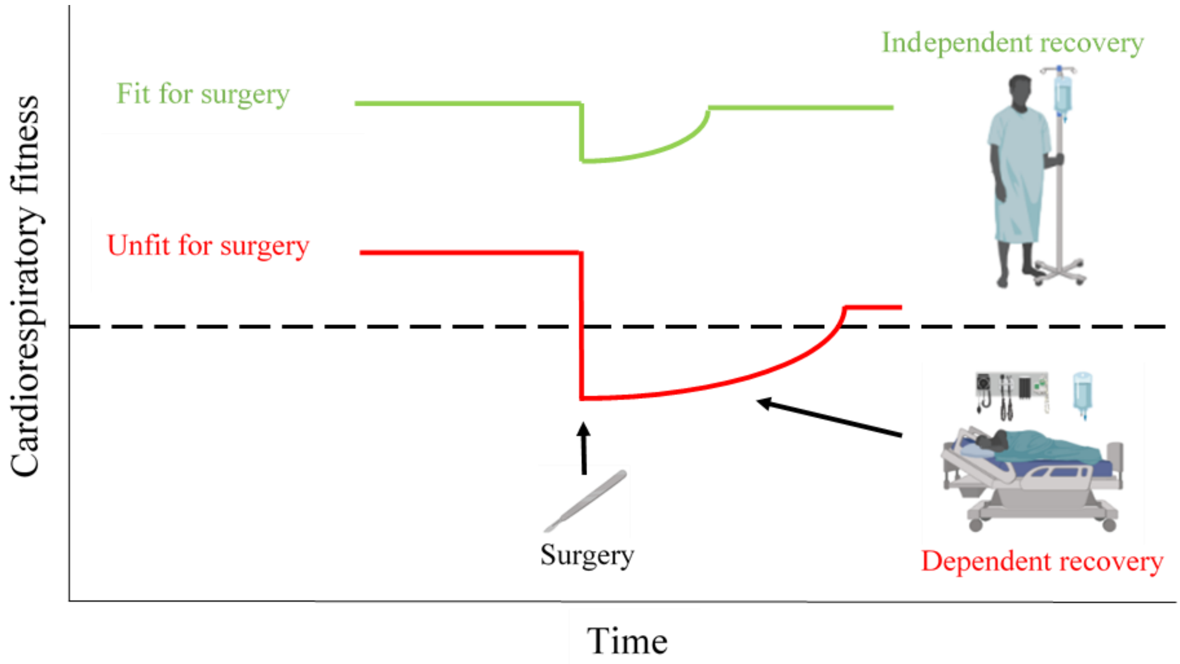


Figure 6. The insult of surgery and potential for change in patient recovery, adapted from Clegg et al. (2013). The green plot represents a patient considered (CRF) 'fit' for surgery whereas the red plot represents a patient classified as 'unfit'. The dashed line represents the cut-off between independent patient recovery typically requiring Ward based care, and dependent recovery requiring HDU or ICU admission.

Given the importance of assessing CRF in clinical practice, the American Heart Association (AHA) have published a scientific statement promoting CRF as a clinical vital sign (Ross et al., 2016).

2.5. Mechanistic link between CRF and postoperative outcome

The model presented (Figure 6) presumes the existence of an obligatory baseline level of CRF (such as the threshold values for AT, $\dot{V}O_2$ peak or $\dot{V}_E/\dot{V}CO_2$ found in Table 1) to survive an increased demand for O_2 during the perioperative period. If unable to meet this presumed O_2 demand, chronic hypoxemia may be responsible for increased morbidity and mortality for any severity of disease. Whilst a detailed mechanistic understanding explaining why impaired CRF is associated with poor postoperative outcome remains to be elucidated, the presence of an O_2 debt during the perioperative period is fundamental to this model.

The surgical stress response is characterised by an increased O_2 demand as originally demonstrated by Ciaffoni et al. (2016), measured directly (via in-airway sensors) beginning in the intraoperative period (Figure 7). The underlying mechanisms responsible for the perioperative elevation in $\dot{V}O_2$ can be explained by complex changes in metabolic demand. These comprise hormonal, haematological, and immunological changes, manifested with increased $\dot{Q}$ and O_2 consumption as the delivery of nutrient and O_2-rich blood supports energy processes, tissue repair and protein synthesis (Gillis and Wischmeyer, 2019). Surgery, is also known to result in oxidative stress with consequent increases in free radical formation (Arsalani-Zadeh et al., 2011). This is particularly prominent during abdominal surgery because of potential ischemia-reperfusion, leukocyte activation, mitochondrial dysfunction, and concurrent depletion of antioxidants in the postoperative period due to increased consumption (Thomas and Balasubramanian, 2004, Musil et al., 2005). During laparoscopy for example, increases in intra-abdominal pressure during pneumoperitoneum, driven by inflation-deflation, may cause splanchnic ischemia-reperfusion and subsequent oxidative stress (Leduc and Mitchell, 2006).

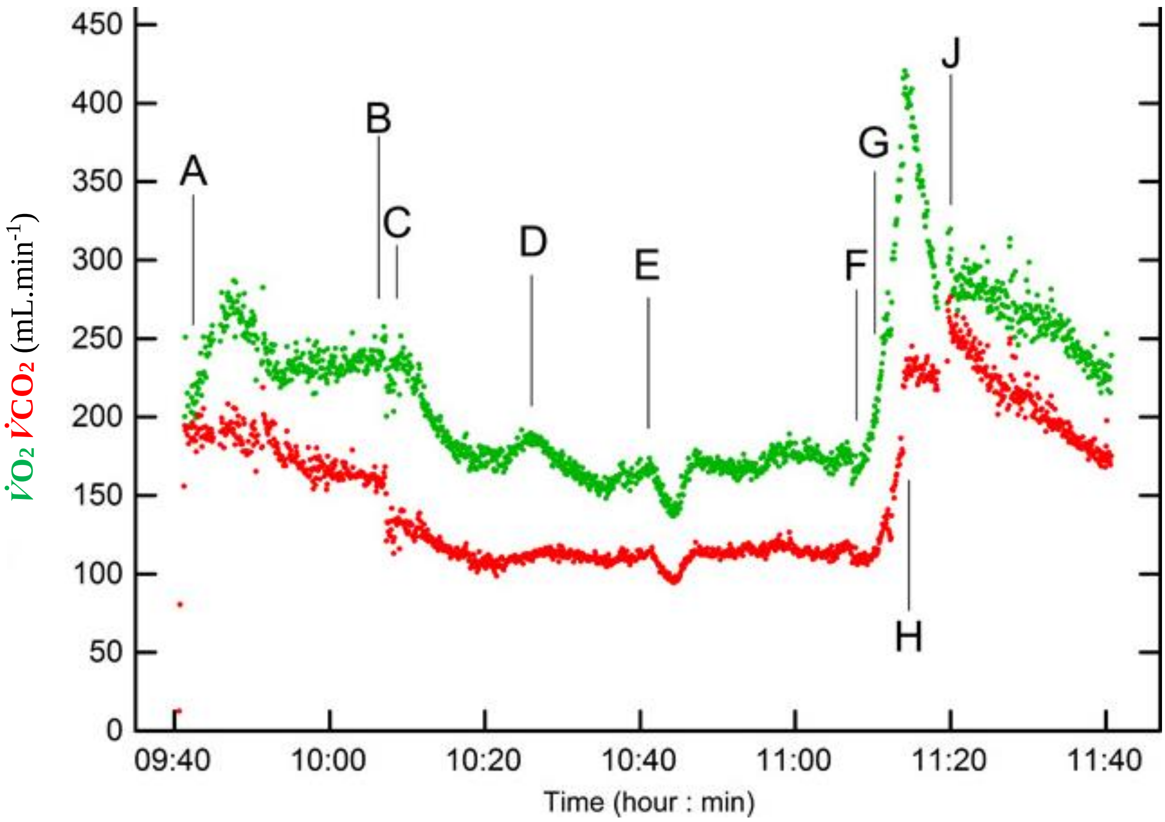


Figure 7. O_2 uptake during the intraoperative period of a patient undergoing AAA repair, taken from Ciaffoni et al. (2016). Events are represented by points as follows: (A) knife to skin; (B) reduction in ventilator driving pressure; (C) aortic clamp applied; (D) fall in blood pressure; (E) metaraminol (fast-acting a-agonist) bolus, infusion rate increased from 2 to 5 ml. hr^{-1}; (F) and (G) sequential removal of iliac artery clamps; (H) increase in ventilator driving pressure; and (J) removal of superior retractor restricting rib cage movement.

Ciaffoni et al. (2016) also demonstrate concurrent elevation of $\dot{V}CO_2$ production during the intraoperative period, which may be equally important in terms of 'clearance' for the maintenance of normal acid-base balance (Bailey et al., 2017), and requires further mechanistic investigation.

The additional demand for O_2 is not solely constrained to the intraoperative period however. Shoemaker et al. (1992) measured $\dot{V}O_2$ in 253 high-risk patients (defined by criteria with a

>30% surgical mortality rate) before, during, and immediately after major surgery. These values were compared with the estimated $\dot{V}O_2$ requirements of the patients (using resting preoperative control values) to calculate the magnitude of $\dot{V}O_2$ deficit. Patients who died (n=64) had organ failure and a mean $\dot{V}O_2$ deficit of 33.2 L.m^{-2}, compared with 21.6 L.m^{-2} for survivors with organ failure (n=31), and 9.2 L.m^{-2} for survivors without organ failure or major complications (n=158). Their findings demonstrated the presence of an O_2 deficit across the perioperative period and its magnitude was associated with the development of organ failure and ultimately death as illustrated in Figure 8.

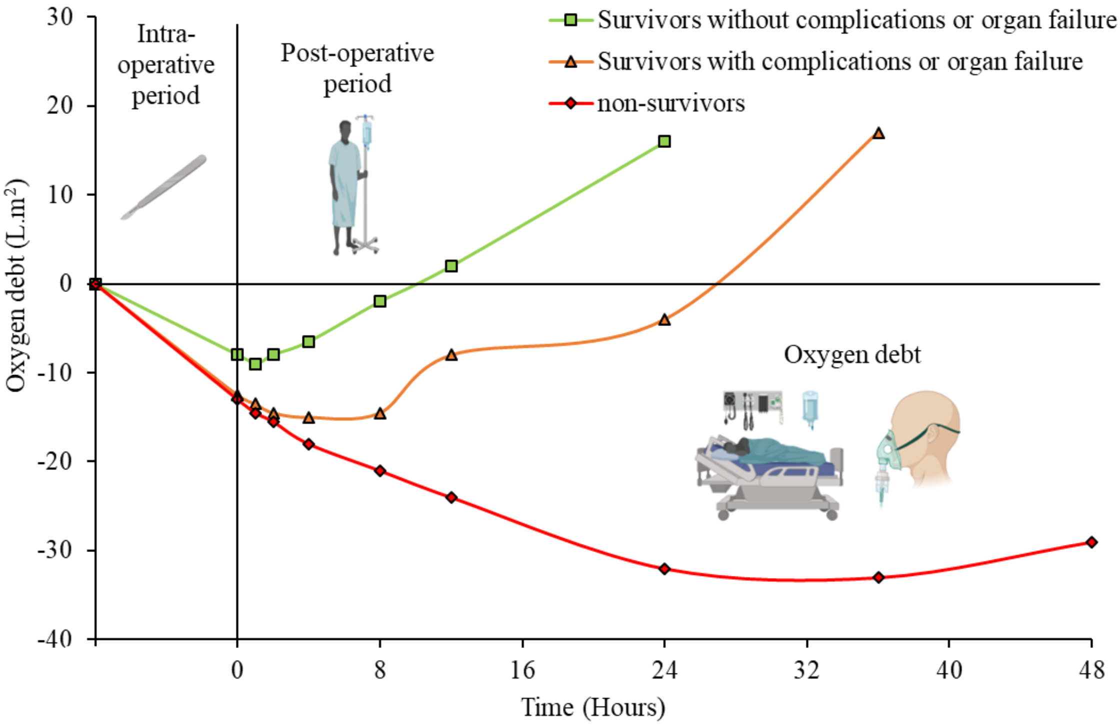


Figure 8. The cumulative O_2 deficit associated with survivors without complications or organ support, with complications or organ support, and non-survivors. Adapted from Shoemaker et al. (1992).

Furthermore, the authors also investigated the time-course and types of emerging complications up to 10 days following surgery as illustrated in Figure 9, again adapted from Shoemaker et al. (1992).

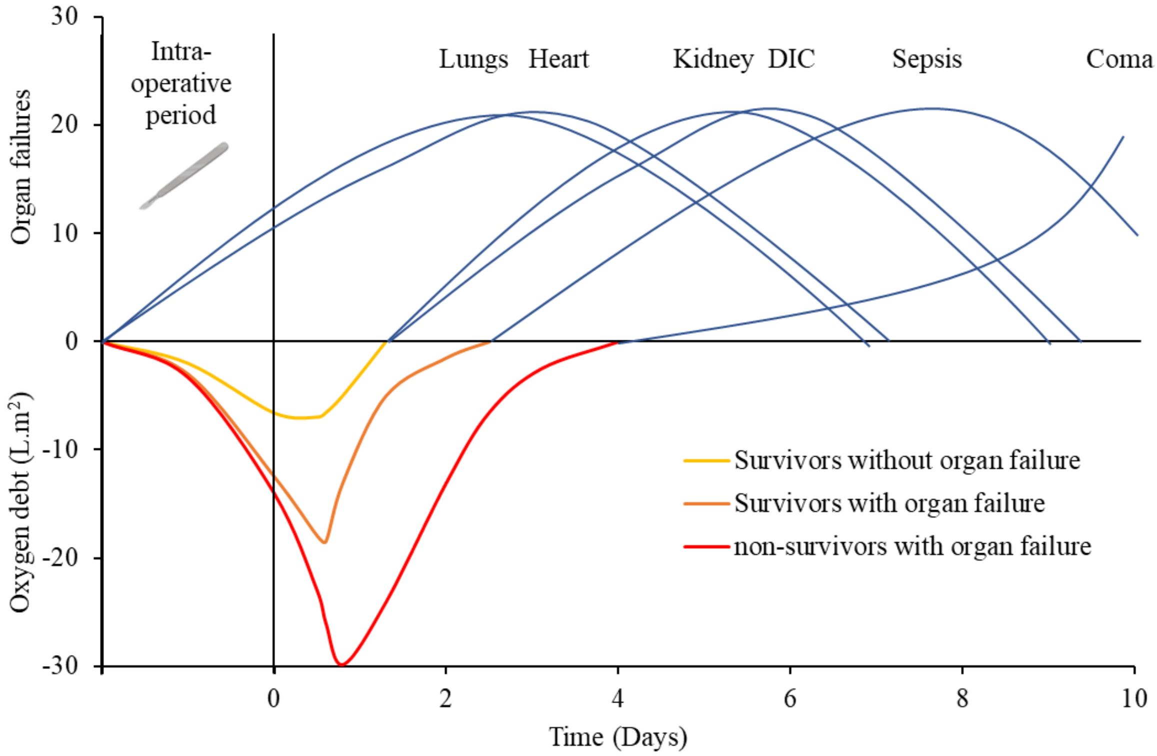


Figure 9. Time course of O_2 debt in survivors with and without organ failure and non-survivors, and the relationship with the emergence and type of organ failures over time, adapted from Shoemaker et al. (1992). Cardiopulmonary complications typically emerge first after surgery, followed by kidney, disseminated intravascular coagulation (DIC), then sepsis and coma.

Interestingly, the recovery ‘slopes’ of the O_2 debt in Figure 9 are much the same, between survivors (with organ failure) vs. non-survivors, and just the intraoperative and early postoperative magnitude is greater which may suggest this to be the more critical component.

2.6. Potential mechanisms that enhance survival

Whilst mechanistic bases explaining the link between (elevated) CRF and postoperative outcome require further elucidation, evidence demonstrates that patients with low CRF are associated with poor postoperative outcome, likely explained by a magnitude of perioperative O_2 debt. Importantly, CRF is a modifiable risk factor and a primary component of prehabilitation strategies (Macmillan, 2019, Tew et al., 2018). Prehabilitation represents an opportunity to improve patient readiness for surgery and is multi-modal in nature comprising exercise training, and improving nutritional and psychological status (Scheede-Bergdahl et al., 2019). Prehabilitation aims to improve patient CRF to better tolerate the surgical stress response, leading to a reduced risk of perioperative complications and improved postoperative outcome (Tew et al., 2018). The theoretical potential for this strategy is demonstrated in Figure 10.

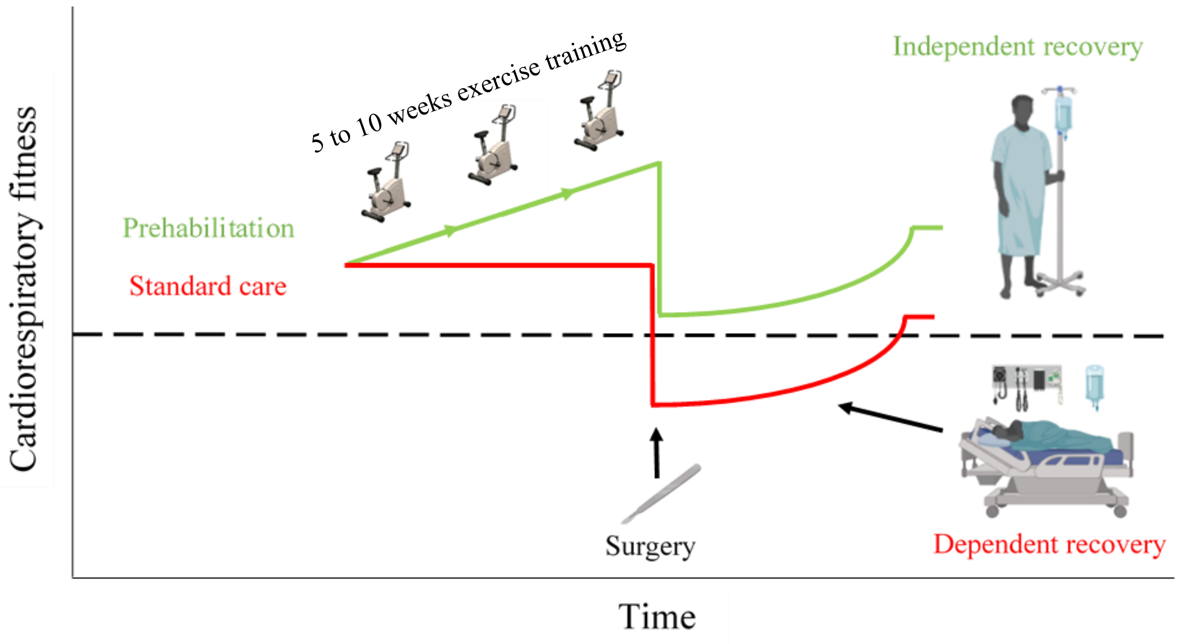


Figure 10. The principle of prehabilitation whereby CRF is improved prior to surgery, thus reducing the risk of poor postoperative outcomes, and enhancing recovery as indicted by the green plot. Adapted from Clegg et al. (2013). The dashed line represents the cut-off between independent (Ward based care) and dependent (HDU, ICU) patient recovery.

Few studies have effectively investigated the potential to improve CRF prior to surgery using exercise interventions and mainly comprise small sample sizes demonstrating proof of principle. West et al. (2015) used an exercise intervention in patients following neoadjuvant chemoradiotherapy prior to surgery. The intervention groups comprised 22 patients, vs. 17 controls, who followed a HIIT protocol, three times per week for six weeks. Following neoadjuvant chemoradiotherapy, O_2 uptake at AT was significantly reduced by 1.9 $mL.kg^{-1}.min^{-1}$ in all subjects. Conversely, six weeks of subsequent HIIT increased O_2 uptake at AT by 2.1 $mL.kg^{-1}.min^{-1}$, whereas it did not change in the controls. In a systematic review, Loughney et al. (2016) concluded that preoperative exercise interventions are safe and feasible, but there are insufficient controlled trials in this area to draw reliable conclusions about the efficacy of these interventions. Recently, clinical guidelines and recommendations for preoperative exercise training in patients awaiting major non-cardiac surgery have been published (Tew et al., 2018), however it is again acknowledged that further research is needed to identify the optimal exercise prescription in different clinical scenarios.

Whilst interest lies in preoperative exercise training, clear translational evidence to improved postoperative outcomes is yet to be established, with studies such as West et al. (2015) underpowered for this endpoint. The most current systematic review (of 22 studies) with meta-analysis claimed that whilst prehabilitation improved preoperative functional capacity (measured by 6 min walk distance, albeit unlike West et al., 2015 objective measures of CRF like $\dot{V}O_2$ peak and AT were not improved) and substantially reduced hospital stay, it did not significantly change postoperative complications, 30-day hospital readmissions or postoperative mortality (Waterland et al., 2021). These findings require caution given the small sample sizes, heterogeneity of exercise interventions, limited reporting of objective measures of CRF, and lack of consensus on standardised endpoints of included studies. Clearly, there is a requirement for a higher quality of evidence from large, randomised control trials, and clinical trials are ongoing with results awaited. Examples include: Van Rooijen et al., (2019), an international multicentre multimodal prehabilitation intervention including exercise, nutrition, and psychological coping strategies within an Enhanced Recovery After Surgery (ERAS) protocol (Trial ID NTR5947); a comparison of hospital based supervised exercise, supported home based exercise vs. usual care to investigate patient recovery after bowel cancer surgery (PREPARE-ABC, 2020; Trial ID ISRCTN82233115); and Wessex Fit-4 Cancer Surgery (Southampton University, 2020) investigating the effectiveness of a community based structured responsive exercise training program with or without psychological support (Trial ID NCT03509428).

From a mechanistic perspective, similarities exist between the physiological insult of surgery and the acute response to an exercise stimulus. Primarily, an increased cellular demand for O_2, consequent to oxidative phosphorylation required to regenerate ATP is required to enable continued physical activity. As a chronic adaptive response to exercise, an improved ability to increase $\dot{V}O_2$ is associated with elevated peroxisome proliferator-activated receptor gamma coactivator 1-alpha mRNA (Gibala et al., 2009), a moderator of skeletal muscle mitochondrial biogenesis. An increase in citrate synthase (a marker of muscle oxidative capacity) has also been reported (Burgomaster et al., 2005), and an increase in oxidative stress (Bailey et al., 2018, Davies et al., 1982, Radák et al., 1999) which is attenuated following exercise training (Fatouros et al., 2004). The mechanisms of this exercise induced response have been linked to improvements in total antioxidant capacity (Fatouros et al., 2004, Radák et al., 1999) which is considered a marker of the bodies defence system to neutralise excessive and deleterious reactive oxygen species (ROS) formation (Ghiselli et al., 2000). Total antioxidant capacity has been enhanced following exercise training in both animal (Liu et al., 2000) and human models

(Fatouros et al., 2004). However, whether the long-term exercise-induced increase in total antioxidant capacity and thus reduction in oxidative stress is a key factor in improving postoperative outcomes remains to be elucidated. Not only has exercise training been associated with a reduction in oxidative stress, but also with improved vascular function and consequent O_2 transport (Wray et al., 2011). Systemic and cerebrovascular function has been shown to improve following HIIT (Calverley et al., 2020, Molmen-Hansen et al., 2012), the potential consequence of an 'optimised' blood flow-shear phenotype, triggering calcium influx into the hyperpolarised endothelial cells (Cooke et al., 1991) upregulating endothelial nitric oxide synthase (Bolduc et al., 2013).

2.7. Optimising risk quantification and patient management

The evidence reviewed suggests that impaired CRF is both an independent and modifiable risk factor associated with postoperative outcome. Yet the strength of this relationship, used to predict postoperative outcome, is not effectively compared to traditional risk factors like ischaemic heart disease, lung disease, or diabetes and obesity. This comparison has been addressed epidemiologically for all-cause deaths (outside of the surgical setting) within the Aerobics Centre Longitudinal Study, and low CRF was found to be a greater risk factor than hypertension, smoking, high cholesterol, diabetes and obesity (Blair, 2009).

Attributable fractions describe the percentage of deaths that would not occur if a risk factor were removed from a population and account for both the risk of mortality associated with that condition and its prevalence in the population, as illustrated in Figure 11. This approach could be conducted in the surgical setting to help optimise risk quantification and highlight the importance of CRF relative to traditional risk factors.

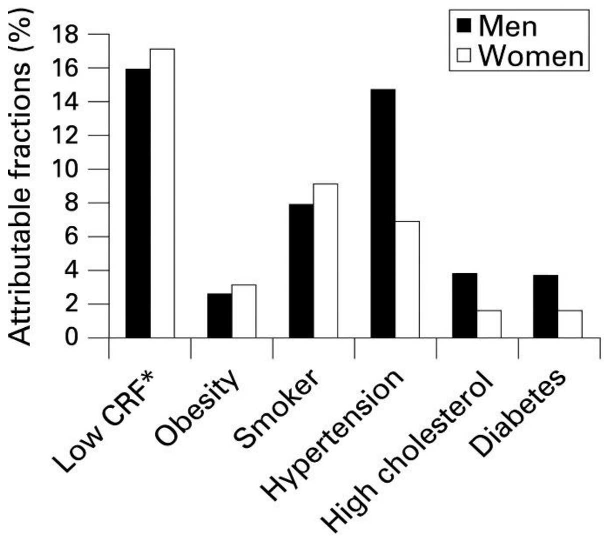


Figure 11. Attributable fractions (%) for all-cause deaths in the Aerobics Center Longitudinal Study, taken from Blair (2009). *Cardiorespiratory fitness determined by a maximal exercise test on a treadmill.

Like most biomarkers, CRF is a dynamic metric subject to variation and thus needs to be interpreted with caution. Such variation encompasses both analytical and biological components. Whilst studies have investigated the reliability of pertinent PCPET variables (Kothmann et al., 2009b), their translational impact upon patient fitness stratification has not been adequately examined.

Patient stratification should be optimised using the most effective metrics of CRF, with accompanying threshold values, which are indicative of risk specific to patient populations and surgical procedures. Table 1 highlights that many studies, including the seminal work of Older et al. (1993), have simply adopted threshold values developed by other studies sometimes using different patient populations and surgical procedures. Furthermore, CRF is commonly described using the AT, $\dot{V}O_2$ peak or $\dot{V}_E/\dot{V}CO_2$ as discussed, however alternative metrics may provide superior prognostic utility in some settings. For example, if a patient is unable or unwilling to exercise to exhaustion, a submaximal measure of CRF relating O_2 consumption to workload achieved, such as the O_2 uptake efficiency slope (OUES; Hollenberg and Tager, 2000) may be more effective.

Surprisingly, despite evidence that CRF is lower in females across the lifespan, given smaller body size, skeletal muscle mass, peak cardiac output and Hb concentration (Jackson et al., 2009, Fleg et al., 2005), sex is not considered during surgical risk stratification. If a simple dose-response relationship exists between low CRF and postoperative survival, we would expect females to be at increased risk given these congenital constraints. Furthermore, other risk factors such as cardiovascular disease (CVD), which may vary between the sexes, require investigation to appraise a potential compensatory effect for CRF and consequent changes in its prognostic potential on postoperative outcome.

Conclusion

The current review has explored the intimate relationship between O_2 transport and postoperative outcome, emphasising how preoperative CRF is an independent risk factor for postoperative mortality and morbidity, when patients undergo major intra-abdominal surgery. There is increased O_2 demand during the perioperative period and patients must meet this demand to avoid debt, the presence and magnitude of which is related to morbidity and mortality. This relationship can be used to assess patient risk, plan perioperative care, and optimise patient management using exercise as a modifiable intervention. However, there is a clear need to improve the detection and interpretation of CRF, better quantify risk to specific populations, sex, and surgical procedure, and better understand the optimal management of patients including mode of exercise to improve CRF. Collectively, a better understanding of CRF used to determine fitness for surgery, will enable clinicians to help direct patient care and improve survival.

2.8. Objective, Aims and Hypotheses

Considering the knowledge gaps outlined, the overarching objective of this thesis was to explore the 'potential' relationship between CRF and postoperative outcome (morbidity and survival) in patients undergoing major intra-abdominal surgery. Three aims were established to: 1) Improve the detection and interpretation of CRF, 2) Explore more sensitive thresholds of CRF predictive of postoperative outcome, and 3) Improve patient risk stratum using exercise.

Improving the detection and interpretation of CRF

To establish robust quality control procedures, the aim of *Study 1* was to firstly determine the magnitude of natural variation described by the 'noise' associated with biological and analytical variation when measuring CRF, which may be a result of time of day, dietary status, and equipment imprecision for example. Secondly, and for the first time within the clinical setting, the corresponding implications for patient fitness stratification were considered if natural variation is not accounted for. It was hypothesised that natural variation is present in markers of CRF and will thus impact upon patient fitness stratification.

Exploring more sensitive thresholds of CRF predictive of postoperative outcome

In *Study 2,* the aims were also two-fold. Firstly, the extent to which CRF is impaired in a cohort of patients undergoing vascular surgery for AAA repair was examined, and secondly, CPET variables and their threshold scores that hold prognostic significance for postoperative survival were defined. It was hypothesised that CRF is impaired in patients with AAA disease, and that the magnitude of impairment can be used to predict postoperative survival, which may help to direct care provision.

The aim of *Study 3* was to firstly investigate the association between CRF and postoperative outcome in a large cohort of (pooled male and female) patients undergoing colorectal surgery and compare the contribution of CRF to mortality against tradition CVD risk factors. Secondly, this study aimed to compare for the first time, the sensitivity to CRF between the sexes and determine if there is need for sex-specific thresholds of fitness to better predict mortality. It was hypothesised that a lower level of CRF would be found in females which would translate into worse outcomes following major colorectal surgery than male counterparts.

Enhancing patient management using exercise

Finally, *Study 4,* a clinical case-study was conducted with the aim to demonstrate the efficacy, feasibility, and potential benefits of HIIT in a high-risk patient requiring oesophageal reconstruction to enable surgery and improve post-operative outcome. It was hypothesised that HIIT prior to major elective surgery is well tolerated and associated with objective cardiopulmonary improvement.

Chapter 3

General Methodology

This chapter describes the equipment used, testing procedures, and analyses performed. Four studies were conducted to explore the relationship between CRF and postoperative outcome, and their details follow.

3.1. Ethics

All procedures were carried out in accordance with the Declaration of Helsinki of the World Medical Association (Williams, 2008). Approval was obtained from The University of South Wales Ethics Committee (LSE1636GREO), and Cardiff and Vale University Health Board Research & Development Office (15/AIC/6352) to analyse databases held at the University Hospital of Wales, Cardiff, Department of Anaesthetics (Appendix B). Patient consent was waived for the first three studies following formal consultation/confirmation with the ethics committee as this work was deemed a service evaluation of standard practice. Written informed consent was obtained for participants in the comparative control arms for S*tudy 1* and *2*, and the patient supporting the clinical case report outlined in *Study 4*.

3.2. Patients

The first three studies used data from consecutive patient visits who underwent CPET as part of a preoperative assessment clinic between January 2010 and December 2016. Only patients who proceeded to surgery and had subsequent complete postoperative records for length of stay, complications, and mortality were included in the analysis.

3.3. Experimental Design

To test the hypotheses, the experimental methodology was divided into four studies. The studies were designed to optimise the assessment and interpretation of CRF, evaluate the association between preoperative CRF and postoperative outcome, and assess the impact that an exercise intervention may have in a prehabilitation setting.

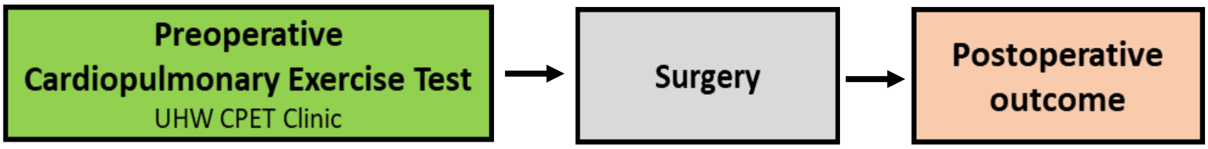


Figure 12. General experimental design for the retrospective analysis of databases. Preoperative CPET were conducted at the University Hospital Wales, Cardiff and results tested for association with postoperative morbidity and mortality.

A retrospective, cross-sectional analysis was conducted of anonymised, longitudinal hospital databases that were prospectively populated at a single NHS centre (University Hospital of Wales, Cardiff). A central CPET Database was collated using merged data from a Colorectal Surgeons Database, Critical Care Database, and longitudinal Office for National Statistics (ONS) mortality records.

3.3.1 Study 1

In a two-armed study focussing on quality control, the magnitude of natural variation associated with repeated measures for selected CPET variables (previously reported as independent predictors of postoperative outcome) was first calculated in a young apparently healthy population. Subsequently, these defined ranges of natural variation were retrospectively applied to an anonymised database of patients who underwent CPET prior to colorectal surgery, to re-appraise fitness stratification.

3.3.2 Study 2

A retrospective cross-sectional analysis of AAA patients was first compared with a matched apparently healthy cohort to determine the magnitude of impaired CRF. Subsequently, the association between impaired CRF and postoperative outcome was investigated in these AAA patients.

3.3.3 Study 3

This study employed a retrospective cross-sectional analysis of patients (female vs. male) undergoing CPET prior to elective colorectal surgery. Firstly, the association between impaired CRF and postoperative outcome was examined for the whole cohort. Preoperative CRF and postoperative outcome was then compared between the sexes, to determine if sex-specific CRF should be considered when interpreting the association between CRF and postoperative outcome.

3.3.4 Study 4

The final study, a case report, constituted a preoperative exercise intervention in a 'high-risk' patient, comparing the efficacy of supervised HITT to improve perioperative risk with a prior home-based unsupervised moderate intensity steady state (MISS) approach.

Figure 13 illustrates the experimental designs employed in each of these studies.

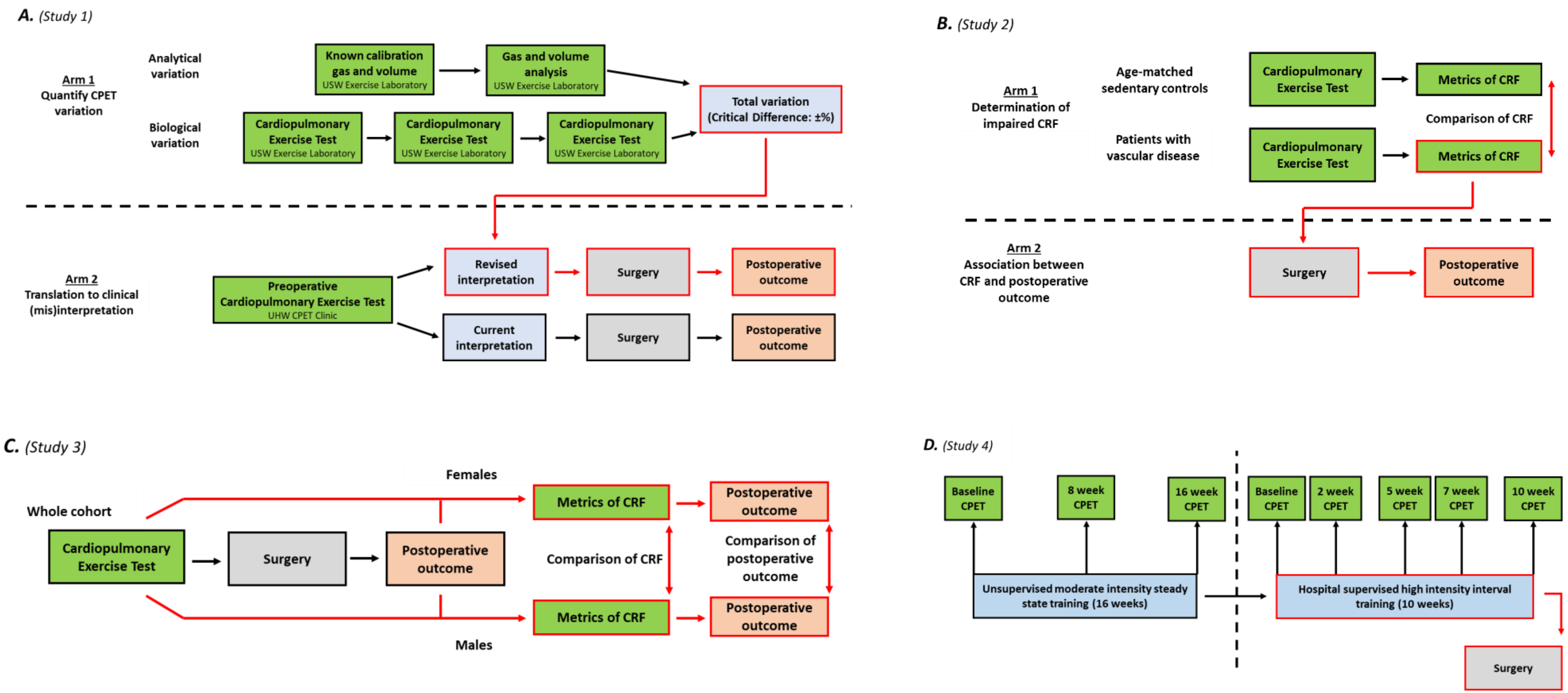


Figure 13. Experimental designs to investigate: **A.** (*Study 1*) the magnitude of variation in CPET test results and potential to inform the misclassification of fitness; **B.** (*Study 2*) the impairment of CRF and association with postoperative outcome in vascular disease; **C.** (*Study 3*) CRF as an independent risk factor compared to traditional risk factors, and sex-specific differences in CRF and association with postoperative outcome in colorectal disease; **D.** (*Study 4*) High intensity exercise training in the 'high-risk' patient. CPET, cardiopulmonary exercise test; CRF, cardiorespiratory fitness.

3.4. Preoperative Assessment

Fundamental to all studies was the assessment of patient CRF using CPET. Whilst the studies comprised retrospective analyses of anonymised databases, all data was collected prospectively as part of usual patient care at a preoperative assessment clinic and thus patient selection was conducted by chronological order.

Prior to the patient's CPET clinic visit, each patient received an information sheet detailing the purpose of this preoperative testing. In the CPET clinic, relevant clinical information and risk factors were recorded in the CPET database, which included comorbidities such as ischaemic heart disease (IHD), heart failure, diabetes, chronic obstructive pulmonary disease (COPD), and cerebrovascular accident (CVA), medications, smoking history, accustomed activity levels, biomarkers (Hb concentration and creatinine). Anthropometric measures for stature (Seca, Hamburg, Germany) and body mass (Seca, Hamburg, Germany) were recorded and body mass index (BMI) calculated. Each patient then had a physical examination of the heart and lungs.

Pulmonary function tests were conducted to determine forced vital capacity (FVC), forced expiratory volume in 1-second (FEV_1), FEV_1/FVC ratio, Slow Vital Capacity and a predicted maximal voluntary ventilation (MVV) by multiplying FEV_1 by 40 (Campbell, 1982). These measures were collected in the best of three single maximal exhalations, followed by a single slow maximal exhalation.

3.4.1 Cardiopulmonary Exercise Test

All CPET were conducted in accordance with the perioperative CPET consensus clinical guidelines (Levett et al., 2018).

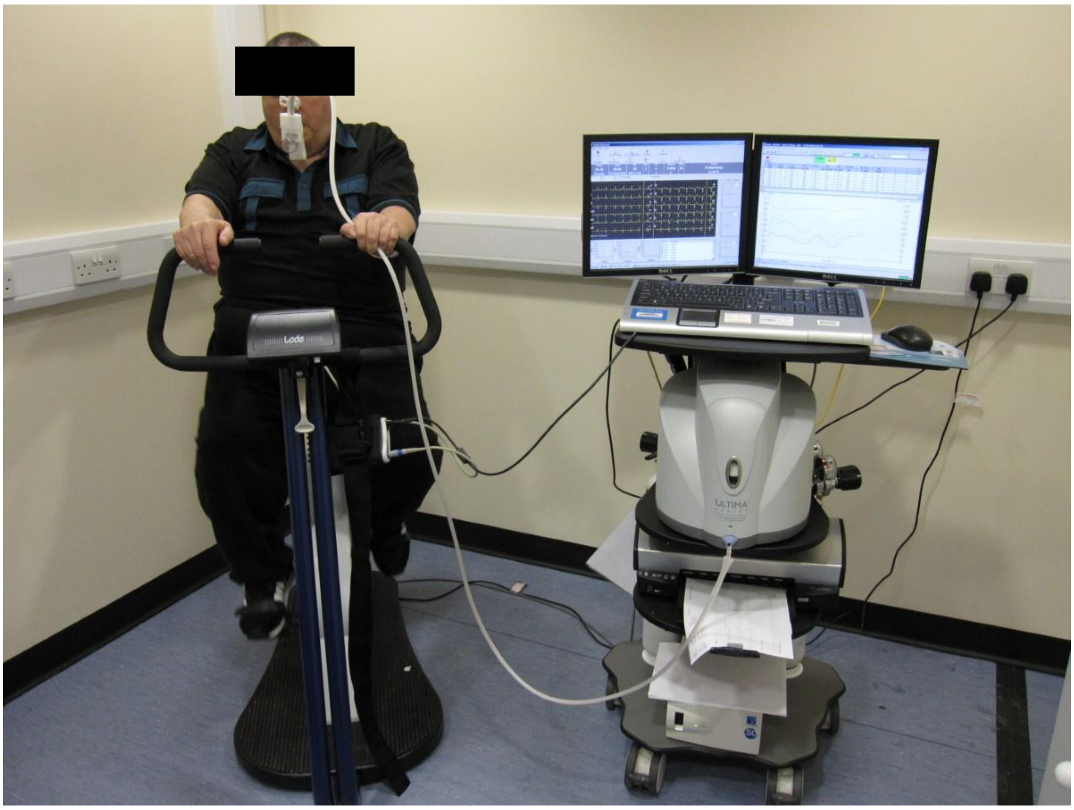


Figure 14. The cardiopulmonary exercise test (CPET).

An electromagnetically-braked cycle ergometer (Lode, Gronigen, The Netherlands) was used for all preoperative CPET. Patients were instructed on how to mount the cycle ergometer and saddle height adjusted. A Medgraphics Ultima metabolic cart (MedGraphics^{TM,} Gloucester, UK) was used to measure respiratory gas concentration for O_2 and CO_2 and flow volume. Calibration was undertaken in accordance with manufacturer's guidelines using a 3-litre volume syringe (Hans Rudolph, Kansas City, USA) for flow calibration, and reference gases (12% O_2, 5% CO_2, and balance Nitrogen) for gas analyser calibration. Periodical biological calibration was also conducted using the responses of a member of the clinic staff familiar with testing procedures. The subject performed two sub-AT constant work rate tests of 6 minutes duration, with the steady-state $\dot{V}O_2$, $\dot{V}CO_2$, and minute ventilation ($\dot{V}_E$) responses at each work rate being obtained by averaging data over the final 2 min of the test with a steady state response observed (Levett et al., 2018).

Prior to commencing exercise, a resting 12-lead electrocardiogram (ECG) was performed (Welch Allyn, New York, USA), nose clip fitted and checked for leaks, and mouthpiece inserted. At least 2 minutes of resting data was obtained. In the event of a high respiratory exchange ratio (RER), the resting phase was extended to allow RER values to approach 1 or below.

An exercise protocol (Wasserman, 2012) was employed whereby patients cycled at 50 to 60 revolutions per minute (RPM) for three minutes in an unloaded freewheeling state followed by a progressively ramped period of exercise (5 to 15 W. min^{-1} based on mass, stature, age, and sex). The work-rate increment was calculated to reach the patient's estimated power at $\dot{V}O_2$ peak in 10 minutes. Blood pressure was measured prior to commencement, and every three minutes during exercise using an automated inflatable cuff and auscultation BP monitor (Phillips Suresigns VS3, Guildford, UK). Arterial blood oxygen saturation was measured at the index or middle finger using pulse oximetry (Nonin 7500, Plymouth, USA) throughout the exercise test. Exercise tests ended when the patient reached volitional exhaustion, or symptom limited termination. Criteria for termination were an ST segment deviation ≥2mm indicated by ECG, arterial O_2 saturation ≤80%, an abnormal blood pressure response to exercise (hypertension defined as >250 mm Hg systolic pressure, or a fall in systolic pressure >20 mm Hg from the highest value during progressive exercise), sudden pallor, loss of coordination, and signs of respiratory failure (Levett et al., 2018).

During exercise, the mid 5 of 7 breaths was averaged. Medgraphics Breeze™ software automatically determined $\dot{V}O_2$ peak (defined as the highest $\dot{V}O_2$ recorded that more often occurred during, albeit not limited to, the final 20 s of a test), OUES (Hollenberg and Tager, 2000), and peak oxygen pulse (O_2 pulse). The AT was manually interpreted by the attending clinician using the V-slope method (Beaver et al., 1986) to 'eyeball' and mark an observed deflection point in the $\dot{V}CO_2$ to $\dot{V}O_2$ plot, supported by comparison of end tidal oxygen tension (ETO_2) and $\dot{V}_E/\dot{V}O_2$ plots at the same marked timepoint. This procedure is described in greater detail in the following paragraphs and supporting Figures 15 and 16. The $\dot{V}_E/\dot{V}CO_2$ was identified at the AT as reported in the software.

The test interpretation procedures were conducted in accordance with the latest Perioperative Exercise Testing and Training Society (POETTS) cardiopulmonary exercise testing consensus clinical guidelines (Levett et al., 2018), the standard to which staff were trained at this centre. This interpretative guidance has published inter-observer agreement, using intra-class correlation coefficients (ICC), for numerical values of AT [ICC 0.83 (0.75-0.90)] and $\dot{V}O_2$ peak [ICC 0.88 (0.84-0.92)] indicating good to excellent reliability (Abbott et al., 2018).

Using the V-slope method, the AT is defined by an inflection point in the $\dot{V}CO_2$ to $\dot{V}O_2$ relationship in the plot of the rate of increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ (Figure 15). This point is identified as the intersection of the linear regression lines of S_1 (below AT) and S_2 (above AT) components. Also, at this point, there is an increase in ETO_2 and $\dot{V}_E/\dot{V}O_2$. The initial two minutes of exercise data were discarded due to the O_2 uptake kinetics response, along with the portion above a respiratory compensation point should an additional deflection in $\dot{V}CO_2$ be observed during the latter stages of exercise.

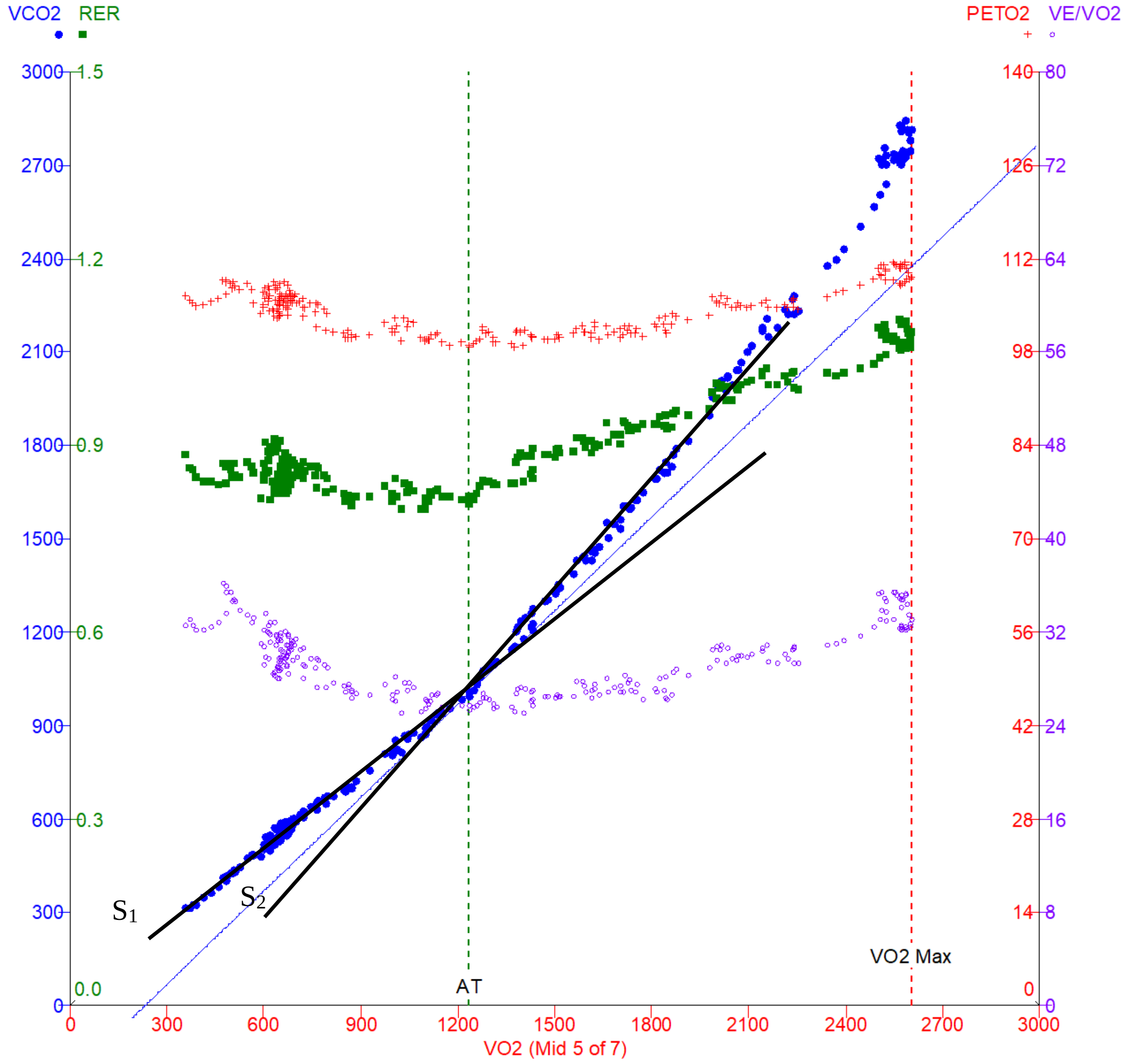


Figure 15. Identification of the AT using the 'V-Slope' method (Beaver et al., 1986). This point is identified as the intersection of the linear regression lines of S_1 (below AT) and S_2 (above AT).

The identified point of AT using the V-slope method was then checked for agreement with a separate plot containing the ventilatory equivalents for O_2 and CO_2. In this second plot, the AT is identified at a point where $\dot{V}_E/\dot{V}O_2$ reaches a nadir after which there is a sustained increase, and at the same time point; $\dot{V}_E/\dot{V}CO_2$ is either still falling or has reached a plateau (Figure 16). Where discrepancies existed, the V-slope method was considered the gold standard.

