Validation of submaximal heart rate recovery as a perioperative risk measure

Dr. Cara Mae Hughes

BM, MSc, FRCA

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College of Medical, Veterinary and Life Sciences

University of Glasgow

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Abstract

The number and complexity of patients presenting for surgery is increasing, with postoperative morbidity placing considerable burden on the health service, as well as negatively impacting patients' quality and length of life. Effective preoperative risk stratification assesses the likelihood of poor postoperative outcomes so appropriate perioperative strategies can be implemented to reduce the incidence and severity of complications. Current risk stratification modalities include risk scores, biomarkers and assessment of cardiorespiratory fitness via exercise testing. The predictive value of these modalities however is variable. Preoperative risk scores involve a degree of subjectivity, particularly in the assessment of functional capacity. Cardiorespiratory fitness as measured by cardiopulmonary exercise testing (CPET) is an objective measure and associated with postoperative outcome. However, CPET is resource-intensive and not appropriate for all patients.

The aim of this thesis was to assess the utility of heart rate recovery (HRR) after submaximal exercise as a preoperative risk measure. Heart rate recovery is a marker of cardiac vagal tone and is prognostic for mortality and cardiovascular events in patients with cardiovascular disease and the general population. Systematic review performed as part of this thesis demonstrated that impaired HRR is associated with poor postoperative outcomes in individual studies, although evidence is limited (Chapter 2). Subsequently it was hypothesised that submaximal HRR could provide an objective preoperative risk prediction measure with broad applicability.

The validity of submaximal HRR in the perioperative population was investigated. The study was performed in three hospitals in the West of Scotland. Eighty-four patients (aged over 50 years) performed a submaximal step test in pre-assessment clinic or the ward prior to elective noncardiac surgery, with continuous electrocardiography for determination of HRR parameters. Perioperative data was collected, including cardiac troponins for the primary outcome of postoperative myocardial injury (PMI). Criterion, predictive, face, construct and concurrent validity were assessed in a series of investigations.

The first investigation of this thesis (Chapter 6) explored the predictive value of submaximal HRR in a cohort of 64 patients who underwent the step test and surgery, with PMI data for analysis. A range of different HRR parameters were assessed for predictive value for PMI, including absolute values, area under the heart rate recovery versus time curve and effort-corrected values, to both proportion of age-predicted maximum HR and proportion of predicted maximum power output reached. Six of the parameters demonstrated predictive value for PMI (area under the receiver operator curve (AUROC) > 0.64 for all), comparable to preoperative risk prediction measures currently in use. Submaximal HRR measured one minute after exercise cessation (HRR_1) demonstrated fair predictive value for PMI (AUROC 0.69, 95% confidence interval 0.55 – 0.82). Furthermore, addition of submaximal HRR_1 improved the predictive performance of a selection of preoperative risk scores in current use.

Secondary analyses (Chapter 7) explored the face validity of submaximal HRR in 72 patients who underwent both the step test and surgery. Submaximal HRR_1 was associated with renal complications and intensive care admission, indicating face validity. However, there was no association between other secondary outcomes and HRR parameters.

The third investigation (Chapter 8) explored construct validity of submaximal HRR in 81 patents who underwent the step test and NT-ProBNP measurement, DASI, SORT, RCRI and POSSUM risk calculation. Submaximal HRR_1 demonstrated construct validity via significant association with SORT mortality; ACS NSQIP SRC risk of any postoperative complication and length of hospital stay; DASI; RCRI and POSSUM mortality and morbidity risk.

The fourth investigation (Chapter 9) explored both criterion and concurrent validity of submaximal HRR in 12 patients who underwent the submaximal step test and CPET. Submaximal HRR did not demonstrate association with anaerobic threshold (AT), peak oxygen consumption or the ventilatory equivalent of carbon dioxide at AT and so criterion validity was not demonstrated. Concurrent validity was not reliably demonstrated, which may reflect the different aspects of cardiorespiratory fitness measured by HRR and CPET. Patients tolerated both

exercise tests well but found the step test more comfortable and acceptable to perform (Chapter 10).

The work within this thesis confirms that submaximal HRR is a well-tolerated, feasible and valid measure in the perioperative population. From the range of HRR parameters measured, submaximal HRR_1 consistently performed well, demonstrating predictive, face and construct validity. Future work may focus on the incorporation of submaximal HRR_1 into preoperative risk assessment models; HRR measurement in the community; and integration of submaximal HRR into prehabilitation programmes.

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Author's Declaration

I declare that, except where reference is made to the contribution of others, this thesis is a result of my own work, written entirely by myself and has not been submitted for any other degree at the University of Glasgow or any other institution.

Recruitment to the study, data analysis, and the writing of this thesis was performed solely by myself. I performed the majority of data collection, with the remainder carried out by individuals acknowledged.

The section on postoperative myocardial injury (Section 1.6) is adapted from an article written by myself and published in BJA Education in October 2023. I was the primary author with guidance from Prof. Ben Shelley and Prof. Gareth Ackland.

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Definitions/Abbreviations

4AT	4 A's test for delirium
6MWT	Six-minute walk test
AAA	Abdominal aortic aneurysm
ACE	Angiotensin-converting enzyme
ACS	American College of Surgeons
AF	Atrial fibrillation
AHA	American Heart Association
AKI	Acute kidney injury
ANS	Autonomic nervous system
ASA	American Society of Anaesthesiologists
AT	Anaerobic threshold
ATS	American Thoracic Society
AUC	Area under the curve
AUROC	Area under the receiver operating characteristic
BMI	Body mass index
BNP	B-type natriuretic peptide
BPM	Beats per minute
CCB	Calcium channel blocker
CFS	Clinical Frailty Score
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPC	Cardiopulmonary complications
CPET	Cardiopulmonary exercise test
CPOC	Centre for Perioperative Care
CRF	Case report form
CV	Coefficient of variation
CVS	Cardiovascular system
DaOH	Days alive and out of hospital
DASI	Duke Activity Status Index
ECG	Electrocardiography
ECHR	Effort-corrected to proportion of age-predicted maximum heart rate reached

ECW	Effort-correction to proportion of maximum predicted power output reached
eGFR	Estimated glomerular filtration rate
ENT	Ear, nose and throat
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
FWA	Full waveform analysis
GI	Gastrointestinal
GJNH	Golden Jubilee National Hospital
HR	Hazard ratio
HR_{max}	Maximum heart rate
HRR	Heart rate recovery
HRV	Heart rate variability
hs-TnT	High-sensitivity Troponin T
IBI	Inter-beat interval
ICC	Intra-class coefficient
ICU	Intensive care unit
IHD	Ischaemic heart disease
IQR	Interquartile range
MACE	Major adverse cardiovascular events
MAKE	Major adverse kidney events
MAP	Mean arterial pressure
METS	Measurement of Exercise Tolerance before Surgery
MI	Myocardial infarction
MINS	Myocardial injury after noncardiac surgery
NADPH	Nicotinamide adenine dinucleotide phosphate
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NIBP	Non-invasive blood pressure
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRI	Net reclassification index
NSQIP	National Surgical Quality Improvement Program
NT-ProBNP	N-terminal pro b-type natriuretic peptide

OR	Odds ratio
PACU	Post-anaesthesia care unit
PCPIE	Patient, Carer and Public Involvement and Engagement
$P_{ET}CO_2$	Partial pressure of end-tidal carbon dioxide
$P_{ET}O_2$	Partial pressure of end-tidal oxygen
PMI	Postoperative myocardial injury
PNS	Parasympathetic nervous system
POD	Postoperative day
POETTS	Perioperative Exercise Testing and Training Society
POMS	PostOperative Morbidity Survey
POSSUM	Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
PVD	Peripheral vascular disease
QoR-15	Quality of Recovery 15
QUIPS	Quality in Prognostic Studies
RCRI	Revised Cardiac Risk Index
RCT	Randomised controlled trial
RER	Respiratory exchange ratio
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
RPE	Rating of perceived exertion
SBP	Systolic blood pressure
SD	Standard deviation
SET	Submaximal exercise test
SG	Savitzky-Golay
SIRS	Systemic inflammatory response syndrome
SNS	Sympathetic nervous system
SORT	Surgical Outcome Risk Tool
SRC	Surgical Risk Calculator
STeP-COMPAC	Standardized Endpoints in Perioperative Medicine – Core Outcome Measures in Perioperative and Anaesthetic Care
T2DM	Type 2 diabetes mellitus
TNF	Tumour necrosis factor
UHC	University Hospital Crosshouse
UHH	University Hospital Hairmyres

UK	United Kingdom
USA	United States of America
VCO_2	Carbon dioxide production
VE	Minute ventilation
VERVE	Validation of heart rate recovery as a Perioperative risk measure
VISION	Vascular Events in Noncardiac Surgery Patients Cohort Evaluation
VO2	Oxygen consumption
VT	Tidal volume

Chapter 1 Introduction

1.1 Perioperative risk

1.1.1 Epidemiology of postoperative complications

There are approximately 1.5 million major[A] operations performed in the UK annually[2], with the majority carrying an intermediate (1-5%) or high (>5%) mortality risk[3,4]. The number of operations performed annually is increasing[5] with it being estimated that approximately 60% of people in England will undergo surgery in their lifetime[6]. This increase in numbers is coupled with an increase in both population age and prevalence of comorbidities leading to a larger number of complex perioperative patients presenting for surgery[7]. Patients with chronic disease[B] have a nearly ten-fold increase in the risk of postoperative death within 90 days of surgery[9]. Even with these challenges, surgical mortality is reducing; in 2017 all major NHS surgery was found to have a 30-day mortality of 1.1%[2]. However despite reducing mortality, postoperative morbidity and complications remain a significant problem placing a large burden on both the NHS and wider society. A meta-analysis of postoperative morbidity found an overall complication rate of 22.6% across over 130000 operations, with associated reduced survival[10]. Postoperative morbidity has an immediate increased cost to the health service, resulting in longer hospital stays, potential need for higher levels of care and potential requirement for re-operation. In the longer term, postoperative morbidity can result in increased disability requiring long term care or hospital re-admissions[11]. Postoperative complications worsen patients' quality of life with this effect dependent on the severity of the complication[12,13]. Postoperative complications affect wider society by adding a financial burden on limited NHS resources, and reducing the ability of patients and their carers to contribute towards the economy[14].