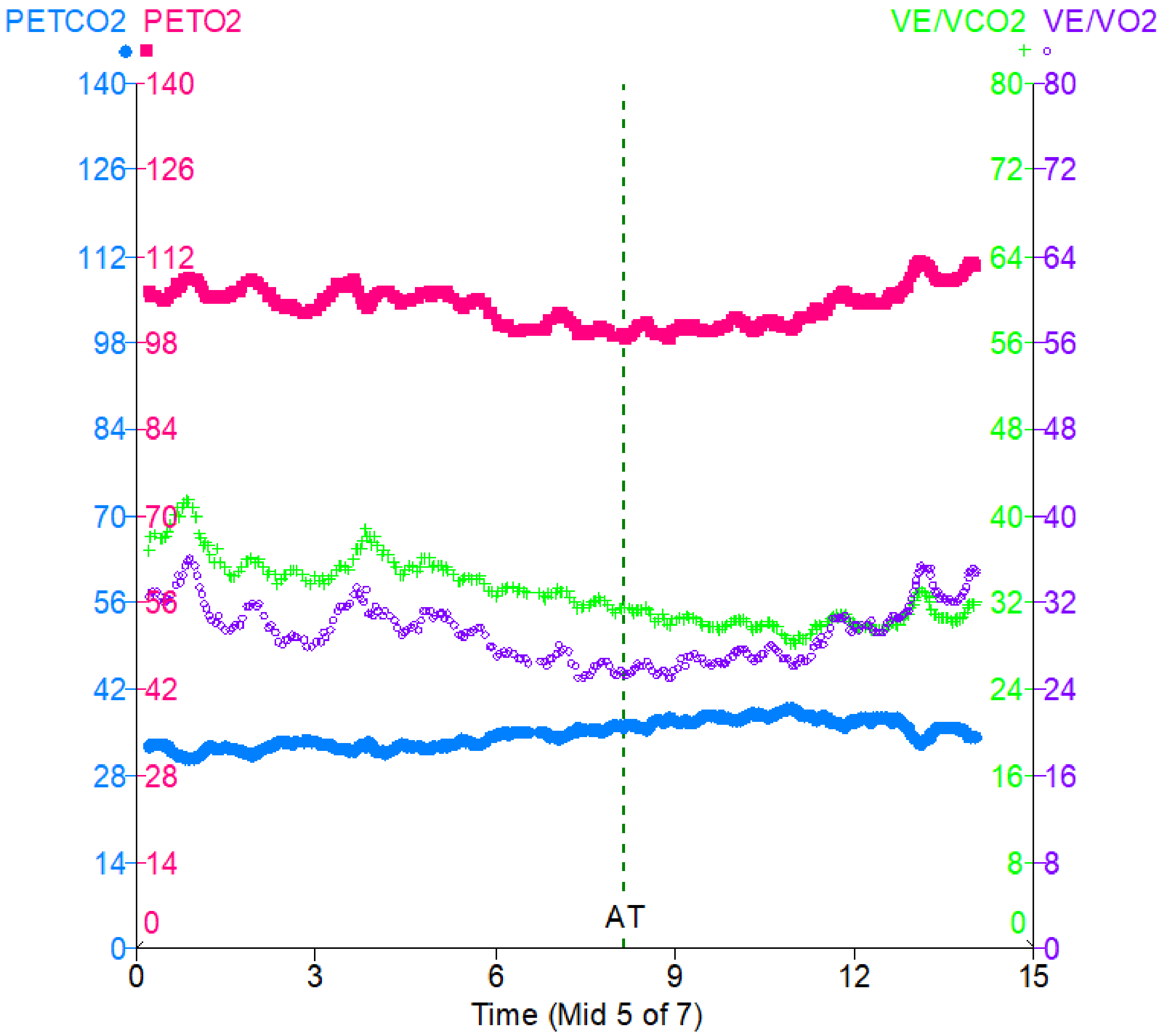


Figure 16. Identification of the anaerobic threshold by comparison of the ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$). The AT is identified at a point where $\dot{V}_E/\dot{V}O_2$ reaches a nadir after which there is a sustained increase, and at the same time point; $\dot{V}_E/\dot{V}CO_2$ is either still falling or has reached a plateau.

All CPET results, alongside patient demographics, diagnosis, comorbidities, and risk factors were then exported into an excel spreadsheet which formed the ‘master’ database into which all postoperative outcome data was added. In the event of a patient attending for CPET and only being able to complete pulmonary function tests; “unable to CPET” was recorded. If a patient achieved only a short duration test (e.g., stopped during the unloaded phase) and/or the

AT was indeterminate from the V-slope or ventilatory equivalent methods, then an AT value was not recoded, and the patient stratified “unable to AT”.

3.5. Postoperative Outcome

Postoperative outcome data were sourced from a hospital Surgeons Database, Critical Care Minimum Data Set, and longitudinal ONS mortality records, cross-referenced with the CPET Database by patient hospital identification number and NHS number. Only patients scheduled for elective surgery were included and minor procedures removed. Details of the surgical procedures were obtained from the Surgeons Database and comorbidities confirmed. Considerable work was required to collate this information into one central database (the CPET master database) as described. Once complete, the central CPET master database was audited using a sample containing 20% of patients which was cross-referenced back to the original independent databases to confirm accuracy of data.

3.5.1 Morbidity

The Surgeons Database provided records of the level of care required by patients following surgery, and contained postoperative destination on either the Ward, Post-Anaesthesia Care Unit (PACU), HDU, or ICU. Subsequent complications were recorded under the following categories: Surgical (return to theatre or unplanned admission to critical care), Cardiovascular, Respiratory, Gastrointestinal, Renal, Neurological, Thromboembolic, Haematological, Infections, Metabolic, Multi-organ failure, Death, Social delay, or High output stoma. Retrospective Clavien-Dindo scores (Dindo et al., 2004) were calculated based on recorded complications, returns to theatre, and in-hospital mortality records. Length of stay was recorded for total postoperative hospital, HDU, and ICU days in the Surgeons Database and Critical Care Database.

3.5.2 Mortality

The National Wales Information Service (NWIS) accessed ONS records using the patient hospital and NHS number and a data set was created for patients identified in the CPET database. To calculate mortality, patient survival status was established at a census date of 30th June 2017 for *Study 2* (patients undergoing vascular surgery) and 27th March 2018 for *Study 3* (patients undergoing colorectal surgery). All patients in the CPET database were returned with a corresponding survival status which was binary coded. Survival days were calculated using an excel spreadsheet formula comparing the date of surgery to the census date if alive, or to the date of death if deceased. Subsequent binary coding was undertaken to determine status at 30-day, 90-day, and 2 years post-surgery. Only patients that had survival days for the complete duration of the specified time points (or a death date within them) were included for analysis. In patients undergoing vascular surgery, these time points were selected to represent both short and mid-term mortality for comparison with previous published data at 30-days (Hartley et al., 2012) and 2-years (Carlisle and Swart, 2007). Ninety-day survival was used as the primary endpoint for patients undergoing colorectal surgery in line with National Bowel Cancer Audit data reporting (NBOCA, 2017) and previous studies (Wilson et al., 2010, Wilson et al., 2019).

3.6. Exercise Training

An initial CPET, as described previously, was conducted prior to commencing exercise intervention. The purpose of the CPET was to measure baseline CRF, define exercise intensities used for training sessions, and to identify the presence of cardiovascular risk factors during dynamic exercising conditions. Subsequently, a 10-week HIIT exercise programme jointly supervised by an exercise physiologist and clinician was undertaken in the hospital setting.

The HIIT consisted of three exercise sessions per week on an electromagnetically braked cycle ergometer (Lode, Gronigen, The Netherlands). Exercise training was completed on Mondays, Wednesdays, and Fridays, with each session lasting 40 minutes in duration. Individual sessions comprised six, two-minute bouts of heavy exercise (50% difference between power output at peak exercise and AT) interspersed with three minutes of moderate exercise (80% power at AT) based on previous research by West et al. (2015) and highlighted in Table 2. Five minutes of unloaded cycling was performed at the start and end of the protocol allowing for a warm-up and cool-down. Heart rate (3-lead ECG, Welch Allyn, New York, USA), blood pressure (Phillips Suresigns VS3, Guildford, UK) and O_2 saturations by finger pulse oximetry (Nonin 7500, Plymouth, USA) were monitored continuously during exercise. The patient was instructed that exercise sessions could be terminated at any time on her instruction, or alternatively by the supervisor if any adverse criteria to stop were met, based on the CPET safety guidelines (ATS/ACCP, 2003).

A CPET was conducted every two weeks and HIIT intensity adjusted accordingly for subsequent exercise training sessions in the event of measured changes in CRF. Following completion of the 10-week exercise intervention, a final and further CPET was performed two weeks prior to surgery to assess changes in functional capacity following HIIT.

Table 2. An individual exercise session.

40 mins exercise (including 5 mins warm-up and 5 mins cool-down)											
3 mins 80% AT	2 mins 50% Δ	3 mins 80% AT	2 mins 50% Δ	3 mins 80% AT	2 mins 50% Δ	3 mins 80% AT	2 mins 50% Δ	3 mins 80% AT	2 mins 50% Δ	3 mins 80% AT	2 mins 50% Δ

80%AT, 80% of the power output at anaerobic threshold (determined by previous CPET); 50%Δ, 50% of the difference between the power output at peak exercise and the power output at AT (For example if power output at AT is 50W and power output at peak exercise is 100W, then 50%Δ = 75W). A 5-minute warm-up and cool-down of unloaded cycling was applied.

Chapter 4

Research Studies

4.1. Study 1

The Cardiopulmonary Exercise Test Grey Zone; Optimising Fitness Stratification by Application of Critical Difference

4.1.1. Introduction

CPET is a non-invasive procedure to determine the level of CRF of patients during a progressive exercise challenge to symptom limited maximum. CPET is used as a tool for preoperative assessment of physical fitness for intra-abdominal surgery to aid clinical decision-making given its increasingly proven association with post-operative outcome (West et al., 2016, Grant et al., 2015, Carlisle and Swart, 2007, Lai et al., 2013, Prentis et al., 2012, Snowden et al., 2013, West et al., 2014b). Furthermore, The AHA has published a scientific statement promoting CRF as a clinical vital sign (Ross et al., 2016). Despite increasing support for CPET, the mechanisms underpinning CRF that provide protection require further investigation.

The seminal work of Older and colleagues (Older et al., 1993) documented an 18% mortality rate in elderly surgical patients with a pulmonary oxygen uptake at the anaerobic threshold ($\dot{V}O_2$-AT) of < 11mL O_2 kg^{1} min^{-1} compared to 0.8% recorded in patients with a $\dot{V}O_2$-AT ≥ 11mL O_2 kg^{-1} min^{-1}. Other biomarkers including $\dot{V}O_2$ peak <15mL O_2 kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}CO_2$-AT > 42 have predicted post-operative survival following AAA surgery (Grant et al., 2015). Studies have further attempted to define threshold values in an effort to optimise risk prediction; for example a range of AT values from 9.0 to 11mL O_2 kg^{-1} min^{-1} have been reported, (Older et al., 1993, Junejo et al., 2012, Prentis et al., 2012, Hartley et al., 2012, Lai et al., 2013) thus demonstrating that variation is present and that a single cut-point cannot be recommended.

Like most biomarkers, CRF is a dynamic metric subject to natural variation and thus needs to be interpreted with caution. Such variation encompasses both analytical and biological components that collectively contribute to the critical difference (CD; Fraser and Fogarty, 1989). The CD represents random variation around a homeostatic point indicative of the change that must occur before a true difference of clinical significance can be claimed. The concept of CD, yet to be applied to clinical CPET variables, emanates from the field of clinical biochemistry and has been applied to metabolic biomarkers of exercise stress and clinical patients (Davison et al., 2012, Bailey et al., 2016).

The current study reflects the first attempt within the clinical setting to quantify the CD of established CPET markers of CRF with corresponding implications for patient management. It is hypothesised that natural variation is present in markers of CRF and will thus impact upon patient fitness stratification.

4.1.2. Methodology

4.1.2.1. Ethics

The University of South Wales Ethics Committee (LSE1636GREO), and Cardiff and Vale University Health Board (15/AIC/6352) approved the study. All procedures were carried out in accordance with the Declaration of Helsinki of the World Medical Association (Williams, 2008). Written informed consent was obtained from participants in study arm 1. Study arm 2 constituted a retrospective analysis of an anonymized database and thus patient consent was waived.

4.1.2.2. Experimental design

A two-armed study was conducted. First, to determine the CDs of selected CPET variables (reported as independent predictors of post-operative outcome), analytical variation was calculated, and biological variation derived using repeated CPET results from a young apparently healthy population (Arm 1). Subsequently, these CD values were retrospectively applied to an anonymised database of patients who underwent PCPET prior to elective colorectal surgery, to re-appraise fitness stratification (Arm 2).

Study arm 1: CD determination

Analytical variation (CV_A); the first component of CD, was determined by repeatedly passing inspired and expired gases through a Medgraphics Ultima metabolic cart (MedGraphics™, Gloucester, UK) in a manner that replicated typical ventilatory responses during the latter stages of a patient CPET (i.e., pulmonary minute ventilation of 25 $L.min^{-1}$). In a series of eight repeated trials each lasting ten respiratory cycles, a 250 L Douglas bag containing saturated expired gas (17% O_2, 5% CO_2) and an equivalent volume of ambient gas was passed through a pneumotach and gas analyser. Inspiration and expiration were simulated using two-way non-rebreathing valves (2700 Series) connected to two factory calibrated 3 L syringes (Hans Rudolph, Kansas City, USA) operated simultaneously (Figure 17). Prior to sampling, calibration was undertaken in accordance with manufacturer's guidelines using a 3 L syringe and a known precision gas. During data collection the middle five of seven breaths were averaged.

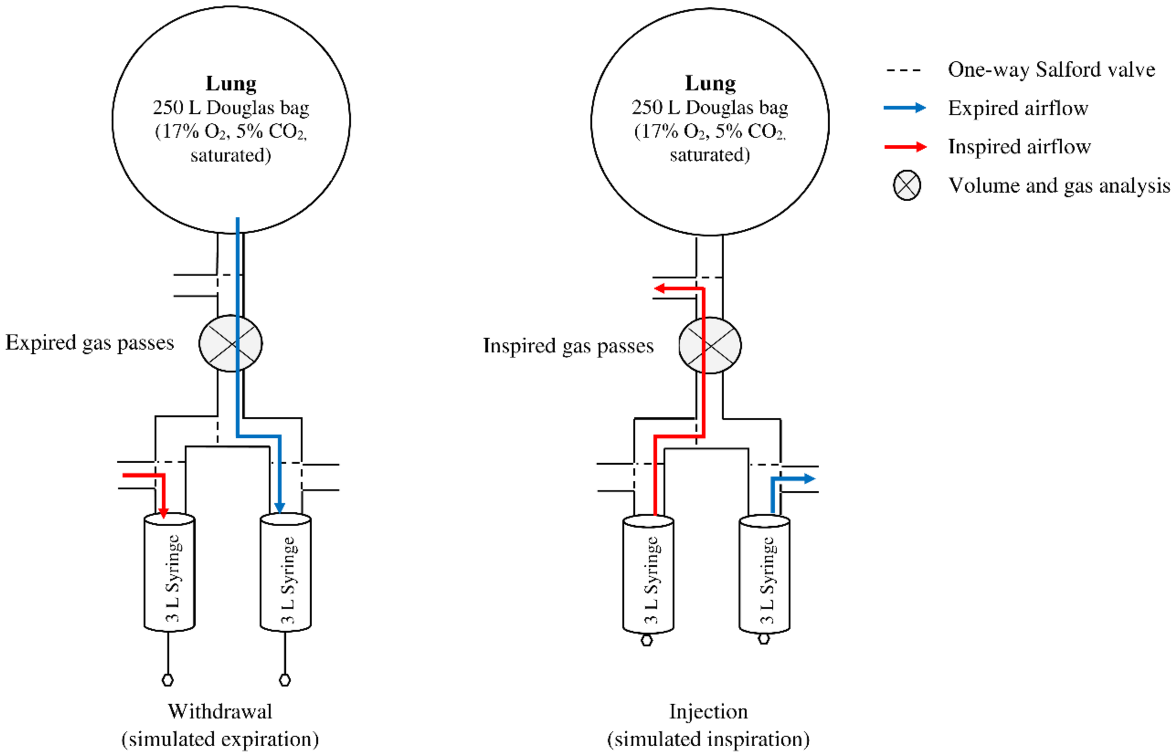


Figure 17. The determination of CV_A for PCPET metrics using simulated expiration and inspiration. CV_A, analytical coefficient of variation; PCPET, preoperative cardiopulmonary exercise test. Simulated oxygen uptake for trials ~ $13 mL.kg^{-1}.min^{-1}$

The within participant coefficient of variation (CV_W) from which biological variation could be calculated, was determined by completion of three repeat CPETs separated by a minimum of 24 hours, for 12 healthy participants (Table 3). Tests were conducted in a randomised order at three time points across operating hours for patient PCPET clinics (09:00 to 10:30, 12:00 to 13:30, and 15:00 to 17:00). All CPETs were conducted to volitional fatigue using the Wasserman (2012) protocol, the same metabolic cart and investigator, and calibration undertaken as previously described. Following three minutes of resting data collection, participants cycled at 60 revolutions per minute on an electromagnetically braked cycle ergometer (Lode, Gronigen, The Netherlands) for three minutes in an unloaded 'freewheeling' state. A progressively ramped period of exercise (10 to 30 W min^{-1} based on stature, age, and predicted $\dot{V}O_2$; Wasserman, 2012) was then undertaken to volitional termination and followed by three minutes recovery. Heart rate (Polar electro, Oy, Finland) was recorded throughout.

Medgraphics Breeze™ software automatically determined $\dot{V}O_2$ peak (defined as the highest $\dot{V}O_2$ recorded that more often occurred during, albeit not limited to, the final 20 s of a test), OUES, and O_2 pulse. The AT was manually interpreted by a clinician using the V-slope method (Beaver et al., 1986), supported by $\dot{V}_E/\dot{V}CO_2$-AT, and $\dot{V}_E/\dot{V}O_2$-AT.

Critical Difference

The CD, taken from the field of clinical biochemistry, is known as the reference change value used as a parameter to interpret test results. CD represents the smallest difference between patient results which when exceeded, likely indicates a true change in the patient. The CD can be expressed as a percentage (applied as ±) or an absolute value in measurement units of the variable concerned. In the setting of CPET, this can be viewed as natural variation which is described by the magnitude of CD and determines the difference in CRF required to demonstrate change not simply due to the 'noise' associated with analytical imprecision (represented by CV_A) and biological variation (represented by CV_B), in order for it to be considered clinically meaningful (Fraser and Fogarty, 1989, Davison et al., 2012). Critical difference uses analysis of variance (ANOVA) to determine the magnitude of random fluctuation around a homeostatic set point within which there is 95% probability that repeated measures will fall. The CD can be set for different probability levels, however, is commonly placed at the 95% confidence limit. The 95% probability is represented by a constant k (2.77) which is calculated from $\sqrt{2} * 1.96$ where 1.96 (two standard deviations) is the factor for 95% probability of a true change in either direction (2-tailed). The constant was multiplied by the square root of the analytical and within-subject biological coefficients of variation combined to make the total variation, thus calculating CD (Equation 1). The coefficients of variation were calculated dividing the standard deviation by the mean score and converted into a percentage as shown in the example of CV_A (Equation 2). The coefficient of analytical variation was subtracted from the CV_W determined from the repeated trials to calculate CV_B (Equation 3).

$$CD = k\sqrt{CV_A^2 + CV_B^2} \qquad \text{(Eq 1)(Fraser and Fogarty, 1989)}$$

Where:

k = constant equal to 2.77 at $P < 0.05$

CV_A = coefficient of analytical variation

CV_B = coefficient of biological variation

CV_A was calculated using the following equation:

$$CV_A = \frac{SD}{\bar{x}} \times 100\ (\%) \qquad \text{(Eq 2)}$$

Where:

SD = standard deviation

$\bar{x}$ = mean

CV_B was calculated from $\dot{V}O_2$ data from each participant, collected at periodic times as described, using the following equation:

$$CV_B = CV_W\,(\%) - CV_A\,(\%) \qquad \text{(Eq 3)}$$

Where:

CV_W = coefficient of within participant variation

Consequently, when interpreting CPET results, and to address the presence of natural variation, the CD (applied above and below an observed score) must be considered to determine the range in which a patient can present without any change in CRF (i.e., before clinical significance can be claimed).

Study arm 2: application of CD metrics to patients

A consecutive sample of 213 patients (Table 3) scheduled for elective colorectal surgery who had undergone CPET testing was retrospectively examined. CPETs were conducted in accordance with the American Thoracic Society/ American College of Chest Physician Statement on Cardiopulmonary Exercise Testing (2003) using identical equipment, investigators, and protocols as outlined in Study arm 1.

Calculated CD metrics were subsequently applied to CPET metrics with established evidence to independently identify unfit patients during pre-surgical assessment (Carlisle and Swart, 2007, Grant et al., 2015, Hartley et al., 2012, Lai et al., 2013, West et al., 2014a, West et al., 2016, Wilson et al., 2010, Snowden et al., 2013). Reference CRF threshold values were established from the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)/AHA Scientific Statement: $\dot{V}O_2$-AT < 11mL O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak < 16mL O_2 kg^{-1} min^{-1}, and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 36 (Guazzi et al., 2016). The CD for additional CPET metrics was calculated for $\dot{V}_E/\dot{V}O_2$-AT (Carlisle and Swart, 2007, Junejo et al., 2014, West et al., 2014a) and peak O_2 pulse (Epstein et al., 2004, Junejo et al., 2012, Prentis et al., 2012, West et al., 2014b).

The calculated CD range above and below an observed score acts as an interval within which we have 95% confidence that repeated measures will fall and was therefore used to redefine and optimise threshold values for CRF used to stratify patient risk. For example, if a patient's $\dot{V}O_2$ peak was measured to be greater than the magnitude of CD above or below the threshold score indicative of low fitness (< 16mL O_2 kg^{-1} min^{-1}), then we have at least 95% confidence that the patient does indeed belong in that fitness strata (a true +ve).

To determine the impact of natural variation on fitness stratification, patient counts were calculated for uncorrected (observed) fit and unfit categories according to EACPR/AHA threshold values, positively corrected (+CD), and negatively corrected (-CD) values. A revised fitness stratification model for each CPET metric was created by applying ±CD to threshold values, thus creating upper and lower boundaries associated with natural variation, and the area in-between the newly defined boundaries classified as indeterminate fitness. Finally, patient counts were compared for current versus newly revised models.

Table 3. Participant and patient characteristics.

	Study arm 1 Apparently healthy participants (n = 12)	***Study arm 2*** Colorectal patients (n = 213)
Demographics:		
Age (years) ˜	22 (20-26)	69 (32-90)
BMI	26 (3.1)	28.3 (5.8)
Sex*		
male	12 (100)	126 (59)
female	0 (0)	87 (41)
Risk factors:		
Smoking*		
no	12 (100)	71 (33)
yes (active/former)	0 (0)	142 (67)
Hypertension*	0 (0)	79 (37)
Diabetes*	0 (0)	34 (16)
IHD*	0 (0)	37 (17)
COPD*	0 (0)	21 (10)
Haemoglobin (g L^{-1})	-	12.7 (1.9)
Creatinine (µmol L^{-1})	-	79.2 (19.7)
Cardiopulmonary function:		
Baseline heart rate (beats min^{-1})	65 (5)	83 (19)
Peak heart rate (beats min^{-1})	178 (5)	124 (28)
$\dot{V}O_2$ peak (mL kg^{-1} min^{-1})	43.8 (6.0)	16.3 (4.9)
RER at peak $\dot{V}O_2$	1.3 (0.1)	1.1 (0.1)
AT (mL O_2 kg^{-1} min^{-1})	23.8 (3.6)	11.0 (3.0)
$\dot{V}_E/\dot{V}CO_2$-AT	23.5 (1.4)	33.6 (5.3)
$\dot{V}_E/\dot{V}O_2$-AT	23.5 (4.7)	30.6 (5.9)
O_2 pulse (mL $beat^{-1}$)	20.7 (0.9)	10.5 (3.8)
Workload at AT (W)	160 (28)	52 (28)
Workload at peak (W)	300 (45)	91 (47)

Data are shown as mean (± standard deviation) or ˜(range), and *n (%). n, number; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; $\dot{V}O_2$ peak, peak oxygen consumption; RER, respiratory exchange ratio; AT, estimated anaerobic threshold; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; O_2 pulse, oxygen pulse at peak exercise; Workload at AT, workload at estimated anaerobic threshold; Workload at peak, workload at peak exercise.

4.1.2.3. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 23.0 Armonk, NY). Distribution normality was confirmed using Shapiro-Wilk *W* tests. Within-subject practice or washout effect between repeated trials, and time of day difference in CPET performance was assessed using Bonferroni corrected repeated measures analysis of variance. Patient counts were analysed using Chi-Square tests. Continuous data are presented as mean (standard deviation) or median (range), and categorical data as absolute values (%). Significance for all two-tailed tests was established at $P < 0.05$. Retrospective sample size calculations were conducted attaining 80% power at the $P < 0.05$ level with the minimum effect of clinical importance represented by the calculated CD (from study arm 1, Table 4) and between-patient standard deviations (from study arm 2, Table 3; Altman, 1980).

4.1.3. Results

Natural variation

No within-subject practice or washout effects were detected for $\dot{V}O_2$ peak [Trial 1: 43.5 (7.8), Trial 2: 44.9 (6.0), and Trial 3: 43.1 (5.8) mL kg^{-1} min^{-1}, $P = 0.424$], $\dot{V}O_2$-AT [Trial 1: 23.8 (3.7), Trial 2: 24.6 (5.0), and Trial 3: 22.8 (3.6) mL kg^{-1} min^{-1}, $P = 0.193$], and $\dot{V}_E/\dot{V}CO_2$-AT [Trial 1: 23.8 (1.6), Trial 2: 23.5 (1.6), and Trial 3: 23.1 (1.9), $P = 0.292$] respectively. The time of day that CPET was conducted also had no effect in measured metrics ($\dot{V}O_2$-AT: $P = 0.40$, $\dot{V}O_2$ peak: $P = 0.81$, and $\dot{V}_E/\dot{V}CO_2$-AT: $P = 0.75$).

Study arm 1 identified a CD of 19% for $\dot{V}O_2$-AT (CV_A 2.2%, CV_B 6.5%), 13% for $\dot{V}O_2$ peak (CV_A 2.2%, CV_B 3.9%), and 10% for $\dot{V}_E/\dot{V}CO_2$-AT (CV_A 0.6%, CV_B 3.6%) (Table 4.). When CD was applied to current CPET fitness threshold values of $\dot{V}O_2$-AT: 11mL O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak: 16mL kg^{-1} min^{-1}, and $\dot{V}_E/\dot{V}CO_2$-AT: 36, a variation of ±2.1mL O_2 kg^{-1} min^{-1}, ±2.0mL kg^{-1} min^{-1}, and ±3.7 respectively was observed.

Table 4. Biological variation and critical difference for cardiopulmonary exercise test variables (Study arm 1, n=12).

Parameter	CV_A (%)	CV_B (%)	Critical difference (%)
AT (mL O_2 kg^{-1} min^{-1})	2.2	6.5	19.1
$\dot{V}O_2$ peak (mL kg^{-1} min^{-1})	2.2	3.9	12.5
$\dot{V}_E/\dot{V}CO_2$-AT	0.6	3.6	10.2
$\dot{V}_E/\dot{V}O_2$-AT	1.7	3.0	9.6
O_2 pulse (mL $beat^{-1}$)	2.2	2.3	8.9
OUES	2.2	3.8	12.1
RER at peak exercise	1.4	5.3	15.2

CV_A, coefficient of analytical variation; CV_B, coefficient of biological variation; AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; O_2 pulse, oxygen pulse at peak exercise; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio.

Potential for incorrect fitness stratification

The CD was applied to positively and negatively correct (the range of) patient CPET scores around their observed (single-point estimate) scores, and subsequently calculated the number of 'false positive' and 'false negative' results. While these terms are not technically correct given the unavoidable uncertainty associated with biological variation and corresponding inability to determine an individual's 'true' level of CRF at any given point in time, it nonetheless provides a conceptual framework to illustrate how blunt application of current thresholds has the potential to affect perioperative planning for a large proportion of patients undergoing major elective surgery.

The application of natural variation (±CD) presented a mathematical possibility for patient results to transcend current fitness stratification boundaries thus demonstrating potential for misclassification (Figure 18) using $\dot{V}O_2$-AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT ($P < 0.001$ in all cases). Differences in patient counts assigned to a given fitness category resulted in false negatives (whereby patients were stratified as fit with variation positively corrected when they were originally unfit), and false positives (whereby patients were stratified as unfit with variation negatively corrected when they were originally fit). Thus, natural variation may have caused up to 59 (28%) false negatives and 69 (32%) false positives at the AT, 33 (15%) false negatives and 35 (16%) false positives at peak $\dot{V}O_2$, and 37 (17%) false negatives and 43 (20%) false positives at the $\dot{V}_E/\dot{V}CO_2$-AT.

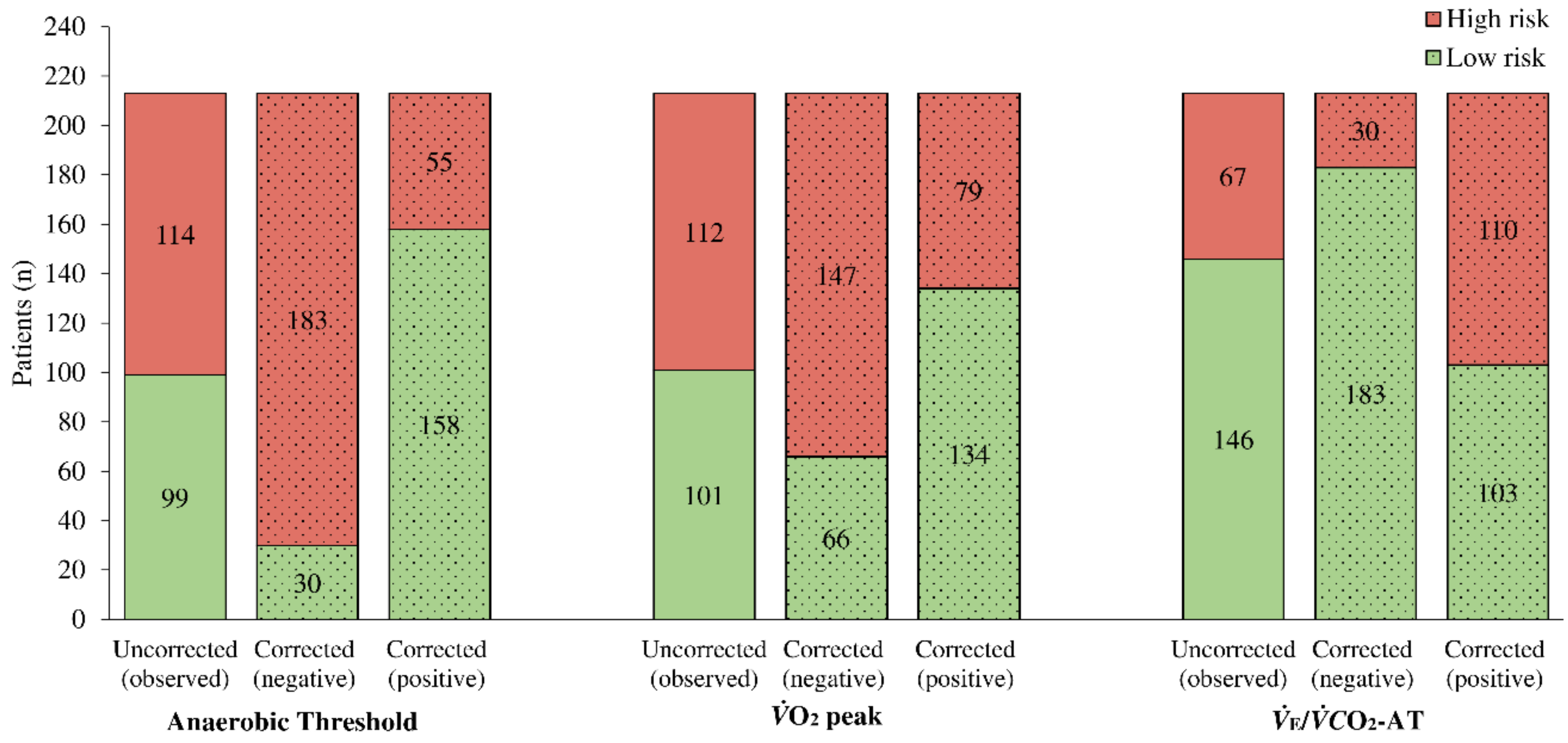


Figure 18. Potential for incorrect patient risk stratification if natural variation is not considered. Patient counts are presented for high (AT < 11mL $O_2.kg^{-1}.min^{-1}$, $\dot{V}O_2$ peak < 16 $mL.kg^{-1}.min^{-1}$, $\dot{V}_E/\dot{V}CO_2 \geq 36$) and low (AT ≥ 11mL $O_2.kg^{-1}.min^{-1}$, peak $\dot{V}O_2 \geq 16$ $mL.kg^{-1}.min^{-1}$, $\dot{V}_E/\dot{V}CO_2 < 36$) risk categories. AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; Observed, uncorrected scores indicative of current risk stratification; Positive, corrected scores by addition of CD; Negative, corrected scores by subtraction of CD. $P < 0.001$ across all pairwise comparisons for corrected scores. Natural variation caused 59 (28%) false negatives and 69 (32%) false positives at the AT, 33 (15%) false negatives and 35 (16%) false positives at $\dot{V}O_2$ peak, and 37 (17%) false negatives and 43 (20%) false positives at the $\dot{V}_E/\dot{V}CO_2$-AT.

Revised model

A revised fitness stratification model (Figure 19) was created with CD defining asymmetrical upper and lower boundaries for absolute values (13.6 and 9.2mL O_2 kg^{-1} min^{-1} for AT, 18.3 and 14.2mL kg^{-1} min^{-1} for $\dot{V}O_2$ peak, 40.1 and 32.7 for $\dot{V}_E/\dot{V}CO_2$-AT) that were independent of fitness misclassification based on natural variation. The resultant area between the upper and lower boundaries represented a newly defined and additional category labelled "Indeterminate-risk".

The indeterminate-fitness category accounted for 60, 32, and 40% of patients for the AT, $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT metrics respectively (Figure 20), and thus fewer patients were stratified as unfit or fit.

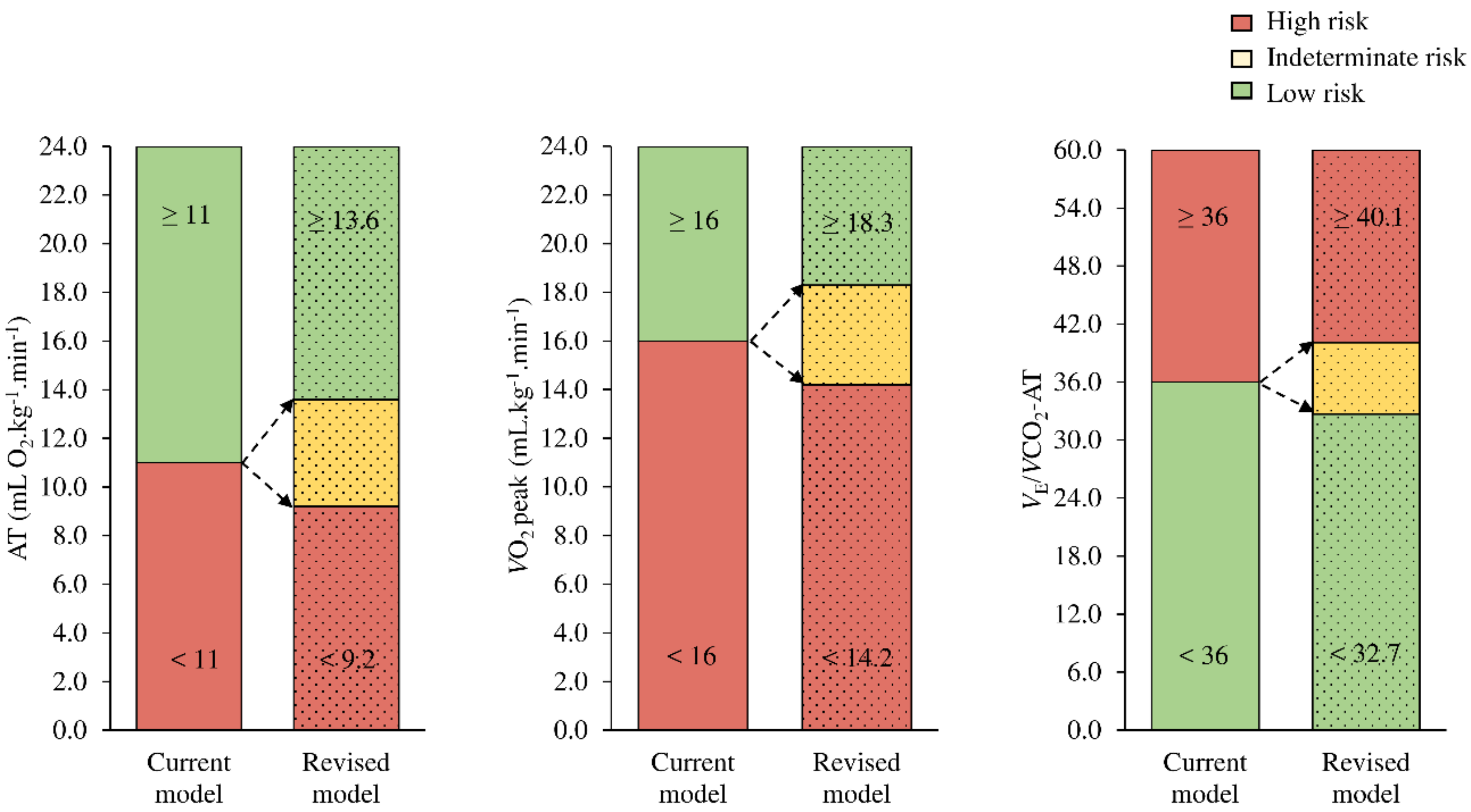


Figure 19. Revised risk stratification model following incorporation of the critical difference for the anaerobic threshold, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT. AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide. Natural variation demonstrates the magnitude of variation present. The lower and upper boundaries define clinically meaningful boundaries not affected by natural variation whilst the area in-between is classified as indeterminate risk.

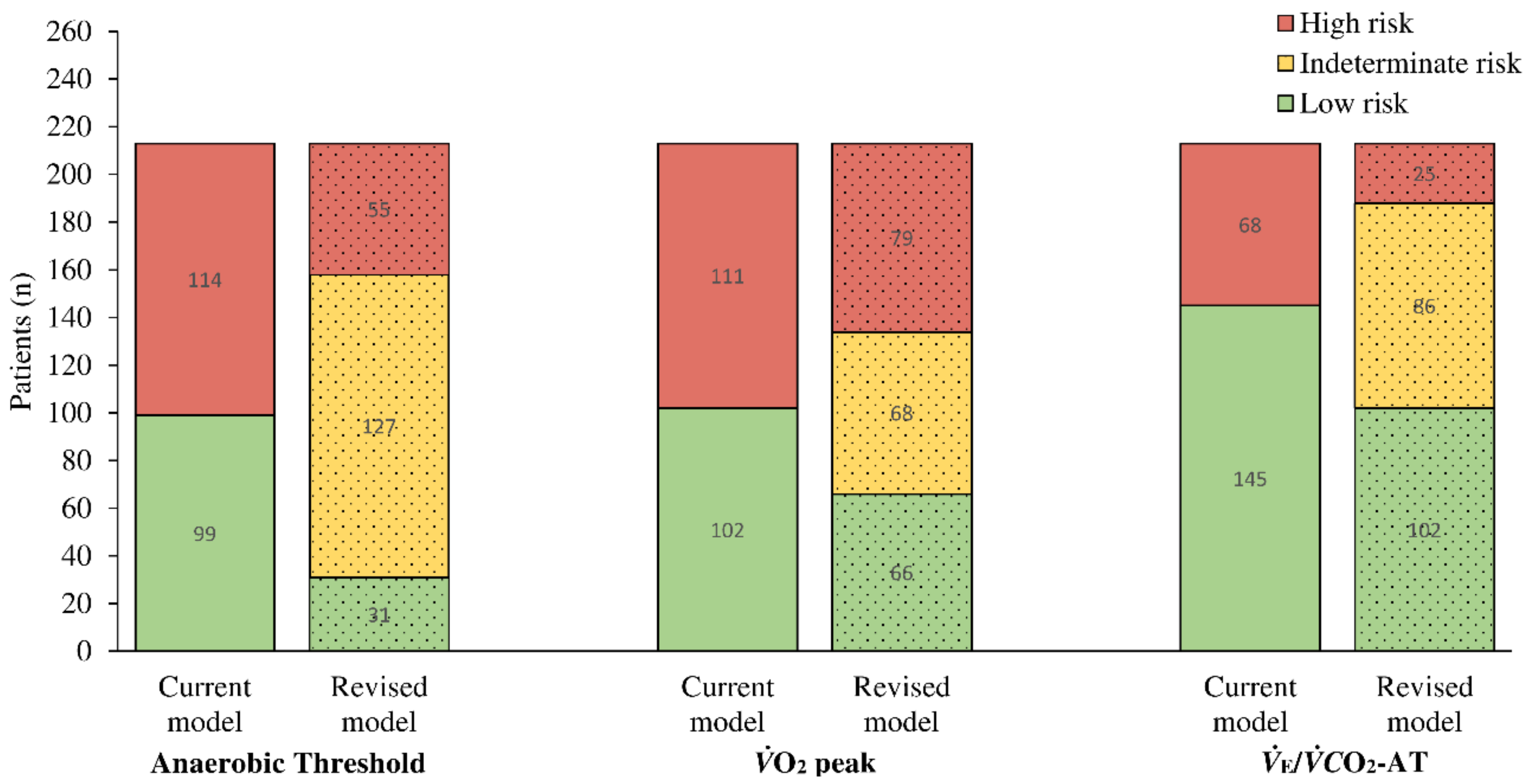


Figure 20. Current versus revised model identification of patient counts by risk category. AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide. The revised model demonstrates large numbers of patients that are classified with indeterminate risk.

4.1.4. Discussion

The present findings highlight the potential for incorrect patient fitness stratification when natural variation is not considered. A revised model was formulated (accounting for natural variation) which established that many patients were stratified with indeterminate fitness. Thus, clinicians should be aware of natural variation and its implications for fitness stratification and this concept should be applied to markers of CRF to further optimise patient management. Whilst this investigation aims to improve the prognostic interpretation of CPET results, it is acknowledged and advocated that clinical decision making does not rely on the application of threshold values alone. There are clear dangers of just using a single point estimate, even if it may be a better number when natural variation is considered. A multitude of additional variables such as work rate, heart rate, duration of exercise, reason for stopping the exercise all go into a composite estimate of functional capacity to be considered alongside other clinical measures when planning perioperative care.

Potential for incorrect patient fitness stratification

The mean CPET score for patients undergoing colorectal surgery was identical to the threshold marker value for AT, within 0.3mL O_2 kg^{-1} min^{-1} for $\dot{V}O_2$ peak, and 2.4 lower for $\dot{V}_E/\dot{V}CO_2$-AT. Thus, when patient scores were positively or negatively corrected with CD, large numbers of patients transcended the EACPR/AHA threshold CRF boundaries demonstrating that natural variation may cause significant rates of incorrect fitness stratification. Of the three primary CPET metrics reported, the AT demonstrated the most incorrectly stratified patients, closely followed by peak $\dot{V}O_2$, and to a lesser albeit significant extent $\dot{V}_E/\dot{V}CO_2$-AT in line with magnitudes of reported CD values and proximity of patient scores to threshold boundaries. Furthermore, a valid and reliable identification of $\dot{V}O_2$-AT is not always possible and has been well documented in patients with heart failure (Arena et al., 2007), and thus may contribute to greater variance in AT.

Revised fitness stratification

The newly revised model (with its wider boundaries accounting for natural variation) excluded many patients from both unfit and fit categories, and thus large numbers were stratified in the indeterminate-fitness category (Figure 20). Not only does this occurrence confirm the impact of natural variation, but consequently presents the challenge of planning perioperative care for patients within this additional fitness category. Concerns may be associated with the introduction of an additional fitness category. For example, patients undergoing colorectal surgery who fell into an intermediate-fitness group (albeit not comparable with the indeterminate-fitness category) have reported a higher rate of serious complications if admitted to the ward rather than HDU (Swart et al., 2017).

The most effective way to assess patient risk is likely a combined approach using clinical variables, biomarkers of susceptibility to disease, and physiological (CPET) testing (Grocott, 2009). Further development of this model is recommended with inclusion of known risk factors independent of CRF to optimise perioperative care.

Limitations

This study has limitations and simply reflects a ‘proof of principle’ concept. Measures of CD were derived from young healthy participants and applied to a cohort of older patients. It may have been possible to recruit a healthy cohort that was better matched in terms of age, sex and BMI which may be assumed to give more generalizable data. However, the repeatability of CPET parameters in healthy subjects has been demonstrated with no significant differences in sex, age, and fitness level (Decato et al., 2018). Comparative values for older controls were not available and would present considerable ethical challenges to determine given that repeat CPET to volitional exhaustion would be required. The CV_W (given by $CV_A + CV_B$ from Table 4) of 6.1% for $\dot{V}O_2$ peak is comparable with chronic obstructive pulmonary disease (6.6%) and congestive heart failure patients observed between 5.7 and 6.0% (Janicki et al., 1990, Owens et al., 1986, Elborn et al., 1990). Furthermore, the CV_W for AT (8.7%) is consistent with patient data (6.8%, 9.2% and 10%; Keteyian et al., 2010, Janicki et al., 1990, Kothmann et al., 2009b), and in excess of CV_W values for $\dot{V}O_2$ peak, the probable consequence of observer error when determining AT via the V-slope method (Beaver et al., 1986). Thus, the method has potential application to clinical populations. Furthermore, our young healthy controls, selected by convenience, may further highlight the necessity to account for natural variation as the reported metrics for CD may reflect a best-case scenario (i.e., lowest CD) if natural variation increases with age and/or pathology. Poole and Jones (2012) demonstrate that slow $\dot{V}O_2$ kinetics during exercise are associated with older and diseased patients, present a greater challenge to homeostasis, and presages poor exercise tolerance. Thus, an even greater magnitude of natural variation may occur in patient populations.

Study arm 1 comprised of men only, whilst the calculated CD was subsequently applied to a population of whom 41% were women. For the $\dot{V}O_2$ peak and $\dot{V}O_2$-AT metrics, the coefficients of variation were comparable with the studies previously stated which also included female data. Metrics represented by ventilatory equivalents however must be treated with caution (for female comparison) as any disparity between the sexes is not accounted for.

Many CPET metrics are scaled to body mass. Further investigation is required to determine if there are any effects on the magnitude of asymmetry for absolute values reported around the zones of indeterminate fitness resulting from scaling to body mass.

Data were collected on a single system in both arms of this study. Analytical precision is likely to vary widely between different manufacturers thus affecting CV_A and consequently CD. Therefore, the results can only be applied with certainty to clinical tests using Medgraphics equipment. At the time of conducting the study the author did not have access to a metabolic calibrator used to calculate CV_A however confidence remains in the findings (up to 2.2%) which are comparable with data produced from such devices, which typically report with accuracy of ±2% (Huszczuk et al., 1990).

It is acknowledged that within the CD range, the further a measured value for a given metric falls from a boundary separating risk stratification, the probability of a false stratification likely becomes smaller. There is no way of knowing an individual's 'true' score as there is no such yardstick (CRF is a moving value resultant of biological variation) and the CD represents a zone of measures within which we have 95% certainty that repeated measures will fall. Furthermore, there is no certainty around the distribution of measured scores within the CD boundary. In biological rhythms we may assume an oscillatory or random spread of measured scores between defined boundaries, however we are not aware of any data for CRF and therefore cannot comment on whether there would be an equal distribution between CD boundaries or a likely bias in any direction. To calculate a difference in probability of a false negative, for example, within the CD range using Bayesian methodologies, further studies would be required to first determine the distribution of many repeated measures within the CD boundaries. Thus, we only state the application of natural variation (±CD) presents a mathematical possibility of a theoretical largest number of patient results that can transcend current risk stratification boundaries.

Prospective sample size calculations

From an experimental design perspective, these observations are interesting when prospectively determining sample sizes for future randomised controlled exercise trials. Studies often rely on minimal clinically important difference (MCID) values such as a $\dot{V}O_2$-AT of 2mL kg^{-1} min^{-1} for example (Kothmann et al., 2009a). This (arbitrarily) defined MCID of 2mL O_2 kg^{-1} min^{-1} falls within the calculated CD of 2.1mL O_2 kg^{-1} min^{-1} (i.e., this is part of normal variation). For comparative purpose, in a worked example using the arbitrary MCID metric of 2mL O_2 kg^{-1} min^{-1} and a standard deviation of 3.0mL O_2 kg^{-1} min^{-1} for $\dot{V}O_2$-AT (derived from the sample of 213 colorectal patients in Table 3) a prospective power calculation indicates that a two-armed exercise intervention study would require a minimum of 36 patients per group (excluding potential dropout) to detect a treatment effect with 80% power at the $P < 0.05$ level. However, to find an effect equal to the CD (using our calculated CD of 2.1mL O_2 kg^{-1} min^{-1} in place of 2mL O_2 kg^{-1} min^{-1}) would reduce the sample size (to 33 patients per group). Furthermore, in an interventional case study design, CD can determine the magnitude of improvement in CRF required, which exceeds natural variation, to indicate an authentic improvement in CRF.

The sample size calculation is based upon a CD determined from a sample of 12 subjects and is limited to a single (Medgraphics) system. Further research (with larger sample sizes, additional metabolic carts, and calculations across the spectrum of age, health and CRF) is encouraged to better support the prospective calculation of sample sizes.

Patient management

Many patients were reclassified into the ‘indeterminate risk’ category which presents the problem of how to clinically manage them. Ideally a high-risk group would be small in numbers allowing appropriate allocation of extensive post-operative care. Wilson (2018) subsequently confirmed a high proportion of patients falling in the ‘indeterminate risk’ category, especially for the AT metric. In Wilson (2018)’s centre these patients would be admitted to an area of a surgical ward with enhanced monitoring with potential to upgrade care and similarly at this centre, a Post-Anaesthesia Care Unit (PACU) could be utilised. This is not an ideal scenario however and still requires much resource, therefore, and from a research perspective, it is recommended that other CPET metrics of CRF with better predictive utility and lower CD magnitudes be investigated. For example, $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT may be better predictors of postoperative mortality with their smaller CD magnitudes, thus defining smaller populations with indeterminate risk. Furthermore, Table 1 highlights many studies that have simply adopted CPET threshold values, often from heterogeneous sources, rather than define them within their own data. Further research can define optimal metrics inclusive of natural variation that better identify high-risk patients.

Conclusions

These findings demonstrate the extent of natural variation in CPET data. Natural variation also has potential to influence patient fitness stratification. Therefore, clinicians should not consider fitness as a single point estimate, but instead as a dynamic range of values defined by natural variation and calculated using critical difference. The use of CRF threshold values inclusive of natural variation to optimise risk prediction models and encourage clinicians to be aware of natural variation and its implications when determining the appropriate level of post-operative care following major surgery is recommended.

4.2. Study 2

Cardiorespiratory Fitness is Impaired and Predicts Mid-Term Postoperative Survival in Patients with Abdominal Aortic Aneurysm Disease

4.2.1. Introduction

Abdominal Aortic Aneurysm is a permanent focal dilatation of the infra-diaphragmatic aorta by 1.5 times the expected normal diameter or greater than 3 cm (Golledge et al., 2006). It can be classified anatomically as supra-renal, juxta-renal, or infra-renal in relation to the renal arteries, with infra-renal AAA being the most common. Rupture of a AAA is associated with a mortality rate of between 65% and 85% resulting in up to 8,000 deaths annually in the UK with approximately half of the deaths attributed to rupture occurring before the patient reaches hospital (Ashton et al., 2002, Basnyat et al., 1999).

Elective AAA surgery is thus indicated for healthy males with aneurysms of 5.5 cm or greater. The corresponding UK in-hospital postoperative mortality for elective open and endovascular (EVAR) AAA repair are considerably lower at 2.9% and 0.4% respectively (VSQI, 2017). However, the physiological insult of major surgery presents an increased O_2 demand during the perioperative period and patients need to achieve a sufficient O_2 delivery to fulfil cellular demand and attain a successful recovery. Shoemaker *et al*. (1992) demonstrated a strong relationship between the magnitude and duration of O_2 deficit in the intraoperative and early postoperative period, and the risk of organ failure and ultimately death. Robust preoperative risk assessment is therefore necessary to identify high-risk patients and optimise care during the perioperative period.

CPET is a non-invasive procedure used to determine the level of CRF of patients during a progressive exercise challenge to symptom limited maximum. In 2016, 47 % of patients in the UK had their fitness measured by CPET as part of a preoperative risk assessment prior to AAA surgery (VSQIP, 2017). A cross-sectional association has been demonstrated between CRF and improved postoperative survival, and reduced morbidity including length of hospital stay (Grant et al., 2015, Hartley et al., 2012, Carlisle and Swart, 2007, Goodyear et al., 2013, Prentis et al., 2012) with values such as an AT < 10.2 mL $O_2.kg^{-1}.min^{-1}$, $\dot{V}O_2$ peak < 15 mL $O_2.kg^{-1}.min^{-1}$, and a $\dot{V}_E/\dot{V}CO_2$-AT > 42 used as threshold scores. However, as with many other preoperative tests, the use of CPET needs to be optimised (Hollingsworth et al., 2015). Thus, the primary aims of the present study were two-fold. First to confirm the extent to which CRF is impaired in AAA patients and define threshold CPET variable scores that hold prognostic significance for postoperative survival.

4.2.2. Methodology

4.2.2.1. Ethics

The Cardiff and Vale University Health Board (15/AIC/6352) approved the retrospective analysis of an anonymised database and thus patient consent was waived. For the healthy control participants, ethical approval was granted by American Medical International (Texas, USA) and the (former) University of Glamorgan (South Wales, Pontypridd, UK). All procedures were carried out in accordance with the Declaration of Helsinki of the World Medical Association (Williams, 2008). The study was not registered in a database.

4.2.2.2. Experimental design

A retrospective cross-sectional analysis of AAA patients (anonymised longitudinal hospital-based database) with a matched apparently healthy cohort was conducted.

4.2.2.3. Participant/patient groups

Healthy participants

For the purposes of comparing baseline CRF, 108 historical controls who had previously engaged in a health-screening program were selected (Table 5). The controls came from a sample of 284 participants (Bailey et al., 1998) and were manually matched for sex, BMI, and age, whilst blinded for $\dot{V}O_2$ peak, the sole measure of CRF recorded.

AAA patients

One hundred and twenty-four consecutive patients of similar age underwent CPET to assess risk for aneurysm repair between 2008 and 2016 (Table 5). Patient data was gathered from medical notes and recorded by the clinician conducting CPET and comprised of BMI, smoking history, presence of IHD, COPD, hypertension, renal disease, and anaemia. Postoperative mortality was determined by review of ONS records and included cause of death. Mid-term survival was calculated by comparison of surgery date and two-year follow up status, a period selected for clinical importance (Grant et al., 2015) and to reduce the interpretive complications associated with surgical intervention (open vs EVAR) upon survival (EVAR trial participants, 2010).

Table 5. Patient and participant demographics.

	Healthy Participants (n = 108)	AAA Patients (n = 124)
Demographics:		
Age (years)	70 ± 7	72 ± 7*
Male/female (n)	80/28	102/22
BMI (kg/m^2)	27.1 ± 3.6	27.5 ± 4.7
Risk factors:		
Smoker/non-smoker (n)	33 (75)	113 (11)*
Hypertension	4 (4)	62 (50)*
Diabetes	7 (6)	7 (6)
IHD	0 (0)	23 (19)
COPD	0 (0)	20 (16)
Surgical approach:		
Open	N/A	88 (71)
EVAR	N/A	13 (10)
Conservative treatment	N/A	23 (19)

Values are mean ± SD or number (%). AAA, abdominal aortic aneurysm; BMI, body mass index; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; EVAR, endovascular aneurysm repair. *Different *vs* Healthy Participants ($P < 0.05$).

4.2.2.4. Measurements

CPET

Healthy participants (comparative analysis)**:** Participants were retrospectively selected based on a normal 12-lead ECG response to a standardised incremental exercise test to volitional exhaustion using the same protocol as outlined for patients. Endpoint determination was assessed by the supervising clinician if the participant developed fatigue, inappropriate dyspnoea, angina, ST segment depression or elevation of 1 mm, significant dysrhythmias, atrioventricular conduction disturbances or defective chronotropic responses. There were no adverse events during the exercise or recovery periods of the tests. All participants were asymptomatic and defined as sedentary since they did not engage in any formal recreational activity outside of everyday living (Bailey et al., 2013a).

AAA patients (correlational analysis): Preoperative CPET were conducted using an electromagnetically braked cycle ergometer (Lode, Gronigen, The Netherlands) and a Medgraphics Ultima metabolic cart (MedGraphics™, Gloucester, UK). Calibration was undertaken in accordance with manufacturer's guidelines using a 3-litre volume syringe (Hans Rudolph, Kansas City, USA) and reference calibration gases. During data collection, the middle five of seven breaths were averaged. An exercise protocol was employed whereby patients cycled at 60 revolutions per minute for three minutes in an unloaded freewheeling state followed by a progressively ramped period of exercise (5 to 15 $W.min^{-1}$ based on mass, stature, age, and gender) to volitional or symptom limited termination, followed by three minutes recovery (Wasserman, 2012). Medgraphics Breeze™ software automatically determined $\dot{V}O_2$ peak (defined as the highest $\dot{V}O_2$ recorded that more often occurred during, albeit not limited to, the final 20 s of a test), OUES (Hollenberg and Tager, 2000), and O_2 pulse. The AT was manually interpreted by a clinician using the V-slope method (Beaver et al., 1986), and supported by comparison of ETO_2 and $\dot{V}_E/\dot{V}O_2$ plots. The $\dot{V}_E/\dot{V}CO_2$ was identified at the AT.

4.2.2.5. Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 23.0 Armonk, NY). Distribution normality was confirmed using repeated Shapiro-Wilk *W* tests. ***Analysis 1 (Comparative):*** Continuous data are presented as mean (standard deviation), and dichotomous variables as number (percentage). Differences in CRF between groups was established using independent samples Student *t*-tests with analysis of covariance performed to adjust for age. Patient counts were analysed using Chi-Square tests. Significance for all two-tailed tests was established at $P < 0.05$.

Analysis 2 (Correlational): The secondary outcome measure, postoperative mortality was assessed using Cox proportional hazards (PHs) regression models. The PH assumption was tested with Schoenfeld residuals (Grambsch and Therneau, 1994). Continuous and dichotomous variables, selected by clinical acumen and without missing values, were first assessed using univariable Cox PH regression. They consisted of age, sex and BMI for demographic risk factors, aneurysm diameter, infra-renal or supra/juxta-renal location, statin therapy, COPD, hypertension and diabetes for clinical risk factors, and the cardiorespiratory variables: $\dot{V}O_2$ peak, $\dot{V}O_2$-AT, $\dot{V}_E/\dot{V}CO_2$-AT, $\dot{V}_E/\dot{V}O_2$-AT, O_2 Pulse, OUES, Workload-AT and Workload-peak. Subsequent multivariable Cox PH models were developed with inclusion criteria of variables at the $P < 0.20$ level (from univariable analysis). Variables were also removed if potential to introduce collinearity to the model was identified by correlation coefficients > 0.80 consistent with Grant et al., (2014). A backward stepwise approach was then employed with exclusion set at the $P < 0.10$ level to yield a final model used to identify independent predictors of postoperative mortality.

Receiver operating characteristic (ROC) curves were constructed for subsequent markers of CRF identified as independent predictors of postoperative mortality. For a marker of CRF to be considered a valid independent predictor of mortality, an area under ROC curve (AUROC) greater than 0.7 was required (Hosmer & Lemeshow, 2013). Optimal threshold values for markers fulfilling this criterion were subsequently calculated by examination of the minimum distance between ROC plots and the upper left corner and presented with sensitivity and specificity. Dichotomised CPET variables were employed to represent sub-threshold CPET values and examined graphically using Kaplan-Meier plots which were compared using a log-rank test to demonstrate postoperative survival with significance established at $P < 0.05$. Confidence intervals (CI) were presented for all survival statistics.

4.2.3. Results

Patient outcomes: Two patients experienced AAA rupture prior to elective surgery and were discounted from the overall analysis. Ninety-nine patients were observed for a median time of 1,034 days following surgery, of which 76 were alive at the time of study analysis. Thirty-day and 90-day mortality was observed for one and seven patients, respectively. Twenty-three patients were treated conservatively, of which 17 died with a median survival of 797 days at the time of study analysis.

Analysis 1 (Comparative): AAA patients were defined by lower CRF across a range of CPET values when compared with similar aged apparently healthy sedentary controls. A mean difference of 13.6 (95% CI 12.0 to 15.2, $P < 0.001$) mL $O_2.kg^{-1}.min^{-1}$ was reported for $\dot{V}O_2$ peak (Figure 21). Covariate analysis for $\dot{V}O_2$ peak demonstrated an age-adjusted mean difference of 12.5 (95% CI 11.1 to 13.9, $P < 0.001$) mL $O_2.kg^{-1}.min^{-1}$ between groups.

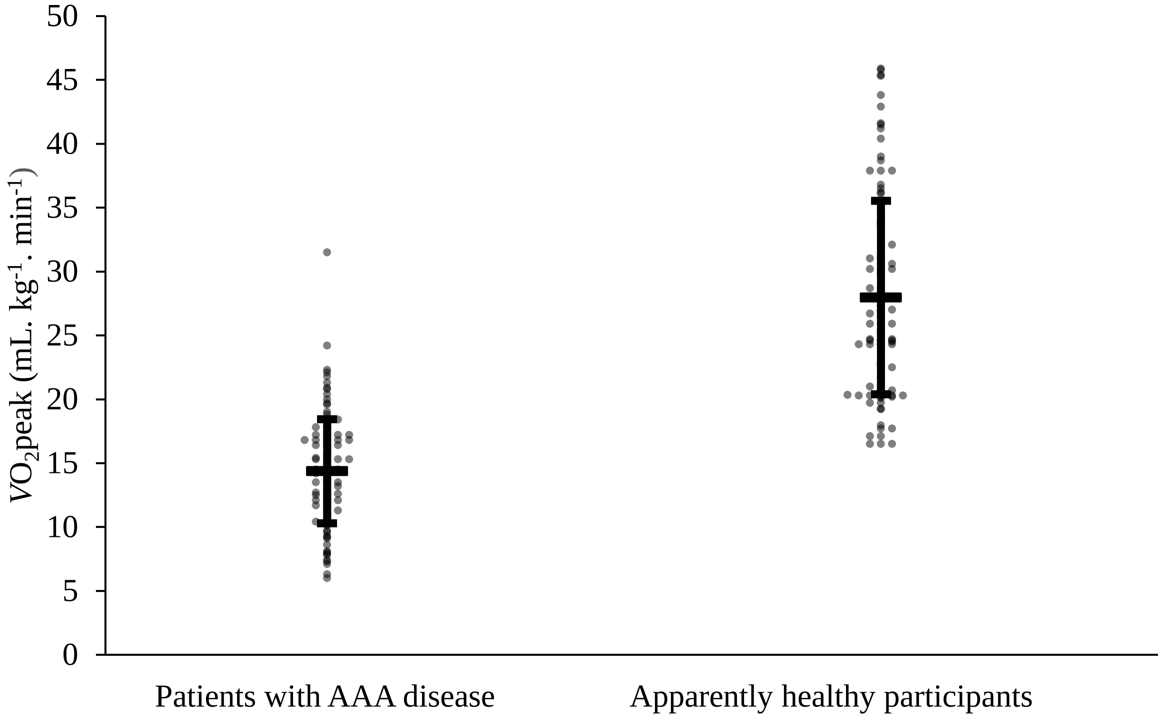


Figure 21. Comparison of peak oxygen consumption between patients with AAA disease and apparently healthy participants. Bars represent mean and standard deviation. *Different *vs* apparently healthy participants (P < 0.05).

Analysis 2 (Correlational): One patient died within 30 days of surgery and 20 deaths were reported two years post-surgery, of which half (10/20) were independent of AAA disease (ONS I71 code; abdominal aortic aneurysm with or without mention of rupture). After univariable analysis, age and all cardiorespiratory variables were significant at the $P < 0.20$ level. In the subsequent multivariable analysis, Workload-peak and $\dot{V}_E/\dot{V}O_2$-AT were removed due to collinearity with $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT, thus the model contained age, $\dot{V}O_2$ peak, $\dot{V}O_2$-AT, $\dot{V}_E/\dot{V}CO_2$-AT, O_2 Pulse, OUES, and Workload-AT. Following stepwise multivariable analysis, the final model step (which was significantly different from the null model, $P = 0.008$) contained age, and both $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT which were found to be independent predictors of mid-term (2 year) postoperative mortality (Table 6). A hazard ratio of 0.84 (95% CI 0.72 to 0.99) was observed for each unit (mL $O_2.kg^{-1}$ min^{-1}) increase in $\dot{V}O_2$ peak.

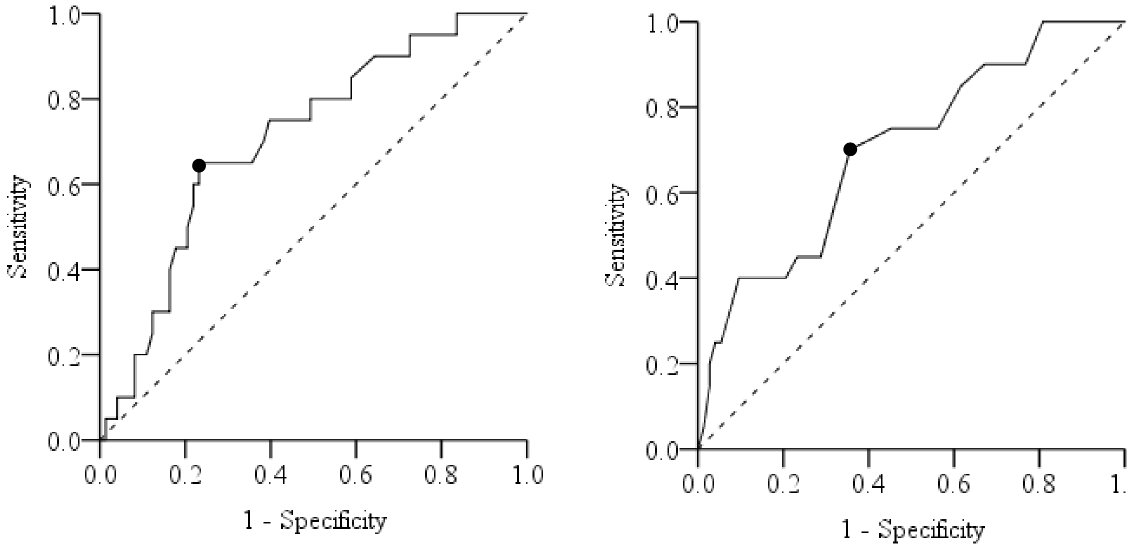
Conversely, a hazard ratio of 1.11 (95% CI 1.03 to 1.20) was observed for each unit increase of $\dot{V}_E/\dot{V}CO_2$-AT.

Table 6. Risk factor relationships with two-year postoperative mortality in AAA patients

	Hazard ratio (95% CI)	*P*-value
Univariable		
Demographics		
Age (years)	1.08 (0.99 – 1.17)	0.08
Female	0.49 (0.06 – 3.73)	0.49
BMI ($kg.m^{-2}$)	1.01 (0.87 – 1.16)	0.93
Clinical		
Aneurysm diameter (cm)	1.06 (0.53 – 2.13)	0.87
Infra-renal	0.44 (0.09 – 2.21)	0.32
Supra/juxta-renal	2.25 (0.45 – 11.18)	0.32
Statin	0.78 (0.24 – 2.52)	0.68
COPD	1.42 (0.32 – 6.42)	0.65
Hypertension	1.48 (0.48 – 4.51)	0.50
Diabetes	1.35 (0.18 – 10.35)	0.78
Cardiorespiratory		
$\dot{V}O_2$ peak ($mL.kg^{-1}.min^{-1}$)	0.81 (0.69 – 0.95)	0.01
$\dot{V}O_2$-AT ($mL.kg^{-1}.min^{-1}$)	0.74 (0.55 – 0.98)	0.03
$\dot{V}_E/\dot{V}CO_2$-AT	1.11 (1.03 – 1.20)	0.01
$\dot{V}_E/\dot{V}O_2$-AT	1.07 (0.98 – 1.18)	0.14
O_2 Pulse ($mL.beat^{-1}$)	0.85 (0.73 – 0.98)	0.03
OUES	1.00 (1.00 – 1.00)	0.12
Workload-AT (W)	0.98 (0.95 – 1.00)	0.06
Workload-peak (W)	0.98 (0.96 – 0.99)	0.01
Multivariable		
Age	1.08 (0.98 – 1.19)	0.14
$\dot{V}O_2$ peak ($mL.kg^{-1}.min^{-1}$)	0.84 (0.72 – 0.99)	0.04
$\dot{V}_E/\dot{V}CO_2$-AT	1.10 (1.01 – 1.19)	0.03

BMI, body mass index; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; AT, anaerobic threshold; O_2 Pulse, oxygen pulse at peak oxygen consumption; OUES, oxygen uptake efficiency slope.

An AUROC (Figure 22) of 0.708 (95% CI 0.585 to 0.830; P = 0.005) was observed for $\dot{V}O_2$ peak with an associated cut-off point of < 13.1 mL O_2.kg^{-1} min^{-1} (sensitivity 65%, specificity 77%). The AUROC curve for $\dot{V}_E/\dot{V}CO_2$-AT was 0.702 (95% CI 0.574 to 0.830; P = 0.006) with an associated cut point of ≥ 34 (sensitivity 70%, specificity 64%).



A. $\dot{V}O_2$ peak **B.** $\dot{V}_E/\dot{V}CO_2$-AT

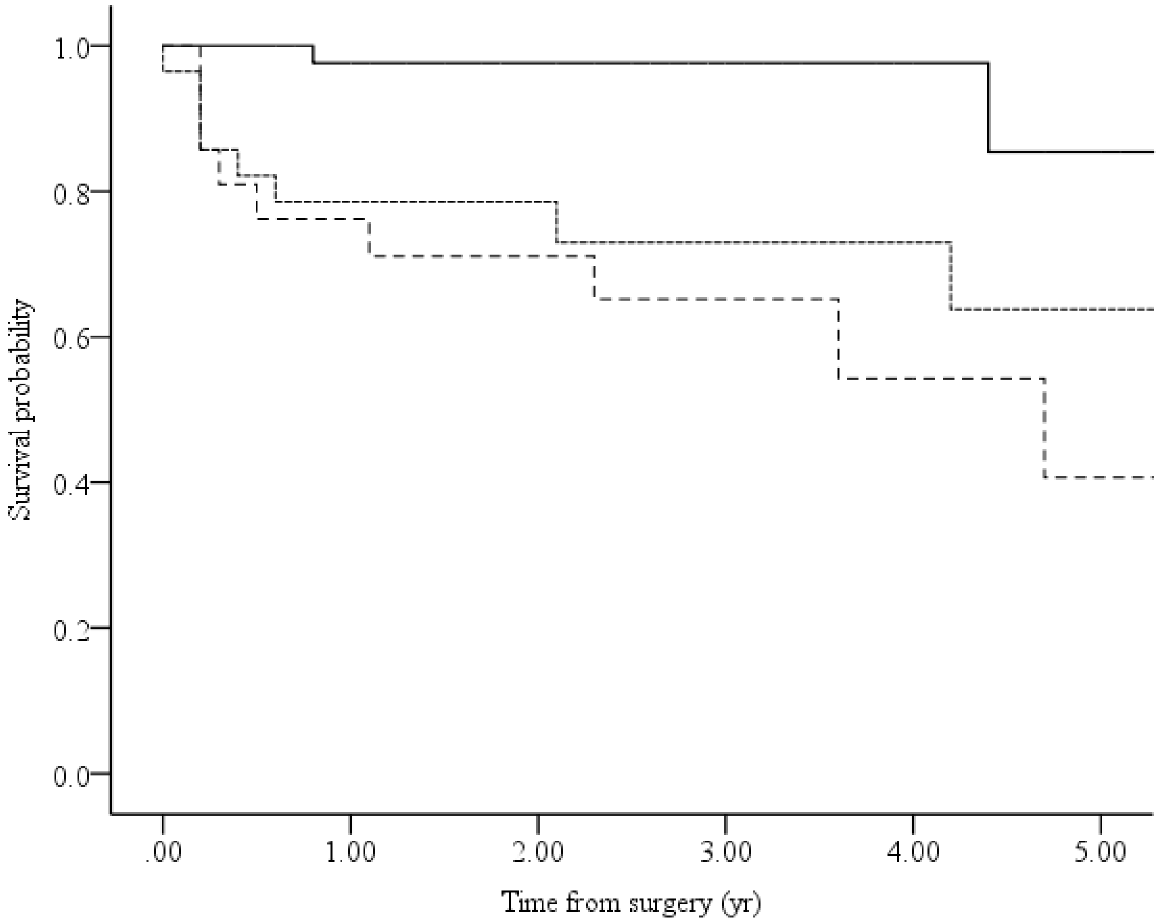
Figure 22. Area under Receiver Operating Characteristic curves. **A:** $\dot{V}O_2$ peak and **B:** $\dot{V}_E/\dot{V}CO_2$-AT. ● Symbols represent optimal cut points. Area under curve: **A** 0.708 (95% CI 0.585 to 0.830; P = 0.005; cut point 13.1 mL.kg^{-1}.min^{-1}); **B** 0.702 (95% CI 0.574 to 0.830; P = 0.006; cut point 34). $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.

The defined cut points for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT (herein defined as sub-threshold CPET values) were applied to stratify patients into high or low-risk subgroups. Subsequently, when entered into a further regression model, hazard ratios of 5.27 (95% CI 1.62 to 17.14, $P = 0.006$) for $\dot{V}O_2$ peak < 13.1 $mL.kg^{-1}.min^{-1}$ and 3.26 (95% CI 1.00 – 10.59, $P = 0.049$) for $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 were apparent (Table 7). Thus, $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT were independent predictors of mid-term survival and patients with one or two sub-threshold CPET values demonstrated reduced postoperative survival ($P = 0.01$) as illustrated in Figure 23.

Table 7. Regression analysis for selected CPET sub-threshold values predictive of two-year postoperative mortality in AAA patients

	Hazard ratio (95% CI)	***P*-value**	**2-year mortality n (%)**
$\dot{V}O_2$ peak < 13.1 $mL.kg^{-1}.min^{-1}$	5.27 (1.62 – 17.14)	0.006	13 (11) *
$\dot{V}O_2$ peak ≥ 13.1 $mL.kg^{-1}.min^{-1}$	Reference group		7 (6)
$\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 units	3.26 (1.00 – 10.59)	0.049	15 (13) *
$\dot{V}_E/\dot{V}CO_2$-AT < 34 units	Reference group		5 (4)

*$P < 0.05$. $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.



Sub-threshold values		No, at risk					
0	———	43	38	30	16	8	5
1	--------	27	19	15	10	7	4
2	- - - - -	20	14	12	7	4	2

Figure 23. Kaplan-Meier plot for survival following AAA surgery stratified by the number of sub-threshold CPET values. P = 0.01, log rank test. Sub-threshold CPET values: $\dot{V}O_2$ peak < 13.1 ml.kg^{-1}.min^{-1}, and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34.

Previous work from this group (Rose et al., 2018b) has demonstrated that natural variation is present in magnitudes of up to ±13 and 10% respectively for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT, and therefore sub-threshold CPET values should take account of this variation when optimising patient fitness stratification. Three zones were calculated whereby patients were either "fit" (≥ 13.1 mL.kg^{-1}.min^{-1} and < 34 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT with natural variation accounted for), "intermediate fitness" (scores that could transcend the sub-threshold values when natural variation is considered), and "unfit" (< 13.1 mL.kg^{-1}.min^{-1} and ≥ 34 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT with natural variation accounted for). Therefore, the defined threshold values produced zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 mL.kg^{-1}.min^{-1} for $\dot{V}O_2$ peak and <31, 31 to 38, and >38 for $\dot{V}_E/\dot{V}CO_2$-AT. Subsequent mortality rates for patients stratified into each zone of fitness are presented in Table 8.

Table 8. CPET variables predictive of postoperative mortality, defined with zones inclusive of natural variation.

	Hazard ratio (95% CI)	***P*-value**	**Mortality n (%)**
$\dot{V}O_2$ peak (mL.kg^{-1}.min^{-1})			
Unfit < 11.6	4.69 (1.21 – 18.26)	0.026	6 (35)*
Intermediate 15 to 11.6	3.10 (0.93 – 10.27)	0.065	9 (26)
Fit > 15	Reference group		5 (10)
$\dot{V}_E/\dot{V}CO_2$-AT (units)			
Unfit ≥ 34	8.59 (1.87 – 39.41)	0.006	8 (47)*
Intermediate ≥ 34	2.12 (0.53 – 8.52)	0.289	9 (18)
Fit < 34	Reference group		3 (9)

*$P < 0.05$ different from reference group. $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.

4.2.4. Discussion

Consistent with the original hypotheses, this study has revealed two findings. First, CRF was shown to be impaired in AAA disease relative to an apparently healthy sedentary population of comparable age. Second, both $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT were able to independently identify patients at high-risk of mid-term postoperative mortality, but not during the intraoperative period. Collectively, these findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients which may help direct care provision.

In the context of the present study, it is speculated that impaired vascular function precipitated by inadequate antioxidant defence and corresponding elevation in oxidative-nitrosative stress, collectively associated with impaired CRF (Bailey et al., 2013b) and AAA disease (Bailey et al., 2006), may be responsible for inferior postoperative outcomes. Impaired vascular endothelial function has been observed in the early postoperative period following major colon cancer surgery (Ekeloef et al., 2017) and warrants further investigation in this population. Furthermore, in addition to impaired $\dot{V}O_2$ peak, patients with high risk of postoperative mortality demonstrated elevated $\dot{V}_E/\dot{V}CO_2$-AT suggesting that inefficient ventilation of the lungs consequent to the mismatching of ventilation to perfusion is a significant risk factor.

As expected, CRF was impaired in AAA disease. This study used an effectively controlled research design with a comparative sample of participants selected by convenience to account for the effect of age, gender, and activity levels. Furthermore, the objectively determined 12-lead ECG assessments confirmed that the control participants were asymptomatic and free of any overt cardiovascular/ischaemic heart disease given a negative functional diagnostic exercise stress test. Of interest, increased prevalence of aneurysmal disease has been linked to populations exhibiting low levels of CRF and reduced blood flow, as demonstrated in amputees and spinal injury, which has been hypothesised as a causative factor (Yeung et al., 2006, Vollmar et al., 1989).

The mean $\dot{V}O_2$ peak for patients with AAA disease reported in this study (14.4 $mL.kg^{-1}.min^{-1}$) was like that reported by Prentis *et al.* (2012). The $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT in this study were independent predictors of postoperative survival in agreement with previous studies (Carlisle & Swart, 2007; Hartley *et al.*, 2012). However, the defined sub-threshold values of < 13.1 $mL.kg^{-1}.min^{-1}$ and ≥ 34 were lower than those previously reported emphasising the need for a more conservative approach. Of interest and contrary to other studies (Grant et al., 2015, Hartley et al., 2012), AT did not predict survival in our cohort of patients.

Studies with larger sample sizes have previously reported an association between CPET values and postoperative survival however limitations are evident. The largest study which recruited 506 patients (Grant et al., 2015) did not define sub-threshold CPET values from their own dataset and instead adopted values from a study (Carlisle and Swart, 2007) with a similarly sized cohort to the present study. Furthermore, another large study (Hartley et al., 2012) adopted sub-threshold CPET values used to predict postoperative morbidity in heterogeneous populations (Snowden et al., 2010). Thus, the current findings demonstrating a lower than previously reported $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT, and no association for AT, hold novel value of clinical importance for patients undergoing surgery for AAA repair.

The value of reporting mid-term survival (defined as two years post-surgery in our data) for patients undergoing AAA repair is supported as in-hospital mortality is now reported at relatively low levels of 2.9% and 0.4% for open and EVAR approaches respectively (VSQIP, 2017). Furthermore, surgery is undertaken not to cure the disease, but to prevent future risk of rupture and thus decision making needs to account for a long-term risk assessment (Howell, 2017). Of the 20 deaths reported in this study at two years post-surgery, half (10/20) were independent of AAA disease (ONS I71 code; abdominal aortic aneurysm with or without mention of rupture). The current findings did not support the ability of CRF to identify patients at high-risk of intraoperative mortality as only one patient died within 30 days of surgery. It is acknowledged that the sample size (Altman, 1980) was based upon the primary outcome variable; to determine if CRF was impaired for patients with AAA disease when compared with age-matched apparently healthy sedentary controls, and retrospective analysis demonstrated > 0.999 power at the $P < 0.05$ level for our given effect size (2.05). The sample size used in Cox regression modelling, however, was low and findings should be considered with caution. Although variables of CRF were significant, the potential for appropriately selecting the best model may have been compromised (Ogundimu et al., 2016).

Few studies have defined sub-threshold CPET values indicative of increased postoperative risk in patients with AAA disease. Instead, many rely on previously defined values, which in some cases may have been determined from different patient populations. It is therefore suggested that these defined threshold values hold potential to improve future identification of high-risk patients. Either $\dot{V}O_2$ peak or $\dot{V}_E/\dot{V}CO_2$-AT should be considered for risk appropriation, and if sub-threshold scores for both are presented, a cumulative effect is likely as demonstrated in Figure 23. Recent work from this group (Rose et al., 2018b) recommends that clinicians should not consider fitness as a single point estimate, but instead as a dynamic range of values defined by natural variation and calculated using critical difference (Fraser and Fogarty, 1989, Davison et al., 2012). Thus, rather than advocating specific binary threshold values, zones along a spectrum of fitness should be adopted (Wilson, 2018). Using this methodology as calculated in the current results, it is recommended that clinicians adopt zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 mL.kg^{-1}.min^{-1} and <31, 31 to 38, and >38 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT respectively. When accounting for natural variation, postoperative mortality was significantly higher in the unfit group, albeit not the intermediate group, compared with fit patients. Findings, however, require caution given the further reduction in group numbers.

Given this data, it was not possible to predict perioperative risk based upon the application of CRF (likely due to the relatively low levels of reported in-hospital mortality and underpowered sample size), and interest arises as to why, in this vascular impaired population, there is an apparent need to wait for two years for the benefit of improved CRF to become apparent? Furthermore, a well-established mechanistic grounding for the protective benefits of improved CRF is yet to be fully established.

Limitations

An association between CPET and mid-term postoperative survival has been reported. However, in order to demonstrate an improved ability to identify high-risk patients, CPET values should also be compared against, or in conjunction with, other risk prediction models such as the Revised Cardiac Risk Index (RCRI), POSSUM, National Surgical Quality Improvement Program (NSQIP), and Surgical Outcome Risk Tool (SORT) (Reeves et al., 2018). Whilst CRF was shown to be impaired in AAA disease relative to a healthy sedentary population of comparable age, it was not possible to determine if any of the control population exhibited AAA disease as they were not screened via Duplex ultrasonography. The (nested) sample of patients who underwent CPET were not representative of the whole population who underwent surgery for aneurysmal repair at this centre and only included those who were referred for CPET. Further investigation of the referral process is required to determine how many patients did not undergo CPET and what the underlying reasons were. The decision to operate (or treat conservatively) was likely influenced by CPET results as patients were routinely referred for CPET to aid risk stratification. Patients treated conservatively demonstrated lower levels of CRF with $\dot{V}O_2$ peak reported at 12.1 mL.kg^{-1}.min^{-1}, a reduction of 2.3 (95% CI 0.29 to 4.28, P = 0.025) mL.kg^{-1}.min^{-1}. The type of surgery (open vs EVAR) can impact in-hospital mortality albeit at 2 years, survival is equal (EVAR trial participants, 2010). It was not possible to determine the number of cases where CPET results influenced treatment decisions, and this may introduce potential for bias. Most patients received open surgery (88% of all elective cases) and therefore findings should be generalised to this approach with greater confidence than EVAR. Despite these limitations, a clear impairment of CRF has been demonstrated in AAA disease, the extent of which may hold predictive value when assessing surgical risk.

Conclusions

This study defines the magnitude of impaired CRF demonstrated in AAA disease. CPET values were unable to identify patients at high-risk of intraoperative mortality. However, these findings add to the body of evidence supporting the measurement of CRF used to identify patients at high-risk of mid-term postoperative mortality. In this specific subset of patients, $\dot{V}O_2$ peak of < 13.1 mL O_2.kg^{-1}.min^{-1} and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 34 allowed for the discrimination of patients at increased risk of mid-term postoperative mortality and it is therefore recommended that zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 mL.kg^{-1}.min^{-1} and <31, 31 to 38, and >38 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT respectively be adopted. Collectively, these findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients which may help direct care provision.

4.3. Study 3

Sex Matters when Assessing Cardiorespiratory Fitness for Preoperative Risk Stratification

4.3.1. Introduction

The routine determination of CRF using CPET is increasingly accepted in patient populations undergoing major surgery, given the information obtained facilitates risk prediction (Guazzi et al., 2016, Myers et al., 2009, Balady et al., 2010). Indeed, there is a case for CRF to be considered a clinical biomarker presenting health professionals with unique opportunities to improve patient management and care (Ross et al., 2016). Preoperative CPET is used to identify patients with low CRF and is a predictor of survival following major intra-abdominal surgery (Moran et al., 2016, Lai et al., 2013, West et al., 2014b, West et al., 2016, Wilson et al., 2010), however the attributable risk of death from low CRF has not been compared with other established independent risk factors for CVD. Nonetheless, the use of CPET as a routine preoperative risk assessment tool has expanded (Reeves et al., 2018).

Despite evidence that CRF is lower in females across the lifespan given smaller body size, skeletal muscle mass, peak cardiac output, Hb concentration, conducting airways, greater O_2 cost of breathing, and augmented vascular ageing (Jackson et al., 2009, Fleg et al., 2005, Beale et al., 2018, Sheel et al., 2016), sex is not considered during surgical risk stratification using CPET data. Current practice commonly adopts universal thresholds of CRF to stratify patients as 'high risk' for surgery (combination of AT <11 ml O_2 kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}CO_2$-AT >34; Wilson et al., 2010, Older et al., 1999, Carlisle and Swart, 2007, Wilson et al., 2019). If a simple dose-response relationship exists between CRF and postoperative survival, females would be expected to be at increased risk given these physiological constraints. However, sex differences in post-operative outcomes following major colorectal surgery remain equivocal, with limited evidence highlighting lower (Byrne et al., 2013) or comparable (Mayr et al., 2019) mortality in females, though none have stratified outcome according to preoperative CRF.

This study was the first to investigate what extent CRF alters the surgical risk stratification of patients undergoing colorectal surgery when expressed relative to sex. First, (Phase 1: Pooled analysis) analysis was conducted to confirm the (inverse) relationship between CRF and mortality of pooled male and female patients whilst adding novel apportioning of the risk associated with being unfit against traditional CVD risk factors. This assumes that CRF is not a 'predictive panacea'! It is but a composite biomarker that must also be considered alongside other risk factors (that contribute to mortality). Second, (Phase 2: Comparative analysis) subsequent investigation was conducted on the simple comparison of between-sex postoperative outcome based on CRF, as a natural experiment to confirm that females are 'congenitally constrained' by lower CRF yet may have fewer CVD risk factors and do better postoperatively compared to males. Furthermore, risk factors (from Phase 1) were stratified by sex to investigate if differences in sensitivity to CRF exist. This emphasises the need to consider the 'collective burden of disease' in addition to sex, and thus consider new thresholds of CRF to optimise the prediction of postoperative outcomes.

4.3.2. Methodology

4.2.2.1. Ethics

The University of South Wales Ethics Committee (LSE1636GREO), and Cardiff and Vale University Health Board (15/AIC/6352) approved the study. Written informed consent was waived as this study constituted a service evaluation. Procedures were conducted in accordance with guidelines set forth by the Declaration of Helsinki of the World Medical Association (Williams, 2008).

4.3.2.2. Experimental Design

A retrospective cross-sectional population-based observational study was conducted in accordance with the STROBE statement (von Elm et al., 2014). This constituted analysis of anonymised longitudinal hospital databases that were prospectively populated at a single NHS centre, University Hospital of Wales, Cardiff. A central CPET Database was collated with merged data from a Colorectal Surgeons Database, Critical Care Database, and longitudinal ONS mortality records. Males and females were stratified based upon chronological order of visit date logged in the longitudinal CPET Database.

4.3.2.3. Patients

Inclusion/exclusion criteria

Consecutive patients (*n* = 1,110, 618 males *vs*. 492 females) who underwent CPET at a preoperative assessment clinic between January 2010 and December 2016 were considered for inclusion (Figure 24). Patients were excluded from the final analysis if there was no record of surgery (*n* = 174), or surgery performed more than 365 days following CPET (*n* = 191). In the case of multiple CPET visits, the visit closest to subsequent surgery was included. Patients undergoing minor or exploratory procedures were also removed (*n* = 105). Inability to CPET was defined as having completed pulmonary function tests but unable to perform cycle ergometry with expiratory gas analysis due primarily to musculoskeletal complications (*n* = 21, 6 males *vs.* 15 females).

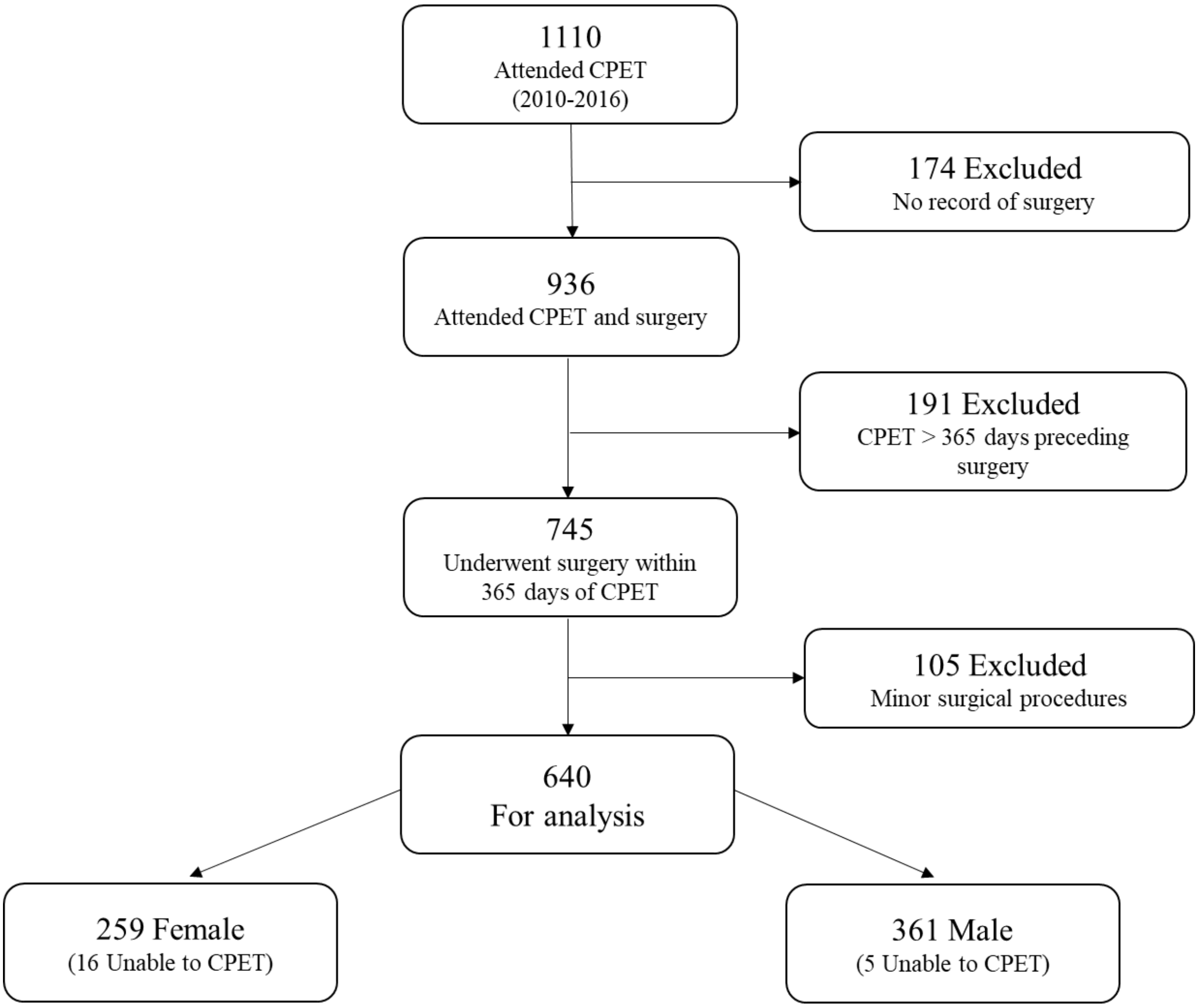


Figure 24. Consort diagram of patient recruitment and selection process. CPET, cardiopulmonary exercise test.

Demographics

Patient demographics including risk factors were gathered from medical notes at the preoperative evaluation by the consultant anaesthetist and included age, body mass, statue, BMI, cancer diagnosis, smoking history, hypertension, diabetes, IHD, COPD, cerebrovascular accident (CVA), statin use, renal disease, anaemia, and ASA physical status classification (Saklad, 1941). Only variables with less than 20% missing data were included and a complete case analysis completed.

4.3.2.4. Measurements

Cardiorespiratory fitness

Following clinical examination and flow loop spirometry, preoperative CPET was conducted using an electromagnetically-braked cycle ergometer (Lode, Gronigen, The Netherlands) and a Medgraphics Ultima metabolic cart (MedGraphics™, Gloucester, UK) as previously described (Rose et al., 2018a, Rose et al., 2018b). Calibration was conducted in accordance with the manufacturer's guidelines using a 3-litre volume syringe (Hans Rudolph, Kansas City, USA) and reference calibration gases. During data collection, the middle five of seven breaths were averaged. Patients cycled at 60 revolutions per minute for three minutes in an unloaded freewheeling state followed by a progressively ramped period of exercise (5 to 15 W min^{-1} based on weight, height, age and sex) to volitional exhaustion or symptom limited termination, followed by a three minute recovery period (Wasserman, 2012). Medgraphics Breeze™ software automatically determined $\dot{V}O_2$ peak defined as the highest $\dot{V}O_2$ recorded that more often occurred during, albeit not limited to, the final 20 s of a test. OUES (Hollenberg and Tager, 2000) which relates O_2 uptake to total ventilation during exercise, and O_2 pulse were also automatically determined by the software. The AT was manually interpreted by the supervising consultant using the V-slope method (Beaver et al., 1986), supported by comparison of $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ plots. Sub-categories “Unable to CPET” and “AT not detected” were recorded if patients were unable to perform a CPET because of their clinical status, or if insufficient data was available for clear identification of the AT. In current practice, patients are classified ‘high risk’ if CPET demonstrates a combination of AT <11 mL O_2 kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}CO_2$ -AT >34 as those with reduced AT or impaired ventilatory efficiency are more likely to die after major intra-abdominal surgery, whether or not they have associated cardiovascular risk factors (Wilson et al., 2010, Older et al., 1999, Carlisle and Swart, 2007, Wilson et al., 2019). Recent evidence, however, suggests caution when adopting the AT which is a less reliable measure and subject to high levels of natural variation (Rose et al., 2018a). Therefore, optimised metrics of CRF were calculated to better stratify patients at high risk. Patients unable to perform CPET, typically characterized by poor postoperative outcome (Lai et al., 2013), were also classified as high risk.

Surgical procedures

Procedures were obtained from the surgical database and included right or left hemicolectomy, transverse, sigmoid or subtotal colectomy, anterior or abdominoperineal resection and Hartmann’s procedures. Open or laparoscopic technique were recorded. Major procedures outside these categories (such as panproctocolectomy) were classified as “Other”.

Postoperative mortality

Postoperative mortality was determined by review of Office ONS records calculated by comparison of surgery date with 30-day, 90-day, 1-year, and 2-year follow-up status in accordance with commonly reported timepoints to align with UK National Bowel Cancer Audit (NBOCA, 2017) data. Postoperative mortality at 1 year was selected as the primary endpoint. Whilst 90-day mortality may be preferable from a surgical perspective, sufficient events for meaningful survival analysis was unlikely. Furthermore, excess postoperative mortality may endure for one year following surgery (Dekker et al, 2011) justifying this primary timepoint for analysis. At two years post-surgery, the possibility of non-related mortality causes would be increased as many patients were on a curative treatment pathway. 90-day outcomes were conducted as a post-hoc sensitivity analysis to demonstrated if results were consistent for this clinically important survival period closer to the time of surgery.

Postoperative morbidity

Postoperative morbidity was determined by analysis of the surgical and critical care databases. Records were collated and analysed detailing length of stay for hospital, HDU, and ITU days, cardiopulmonary complications, all other major complications, and postoperative destinations to either Ward, PACU, HDU or ITU, alongside any subsequent returns to theatre. The type and extent of complications recorded for each patient were subsequently and retrospectively used to construct Clavien-Dindo scores on an 8-point scale of severity (Dindo et al., 2004). Cardiopulmonary complications were selected as the secondary endpoint as they are a leading cause of poor surgical outcomes and significantly increase early postoperative mortality and ICU admission (Fernandez-Bustamante et al., 2017).

4.3.2.5. Analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 25.0 Armonk, NY). Distribution normality was confirmed using repeated Shapiro-Wilk *W* tests. Continuous data are presented as mean (standard deviation), and dichotomous variables as number (percentage).

Demographics

Between-sex differences were established using independent samples *t*-tests for continuous data, or χ^2 tests for patient frequency counts. Significance for all two-tailed tests was established at $P < 0.05$.

Prognostic utility of CPET for all patients

First, it was necessary to determine whether CRF was associated with postoperative mortality (at 1 year) using Cox proportional hazards (PHs) regression models. The PH assumption was tested with Schoenfeld residuals (Grambsch and Therneau, 1994). Continuous and dichotomous variables, selected by clinical acumen and without missing values, were first assessed using univariable Cox PH regression. They consisted of age and BMI for demographic risk factors, CVA, IHD, HTN, COPD, statin therapy and diabetes for clinical risk factors, and the cardiorespiratory variables: $\dot{V}O_2$ peak, $\dot{V}O_2$-AT, $\dot{V}_E/\dot{V}CO_2$-AT, $\dot{V}_E/\dot{V}O_2$-AT, O_2 Pulse, OUES, Workload-AT and Workload-peak. Subsequent multivariable Cox PH models were developed with inclusion criteria of variables at the $P < 0.20$ level (from univariable analysis). Variables were also removed if potential to introduce collinearity to the model was identified by correlation coefficients > 0.8 consistent with Grant et al., (2014). A backward stepwise approach was then employed with exclusion set at the $P < 0.10$ level to produce a final model used to identify independent predictors of postoperative mortality.

The weighting that each risk factor contributed towards 1-year mortality was also determined using attributable fractions, the estimated fraction of all deaths that would not have occurred had there been no exposure (Blair, 2009). attributable fractions were calculated using the following equation (Mansournia and Altman, 2018):

$AF = P_c (1 - 1/HR)$ (Eq 4)

Where P_c = the prevalence of exposure among cases and HR = hazard ratio for the exposure calculated from the Cox PH model.

Long term survival was compared between dichotomized CRF strata (high risk *vs.* low risk defined from the Cox PH model) and examined graphically using Kaplan-Meier plots with log-rank tests (significance established at $P < 0.05$).

Cardiopulmonary complications were assessed using binary logistical regression with the same variables entered into the model as described for survival.

Sex differences: CRF

Mean values for peak workload, O_2 uptake at AT, $\dot{V}O_2$ peak, $\dot{V}_E/\dot{V}CO_2$ –AT, O_2 pulse and OUES were compared between the sexes using independent samples *t*-tests.

Sex differences: Postoperative outcome

A primary unadjusted Cox PH model was used to compare female and male survival across the full follow-up duration with log-rank test for differences in respective curves. To account for between-sex differences in CVD, CRF, and surgical procedures, Cox PH regression models included the significantly different risk factors and surgical procedures identified in Table 9 and differences in CRF (defined using optimised metrics from the Cox PH multivariable survival analysis), allowing for comparison of adjusted survival curves. χ^2 tests were used to compare frequency counts for all complications, and cardiopulmonary complications between the sexes. Length of hospital stay was reported by median values assessed using Mann-Whitney *U* tests.

Defining sex-specific fitness thresholds

Area under receiver operating characteristic curves were constructed for markers of CRF identified as predictors for 1-year postoperative mortality, cardiopulmonary complications, and a further sensitivity analysis for mortality at 90-days post-surgery. For a marker of CRF to be considered a valid predictor of mortality, an AUROC of > 0.7 ($P < 0.05$) was used (Hosmer & Lemeshow, 2013). Threshold values for markers of CRF fulfilling this criterion were subsequently calculated for pooled, male, and female patients by examination of the minimal distance between AUROC plots and the upper left corner, optimizing sensitivity and specificity.

To assess the impact of sex-specific thresholds on the prediction of 1-year postoperative mortality, three risk stratification models were created. Each model used the Cox PH multivariable analysis previously described, but with scale metrics of CRF replaced with a single and dichotomised variable indicating patient risk (high *vs.* low). Model 1 reflected current practice (combination of AT <11 ml O_2 kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}CO_2$-AT >34 to determine risk) and was used as the baseline comparator. Model 2 included the optimised metrics of CRF defined from the original multivariable Cox PH survival model, to dichotomise patient risk. Model 3 included the optimised metrics of CRF from Model 2, but with threshold values (re)defined relative to sex to dichotomise patient risk.

4.3.3. Results

Patient flow

Following exclusion, 640 of 1110 patients were included in the final analysis (Figure 24). Females accounted for 274 (43%) of the sample. Twenty-one patients were unable to perform CPET, of which 16 were females and two died within 90 days of the CPET visit date. No serious adverse events were reported during CPET visits.

Demographics

Males exhibited a higher BMI, greater proportion of smokers, and greater prevalence of diabetes, IHD and COPD, whilst ASA scores were similar (Table 9). More patients underwent laparoscopically assisted vs, open surgery with equal distribution between the sexes, however more females underwent right hemicolectomy (39% *vs* 27%, P=0.002) and fewer underwent anterior resection (24% *vs* 38%, P<0.001).

Table 9. Patient demographics.