[A] "Major" in this context is identified as per the British United Provident Association Schedule of Procedures[1]

[B] Defined in this context by the WHO International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] codes[8]

1.1.2 The surgical stress response and development of postoperative complications

The trauma of surgery places physiological stress on the body, often referred to as the surgical stress response. This response results in an increase in oxygen consumption, primarily via entering a catabolic state which can continue for several days postoperatively[15]. Both the severity and duration of the surgery, and the patient's preoperative health contribute to the extent of the surgical stress response. Although an adaptive response to tissue injury, the surgical stress response can be detrimental, increasing the risk of postoperative morbidity and organ injury. Broadly, the surgical stress response consists of a neuroendocrine-metabolic response and an inflammatory-immune response (Figure 1)[16].

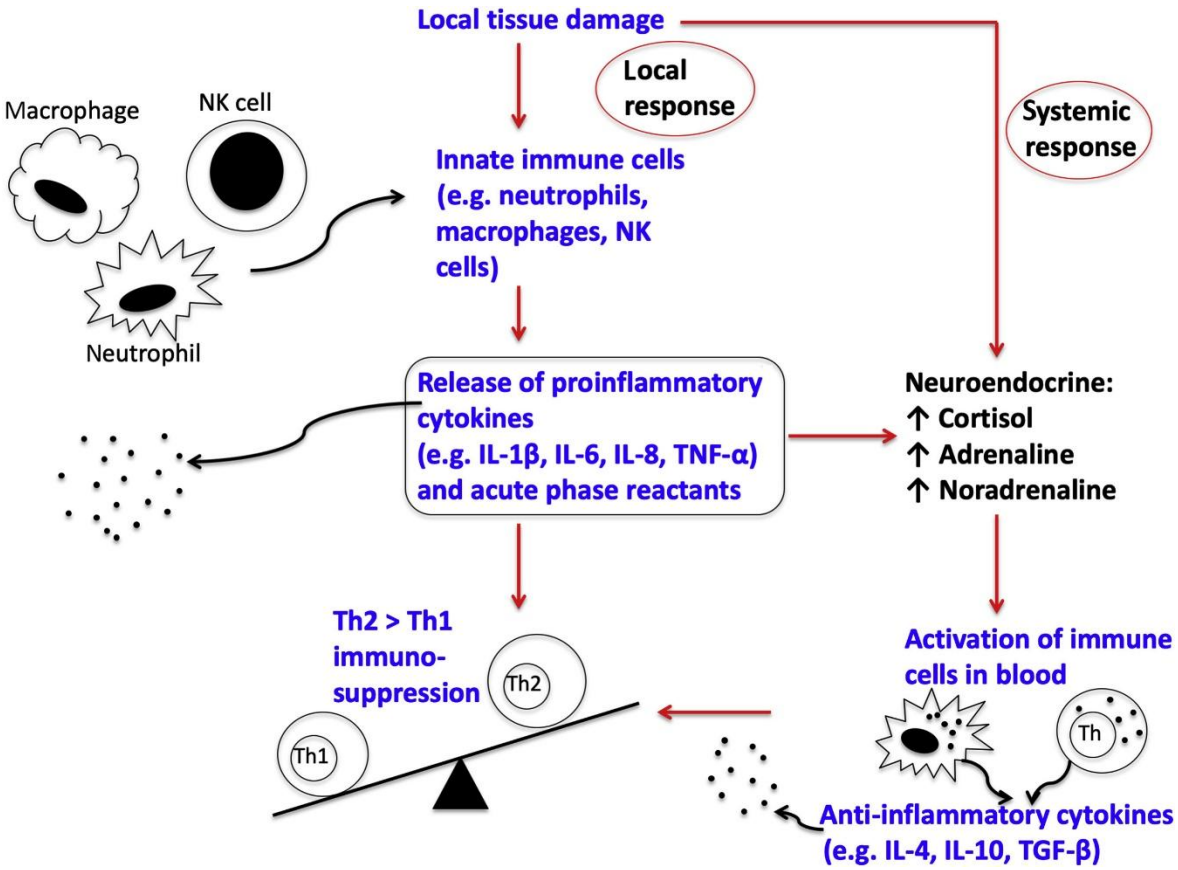


Figure 1 Local and systemic immunological response to surgical tissue damage including neuroendocrine effects (surgical stress). Image from Cusack & Buggy[16].

Tissue damage leads to activation of the sympathetic nervous system (SNS) increasing blood flow to the site of surgery and active muscles but reducing

blood flow to organs such as the kidneys and gastrointestinal tract. Glycogenolysis and hepatic and muscle lipolysis increase leading to hyperglycaemia. The metabolic response consists of increased cortisol secretion which can remain high for at least seven days after major surgery. Cortisol promotes catabolism, antagonises the action of insulin and is immunosuppressant[17]. Catabolism frees up substrates used for tissue repair but, if severe or prolonged, leads to loss of skeletal muscle (sarcopenia), impaired wound healing and increased rates of infection[18]. Sarcopenia in particular is associated with loss of function and independence postoperatively[19]. Tissue injury causes an inflammatory response, which if imbalanced (pro-inflammatory cytokines outweigh anti-inflammatory modulators) can lead to a systemic inflammatory response syndrome (SIRS), immunodeficiency and sepsis. More specifically, there is also a relative increase in the T-helper 2:T-helper 1 ratio which is associated with impaired wound healing, sepsis, cancer recurrence and multi-organ failure[20].

Patients may be predisposed to a more detrimental response to surgery and the surgical stress response if their neuroendocrine, metabolic and immune system are already impaired. For example, increasing age is associated with both increased secretion of cortisol and loss of diurnal variation, and autonomic imbalance with loss of vagal tone. Frailty and pre-existing cardiovascular deconditioning are also linked to chronic neuroendocrine dysfunction[15]. Preoperative metabolic syndrome, consisting of obesity, insulin resistance and hyperlipidaemia is associated with a significantly increased risk of postoperative morbidity and mortality[21]. Preoperative inflammation has been associated with postoperative complications after 30-days[22] and postoperative myocardial injury[23].

Cardiorespiratory fitness is the ability of the cardiovascular and respiratory systems to supply oxygen to working skeletal muscles plus the efficiency of the muscles to utilise the oxygen to produce energy for movement[24]. Pre-existing comorbidity, including specific diseases but also chronic inflammatory, neuroendocrine and autonomic impairment, can lead to reduced cardiorespiratory fitness[15,24]. Comorbidity and fitness are inextricably linked, with comorbidity reducing the ability to perform exercise and contributing to

mechanisms which worsen cardiorespiratory fitness; and a lack of physical activity and declining cardiorespiratory fitness contributing to maladaptive mechanisms described above including autonomic dysfunction and loss of vagal tone. The term “functional capacity” can be used to describe the ability of the body to increase and maintain tissue oxygen delivery in response to the physiological stress and increased oxygen demand that surgery places on the body. Although the mechanisms are different to exercise, inability to compensate for this increased oxygen demand increases the risk of postoperative complications including delayed wound healing, impaired immune function and organ failure[16]. Therefore, an individual with a higher functional capacity is likely able to maintain oxygen delivery under surgical stress better than an “unfit” individual. Although a broad term, functional capacity encompasses the underlying physiological reserve a patient has against the insult of surgery and so provides a marker of both underlying comorbidity and cardiorespiratory fitness.

1.2 Assessment of perioperative risk

1.2.1 Purpose

Assessment of pre-existing comorbidity and functional capacity forms the fundamental pretext underlining preoperative assessment and risk stratification for patients. A patient’s capacity to exercise is a surrogate marker for how their body will cope with the increased physiological demand of surgery and attenuate the maladaptive effects of the surgical stress response. Effective risk stratification can guide shared-decision making conversations with patients and guide both intraoperative and postoperative decision making such as the postoperative level of care required. Current modalities for preoperative risk stratification range from subjective assessments, validated scoring systems, measurement of biomarkers such as brain natriuretic peptide (BNP), and exercise testing including cardiopulmonary exercise testing (CPET), an objective measure of cardiorespiratory fitness.