	Pooled	***Male***	***Female***	***P-value***
Sample size, *n* (%)	640	366 (57)	274 (43)	
Age, mean (range), years	69 (23-90)	69 (23-90)	70 (24-89)	0.877
Risk factors:				
BMI, mean (SD), kg m^{-2}	28.2 (5.6)	28.7 (5.4)	27.5 (5.9)	0.009
Cancer, *n* (%)	540 (84)	314 (86)	226 (83)	0.254
Smoker, *n* (%)	396 (62)	254 (70)	142 (52)	<0.001
Hypertension, *n* (%)	332 (52)	197 (54)	135 (50)	0.274
Diabetes, *n* (%)	114 (18)	79 (22)	35 (13)	0.004
IHD, *n* (%)	108 (17)	76 (21)	32 (12)	0.002
COPD, *n* (%)	139 (22)	91 (25)	48 (18)	0.028
CVA, *n* (%)	49 (8)	33 (9)	16 (6)	0.135
Statin, *n* (%)	265 (41)	166 (45)	99 (36)	0.019
Haemoglobin, mean (SD), g L^{-1}	128 (19)	133 (19)	122 (17)	<0.001
Creatinine, mean (SD), µmol L^{-1}	79 (25)	86 (28)	70 (18)	<0.001
ASA, *n* (%)				
I	19 (3)	9 (3)	10 (4)	0.481
II	382 (61)	215 (60)	167 (63)	0.625
III	219 (35)	132 (37)	87 (33)	0.274
IV	6 (1)	4 (1)	2 (1)	0.704
Surgery:				
Method, *n* (%)				
Laparoscopic	336 (53)	185 (51)	151 (55)	0.264
Procedure, *n* (%)				
Right hemicolectomy	205 (32)	99 (27)	106 (39)	0.002
Transverse hemicolectomy	4 (1)	3 (1)	1 (0)	0.639
Left hemicolectomy	20 (3)	13 (4)	7 (3)	0.503
Subtotal colectomy	13 (2)	6 (2)	7 (3)	0.573
Anterior resection	205 (32)	140 (38)	65 (24)	<0.001
Hartmann's procedure	47 (7)	27 (7)	20 (7)	1.000
APR	47 (7)	24 (7)	23 (8)	0.444
Sigmoid colectomy	45 (7)	27 (7)	18 (7)	0.756
Other	54 (8)	27 (7)	27 (10)	0.315

BMI; body mass index; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ASA, American Society of Anesthesiologists physical status classification; APR, abdominoperineal resection. *P*-values refer to male *vs*. female comparisons.

CRF and postoperative outcome

Forty-nine deaths occurred within 1-year of surgery in the 640 patients included in the final analysis (7.7%). The Cox PH multivariable model presented both $\dot{V}O_2$ peak [HR 0.87 (0.80-0.95), *P*=0.002] and $\dot{V}_E/\dot{V}CO_2$-AT [HR 1.05 (1.00-1.11), *P*=0.037] as scale variables independently associated with mortality. BMI was also present [HR 0.91 (0.85-0.98), *P*=0.006]. Threshold values defined at <14.3 mL kg^{-1} min^{-1} for $\dot{V}O_2$ peak and >34 for $\dot{V}_E/\dot{V}CO_2$-AT were then used to stratify patients with high risk. Using these optimised metrics, 149 (23%) of patients that underwent CPET were considered high risk. These patients experienced greater mortality with a 4.8-fold increased risk at 1-year (Figure 25) relative to the low risk group. When compared with traditional CVD risk factors, being high risk (adjusted for all other CVD risk factors) accounted for the largest proportion (17%) of deaths. High risk patients also exhibited more postoperative cardiopulmonary complications [HR 3.82 (1.50 – 5.35), *P*=0.001] and a 2-day longer hospital stay (9 *vs.* 7 days, *P*=0.011).

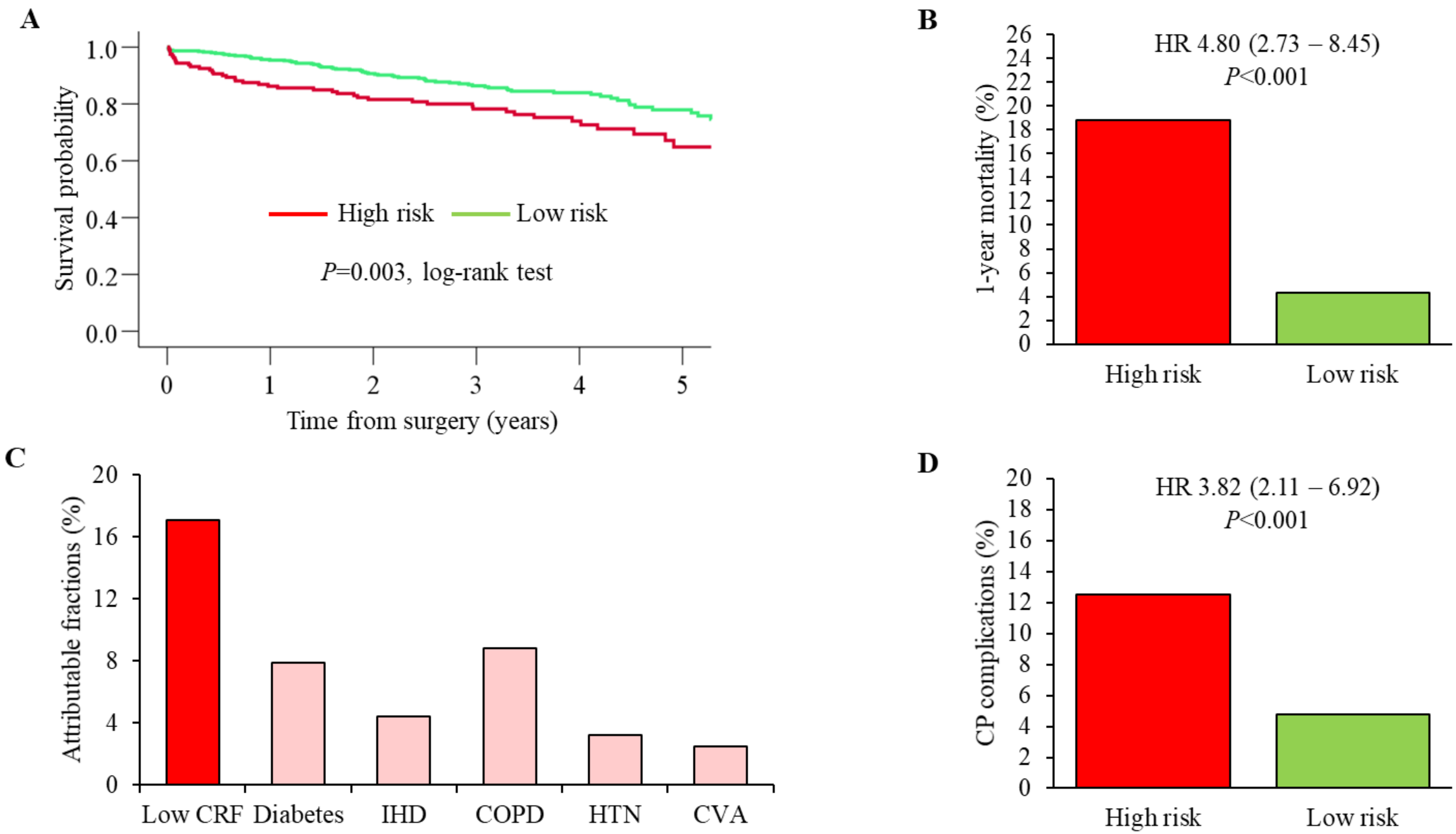

A
1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
High risk
Low risk
P=0.003, log-rank test
0
1
2
3
4
5
Time from surgery (years)
B
HR 4.80 (2.73 – 8.45)
P<0.001
1-year mortality (%)
26
24
22
20
18
16
14
12
10
8
6
4
2
0
High risk
Low risk
C
Attributable fractions (%)
20
16
12
8
4
0
Low CRF
Diabetes
IHD
COPD
HTN
CVA
D
HR 3.82 (2.11 – 6.92)
P<0.001
CP complications (%)
20
18
16
14
12
10
8
6
4
2
0
High risk
Low risk

Figure 25. Postoperative survival following colorectal surgery (*n* = 640) stratified by cardiorespiratory fitness. Patients who were high risk for surgery were characterised by higher mortality rates. Being high risk was determined by optimised metrics of preoperative cardiopulmonary exercise test (if both $\dot{V}O_2$ peak < 14.3 mL kg^{-1} min^{-1} and ventilatory equivalent for carbon dioxide at anaerobic threshold >34 units). **A.** Kaplan-Meier plot demonstrating superior survival in low risk patients over a 5 years follow-up following surgery; $P = 0.003$, log-rank test. **B.** The hazard ratio (HR) for 1-year postoperative mortality (95% confidence interval) demonstrated a 4.8-fold greater risk of mortality if patients were high risk. **C.** Attributable fractions for 1-year postoperative mortality adjusted for age, body mass index, smoking history and each other item in the figure. **D.** The HR for postoperative cardiopulmonary (CP) complications demonstrated a 3.8-fold greater risk if patients were high risk.

Sex differences

CRF

Females exhibited lower CRF in all measured CPET metrics (Figure 26) with observed reductions of 39% (70 *vs.* 115 W, $P < 0.001$) for work-load peak, 7% (10.5 *vs.*11.3 ml O_2 min^{-1} kg^{-1}, $P = 0.001$) for AT, 18% (14.5 *vs.* 17.6 mL kg^{-1} min^{-1}, $P < 0.001$) for $\dot{V}O_2$ peak, 6% (35 *vs.* 33, $P = 0.007$) for $\dot{V}_E/\dot{V}O_2$-AT, 34% (8 *vs.* 12 mL $beat^{-1}$, $P < 0.001$) for O_2 pulse, and 29% (1321 *vs.* 1864 [(mL min^{-1} O_2)/ (L min^{-1} $\dot{V}_E$)] , $P < 0.001$) for OUES.

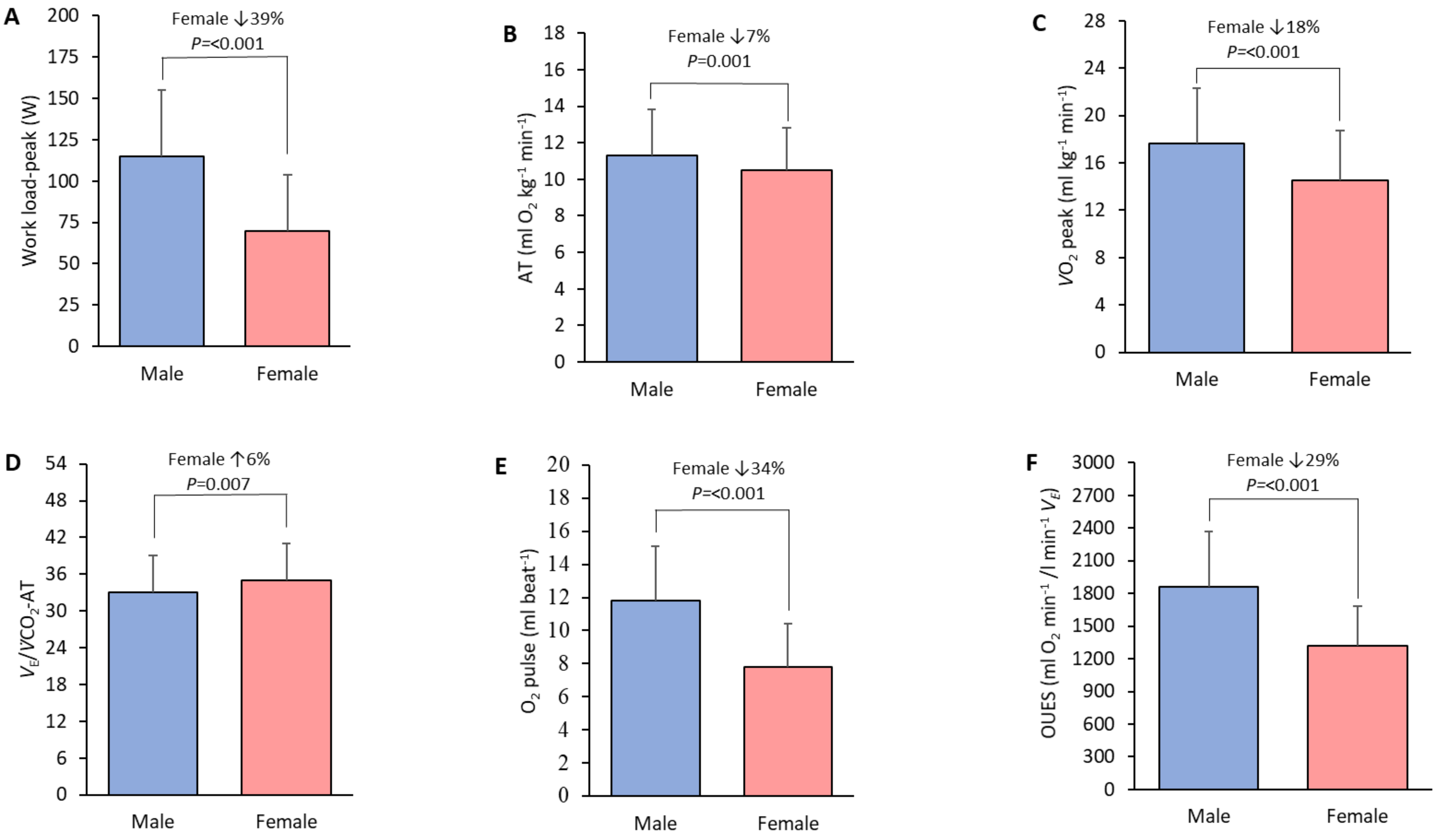

A
Work load-peak (W)
Female ↓39%
P=<0.001
Male
Female
B
AT (ml O2 kg-1 min-1)
Female ↓7%
P=0.001
Male
Female
C
VO2 peak (ml kg-1 min-1)
Female ↓18%
P=<0.001
Male
Female
D
VE/VCO2-AT
Female ↑6%
P=0.007
Male
Female
E
O2 pulse (ml beat-1)
Female ↓34%
P=<0.001
Male
Female
F
OUES (ml O2 min-1 /l min-1 VE)
Female ↓29%
P=<0.001
Male
Female

Figure 26. Sex-differences in preoperative cardiorespiratory fitness. Females were characterised by lower test values for **A.** Workload at peak exercise, **B.** Oxygen uptake at anaerobic threshold (AT), **C.** Peak oxygen consumption ($\dot{V}O_2$ peak), **D.** Ventilatory equivalent for carbon dioxide at anaerobic threshold ($\dot{V}_E/\dot{V}O_2$-AT), **E.** Oxygen pulse at peak exercise (O_2 pulse), **F.** Oxygen uptake efficiency slope (OUES).

Postoperative outcome

No between-sex differences were observed for postoperative outcomes (Table 10). Male and female mortality was 2.7 *vs.* 2.2% at 30 days, 3.3 *vs.* 2.6% at 90 days, and 12% at 2-years (*P* = 0.664, 0.646, and 0.882 respectively). Similarly, male, and female morbidity was not different for complications (43 *vs.* 38%, *P* = 0.234), cardiopulmonary complications (7.4 *vs.* 6.6% *P* = 0.693), and length of hospital stay (8 days, *P* = 0.427). Postoperative destination, Clavien Dindo scores, return to theatre, and length of HDU and ITU stay were also the same.

Table 10. Postoperative outcomes

	Pooled (n=640)	***Male (n= 366)***	***Female (n=274)***	***P-value***
Mortality, *n* (%)				
30-day	16 (2.5)	10 (2.7)	6 (2.2)	0.664
90-day	19 (3.0)	12 (3.3)	7 (2.6)	0.646
1-year	49 (7.7)	26 (7.1)	23 (8.4)	0.544
2-year	78 (12)	44 (12)	34 (12)	0.882
Destination, *n* (%)				
Ward	460 (72)	261 (71)	199 (73)	0.714
PACU	80 (13)	44 (12)	36 (13)	0.672
HDU	75 (12)	46 (13)	29 (11)	0.440
ITU	25 (4)	15 (4.1)	10 (3.6)	0.772
Complications, *n* (%)				
All	260 (41)	156 (43)	104 (38)	0.234
Cardiopulmonary	45 (7)	27 (7.4)	18 (6.6)	0.693
Clavien Dindo, *n* (%)				
0	371 (58)	204 (56)	167 (61)	0.186
I	35 (5.5)	20 (5.5)	15 (5.5)	0.996
II	151 (24)	90 (25)	61 (22)	0.493
IIIa	9 (1.4)	4 (1.1)	5 (1.8)	0.437
IIIb	42 (6.6)	25 (6.8)	17 (6.2)	0.752
IVa	11 (1.7)	9 (2.5)	2 (0.7)	0.096
IVb	2 (0.3)	1 (0.3)	1 (0.4)	0.839
V	19 (3)	12 (3.3)	7 (2.5)	0.593
RTT, *n* (%)	63 (10)	38 (10.4)	25 (9.1)	0.589
LoS, days (median, IQR)				
Hospital	8 (7)	8 (8)	8 (7)	0.427
HDU	2 (0)	2 (0)	2 (0)	0.873
ITU	3 (4.25)	3 (4)	2 (17)	0.937

PACU, post anaesthetic care unit; HDU, high dependency unit; ITU, Intensive trauma unit; RTT, returns to theatre; LoS, length of stay. *P*-values refer to male *vs.* female comparisons.

Survival curve analysis demonstrated no difference (*P* = 0.509) in unadjusted postoperative mortality up to 5 years follow-up between the sexes (Figure 27A). When survival was adjusted for observed between-sex differences in CVD risk factors and surgical procedures, there were no divergences in survival curves (Figure 27B). In contrast, when adjusted for differences in CVD risk factors and surgical procedures ‘inclusive of CRF’, a distinct survival advantage became apparent in females (Figure 27C).

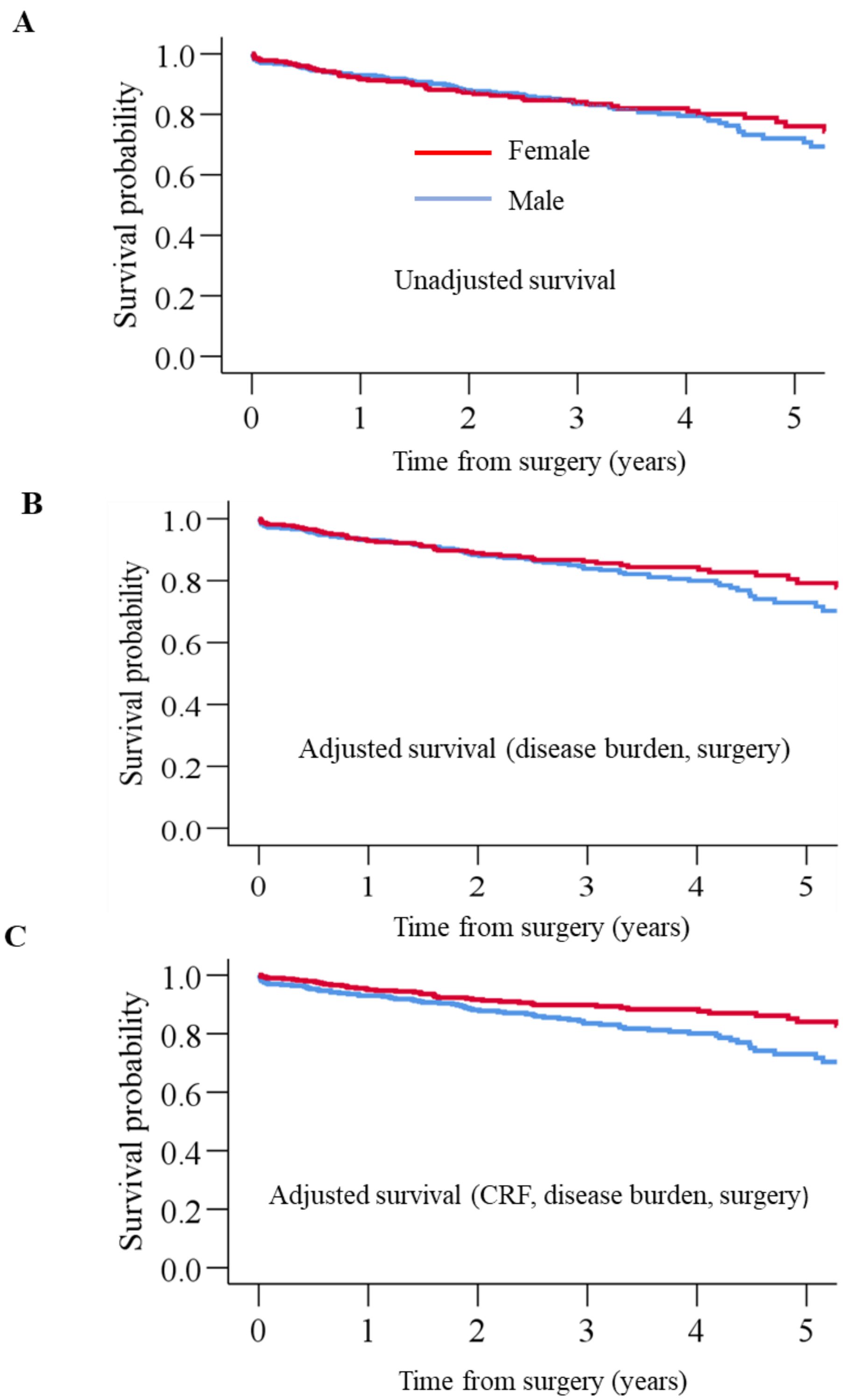


Figure 27. Sex-differences in survival. No sex differences were observed for **A.** Unadjusted survival (Kaplan-Meier plot; P = 0.509, log-rank test), and **B.** Survival adjusted for CVD and type of surgery by Cox PH regression. Superior female survival was observed in **C.** Survival adjusted for CVD, type of surgery, and CRF (using optimised metrics) by Cox PH regression.

Sex-specific fitness thresholds

Analysis of AUROC curves (Table 11) demonstrated that $\dot{V}O_2$ peak, $\dot{V}_E/\dot{V}CO_2$-AT, Peak workload, and OUES were predictive of 1-year mortality for both pooled and respective sex-specific data (AUROC > 0.7, $P < 0.05$ in all cases). Of primary interest however, binary cut-points indicative of increased mortality risk consistently presented at lower levels of CRF in females than males for all predictive markers ($\dot{V}_E/\dot{V}CO_2$-AT >35 *vs*. >33, $\dot{V}O_2$ peak 11.9 *vs.* 14.9 mL kg^{-1} min^{-1}, Peak workload <50 *vs.* <100 W, and OUES <1148 *vs*. <1681 respectively). Similarly, in the sensitivity analysis, markers predictive of 90-day postoperative mortality also presented at binary cut-offs indicative of lower CRF in females ($\dot{V}_E/\dot{V}CO_2$-AT >39 *vs*. >33, $\dot{V}O_2$ peak 10.9 *vs.* 15.8 mL kg^{-1} min^{-1}, Peak workload <61 *vs.* <94 W, and OUES <1078 *vs*. <1537 respectively).

Postoperative cardiopulmonary complications were predicted by fewer CPET markers: $\dot{V}_E/\dot{V}CO_2$-AT for pooled, male, and female cohorts, $\dot{V}O_2$ peak in the male cohort, and Peak workload in both male and female cohorts. Interestingly, and in agreement with mortality data, sex-specific cut-points again occurred at lower levels of CRF for females ($\dot{V}_E/\dot{V}CO_2$-AT >37 *vs*. >33, and Peak workload <64 *vs.* <98 W for males).

Table 11. Area under receiver operating characteristic curves for preoperative CPET variables predictive of mortality and morbidity

	Pooled		***Male***			***Female***		
	AUROC	Cut-point	AUROC	Δ AUROC (*vs.* pooled)	Cut-point	AUROC	Δ AUROC (*vs.* pooled)	Cut-point
1-year mortality:								
AT (mL O_2 kg^{-1} min^{-1})	0.62 (0.53-0.71)		0.59 (0.47-0.71)	-0.02		0.66 (0.53-0.79)	+0.04	
$\dot{V}_E/\dot{V}CO_2$-AT	0.74 (0.66-0.82)	>34	0.76 (0.66-0.86)	+0.02	>33	0.71 (0.59-0.83)	-0.03	>35
$\dot{V}O_2$ peak (mL kg^{-1} min^{-1})	0.72 (0.64-0.79)	<14.3	0.70 (0.60-0.80)	-0.02	<14.9	0.76 (0.65-0.86)	+0.04	<11.9
Peak workload (W)	0.72 (0.65-0.79)	<91	0.75 (0.67-0.84)	+0.04	<100	0.78 (0.67-0.89)	+0.03	<50
O_2 pulse (mL $beat^{-1}$)	0.70 (0.62-0.79)	<8.5	0.68 (0.56-0.80)	-0.02		0.80 (0.71-0.89)	+0.10	<6.5
OUES (mL min^{-1} O_2)/ (L min^{-1} $\dot{V}_E$)	0.73 (0.65-0.80)	<1461	0.74 (0.64-0.83)	+0.01	<1681	0.82 (0.74-0.89)	+0.09	<1148
90-day mortality (sensitivity analysis)								
AT (mL O_2 kg^{-1} min^{-1})	0.62 (0.44-0.79)		0.61 (0.41-0.80)	-0.01		0.72 (0.38-1.00)	+0.10	
$\dot{V}_E/\dot{V}CO_2$-AT	0.81 (0.72-0.90)	>34	0.81 (0.71-0.91)	0	>33	0.85 (0.74-0.97)	+0.04	>39
$\dot{V}O_2$ peak (mL kg^{-1} min^{-1})	0.73 (0.61-0.84)	<13.8	0.74 (0.61-0.87)	+0.01	<15.8	0.84 (0.71-0.96)	+0.11	<10.9
Peak workload (W)	0.71 (0.60-0.82)	<68	0.76 (0.65-0.88)	+0.05	<94	0.83 (0.69-0.98)	+0.12	<61
O_2 pulse (mL $beat^{-1}$)	0.62 (0.48-0.77)		0.63 (0.47-0.79)	+0.01		0.85 (0.74-0.95)	+0.23	<6.5
OUES (mL min^{-1} O_2)/ (L min^{-1} $\dot{V}_E$)	0.70 (0.57-0.83)	<1537	0.78 (0.65-0.91)	+0.08	<1537	0.88 (0.77-0.97)	+0.18	<1078
Cardiopulmonary complications:								
AT (mL O_2 kg^{-1} min^{-1})	0.61 (0.53-0.69)		0.68 (0.57-0.78)	+0.07		0.51 (0.38-0.64)	-0.10	
$\dot{V}_E/\dot{V}CO_2$-AT	0.74 (0.67-0.81)	>34	0.76 (0.68-0.84)	+0.02	>33	0.73 (0.61-0.84)	-0.01	>37
$\dot{V}O_2$ peak (mL kg^{-1} min^{-1})	0.68 (0.62-0.75)		0.72 (0.64-0.81)	+0.04	<15.3	0.67 (0.57-0.78)	-0.01	
Peak workload (W)	0.66 (0.58-0.73)		0.70 (0.61-0.79)	+0.04	<98	0.70 (0.59-0.80)	+0.04	<64
O_2 pulse (mL $beat^{-1}$)	0.59 (0.50-0.67)		0.62 (0.52-0.72)	+0.03		0.65 (0.52-0.77)	+0.07	
OUES (mL min^{-1} O_2)/ (L min^{-1} $\dot{V}_E$)	0.63 (0.55-0.71)		0.69 (0.58-0.80)	+0.06		0.58 (0.47-0.70)	-0.05	

AUROC curves better predict mortality when expressed relative to sex with female cut-points occurring at lower levels of CRF than males. AUROC curves are presented with 95% confidence intervals. Cut-points are calculated for variables with AUROC >0.7 and $P < 0.05$. AT, anaerobic threshold; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$ peak, peak oxygen consumption; O_2 pulse, oxygen pulse at peak oxygen consumption; OUES, oxygen uptake efficiency slope.

In both current practice (Model 1) and newly optimised CPET metrics (Model 2) predictive of 1-year mortality, more females were stratified high risk compared with males (36 *vs*. 22%, $P < 0.001$, and 32 *vs.* 17%, $P < 0.001$ respectively; Table 12). Conversely, when fitness was stratified using optimized sex-specific thresholds (Model 3), an equal portion of females and males were classified high risk compared with current practice (20 *vs*. 21%, $P = 0.702$), thus correcting the disparity of between-sex risk stratification. This correction was achieved with improved specificity (74 to 82%) albeit with a small reduction in sensitivity (59 to 55%). The overall predictive utility of each subsequent model improved AUROC curve values [Model 1: 0.67 (0.58-0.75), Model 2: 0.69 (0.61-0.78)), and Model 3 0.70 (0.61-0.78)] and the refined cut-points provided greater discrimination of risk with hazard ratios increasing respectively [Model 1: HR 3.61 (2.05-6.36), Model 2: HR 4.80 (2.73-8.45), and Model 3: HR 5.13 (2.92-9.01)].

Table 12. Optimisation of fitness stratification predictive of 1-year postoperative mortality. Reformulation of sex-specific CRF thresholds with corresponding lower 'cut-offs' corrected the excess identification of high risk females (*vs.* males) and improved mortality prediction.

Model	Thresholds indicating high risk	High risk patients identified n (%) Male/ Female	AUROC (95% CI)	Sensitivity/ Specificity (%)	Mortality (%) High risk/ Low risk	Hazard ratio (95% CI) *vs.* low risk
1 Current practice	AT<11 mL O_2.kg^{-1}.min^{-1} $\dot{V}_E/\dot{V}CO_2$-AT>34 units	**83 (23)/ 99 (36)***	0.67 (0.58-0.75)	59 / 74	16 / 4*	3.61 (2.05-6.36)
2 Optimised metrics	$\dot{V}O_2$ peak<14.3 mL kg^{-1} min^{-1} $\dot{V}_E/\dot{V}CO_2$-AT>34 units	**61 (17)/ 88 (32)***	0.69 (0.61-0.78)	57 / 79	19 / 4*	4.80 (2.73-8.45)
3 Optimised metrics, sex-specific	*Male* $\dot{V}O_2$ peak<14.9 mL kg^{-1} min^{-1} $\dot{V}_E/\dot{V}CO_2$-AT>33 units *Female* $\dot{V}O_2$ peak<11.9 mL kg^{-1} min^{-1} $\dot{V}_E/\dot{V}CO_2$-AT>35 units	**78 (21)/ 55 (20)**	0.70 (0.61-0.78)	55 / 82	20 / 4*	5.13 (2.92-9.01)

*$P < 0.05$ for between-sex differences. $\dot{V}O_2$ peak, peak oxygen consumption; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.

4.3.4. Discussion

This study has identified two primary findings. First, CRF was identified as the principal independent risk factor for postoperative mortality in major colorectal surgery and being high risk accounted for disproportionately more deaths than other, more traditional CVD risk factors. Second, the link between low preoperative CRF and increased mortality necessitates the assignment of 'sex-specific' CRF thresholds to better inform surgical risk stratification and further optimize patient care/management.

CRF and mortality

Being high risk was associated with poor postoperative outcome following major colorectal surgery with lower survival at all postoperative timepoints, including a disproportionate 4.8-fold increased risk of 1-year mortality, a 3.8-fold greater risk of cardiopulmonary complications, and a 2-day increased hospital length of stay. This supports existing evidence in patients undergoing major colorectal surgery (Wilson et al., 2010, Lai et al., 2013, West et al., 2016, Wilson et al., 2019). Novel application of attributable fractions highlighted that having low CRF was responsible for 17% of deaths, greater than any of the traditional CVD risk factors. This highlights low CRF as the most important risk factor for postoperative mortality, similar to its relationship with 'all-cause' mortality outside of the perioperative setting (Blair, 2009). The confounding potential of advancing age and corresponding reduction in CRF is important and has an annual mortality HR of 1.06 (Carlisle, 2019). The attributable fractions and survival curves were age-adjusted, and furthermore the mean age between the sexes was not different.

Sex differences

Lower preoperative CRF in females was reflected in all CPET metrics and agrees with previous findings (Jackson et al., 2009, Fleg et al., 2005), and likely reflects lower skeletal muscle mass and differences in convective/diffusive components of O_2 transport. The lesser lung size of females accompanied by smaller conducting airways relative to males, predispose greater mechanical ventilatory constraints to exercise hyperpnea, and at a given ventilation, women have a higher work and oxygen cost of breathing (Sheel et al., 2016), Hg concentration was lower in females, closely agreeing with a reported reduction of 12% compared with males (Murphy, 2014). Peak cardiac output is lower in females who, even after indexing for body size, have smaller left ventricular chambers and accordingly lower stroke volumes (Beale et al., 2018). Vascular ageing is also further augmented in females, characterized by greater arterial elastance, higher pulse pressure, smaller and stiffer aortic arches, and earlier wave reflection than men, independent of body size and heart rate (Redfield et al., 2005).

The lower CRF in females meant that a greater proportion were disproportionately stratified high risk when compared with males using both current practice (Model 1) and optimised CPET metrics (Model 2). This finding agreed with a previous study in major colorectal surgery (Wilson et al., 2010). Given the widely presumed existence of a dose-response relationship between CRF and postoperative survival, we would have expected higher mortality and morbidity in females given physiological constraints in convective/diffusive O_2 transport. However, to the contrary, data indicate comparable (i.e. not elevated) mortality and morbidity between the sexes with lower 30 and 90-day mortality reported in females over males, albeit for reasons that remain to be resolved (Byrne et al., 2013). This highlights the need to consider other CVD risk factors that ultimately contribute to the ‘collective’ disease burden.

Although CRF was lower in females, the collective CVD burden was higher in males and therefore may have counteracted the vascular protective benefits of elevated CRF, resulting in similar survival. The fact that the type of surgery was different (i.e., less complicated) in females who underwent fewer anterior resections and more right hemicolectomies (West et al., 2016) may have contributed to improved postoperative outcome. However, despite between-sex differences in CVD risk burden and type of surgery, survival remained unchanged, even when adjusted for these unavoidable confounders. Of note, when survival was further adjusted to include CRF, a distinct advantage became apparent in fitter females, highlighting their heightened sensitivity to CRF.

Preoperative risk re-stratification

These findings call for a reappraisal of the currently used CRF thresholds for preoperative risk stratification, highlighting the importance of defining sex-specific thresholds that can better predict postoperative outcome. This has major implications for surgical risk stratification and perioperative care. These findings indicate that a disproportionate number of females are incorrectly stratified as being high risk in current practice, which may result in an overly risk-averse approach with excess resource utilisation (e.g., HDU beds) and associated cost implications. Fewer females were stratified high risk when reformulated CRF thresholds with corresponding lower 'cut-offs' were applied, thus providing a balanced proportion between the sexes, and importantly, also improved the prediction of postoperative mortality. The findings are also consistent with females undergoing heart transplantation who, despite lower CRF ($\dot{V}O_2$ peak), have a superior 1-year transplant-free survival (Elmariah et al., 2006), further reinforcing the need for sex-specific fitness thresholds that extend beyond major colorectal surgery.

When males were compared with pooled data, the newly defined sex-specific thresholds moved in the opposite direction to females (to produce higher 'cut-offs' indicative of greater CRF) albeit by a much smaller magnitude. This may partially be explained by the larger weighting of males (58%) in the pooled sample. Consequently, the clinical implications for men were largely unchanged with a similar proportion being stratified high risk when compared with current practice.

Further optimisation of the sex-specific thresholds is possible. *Study 1* (Rose et al., 2018b) demonstrated the presence of natural variation in CRF and the corresponding potential for incorrect surgical risk stratification if not accounted for. Therefore, threshold values inclusive of CD (as previously described) produced zones for fit, intermediate fitness, and unfit of >17, 17 to 13.2, and <13.2 $mL.kg^{-1}.min^{-1}$ for $\dot{V}O_2$ peak and <30, 30 to 37, and >37 for $\dot{V}_E/\dot{V}CO_2$-AT for males, and >13.6, 13.6 to 10.6, and <10.6 $mL.kg^{-1}.min^{-1}$ for $\dot{V}O_2$ peak and <32, 32 to 39, and >39 for $\dot{V}_E/\dot{V}CO_2$-AT for females. CD was only determined in male controls however and may result in differences in reclassification between women and men, albeit this is unlikely as between-sex repeatability of CPET parameters has been equally demonstrated (Decato et al., 2018).

Given the recent adoption of multimodal prehabilitation strategies, with exercise training identified as the most fundamental component (Scheede-Bergdahl et al., 2019), these findings redefine 'target thresholds' of CRF relative to sex, and highlight the increased importance of CRF for females in whom lower levels of CRF may respond more favourably to exercise intervention.

Conclusions

This study is the first to highlight CRF as the principal independent risk factor for postoperative mortality; being high risk accounted for disproportionately more deaths than other, more traditional CVD risk factors, and was further compounded in females. These findings have facilitated the assignment of ‘sex-specific’ CRF thresholds that better inform surgical risk stratification to further optimize clinical decision-making and patient care.

4.4. Study 4

High-Intensity Exercise Training Improves Perioperative Risk Stratification in the High-Risk Patient

4.4.1. Introduction

Poor CRF is associated with an increased risk of adverse peri-operative outcomes including major morbidity, mortality, increased length of stay in hospital (Moran et al., 2016) and reduced health-related quality of life (Tew et al., 2018) following major surgery. The AHA guidelines (2014) recommend functional assessment for evaluating peri-operative risk (Fleisher et al., 2014). CPET is used to objectively measure functional capacity and can identify the causes of exercise limitation. CPET can evaluate chronic comorbidities and allow identification of new pathology that requires treatment or optimisation. This data can be used to facilitate shared decision making, to allow appropriate utilisation of postoperative critical care and to direct prehabilitation programs. Approximately 30,000 preoperative CPET are conducted in the UK each year to assess patient risk and plan care (Reeves et al., 2018). With the rapid uptake of CPET, an international Perioperative Exercise Testing and Training Society has been established to promote the highest standards of care for patients undergoing exercise testing, training, or both in the perioperative setting (Levett et al., 2018). There is increasing evidence that preoperative exercise training can improve CRF (West et al., 2015) by creating improved physiological reserve to deal with the stress response to surgery. Typically, studies recruit by convenience with younger and physically active patients more likely to participate. Thus, the feasibility and efficacy of exercise interventions in ‘unfit’ patients deemed high-risk for surgery is not adequately addressed and warrants further investigation.

It is well established that MISS exercise can improve CRF reducing the risk of cardiovascular disease and all-cause mortality across the human aging continuum (Blair et al., 1989). However, the optimal modality, frequency and duration remain a constant source of debate. Furthermore, clinical urgency and time demands may be potential barriers to participation (Reichert et al., 2007). As a consequence, attention has since turned to an alternative exercise modality, HIIT, given its capacity to further potentiate metabolic, cardiopulmonary and systemic vascular adaptation with the added attraction of reduced exercise duration even in patients who are deemed 'high risk' (Gibala et al., 2006). With this in mind, we describe a clinical case study to highlight the feasibility and potential benefits of HIIT in a high-risk patient requiring oesophageal reconstruction to improve post-operative outcome.

4.4.2. Methodology

4.4.2.1. Ethics

Cardiff and Vale University Health Board Ethics Committee was informed, and formal approval was deemed unnecessary as this was part of the proposed preoperative optimisation strategy. The patient provided written informed consent and all procedures adhered to guidelines set forth in the Declaration of Helsinki.

4.4.2.2. Patient

A 70-year-old Caucasian female with a body mass of 24 kg.m-2, haemoglobin of 12 g.dL-1 and normal renal and liver function underwent transhiatal oesophagectomy for oesophageal cancer but developed postoperative ischaemia of the gastric conduit. Following a problematic course on critical care she required further emergency surgery and was left with a pharyngostomy and a feeding jejunostomy. The patient attended the anaesthetic preoperative clinic for assessment of CRF for colonic interposition to restore gastrointestinal tract continuity. Her medical history included myocardial infarction, coronary artery bypass surgery, hypertension, pulmonary embolism, and a right hemi-colectomy for caecal cancer. Her drug treatment included apixaban, ramipril, bisoprolol and atorvastatin. She denied symptoms of angina and had a good self-reported tolerance to physical activity despite a 30-pack year smoking history.

4.4.2.3. Experimental Design

Exercise interventions

Following initial CPET, she was stratified as high risk for surgical intervention and the patient attempted to improve her functional capacity with unsupervised training at home using a treadmill walking for 20 mins, three times per week (MISS training).

A second CPET, eight weeks later, demonstrated no difference to her risk stratification and she agreed to train further using a home fitness video three times per week. Despite being well motivated, the patient's own efforts failed to improve her CPET metrics. This led to further detailed discussion of perioperative risk and adequate preoperative preparation, and she agreed to undertake a 10-week HIIT exercise programme jointly supervised by an exercise physiologist and clinician.

HIIT consisted of three exercise sessions per week on a cycle ergometer, each of 40 minutes duration. Sessions comprised six, two-minute bouts of heavy exercise (50% difference between power output at peak exercise and AT) interspersed with three minutes of moderate exercise (80% power at AT) based on previous research (West et al., 2015). Heart rate (3-lead ECG), blood pressure and oxygen saturations by finger pulse oximetry were monitored during exercise. A CPET was conducted approximately every two weeks and HIIT intensity adjusted accordingly. A final CPET was performed two weeks prior to surgery to assess changes in functional capacity following HIIT.

4.4.2.4. Measurements

CPET

Objective assessment of functional capacity was performed using CPET. All CPETs were conducted to volitional fatigue using a MedGraphics Ultima metabolic cart (MedGraphicsTM, Gloucester, UK) and an electromagnetically braked cycle ergometer (Lode, Groningen, The Netherlands) in accordance with UK national guidelines for CPET (Levett et al., 2018). Breath-by-breath measurements of gas exchange were obtained using a mouthpiece connected to a MedGraphics preVentTM pneumotach device with a nose-clip to measure both inspired and expired oxygen and carbon dioxide levels and respiratory flow. Following 3 minutes of resting data collection, the subject cycled at 60 rpm for 3 minutes in an unloaded 'freewheeling' state. A progressively ramped period of exercise at 10 W min-1 based on her stature, age, and predicted $\dot{V}O_2$ peak was then undertaken to symptom limited termination and followed by 1-5 min recovery period.

During each CPET, the following measurements were recorded:

Cardiovascular. Heart rate and electrocardiogram ST segment analysis were recorded continuously.

Pulmonary. O_2 uptake, CO_2 output, expiratory minute ventilation, and respiratory frequency were recorded breath by breath throughout. MedGraphics BreezeSuiteTM software automatically determined $\dot{V}O_2$ peak (defined as the highest oxygen uptake during the final 20 s of exercise reported) and OUES. The AT was manually interpreted by a clinician using the modified V-slope method (Whipp et al., 1986), supported by $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$, and ETO_2 and $ETCO_2$ in accordance with UK national guidelines for perioperative CPET (Levett et al., 2018). Breath-by-breath data was averaged using middle five of seven breaths. Pulse oximetry was recorded throughout.

4.4.2.5. Data Interpretation

CPET values

Reference CRF threshold values for perioperative risk from the EACPR/AHA Scientific Statement were used: $\dot{V}O_2$-AT < 11 ml $O_2.kg^{-1}.min^{-1}$, $\dot{V}O_2$peak < 16 ml $O_2.kg^{-1}.min^{-1}$, and $\dot{V}_E/\dot{V}CO_2$ at AT >36. Failure to reach one or more of these thresholds cumulatively increases the perioperative risk reference (Guazzi et al., 2016). Changes in CRF were also compared with known test-retest coefficients of variation (CV_A and CV_B) associated with both biological variation and analytical variation, indicative of CD. Based on previously published works, CD represents the magnitude of change required to demonstrate a meaningful physiological change (Rose et al., 2018b).

Critical difference: CRF is a dynamic metric subject to natural variation encompassing both analytical and biological components that collectively contribute to the critical difference (Fraser and Fogarty, 1989) given by:

$$CD = k\sqrt{CV_A^2 + CV_B^2} \qquad \text{(Eq 1)}$$

Where:

k = constant equal to 2.77 at $P < 0.05$

CV_A = coefficient of analytical variation

CV_B = coefficient of biological variation

Natural variation is described by the magnitude of CD and determines the difference in CRF required to demonstrate change not simply due to the 'noise' associated with analytical imprecision (represented by CV_A) and biological variation (represented by CV_B), to determine if any change is to be considered 'clinically meaningful'. Previous work from this thesis has calculated the CD for $\dot{V}O_2$-AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT to be 19%, 13%, and 10%, respectively (Rose et al., 2018b). Changes in the observed CRF metrics were retrospectively compared against these values to provide clearer insight into the true physiological benefit conferred by the respective exercise interventions.

4.4.3. Results

Despite good self-reported exercise capacity, an initial baseline CPET conducted 9 months after her failed oesophagectomy demonstrated poor CRF, achieving peak work 73W, AT 7.8 ml $O_2.kg^{-1}.min^{-1}$, $\dot{V}O_2$ peak 14.7 ml $O_2.kg^{-1}.min^{-1}$ and $\dot{V}_E/\dot{V}CO_2$-AT 28 (Table 12). This CPET performance was like that achieved prior to her original oesophagectomy.

A second CPET, eight weeks later after self-directed, unsupervised home training on a treadmill, demonstrated minimal change in AT (7.8-7.7 ml O_2. $kg^{-1}.min^{-1}$; -1%), but small improvements in $\dot{V}O_2$ peak (14.7-16.2 ml O2. kg-1.min-1; +10%), and minute ventilation (38.0-47.8 L.min-1; +26%). Following further training with a home fitness video, a third CPET 16 weeks later, demonstrated worsening of her exercise capacity (Table 12).

Table 12. CPETs during unsupervised, moderate intensity steady-state (MISS) training.

	Pre-oesophagectomy	Pre-MISS baseline (9 months post-oesophagectomy)	8 weeks MISS completed	16 weeks MISS completed	% change required based on CD	% change observed from baseline to 16 weeks
$\dot{V}O_2$-AT (ml O_2.kg^{-1}.min^{-1})	8.4	7.8	7.7	8.3	19%	+6%
$\dot{V}O_2$ peak (ml O_2.kg^{-1}.min^{-1})	13.1	14.7	16.2	13.7	13%	-7%
Power at $\dot{V}O_2$ peak (Watts)	91	73	77	70		-4%
$\dot{V}_E$ (L.min^{-1})	41.3	38.0	47.8	35.8		-6%
$\dot{V}_E/\dot{V}CO_2$-AT	32	28	31	30	10%	+7%
RER at peak	1.27	1.44	1.47	1.38	15%	-4%
Heart rate peak (b.min^{-1})	125	131	125	100		-24%
OUES	1110	858	986	923	12%	+8%
Power at AT (Watts)	50	39	36	40		+3%

AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen uptake, $\dot{V}_E$, peak minute ventilation; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for oxygen at AT; RER, respiratory exchange ratio; OUES, oxygen uptake efficiency slope; CD, critical difference.

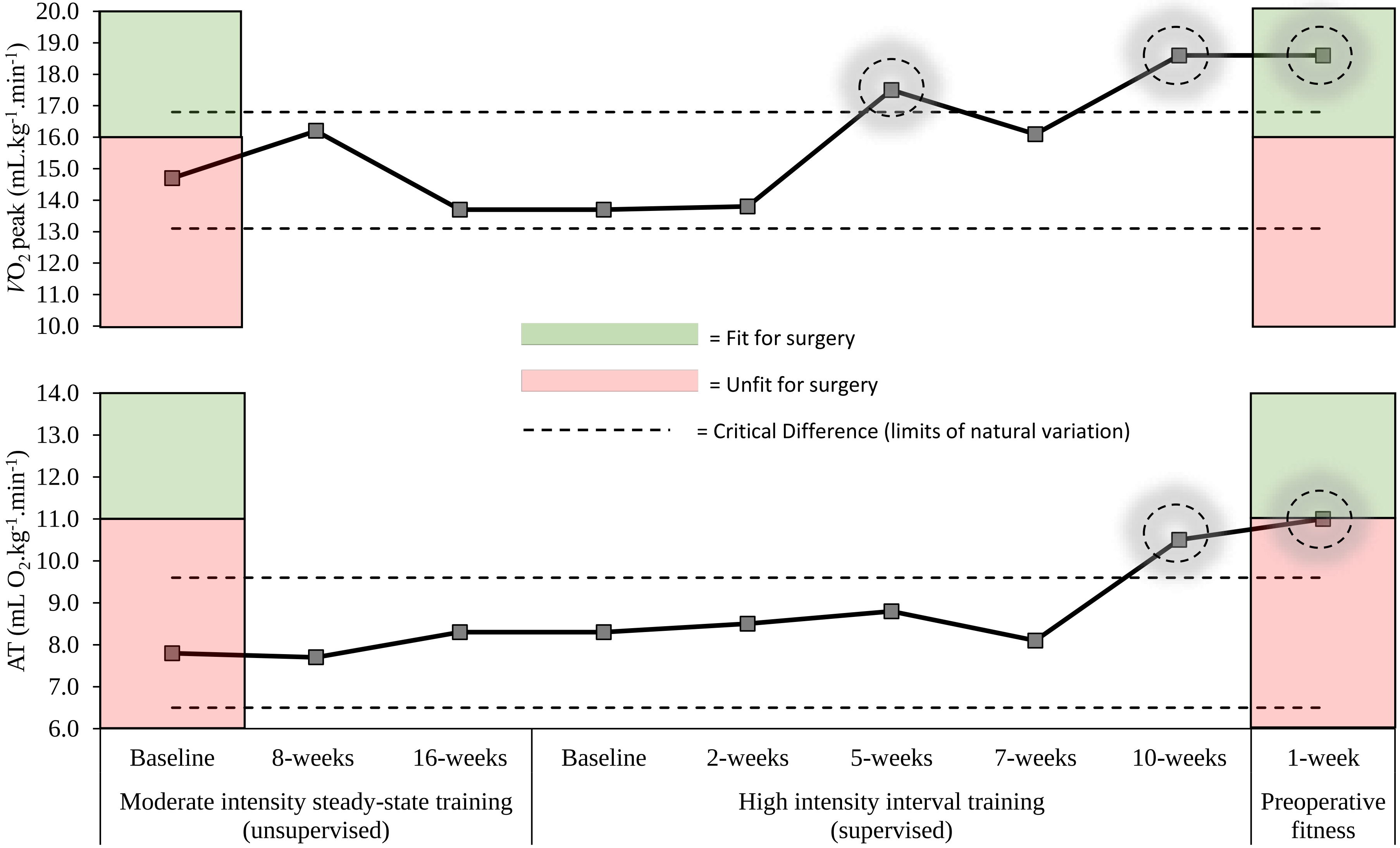
The 10-week, supervised, HIIT programme was well tolerated with no adverse events identified. She completed 29 of the prescribed 30 sessions (one training session was not completed due to illness). Her Hg levels were normal throughout the training programmes and her body mass remained constant.

HIIT resulted in increases (Table 13, Figure 28) in $\dot{V}O_2$ peak (13.7-18.6 mL.kg^{-1}.min^{-1}; +36%), $\dot{V}O_2$-AT (8.3-10.5 mL.kg^{-1}.min^{-1}; +27%), peak power (70-102W; +46%), minute ventilation (35.8-57.7 L.min^{-1}; +61%) and OUES (923-1079; +17%). $\dot{V}_E/\dot{V}CO_2$-AT decreased (30-28; -7%). Peak heart rate increased 33% (100-133 b.min^{-1}).

Table 13. Cardiopulmonary exercise test results during supervised high-intensity interval training (HIIT).

	Pre-HIIT baseline	2 weeks HIIT completed	5 weeks HIIT completed	7 weeks HIIT completed	10 weeks HIIT completed	% change required based on CD	% change from baseline to 10 weeks
$\dot{V}O_2$-AT (ml O_2.kg^{-1}.min^{-1})	8.3	8.5	8.8	8.1	10.5	19%	+27%
$\dot{V}O_2$ peak (ml O_2.kg^{-1}.min^{-1})	13.7	13.8	17.5	16.1	18.6	13%	+36%
Power at $\dot{V}O_2$ peak (Watts)	70	76	91	95	102		+46%
$\dot{V}_E$ (L.min^{-1})	35.8	32.7	49.1	51.4	57.7		+61%
$\dot{V}_E/\dot{V}CO_2$-AT	30	28	30	28	28	10%	-7%
RER at peak	1.38	1.42	1.38	1.60	1.55	15%	+12%
Heart rate peak (b.min^{-1})	100	120	118	120	133		+33%
OUES	923	969	1000	944	1079	12%	+17%
Power at AT (Watts)	40	36	40	40	52		+30%

AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen uptake; $\dot{V}_E$, peak minute ventilation; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for oxygen at AT; RER, respiratory exchange ratio; OUES, oxygen uptake efficiency slope; CD, critical difference.



20.0
19.0
18.0
17.0
16.0
15.0
14.0
13.0
12.0
11.0
10.0
VO2 peak (mL.kg-1.min-1)
= Fit for surgery
= Unfit for surgery
= Critical Difference (limits of natural variation)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
AT (mL O2.kg-1.min-1)
Baseline
8-weeks
16-weeks
Baseline
2-weeks
5-weeks
7-weeks
10-weeks
1-week
Moderate intensity steady-state training (unsupervised)
High intensity interval training (supervised)
Preoperative fitness

Figure 28. Cardiorespiratory fitness at baseline and during MISS and HIIT exercise intervention. Following ten weeks of HIIT (three sessions per week), fitness was maintained until the time of surgery by completion of a further two HIIT sessions per week. For comparative purposes, a literature-based age-matched control would demonstrate a $\dot{V}O_2$ peak of 22 mL $O_2.kg^{-1}.min^{-1}$ (Wasserman, 2012). AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen uptake.

4.4.4. Discussion

The patient's CRF at baseline was considerably lower than literature-based age-matched controls and confirmed a high level of risk for major surgery when compared with reference CRF threshold values for perioperative risk stratification. Supervised HIIT training enabled objective improvement greater than the magnitude of natural variation, thus was clinically significant based on application of the critical difference. The patient's improved CRF as demonstrated by her CPET metrics resulted in the reclassification of her risk for major surgery into a low-risk group. This clinical case study highlights that HIIT in the high-risk patient preparing for major intra-abdominal surgery is effective. High-intensity interval training improvements in CRF were incurred over a short period of time and were considered clinically meaningful enabling the patient to transcend the 'fitness' boundary ahead of major surgery. Collectively, these findings support the implementation of HIIT as an effective prehabilitation strategy with the potential to optimise perioperative outcome.

The 'high-risk surgical patient' accounts for 13% of cases in the United Kingdom but contributes to over 80% postoperative deaths and complications (Pearse et al., 2006). The principle of prehabilitation is to improve cardiovascular, respiratory and muscular conditioning and can be considered analogous to the preparation of an individual for a marathon event (Wynter-Blyth and Moorthy, 2017). Improving a patient's physiological reserve allows them to meet the demands of this perioperative stress, reducing the risk of complications and death. A multimodal prehabilitation programme allows other factors such as smoking, alcohol, nutrition and anaemia to be addressed (Tew et al., 2018). The optimum components of an exercise program have yet to be elucidated as much of the evidence is relatively recent (Minnella and Carli, 2018). Given the short time that cancer patients have between diagnosis and surgery, HIIT training seems to confer the greatest advantages and current trials are ongoing to determine this (Woodfield et al., 2018).

It is acknowledged that idiosyncrasies are present when comparing the type of exercise intervention (supervised vs. unsupervised), intensity of exercise (HIIT vs. MISS), and mode of exercise (walking vs. cycling), and that a controlled experiment with an age-matched healthy participant was outside the scope of this work. The study simply aimed to demonstrate the impact of a theoretically effective exercise intervention on a single patient to improve clinical outcome. The efficacy of the HIIT intervention may be attributed to some key factors. Firstly, the HIIT programme was individualised using the cycle ergometer to adjust work rate based on the patient's power output at two measured physiological parameters (AT and $\dot{V}O_2$ peak). This allowed targeted training using a planned programme of exercise. Secondly, the HIIT programme was supervised throughout by both a medical professional and exercise physiologist. This joint supervision allowed for psychological, behavioural, and environmental factors to be addressed through regular encouragement, reassurance, and motivation in a safe and secure environment. Whilst the patient ultimately must do the training, the health professionals must supervise the HIIT programme to harness and maintain patient motivation while ensuring safety. Whilst this work demonstrated beneficial increases in CRF, the present HIIT programme is admittedly resource intensive in terms of equipment and professional input. Further research is required to evaluate the potential for its widespread implementation in the pre-operative setting, given the inevitable financial and logistical constraints.

Studies in healthy participants and patients with established cardiometabolic disease have consistently demonstrated a greater increase in $\dot{V}O_2$ max following HIIT compared to MISS (Milanovic et al., 2015). This demonstrate that despite shorter bouts of activity, albeit at higher intensity, HIIT has the capacity to further potentiate physiological adaptation compared to MISS, which lies at the heart of its current popularity. Indeed, this study demonstrated that most of the adaptive benefit was incurred within the first five weeks of HIIT, suggesting that training interventions as short as this may prove ‘sufficient’ allowing the patient to transcend the ‘fitness for surgery’ boundary.

This case study has demonstrated very encouraging findings; however, further research is required before such an approach could be recommended to improve fitness for surgery. Firstly, adequately powered studies are required before HIIT is widely adopted to improve fitness for surgery (Calverley et al., 2020). Based upon previous data describing a large cohort of patients undergoing colorectal surgery (Rose et al., 2018b), a prospective power calculation indicates that a two-armed exercise intervention study would require a minimum of 36 patients per group (excluding potential dropout) to detect a treatment effect with 80% power at the $P < 0.05$ level. Patient selection should be determined by completion of CPET, not only to provide a gold standard objective determination of fitness and to individualize training intensity, but also to identify pathophysiological responses of patients unsuitable for intervention. Selection bias and non-randomised trials are problematic and have produced discouraging findings. Boereboom et al., (2019) claimed that short-term pre-operative HIIT does not improve fitness of colorectal cancer patients. The baseline fitness of their cohort exhibited a mean $\dot{V}O_2$ peak of 23.9 mL $O_2.kg^{-1}.min^{-1}$ indicating that that they were already fit for surgery and would be stratified low risk even with natural variation (Rose et al., 2018b) accounted for. The overwhelming strength of our case study was the targeted approach of a HIIT intervention for a high-risk patient and given the high-risk patient may account for over 80% of postoperative deaths (Pearse et al., 2006), future studies should recruit patients with significantly impaired CRF typical of current practice, whilst ensuring safety by screening with CPET.

Caution must be applied however, and the risk of adverse events adequately established when using exercise. Additional adaptive benefits such as the upregulation of angiogenesis and anti-oxidative/inflammatory related genes resultant of the increased sinusoidal shear stress provided by HIIT are evident (Calverley et al., 2020), however this increase in shear stress may be problematic in the acute setting. For example, it remains to be established if vascular patients with large diameter aortic aneurysms are at greater risk of rupture. Thus, recommendations for exercise must address the benefit to risk ratio specific to baseline CRF, disease state, and surgical procedure.

In conclusion, HIIT was shown to be a feasible, safe, and well tolerated exercise intervention that was associated with impressive improvements in CRF enabling a single patient to be classified as ‘fit’ for major surgery. Collectively, these findings support the detailed investigation of HIIT as an effective prehabilitation strategy with the potential to optimise peri-operative outcome.

Chapter 5

Synthesis of Findings

5.1. Overview

The overall objective of this thesis was to explore the 'potential' relationship between CRF and postoperative outcome (morbidity and survival) in patients undergoing major intra-abdominal surgery. Although growing evidence suggests that low CRF may be an independent predictor of (poor) postoperative outcome, several limitations can complicate clinical interpretation and remain to be addressed. To that end, three aims were established to: 1) Improve the detection and interpretation of CRF, 2) Explore more sensitive thresholds of CRF to further improve prediction of postoperative outcome, and 3) Provide evidence that an exercise intervention directly improves patient risk stratum.

This body of work supports the over-arching hypothesis that impaired CRF is associated with inferior postoperative outcome for patients undergoing vascular and colorectal surgery. *Study 3* detailed the principal findings that low CRF accounted for more deaths than any other CVD risk factor and was associated with inferior postoperative outcome, which was further supported by *Study 2*.

The first aim was addressed in *Study 1* where the identification of natural variation improved the interpretation of CRF. The hypothesis stating that natural variation is present in markers of CRF and will thus impact upon patient fitness stratification was supported.

The second aim was addressed using a multitude of integrated findings from *Study 2* and *3.* Low CRF was identified in vascular and colorectal patient populations and novel thresholds, relative to the type of surgery and sex of patients, were developed to improve the prediction of postoperative outcome. The hypothesis stating that CRF is impaired in patients with AAA disease, and that the magnitude of impairment can be used to predict postoperative survival was supported. However, the hypothesis stating that a lower level of CRF would be found in females which would translate into worse outcomes following major colorectal surgery than male counterparts was not supported.

Finally, the third aim was explored in *Study 4* where efficacy of a preoperative HITT intervention was demonstrated in a high-risk patient. The hypothesis that HIIT prior to major elective surgery is well tolerated and associated with objective cardiopulmonary improvement was supported.

A summary of the thesis findings with key take-home messages is provided in Figure 30 and demonstrates how the body of work addresses the overall objective and established aims.

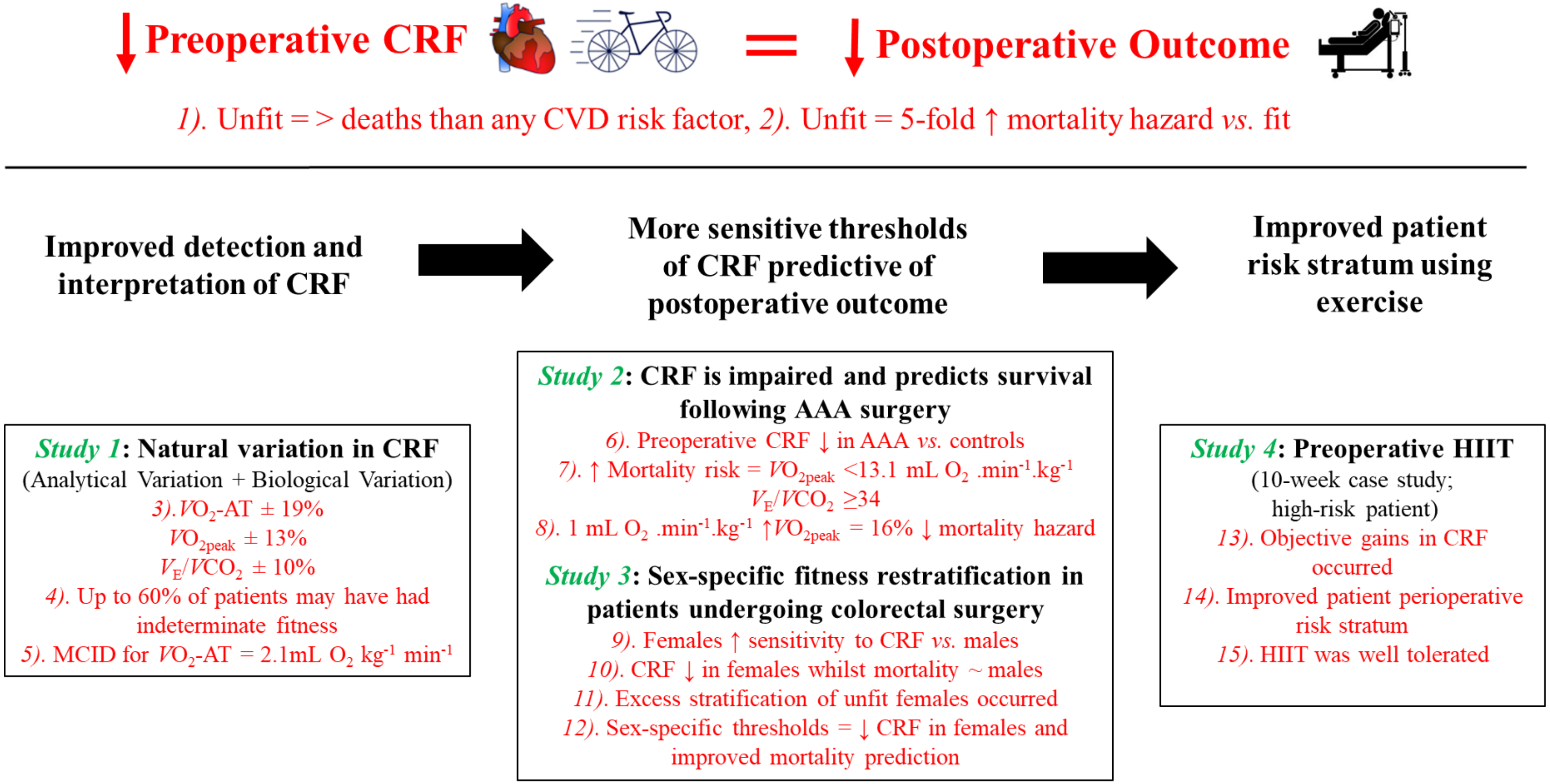


Figure 30. Summary of thesis findings with numbered key take-home messages. CRF, cardiorespiratory fitness; CVD, cardiovascular disease; $\dot{V}O_2$-AT, oxygen uptake at anaerobic threshold; $\dot{V}O_2$ peak, oxygen uptake at peak exercise; $V_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; AAA, abdominal aortic aneurysm; HIIT, high intensity interval training; MCID, minimal clinically important difference.

5.2. Integration of Findings and Emerging Concepts

In agreement with the seminal work of Older et al., (1993) and more recent systematic review of Moran et al., (2016), the current work supports the premise that impaired CRF is associated with inferior postoperative outcome for patients undergoing major intra-abdominal surgery. The principal findings from the largest cohort of 640 patients (in *Study 3)* who underwent CPET prior to colorectal surgery also confirmed, for the first time using attributable fractions, that **1) being unfit accounted for more patient deaths than any other CVD risk factor**. Furthermore, **2) unfit patients experienced 5-fold greater risk of death than fit patients** and a similarly increased (3 to 5-fold) risk of mortality was observed for the unfit patients undergoing vascular surgery in *Study 2*. Given the importance of CRF as a primary biomarker which may be used to optimise patient care and plan resource, a detailed appraisal of the established aims follows.

Improved detection and interpretation of CRF (Study 1)

Study 1 was the first of its kind to determine the extent of natural variation, comprising both analytical and biological components (critical difference), for patient surgical risk stratification. This is important because in practice, patients typically undergo just one CPET test to determine CRF, and thus risk is clinically evaluated on a single point estimate. This study demonstrated that natural variation indeed induced large magnitudes of variation in CRF. As such, these findings demonstrated that **3) critical differences of ± 19%, 13%, and 10% for $\dot{V}O_2$-AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT were present**. Of particular interest, and somewhat ironically given that the development of preoperative CPET emanated from the use of $\dot{V}O_2$-AT as the principal variable used to predict postoperative mortality (Older et al., 1993), this metric exhibited the highest magnitude of variance and presented a theoretical potential that **4) up to 60% of patients may have indeterminate fitness**. Since the publication of this work, studies have cited this finding as a possible explanation for why alternative metrics of CRF, determined by CPET, have exhibited superior prognostic utility (Rose et al., 2018a, Wilson, 2018, Wilson et al., 2019, van Dellen et al., 2019, Fisher et al., 2019). Given the effect natural variation has on the measurement of CRF, it is recommended that future work describing thresholds of CRF be inclusive of natural variation. Indeed, this point was emphasised in a subsequent editorial response (Wilson, 2018, p.1146) stating that "it is time to call into question over-reliance on specific binary cut-offs and think more in terms of strata or zones along a spectrum of fitness, and hence risk". To clarify the interpretive context of the critical difference, a stated value (±*x*%) represents the magnitude of change from a threshold boundary which determines fitness stratification, that a patient is required to achieve for a true stratum of fitness to be assigned. In the context of improving CRF through exercise intervention, the critical difference represents the magnitude of change which needs to be exceeded before a true change in fitness can be claimed.

The concept of critical difference was applied to the findings of *Study 2* whereby binary cut-offs that predicted postoperative mortality included $\dot{V}O_2$ peak <13.1 mL $O_2.min^{-1}.kg^{-1}$ and $\dot{V}_E/\dot{V}CO_2$-AT ≥34. Subsequently, with natural variation accounted for (±13 and 10%), it was recommended that clinicians adopt zones for fit, intermediate fitness, and unfit of >15, 15 to 11.6, and <11.6 $mL.kg^{-1}.min^{-1}$ and <31, 31 to 38, and >38 for $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT respectively when identifying patients at risk of mid-term (2 year) postoperative mortality. The recommended zones advance upon existing binary stratification models (Grant et al., 2015, Hartley et al., 2012) whereby patients are either fit or unfit based upon $\dot{V}O_2$ peak (of ≥15 or <15 mL $O_2.min^{-1}.kg^{-1}$) and a true score may transcend the stratification boundary due to the presence of natural variation, thus allowing potential for mis-assignment of surgical risk.

Critical difference can also be used to determine a MCID for metrics of CRF, thus informing prospective sample size calculations for future randomised controlled exercise trials. To date, studies have failed to determine a MCID for CRF that has translated to a change in postoperative outcome measures following an exercise intervention, and typically rely on MCIDs that appear to lack a well-established scientific basis. The worked example provided, based upon data from the colorectal patient cohort, determined **5) a MCID of 2.1 mL $O_2.kg^{-1}.min^{-1}$ for $\dot{V}O_2$-AT** which is recommended to inform future sample size calculations. Therefore, to conduct a two-armed exercise intervention study to detect a change in CRF (of 2.1 $mL.kg^{-1}.min^{-1}$) within accepted parameters for making a type I error with a false positive conclusion ($P < 0.05$) and type II error with a false negative conclusion (80% power), a minimum of 36 patients per group (intervention and control) would be required excluding dropouts.

More sensitive thresholds of CRF predictive of postoperative outcome (Study 2 and 3)

Prior to identifying CRF thresholds that may predict postoperative outcome, the preliminary objective of *Study 2* was to put into clearer perspective just how physically unfit patients were. Interestingly, no studies have compared the preoperative CRF of patients undergoing major vascular surgery with age and (in)activity-matched matched (non-surgical) controls. The results demonstrated that **6) patients scheduled for vascular surgery had lower CRF than controls by an age-adjusted mean difference of 12.5 mL $O_2.kg^{-1}.min^{-1}$**.

The study subsequently focused on identifying CRF thresholds predictive of postoperative mortality and established that **7) in a cohort of patients undergoing CPET prior to AAA repair, <13.1 mL $O_2.min^{-1}.kg^{-1}$ for $\dot{V}O_2$ peak and ≥34 for $\dot{V}_E/\dot{V}CO_2$-AT were independent predictors of postoperative mortality at 2-years**. Interestingly, the $\dot{V}O_2$-AT was not predictive of mortality, likely because of the high magnitude of natural variation identified in S*tudy 1*. Mortality was prospectively employed as the (hypothesis driven) primary postoperative outcome variable for investigation given that it is the most clinically relevant measure available.

Interestingly, the findings only demonstrated CRF to be an independent predictor of mortality at two-years following surgery, and not during the perioperative period. The sample contained 101 patients who underwent surgery following CPET, of which one died within 30-days and seven within 90-days, thus it was not surprising that CRF did not predict mortality in the perioperative period due to the (small) sample size. At the time of study conduct, the corresponding UK in-hospital postoperative mortality for elective open and endovascular AAA repair was 2.9% and 0.4% respectively (VSQI, 2017). A mid-term postoperative measure such as 2-year mortality was deemed an important finding for patients undergoing AAA repair, as surgery is not undertaken to cure the disease, but to prevent future risk of rupture, thus decision making needs to account for risk assessment extending beyond the perioperative period (Howell, 2017). Furthermore, quality of life needs to be considered given that six months following major surgery, approximately 50% of patients return to preoperative levels of functional capacity (Jensen et al., 2011). Of additional interest, 23 of the 124 patients who underwent preoperative CPET in the current study did not proceed to surgery and these patients exhibited lower CRF (2.3 mL $O_2.min^{-1}.kg^{-1}$, $P = 0.025$) which probably influenced the decision to treat conservatively.

Following multivariable analysis, a hazard ratio determining postoperative mortality of 0.84 was present in this cohort for $\dot{V}O_2$ peak Albeit based upon association, this suggests that 8) for each unit ($mL.min^{-1}.kg^{-1}$) increase in $\dot{V}O_2$ peak, patients were 16% less likely to die. This provides justification for exercise intervention to modify CRF, and hence investigate the potential causative link to subsequent (improved) postoperative outcome. AAA patients may be considered high-risk for exercise intervention, however are not a contraindication to low intensity aerobic exercise (Benson et al., 2019). This warrants further investigation and provided impetus to conduct *Study 4* investigating the feasibility and efficacy of a HIIT intervention in a high-risk patient, albeit to undergo upper gastrointestinal surgery in this instance.

Whilst a growing body of evidence supports the 'potential' relationship between CRF and postoperative outcome (Moran et al., 2016), surprisingly there is no evidence that compares sex-differences within this relationship and current practice adopts universal thresholds of CRF, irrespective of sex, to stratify patients. Given the premise that a simple dose-response relationship exists between CRF and postoperative survival, much like a natural experiment, females would be expected to carry increased risk given physiological constraints of lower CRF consequent to smaller body size, skeletal muscle mass, peak cardiac output and Hg concentration (Jackson et al., 2009, Fleg et al., 2005). Thus, *Study 3* was a first of its kind to comprehensively determine sex-differences in CPET and corresponding postoperative outcomes in a large cohort of patients undergoing major intra-abdominal surgery (colorectal surgery, in this instance), and evaluate the need for sex-specific fitness thresholds.

The analysis of the pooled cohort, which determined the principal findings of this thesis (that being unfit accounted for more patient deaths than any other CVD risk factor), was repeated in the comparative (female *vs.* male) samples. Importantly, **9) females were more sensitive to CRF as when survival curves were adjusted for CRF between the sexes, female survival was superior to male counterparts.** When between-sex preoperative CRF and postoperative survival was compared, **10) females had lower CRF (between 6 and 39% across CPET metrics), whilst mortality was equal to that of males**. This challenges the traditional dose-response premise between CRF and postoperative outcome, and other risk factors like CVD which indeed did vary between the sexes could titrate prognostic potential, and thus required investigation to assess the 'neutralising' impact of CRF on postoperative outcome. This finding led to the investigation of sex-specific thresholds of fitness and their comparative prediction of mortality. Furthermore, given that current practice universally adopts thresholds of CRF irrespective of sex, and lower CRF is evident in females despite equivalent mortality, current methods of stratification require revision. Indeed, **11) an excessive number of females were incorrectly stratified unfit (33 *vs.* 21% of males) in current practice**.

Both sex-related differences in CVD risk factors and surgical procedures were evident in this study and whilst male patients had superior CRF, they also carried a higher burden of CVD, greater frequency of anterior resections, and fewer right hemicolectomies. Nevertheless, when survival curves for females and males were adjusted for these confounding variables, no differences were found, unlike when further adjusted for CRF which subsequently demonstrated advantage to females, which also supports that female are more sensitive to CRF.

These findings facilitated the first assignment of sex-specific CRF thresholds in intra-abdominal surgery and identified **12) CRF threshold values were lower in females and improved mortality prediction**. Sex-specific differences in preoperative $\dot{V}O_2$ peak and postoperative outcome have been observed in cardiac transplantation (Elmariah et al., 2006), where women had lower $\dot{V}O_2$ peak (14.0 vs. 16.6 $ml.kg^{-1}.min^{-1}$; $P < 0.0001$) yet, the one-year transplant-free survival was significantly lower for men (81% vs. 94%, $P < 0.0001$). This suggests that sex-specific CRF thresholds should be defined not just for patients undergoing intra-abdominal surgery alone, but require investigation for all patients who undergo preoperative CPET.

Improved patient risk stratum using exercise

As a modifiable risk factor, interventions aiming to improve CRF prior to surgery justify consideration. *Study 4* employed a short duration (10-week) time efficient HIIT exercise protocol to firstly investigate the efficacy of this intervention, and secondly to establish feasibility in a high-risk patient with low CRF. This was important because whilst preoperative exercise interventions have demonstrated improvement in CRF (West et al., 2015), the baseline CRF of patients recruited is typically higher than that found in practice (and indeed this body of work). If exercise is to be increasingly adopted as a prime component of multimodal prehabilitation, the response of the high-risk patient with corresponding low CRF requires consideration.

Study 4 demonstrated that **13) objective gains in CRF occurred** that were ‘authentic’, that is, could not be accounted for solely by natural variation. The improvements in CRF were compared with and exceeded the previously calculated critical differences for both $\dot{V}O_2$ peak and $\dot{V}O_2$-AT outlined in *Study 1* (12.5% for $\dot{V}O_2$ peak and 19.1% for $\dot{V}O_2$-AT and 19.1%; Rose et al., 2018b). Furthermore, the objective improvements in CRF transcended stratification boundaries determining fitness for surgery (Fleisher et al., 2014) as the patient moved from a high-risk to low-risk stratum for CRF, thus **14) HIIT improved perioperative risk stratum**. As expected, the gain in CRF exceeded that conferred by its moderate intensity counterpart. Finally, excellent adherence to the intervention was recorded (29 of 30 scheduled sessions were completed), therefore **15) HIIT was well tolerated in the high-risk patient**. These outcomes support the implementation of HIIT as an effective prehabilitation strategy with the potential to optimise peri-operative outcome.

5.3. Clinical Recommendations

The findings outlined in this thesis highlight the importance of CRF as an independent risk factor for postoperative mortality and morbidity in patients undergoing intra-abdominal surgery. Given the new knowledge gained, the following recommendations are tentatively advanced to improve current clinical practice:

1) ***Place CRF front and central***. The measurement of CRF determined by CPET should be considered a prime component of a preoperative assessment clinic to assess risk and inform a patient work-up prior to surgery. Multiple metrics of CRF exists and this work has demonstrated both $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT to be of prime importance. Patients present with impaired CRF compared to sedentary people of similar age. Furthermore, these data place greater prognostic value in CRF than traditional CVD risk factors when predicting postoperative outcomes. Whilst superior CRF may counteract the risk presented by CVD, a combination of both low CRF and CVD should be noted with caution and is indicative of high surgical risk (Wilson et al., 2010). This research group has also demonstrated that centres that have onsite CPET facilities are associated with an 18% reduction [relative risk (RR) 0.82, 95% CI 0.70–0.96, $P = 0.0157$] in 90-day mortality *vs*. centres that did not offer CPET (Davies et al., 2018).
2) ***Consider natural variation in CRF during surgical risk stratification***. Patients typically undergo one CPET in current clinical practice and risk stratification is based upon a single point estimate. Sources of variation (mostly biological) occur in metrics of CRF and if not accounted for, can result in up to 60% of patients to have incorrectly

stratified fitness. It is recommended that zones of fitness are used instead, directed by the critical differences presented for respective metrics of CRF, thus allowing certainty (with 95% limits of agreement) that a patient can rightfully be classified as fit or unfit, or be placed in a new stratum (in between) that represents a zone of indeterminate fitness. A significant proportion of patients will be stratified in the indeterminate fitness zone which presents the problem of how to care for them. They could be admitted to HDU after surgery 'just in case' however this presents substantial resource requirement. In an editorial response following publication of *Study 3*, Wilson (2018) confirmed similar proportions of patients falling into the indeterminate fitness category (a potential for up to 63% in their case). In their hospital, these patients are admitted to a surgical ward with enhanced monitoring by perioperative physicians and care upgraded if necessary. Similarly, a PACU is available for monitoring these patients at the research site of the studies in this thesis (University Hospital of Wales, Cardiff).

3) ***Stratify CRF relative to surgical procedure.*** Patient groups present with different pathology and are subjected to different magnitudes of physiological insult when undergoing surgery. Thus, metrics of CRF predictive of postoperative outcome need to be optimised accordingly. These data suggest using $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT for patients undergoing vascular AAA surgery, whilst the most predictive metric for patients undergoing colorectal surgery was the $\dot{V}_E/\dot{V}CO_2$-AT.

4) ***Apply caution to the AT.*** Since the landmark studies of Older et al. (1999, 1993), an AT <11 mL $O_2.min^{-1}.kg^{-1}$ has been arbitrarily used in practice to identify the high-risk patient, unfit for surgery. Indeed, many subsequent studies adopted this risk threshold without confirming it to be the optimal metric of CRF predicting postoperative outcome in their patient populations. In the present body of work, the $\dot{V}O_2$-AT alone was not predictive of mortality or morbidity in both vascular and colorectal patient groups,

likely due to a high magnitude of natural variation identified. Also, traditionally, identification of the AT has been plagued by subjective complications and we are still not really clear what it all means from a physiochemical perspective (Hopker et al., 2011). In a similarly large cohort of patients undergoing colorectal surgery to those in Study 3, Wilson et al. (2019) also found that the AT was not predictive of postoperative outcome and instead reported the $\dot{V}_E/\dot{V}CO_2$-AT as the optimal metric. Superior metrics defined for respective patient populations are therefore recommended such as $\dot{V}O_2$ peak and $\dot{V}_E/\dot{V}CO_2$-AT for example in this thesis. When interpreting a CPET report, much time (and lively discussion between clinicians/physiologists) is required in the exact determination of the AT, however this metric is likely of lesser importance.

5) ***Stratify CRF relative to sex.*** Female patients have lower preoperative CRF than male counterparts. Females are also shown to be more sensitive to CRF, meaning that low CRF is attributable (through association) to a greater proportion of deaths than that found in males. Despite the lower preoperative CRF of females, equal postoperative outcomes (mortality and morbidity) are observed between the sexes. Consequently, an excess of female patients are stratified unfit in current practice which presents opportunity to save resource. To address this problem and improve the prediction of postoperative outcome, it is recommended that sex-specific thresholds of CRF are used which are characterised by lower values for females.

6) ***Embrace exercise intervention.*** Most existing evidence supporting the efficacy and feasibility of exercise intervention has been investigated using participants who are likely younger and fitter than typical patient cohorts. Nevertheless, *Study 4* supported the use of HIIT in the high-risk patient with poor baseline CRF. HIIT is a time efficient mode of exercise that in 5 to 10 weeks, may enable a patient to transcend (upwards) fitness stratification boundaries. This is important because a cancer patient, for example, has a limited window of 'opportunistic intervention' prior to surgery and this data implies feasibility and efficacy.

5.4. Limitations

In addition to study-specific limitations (outlined in *Chapter 4*), there are some more general limitations that warrant critical consideration:

Patient CRF lower than that typically encountered

The patients who underwent CPET prior to vascular and colorectal surgery in this work, resided in South Wales, UK and underwent CPET at the University Hospital of Wales, Cardiff. The mean $\dot{V}O_2$-AT prior to colorectal surgery of 10.9 mL $O_2.min^{-1}.kg^{-1}$ was considerably lower than values reported elsewhere in the UK for patients undergoing equivalent surgery, such as 12.1 units in a cohort from Liverpool (West et al., 2014b), and 13.0 units in a cohort from Plymouth (Lai et al., 2013). Indeed, when the mean AT of the colorectal patients was compared with 30 other sites across the UK performing CPET prior to major intra-abdominal surgery (mean AT range of 15.3 to 10.3mL $O_2.min^{-1}.kg^{-1}$), the Cardiff cohort ranked 24^{th} lowest (Davies, 2019). Furthermore, less favourable postoperative outcomes have been identified in previous national bowel cancer audits for this hospital compared to UK averages (NBOCA, 2016, NBOCA, 2017). Therefore, the present work likely involves considerably more unfit and hence high-risk patients than typically encountered. This may equally be considered a strength however, given that the 'high-risk surgical patient' contributes to over 80% postoperative deaths and complications (Pearse et al., 2006).

Single NHS centre

The findings from *Study 1, 2 and 3* included patients from a single NHS centre. Whilst sufficient sample sizes were robustly used to support conclusions, inference to wider patient populations should be treated with caution.

Weighting of risk factors

Literature has not addressed the weighting of CRF in determining postoperative outcome compared to other, arguably more established, risk factors for CVD. Furthermore, the greatest weighting of risk likely comes from the type and urgency of surgical procedure. *Study 3* marks a considerable progression whereby the number of postoperative deaths attributed to low CRF was directly compared with that of traditional CVD risk factors (and shown to be most important).

It is important to note that the deaths attributable to (low) CRF and other independent risk factors for CVD still represent a minority of global mortality; most deaths can likely be accounted for by surgical procedure (and skill of the operating surgeon) and patient management during the perioperative period (the anaesthetist). Consideration of all risk factors, including CRF, including novel methods to quantify the extent of surgical insult and effectiveness of intraoperative patient management will further improve risk prediction and likely further highlight the critical importance of (adequate) CRF.

5.5. Future Research

The potential use of CRF in risk stratification and prediction requires further research and the results from this body of work can be interpreted to both aid risk prediction, and to generate hypotheses in aetiological research thus identifying potential targets for intervention. Whilst

CRF can be used in both contexts, the research that needs to come next and subsequent clinical applications are very different.

Refining metrics, models, and wider applications to aid risk prediction

To confirm and further refine findings, the present studies require replication across large national databases including patients from different socioeconomic and geographical backgrounds. At a national level, our research group is involved in the creation of a multi-centre CPET database for Wales to provide greater numbers of test results for comparison with postoperative outcome. At an international level, we are exploring potential to conduct multisite comparative studies between different main hospital clinics with different patient socioeconomic and CRF status, such as with colleagues and collaborators in the Rigshospitalet, Copenhagen. A protocol revision has also been submitted, and approval granted to expand analysis of the current CPET database to investigate the relationship between CRF and postoperative outcome in hepatobiliary and pancreatic, urology, gynaecology, renal, cardiology, general surgery and ear nose and throat patients that are now also routinely referred to undergo PCPET prior to major surgery.

For risk prediction, a focus on determining whether the inclusion of CRF improves existing prognostic modelling, over and above traditional risk factors is required. For example, albeit outside of the surgical setting, Argyridou et al., (2020) reported that a simple self-reported measure of walking pace improved risk prediction for all-cause and cardiovascular mortality when added to established risk factors. Further work is required to optimise risk prediction in the surgical setting by using PCPET values in conjunction with risk prediction models such as the RCRI, POSSUM, NSQIP, and SORT (Reeves et al., 2018). Models such as NSQIP and SORT importantly include the type and severity of surgical procedure and the urgency (elective vs. emergency for example) alongside CVD and consequently report strong AUROC values, also referred to as 'C-statistics', of 0.81 to 0.94 (Protopapa et al., 2014, Bilimoria et al., 2013). For reference, an AUROC or C-statistic value of 1 would indicate a model that perfectly discriminates patients with postoperative mortality or morbidity against those without. Impressively, optimised metrics of CRF, alone, produced AUROC values up to 0.88 in *Study 3* (Table 13) and may therefore further improve these risk prediction models if incorporated. Thus, inclusion of a primary measure of CRF (such as $\dot{V}O_2$ peak) to these models would allow direct comparison of subsequent C-statistics and demonstrate if revised models do indeed optimise prediction, much like the example of Argyridou et al., (2020). To date, only one risk calculator (Carlisle et al., 2015) has incorporated preoperative CPET values for $\dot{V}O_2$ peak, peak power output and $\dot{V}_E/\dot{V}CO_2$-AT alongside other preoperative variables to predict long term survival in patients following AAA repair. However, comparison of mortality prediction against the same model without metrics of CRF included was not presented.

A deeper mechanistic understanding to improve risk prediction and aetiological research

The mechanisms underlying the postoperative protective benefits conferred by CRF remain to be fully established. In addition to metabolic changes, the stress response to surgery also gives rise to hormonal and immunological changes (Reuter et al., 2010). The mechanical impact of surgery alone is sufficient to cause tissue damage that can activate (local and systemic) oxidative-inflammatory-nitrosative stress (OXINOS) to modulate (impair) vascular O_2 transport. Conversely, anaesthesia inhibits the stress response to surgery thus counteracting resultant oxidative and inflammatory responses, albeit less effectively in thoracic and upper abdominal procedures whereby the use of agents such as fentanyl, for example, causes respiratory depression which may consequently require ventilatory support in the postoperative period (Klingstedt et al., 1987).

Systemic inflammation, consequent to surgery, may also lead to an increase in reactive nitrogen species (RNS), in addition to the upstream increase in oxidative stress and ROS, which requires consideration. Oxidative and nitrosative stress is a normal product of metabolism, maintaining homeostasis as signalling molecules, and is beneficial in pathophysiological conditions such as phagocytic cells using ROS to destroy pathogens, while nitric oxide (NO) is pivotal to flow-mediated vasodilation of the vascular endothelium (Gielis et al., 2017). However, much like ROS, RNS are also characterised by molecules that contain an unpaired electron on their outer electron shell, and cause structural membrane damage, mitochondrial dysfunction and inflammation (Berg et al., 2011). Work from this research group has also demonstrated that elevated OXINOS stress is associated with impaired systemic vascular dysfunction (Bailey, 2018, Bailey et al., 2013b). A theoretical model (Figure 31) proposing molecular mechanisms describing the maladaptive response to surgery in the unfit patient is provided which may provide a framework for future research focus.

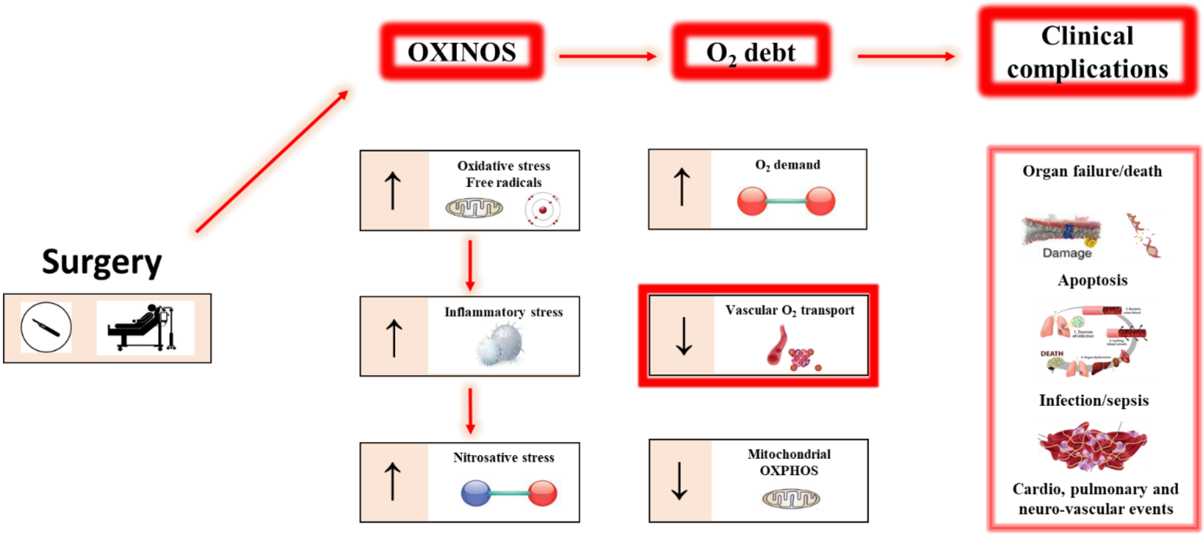


Figure 31. A theoretical model proposing molecular mechanisms describing the maladaptive response to surgery in the unfit patient. OXINOS, oxidative-inflammatory-nitrosative stress; OXPHOS, oxidative phosphorylation.

Novel biomarkers predictive of postoperative outcome may therefore arise following investigation of OXINOS and offer a deeper mechanistic insight. Interestingly, a recent study (Ekeloef et al., 2017) investigated endothelial dysfunction in the early postoperative period to help better understand the mechanisms for myocardial injury after non-cardiac surgery. They identified systemic vascular endothelial dysfunction (measured using the reactive hyperaemia index, assessed non-invasively using digital pulse tonometry) in the early postoperative period following major colorectal surgery. Given the expertise of the present research group, it is intended to conduct the measurement of preoperative OXINOS alongside established systemic PCPET derived measures of CRF. Indeed, a recent collaboration has investigated the addition of a systemic inflammatory marker (C-reactive protein) alongside physiological performance ($\dot{V}O_2$ peak) as indicators of complications after oesophageal cancer surgery (Powell et al., 2020) and vascular surgery (Bailey, 2021).

A striking observation in this field of research is the omission of the brain when discussing the potential mechanisms that may help better understand the relationship between CRF and postoperative outcome. Current funding applications are being sought by this research group (given the expertise and resource within this laboratory) to investigate OXINOS alongside cerebrovascular measures and their (mechanistic) relationship with postoperative outcome. Interestingly, important new evidence demonstrates high occurrences of perioperative covert stroke following non-cardiac major surgery, which is associated with an increased risk of cognitive decline one year later (Mrkobrada et al., 2019). Prior work from this group has demonstrated that elevated OXINOS stress in human disease is associated with impaired cerebrovascular function in the form of blunted cerebral perfusion and vascular reactivity that precedes cognitive impairment and depression, helping identify those in need of more specialist clinical support (Bailey, 2018).

This approach highlights not only the possibility to improve risk prediction by integration of novel biomarkers to existing models, but also the development of interventions, both pharmacological and using exercise in aetiological research.

Optimising exercise training prior to major surgery: an aetiological perspective

Albeit a single case study, the findings from Study 4 demonstrate the potential to improve preoperative CRF, and similarly, evidence from small sample studies is emerging (Simonson et al., 2020). The understanding of improved CRF consequent to exercise training requires further investigation both from a mechanistic perspective and translation to postoperative outcomes, to tailor and optimise dosage for specific patient groups. Interestingly, many similarities exist between the physiological insult of surgery and the acute response to an exercise stimulus.

As described more extensively in *Chapter 2*, adaptations to exercise include elevated peroxisome proliferator-activated receptor gamma coactivator 1-alpha mRNA which moderates mitochondrial biogenesis (Gibala et al., 2009), increased citrate synthase concentrations indicative of muscle oxidative capacity (Burgomaster et al., 2005), and oxidative stress observed following acute exercise (Bailey et al., 2018) attenuated with chronic exercise stimulus (Fatouros et al., 2004) consequent to improved antioxidant capacity (Fatouros et al., 2004, Radák et al., 1999). Furthermore, and possibly of greatest importance, improved vascular function is apparent following exercise (Wray et al., 2011), and further optimised with HIIT (Molmen-Hansen et al., 2012) and consequent upregulation of endothelial nitric oxide synthase (Bolduc et al., 2013). Collectively, the theoretical and proven adaptive responses by patients undergoing exercise interventions are likely able to improve CRF, increase antioxidant defences, immune response, and endothelial function, which may in turn promote superior postoperative outcomes as highlighted in Figure 32.

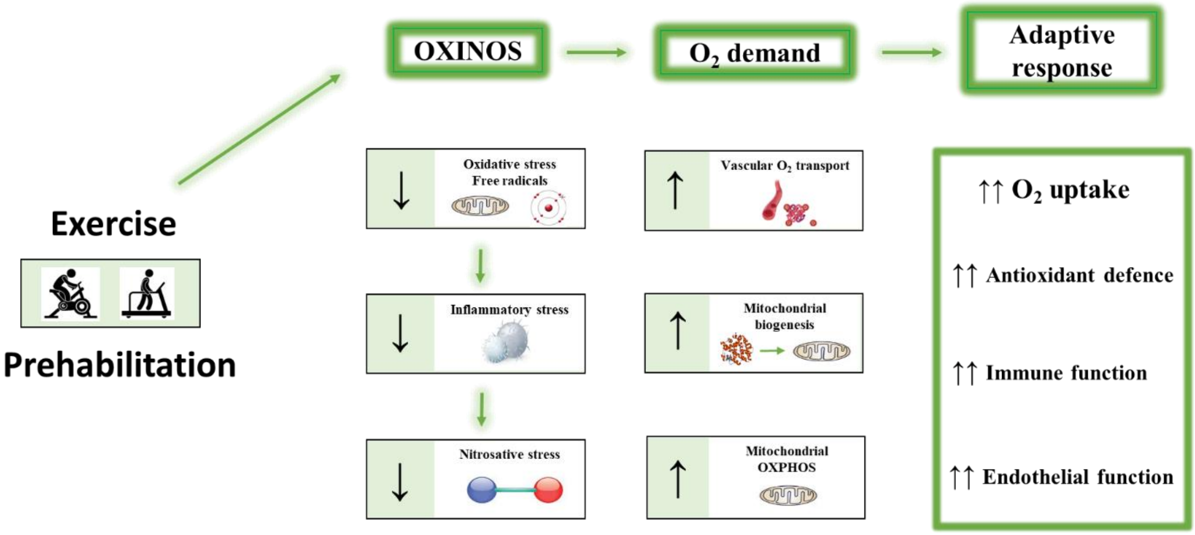


Figure 32. A theoretical model proposing mechanisms that describe the chronic adaptive response to exercise, as part of a prehabilitation strategy prior to surgery, that may protect against the surgical stress response.

Research into the development of preoperative exercise interventions to optimise the modifiable components of CRF is ongoing and, as previously described, large clinical trials are set to report findings soon. This is important because we still do not know what mode, duration, or intensity of exercise is optimal to provide the most effective benefits. Furthermore, for exercise interventions to be effective and essential components of multimodal prehabilitation strategies, they should be tailored to patient needs, specific to their level of fitness, time to surgery, and resource availability.

Finally, there is little focus on the effects of preoperative CRF on surgical outcomes in the long term. Whilst, such longitudinal studies are difficult to conduct, our research team is currently providing a local (exercise) intervention arm, for the South Wales region, supporting CHALLENGE; a randomised controlled trial comprising a phase III study of the impact of a physical activity programme (3 years duration) on disease-free survival in patients with high risk stage II or stage III colon cancer (Courneya et al., 2014, Courneya et al., 2008; Trial ID NCT00819208). At a local level, CHALLENGE has recruited patients from the cohort investigated in *Study 3* of the present work. Results are yet to be reported and are awaited with interest especially from a comparative perspective with the exercise prehabilitation trials.

5.6. Conclusions

Preoperative CRF was associated with postoperative outcome in patients undergoing major colorectal and vascular surgery, and thus CPET should be considered a principal component of surgical risk assessment. This work highlights the importance of CRF above that of traditional CVD comorbidities when assessing surgical risk, and low CRF was associated with a 3 to 5-fold greater risk of mortality. The measurement and interpretation of CRF has been optimised considering sources of variation and their potential to (mis)inform risk, which may lead to up to 60% of patients being incorrectly stratified. New and improved threshold values for metrics of CRF have been defined relative to surgical procedure and patient sex, which better predict postoperative outcome than current practice. Finally, potential to objectively improve CRF in the high-risk patient, thus reducing surgical risk, has been demonstrated through exercise intervention and theoretical review.

Collectively, the novel findings reported have extended the current body of knowledge and can inform future practice to change and optimise patient risk stratification. This may inform perioperative care and improve patient outcomes following major intra-abdominal surgery.

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Appendix A – Ethical Approval

GIG CYMRU NHS WALES
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Cardiff and Vale University Health Board

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University Hospital of Wales

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From: Professor C Fegan
R&D Director
R&D Office, 2nd Floor TB2
University Hospital of Wales
Cardiff
CF14 4XW

01 March 2016

Dr Richard Davies
Consultant Anaesthetist
University Hospital of Wales
Heath
Cardiff
CF14 4XW

Dear Dr Davies

Cardiff and Vale UHB Ref and Study Title : 15/AIC/6352 : Impaired Cardiopulmonary Fitness And Post-Operative Survival

IRAS Project ID: 181114

The above research project was forwarded to Cardiff and Vale University Health Board R&D Office by the Health and Care Research Wales Permissions Coordinating Unit. A Governance Review has now been completed on the project.

Documents approved for use in this study are:

Document	Version	Date
NHS R&D Form	5.2	11/12/2015
SSI Form	5.2	11/12/2015
Protocol	2	08/02/2016
Anaesthesia for Enhanced Recovery Document	-	Sep-10

I am pleased to inform you that the UHB has no objection to your proposal and that this study has been classed as pathway-to-portfolio. You have informed us that

University of South Wales is willing to act as Sponsor under the Research Governance Framework for Health and Social Care.

Please accept this letter as confirmation of permission for the project to begin within this UHB.

In order to comply with Health and Care Research Wales reporting requirements, you must inform the R&D Office of the date which this site opens to recruitment and the date that the first patient is recruited at this site. Please email this information to CAV research.development@wales.nhs.uk

May I take this opportunity to wish you success with the project and remind you that as Chief / Principal Investigator you are required to:

- Inform the R&D Office if this project has not opened within 12 months of the date of this letter. Failure to do so may invalidate R&D approval.
- Inform the Health and Care Research Wales Permissions Coordinating Unit and the UHB R&D Office if any external or additional funding is awarded for this project in the future
- Ensure that all study amendments are submitted to the Health and Care Research Wales Permissions Coordinating Unit by the Chief Investigator
- Ensure the Health and Care Research Wales Permissions Coordinating Unit is notified of the study's closure
- Ensure that the study is conducted in accordance with all relevant policies, procedures and legislation
- Provide information on the project to the UHB R&D Office as requested from time to time, to include participant recruitment figures

Yours sincerely,

Professor Christopher Fegan
R&D Director / Chair of the Cardiff and Vale Research Review Service (CaRRS)

CC **R&D Lead: Dr Naomi Goodwin**
Chief Investigator, Professor Damian Bailey, University of South Wales
Sponsor Contact: Louise Bright, University of South Wales
Student: Mr George Rose
Finance: Anthony Williams, University Hospital of Wales
Clinical Board Assistant Head of Finance: Rebeka Warren, University Hospital of Wales

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UMAL

TO WHOM IT MAY CONCERN

23rd November 2015

Dear Sir/Madam

UNIVERSITY OF SOUTH WALES AND ALL ITS SUBSIDIARY COMPANIES

Project: Impaired cardiopulmonary fitness and postoperative survival

We confirm that the above Institution is a Member of U.M. Association Limited, and that the following covers are in place:

1. **EMPLOYERS' LIABILITY**

Certificate No.	Y016458QBE0115A/085
Period of Cover	1 August 2015 to 31 July 2016
Limit of Indemnity	£30,000,000 any one event unlimited in the aggregate.
Includes	Indemnity to Principals
Cover provided by	QBE Insurance (Europe) Limited and Excess Insurers.