1.2.2 Surgical Outcome Risk Tool (SORT)

The SORT is a surgical preoperative calculator, originally developed in 2014, for prediction of the risk of death within 30-days of non-cardiac surgery[25]. The six

original variables (American Society of Anaesthesiologists (ASA) physical status grade, urgency of surgery, surgical severity, surgical specialty, presence of cancer and patient age) were prospectively derived from National Confidential Enquiry into Patient Outcome and Death (NCEPOD) data from 11219 patients and validated using data from 5569 patients in the UK. The tool was updated in 2020 with the addition of clinician's assessment of risk, thereby incorporating both objective and subjective assessment[26]. The investigators of this large cohort study found that SORT with clinical assessment of risk demonstrated improved discrimination (AUROC 0.92 (0.90-0.94)) compared to SORT alone (AUROC 0.90 (0.88-0.92)) and subjective assessment alone (AUROC 0.89 (0.86-0.91)). Subsequent external validation studies have duplicated the excellent discrimination value of the SORT in different clinical settings[27,28]. However, there are limitations; the tool is only valid to provide an estimated risk of 30-day mortality, an outcome which is rare and increasingly less important to patients[29]; and has only been validated in resource-rich countries, therefore its validity in resource-poor settings is unknown. Although intuitive that high-risk of death is equal to high-risk of complications, as the SORT score quantifies a patient's 30-day risk for mortality, it has an unproven inference for risk of postoperative complications. Its main utilisation is to facilitate discussions around postoperative destination for high-risk patients and to aid shared-decision making conversations with patients providing an objective, quantifiable risk of death. However, due to its lack of specificity in potential causes of death, it has limited use in targeted system/comorbidity-specific preoperative optimisation.

1.2.3 American College of Surgeons National Surgical Quality Improvement Program Surgical Risk calculator (ACS NSQIP SRC)

The ACS NSQIP SRC estimates the risk of postoperative complications, including death and predicted length of hospital stay within 30-days of surgery. The estimate is initially based on the type of procedure, alongside further preoperative data including age, sex, functional status, ASA physical status and comorbid status plus additional information if the patient is aged over 65 years. For each outcome, the risk for the individual patient is given alongside the

average risk. A colour-coded graph is also provided with above, average, or below-average risk given to aid communication with patients (Figure 2).

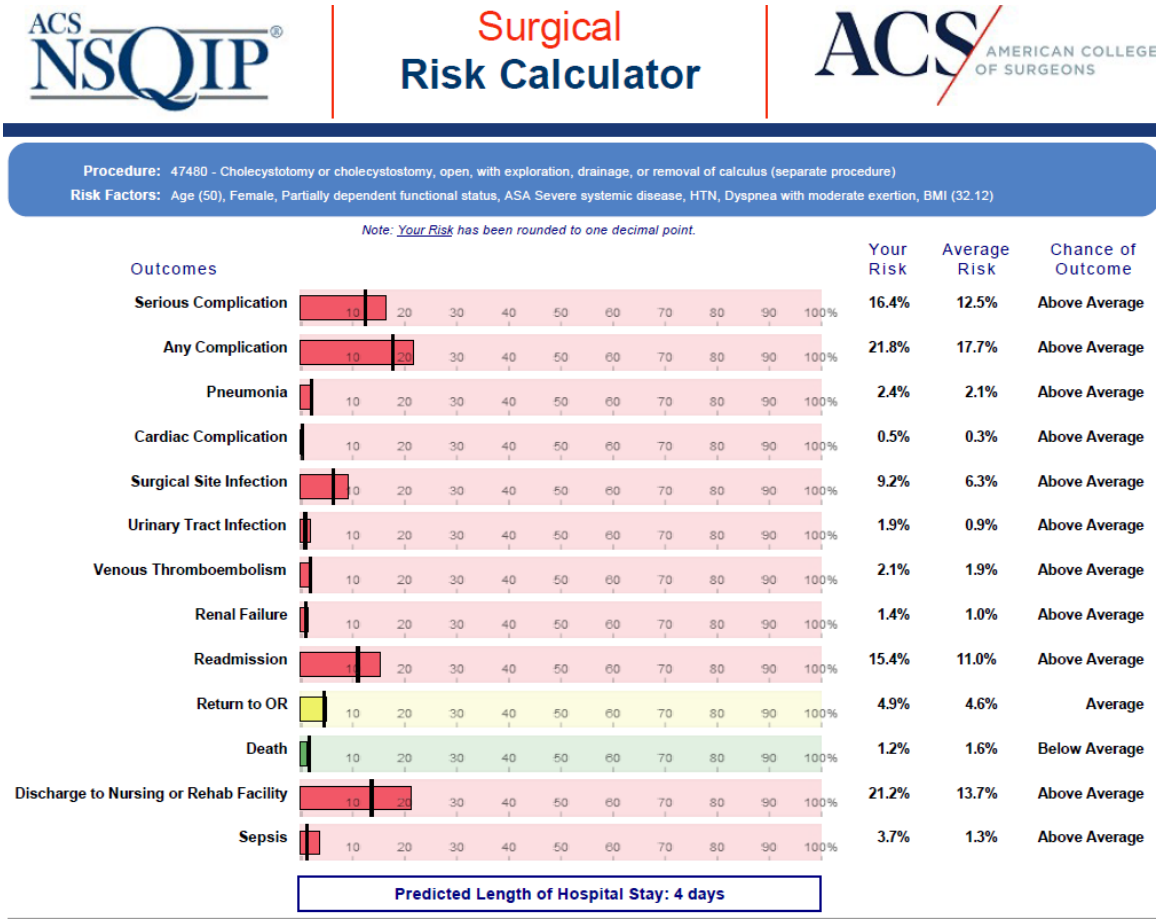


Figure 2 Example of outcomes output from ACS NSQIP SRC for hypothetical patient undergoing cholecystectomy[30].

The SRC aims to guide surgical decision-making and informed consent for a shared decision-making conversation regarding the suitability of surgery for the patient, rather than guiding perioperative conduct. The original calculator was developed in 2013 via logistic regression modelling using standardised clinical data from 393 North American hospitals participating in the ACS NSQIP, incorporating data from over one million patients. It demonstrated excellent predictive value with AUROCs of 0.94 (confidence intervals not described) for mortality and 0.82 for morbidity[31]. The current risk calculator was developed using data collected from over five million operations in the USA from 2016 to 2020, with the current iteration using machine-learning to recalibrate and update the model. The machine-learning model demonstrated improved discrimination and calibration[32].

The SRC is based on data predominantly from American hospitals with external validation studies out with North America demonstrating mixed results[33,34]. One from the Netherlands in 682 patients aged ≥70 years old, undergoing elective colorectal surgery, demonstrated SRC accurately predicted readmission rate, overestimated the rate of discharge not to home and underestimated all other outcomes. The AUROC for post-operative pneumonia in this population was 0.75 (0.67-0.83) and 0.70 (0.62-0.78) for discharge not to home, but poor for all other outcomes[33]. A retrospective validation study in 200 consecutive Australian patients undergoing head and neck microsurgery reconstruction found that the SRC demonstrated predictive value for pneumonia (AUROC 0.91 (0.85-0.98)) and urinary tract infection (AUROC 0.84 (0.67-0.92)) but for all other complications demonstrated an AUROC of ≤0.80[34]. These external validation studies show the potential discrepancy between the ability of risk scores to predict outcome when performed in different populations to the original data source population. Nonetheless it is widely utilised globally with recommendations for use in Europe (further detail in Section 1.2.8).

1.2.4 Duke Activity Status Index (DASI)

The Duke Activity Status Index is a 12-question assessment of functional status which determines how much activity a patient can do, with each answer weighted to give a maximum score of 58.2 (Table 1).

Table 1 Duke Activity Status Index questions with associated weighted score if the patient is able to do that activity[35].

Are you able to:	Score if "Yes" answered
Take care of yourself, that is, eat, dress, bathe or use the toilet?	2.75
Walk indoors, such as around your house?	1.75
Walk a block or two on ground level?	2.75
Climb a flight of stairs or walk up a hill?	5.50
Run a short distance?	8.00
Do light work around the house like dusting or washing dishes?	2.70
Do moderate work around the house like vacuuming, sweeping floors or carrying groceries?	3.50
Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	8.00
Do garden work like raking leaves, weeding or pushing a lawn mower?	4.50
Have sexual relations?	5.25
Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis or throwing a ball?	6.00
Participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?	7.50

The index was originally described in 1989 where the peak oxygen uptake (VO_{2peak})[C] of 50 participants was compared with their ability to perform activity. The index was then validated in another 50 participants, with DASI correlating significantly with VO_{2peak} (Spearman's correlation coefficient (ρ) 0.58, $p<0.0001$)[35]. The DASI is established for use as self-reported functional capacity in stable cardiac patients (undergoing elective diagnostic coronary angiography without acute coronary syndrome) with incremental prognostic value for significant angiographic coronary artery disease (adjusted hazard ratio (HR) 2.89

[C] Peak oxygen uptake is the oxygen uptake at the end of an incremental test and is indicative of peak exercise capacity (discussed more in Section 1.2.10.1)[36]