2. **PUBLIC AND PRODUCTS LIABILITY**

Certificate of Entry No.	UM085/08
Period of Cover	1 August 2015 to 31 July 2016
Includes	Indemnity to Principals
Limit Of Indemnity	£50,000,000 any one event and in the aggregate in respect of Products Liability and Unlimited in the aggregate in respect of Public Liability.
Cover provided by	U.M. Association Limited and Excess Cover Providers led by QBE Insurance (Europe) Limited

If you have any queries in respect of the above details, please do not hesitate to contact us.

Yours faithfully

Susan Wilkinson

Susan Wilkinson
For U.M. Association Limited

ISO 9001 REGISTERED FIRM

U.M. Association Limited
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Appendix B – Publications Arising from this Thesis

B.1. Journal Papers

Received: 29 March 2022 | Accepted: 11 May 2022

DOI: 10.1113/EP090156

Experimental Physiology WILEY

REVIEW ARTICLE

'Fit for surgery': the relationship between cardiorespiratory fitness and postoperative outcomes

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Edited by: Jeremy Ward

Abstract

Surgery accounts for 7.7% of all deaths globally and the number of procedures is increasing annually. A patient's 'fitness for surgery' describes the ability to tolerate a physiological insult, fundamental to risk assessment and care planning. We have evolved as obligate aerobes that rely on oxygen (O_2). Systemic O_2 consumption can be measured via cardiopulmonary exercise testing (CPET) providing objective metrics of cardiorespiratory fitness (CRF). Impaired CRF is an independent risk factor for mortality and morbidity. The perioperative period is associated with increased O_2 demand, which if not met leads to O_2 deficit, the magnitude and duration of which dictates organ failure and ultimately death. CRF is by far the greatest modifiable risk factor, and optimal exercise interventions are currently under investigation in patient prehabilitation programmes. However, current practice demonstrates potential for up to 60% of patients, who undergo preoperative CPET, to have their fitness incorrectly stratified. To optimise this work we must improve the detection of CRF and reduce potential for interpretive error that may misinform risk classification and subsequent patient care, better quantify risk by expressing the power of CRF to predict mortality and morbidity compared to traditional cardiovascular risk factors, and improve patient interventions with the capacity to further enhance vascular adaptation. Thus, a better understanding of CRF, used to determine fitness for surgery, will enable both clinicians and exercise physiologists to further refine patient care and management to improve survival.

KEYWORDS
cardiorespiratory fitness, mortality, oxygen transport, physical activity, surgery

1 | INTRODUCTION

Surgery is amongst the leading risk factors for mortality and has been estimated to account for 7.7% of all deaths globally (Nepogodiev et al., 2019). By 2030, it is estimated that one-fifth of people aged 75 years and older in the United Kingdom alone will undergo surgery (Fowler et al., 2019). Therefore, to better understand and mitigate this risk, we need to consider not just the disease or surgical procedure, but also the phenotypical response and ability to cope with the physiological insult posed by major surgery. Furthermore, prophylactic intervention targeting modifiable risk factors prior to surgery, a process known as 'prehabilitation', requires investigation and optimisation. This review explores our relationship with oxygen (O_2), the elixir of life, and how its transport and use in the human body determines 'fitness for surgery'.

2 | ORIGIN OF O_2 AND OUR DEPENDENCY ON OXIDATIVE METABOLISM

When the solar system emerged 4.6 billion years ago (Dickerson, 1978), Earth's atmosphere was devoid of O_2, a vast difference compared with the modern day atmospheric inspired fraction of 20.93%. The emergence of life, likely originating in alkaline thermal vents at the bottom of the oceans, initially gave rise to the domains of archaea and bacteria (Miller & Bada, 1988). Approximately 1.5 billion years ago, cyanobacteria began to release O_2 into the atmosphere (Nisbet & Sleep, 2001). The organic compounds that emerged from the 'primordial soup' were photosynthetic, capturing solar radiation and creating the organic molecule glucose. In turn, the O_2 released into the atmosphere signalled a major evolutionary event, arguably described by two oxidation 'pulses', the Great Oxidation Event and the Neoproterozoic Event, or as a progressive evolution, the Great Oxidation Transition (Lyons et al., 2014). This gave rise to atmospheric O_2 and the evolution of O_2-dependent organisms, from primitive eukaryotic unicellular structures performing metabolism, locomotion and reproduction to present day *Homo sapiens*.

Figure 1 describes the production of paleo-atmospheric O_2 and the entire dependency of the respiring mammalian cell for the constancy of electron flow, with molecular O_2 serving as the terminal electron acceptor in mitochondrial oxidative phosphorylation. *Homo sapiens*, like all mammals, has a remarkable ability to harness O_2, allowing a rapid turnover of adenosine triphosphate (ATP) and affording cells, tissue and organs a coordinated stasis sustaining life. Mammalian evolution has thus produced a structural, functional and physiological organisation that efficiently coordinates the convective delivery and diffusive uptake of O_2, essential for successful life.

3 | FROM MOUTH TO MITOCHONDRIA: CONVECTIVE AND DIFFUSIVE DETERMINANTS OF O_2 TRANSPORT

Early measurements describing O_2 uptake ($\dot{V}_{O_2}$) in humans at the onset of intense movement were conducted by Hill and Lupton (1923) and demonstrated a rapid and exponential response, as skeletal muscle has the capacity to increase rate of metabolism by an astounding 50- to 100-fold above its resting requirements. This challenges a rapid delivery of O_2 to the mitochondrial inner membrane for use as the terminal electron acceptor, whereby oxidative phosphorylation generates ATP. O_2 is transported by convection, which describes its movement within the airways and circulation-driven aero- and hydrostatic pressure gradients, and by diffusion, the passive movement down a concentration gradient such as between the alveolar compartment and pulmonary capillary bed and between the systemic microcirculation and tissue.

Figure 2 illustrates the major organs and processes, both convective and diffusive, that describe the 'O_2 cascade'. Following inspiration of air into the lungs, O_2 diffuses down a concentration gradient at the alveolar–capillary membrane, minimally dissolves in plasma and predominantly binds with haemoglobin (Hb), an allosteric protein with affinity for four molecules of O_2. Deoxygenated venous blood is therefore saturated with O_2 in the pulmonary capillaries, the concentration of which is proportional to the concentration of Hb, its P_{50} and the partial pressure exerted by O_2 on the plasma at a given temperature (Henry's law). Oxygenated blood then travels the vascular system driven by the heart. This convective component is referred to as 'O_2 delivery' ($\dot{Q}_{O_2}$), the product of cardiac output ($\dot{Q}$) and arterial O_2 content ($\dot{Q} \times C_{aO_2}$), and is complete when O_2 diffuses across the microcirculatory capillary beds and reaches the mitochondrial matrix where it is used as the terminal electron carrier. $\dot{V}_{O_2}$ as described by Fick's principle is equal to the product of $\dot{Q}$ and the difference between arterial and mixed venous oxygen content ($C_{aO_2} - C_{\bar{v}O_2}$). Notably, in health, the principal 'rate limiting' steps for maximal O_2 uptake ($\dot{V}_{O_2max}$) are attributed to the perfusive ($\dot{Q}_{O_2}$) and diffusive components of the cascade (Wagner, 2000).

4 | METRICS AND MEANING: ASSESSMENT OF CARDIORESPIRATORY FITNESS

The advent of breath-by-breath measurement technology has allowed us to measure the capacity of the O_2 transport system and determine metrics describing the magnitude of cardiorespiratory fitness (CRF), which not only describes an individual's ability to perform physical activity, but is linked to cardiovascular health (Ross et al., 2016) and

New Findings

- **What is the topic of this review?**
  The relationships and physiological mechanisms underlying the clinical benefits of cardiorespiratory fitness (CRF) in patients undergoing major intra-abdominal surgery.
- **What advances does it highlight?**
  Elevated CRF reduces postoperative morbidity/mortality, thus highlighting the importance of CRF as an independent risk factor. The vascular protection afforded by exercise prehabilitation can further improve surgical risk stratification and postoperative outcomes.

longevity (Blair et al., 1989). Cardiopulmonary exercise testing (CPET) is used to objectively measure the ability of a patient to uptake O_2 and typically involves an incremental exercise test to symptom-limited exhaustion. CPET can also identify underlying pathology and evaluate the impact of chronic comorbidities on O_2 uptake. Recently, the use of CPET has been widely adopted in patients prior to major surgery and approximately 30,000 tests are conducted annually in the UK alone (Reeves et al., 2018). These data are used to support patient care decisions, plan appropriate postoperative critical care, and direct pre-habilitation programs aimed at improving CRF (Levett et al., 2018). Three primary metrics describing CRF are typically reported when conducting CPET:

1. Peak oxygen consumption ($\dot{V}_{O_2peak}$), defined as the $\dot{V}_{O_2}$ attained during an incremental test to exhaustion, expressed in absolute terms (ml min^{-1}) or relative to body mass (ml kg^{-1} min^{-1}), which can be subject to allometric scaling, and measured as the highest value recorded, often occurring during the final 20 s of a test. Whilst $\dot{V}_{O_2peak}$ is reflective of a patient's 'best effort', it may not necessarily reflect a true highest value, defined as $\dot{V}_{O_2max}$ with an observed plateau present in the O_2 uptake work-rate slope of Hill & Lupton (1923) demonstrated in Figure 3. Controversy exists here, and evidence suggests only a minority of continuous tests, even in young healthy people, yield a measurable plateau (Day et al., 2003; Poole & Jones, 2017). Nevertheless, an exercise test to exhaustion is important since it allows for the site of transport limitation across the O_2 cascade to be identified (Wagner, 2000).
2. Anaerobic threshold (AT), a submaximal index of CRF defined as the $\dot{V}_{O_2}$ above which anaerobic metabolism supplements oxidative phosphorylation with additional carbon dioxide (CO_2) production, creating a deflection point on a plot of pulmonary CO_2 output versus O_2 uptake (Figure 4). The AT is also commonly reported as a percentage of $\dot{V}_{O_2peak}$ or $\dot{V}_{O_2max}$. Whilst the AT signifies a transition where increased glycolysis raises the muscles lactate efflux into the blood above its removal rate with associated metabolic acidosis, a multitude of definitions and controversies exist (Poole et al., 2021). Thus in the context of preoperative CPET, AT refers to the gas exchange threshold (GET, sometimes also referred to as the ventilatory threshold), typically measured using the 'gold standard' V-slope (Beaver et al., 1986) method of determination. GET is expressed in ml kg^{-1} min^{-1} or ml min^{-1}.
3. The ventilatory equivalent for carbon dioxide (V_{eqCO_2}), defined as a ratio of minute ventilation to CO_2 production and usually reported at the GET. V_{eqCO_2} reflects the composite efficiency

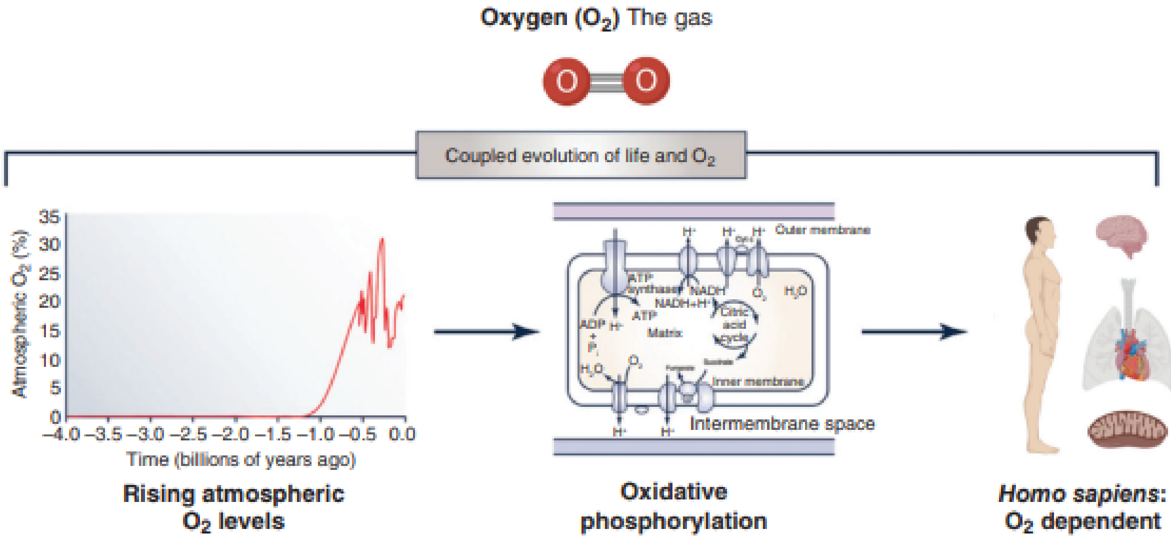

FIGURE 1 The production of oxygen (O_2), dependency of mitochondrial oxidative phosphorylation upon O_2, and the evolution of *Homo sapiens* to support O_2 delivery. Adapted from Bailey (2019)

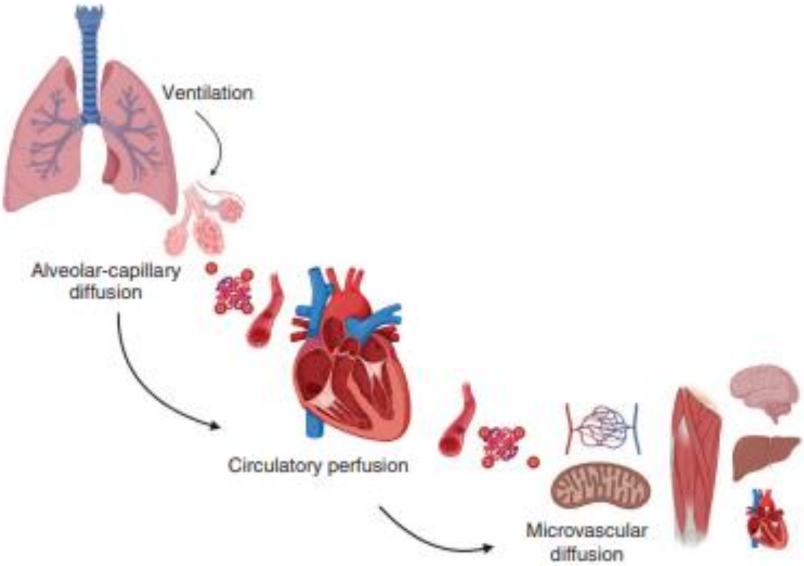

FIGURE 2 The oxygen (O_2) transport system characterised by pulmonary ventilation, alveolar–capillary diffusion, circulatory perfusion driven by the cardiovascular system and diffusion across the microcirculatory capillary beds. The volume of O_2 transport, described by Fick's principle, is determined by the product of convective (cardiac output) and diffusive O_2 transport terms (and is the product of cardiac output and the difference between the O_2 content of arterial and venous blood)

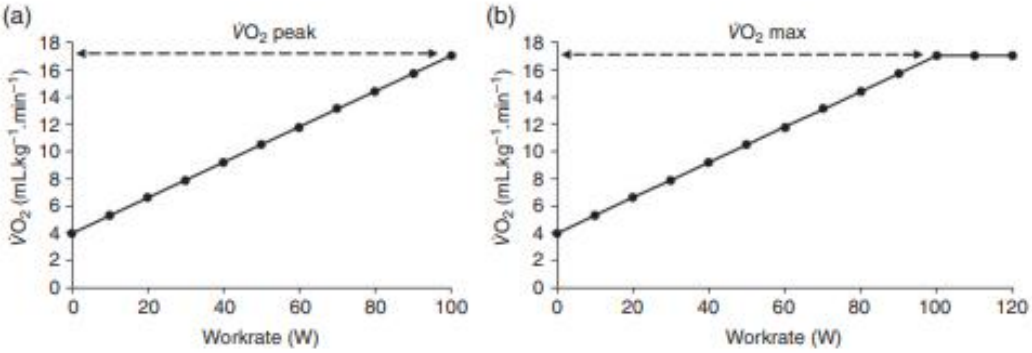

FIGURE 3 Schematic representation of O_2 consumption at the limit of exercise tolerance during CPET. (a) $\dot{V}_{O_2peak}$ reported as the highest value recorded. (b) $\dot{V}_{O_2max}$ idealised as a true highest value with observed plateau present. $\dot{V}_{O_2peak}$, peak oxygen consumption; $\dot{V}_{O_2max}$, maximal oxygen uptake

of the ventilatory response, including the breathing pattern and adaptive changes in pulmonary gas exchange in response to exercise. Elevated values for V_{eqCO_2} occur in heart failure, respiratory disease and pulmonary hypertension (ATS/ACCP, 2003; Snowden et al., 2010; Sun et al., 2001) consequent to diminished perfusion, ventilation–perfusion mismatching, or diffusion limitation and changes in breathing pattern, which increase dead space ventilation.

5 | CRF AND SURGERY: LINK TO SURVIVAL

Mortality following major surgery is a significant risk despite progress being made in surgical technologies, anaesthesia and peri-operative care. In colorectal surgery, mortality is reported at 3.2% within 90 days (NBOCA, 2017) with complication rates above 30% (Lucas & Pawlik, 2014). Similarly, in-hospital mortality for elective abdominal aortic aneurysm (AAA) repair is 2.9% for open repair and 0.4% for endovascular repair (VSQI, 2017). Furthermore, the insult of major colorectal surgery has been shown to reduce CRF by ~40%, with hospital stays of 7–9 days, and only 50% of patients regaining pre-operative CRF levels after 6 months (Jensen et al., 2011).

Accurate prediction of surgical risk is required to facilitate shared decision making, improve patient outcomes and plan peri-operative care. Traditionally, subjective clinical acumen alone was used; however, objective scoring systems are available including the Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM; Whiteley et al., 1996), American Society of Anaesthesiologists (ASA) physical status, Charlson Comorbidity Index, and measures of cardiac function (Moyes et al., 2013). These systems are generally weak, and complementary 'biomarkers' are needed. CRF, a modifiable risk factor, has long been (inversely) associated with all-cause mortality (Kokkinos et al., 2010; Mandsager et al., 2018), and evidence also suggests that impaired CRF

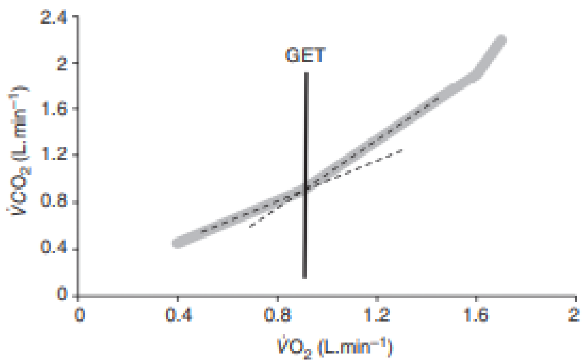

FIGURE 4 Schematic representation of the V-slope method (Beaver et al., 1986) for estimation of the gas exchange threshold (GET) during CPET. GET is identified at the intersection of two linear sections of the $\dot{V}_{CO_2}$–$\dot{V}_{O_2}$ relationship, represented by the continuous black line. A further deflection point in the relationship may be observed during the latter stages of CPET and represents respiratory compensation

(see Older et al., 1993, below) is associated with reduced survival and increased morbidity following major surgery (Moran et al., 2016; Smith et al., 2013).

The seminal work of Older et al. (1993) first described an association between preoperative CRF and postoperative outcome. They studied 184 elderly patients undergoing elective major intra-abdominal surgery and established that patients classified as 'unfit' exhibited markedly higher mortality rates than those deemed 'fit' (18% vs. 0.8%, $P < 0.001$). Patients were considered unfit by preoperative CPET if O_2 uptake at GET was <11 ml O_2 kg^{-1} min^{-1}, a value originally described by Weber and Janicki (1985) that characterised the GET in patients with moderate to severe heart failure. Studies have since used the GET as a measure of CRF, and further supported the inverse association between CRF and postoperative mortality and morbidity in patients undergoing a variety of intra-abdominal surgeries (Table 1).

A theoretical model (Figure 5) originally developed by Clegg et al. (2013) helps visualise why elevated CRF is associated with improved postoperative outcome. The model describes potential differences in surgical outcome between a hypothetical patient who is unfit for surgery (for example with a GET < 11 ml O_2 kg^{-1} min^{-1}) compared to a patient deemed fit (GET ≥ 11 ml O_2 kg^{-1} min^{-1}). The unfit patient is more likely to require care in a high dependency unit or intensive care unit with a greater likelihood of complications and risk of mortality, whereas the fit patient may experience a normal and faster recovery on the ward.

Given the importance of assessing CRF in clinical practice, the American Heart Association has published a scientific statement promoting CRF as a clinical vital sign (Ross et al., 2016).

6 | MECHANISTIC LINK BETWEEN CRF AND POSTOPERATIVE OUTCOME

The model presented (Figure 5) presumes the existence of an obligatory baseline level of CRF (such as the threshold values for $\dot{V}_{O_2peak}$, GET or V_{eqCO_2} found in Table 1) to survive an increased demand for O_2 during the perioperative period. If the patient is unable to meet this presumed O_2 demand, chronic hypoxaemia and limited $\dot{Q}_{O_2}$ may be responsible for increased morbidity and mortality for any severity of disease. Whilst a detailed mechanistic understanding explaining why impaired CRF is associated with poor postoperative outcome remains to be elucidated, the presence of an O_2 deficit during the perioperative period is fundamental to this model.

The surgical stress response is characterised by an increased O_2 demand as demonstrated by Ciaffoni et al. (2016), measured directly (via in-airway sensors) beginning in the intraoperative period (Figure 6). The underlying mechanisms responsible for the perioperative elevation in $\dot{V}_{O_2}$ can be explained by complex changes in metabolic demand. These comprise hormonal, haematological and immunological changes, manifest by increased $\dot{Q}$ and O_2 consumption as the delivery of nutrient and O_2-rich blood supports energy processes, tissue repair and protein synthesis (Gillis & Wischmeyer, 2019). Shoemaker et al. (1988) also describe a substantial increase in O_2 demand, from an average of 110 ml min^{-1} m^{-2} at rest to

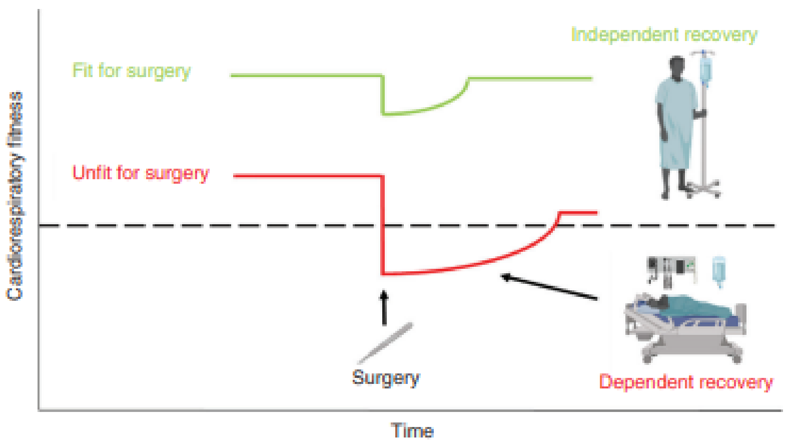

FIGURE 5 Physiological insult of surgery and potential for change in patient recovery, adapted from Clegg et al. (2013). The green plot represents a patient considered (CRF) 'fit' for surgery whereas the red plot represents a patient classified as 'unfit'. The dashed line represents the cut-off between independent patient recovery typically requiring ward-based care, and dependent recovery requiring high dependency unit or intensive care unit admission

TABLE 1 Studies demonstrating an association between CRF and postoperative outcome following non-cardiac intra-abdominal surgery, adapted from (Moran et al., 2016)

Author	Patients (n)	$\dot{V}_{O_2peak}$ risk threshold (ml kg^{-1} min^{-1})	GET risk threshold (ml O_2 kg^{-1} min^{-1})	V_{eqCO_2} risk threshold	Risk thresholds defined/adopted	Postoperative outcome
Intra-abdominal surgery						
Older et al. (1993)	187	Not measured	Yes <11.0	Not measured	Adopted	Hospital mortality
Older et al. (1999)	548	Not measured	Yes <11.0	No	Adopted	Hospital mortality
Wilson et al. (2010)	847	Not measured	Yes <10.9	Yes >34	Adopted	Mortality 90 days
Snowden et al. (2010)	116	No	Yes <10.1	No	Defined	Morbidity: comp
Vascular AAA surgery						
Carlisle and Swart (2007)	130	Yes	Yes	Yes >42	Defined	Mortality: 2 years
Hartley et al. (2012)	415	Yes <15.0	Yes <10.2	Yes >42	Adopted	Mortality: 30 days, 90 days
Prentis et al. (2012)	185	No	Yes <10.0	No	Defined	Morbidity: LoS
Goodyear et al. (2013)	188	Not measured	Yes <11.0	Not measured	Adopted	Mortality: 30 days Morbidity: LoS
Grant et al. (2015)	506	Yes <15.0	Yes <10.2	Yes >42	Adopted	Mortality: 3 years
Rose et al. (2018a)	124	Yes <13.1	No	Yes ≥34	Defined	Mortality: 2 years
Colorectal surgery						
Lai et al. (2013)	269	Not measured	Yes <11.0	Not measured	Adopted	Mortality: 2 years Morbidity: LoS
West et al. (2014b)	136	Yes <16.7	Yes <10.1	Yes >32	Defined	Morbidity: comp
West et al. (2014a)	105	Yes <18.6	Yes <10.6	No	Defined	Morbidity: comp
Wilson et al. (2019)	1375	Not measured	No	Yes >39	Defined	Mortality: 90 days
Upper gastrointestinal surgery						
McCullough et al. (2006)	109	Yes <15.8	No	No	Defined	Morbidity: comp
Nagamatsu et al. (2001)	91	Yes <800 ml	Yes	Not measured	Defined	Morbidity: comp
Moyes et al. (2013)	108	No	Yes <9.0	No	Defined	Morbidity: comp
Patel et al. (2019)	120	Yes <17.0	No	No	Defined	Morbidity: comp

Risk thresholds relate to a level of CRF below which an inferior postoperative outcome has been observed and are either defined from the respective study data or have been adopted from other studies and applied to the study data. Abbreviations: AAA, (open) abdominal aortic aneurysm; comp, complications; GET, gas exchange threshold; LoS, hospital length of stay; V_{eqCO_2}, ventilatory equivalent for carbon dioxide; $\dot{V}_{O_2peak}$, peak oxygen consumption.

170 ml min^{-1} m^{-2} following major surgery, consequent to the strong systemic inflammatory response. Thus, a patient with greater $\dot{V}_{O_2}$ reserve may help mitigate this cardiovascular burden.

Surgery, is also known to result in oxidative stress with consequent increases in free radical formation (Arsalani-Zadeh et al., 2011; Bailey et al., 2006, 2007). This is particularly prominent during abdominal surgery given the potential for ischemia–reperfusion, leukocyte activation, mitochondrial dysfunction and concurrent depletion of anti-oxidants in the postoperative period due to increased consumption (Bailey et al., 2006; Musil et al., 2005; Thomas & Balasubramanian, 2004). During laparoscopic surgery, for example, increases in intra-abdominal pressure during pneumoperitoneum may cause splanchnic ischemia–reperfusion and subsequent oxidative stress (Leduc & Mitchell, 2006). Furthermore, a reduction in $\dot{Q}$ contributing to decreased O_2 delivery is observed as systemic venous return is reduced to the right side of the heart and pulmonary venous return reduced to the left side of the heart. The conformational changes in ventricular architecture combine to decrease $\dot{Q}$ and are compounded by an increase in systemic vascular resistance. Ciaffoni et al. (2016) also demonstrated concurrent elevation of CO_2 production during the intraoperative period, which may be equally important in terms of 'clearance' for the maintenance of normal acid–base balance (Bailey et al., 2017) and requires further mechanistic investigation.

The contribution of anaesthesia to the production of reactive oxygen species (ROS) in the perioperative period is also important. O_2 is one of the most used drugs in anaesthetic practice. Reducing cellular hypoxia is a clinical priority, and thus the sickest patients who are likeliest to suffer the adverse consequences of hyperoxia and ROS formation are the likeliest to receive supplemental O_2. There is a good case for accepting lower levels of arterial oxygenation to minimise ROS damage in the perioperative period. However, because of genetic variability in susceptibility to damage by ROS it is impossible to

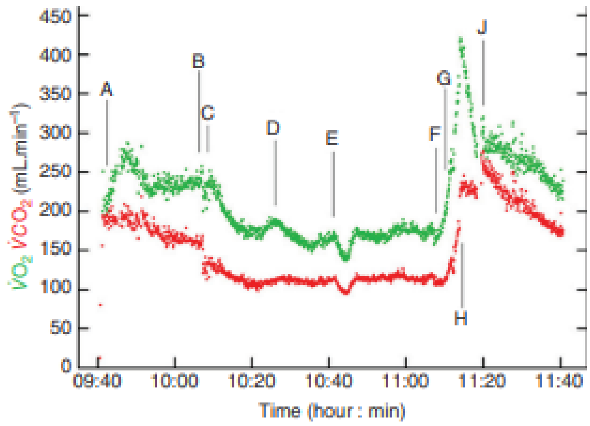

FIGURE 6 Pulmonary O_2 uptake during the intraoperative period of a patient undergoing abdominal aortic aneurysm repair, taken from Ciaffoni et al. (2016). Events are represented by knife to skin (A); reduction in ventilator driving pressure (B); aortic clamp applied (C); fall in blood pressure (D); metaraminol (fast-acting α-agonist) bolus, infusion rate increased from 2 to 5 ml h^{-1} (E); sequential removal of iliac artery clamps (F, G); increase in ventilator driving pressure (H); and removal of superior retractor restricting rib cage movement (I)

predict which patients would be most vulnerable and when. Furthermore, some anaesthetics (e.g., ketamine) have been shown to interfere with mitochondrial function, promote dismutase activity and affect ROS handling, albeit in animal studies (Venâncio et al., 2015).

The additional demand for O_2 is not solely constrained to the intraoperative period. Shoemaker et al. (1992) measured $\dot{V}_{O_2}$ in 253 high-risk patients (defined by criteria with a >30% surgical mortality rate) before, during and immediately after major surgery. These values were compared with the estimated $\dot{V}_{O_2}$ requirements of the patients (using resting preoperative control values) to calculate the magnitude of O_2 deficit. Patients who died (n = 64) had organ failure and a mean O_2 deficit of 33.2 l m^{-2}, compared with 21.6 l m^{-2} for survivors with organ failure (n = 31), and 9.2 l m^{-2} for survivors without organ failure or major complications (n = 158). These findings highlight the clinical significance of the cumulative O_2 deficit across the perioperative period and corresponding implications for development of organ failure and ultimately death (Figure 7). Furthermore, the authors also investigated the time course and types of emerging complications up to 10 days following surgery as illustrated in Figure 8. Interestingly, the recovery 'slopes' of the O_2 deficit in Figure 8 are much the same between survivors (with organ failure) and non-survivors, and just the intraoperative and early postoperative magnitude is greater, which may suggest this to be the more critical component.

7 | POTENTIAL MECHANISMS THAT ENHANCE SURVIVAL

Whilst mechanistic bases explaining the link between (elevated) CRF and postoperative outcome require further elucidation, evidence demonstrates that patients with low CRF are associated with poor postoperative outcome, likely explained by the prevailing magnitude of perioperative O_2 deficit. Importantly, CRF is a modifiable risk factor and a primary component of prehabilitation strategies (Macmillan, 2019; Tew et al., 2018). Prehabilitation represents an opportunity to improve patient preparation for surgery and is multi-modal in nature comprising exercise training and improving nutritional and psychological status (Scheede-Bergdahl et al., 2019). Prehabilitation aims to improve patient CRF to better tolerate the surgical stress response, leading to a reduced risk of perioperative complications and improved postoperative outcome (Tew et al., 2018). The theoretical potential for this strategy is illustrated in Figure 9.

Few studies have investigated the potential to improve CRF prior to surgery using exercise interventions and those that have mainly comprise small sample sizes demonstrating proof of principle (Rose et al., 2020; Simonsen et al., 2020). West et al. (2015) deployed an exercise intervention in patients following neoadjuvant chemoradiotherapy prior to surgery. The intervention group comprised 22 patients with 17 controls who followed a high intensity interval training (HIIT) protocol, three times per week for 6 weeks. Following neoadjuvant chemoradiotherapy, $\dot{V}_{O_2}$ at GET was significantly reduced by a mean of 1.9 ml kg^{-1} min^{-1}. Conversely, 6 weeks of subsequent HIIT sessions increased O_2 uptake at GET by 2.1 ml kg^{-1} min^{-1}, whereas it did not change in the controls. In a systematic review, Loughney et al. (2016) concluded that preoperative exercise interventions are safe and feasible, yet there are insufficient controlled trials to draw reliable conclusions about their efficacy and feasibility. Recently, clinical guidelines and recommendations for preoperative exercise training in patients awaiting major non-cardiac surgery have been published (Tew et al., 2018). However, it is again acknowledged that further research is needed to identify the optimal exercise prescription in different clinical scenarios, particularly in the short preoperative time frame encountered in urgent cancer surgery.

While interest lies in preoperative exercise training, clear translational evidence to improved postoperative outcomes is yet to be established, with studies by West et al. (2015) underpowered for this endpoint. The most current systematic review (of 22 studies) with meta-analysis claimed that whilst prehabilitation improved preoperative functional capacity (measured by 6-min walk distance, albeit unlike West et al. (2015) objective measures of CRF including $\dot{V}_{O_{2peak}}$ and GET were not improved) and substantially reduced hospital stay, it did not reduce postoperative complications, 30-day hospital readmissions or postoperative mortality (Waterland et al., 2021). These findings need to be considered cautiously given the small sample sizes, heterogeneity of exercise interventions, limited reporting of objective measures of CRF, and lack of consensus on standardised endpoints of included studies.

Clearly, there is a requirement for a higher quality of evidence from large, randomised control trials, and clinical trials are ongoing with results awaited. Examples include: Van Rooijen et al. (2019), an international multicentre multimodal prehabilitation intervention including exercise, nutrition and psychological coping strategies

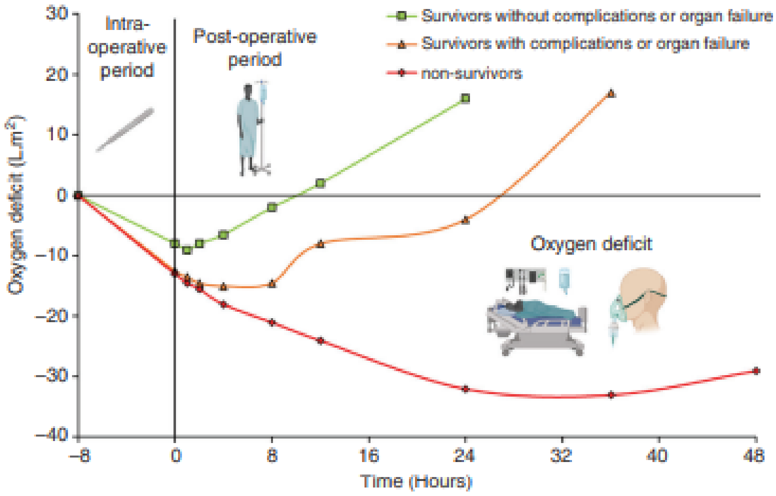

FIGURE 7 The cumulative O_2 deficit associated with survivors without complications or organ support, with complications or organ support, and non-survivors. Adapted from Shoemaker et al. (1992)

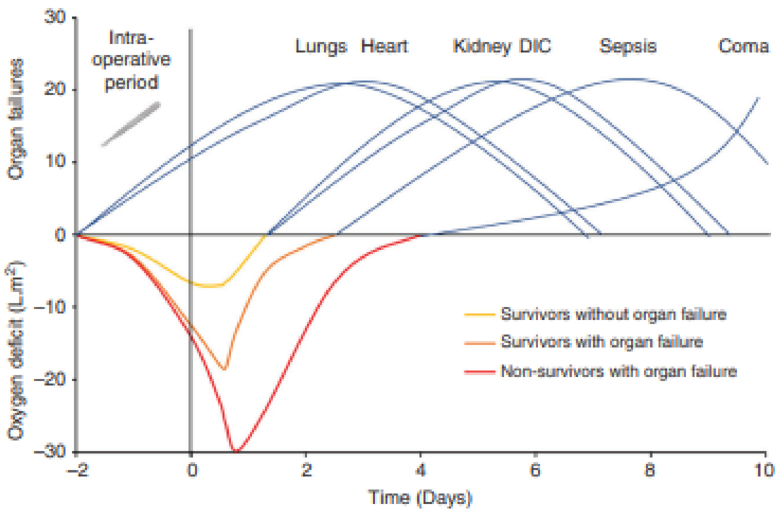

FIGURE 8 Time course of O_2 deficit in survivors with and without organ failure and non-survivors, and the relationship with the emergence and type of organ failures over time, adapted from Shoemaker et al. (1992). Cardiopulmonary complications typically emerge first after surgery, followed by kidney, disseminated intravascular coagulation (DIC), then sepsis and coma

within an enhanced recovery after surgery (ERAS) protocol (Trial ID NTR5947); a comparison of hospital-based supervised exercise, supported home-based exercise versus usual care to investigate patient recovery after bowel cancer surgery (PREPARE-ABC, 2020; Trial ID ISRCTN82233115); and Wessex Fit-4 Cancer Surgery (Southampton University, 2020) investigating the effectiveness of a community-based structured responsive exercise training programme with or without psychological support (Trial ID NCT03509428).

From a mechanistic perspective, similarities exist between the physiological insult of surgery and the acute response to an exercise stimulus. Primarily, an increased cellular demand for O_2, consequent to oxidative phosphorylation required to regenerate ATP, is required to enable continued physical activity. As a chronic adaptive response to exercise, an improved ability to increase $\dot{V}_{O_2}$ is associated with elevated mRNA of peroxisome proliferator-activated receptor γ coactivator 1-α (Gibala et al., 2009), a moderator of skeletal muscle mitochondrial biogenesis. An increase in citrate synthase (a marker of muscle oxidative capacity) has also been reported (Burgomaster et al., 2005), and an increase in oxidative stress (Bailey et al., 2010, 2018; Davies et al., 1982; Radák et al., 1999), which is attenuated following exercise training (Fatouros et al., 2004).

The mechanisms of this exercise-induced response have been linked to improvements in total antioxidant capacity (Fatouros et al., 2004; Radák et al., 1999), which is considered a marker of the body's defence system to neutralise excessive and deleterious free radical and associated ROS formation (Ghiselli et al., 2000). Total antioxidant capacity has been enhanced following exercise training in both animal (Liu et al., 2000) and human (Fatouros et al., 2004) models. However, whether the long-term exercise-induced increase in total antioxidant capacity, and thus reduction in oxidative stress, is a key factor in improving postoperative outcomes remains to be elucidated. Exercise training been associated not only with a reduction in oxidative stress, but also with improved vascular function and consequent O_2 transport (Wray et al., 2011). Systemic and cerebrovascular function has

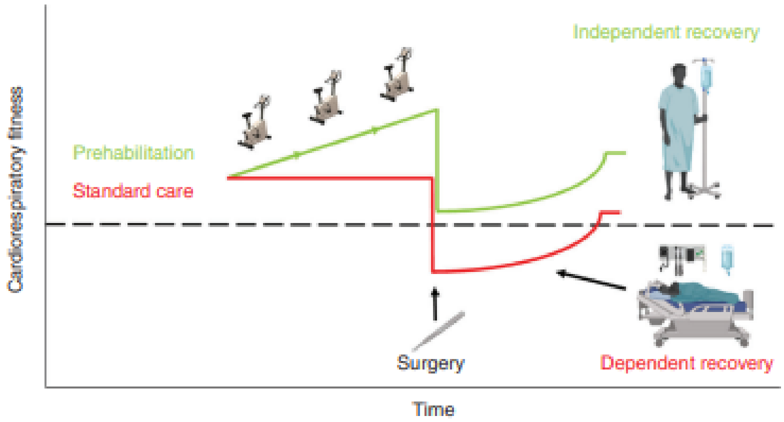

FIGURE 9 The fundamental principle underlying exercise prehabilitation whereby CRF is improved prior to surgery, thus reducing the risk of postoperative complications, and enhancing recovery as indicted by the green plot. Adapted from Clegg et al. (2013). The dashed line represents the cut-off between independent (ward-based care) and dependent (high dependency unit, intensive care unit) patient recovery

been shown to improve following HIIT (Calverley et al., 2020; Molmen-Hansen et al., 2012), the potential consequence of an 'optimised' blood flow-shear phenotype, triggering calcium influx into the hyper-polarised endothelial cells (Cooke et al., 1991) upregulating endothelial nitric oxide synthase (Bolduc et al., 2013).

8 | OPTIMISING RISK QUANTIFICATION AND PATIENT MANAGEMENT

The evidence reviewed suggests that impaired CRF is both an independent and a modifiable risk factor associated with postoperative outcome. Yet the strength of this relationship, used to predict post-operative outcome, is not effectively compared against traditional cardiovascular risk factors such as ischaemic heart disease, lung disease, or diabetes and obesity. This comparison has been addressed epidemiologically for all-cause deaths (outside of the surgical setting) within the Aerobics Centre Longitudinal Study, in which low CRF was found to be a greater risk factor than hypertension, smoking, high cholesterol, diabetes and obesity (Blair, 2009).

Attributable fractions describe the percentage of deaths that would not occur if a risk factor were removed from a population and account for both the risk of mortality associated with that condition and its prevalence in the population, as illustrated in Figure 10. This approach could be conducted in the surgical setting to help optimise risk quantification and further highlight the clinical importance of CRF relative to traditional risk factors.

Like all biomarkers, CRF is a dynamic metric subject to natural variation and thus needs to be interpreted with caution. Such variation encompasses both analytical and biological components which can be described using the concept of critical difference, indicative of the magnitude of variation around a true homeostatic point at any given time. Rose et al. (2018b) introduced the concept of critical difference to preoperative CPET and found differences of ± 19%, 13% and 10% for $\dot{V}_{O_2}$-GET, $\dot{V}_{O_2peak}$ and V_{eqCO_2}-GET. The translational impact upon patient fitness stratification in their study demonstrated that up to 60% of patients were of indeterminate fitness, where for example, they could not be sure that a patient had a 'true' GET < 11 ml O_2 kg^{-1}

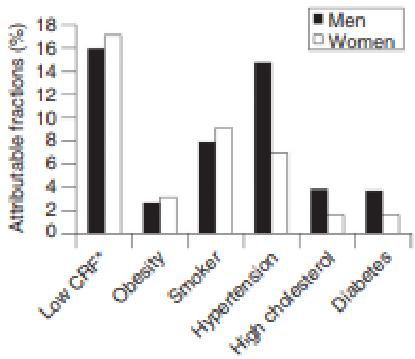

FIGURE 10 Attributable fractions (%) for all-cause deaths in the Aerobics Centre Longitudinal Study, taken from Blair (2009). *Cardiorespiratory fitness determined by a maximal exercise test on a treadmill

min^{-1} when variation was accounted for. A revised stratification model was formulated using zones along a spectrum of fitness; thus, clinicians are advised to look beyond a single cut-point and instead advocate a dynamic range of CPET values indicative of surgical risk (Wilson, 2018).

Furthermore, whilst inter-observer agreement, using intra-class correlation coefficient (ICC), for numerical values of GET (ICC 0.83 (0.75–0.90)) and $\dot{V}_{O_2peak}$ (ICC 0.88 (0.84–0.92)) indicating good to excellent relative reliability (Abbott et al., 2018), inter-observer agreement regarding whether or not a reportable value existed was less consistent. This suggests that guidance for identification of reportable values could be improved.

Patient stratification should be optimised using the most effective metrics of CRF, with accompanying threshold values, which are indicative of risk specific to patient populations and surgical procedures. Table 1 highlights that many studies, including the seminal work of Older et al. (1993), have simply adopted threshold values developed by other studies sometimes using different patient populations and surgical procedures. Furthermore, CRF is commonly described using $\dot{V}_{O_2peak}$, GET or V_{eqCO_2} as discussed; however, alternative metrics may provide superior prognostic utility in some settings. For example, if a patient is unable or unwilling to exercise to exhaustion, a submaximal measure of CRF relating O_2 consumption to workload achieved, such as the O_2 uptake efficiency slope (OUES; Hollenberg & Tager, 2000; Bongers et al., 2017), may be more effective.

Female inclusion rate in peer-reviewed publications of perioperative CPET is reported at only 31% and may have a bearing on the interpretation of data (Thomas et al., 2020). Surprisingly, despite evidence that CRF is lower in females across the lifespan, given smaller body size, skeletal muscle mass, peak cardiac output and Hb concentration (Jackson et al., 2009; Fleg et al., 2005), sex is not considered during surgical risk stratification. If a simple dose–response relationship exists between low CRF and postoperative survival, we would expect females to be at increased risk given these congenital constraints. Furthermore, other risk factors such as cardiovascular disease (CVD), which may vary between the sexes, require investigation to appraise a potential compensatory effect for CRF and consequent changes in its prognostic potential on postoperative outcome.

9 | CONCLUSION

The current review has explored the intimate relationship between O_2 transport and postoperative outcome, emphasising how preoperative CRF is an independent risk factor for postoperative mortality and morbidity, when patients undergo major intra-abdominal surgery. There is increased O_2 demand during the perioperative period and patients must meet this demand to avoid tissue hypoxia, the presence and magnitude of which dictates postoperative morbidity and mortality. This relationship can be used to assess patient risk, plan perioperative care and optimise patient management using exercise as a modifiable intervention. However, there is a clear need to improve the physiological detection and interpretation of CRF, better quantify risk to specific populations, sex and surgical procedure, and better understand the optimal management of patients including the mode of exercise intervention and its timing. Collectively, a better understanding of CRF used to determine fitness for surgery will enable clinicians and physiologists alike to direct patient care more effectively and ultimately improve survival.

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COMPETING INTERESTS

D.M.B. is Chair of the Life Sciences Working Group and member of the Human Spaceflight and Exploration Science Advisory Committee to the European Space Agency and member of the Space Exploration Advisory Committee to the UK Space Agency.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Clinical Practice

The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference

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Abstract

Background: Cardiorespiratory fitness can inform patient care, although to what extent natural variation in CRF influences clinical practice remains to be established. We calculated natural variation for cardiopulmonary exercise test (CPET) metrics, which may have implications for fitness stratification.

Methods: In a two-armed experiment, critical difference comprising analytical imprecision and biological variation was calculated for cardiorespiratory fitness and thus defined the magnitude of change required to claim a clinically meaningful change. This metric was retrospectively applied to 213 patients scheduled for colorectal surgery. These patients underwent CPET and the potential for misclassification of fitness was calculated. We created a model with boundaries inclusive of natural variation [critical difference applied to oxygen uptake at anaerobic threshold ($\dot{V}O_2$-AT): 11 ml O_2 kg^{-1} min^{-1}, peak oxygen uptake ($\dot{V}O_2$ peak): 16 ml O_2 kg^{-1} min^{-1}, and ventilatory equivalent for carbon dioxide at AT (V_E/VCO_2-AT): 36].

Results: The critical difference for $\dot{V}O_2$-AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT was 19%, 13%, and 10%, respectively, resulting in false negative and false positive rates of up to 28% and 32% for unfit patients. Our model identified boundaries for unfit and fit patients: AT <9.2 and ≥13.6 ml O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak <14.2 and ≥18.3 ml kg^{-1} min^{-1}, $\dot{V}_E/\dot{V}CO_2$-AT ≥40.1 and <32.7, between which an area of indeterminate-fitness was established. With natural variation considered, up to 60% of patients presented with indeterminate-fitness.

Conclusions: These findings support a reappraisal of current clinical interpretation of cardiorespiratory fitness highlighting the potential for incorrect fitness stratification when natural variation is not accounted for.

Keywords: anaerobic threshold; cardiopulmonary exercise test; risk assessment

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Editor's key points

- Cardiorespiratory fitness affects outcome from major surgery and may be assessed using cardiopulmonary exercise testing (CPET) but there are few data on the natural variation in CPET measures.
- The critical difference accounts for both imprecision in measurements and biological variation and indicates clinically important changes in a variable.
- This study found significant variability in the critical differences in CPET values in healthy adults and when applied retrospectively to a patient cohort.
- Using the boundaries of critical difference, a large proportion of patients were classified as being of indeterminate fitness for surgery.
- If confirmed, this suggests that fitness stratification should be based on a range of values for a CPET variable rather than a single value.

Cardiopulmonary exercise testing (CPET) is a non-invasive procedure to determine the level of cardiorespiratory fitness (CRF) of patients during a progressive exercise challenge to symptom limited maximum. CPET is used as a tool for preoperative assessment of physical fitness for intra-abdominal surgery to aid clinical decision-making given its increasingly proved association with postoperative outcome.[1–7] Furthermore, The American Heart Association recently published a scientific statement promoting CRF as a clinical vital sign.[8] Despite increasing support for CPET, the mechanisms underpinning CRF that provide protection require further investigation.

The seminal work of Older and colleagues[9] documented an 18% mortality rate in elderly surgical patients with a pulmonary oxygen uptake at the anaerobic threshold ($\dot{V}O_2$-AT) of <11 ml oxygen (O_2) kg^{-1} (total body mass) min^{-1} compared with 0.8% recorded in patients with a $\dot{V}O_2$-AT$\geq$11 ml O_2 kg^{-1} min^{-1}. Other biomarkers including peak oxygen uptake ($\dot{V}O_2$ peak) <15 ml O_2 kg^{-1} min^{-1} and ventilatory equivalent for carbon dioxide at AT ($\dot{V}_E/\dot{V}CO_2$-AT) >42 have predicted postoperative survival after abdominal aortic aneurysm surgery.[2] Studies have further attempted to define threshold values in an effort to optimise risk prediction; for example a range of AT values from 9.0 to 11 ml O_2 kg^{-1} min^{-1} have been reported,[4,5,9–12] thus demonstrating that variation is present and that a single cut-point cannot be recommended.

Like most biomarkers, CRF is a dynamic metric subject to natural variation and thus needs to be interpreted with caution. Such variation encompasses both analytical and biological components that collectively contribute to the critical difference (CD) as originally described by Fraser and Fogarty.[13] The CD represents random variation around a homeostatic point indicative of the change that must occur before a true difference of clinical significance can be claimed. The concept of CD, yet to be applied to clinical CPET variables, emanates from the field of clinical biochemistry and has been applied to metabolic biomarkers of exercise stress and clinical patients.[14,15]

The current study reflects the first attempt within the clinical setting to quantify the CD of established CPET markers of CRF with corresponding implications for patient management. We hypothesise that natural variation is present in markers of CRF and will thus impact upon patient fitness stratification.

Methods

Ethical approval

The University of South Wales Ethics Committee (LSE1636-GREO), and Cardiff and Vale University Health Board (15/AIC/6352) approved the study. All procedures were carried out in accordance with the Declaration of Helsinki of the World Medical Association.[16] Written informed consent was obtained from participants in study arm 1. Study arm 2 constituted a retrospective analysis of an anonymised database and thus patient consent was waived.

Design

We conducted a two-armed study. First, to determine the CDs of selected CPET variables (reported as independent predictors of postoperative outcome), analytical variation was calculated, and biological variation derived using repeated CPET results from a young apparently healthy population (arm 1). Subsequently, these CD values were retrospectively applied to an anonymised database of patients who had CPET before colorectal surgery, to re-appraise fitness stratification (arm 2).