(2.39-3.50)) and major adverse cardiac events (MACE[D], AUROC 0.67 (0.66-0.69)) at three years[37]. More recently, the Measurement of Exercise Tolerance before Surgery (METS) trial demonstrated that only DASI scores were associated with predicting death or myocardial infarction (MI) within 30-days of surgery whereas subjective assessment, NT pro-BNP and cardiopulmonary exercise testing (CPET) were not associated with this outcome[38]. The METS trial was a multicentre international prospective study recruiting 1401 patients aged over 40 undergoing major non-cardiac surgery with one or more cardiovascular risk factor. All patients had functional capacity assessed via clinician subjective opinion (reported as metabolic equivalents), DASI questionnaire and VO_{2peak} via CPET plus preoperative NT-ProBNP was measured. The primary outcome was death or MI within 30-days of surgery, with myocardial injury a secondary outcome. The study found that clinician subjective opinion had no association with the study outcomes; VO_{2peak} only demonstrated an association with moderate or severe postoperative complications (adjusted odds ratio (OR) 0.86 (0.78-0.97)) and NT-ProBNP showed significant association with death or myocardial injury (adjusted OR 1.78 (1.21-2.62)) within 30-days of surgery. The DASI performed best with an adjusted OR of 0.91 (0.83-0.99)). Addition of DASI to the baseline model (Revised Cardiac Risk Index (RCRI)) improved prediction of 30-day MI or death (AUROC 0.59 to 0.67) and 30-day myocardial injury or death (AUROC 0.70 to 0.71). The DASI also demonstrated only moderate correlation with VO_{2peak} (ρ 0.41, $p<0.0001$). The authors suggest that DASI performs so well as it encompasses more than purely a patient's cardiovascular capacity, possibly also appraising frailty, musculoskeletal strength and self-imposed physical limitations[38]. The ultimate conclusion from the METS trial was that DASI score and NT-ProBNP (or similar natriuretic peptides) should supplant subjective assessment for the estimation of perioperative cardiac risk. A subsequent nested cohort analysis of the METs trial identified a DASI score of less than 34 as a cut-off for identification of patients at increased risk for MI, myocardial injury, moderate to severe postoperative complications and new disability[39]. The DASI questionnaire is an easy, inexpensive and understandable measure for patients

[D] MACE is a composite outcome of death, nonfatal myocardial infarction or stroke

to complete, which assesses true functional capacity rather than purely cardiovascular components.

1.2.5 Revised Cardiac Risk Index (RCRI)

The RCRI is a score formulated to identify the risk of cardiovascular complications after non-cardiac surgery. It was developed in 1999 by identifying six independent predictors of major cardiac complications in 4315 patients ≥50 years old undergoing elective major non-cardiac surgery in a single tertiary-care hospital. The independent predictors are: high-risk surgery, history of ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative insulin therapy and a preoperative serum creatinine >176.8μmol/L. Each predictor carries a score of one, with the total score indicating the patient's risk of major postoperative cardiovascular complications: zero corresponds to 0.5% risk, one to 1.3% risk, two to 4.0% risk and three or more to 9.0% risk. The RCRI also demonstrated predictive value for major cardiovascular complications with an AUROC of 0.78±0.02 in the entire study population[40]. The RCRI has been further validated in a large systematic review of cohort studies demonstrating association with major cardiac complications or death, either within 30-days of surgery or in hospital. Eighteen studies (124,032 patients) reported postoperative cardiac complications with a median AUROC of 0.69 (IQR 0.62-0.75). Pooled analysis was not performed due to high heterogeneity. The predictive value was lower for the seven separate vascular studies (pooled AUROC 0.64 (0.61-0.68)). The median AUROC for mortality was 0.62 (range 0.54 – 0.78) as reported by six studies. The conclusions from this systematic review were limited by poor quality studies but the authors suggest it is reasonable to use the RCRI to discriminate between high and low-risk patients (≥3 risk factors and <3 risk factors, respectively) undergoing mixed non-cardiac surgery[41]. The RCRI is easy to use and can act as a screening tool but is only validated to predict cardiovascular complications. Despite this is it utilised widely to guide perioperative decision making and is recommended for perioperative risk stratification by the Canadian Cardiovascular Society[42] (discussed further in Section 1.2.8).

1.2.6 Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM)

The POSSUM scores combine patients' physiological parameters and operative severity scores to calculate postoperative mortality and morbidity risk. The Portsmouth POSSUM (P-POSSUM) is validated for use in general surgery and the V-POSSUM for use in patients undergoing Vascular surgery. The original POSSUM score[43] (developed as an audit tool) grossly overestimated the risk of death. The P-POSSUM was developed by performing logistic regression on 1485 patients with alteration of the logistic regression equation for mortality but using the same physiological and operative parameters as in the original score (Table 2)[44].

Table 2 Physiological and operative parameters of the Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (P-POSSUM)[44].

Physiological Parameters	Operative Parameters
Age	Operative severity
Cardiac history	Multiple procedures
Respiratory history	Total blood loss
Blood pressure	Peritoneal soiling
Pulse rate	Presence of malignancy
Glasgow coma score	Mode of surgery
Haemoglobin level	
White cell count	
Urea concentration	
Sodium level	
Potassium level	
Electrocardiography	

The V-POSSUM was developed specifically for major arterial surgery to allow for the high-risk of these elective procedures. A separate POSSUM score exists for ruptured aortic aneurysm repair (rAAA-POSSUM) as this operation inherently carries a high mortality which is not comparable to most other (non-cardiac) operations[45]. In a large, retrospective external validation study comparing mortality risk scores in 31153 patients, P-POSSUM demonstrated predictive value for 30-day mortality (AUROC 0.89 (confidence intervals not described)) although this was less than the SORT score (AUROC 0.92)[27]. In a prospective study comparing SORT and P-POSSUM with subjective clinical opinion in 22631 patients, both methods overpredicted risk of 30-day mortality. Again, SORT demonstrated the best discrimination (AUROC 0.90 (0.88-0.92)) compared to P-POSSUM (AUROC 0.89 (0.88-0.91))[26].

There is conflict within the literature regarding the purpose of POSSUM scoring. Some maintain it was developed for audit purposes and to review either individual or departmental surgical performance; others purport its use as an individual perioperative risk estimation tool which can be used to convey information to patients. It is only validated as a tool for 30-day mortality and gives an indiscriminate risk for postoperative morbidity. The P-POSSUM is now 26 years old and so, as with all risk scores developed by logistic regression on a historical sample, will overestimate risk as surgical procedures and perioperative conduct become safer.

1.2.7 NT-ProBNP

B-type natriuretic peptide (BNP) is a hormone released by cardiac myocytes in response to stress, particularly mechanical stretch. There is also evidence that BNP is released in response to catecholamines and hypoxia[46]. It is synthesised as a prohormone (proBNP) and on release, it is split into the biologically active BNP and its inactive N-terminal proBNP (NT-ProBNP). Both can be measured within the blood, with NT-ProBNP demonstrating a longer half-life. B-type natriuretic peptide causes diuresis, vasodilation and reduced renin and aldosterone secretion thereby reducing cardiac preload and therefore myocardial stretch.

Measurement of BNP and NT-ProBNP is established in management of heart failure, where it is used as a screening tool, a prognostic tool and to assess response to therapy[47]. It demonstrates association with both the New York Heart Association class of severity of heart failure symptoms and echocardiographic findings. BNP has also been found to be a risk predictor in coronary artery disease and acute coronary syndrome, independent of heart failure[48]. In the perioperative setting, BNP and NT-ProBNP have demonstrated prognostic value for both cardiovascular complications and mortality in high-risk patients undergoing non-cardiac surgery[49]. NT-ProBNP has recently demonstrated predictive value (AUROC 0.70, no confidence interval described) for a composite of vascular death and myocardial injury after non-cardiac surgery (MINS, see Section 1.5) within 30-days of non-cardiac surgery, with improvement in prediction when combined with the RCRI (Section 1.2.5)[50]. In a prospective observational study of 200 patients undergoing intermediate/high-risk non-cardiac surgery, NT-ProBNP demonstrated a predictive value for a composite

endpoint of postoperative morbidity[E] (AUROC 0.68 (0.60-0.76)) when dichotomised by a threshold of 433 pg/ml[51]. Both BNP and NT-proBNP are recommended by the European Society of Cardiology for cardiac risk stratification in patients undergoing intermediate and high-risk non-cardiac surgery with cardiovascular risk factors[F52]. The Canadian Cardiovascular Society recommends measuring BNP or NT-ProBNP in patients aged ≥65 years, or ≥45 years with cardiovascular risk factors or with an RCRI >1 undergoing non-cardiac surgery. Identification of raised NT-ProBNP (>300pg/ml) indicates that patients should have heightened postoperative surveillance for cardiovascular complications including postoperative troponin measurement and ECG[42]. It is not common practice in the UK currently to measure NT-ProBNP in all high-risk surgical patients, predominantly due to the cost implications of the assay and uncertainty in how to subsequently investigate and manage the result. However, some centres may use it as a screening tool for further cardiovascular imaging e.g. preoperative transthoracic echocardiogram and/or "cardiovascular optimisation."

1.2.8 National Institute for Health and Care Excellence (NICE) and international guidelines on perioperative risk stratification

The National Institute for Health and Care Excellence (NICE) guidance document 'Perioperative Care in Adults' recommends using:

> *"a validated risk stratification tool to supplement clinical assessment when planning surgery, including dental surgery. Discuss the person's risks and surgical options with them to allow for informed shared decision making."*

However it provides no recommendations on which tools to use[53]. In the evidence review for the Guideline, the committee assessed the predictive value of the P-POSSUM, SORT and ACS-NSQIP SRC for postoperative mortality and morbidity. The quality of evidence was found to be low or very low with variable

[E] In this context, the primary outcome "postoperative morbidity" was a composite of rehospitalisation, acute decompensated heart failure, acute kidney injury and infection within 30-days of surgery

[F] Established cardiovascular disease, ≥65 years or ≥45 years with hypertension, dyslipidaemia, diabetes, smoker or family history of cardiovascular disease

predictive power, ranging from AUROCs of 0.6 to 0.9 for mortality and 0.6 to 0.7 for morbidity. Hence no firm recommendations were made by the panel, but the usefulness of a validated risk stratification tool to frame discussion about risk and, along with clinical judgement, to guide perioperative conduct was acknowledged[54]. In June 2021, the Centre for Perioperative Care (CPOC) endorsed comprehensive guidelines on preoperative assessment and optimisation[55]. Although recognising the lack of evidence base for these guidelines, they are more prescriptive, suggesting that all patients should be assessed for the impact of comorbid conditions on functional capacity and surgical outcome. They recommend all patients should have their individualised risk assessed using objective measures, with the SORT highlighted as it has been validated in a UK population. The DASI is recommended as a screening measure for functional capacity, with patients identified as having reduced capacity progressing to more objective measures of fitness e.g. CPET where available. These guidelines represent an aspirational service to patients, with little analysis of the quality of evidence or the impact of decisions based on scoring systems on patient outcomes. Additionally, a cost-analysis of investigations and subsequent changes to perioperative care was not undertaken.

International guidelines on preoperative risk stratification vary depending on patient population, local validation of measures and funding strategies. The joint European Society of Anaesthesiology and European Society of Cardiology Guidelines on cardiovascular assessment and management for non-cardiac surgery recommend the use of clinical risk indices, but not one particular score. Consideration of preoperative biomarker use is also advised (in contrast to UK guidelines), predominantly preoperative troponin and NT-ProBNP measurement in high-risk patients only. Similar to the NICE guidelines, the authors state that risk stratification tools should be used in conjunction with clinical assessment and should not dictate management decisions alone[52].

The Canadian Cardiovascular Society Guidelines recommend risk stratification of high-risk patients with the RCRI plus NT-ProBNP/BNP measurement (as per Section 1.2.7)[42]. If NT-ProBNP is ≥300 pg/ml or unavailable, they recommend postoperative cardiac troponin screening, a postoperative ECG and multidisciplinary postoperative care. Again, the authors acknowledge the limited

quality of evidence for these recommendations. The use of NT-ProBNP is based on cost-analysis of measurement compared with cardiac imaging and non-invasive cardiac stress testing.

Finally, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines recommend the use of a validated risk prediction tool to predict MACE with patients identified as low-risk not requiring further testing[56]. They recommend both the RCRI and ACS-NSQIP SRC as prediction tools. The ACS-NSQIP SRC is derived and validated from a North American population. Routine preoperative biomarker measurement is not recommended. Functional capacity assessment is recommended either via subjective metabolic equivalents questioning or the DASI. If a patient is identified to be high-risk via risk stratification tools and functional capacity assessment, pharmacological stress testing is recommended prior to surgery to identify patients who may benefit from cardiac optimisation prior to surgery[56].

1.2.9 Exercise testing

1.2.10 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing is a non-invasive, objective measurement of the body's response to the physiological stress of maximal exercise. Usually performed on a cycle ergometer, the patient begins at rest and progressively pedals at an increasing load until they are unable to continue, either due to patient fatigue or symptoms, or due to adverse signs such as ST segment changes. Cardiopulmonary exercise tests are considered maximal to the limit of patient tolerance. During the test, cardiovascular parameters are measured (ECG, non-invasive blood pressure (NIBP)) and both expired respiratory gases (oxygen (O_2) and carbon dioxide (CO_2)) and minute ventilation measured via a face mask connected to a rapid gas analyser and pressure-differential pneumotachograph, respectively. The test provides a comprehensive, integrated assessment of the patient's cardiovascular, respiratory, metabolic and muscular capacity, and is subsequently considered the gold standard exercise test for measuring aerobic capacity. Cardiopulmonary exercise testing has many applications including diagnostic and prognostic. It can be used to aid diagnosis of cardiorespiratory pathology in patients with significant dyspnoea or exercise

limitation; assess severity and response to treatment, particularly in heart failure or chronic obstructive pulmonary disease; and is validated to assess functional capacity in the perioperative setting. Many cardiorespiratory variables are both measured and derived during CPET with measurements displayed on a nine-panel plot for interpretation (Figure 3). However, peak oxygen consumption (VO_{2peak}), oxygen consumption at anaerobic threshold (AT) and the ventilatory equivalent of carbon dioxide at AT (VE/VCO_2) are the most widely described and subsequently shown to be the variables with the best predictive capability[57-60].

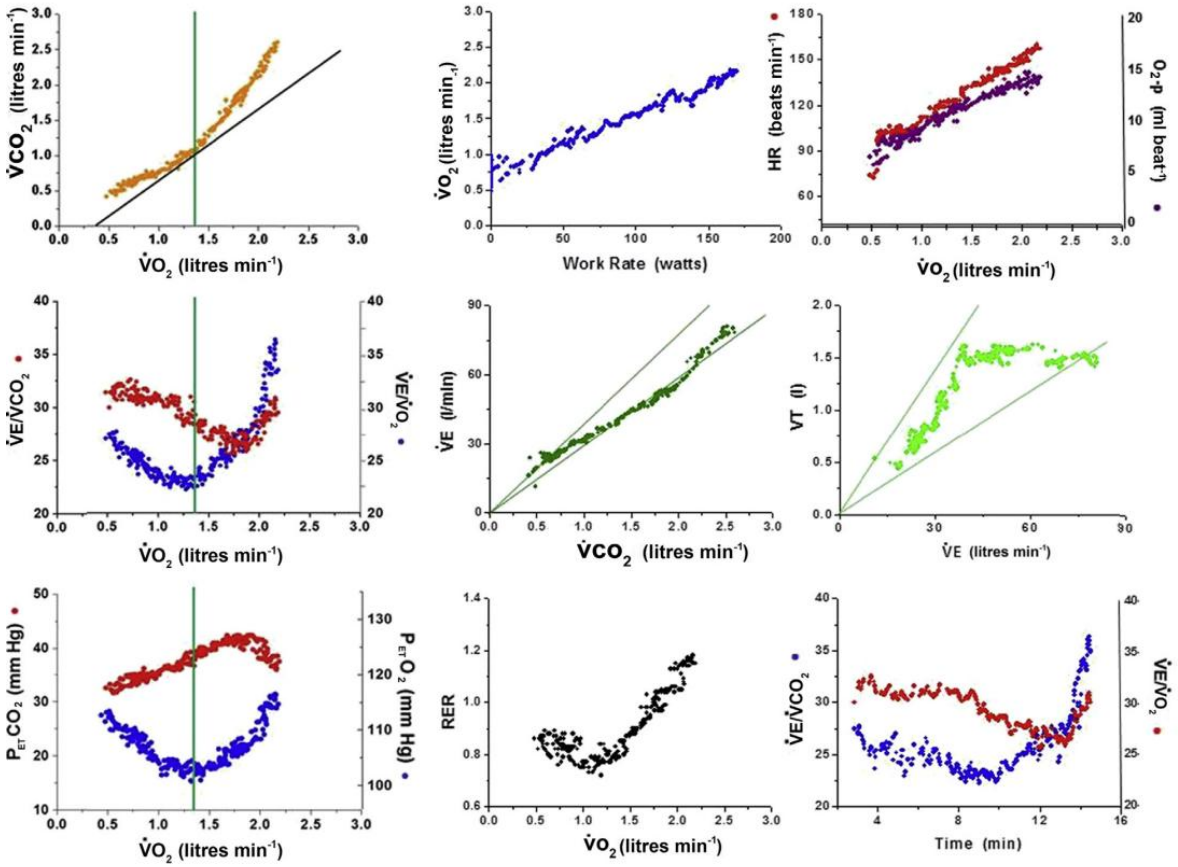


Figure 3 Example of a nine-panel plot in a healthy individual. Taken from Levett et al[57]. VCO_2: carbon dioxide production; VO_2: oxygen consumption; O_2.p: oxygen pulse (oxygen consumption divided by heart rate); VE: minute ventilation; VT: tidal volume; $P_{ET}CO_2$: end-tidal partial pressure of carbon dioxide; $P_{ET}O_2$: end-tidal partial pressure of oxygen; RER: respiratory exchange ratio (VCO_2/VO_2). Green vertical line: anaerobic threshold estimation.

1.2.10.1 Peak Oxygen Consumption

Oxygen consumption (VO_2) is the product of cardiac output and arterio-venous oxygen content difference and is an expression of oxygen use by tissues. Peak oxygen consumption is the highest oxygen uptake measuredand is effort-

dependent (Figure 4). It is measured directly as the peak volume (ml) of oxygen uptake averaged over approximately 20 seconds and is usually normalised to patient mass (kg). It is subtly different to maximum oxygen consumption (VO_{2max}), usually described in sports physiology, which is the maximum physiologically attainable oxygen uptake by a person which is reached at true maximal exertion and demonstrated by a sustained plateau in oxygen uptake. Peak oxygen consumption is described in perioperative CPET because this is a more realistic measure for patients where not all individuals will reach true maximum exertion and demonstrate a plateau in oxygen uptake. In the absence of a plateau in VO_2, either a heart rate within 10 bpm of age-predicted maximum or a respiratory exchange ratio (RER) over 1.10 (indicating that more CO_2 is being produced than O_2 utilised and therefore anaerobic metabolism is taking place) indicate a physiologically maximal effort.