Study arm 1: Critical difference determination

Analytical variation (CV_A); the first component of CD, was determined by repeatedly passing inspired and expired gases through a MedGraphics Ultima metabolic cart (MedGraphics™, Gloucester, UK) in a manner that replicated typical ventilatory responses during the latter stages of a patient CPET (i.e. pulmonary minute ventilation of 25 litres min^{-1}). In a series of eight repeated trials, each lasting 10 respiratory cycles, a 250 litre Douglas bag containing saturated expired gas (17% O_2, 5% CO_2) and an equivalent volume of ambient gas was passed through a pneumotach and gas analyser. Inspiration and expiration were simulated using two-way non-rebreathing valves (2700 Series) connected to two factory-calibrated 3 litre syringes (Hans Rudolph, Kansas City, KS, USA) operated simultaneously (Fig 1). Before sampling, calibration was undertaken in accordance with manufacturer's guidelines using a 3 litre syringe and a known precision gas. During data collection the middle five of seven breaths were averaged.

The within participant coefficient of variation (CV_W) from which biological variation could be calculated, was determined by completion of three repeat CPETs separated by a minimum of 24 h, for 12 healthy participants (Table 1). Tests were conducted in a randomised order at three time points across operating hours for patient CPET clinics (09:00–10:30, 12:00–13:30, and 15:00–17:00). All CPETs were conducted to volitional fatigue using the Wasserman protocol,[17] the same metabolic cart and investigator, and calibration undertaken as previously described. Following 3 min of resting data collection, participants cycled at 60 rpm on an electromagnetically braked cycle ergometer (Lode, Groningen, The Netherlands) for 3 min in an unloaded 'freewheeling' state. A progressively ramped period of exercise (10–30 W min^{-1} based on stature, age, and predicted $\dot{V}O_2$)[17] was then undertaken to volitional termination and followed by 3 min recovery. Heart rate (Polar Electro, Oy, Finland) was recorded throughout.

MedGraphics Breeze™ software automatically determined $\dot{V}O_2$ peak (defined as the highest $\dot{V}O_2$ during the final 30 s of exercise reported), oxygen uptake efficiency slope, and peak oxygen pulse (O_2 pulse). The AT was manually interpreted by a

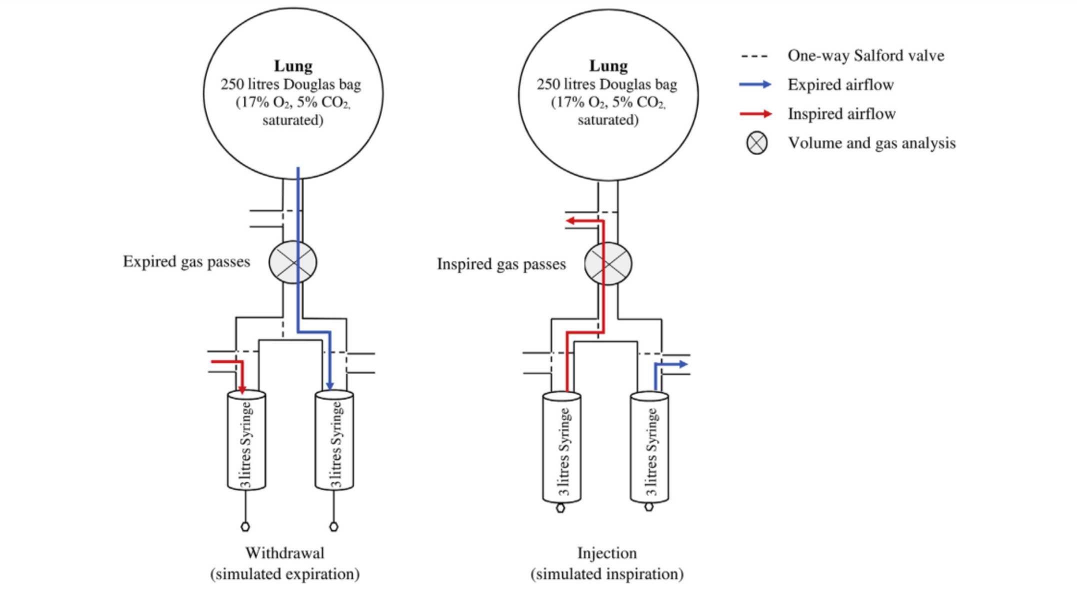

Fig. 1. The determination of CV_A for CPET metrics using simulated expiration and inspiration. CPET, cardiopulmonary exercise test; CV_A, coefficient of analytical variation. Simulated oxygen uptake for trials ~ 13ml kg^{-1} min^{-1}.

clinician using the V-slope method,[18] supported by $\dot{V}_E/\dot{V}CO_2$-AT, and $\dot{V}_E/\dot{V}O_2$-AT.

Critical difference

Natural variation is described by the magnitude of CD and determines the difference in CRF required to demonstrate change not simply because of the 'noise' associated with analytical imprecision (represented by CV_A) and biological variation (represented by CV_B), in order for it to be considered clinically meaningful.[13,14] Critical difference uses ANOVA to determine the magnitude of random fluctuation around a homeostatic set point within which there is 95% probability that repeated measures will occur. The 95% probability is represented by a constant k (2.77) in equation (1) [calculated from $\sqrt{2} \times 1.96$ (two standard deviations)]. Coefficients of variation were calculated dividing the standard deviation by the mean score and converted into a percentage as shown in the example of CV_A [equation (2)]. The coefficient of analytical variation was subtracted from the CV_W determined from the repeated trials to calculate CV_B [equation (3)].[13]

$$CD = k\sqrt{CV_A^2 + CV_B^2} \quad (1)$$

where k = constant equal to 2.77 at $P < 0.05$, CV_A = coefficient of analytical variation, and CV_B = coefficient of biological variation.

CV_A was calculated using the following equation:

$$CV_A = \frac{SD}{\overline{X}} \times 100\ (\%) \quad (2)$$

where SD = standard deviation and $\overline{x}$ = mean.

CV_B was calculated from $\dot{V}O_2$ data from each participant, collected at periodic times as described, using the following equation:

$$CV_B = CV_W(\%) - CA_A(\%) \quad (3)$$

where CV_W = coefficient of within participant variation.

Consequently, when interpreting CPET results, and to address the presence of natural variation, the CD (applied above and below an observed score) must be considered to determine the range in which a patient can present without any change in CRF (i.e. before clinical significance can be claimed).

Study arm 2: application of critical difference metrics to patients

A consecutive sample of 213 patients (Table 1) scheduled for elective colorectal surgery who had undergone CPET testing was examined retrospectively. CPETs were conducted in accordance with the American Thoracic Society/American College of Chest Physician Statement on Cardiopulmonary Exercise Testing,[19] using identical equipment, investigators, and protocols as outlined in study arm 1.

Calculated CD metrics were subsequently applied to CPET metrics with established evidence to independently identify unfit patients during pre-surgical assessment.[1–4,6,11,20,21] Reference CRF threshold values were established from the European Association for Cardiovascular Prevention and Rehabilitation (EACPR)/American Heart Association (AHA) Scientific Statement: $\dot{V}O_2$-AT < 11 ml O_2 kg^{-1} min^{-1}, $\dot{V}O_2$

Table 1 Participant and patient characteristics. Data are shown as mean (SD) or (range), and *n* (%). AT, estimated anaerobic threshold; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; O_2 pulse, oxygen pulse at peak exercise; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}O_2$ peak, peak oxygen consumption; Workload at peak, workload at peak exercise; Workload at AT, workload at estimated anaerobic threshold

	Study arm 1 Apparently healthy participants (*n*=12)	Study arm 2 Colorectal patients (*n*=213)
Demographics		
Age (yr)	22 (20–26)	69 (32–90)
BMI	26 (3.1)	28.3 (5.8)
Gender		
Male	12 (100)	126 (59)
Female	0 (0)	87 (41)
Risk factors		
Smoking		
No	12 (100)	71 (33)
Yes (active/former)	0 (0)	142 (67)
Hypertension	0 (0)	79 (37)
Diabetes	0 (0)	34 (16)
IHD	0 (0)	37 (17)
COPD	0 (0)	21 (10)
Haemoglobin (g litre^{-1})	–	12.7 (1.9)
Creatinine (μmol litre^{-1})	–	79.2 (19.7)
Cardiopulmonary function		
Baseline heart rate (beats min^{-1})	65 (5)	83 (19)
Peak heart rate (beats min^{-1})	178 (5)	124 (28)
$\dot{V}O_2$ peak (ml kg^{-1} min^{-1})	43.8 (6.0)	16.3 (4.9)
RER at $\dot{V}O_2$ peak	1.3 (0.1)	1.1 (0.1)
AT (ml O_2 kg^{-1} min^{-1})	23.8 (3.6)	11.0 (3.0)
$\dot{V}_E/\dot{V}CO_2$-AT	23.5 (1.4)	33.6 (5.3)
$\dot{V}_E/\dot{V}O_2$-AT	23.5 (4.7)	30.6 (5.9)
O_2 pulse (ml beat^{-1})	20.7 (0.9)	10.5 (3.8)
Workload at AT (W)	160 (28)	52 (28)
Workload at peak (W)	300 (45)	91 (47)

peak < 16 ml O_2 kg^{-1} min^{-1}, and $\dot{V}_E/\dot{V}CO_2$-AT ≥ 36.[22] The CD for additional CPET metrics was calculated for $\dot{V}_E/\dot{V}O_2$-AT,[3,20,23] and peak O_2 pulse.[5,7,10,24]

To determine the impact of natural variation on fitness stratification, patient counts were calculated for uncorrected (observed) fit and unfit categories according to EACPR/AHA threshold values, positively corrected (+CD), and negatively corrected (−CD) values. A revised fitness stratification model for each CPET metric was created by applying ±CD to threshold values, thus creating upper and lower boundaries associated with natural variation, and the area in-between the newly defined boundaries classified as indeterminate-fitness. Finally, patient counts were compared for current *vs* newly revised models.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 23.0; Armonk, NY, USA). Distribution normality was confirmed using Shapiro–Wilk W tests. Within-subject time of day difference in CPET performance was assessed using Bonferroni corrected repeated measures analysis of variance. Patient counts were analysed using Chi-Square tests. Continuous data are presented as mean (SD) or median (range), and categorical data as absolute values (%). Significance for all two-tailed tests was established at $P<0.05$. Retrospective sample size calculations were conducted attaining 80% power at the $P<0.05$ level with the minimum effect of clinical importance represented by the calculated CD (from study arm 1, Table 2) and between-patient standard deviations (from study arm 2, Table 1).[25]

Results

Natural variation

Study arm 1 identified a CD of 19% for $\dot{V}O_2$-AT (CV_A 2.2%, CV_B 6.5%), 13% for $\dot{V}O_2$ peak (CV_A 2.2%, CV_B 3.9%), and 10% for $\dot{V}_E/\dot{V}CO_2$-AT (CV_A 0.6%, CV_B 3.6%; Table 2). The time of day that CPET was conducted had no effect in measured metrics ($\dot{V}O_2$-AT: $P = 0.40$, $\dot{V}O_2$ peak: $P = 0.81$, and $\dot{V}_E/\dot{V}CO_2$-AT: $P = 0.75$). When CD was applied to current CPET fitness threshold values of $\dot{V}O_2$-AT: 11 ml O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak: 16 ml kg^{-1} min^{-1}, and $\dot{V}_E/\dot{V}CO_2$-AT: 36, a variation of ±2.1 ml O_2 kg^{-1} min^{-1}, ±2.0 ml kg^{-1} min^{-1}, and ±3.7 respectively was observed.

Potential for incorrect fitness stratification

We applied CD to positively and negatively correct (the range of) patient CPET scores around their observed (single-point estimate) scores, and subsequently calculated the number of 'false positive' and 'false negative' results. While these terms are not technically correct given the unavoidable uncertainty associated with biological variation and corresponding inability to determine an individual's 'true' level of CRF at any given time, it nonetheless provides a conceptual framework to illustrate how blunt application of current thresholds has the potential to affect perioperative planning for a large proportion of patients undergoing major elective surgery.

The application of natural variation (±CD) presented a mathematical possibility for patient results to transcend current fitness stratification boundaries thus demonstrating potential for misclassification (Fig 2) using $\dot{V}O_2$-AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT ($P < 0.001$ in all cases). Differences in patient counts assigned to a given fitness category resulted in false negatives (whereby patients were stratified as fit with variation positively corrected when they were originally unfit), and

Table 2 Biological variation and critical difference for cardiopulmonary exercise test variables (Study arm 1, *n*=12). AT, anaerobic threshold; CV_A, coefficient of analytical variation; CV_B, coefficient of biological variation; O_2 pulse, oxygen pulse at peak exercise; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}O_2$ peak, peak oxygen consumption

Parameter	CV_A (%)	CV_B (%)	Critical difference (%)
AT (ml O_2 kg^{-1} min^{-1})	2.2	6.5	19.1
$\dot{V}O_2$ peak (ml kg^{-1} min^{-1})	2.2	3.9	12.5
$\dot{V}_E/\dot{V}CO_2$-AT	0.6	3.6	10.2
$\dot{V}_E/\dot{V}O_2$-AT	1.7	3.0	9.6
O_2 pulse (ml beat^{-1})	2.2	2.3	8.9
OUES	2.2	3.8	12.1
RER at peak exercise	1.4	5.3	15.2

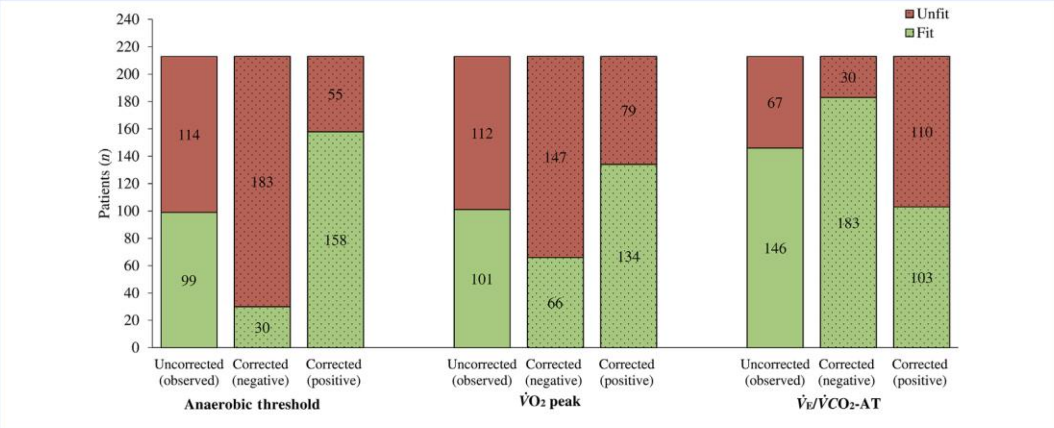

Fig. 2. Potential for incorrect patient fitness stratification if natural variation is not taken into account. Patient counts are presented for unfit (AT < 11ml O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak < 16ml kg^{-1} min^{-1}, $\dot{V}_E/\dot{V}CO_2 \geq 36$) and fit (AT ≥ 11ml O_2 kg^{-1} min^{-1}, $\dot{V}O_2$ peak ≥ 16ml kg^{-1} min^{-1}, $\dot{V}_E/\dot{V}CO_2 < 36$) categories. AT, anaerobic threshold; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$ peak, peak oxygen consumption; Observed, uncorrected scores indicative of current risk stratification; Positive, corrected scores by addition of CD; Negative, corrected scores by subtraction of CD. P<0.001 across all pairwise comparisons for corrected scores. Natural variation caused 59 (28%) false negatives and 69 (32%) false positives at the AT, 33 (15%) false negatives and 35 (16%) false positives at $\dot{V}O_2$ peak, and 37 (17%) false negatives and 43 (20%) false positives at $\dot{V}_E/\dot{V}CO_2$-AT.

false positives (whereby patients were stratified as unfit with variation negatively corrected when they were originally fit). Thus, natural variation may have caused up to 59 (28%) false negatives and 69 (32%) false positives at the AT, 33 (15%) false negatives and 35 (16%) false positives at $\dot{V}O_2$ peak, and 37 (17%) false negatives and 43 (20%) false positives at the $\dot{V}_E/\dot{V}CO_2$-AT.

Revised model

A revised fitness stratification model (Fig 3) was created with CD defining asymmetrical upper and lower boundaries for absolute values (13.6 and 9.2 ml O_2 kg^{-1} min^{-1} for AT, 18.3 and 14.2 ml kg^{-1} min^{-1} for $\dot{V}O_2$ peak, 40.1 and 32.7 for $\dot{V}_E/\dot{V}CO_2$-AT) that were independent of fitness misclassification based on

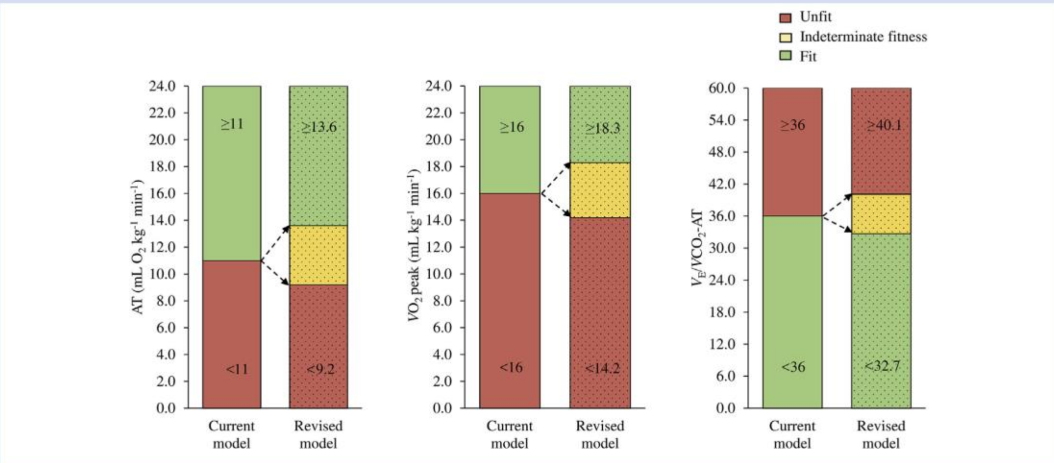

Fig. 3. Revised fitness stratification model following incorporation of the critical difference for the anaerobic threshold, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT. AT, anaerobic threshold; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$ peak, peak oxygen consumption. Natural variation demonstrates the magnitude of variation present. The lower and upper boundaries define clinically meaningful boundaries not affected by natural variation whilst the area in-between is classified as indeterminate-fitness.

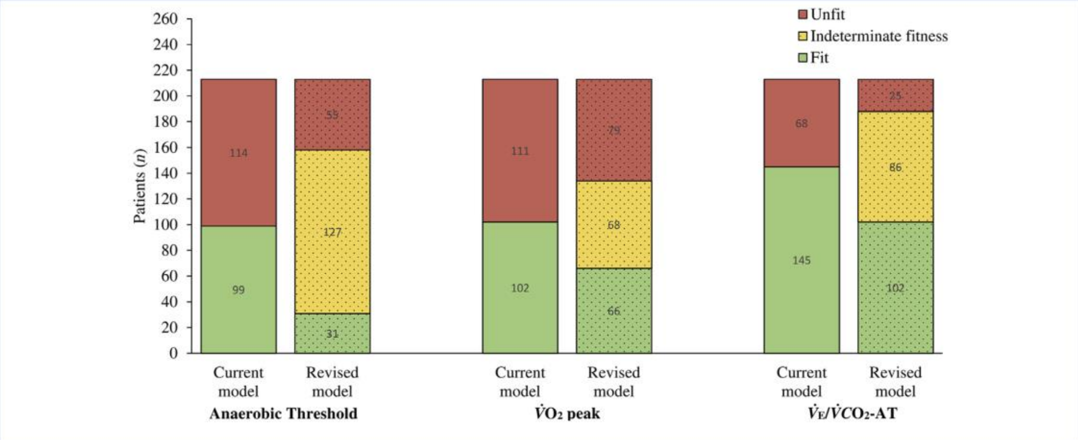

Fig. 4. Current versus revised model identification of patient counts by fitness category. AT, anaerobic threshold; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$ peak, peak oxygen consumption. The revised model demonstrates large numbers of patients that are classified with indeterminate-fitness.

natural variation. The resultant area between the upper and lower boundaries represented a newly defined and additional category labelled 'indeterminate-fitness'. The indeterminate-fitness category accounted for 60, 32, and 40% of patients for the AT, $\dot{V}O_2$ peak, and $\dot{V}_E/\dot{V}CO_2$-AT metrics, respectively (Fig 4), and thus fewer patients were stratified as unfit or fit.

Discussion

The present findings highlight the potential for incorrect patient fitness stratification when natural variation is not considered. We formulated a revised model (accounting for natural variation), which established that many patients were stratified with indeterminate-fitness. We therefore encourage clinicians to be aware of natural variation and its implications for fitness stratification and suggest this concept be applied to markers of CRF to further optimise patient management. Whilst this investigation aims to improve the prognostic interpretation of CPET results, we acknowledge and advocate that clinical decision making does not rely on the application of threshold values alone. There are clear dangers of just using a single point estimate, even if it may be a better number when natural variation is considered. A multitude of additional variables such as work rate, heart rate, duration of exercise, and reason for stopping the exercise all go into a composite estimate of functional capacity to be considered alongside other clinical measures when planning perioperative care.

Potential for incorrect patient fitness stratification

The mean CPET score for patients undergoing colorectal surgery was identical to the threshold marker value for AT, within 0.3 ml O_2 kg^{-1} min^{-1} for $\dot{V}O_2$ peak, and 2.4 lower for $\dot{V}_E/\dot{V}CO_2$-AT. Thus, when patient scores were positively or negatively corrected with CD, large numbers of patients transcended the EACPR/AHA threshold CRF boundaries demonstrating that natural variation may cause significant rates of incorrect fitness stratification. Of the three primary CPET metrics reported, the AT demonstrated the most incorrectly stratified patients, closely followed by $\dot{V}O_2$ peak, and to a lesser, albeit significant, extent $\dot{V}_E/\dot{V}CO_2$-AT in line with magnitudes of reported CD values and close proximity of patient scores to threshold boundaries. Furthermore, a valid and reliable identification of $\dot{V}O_2$-AT is not always possible and has been well documented in patients with heart failure,[26] and thus may contribute to greater variance in AT.

Revised fitness stratification

Our revised model (with its wider boundaries accounting for natural variation) excluded many patients from both unfit and fit categories, and thus large numbers were stratified in the indeterminate-fitness category (Fig 4). Not only does this occurrence confirm the impact of natural variation, but consequently presents the challenge of planning perioperative care for patients within this additional fitness category. Concerns may be associated with the introduction of an additional fitness category. For example, patients undergoing colorectal surgery who fell into an intermediate-risk group (albeit not comparable with our indeterminate-fitness category) have reported a higher rate of serious complications if admitted to the ward rather than HDU.[27]

The most effective way to assess patient risk is likely to be a combined approach using clinical variables, biomarkers of susceptibility to disease, and physiological testing (CPET).[28] We suggest further development of our model by inclusion of known risk factors independent of CRF to optimise perioperative care.

Limitations

We recognise that this study has limitations and simply reflects a 'proof of principle' concept. Measures of CD were derived from young healthy participants and applied to a cohort of older patients. Comparative values for older controls were not available and would present considerable ethical challenges to determine given that repeat CPET to volitional exhaustion would be required. Our CV_W (given by $CV_A + CV_B$ from Table 2) of 6.1% for $\dot{V}O_2$ peak is comparable with chronic obstructive pulmonary disease (6.6%) and congestive heart failure patients (5.7% and 6.0%).[29–31] Furthermore, our CV_W for AT (8.7%) is consistent with patient data (6.8%, 9.2%, and 10%),[30,32,33] and in excess of CV_W values for $\dot{V}O_2$ peak, the probable consequence of observer error when determining AT via the V-slope method.[18] Thus, our method has potential application to clinical populations. However, reported metrics for CD may reflect a best-case scenario (i.e. lowest CD) if natural variation increases with age, pathology, or both.

Study arm 1 included men only, whilst the calculated CD was subsequently applied to a population of whom 41% were women. For the $\dot{V}O_2$ peak and $\dot{V}O_2$-AT metrics, our coefficients of variation were comparable with the studies previously stated, which also included female data. Metrics represented by ventilatory equivalents however must be treated with caution (for female comparison) as any disparity between the sexes is not accounted for.

Many CPET metrics are scaled to body mass. Further investigation is required to determine if there are any effects on the magnitude of asymmetry for absolute values reported around our zones of indeterminate-fitness resulting from scaling to body mass.

Data were collected on a single system in both arms of this study. We are aware that analytical precision is likely to vary widely between different manufacturers, thus affecting CV_A and consequently CD. Therefore, our results can only be applied with certainty to clinical tests using MedGraphics equipment. At the time of conducting the study, the authors did not have access to a metabolic calibrator used to calculate CV_A; however, we are confident that our findings (up to 2.2%) are comparable with data produced from such devices, which typically report with accuracy of ±2%.[34]

Prospective sample size calculations

From an experimental design perspective, our observations have implications when prospectively determining sample sizes for future randomised controlled exercise trials. We suggest that CD be used to determine the minimal clinically important difference (MCID) for any given metric of CRF. Until now, studies investigating whether particular interventions improve CRF often rely on MCID values that appear to lack a well-established scientific basis, such as a $\dot{V}O_2$-AT of 2 ml kg^{-1} min^{-1}, for example.[35] This (arbitrarily) defined MCID of 2 ml O_2 kg^{-1} min^{-1} is in fact incorrect because it falls within our calculated CD of 2.1 ml O_2 kg^{-1} min^{-1} (i.e. this is part of normal variation). In a worked example using the arbitrary metric of 2 ml O_2 kg^{-1} min^{-1}, a prospective power calculation indicates that a two-armed exercise intervention study would require a minimum of 36 patients per group (excluding potential dropout) to detect a treatment effect with 80% power at the $P<0.05$ level. However, considering natural variation (using our calculated CD of 2.1 ml O_2 kg^{-1} min^{-1} in place of 2 ml O_2 kg^{-1} min^{-1}) would further inflate the sample size (to 39 patients per group), highlighting the potential for a type II error.

We recognise that the sample size calculation is based upon a CD determined from a sample of 12 subjects and is limited to a single (MedGraphics) system. Further research (with larger sample sizes, additional metabolic carts, and calculations across the spectrum of age, health, and CRF) is encouraged to better support our prospective calculation of sample sizes.

Conclusions

These findings demonstrate the extent of natural variation in CPET data. Natural variation also has potential to influence patient fitness stratification. Therefore, clinicians should not consider fitness as a single point estimate, but instead as a dynamic range of values defined by natural variation and calculated using critical difference. We suggest the use of cardiorespiratory fitness threshold values inclusive of natural variation to optimise risk prediction models, and encourage clinicians to be aware of natural variation and its implications when determining the appropriate level of postoperative care after major surgery.

Author's contributions

Conception and design: all authors.

CPET tests and data collation: R.G.D, I.R.A, G.A.R.

Analysis: G.A.R. with input from: D.M.B, M.H.L, R.G.D, I.R.A.

Manuscript draft: G.A.R., D.M.B.

Revisions and approval of final version for submission: all authors.

Declaration of interest

The authors declare no conflict of interest.

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RESEARCH PAPER

WILEY EP Experimental Physiology

Cardiorespiratory fitness is impaired and predicts mid-term postoperative survival in patients with abdominal aortic aneurysm disease

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Abstract

Preoperative cardiopulmonary exercise testing is a standard assessment of cardiorespiratory fitness (CRF) and risk stratification. However, to what extent CRF is impaired in patients undergoing surgical repair of abdominal aortic aneurysm (AAA) disease and the corresponding implications for postoperative outcome requires further investigation. We measured CRF during an incremental exercise test to exhaustion using online respiratory gas analysis in patients with AAA disease (n = 124, aged 72 ± 7 years) and healthy sedentary control subjects (n = 104, aged 70 ± 7 years). Postoperative survival was examined for association with CRF, and threshold values were calculated for independent predictors of mortality. Patients who underwent preoperative cardiopulmonary exercise testing before surgical repair had lower CRF [age-adjusted mean difference of 12.5 ml O_2 kg^{-1} min^{-1} for peak oxygen uptake ($\dot{V}_{O_2peak}$), $P < 0.001$ *versus* control subjects]. After multivariable analysis, both $\dot{V}_{O_2peak}$ and the ventilatory equivalent for carbon dioxide at anaerobic threshold ($\dot{V}_E/\dot{V}_{CO_2}$–AT) were independent predictors of mid-term postoperative survival (2 years). Hazard ratios of 5.27 (95% confidence interval 1.62–17.14, $P = 0.006$) and 3.26 (95% confidence interval 1.00–10.59, $P = 0.049$) were observed for $\dot{V}_{O_2peak} < 13.1$ ml O_2 kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}_{CO_2}$–AT ≥ 34, respectively. Thus, CRF is lower in patients with AAA, and those with a $\dot{V}_{O_2peak} < 13.1$ ml O_2 kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}_{CO_2}$–AT ≥ 34 are associated with a markedly increased risk of postoperative mortality. Collectively, our findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients, which may help to direct care provision.

KEYWORDS
abdominal aortic aneurysm, cardiopulmonary exercise test, risk assessment

1 | INTRODUCTION

Abdominal aortic aneurysm (AAA) is a permanent focal dilatation of the infradiaphragmatic aorta by 1.5 times the expected normal diameter or >3 cm (Golledge, Muller, Daugherty, & Norman, 2006). It can be classified anatomically as suprarenal, juxtarenal or infrarenal in relationship to the renal arteries, with infrarenal AAA being the most common. Rupture of an AAA is associated with a mortality rate of between 65 and 85%, resulting in up to 8000 deaths annually in the UK, with approximately half of the deaths attributed to rupture occurring before the patient reaches hospital (Ashton et al., 2002; Basnyat, Biffin, Moseley, Hedges, & Lewis, 1999).

Elective AAA surgery is thus indicated for healthy males with aneurysms of ≥5.5 cm. The corresponding values for UK in-hospital postoperative mortality for elective open and endovascular AAA repair are considerably lower, at 2.9 and 0.4%, respectively (VSQI, 2017). However, the physiological insult of major surgery presents an increased oxygen demand during the perioperative period, and patients need to achieve a sufficient oxygen (O_2) delivery in order to fulfil cellular demand and attain a successful recovery. Shoemaker, Appel, & Kram (1992) demonstrated a strong relationship between the magnitude and duration of O_2 deficit in the intraoperative and early postoperative period and the risk of organ failure and ultimately death. Robust preoperative risk assessment is therefore necessary to identify high-risk patients and optimize care during the perioperative period.

Preoperative cardiopulmonary exercise testing (PCPET) is a non-invasive procedure used to determine the level of cardiorespiratory fitness (CRF) of patients during a progressive exercise challenge to symptom-limited maximum. In 2016, 47% of patients in the UK had their fitness measured by cardiopulmonary exercise testing (CPET) as part of a preoperative risk assessment before AAA surgery (VSQI, 2017). A cross-sectional association has been demonstrated between CRF and improved postoperative survival and reduced morbidity, including length of hospital stay (Carlisle & Swart, 2007; Goodyear et al., 2013; Grant et al., 2015; Hartley et al., 2012; Prentis et al., 2012), with values such as an anaerobic threshold (AT) < 10.2 ml O_2 kg^{-1} min^{-1}, peak oxygen uptake ($\dot{V}_{O_2peak}$) < 15 ml O_2 kg^{-1} min^{-1} and a ventilatory equivalent for carbon dioxide at the anaerobic threshold ($\dot{V}_E/\dot{V}_{CO_2}$–AT) > 42 used as cut-off scores. However, as with many other preoperative tests, the use of CPET needs to be optimized (Hollingsworth, Danjoux, & Howell, 2015). Thus, the primary aims of the present study were twofold: (i) to confirm the extent to which cardiorespiratory fitness is impaired in AAA patients; and (ii) to define threshold PCPET variable scores that hold prognostic significance for postoperative survival.

New Findings

- **What is the central question of this study?**
  To what extent cardiorespiratory fitness is impaired in patients with abdominal aortic aneurysmal (AAA) disease and corresponding implications for postoperative survival requires further investigation.
- **What is the main finding and its importance?**
  Cardiorespiratory fitness is impaired in patients with AAA disease. Patients with peak oxygen uptake of <13.1 ml O_2 kg^{-1} min^{-1} and ventilatory equivalent for carbon dioxide at anaerobic threshold ≥34 are associated with increased risk of postoperative mortality at 2 years. These findings demonstrate that cardiorespiratory fitness can predict mid-term postoperative survival in AAA patients, which may help to direct care provision.

2 | METHODS

2.1 | Ethical approval

The Cardiff and Vale University Health Board (15/AIC/6352) approved the retrospective analysis of an anonymized database, and thus patient consent was waived. For the healthy control participants, ethical approval was granted by American Medical International (TX, USA) and the (former) University of Glamorgan (South Wales, Pontypridd, UK). All procedures were carried out in accordance with the *Declaration of Helsinki* of the World Medical Association (Williams, 2008). The study was not registered in a database.

2.2 | Experimental design

We conducted a retrospective cross-sectional analysis of AAA patients (anonymized longitudinal hospital-based database) with a matched apparently healthy cohort.

2.3 | Participant/patient groups

2.3.1 | Healthy participants

For the purposes of comparing baseline CRF, we used 108 consecutive historical control subjects with a mean age of 72 years, who had previously engaged in a health-screening programme (Table 1).

2.3.2 | Abdominal aortic aneurysm patients

One hundred and twenty-four consecutive patients of similar age underwent PCPET to assess the risk for aneurysm repair between 2008 and 2016 (Table 1). Patient data were gathered from medical notes and recorded by the clinician conducting PCPET and consisted of body mass index (BMI), smoking history, presence of ischaemic heart disease, chronic obstructive pulmonary disease, hypertension, renal disease and anaemia. Postoperative mortality was determined by review of Office for National Statistics (ONS) records and included cause of death. Mid-term survival was calculated by comparison of surgery date and 2 year follow-up status.

TABLE 1 Patient and healthy participant demographics

	Healthy participants (n = 108)	AAA patients (n = 124)
Demographics		
Age (years)	70 ± 7	72 ± 7[a]
Male/female (n)	80/28	102/22
BMI (kg m^{-2})	27.1 ± 3.6	27.5 ± 4.7
Risk factors		
Smoker	33 (31)	113 (91)[a]
Hypertension	4 (4)	62 (50)[a]
Diabetes	7 (6)	7 (6)
IHD	0 (0)	23 (19)[a]
COPD	0 (0)	20 (16)[a]
Surgical approach		
Open	n.a.	88 (71)
EVAR	n.a.	13 (10)
Conservative treatment	n.a.	23 (19)

Values are the mean ± SD or number (%). Abbreviations: AAA, abdominal aortic aneurysm; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EVAR, endovascular aneurysm repair; and IHD, ischaemic heart disease.
[a]Different *versus* healthy participants ($P < 0.05$).

2.4 | Measurements

2.4.1 | Cardiopulmonary exercise testing of healthy participants (comparative analysis)

Participants were retrospectively selected based on a normal 12-lead ECG response to a standardized incremental exercise test to volitional exhaustion using the same protocol as outlined for patients. End-point determination was assessed by the supervising clinician if the participant developed fatigue, inappropriate dyspnoea, angina, ST segment depression or elevation of 1 mm, significant dysrhythmias, atrioventricular conduction disturbances or defective chronotropic responses. There were no adverse events during the exercise or recovery periods of the tests. All participants were asymptomatic and defined as sedentary because they did not engage in any formal recreational activity outside of everyday living (Bailey et al., 2013a).

2.4.2 | Cardiopulmonary exercise testing of AAA patients (correlational analysis)

Preoperative CPET was conducted using an electromagnetically braked cycle ergometer (Lode, Gronigen, The Netherlands) and a Medgraphics Ultima metabolic cart (MedGraphics, Gloucester, UK). Calibration was undertaken in accordance with manufacturer's guidelines using a 3 litre syringe (Hans Rudolph, Kansas City, KS, USA) and reference calibration gases. During data collection, the middle five of seven breaths were averaged. An exercise protocol was used whereby patients cycled at 60 r.p.m. for 3 min in an unloaded freewheeling state, followed by a progressively ramped period of exercise (from 5 to 15 W min^{-1} based on mass, stature, age and sex) to volitional or symptom-limited termination, followed by 3 min recovery (Wasserman, 2012). Medgraphics Breeze software automatically determined peak oxygen uptake ($\dot{V}_{O_2peak}$; defined as the highest O_2 uptake during the final 30 s of exercise reported), oxygen uptake efficiency slope (OUES; Hollenberg & Tager, 2000), and peak oxygen pulse (O_2 pulse). The AT was manually interpreted by a clinician using the V-slope method (Beaver, Wassermen, & Whipp, 1986) and supported by comparison of end-tidal oxygen tension (ETO_2) and ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}_{O_2}$) plots. The ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) was identified at the AT.

2.5 | Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 23.0; IBM, Armonk, NY, USA). Distribution normality was confirmed using repeated Shapiro–Wilk *W* tests.

2.5.1 | Analysis 1 (comparative)

Continuous data are presented as the mean (SD), and dichotomous variables as the number (percentage). Differences in CRF between groups were established using unpaired *t* tests with analysis of covariance performed to adjust for age. Patient counts were analysed using χ^2 tests. Significance for all two-tailed tests was established at $P < 0.05$.

2.5.2 | Analysis 2 (correlational)

The secondary outcome measure, postoperative mortality, was assessed using Cox proportional hazards (PHs) regression models. The PH assumption was tested with Schoenfeld residuals (Grambsch & Therneau, 1994). Continuous and dichotomous variables were first assessed using univariable Cox PH regression. Subsequent multivariable Cox PH models were developed with inclusion criteria of variables at the $P < 0.2$ level (from univariable analysis) and a backward stepwise approach was used. Receiver operating characteristic (ROC) curves were constructed for subsequent markers of CRF identified as independent predictors of postoperative mortality. For a marker of CRF to be considered a valid independent predictor of mortality, an area under the ROC of >0.7 was required. Optimal threshold values for markers fulfilling this criterion were subsequently calculated by examination of the minimal distance between ROC plots and the upper left corner and presented with sensitivity and specificity. Dichotomized PCPET variables were used to represent subthreshold PCPET values and examined graphically using Kaplan–Meier plots, which were compared using a log-rank test to demonstrate postoperative survival, with significance established at $P < 0.05$. Confidence intervals (CIs) were presented for all survival statistics.

3 | RESULTS

3.1 | Patient outcomes

Two patients experienced AAA rupture before elective surgery and were discounted from the overall analysis. Ninety-nine patients were observed for a median time of 1034 days after surgery, of whom 76 were alive at the time of study analysis. Thirty day and 90 day mortality was observed for one and seven patients, respectively. Twenty-three patients were treated conservatively, of whom 17 died, with a median survival of 797 days at the time of study analysis.

3.2 | Analysis 1 (comparative)

Abdominal aortic aneurysm patients were defined by lower CRF across a range of PCPET values when compared with apparently healthy sedentary control subjects of a similar age. A mean difference of 13.6 ml O_2 kg^{-1} min^{-1} (95% CI 12.0–15.2, $P < 0.001$) was reported for $\dot{V}_{O_2peak}$ (Figure 1). Covariate analysis for $\dot{V}_{O_2peak}$ demonstrated an age-adjusted mean difference of 12.5 ml O_2 kg^{-1} min^{-1} (95% CI 11.1–13.9, $P < 0.001$) between groups.

3.3 | Analysis 2 (correlational)

One patient died within 30 days of surgery, and 20 deaths were reported 2 years post-surgery, of which half (10/20) were independent of AAA disease (ONS I71 code; abdominal aortic aneurysm with or without mention of rupture). Following multivariable analysis, both $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT were found to be independent predictors of mid-term (2 year) postoperative mortality (Table 2). A hazard ratio

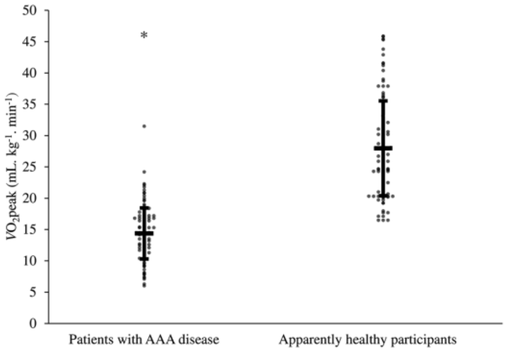

FIGURE 1 Comparison of peak oxygen consumption between patients with abdominal aortic aneurysm disease and apparently healthy participants. Bars represent the mean and SD. *Different *versus* healthy participants ($P < 0.05$), using unpaired *t* test

of 0.84 (95% CI 0.72–0.99) was observed for each unit (ml O_2 kg^{-1} min^{-1}) increase in $\dot{V}_{O_2peak}$. Conversely, a hazard ratio of 1.11 (95% CI 1.03–1.20) was observed for each unit increase of $\dot{V}_E/\dot{V}_{CO_2}$–AT. An area under the ROC curve (Figure 2) of 0.708 (95% CI 0.585–0.830, $P = 0.005$) was observed for $\dot{V}_{O_2peak}$, with an associated cut-off point of <13.1 ml O_2 kg^{-1} min^{-1} (sensitivity 65%, specificity 77%). The area under the ROC curve for $\dot{V}_E/\dot{V}_{CO_2}$–AT was 0.702 (95% CI 0.574–0.830, $P = 0.006$), with an associated cut-point of ≥34 (sensitivity 70%, specificity 64%).

We applied our defined cut-points for $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT (herein defined as subthreshold PCPET values) to stratify patients into high- or low-risk subgroups. Subsequently, when entered into a further regression model, hazard ratios of 5.27 (95% CI 1.62–17.14, $P = 0.006$) for $\dot{V}_{O_2peak}$ < 13.1 ml kg^{-1} min^{-1} and 3.26 (95% CI 1.00–10.59, $P = 0.049$) for $\dot{V}_E/\dot{V}_{CO_2}$–AT ≥ 34 were apparent (Table 3). Thus, $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT were independent predictors of mid-term survival, and patients with one or two subthreshold PCPET values

TABLE 2 Risk factor relationships with 2 year postoperative mortality in AAA patients

	Hazard ratio (95% CI)	*P* Value
Univariable		
Demographics		
Age (years)	1.08 (0.99–1.17)	0.08
Female	0.49 (0.06–3.73)	0.49
BMI (kg m^{-2})	1.01 (0.87–1.16)	0.93
Clinical		
Aneurysm diameter (cm)	1.06 (0.53–2.13)	0.87
Infrarenal	0.44 (0.09–2.21)	0.32
Supra/juxtarenal	2.25 (0.45–11.18)	0.32
Statin	0.78 (0.24–2.52)	0.68
COPD	1.42 (0.32–6.42)	0.65
Cardiorespiratory		
$\dot{V}_{O_2peak}$ (ml kg^{-1} min^{-1})	0.81 (0.69–0.95)	0.01
$\dot{V}_{O_2}$–AT (ml kg^{-1} min^{-1})	0.74 (0.55–0.98)	0.03
$\dot{V}_E/\dot{V}_{CO_2}$–AT	1.11 (1.03–1.20)	0.01
$\dot{V}_E/\dot{V}_{O_2}$–AT	1.07 (0.98–1.18)	0.14
O_2 pulse (ml beat)$^{-1}$	0.85 (0.73–0.98)	0.03
OUES	1.00 (1.00–1.00)	0.12
Workload at AT (W)	0.98 (0.95–1.00)	0.06
Peak workload (W)	0.98 (0.96–0.99)	0.01
Multivariable		
$\dot{V}_{O_2peak}$ (ml kg^{-1} min^{-1})	0.84 (0.72–0.99)	0.04
$\dot{V}_E/\dot{V}_{CO_2}$–AT	1.10 (1.01–1.19)	0.03

Abbreviations: AT, anaerobic threshold; BMI, body mass index; COPD, chronic obstructive pulmonary disease; O_2 pulse, oxygen pulse at peak oxygen consumption; OUES, oxygen uptake efficiency slope; $\dot{V}_E/\dot{V}_{CO_2}$, ventilatory equivalent for carbon dioxide; $\dot{V}_E/\dot{V}_{O_2}$, ventilatory equivalent for oxygen; and $\dot{V}_{O_2peak}$, peak oxygen consumption. $\dot{V}_{O_2}$–AT, oxygen consumption at anaerobic threshold

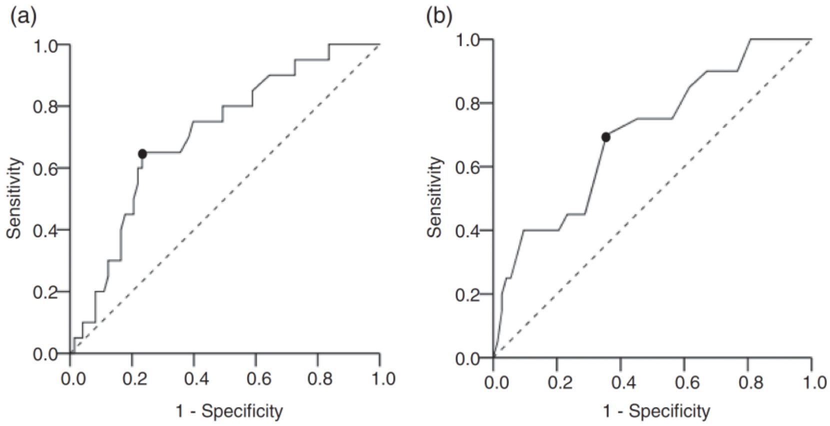

FIGURE 2 Area under receiver operating characteristic curves. (a) Peak oxygen consumption ($\dot{V}_{O_2peak}$). (b) Ventilatory equivalent for carbon dioxide at anaerobic threshold ($\dot{V}_E/\dot{V}_{CO_2}$–AT). Symbols represent optimal cut-points. Area under curve: (a) 0.708 (95% confidence interval 0.585–0.830, $P = 0.005$; cut-point 13.1 ml kg^{-1} min^{-1}); and (b) 0.702 (95% confidence interval 0.574–0.830, $P = 0.006$; cut-point 34)

TABLE 3 Regression analysis for selected cardiopulmonary exercise testing subthreshold values predictive of 2 year postoperative mortality in abdominal aortic aneurism patients

	Hazard ratio (95% CI)	*P* Value	2 year mortality [*n* (%)]
$\dot{V}_{O_2peak} < 13.1$ ml kg^{-1} min^{-1}	5.27 (1.62–17.14)	0.006	13 (11)[a]
$\dot{V}_{O_2peak} \geq 13.1$ ml kg^{-1} min^{-1}	Reference group		7 (6)
$\dot{V}_E/\dot{V}_{CO_2}$–AT ≥ 34 units	3.26 (1.00–10.59)	0.049	15 (13)[a]
$\dot{V}_E/\dot{V}_{CO_2}$–AT < 34 units	Reference group		5 (4)

Abbreviations: CI, confidence interval; $\dot{V}_E/\dot{V}_{CO_2}$–AT, ventilatory equivalent for carbon dioxide at anaerobic threshold; and $\dot{V}_{O_2peak}$, peak oxygen consumption
[a]$P < 0.05$.

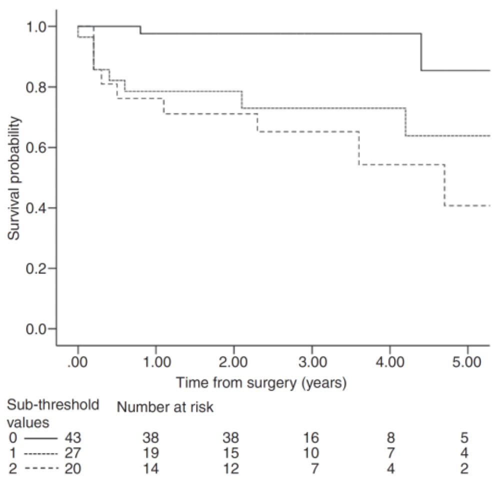

FIGURE 3 Kaplan–Meier plot for survival after abdominal aortic aneurism surgery stratified by the number of subthreshold cardiopulmonary exercise testing (CPET) values. $P = 0.01$, log-rank test. Subthreshold CPET values: $\dot{V}_{O_2peak} < 13.1$ ml kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}_{CO_2}$–AT ≥ 34

demonstrated reduced postoperative survival ($P = 0.01$), as illustrated in Figure 3. Previous work from our group (Rose et al., 2018) has demonstrated that natural variation is present in magnitudes of up to ±13 and ±10%, respectively for $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT, and therefore subthreshold PCPET values should take account of this variation when optimizing patient fitness stratification. Three zones were calculated whereby patients were 'fit' (≥13.1 ml kg^{-1} min^{-1} and <34 for $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT, respectively, with natural variation accounted for), 'intermediate fitness' (scores that could transcend the subthreshold values when natural variation is considered) or 'unfit' (<13.1 ml kg^{-1} min^{-1} and ≥34 for $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT, respectively, with natural variation accounted for). Therefore, our defined threshold values produced zones for fit, intermediate fitness and unfit of >15, 15–11.6 and <11.6 ml O_2 kg^{-1} min^{-1} for $\dot{V}_{O_2peak}$ and <31, 31–38 and >38 for $\dot{V}_E/\dot{V}_{CO_2}$–AT.

4 | DISCUSSION

Consistent with our original hypotheses, our study has revealed two findings. First, CRF was shown to be impaired in AAA disease relative to an apparently healthy sedentary population of comparable age. Second, both $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT were able independently to identify patients at high risk of mid-term postoperative mortality, but not during the intraoperative period. Collectively, our findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients, which may help to direct care provision.

In the context of the present study, we speculate that impaired vascular function precipitated by inadequate antioxidant defences and a corresponding elevation in oxidative-nitrosative stress, collectively associated with impaired CRF (Bailey et al., 2013b) and AAA disease (Bailey et al., 2006), might be responsible for inferior postoperative outcomes. Impaired vascular endothelial function has been observed in the early postoperative period after major colon cancer surgery (Ekeloef et al., 2017) and warrants further investigation in this population. Furthermore, in addition to impaired $\dot{V}_{O_2peak}$, patients with high risk of postoperative mortality demonstrated elevated $\dot{V}_E/\dot{V}_{CO_2}$–AT, suggesting that inefficient ventilation of the lungs consequent to the mismatching of ventilation to perfusion is a significant risk factor.

As expected, CRF was impaired in AAA disease. Our study used an effectively controlled research design, with a comparative sample of participants selected by convenience to account for the effect of age, sex and activity levels. Furthermore, our objectively determined 12-lead ECG assessments confirmed that the control participants were asymptomatic and free of any overt cardiovascular/ischaemic heart disease, given a negative functional diagnostic exercise stress test. Of interest, increased prevalence of aneurysmal disease has been linked to populations exhibiting low levels of CRF and reduced blood flow, as demonstrated in amputees and spinal injury, which has been hypothesized as a causative factor (Vollmar, Pauschinger, Paes, Henze, & Friesch, 1989; Yeung et al., 2006).

The mean $\dot{V}_{O_2peak}$ for patients with AAA disease reported in the present study (14.4 ml O_2 kg^{-1} min^{-1}) was similar to that reported by Prentis et al. (2012). Our reported $\dot{V}_{O_2peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT were independent predictors of postoperative survival, in agreement with previous studies (Carlisle & Swart, 2007; Hartley et al., 2012). However, our defined subthreshold values of <13.1 ml O_2 kg^{-1} min^{-1} and ≥34 were lower than those previously reported, emphasizing the need for a more conservative approach. Of interest and contrary to other studies (Grant et al., 2015; Hartley et al., 2012), AT did not predict survival in our cohort of patients.