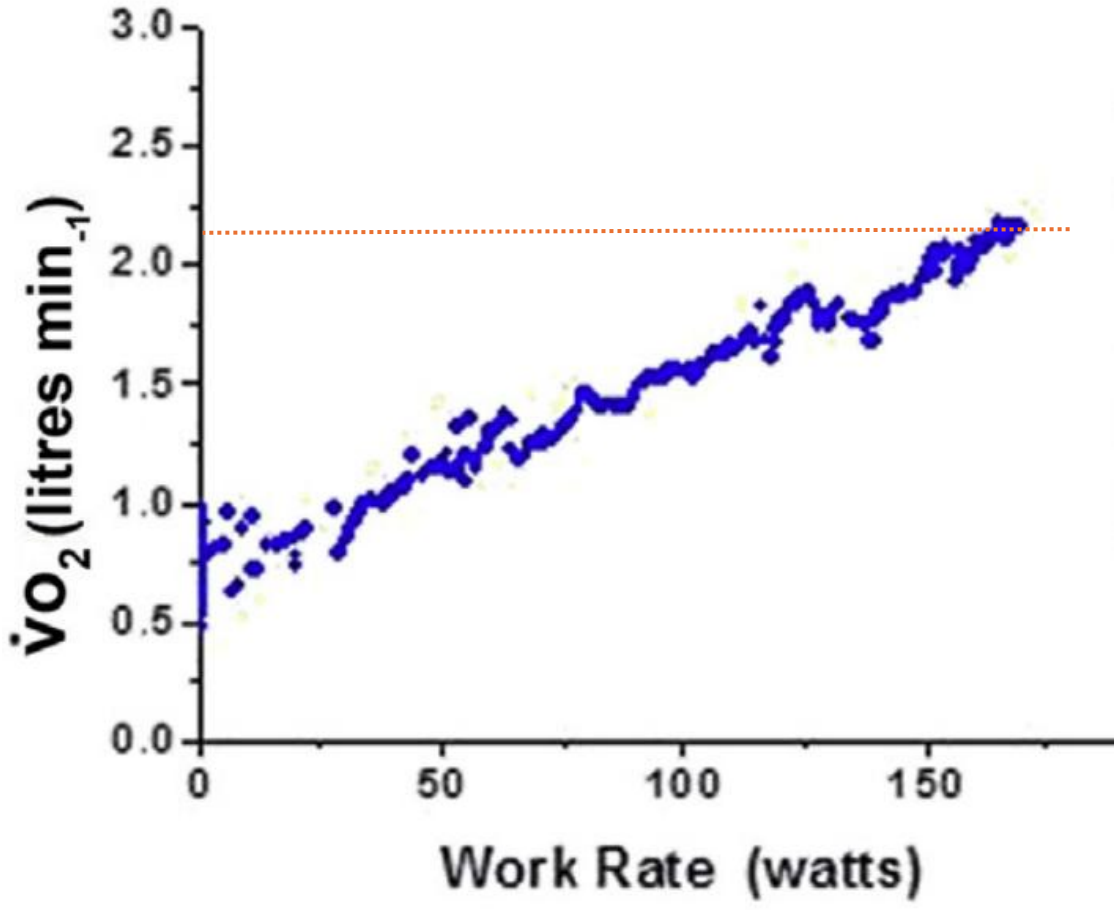


Figure 4 Example of Panel 2: VO_2 vs work rate in a healthy individual performing CPET. Modified from Levett et al[57]. Peak VO_2 at end of exercise is 2.2 L/min (red dotted line), which in a 70 kg person equates to a peak oxygen consumption of approximately 31ml/kg/min. Oxygen consumption does not plateau in this patient so additional criteria (heart rate within 10 bpm of age-predicted maximum or RER >1.10) would need to be demonstrated to confirm a maximal test.

Peak oxygen consumption is an indicator of the integrity of the oxygen transport pathway between the lungs and mitochondria, therefore encompassing respiratory, cardiovascular (oxygen transport) and muscle (oxygen utilisation) function. As an individual measure, VO_{2peak} predicts postoperative mortality and morbidity, and has been demonstrated to be both easy to identify and reproducible[57,61]. Specific thresholds for identifying high-risk patients using VO_{2peak} have been identified but are varied depending on the patient population, indication for CPET and outcome studied. A recent systematic review on preoperative CPET in intra-abdominal surgery (including abdominal aortic aneurysm (AAA) repair) recommended a VO_{2peak} a cut-off of less than 15ml/kg/min for AAA repair to identify patients at high-risk of 90 day mortality[61] and this cut-off appears to have been utilised in subsequent literature[62]. However, despite indicating predictive value of VO_{2peak} for postoperative morbidity and mortality in patients undergoing elective intra-abdominal and thoracic surgery[63], further thresholds could not be recommended.

1.2.10.2 Anaerobic Threshold

The AT is defined as the VO_2 at which blood lactate steadily increases during exercise and is associated with a progressive metabolic acidosis. In perioperative CPET, blood lactate levels are not measured and so there is a three-criterion discrimination technique to most accurately predict the anaerobic threshold in perioperative CPET based on expiratory gas measurement[64]. Criterion one is to identify excess CO_2 production relative to VO_2 via either the V-slope or modified V-slope. The V-slope is the relationship between oxygen uptake and carbon dioxide production. The point (VO_2) at which there is an inflection, indicating excessive CO_2 production compared to oxygen uptake is the anaerobic threshold. The modified V-slope method is an alternative which is useful when there is not a clear inflection point in the VCO_2-VO_2 relationship. A line is made on the graph with gradient $VCO_2/VO_2 = 1.0$. The VO_2 at which the data meets a unitary tangent (line with gradient of change in VCO_2/change in $VO_2 = 1$) is taken at the AT, as data higher than this point indicate proportionally higher VCO_2 than VO_2 (Figure 5).

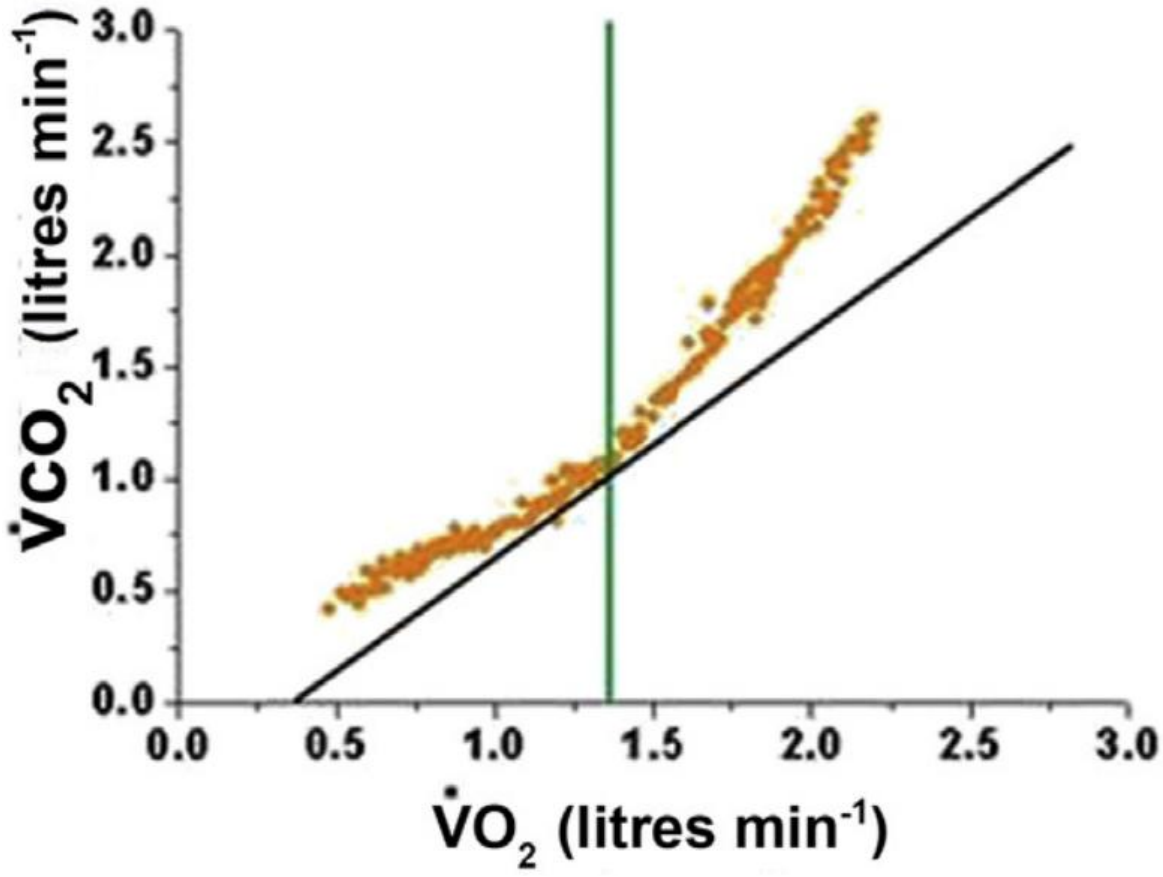


Figure 5 Example of Panel 1: VCO_2 vs VO_2 in a healthy individual. Taken from Levett et al[57]. Orange dots: V-slope (relationship of VCO_2 and VO_2). Green line: point of anaerobic threshold where VCO_2 increases disproportionately to VO_2. Black line: $VCO_2/VO_2 = 1$, used to identify AT using modified V-slope method. In this example, the AT is at a VO_2 of 1.3L/min equating to an AT of approximately 18.5ml/kg/min in a 70 kg person.

Criterion two of AT identification is the point at which there is an increase in minute ventilation (VE) but without an equivalent increase in VO_2. The excess CO_2 produced from anaerobic glycolysis drives ventilation but oxygen consumption is maximal. This is demonstrated by both an increase in VE/VO_2 (ratio of minute ventilation and VO_2) (after reaching a nadir) (Figure 6a) and an increase in alveolar end-tidal PO_2 ($P_{ET}O_2$) relative to VO_2 (Figure 6b).

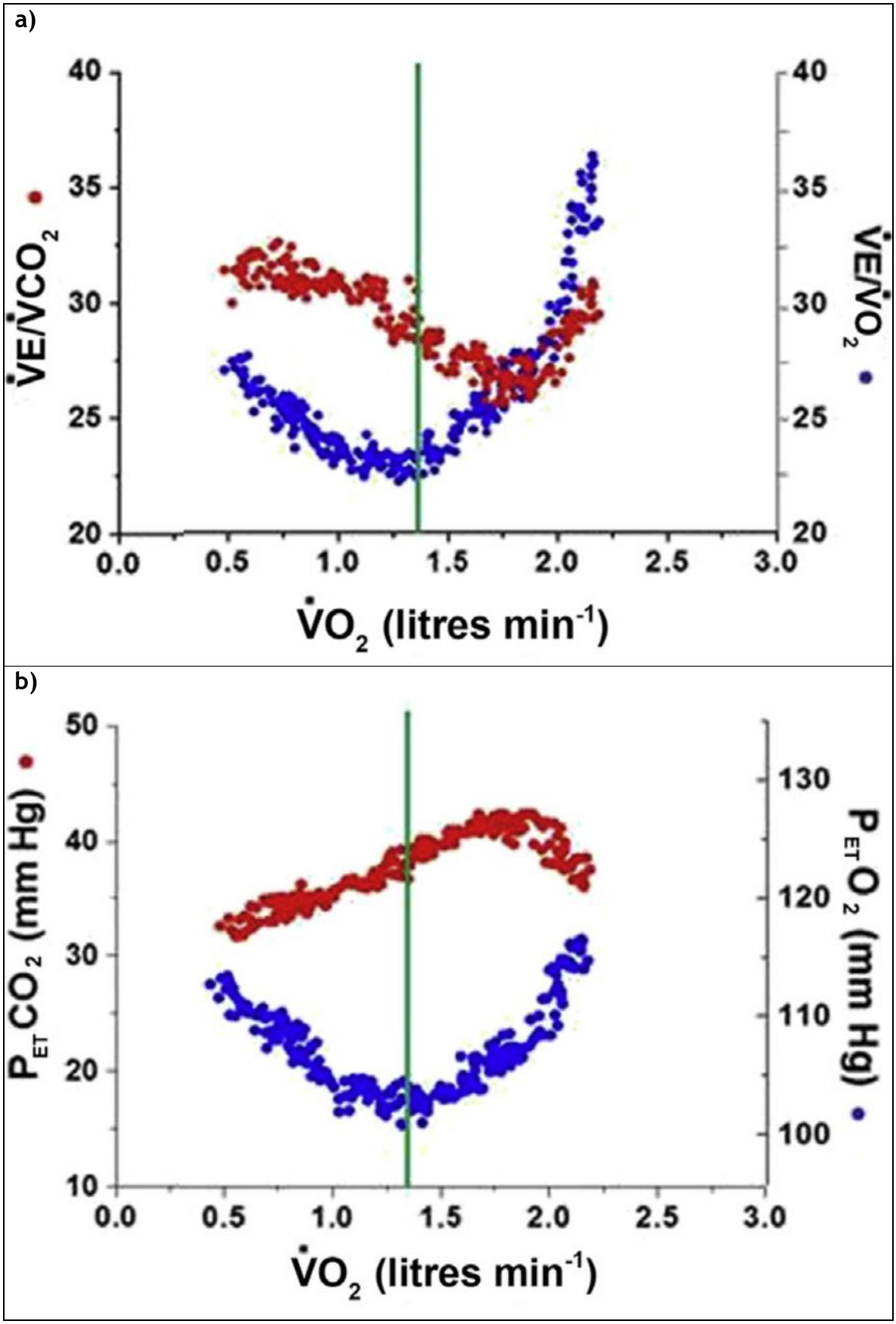


Figure 6 Example of plots 4 and 7 during CPET of healthy individual. Taken from Levett et al[57]. a) VE/VCO_2 (red dots) and VE/VO_2 (blue dots) versus VO_2. Green line: VO_2 at AT identified as point at which VE/VO_2 starts to increase after reaching nadir. b) $P_{ET}CO_2$ (red dots) and $P_{ET}O_2$ (blue dots) versus VO_2. Green line: VO_2 at AT identified as point at which $P_{ET}CO_2$ increases after reaching a nadir.

Criterion three of AT identification aims to confirm that the hyperventilation identified by criteria one and two is not due to anxiety, pain or hypoxaemia. This is done by confirming that VE/VCO_2 is constant or decreasing as VE/VO_2 increases (Figure 6a) and that $P_{ET}CO_2$ does not fall at AT (this happens later during exercise as ventilatory compensation for metabolic acidosis occurs) (Figure 6b). These criteria demonstrate that determination of AT can be complex, particularly if there is noise within the data or in certain disease states such as very severe respiratory disease (e.g. interstitial lung disease) or significant heart failure[36]. The anaerobic threshold is indicative of the effectiveness of cardiovascular oxygen transfer and muscular oxygen utilisation.

Anaerobic threshold is the CPET parameter which has been most extensively investigated in the preoperative risk prediction literature and is associated with postoperative morbidity and mortality[61]. A comprehensive systematic review investigating the predictive value of CPET for postoperative complications in patients undergoing non-cardiac surgery found variable results from 33 reported studies[62]. Anaerobic threshold demonstrated sensitivity ranging from 0.0 – 100.0% and specificity of 41.5 - 92.0% for 30-day mortality; sensitivity ranging from 23.3 - 100.0% and specificity 43.4 – 91.9% for cardiorespiratory complications within 30-days[62]. Six studies reported AUROC to demonstrate predictive value of AT for a range of outcomes. The AUROC for 30-day mortality varied between 0.75 (0.65 – 0.85) and 0.86 (no CI reported); for cardiorespiratory complications within 30-days of surgery AUROC varied from 0.57 (0.30 – 0.85) to 0.83 (0.69 – 0.96)[62]. The authors of this review concluded that CPET parameters are more effective at ruling out low-risk patients than identifying the high-risk perioperative population. The recent METS trial (see Section 1.2.4) rather surprisingly found that AT did not improve baseline model performance for the prediction of 30-day mortality or myocardial infarction, however due to a low incidence of the primary outcome, the study may have been underpowered[38]. A risk threshold of <11ml/kg/min equating to high-risk of postoperative mortality has been used both in clinical practice and perioperative CPET research since 1993[65]. Based on the systematic review findings, Moran et al. recommend a threshold of <9ml/kg/min for 90 day mortality in hepatic transplant and up to 10.9ml/kg/min for mortality in intra-abdominal surgery[61]. There is little and varied literature on specific thresholds for CPET risk

prediction and so this systematic review presents the best (although still limited) evidence for thresholds. It has been noted that within the perioperative CPET risk prediction literature, there has been a downward trend in the AT risk threshold over the years. This has been postulated to be due to improving surgical techniques and perioperative care, although more research is required to determine the underlying cause and whether this effects the utility of perioperative CPET[58] in a population where postoperative complications are becoming less frequent.

1.2.10.3 Ventilatory equivalent for carbon dioxide at AT

Once AT has been identified, the ventilatory equivalent for CO_2 (VE/VCO_2) is recorded at the point of the AT (Figure 7). The ratio of minute ventilation to exhaled CO_2 indicates the efficiency of ventilation and gas exchange. It tends to fall during exercise as ventilation-perfusion mismatch improves and thus higher values are associated with diseases which impair ventilation, perfusion or gas exchange across the lungs including heart failure, pulmonary hypertension and chronic respiratory disease. As with other CPET parameters, risk thresholds depend on the population studied, test indication and outcome, although VE/VCO_2 at AT has been less extensively investigated within the perioperative literature than VO_{2peak} or AT. No recommendations were made for a risk threshold for VE/VCO_2 at AT by Moran et al reflecting the limited evidence base[61]. The American Thoracic Society recommends a cut-off of >34 indicating high-risk patients[66] based on a study in patients undergoing major intra-abdominal surgery which demonstrated that this was a significant predictor for all-cause hospital and 90 day mortality[67].