Studies with larger sample sizes have previously reported an association between PCPET values and postoperative survival;

however, limitations are evident. The largest study, which recruited 506 patients (Grant et al., 2015), did not define subthreshold PCPET values from their own dataset and instead adopted values from a study (Carlisle & Swart, 2007) with a cohort of a similar size to the present study. Furthermore, another large study (Hartley et al., 2012) adopted subthreshold PCPET values used to predict postoperative morbidity in heterogeneous populations (Snowden et al., 2010). Thus, our findings demonstrating a lower than previously reported $\dot{V}_{O_2 peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT, and no association for AT, hold new value of clinical importance for patients undergoing surgery for AAA repair.

We support the value of reporting mid-term survival (defined as 2 years post-surgery in our data) for patients undergoing AAA repair, because in-hospital mortality is now reported at relatively low levels of 2.9 and 0.4% for open and endovascular aneurysm repair approaches, respectively (VSQI, 2017). Furthermore, surgery is undertaken not to cure the disease, but to prevent future risk of rupture, and thus decision-making needs to account for a long-term risk assessment (Howell, 2017). Of the 20 deaths reported in our study at 2 years post-surgery, half (10/20) were independent of AAA disease (ONS I71 code; abdominal aortic aneurysm with or without mention of rupture). Our findings did not support the ability of CRF to identify patients at high risk of intraoperative mortality, because only one patient died within 30 days of surgery. We acknowledge that the sample size (Altman, 1980) was based upon the primary outcome variable; to determine if CRF was impaired for patients with AAA disease when compared with age-matched apparently healthy sedentary control subjects, and retrospective analysis demonstrated 100% power at the $P < 0.05$ level for our given effect size (2.05).

Few studies have defined subthreshold PCPET values indicative of increased postoperative risk in patients with AAA disease. Instead, many rely on previously defined values, which in some cases may have been determined from different patient populations. We therefore suggest that our defined threshold values hold potential to improve future identification of high-risk patients. Either $\dot{V}_{O_2 peak}$ or $\dot{V}_E/\dot{V}_{CO_2}$–AT should be considered for risk appropriation, and if subthreshold scores for both are presented, a cumulative effect is likely, as demonstrated in Figure 3. Recent work from our group (Rose et al., 2018) recommends that clinicians should not consider fitness as a single point estimate, but instead as a dynamic range of values defined by natural variation and calculated using critical difference (Davison et al., 2012; Fraser & Fogarty, 1989). Thus, rather than advocating specific binary threshold values, zones along a spectrum of fitness should be adopted (Wilson, 2018). Using this methodology as calculated in our results, we recommend that clinicians adopt zones for fit, intermediate fitness and unfit of >15, 15–11.6 and <11.6 ml kg^{-1} min^{-1} and <31, 31–38 and >38 for $\dot{V}_{O_2 peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT, respectively, when identifying patients at risk of mid-term (2 year) postoperative mortality.

Given that we were unable to predict perioperative risk based upon the application of CRF (probably as a result of the relatively low levels of reported in-hospital mortality and underpowered sample size), it is interesting to speculate why, in this vascular impaired population, there is an apparent need to wait for 2 years for the benefit of improved CRF to become apparent. Furthermore, a well-established mechanistic grounding for the protective benefits of improved CRF is yet to be established.

4.1 | Limitations

We have reported an association between PCPET and mid-term postoperative survival. However, in order to demonstrate an improved ability to identify high-risk patients, PCPET values should also be compared against, or in conjunction with, other risk prediction models, such as the Revised Cardiac Risk Index (RCRI), Physiological and Operative Score for enumeration of Mortality and Morbidity (POSSUM), National Surgical Quality Improvement Program (NSQIP) and Surgical Outcome Risk Tool (SORT) (Reeves et al., 2018).

Although CRF was shown to be impaired in AAA disease relative to a healthy sedentary population of comparable age, we were unable to determine whether any of the control population exhibited AAA disease, because they were not screened via Duplex ultrasonography.

Our (nested) sample of patients who underwent PCPET were not representative of the whole population who underwent surgery for aneurysmal repair at this centre and included only those who were referred for PCPET. Further investigation of the referral process is required to determine how many patients did not undergo PCPET and the underlying reasons. The decision to operate (or treat conservatively) was probably influenced by PCPET results, because patients were routinely referred for PCPET to aid risk stratification. Patients treated conservatively demonstrated lower levels of CRF, with $\dot{V}_{O_2 peak}$ reported at 12.1 ml kg^{-1} min^{-1}, a reduction of 2.3 ml kg^{-1} min^{-1} (95% CI 0.29–4.28, $P = 0.025$). Despite these limitations, a clear impairment of CRF has been demonstrated in AAA disease, the extent of which might hold predictive value when assessing surgical risk.

4.2 | Conclusions

This study defines the magnitude of impaired CRF demonstrated in AAA disease. The PCPET values were unable to identify patients at high risk of intraoperative mortality. However, our findings add to the body of evidence supporting the measurement of CRF used to identify patients at high risk of mid-term postoperative mortality. In this specific subset of patients, $\dot{V}_{O_2 peak}$ of <13.1 ml kg^{-1} min^{-1} and $\dot{V}_E/\dot{V}_{CO_2}$–AT ≥ 34 allowed for the discrimination of patients at increased risk of mid-term postoperative mortality, and we therefore recommend zones for fit, intermediate fitness and unfit of >15, 15–11.6 and <11.6 ml kg^{-1} min^{-1} and <31, 31–38 and >38 for $\dot{V}_{O_2 peak}$ and $\dot{V}_E/\dot{V}_{CO_2}$–AT, respectively. Collectively, these findings demonstrate that CRF can predict mid-term postoperative survival in AAA patients, which may help to direct care provision.

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AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of study. R.G.D. and I.R.A. supervised the patient CPET tests. Postoperative outcome data were collated by R.G.D. and I.M.W. G.A.R. performed the analysis with input from D.M.B, M.H.L. and I.M.W. The manuscript was drafted by G.A.R. and D.M.B. Funding was obtained by D.M.B. All authors provided revisions, approved the final version for submission and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

COMPETING INTERESTS

None declared.

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CASE REPORT

Physiological Reports

High-intensity exercise training improves perioperative risk stratification in the high-risk patient

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Abstract

Exercise prehabilitation prior to major surgery can improve cardiorespiratory fitness (CRF) and clinical outcome. However, in patients deemed "high--risk" for surgery, the feasibility, optimum training modality and its intensity, duration, and frequency are yet to be defined. We assessed the cardiorespiratory fitness of a 70-year-old female patient requiring major thoraco-abdominal surgery for reconstruction of her esophagus. Cardiopulmonary exercise testing (CPET) on a cycle ergometer was used to determine CRF. A baseline CPET confirmed poor CRF and placed her in a high surgical risk group. This was followed by 16 weeks of unsupervised, home-based, moderate-intensity steady-state (MISS) training followed by 10 weeks of high-intensity interval training (HIIT) under the combined supervision of an exercise physiologist and clinician in hospital. Following MISS training, CPET metrics failed to improve: peak oxygen uptake decreased (14.7–13.7 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; −7%) together with peak power (73–70 W; −4%) and anaerobic threshold (AT) increased (7.8–8.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; +6%). However, HIIT resulted in impressive improvement in CRF. Peak oxygen uptake (13.7–18.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; +36%), AT (8.3–10.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; +27%), peak power (70–102 W; +46%), minute ventilation (35.8–57.7 $L \cdot min^{-1}$; +61%), and peak heart rate (100–133 $b \cdot min^{-1}$; +33%) all increased. Ventilatory equivalents for carbon dioxide at AT ($\dot{V}_E/\dot{V}CO_2$-AT) improved (30–28; −7%). The improvement in CRF resulted in surgical reclassification from high to low risk. In conclusion, preoperative HIIT training can confer a marked improvement in CRF in an elderly surgical patient and is associated with a corresponding reduction in perioperative risk.

KEYWORDS
cardiopulmonary exercise test, exercise training, risk assessment

1 | INTRODUCTION

Poor cardiorespiratory fitness (CRF) is associated with an increased risk of adverse perioperative outcomes including major morbidity, mortality, increased length of stay in hospital (Moran et al., 2016) and reduced health-related quality of life (Tew, Ayyash, Durrand, & Danjoux, 2018) following major surgery. The American Heart Association guidelines

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(2014) recommend functional assessment for evaluating peri-operative risk (Fleisher et al., 2014). Cardiopulmonary exercise testing (CPET) is used to objectively measure functional capacity and can identify the causes of exercise limitation. CPET can evaluate chronic comorbidities and allow identification of new pathology that requires treatment or optimization. These data can be used to facilitate shared decision making, to allow appropriate utilization of postoperative critical care and to direct prehabilitation programs. Approximately 30,000 preoperative CPET are conducted in the UK each year to assess patient risk and plan care (Reeves et al., 2018). With the rapid uptake of CPET, an international Perioperative Exercise Testing and Training Society has been established to promote the highest standards of care for patients undergoing exercise testing, training, or both in the perioperative setting (Levett et al., 2018). There is increasing evidence that preoperative exercise training can improve CRF (West et al., 2015) by creating improved physiological reserve to deal with the stress response to surgery. Typically, studies recruit by convenience with younger and physically active patients more likely to participate. Thus, the feasibility and efficacy of exercise interventions in "unfit" patients deemed high risk for surgery is not adequately addressed and warrants further investigation.

It is well established that moderate intensity steady-state (MISS) exercise can improve CRF reducing the risk of cardiovascular disease and all-cause mortality across the human aging continuum (Blair, Kohl, & Paffenbarger, 1989). However, the optimal modality, frequency, and duration remain a constant source of debate. Furthermore, clinical urgency and time demands may be potential barriers to participation (Reichert, Barros, Domingues, & Hallal, 2007). As a consequence, attention has since turned to an alternative exercise modality, high-intensity interval training (HIIT), given its capacity to further potentiate metabolic, cardiopulmonary, and systemic vascular adaptation with the added attraction of reduced exercise duration even in patients who are deemed "high risk" (Gibala et al., 2006). With this in mind, we describe a clinical case study to highlight the feasibility and potential benefits of HIIT in a high-risk patient requiring esophageal reconstruction in an attempt to improve postoperative outcome.

2 | METHODS

2.1 | Ethics approval

The Cardiff and Vale University Health Board Ethics Committee was informed and formal approval was deemed unnecessary as this was part of the proposed preoperative optimization strategy. The patient provided written informed consent and all procedures adhered to guidelines set forth in the Declaration of Helsinki.

2.2 | Patient

A 70-year-old Caucasian female with a body mass of 24 kg·m^{-2}, hemoglobin of 12 g·dl^{-1} and normal renal and liver function underwent transhiatal esophagectomy for esophageal cancer but developed postoperative ischemia of the gastric conduit. Following a problematic course on critical care she required further emergency surgery and was left with a pharyngostomy and a feeding jejunostomy. The patient attended our anesthetic preoperative clinic for assessment of CRF for colonic interposition to restore gastrointestinal tract continuity. Her medical history included myocardial infarction, coronary artery bypass surgery, hypertension, pulmonary embolism, and a right hemi-colectomy for cecal cancer. Her drug treatment included apixaban, ramipril, bisoprolol, and atorvastatin. She denied symptoms of angina and had a good self-reported tolerance to physical activity despite a 30-pack year smoking history.

2.3 | Design

2.3.1 | Exercise interventions

Following initial CPET, she was stratified as high risk for surgical intervention and the patient attempted to improve her functional capacity with unsupervised training at home using a treadmill walking for 20 min, three times per week (MISS training).

A second CPET, 8 weeks later, demonstrated no difference to her risk stratification and she agreed to train further using a home fitness video three times per week. Despite being well motivated, the patient's own efforts failed to improve her CPET metrics. This led to further detailed discussion of perioperative risk and adequate preoperative preparation, and she agreed to undertake a 10-week HIIT exercise program jointly supervised by an exercise physiologist and clinician.

HIIT consisted of three exercise sessions per week on a cycle ergometer, each of 40 min duration. Sessions comprised six, 2-min bouts of heavy exercise (50% difference between power output at peak exercise and anaerobic threshold [AT]) interspersed with 3 min of moderate exercise (80% power at AT) based on previous research by West et al. (2015). Heart rate (3-lead electrocardiogram), blood pressure, and oxygen saturations by finger pulse oximetry were monitored during exercise. A CPET was conducted approximately every 2 weeks and HIIT intensity adjusted accordingly. A final CPET was performed 2 weeks prior to surgery to assess changes in functional capacity following HIIT.

2.4 | Measurements

2.4.1 | CPET

Objective assessment of functional capacity was performed using CPET. All CPETs were conducted to volitional fatigue using a MedGraphics Ultima metabolic cart (MedGraphics™) and an electromagnetically braked cycle ergometer (Lode, Groningen, The Netherlands) in accordance with UK national guidelines for CPET (Levett et al., 2018). Breath-by-breath measurements of gas exchange were obtained using a mouthpiece connected to a MedGraphics preVent™ pneumotach device with a noseclip to measure both inspired and expired oxygen and carbon dioxide levels and respiratory flow. Following 3 min of resting data collection, the subject cycled at 60 rpm for 3 min in an unloaded "'freewheeling" state. A progressively ramped period of exercise at 10 $W.min^{-1}$ based on her stature, age, and predicted peak oxygen uptake ($\dot{V}O_2$ peak) was then undertaken to symptom limited termination and followed by 1- to 5-min recovery period.

During each CPET, the following measurements were recorded:

- *Cardiovascular*. Heart rate and electrocardiogram ST segment analysis were recorded continuously.
- *Pulmonary*. Oxygen uptake, carbon dioxide output, expiratory minute ventilation, and respiratory frequency were recorded breath by breath throughout. MedGraphics BreezeSuite™ software automatically determined $\dot{V}O_2$ peak (defined as the highest oxygen uptake during the final 30 s of exercise reported) and oxygen uptake efficiency slope (OUES). The AT was manually interpreted by a clinician using the modified V-slope method (Whipp, Ward, & Wasserman, 1986), supported by ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) and end-tidal partial pressures of oxygen and carbon dioxide in accordance with UK national guidelines for perioperative CPET (Levett et al., 2018). Breath-by-breath data were averaged using middle five of seven breaths. Pulse oximetry was recorded throughout.

2.5 | Data interpretation

2.5.1 | CPET values

For comparative purposes, the CRF of a literature-based age-matched control would demonstrate a $\dot{V}O_2$ peak of 22 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Wasserman, 2012). We used reference CRF threshold values for perioperative risk from the European Association for Cardiovascular Prevention and Rehabilitation (EACPR)/American Heart Association (AHA) Scientific Statement: $\dot{V}O_2$ at AT <11 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, $\dot{V}O_2$ peak <16 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, and $\dot{V}_E/\dot{V}CO_2$ at AT > 36. Failure to reach one or more of these thresholds cumulatively increases the perioperative risk reference (Guazzi et al., 2016). We also compared changes in CRF with known test-retest coefficients of variation (CV) associated with both biological variation and analytical variation, indicative of Critical Difference (CD). Based on previously published works, CD represents the magnitude of change required to demonstrate a meaningful physiological change (Rose et al., 2018).

2.5.2 | Critical difference (CD)

CRF is a dynamic metric subject to natural variation encompassing both analytical and biological components that collectively contribute to the critical difference given by (Fraser & Fogarty, 1989):

$$CD = k\sqrt{CV_A^2 + CV_B^2} \tag{1}$$

where: k = constant equal to 2.77 at $p < .05$. CV_A = coefficient of analytical variation. CV_B = coefficient of biological variation.

Natural variation is described by the magnitude of CD and determines the difference in CRF required to demonstrate change not simply due to the "noise" associated with analytical imprecision (represented by CV_A) and biological variation (represented by CV_B), in order to determine if any change is to be considered "clinically meaningful." We have previously calculated the CD for VO_2-AT, VO_2peak, and V_E/VCO_2-AT to be 19%, 13%, and 10%, respectively (Rose et al., 2018). Changes in the observed CRF metrics were retrospectively compared against these values to provide clearer insight into the true physiological benefit conferred by the respective exercise interventions.

3 | RESULTS

Despite good self-reported exercise capacity, an initial baseline CPET conducted 9 months after her failed esophagectomy demonstrated poor CRF, achieving peak work 73 W, AT 7.8 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, $\dot{V}O_2$ peak 14.7 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, and $\dot{V}_E/\dot{V}CO_2$-AT 28 (Table 1). This CPET performance was similar to that achieved prior to her original esophagectomy (Table 1).

A second CPET, 8 weeks later after self-directed, unsupervised home training on a treadmill, demonstrated minimal change in AT (7.8–7.7 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; −1%), but small improvements in $\dot{V}O_2$ peak (14.7–16.2 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; +10%), and minute ventilation (38.0–47.8 $L \cdot min^{-1}$; +26%)

(Table 1). Following further training with a home fitness video, a third CPET 16 weeks later, demonstrated worsening of her exercise capacity (Table 1).

The 10-week, supervised, HIIT program was well tolerated with no adverse events identified. She completed 29 of the prescribed 30 sessions (one training session was not completed due to illness). Her hemoglobin levels were normal throughout the training programs and her body mass remained constant.

HIIT resulted in increases in $\dot{V}O_2$ peak (13.7–18.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; +36%), AT (8.3–10.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; +27%), peak power (70–102 W; +46%), minute ventilation (35.8–57.7 $L \cdot min^{-1}$; +61%), and oxygen uptake efficiency slope (OUES) (923–1,079; +17%). $\dot{V}_E/\dot{V}CO_2$-AT decreased (30–28; −7%). Peak heart rate increased 33% (100–133 b. min^{-1}). (Table 2, Figure 1).

4 | DISCUSSION

The patient's CRF at baseline was considerably lower than literature-based age-matched controls and also confirmed a high level of risk for major surgery when compared with reference CRF threshold values for perioperative risk

TABLE 1 Cardiopulmonary exercise test results during unsupervised, moderate intensity steady-state (MISS) training

	Pre-esophagectomy	Pre-MISS baseline (9 months post-esophagectomy)	8-week MISS completed	16-week MISS completed	% change required based on CD	% change observed from baseline to 16 weeks
$\dot{V}O_2$-AT (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)	8.4	7.8	7.7	8.3	19%	+6%
$\dot{V}O_2$ peak (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)	13.1	14.7	16.2	13.7	13%	−7%
Power at $\dot{V}O_2$ peak (Watts)	91	73	77	70		−4%
$\dot{V}_E$ ($L \cdot min^{-1}$)	41.3	38.0	47.8	35.8		−6%
$\dot{V}_E/\dot{V}CO_2$-AT	32	28	31	30	10%	+7%
RER at peak	1.27	1.44	1.47	1.38	15%	−4%
Heart rate peak ($b \cdot min^{-1}$)	125	131	125	100		−24%
OUES	1,110	858	986	923	12%	+8%
Power at AT (Watts)	50	39	36	40		+3%

Abbreviations: $\dot{V}_E$, peak minute ventilation; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for oxygen at AT; AT, anaerobic threshold; CD, critical difference; $\dot{V}O_2$ peak, peak oxygen uptake; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio.

TABLE 2 Cardiopulmonary exercise test results during supervised high-intensity interval training (HIIT)

	Pre-HIIT baseline	2-week HIIT completed	5-week HIIT completed	7-week HIIT completed	10-weeks HIIT completed	% change required based on CD	% change from baseline to 10 weeks
$\dot{V}O_2$-AT (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)	8.3	8.5	8.8	8.1	10.5	19%	+27%
$\dot{V}O_2$ peak (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)	13.7	13.8	17.5	16.1	18.6	13%	+36%
Power at $\dot{V}O_2$ peak (Watts)	70	76	91	95	102		+46%
$\dot{V}_E$ ($L \cdot min^{-1}$)	35.8	32.7	49.1	51.4	57.7		+61%
$\dot{V}_E/\dot{V}CO_2$-AT	30	28	30	28	28	10%	−7%
RER at peak	1.38	1.42	1.38	1.60	1.55	15%	+12%
Heart rate peak ($b \cdot min^{-1}$)	100	120	118	120	133		+33%
OUES	923	969	1,000	944	1,079	12%	+17%
Power at AT (Watts)	40	36	40	40	52		+30%

Abbreviations: $\dot{V}_E$, peak minute ventilation; $\dot{V}_E/\dot{V}CO_2$-AT, ventilatory equivalent for oxygen at AT; AT, anaerobic threshold; CD, critical difference; $\dot{V}O_2$ peak, peak oxygen uptake; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio.

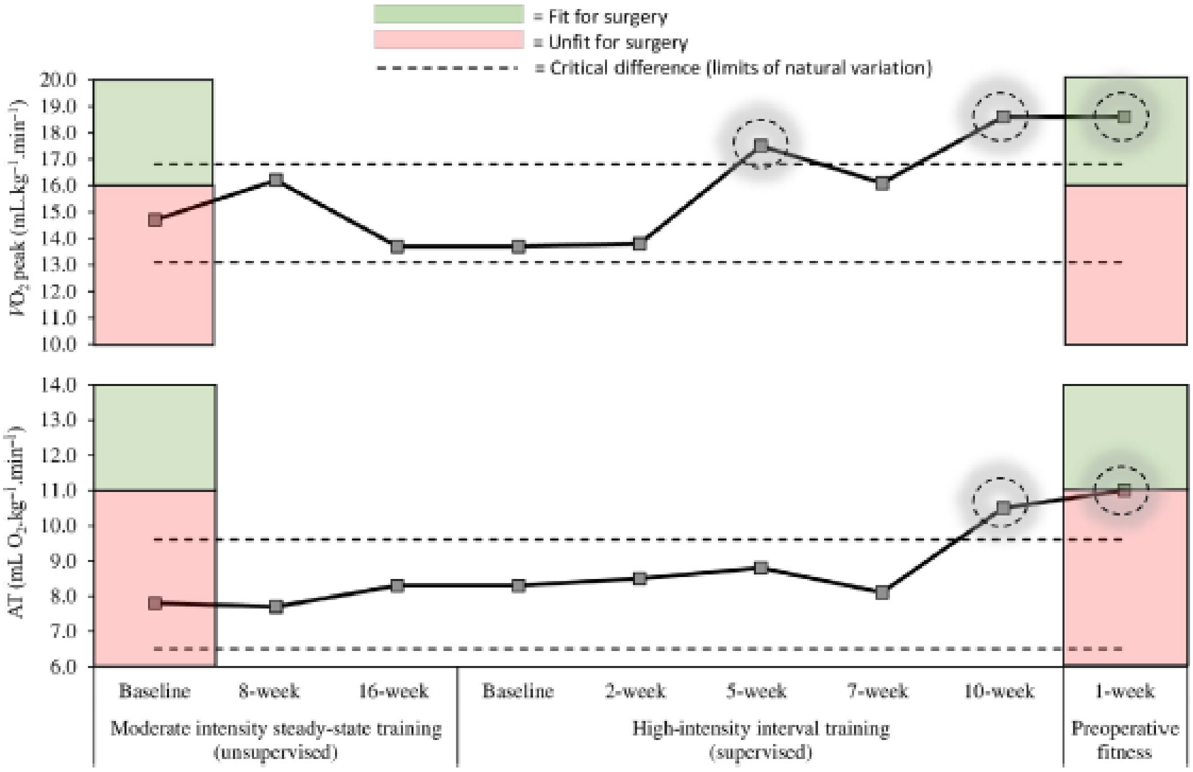

FIGURE 1 Cardiorespiratory fitness at baseline, during moderate intensity steady state (MISS) and high intensity interval training (HIIT) approaches. Following 10 weeks of HIIT (three sessions per week), fitness was maintained until the time of surgery by completion of a further two HIIT sessions per week. For comparative purposes, a literature-based age-matched control would demonstrate a $\dot{V}O_2$ peak of 22 ml O_2·kg^{-1}·min^{-1} (Wasserman, 2012). AT, anaerobic threshold; $\dot{V}O_2$ peak, peak oxygen uptake

stratification. Supervised HIIT training enabled impressive improvement in excess of natural variation and was clinically significant based on application of the critical difference. Our patient's improved CRF as demonstrated by her CPET metrics resulted in the reclassification of her risk for major surgery into a low risk group. This clinical case study highlights that HIIT in the high-risk patient preparing for major intra-abdominal surgery is effective. HIIT improvements in CRF were incurred over a short period of time and were considered clinically meaningful enabling the patient to transcend the "fitness" boundary ahead of major surgery. Collectively, our findings support the implementation of HIIT as an effective prehabilitation strategy with the potential to optimize perioperative outcome.

The "high-risk surgical patient" accounts for 13% of cases in the United Kingdom, but contributes to over 80% postoperative deaths and complications (Pearse et al., 2006). The principle of prehabilitation is to improve cardiovascular, respiratory, and muscular conditioning and can be considered analogous to the preparation of an individual for a marathon event (Wynter-Blyth & Moorthy, 2017). Improving a patient's physiological reserve allows them to meet the demands of this perioperative stress, reducing the risk of complications and death. A multimodal prehabilitation program allows other factors such as smoking, alcohol, nutrition, and anemia to be addressed (Tew et al., 2018). The optimum components of an exercise program have yet to be elucidated as much of the evidence is relatively recent (Minnella & Carli, 2018). Given the short time period that cancer patients have between diagnosis and surgery, HIIT training seems to confer the greatest advantages and current trials are ongoing to determine this (Woodfield et al., 2018).

We acknowledge the idiosyncrasies present when comparing the type of exercise intervention (supervised vs. unsupervised), intensity of exercise (HIIT vs. MISS), and mode of exercise (walking vs. cycling), and that a controlled experiment with an age-matched healthy participant was outside the scope of this work. We simply aimed to demonstrate the impact of a theoretically effective exercise intervention on a single patient to improve clinical outcome. The efficacy of our HIIT intervention may be attributed to some key factors. First, the HIIT program was individualized using the cycle ergometer to adjust work rate based on the patient's power output at two measured physiological parameters (AT and

$\dot{V}O_2$ peak). This allowed targeted training using a planned program of exercise. Second, the HIIT program was supervised throughout by both a medical professional and exercise physiologist. This joint supervision allowed for psychological, behavioral, and environmental factors to be addressed through regular encouragement, reassurance, and motivation in a safe and secure environment. While the patient ultimately must do the training, the health professionals must supervise the HIIT program to harness and maintain patient motivation while ensuring safety. While we have demonstrated beneficial increases in CRF, the present HIIT program is admittedly resource intensive in terms of equipment and professional input. Further research is required to evaluate the potential for its widespread implementation in the preoperative setting, given the inevitable financial and logistical constraints.

Studies in healthy participants and patients with established cardiometabolic disease have consistently demonstrated a greater increase in maximal oxygen consumption ($\dot{V}O_2$ max) following HIIT compared to MISS (Milanovic, Sporis, & Weston, 2015). The associated $\dot{V}O_2$ max increase is associated with elevated peroxisome proliferator-activated receptor gamma coactivator 1-alpha mRNA (Gibala et al., 2009), a moderator of skeletal muscle mitochondrial biogenesis which sits "front and central" in terms of the primary mechanism underpinning its superior cardiopulmonary adaptive benefits. Furthermore, an increase in citrate synthase (a marker of muscle oxidative capacity) has also been reported (Burgomaster, Hughes, Heigenhauser, Bradwell, & Gibala, 2005). Systemic vascular function has also been shown to improve following HIIT (Molmen-Hansen et al., 2012), the likely consequence of an "optimized" blood flow-shear phenotype, triggering calcium influx into the hyperpolarized endothelial cells (Cooke, Rossitch, Andon, Loscalzo, & Dzau, 1991) upregulating endothelial nitric oxide synthase (Bolduc, Thorin-Trescases, & Thorin, 2013). Collectively, these studies demonstrate that despite shorter bouts of activity, albeit at higher intensity, HIIT has the capacity to further potentiate physiological adaptation compared to MISS, which lies at the heart of its current popularity. Indeed, we demonstrated that the majority of adaptive benefit was incurred within the first 5 weeks of HIIT, suggesting that training interventions as short as this may prove "sufficient" allowing the patient to transcend the "fitness for surgery" boundary.

In conclusion, HIIT was shown to be a feasible, safe, and well-tolerated exercise intervention that was associated with impressive improvements in CRF enabling a single patient to be classified as "fit" for major surgery. Collectively, our findings support the detailed investigation of HIIT as an effective prehabilitation strategy with the potential to optimize perioperative outcome.

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CONFLICT OF INTEREST

No conflicts of interest (financial or otherwise) are declared by the authors.

AUTHOR CONTRIBUTIONS

R.D., I.A., and G.R. performed the experiment and supervised the exercise interventions. M.A., R.D., I.A., G.R., and D.M.B. analyzed the data and interpreted the findings. M.A., G.R., R.D., and I.A. drafted the manuscript. All authors edited and revised the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Bowel cancer surgery outcomes and pre-operative cardiopulmonary exercise testing: insights from real-world data

Bowel cancer is the third most common cancer in the UK [1]. Many of these patients will present for surgical treatment. The 2017 Annual Report of the National Bowel Cancer Audit describes data collected from over 30,000 patients diagnosed with bowel cancer between April 2015 and March 2016 in England and Wales [2]. This national audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) and funded by NHS England and Wales. The audit is carried out by the Clinical Effectiveness Unit of the Royal College of Surgeons of England in partnership with the Association of Coloproctology of Great Britain and Ireland and NHS Digital. Sixty-three percent of these patients had undergone a major surgical resection [2].

Centres in the UK are increasingly using pre-operative cardiopulmonary exercise testing (CPET) to risk stratify patients before major surgery. Within the same period, the National Bowel Cancer Audit conducted an organisational survey to determine the availability of on-site services including CPET for the objective evaluation of cardiopulmonary fitness and peri-operative risk at each NHS site [3]. Cardiopulmonary exercise testing-derived metrics have the potential to predict morbidity and mortality after major abdominal surgery [4]. It may also allow individualised risk assessment; inform shared decision making; identify requirement for postoperative critical care; and assesses and identifiy scope for optimisation of comorbidities and prehabilitation [5]. The latest survey of CPET in the UK identified increasing utilisation with over 30,000 tests performed annually [6].

National Bowel Cancer Audit data are publicly available online under the Open Government Licence via NHS Digital. We analysed the two latest datasets [2, 3] to determine if there were any differences between the clinical outcomes of patients who underwent surgery in centres with and without CPET. We compared 90-day mortality between hospitals that provided CPET and those that did not. Statistical analysis was conducted using MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; 2016). Patients were pooled for sites with and without CPET facilities. Relative risk (RR) was calculated for patients treated at sites with and without CPET.

In centres that had onsite CPET facilities, 10,694/17,986 (59%) patients had major surgery. This was associated with an 18% reduction (RR 0.82, 95%CI 0.70–0.96, $p = 0.0157$) in 90-day mortality in centres that had CPET. There was no significant difference in disease severity (patients with distant metastases at the time of surgery) between centres with and without CPET (RR 0.99, 95%CI 0.90–1.09, $p = 0.7947$) or in the volume of patients in each centre on a curative major resection treatment pathway (RR 1.01, 95%CI 0.98–1.05, $p = 0.53$). Although there were more patients recorded as ASA status 1 in centres with CPET (RR 1.1, 95%CI 1.02–1.20, $P = 0.0159$), there was no difference in patients recorded as ASA physical status 2, 3 or 4/5 between centres with and without CPET (ASA 2 RR 0.97, 95%CI 0.95–1.0, $p = 0.067$; ASA 3 RR 0.96, 95%CI 0.91–1.01, $p = 0.090$; ASA 4/5 RR 0.87, 95%CI 0.73–1.04, $p = 0.126$).

National Bowel Cancer Audit data are real-world data that are freely available for analysis and characterises routine clinical practice. Our analysis of this dataset suggests an association between better outcomes and centres that have CPET, which warrants further scrutiny. Exercise-oncology research is expanding and CPET-based prehabilitation has potential to improve outcomes after cancer surgery. Current data submission to the National Bowel cancer Audit includes patient-level CPET data and we would encourage the auditors to describe and refine further any correlation between CPET and outcomes after major colorectal cancer surgery in future reports.

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 doi:10.1111/anae.15451

Science Letter

Effect of a novel viral filter on cardiopulmonary exercise testing during the COVID-19 pandemic

Cardiopulmonary exercise testing (CPET) before major surgery provides the best risk estimate of postoperative morbidity, mortality and consequent prognosis [1], yet is currently suspended because of the hazards associated with aerosol-generating physical exercise and potential infective transmission [2]. While some services have transitioned to secondary, less informative assessments of cardiopulmonary function [3], novel counter-measures are required if surgical outcomes are to be optimised. Moreover, the related effect size is such that by July 2020, COVID-19 disease was associated with an 81-fold increase in the number of patients (n = 83,000) waiting > 1 year for NHS treatment in England alone [4]. Despite the transmission-reducing potential of porous microbacterial/viral filters (BVF), concerns related to water vapour saturation and increased ventilatory resistance raise barriers to implementation [2]. The aim of our study was to investigate the effect of a novel BVF on cardiorespiratory parameters during CPET, in a randomised single-blind crossover study.

Following ethical approval as a service evaluation (Cardiff and Vale University Health Board), 12 healthy, male participants with a mean (SD) age of 45 (10) years completed two separate CPET tests (seven days apart), with BVF and without (true value) BVF, distal to the sampling line. Participants performed a standardised incremental cycling

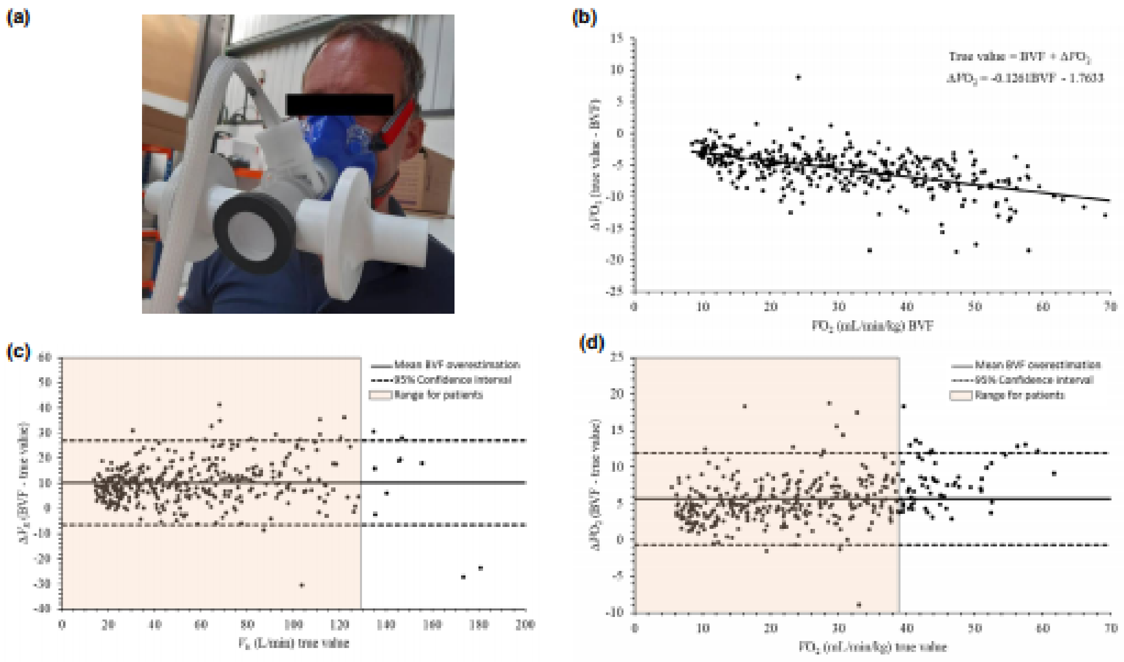

Figure 1 Dynamic changes in select cardiopulmonary metrics during cardiopulmonary exercise testing (CPET) with BVF and without (true value) a BVF. (a) specialist BVF; (b) provides the correction required when conducting CPET with a BVF. Modified Bland-Altman plots display the mean difference between BVF and true values for: (c) Pulmonary ventilation ($\dot{V}_E$), +10.2 $l.min^{-1}$ ($p < 0.001$) and (d) Oxygen uptake ($\dot{V}O_2$), +5.6 $ml.min^{-1}.kg^{-1}$ ($p < 0.001$). Data points represent the middle five of seven breaths subsequently averaged for each 10 W increment of power output. Reference ranges are from patients (n = 3168) who underwent CPET before major surgery; mean (SD) $\dot{V}_E$ 49.8 (17.9) $l.min^{-1}$ and $\dot{V}O_{2\,peak}$ 16.1 (5.0) $mlO_2.min^{-1}.kg^{-1}$.

test to volitional exhaustion with online breath-by-breath respiratory gas analysis (MedGraphics Ultima Series, Saint Paul, MN, USA) [5]. Modified Bland-Altman plots determined mean differences and course of bias. Interpretive implications for surgical risk stratification in a separate group of 618 patients who had previously undergone CPET before surgery for colorectal cancer were used for comparison.

A strong positive correlation was observed between the BVF and true value trials ($r^2 = 0.956$, $p < 0.001$). The BVF resulted in a systematic error and (mean) overestimation of pulmonary ventilation ($\dot{V}_E$, +10.2 $l.min^{-1}$, $p < 0.001$) and corresponding oxygen uptake ($\dot{V}O_2$, +5.6 $ml.min^{-1}.kg^{-1}$, $p < 0.001$) (Figure 1B–D, including corrective equation). Failure to account for these differences would have meant that 2.8 % of colorectal patients would have been misleadingly classified as being unfit (anaerobic threshold < 11 $mlO_2.kg^{-1}.min^{-1}$ [5]) compared with the authentic value of 53%.

Collectively, the findings indicate that CPET can be safely performed with a specialist BVF, minimising potential for transmission of aerosolised particles. The systematic overestimation driven by inflated measurement of gas flow across the mouthpiece pneumotach can be corrected for, allowing metrics of $\dot{V}O_2$ to be (re)calculated with accuracy and precision. These findings should help re-establish safe CPET services in the clinical setting to guide and refine physiological stage-directed patient care.

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B.2. Conference Abstracts

33 Does initial clinical impression predict cardiopulmonary exercise testing performance?

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Recognising frailty in patients pre-operatively is important as they have higher mortality and are less likely to return to baseline functional status post surgery [1]. Valid and reliable assessment of functional capacity is an important part of pre-operative evaluation [2]. Initial clinical impression is considered useful to identify frail patients during pre-operative assessment, though little research exists to validate this. By comparison, cardiopulmonary exercise testing (CPET) reliably predicts postoperative outcomes.

Methods

During pre-operative assessment in our CPET clinic, an initial clinical impression for each patient was prospectively formed by two experienced clinicians before history taking. Each patient was judged 'frail' or 'not frail' by initial subjective assessment. Clinical notes were reviewed and patients considered either 'fit' or 'unfit' based on severity of comorbidities. This information was compared against anaerobic threshold (AT), postoperative risk prediction by CPET and ASA status. Data were analysed using the Chi-square automatic interaction detection decision tree technique method (SPSS).

Results

In total, 133 patients who had CPET testing in 2016 were included (age range 45–89, 44% female, 56% male). The majority (64%) of patients were scheduled for colorectal surgery. Four patients were unable to perform CPET and 18 (14%) had an indeterminate AT. Twenty-six percent of patients who were frail by initial clinical impression were fit by notes review. Of those with an AT < 11 $mlO_2.kg^{-1}.min^{-1}$, 35% were deemed not frail by clinical impression whereas 39% were frail; the remainder of patients had an indeterminate AT. Of those with an AT > 11 $mlO_2.kg^{-1}.min^{-1}$, 26% were deemed frail by clinical impression; 28% of patients who were not frail by clinical impression were intermediate/high risk by CPET criteria.

Discussion

There appears to be poor agreement between first impression 'eyeballing' by clinicians and CPET performance. Approximately one-third of patients deemed fit by first clinical impression or notes review were higher risk by CPET criteria. This study suggests that snapshot clinical opinions of frailty status gained in the first minute of patient encounter often result in inaccurate assessment of patient risk. We have shown that many patients who are deemed fit on clinical impression have CPET results that put them in a higher risk group postoperatively. Caution is warranted when using 'gut instinct' as a predictor of peri-operative risk assessment.

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87 Frailty scoring is moderately associated with cardiopulmonary exercise testing performance in patients scheduled for major intra-abdominal surgery

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Cardiopulmonary exercise testing (CPET) is an objective, dynamic measure of physiological function that informs shared decision making and guides peri-operative care of patients undergoing major intra-abdominal surgery. An anaerobic threshold < 11 $ml.kg^{-1}.min^{-1}$ and peak VO_2 < 15 $ml.kg^{-1}.min^{-1}$ are common cut-points used in peri-operative risk assessment [1]. However, CPET is both costly and time consuming. Frailty scoring is a multidimensional patient evaluation that can identify markers of reduced physiological reserve. Routine pre-operative frailty assessment is recommended by the British Geriatric Society [2]. We hypothesised that frailty scores would identify patients with lower levels of cardiorespiratory fitness.

Methods

We conducted a service evaluation to compare existing frailty scoring systems and their components with CPET performance. We analysed patients age ≥ 65 years presenting to our CPET clinic prior to major elective intra-abdominal surgery over a 6-month period. Patients completed both the Edmonton Frail Scale (EFS) and Hopkins Frailty Score (HFS), which have both been validated in surgical populations [3]. Frailty scoring preceded CPET and followed the guidance of the original authors. Functional measures included grip strength and gait speed.

Results

Data from 52 patients were analysed (23 male), mean age 74.7 years. The EFS identified 3/52 (6%) as frail. The HFS identified 7/52 (13%) with frailty. Mean EFS score was 3.32 (SD 2.47), mean HFS score was 1.27 (SD 1.22). Mean peak VO_2 was 15.9 $ml.kg^{-1}.min^{-1}$ (5.4) and mean anaerobic threshold 11.6 $ml.kg^{-1}.min^{-1}$ (2.7). Anaerobic threshold did not correlate with either frailty scores but 37% (19/52) of patients had either an anaerobic threshold < 11.0 $ml.kg^{-1}.min^{-1}$ or were unable to manage a CPET. However, both frailty scores and their components had moderate but statistically significant correlation with peak VO_2. The walking tests provided the best positive predictive value for peak VO_2.

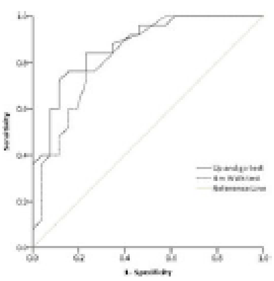

Figure 1 ROC curves for predicting VO_2 peak < 15 $ml.kg^{-1}.min^{-1}$ from the timed up and go test and 4 m walk test. AUC 0.87 – timed up and go test (95% CI 0.78–0.97, p < 0.01) and 0.83–4m walk test (95% CI 0.72–0.94, p < 0.01).

Discussion

Frailty scores had moderate correlation with CPET performance. The frailty domains that assessed actual physical activity (timed up and go test and 4 m walk test) were better predictors of CPET performance. Further work is required to demonstrate whether these frailty tests are better than CPET in predicting postoperative outcomes after major surgery.

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92 Do echocardiographic parameters correlate with cardiopulmonary exercise testing performance?

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In the UK, the most common specialist investigation before major non-cardiac surgery is transthoracic echocardiography, which has a low positive predictive value for identifying peri-operative cardiac events [1]. By comparison, functional cardiorespiratory fitness determined by cardiopulmonary exercise testing (CPET) does predict postoperative outcomes after many surgical interventions [2]. We aimed to assess the correlation between echocardiographic measurement of left ventricular function and CPET performance.

Methods

Using a retrospective analysis of all patients undergoing CPET over a 75-month period, we extracted those who had an echocardiogram within 90 days of CPET (pre- or post-operatively), where there was no history of myocardial infarction between tests. We compared commonly reported CPET variables with echocardiographic measurement of left ventricular function (ejection fraction).

Data were analysed using Spearman rank correlation and Pearson correlation coefficient tests and presented as scatter plots.

Results

There were 1304 patients who had undergone CPET between 2009 and 2016 (461 female, 843 male, age range 18–94 years). Of these, 146 patients had echocardiograms performed within 90 days of CPET testing (54 female and 92 male, age range 24-89 years). The majority of patients (49%) were listed for major colorectal surgery. There was no correlation between anaerobic threshold (AT) ($r = 0.04$, $p = 0.61$), peak VO_2 ($r = -0.10$, $p = 0.23$), ventilatory equivalent for CO_2 (VE/VCO_2) ($r = -0.07$, $p = 0.38$) and exercise time with left ventricular ejection fraction ($r = -0.07$, $p = 0.44$) (Fig. 1).

Discussion

There appears to be no correlation between ejection fraction measured by echocardiography and commonly reported CPET variables. Routine pre-operative echocardiography does not therefore appear to predict functional capacity. CPET variables have been shown to predict outcomes in non-cardiac surgery and these data would suggest that ejection fraction measured by resting echocardiography should not be used as a surrogate for functional capacity in order to infer pre-operative fitness and postoperative survival.

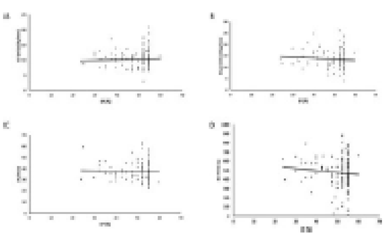

Figure 1 A: AT vs. ejection fraction, B: Peak VO_2 vs. ejection fraction, C: VE/VCO_2 vs. ejection fraction and D: exercise time vs. ejection fraction.

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CONTROL ID: 3024208

TITLE: High intensity exercise training prior to major elective surgery is well tolerated and associated with impressive cardiopulmonary improvement.

PRESENTATION TYPE: General Communication

CURRENT SPECIAL INTEREST GROUP: Human Physiology

AUTHORS (FIRST NAME, LAST NAME): George Rose[1], Thomas A. Calverley[1], Hayato Tsukamoto[1], David Byfield[1], Richard Davies[2], Ian Appadurai[2], Damian M. Bailey[1]

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ABSTRACT BODY:

Abstract Body : Impaired cardiorespiratory fitness (CRF) is associated with poor post-operative outcome following major surgery (Moran et al., 2016). Given its importance, approximately 30,000 preoperative cardiopulmonary exercise tests (CPET) are conducted in the UK each year to assess patient risk and plan care (Levett et al, 2018). Exercise training can improve CRF prior to surgery (West et al. 2015), however the current evidence base is lacking. Thus, we conducted a clinical case study to address feasibility and benefits of high intensity interval training (HIIT).

A 70 year-old female who underwent an oesophagectomy for oesophageal cancer developed ischaemia of the gastric conduit and was left with a pharyngostomy, and feeding jejunostomy. Further surgery for restoration of the upper gastrointestinal tract with a colonic interposition was considered, however the patient's fitness for surgery was stratified as high-risk. The medical history also included a myocardial infarction and coronary artery bypass graft. Following CPET to determine baseline fitness, a 10-week supervised HIIT intervention was conducted. Three exercise sessions of 40 minutes duration separated by 48 hours recovery were completed each week using cycle ergometry. Sessions comprised six, two-minute bouts of heavy exercise (50% difference between power output at peak exercise and anaerobic threshold (AT)) interspersed by three minutes of moderate exercise (80% power at AT) based on previous research (West et al. 2015). Heart rate (12-lead ECG) and blood pressure was monitored during exercise. A CPET was conducted every two weeks and HIIT intensity adjusted accordingly.

The HIIT intervention was well tolerated with no adverse events occurring, and 29 of 30 sessions completed. After 10 weeks, pulmonary oxygen uptake at peak exercise and AT increased by 36 and 27% respectively (18.6 vs 13.7 and 10.5 vs 8.3 $ml.kg^{-1}.min^{-1}$) and traversed a fitness stratification threshold of 15 $ml.kg^{-1}.min^{-1}$ for peak oxygen uptake. The patient was referred for surgery.

Despite the high intensity exercise, HIIT proved feasible, safe, and well tolerated. Impressive cardiopulmonary adaptation occurred in excess of variation typical of repeated measures (Rose et al., 2018). Improved CRF over a short period of time enabled the patient to be classified as "fit" for surgery, and thus supports investigating HIIT in future trials as an adjunct prior to major surgery.

Reference 1: Levett et al. (2018). Br J Anaesth 120, 484-500.

Reference 2: Moran et al. (2016). Br J Anaesth 116, 177-191.

Reference 3: Rose et al. (2018). Br J Anaesth 120, 1187-1194.

Reference 4: West et al. (2015). Br J Anaesth 114, 244-251.

CONTROL ID: 2270444
CURRENT SPECIAL INTEREST GROUP: Cardiovascular, Respiratory and Autonomic Control (CRAC)
CURRENT SUB-CATEGORY: None
PRESENTATION TYPE: General Communication

TITLE: **Sensitivity and specificity of manual versus automated methods of anaerobic threshold detection in patients undergoing colorectal surgery; implications for clinical outcomes?**

AUTHORS (FIRST NAME, LAST NAME): George A. Rose[1], Richard Davies[2], Ian Appadurai[2], Damian Bailey[1]
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ABSTRACT BODY:

Abstract Body : **Background:** Cardiopulmonary exercise testing (CPX) is used to determine cardiorespiratory fitness in patients prior to major surgery given its association with post-operative survival. Typically an automated anaerobic threshold (AT) value of <11.0 ml $O_2.kg^{-1}.min^{-1}$ (Older et al., 1999) has been employed as an objective biomarker of increased perioperative risk. In the present study, we compared to what extent differences between automated versus manual (gold-standard) methods of AT detection have the theoretical potential to influence surgical risk stratification.

Methods: A randomised sample of 213 patients scheduled for elective colorectal surgery who underwent CPX testing were retrospectively examined. Manual AT results were calculated using the gold standard 'V-slope' method (Beaver et al., 1986) and confirmed by two independent clinicians. Automated AT results were compiled using default settings in Breeze software (Medgraphics, UK). Ventilatory equivalent for CO_2 (VE/VCO_2) slope and respiratory exchange ratio (RER) were also recorded at both Manual and Automated ATs. Following confirmation of distribution normality (Shapiro *W* Wilks tests), data were analysed using a combination of paired samples *t*-tests and Chi-Squared tests. Data are expressed as mean ± SD and significance established at $p < 0.05$.

Results: Pulmonary oxygen uptake (VO_2) at the AT was 11.0 ± 3.0 versus 12.5 ± 3.8 $ml.kg^{-1}.min^{-1}$ for the Manual and Automated methods respectively ($p < 0.05$). One hundred and twelve ATs <11.0 ml $O_2.kg^{-1}.min^{-1}$ were reported for the Manual versus 70 for the Automated method ($p < 0.05$). Fifty two false negatives were reported for the Automated method (sensitivity 55%, specificity 91%).

Conclusions: Automated detection of the AT overestimates VO_2 by 13% and is associated with a high rate of type II errors (false negatives). This could result in some patients transcending risk stratification boundaries thus leading to incorrect decision making and inappropriate surgical risk stratification. Despite the ease of use of automated software based AT predictions, clinicians should be encouraged to use the manual and gold standard V-slope method for a more accurate assessment of patient cardiorespiratory fitness.

Reference 1: Beaver et al. (1986). *J Appl Physiol* **60(6),** 2020-2027
Reference 2: Older et al. (1999). *Chest* **116,** 355-362