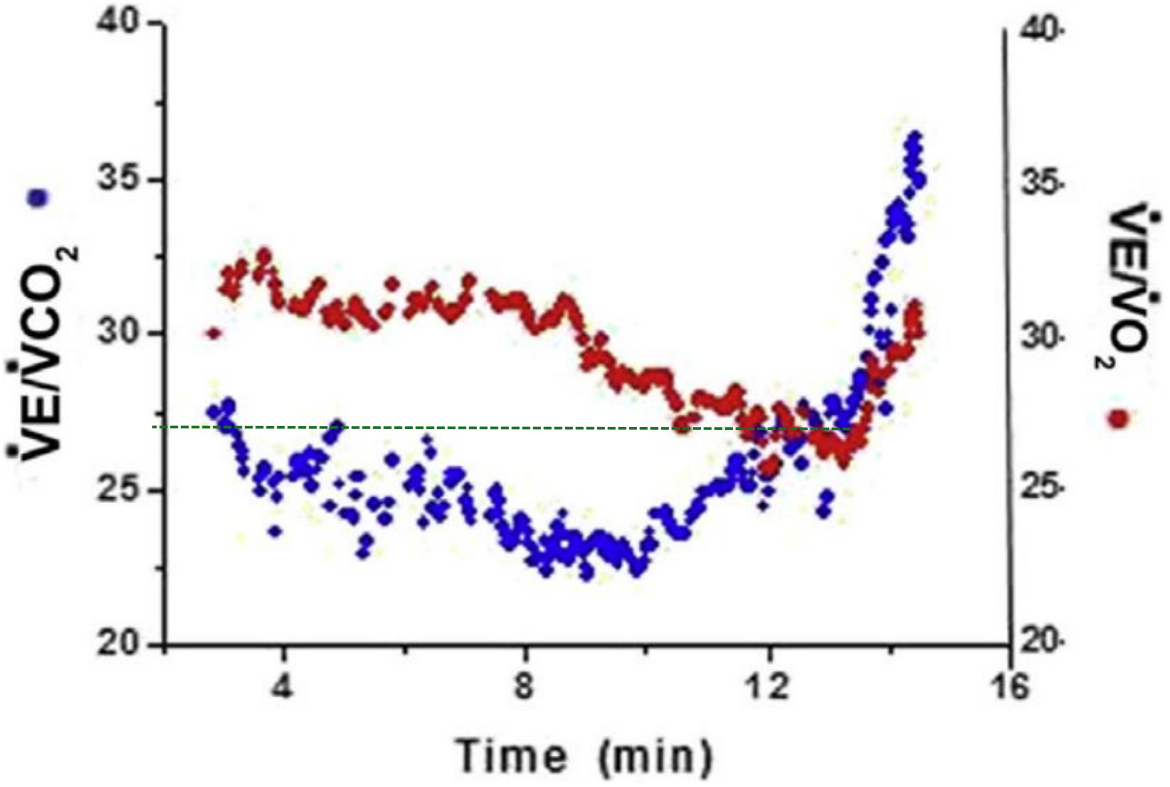


Figure 7 Example of VE/VCO2 and VE/VO2 versus time in a healthy individual. Modified from Levett et al[57]. Dashed green line: VE/VCO_2 at AT identified by point at which VE/VO_2 begins to increase. VE/VCO_2 in this person therefore approximately 27.

1.2.10.4 CPET use within the NHS

The use of preoperative CPET is increasing in the UK, with a national survey from 2016-2017 demonstrating 30000 tests were performed a year; provision had doubled since 2011; and 68.1% of NHS trusts have an established preoperative service[60]. Patient selection was predominantly based on the type of surgery, but also clinician concern. Of the departments who utilise CPET (n = 98), the three most common surgical specialities which use CPET were colorectal (89.5%), upper GI (77.9%) and vascular surgery (68.6%). Interpretation of CPET was predominantly performed by anaesthetists with results used to make recommendations on the suitability of surgery, location of postoperative care, prehabilitation where available and to quantify risk. Interestingly, 10-15% of respondents combine CPET findings with other risk stratification scores to guide their clinical recommendations. The main inhibitory factor to setting up a CPET service was cost (58.5%), although 43.9% of respondents who did not undertake preoperative CPET also cited lack of clinical need and 25.0% reported a lack of evidence of benefit. The average cost of a single CPET is estimated to be £183 in

2016[62] although this has likely increased. In 2016, the National Institute for Health and Care Excellence (NICE) guidelines on routine preoperative tests made no recommendation for CPET due to a lack of clinical evidence. Subsequent to survey publication, the perioperative exercise testing and training society (POETTS) published consensus guidelines on indications, conduct and physiological interpretation of preoperative CPET but recognising limited data precluding specific recommendations for risk thresholds[57]. A further limitation to CPET is that a cohort of patients may not be able to complete it, either due to mobility problems precluding cycle ergometry or severe cardiopulmonary disease limiting the ability to reach AT and therefore the clinical utility of the test. Although there is evidence that inability to complete a test is associated with poor postoperative outcomes itself[68]. In such patients, performance of submaximal exercise tests (SETs) may be more feasible.

1.2.11 Submaximal exercise testing

Submaximal exercise testing (SET) provides an objective measure of functional capacity but without either the intense resources, patient motivation or patient mobility, required for CPET[69]. The most common SET for preoperative risk stratification is the six-minute walk test (6MWT) distance, although this measure is less investigated and validated in the preoperative population than the three main CPET parameters described above.

The 6MWT involves the patient walking as far as possible along a flat unimpeded track for six-minutes. During the test, they may slow down or stop to rest as necessary. The main parameter recorded is the total distance walked, although it is possible to measure physiological variables such as oxygen saturation[70]. The submaximal nature means that the results are dependent on patient volition, and factors such as patient height, age and corridor length can affect results. However, when performed in the same conditions and after practice, 6MWT distance demonstrates good inter-test reproducibility[70]. Initial investigations of 6MWT distance focused on association of 6MWT distance with cardiorespiratory fitness as measured by CPET (primarily AT and VO_{2peak}). Guazzi et al. demonstrated that 6MWT distance was associated with VO_{2peak} (Pearson's correlation coefficient (r) 0.68, $p < 0.001$), AT (r 0.63, $p < 0.001$) and VE/VCO_2 slope (r -0.38, $p = 0.01$) in 253 patients with chronic heart failure. However, this

association of 6MWT distance with markers of cardiorespiratory fitness did not translate to prognostic value[71]. In contrast, a substudy of the METS trial (described in Section 1.2.4) demonstrated poor association between 6MWT distance and both AT (r 0.28) and VO_{2peak} (r 0.36) in the perioperative population. In terms of predictive value for postoperative complications, results for the 6MWT distance are comparable to those of CPET parameters (AUROC 0.70 (0.52 – 0.88) for 30-day mortality or myocardial infarction). In this study, 1% of patients terminated the test early, compared to 14% of patients who undertook CPET[72]. A larger secondary analysis of METS found that a reduced 6MWT distance was associated with an increased adjusted odds ratio for postoperative complications (aOR 1.32 per 100m decrease (95%CI 1.01 – 1.73)); however addition of 6MWT distance to a multivariable regression model comprising age, sex and high-risk surgery did not demonstrate improvement for prediction of postoperative complications[73].

In conclusion, despite being the gold-standard exercise test for assessing functional capacity, the predictive value of CPET in the perioperative population is less clearcut. Analysis of measured variables including oxygen consumption at anaerobic threshold and VO_{2peak} indicate the patient's risk for post-operative morbidity and mortality[59]. Unfortunately, a proportion of patients are unable to perform effective CPET, for example due to arthritis or failure to reach maximal exertion. CPET is also resource-intensive and availability varies. Submaximal exercise tests are advocated because they are better tolerated by patients and are less resource-intensive than maximal exercise testing[69], with some papers demonstrating equivalent predictive value for SETs and CPET in the perioperative population[72]. Six-minute walk test distance however, unless repeated in strict, consistent conditions, can demonstrate poor reproducibility dependent on patient volition. Heart rate recovery after submaximal exercise testing could provide an objective, physiological parameter which remains available for patients to perform and feasible to measure; the physiological basis of which is described in the following sections.

1.3 Cardiovascular physiology

1.3.1 Autonomic nervous system overview

The autonomic nervous system (ANS) regulates involuntary functions and comprises of two competing systems: sympathetic and parasympathetic, which act throughout the whole body. The sympathetic nervous system (SNS) is responsible for the figurative "*flight or fight*" response causing, amongst others, increased cardiac output via tachycardia and increased myocardial contractility, bronchial smooth muscle dilatation, reduced gut motility and mydriasis. Sympathetic preganglionic fibres originate from the thoraco-lumbar region of the spinal cord and synapse in the sympathetic chain close to the spinal cord. Postganglionic fibres follow spinal or visceral nerves to innervate target organs. The primary postganglionic neurotransmitter in the SNS is adrenaline which acts on alpha and beta adrenergic receptors at the target organs[74].

The parasympathetic nervous system (PNS) is responsible for "*rest and digest*" functions such as increased gut peristalsis and tone, salivary gland secretion and relaxation of gut sphincters. Preganglionic PNS fibres originate from the medulla oblongata and sacral nerves (craniosacral outflow) and synapse close to the target organ. The main PNS efferent neurotransmitter is acetylcholine which acts on muscarinic receptors at target organs and nicotinic receptors within the ganglia. The cardiac effects of the PNS are controlled via the vagus nerve (10th cranial nerve) and include reduced heart rate via decreased conduction velocity and reduced myocardial contractility[74].

1.3.2 Cardiac parasympathetic tone

Afferent PNS information from the heart is transmitted to the nucleus tractus solitarius in the medulla oblongata via vagal sensory neurones. The peripheral terminals of cardiac vagal afferents are distributed across the cardiac conduction system, and myocardium of the atria and ventricles. Within the atria and ventricles, cardiac vagal afferents are mechanosensitive, activated by either myocardial stretch (ventricular filling i.e. preload) or myocardial pressure (during systole)[75]. Vagal afferents also transmit information from the aortic baroreceptors in response to aortic stretch and from the lungs in response to

lung stretch. This vasomotor area in the medulla also receives direct chemosensitive inputs from the aortic and carotid bodies, and inputs from the cerebral cortex via the hypothalamus.

The efferent presynaptic fibres of the vagus nerve originate at the nucleus ambiguus and the dorsal nucleus of the vagus nerve in the medulla oblongata. They innervate nodal tissue and the atria, controlling heart rate, atrioventricular conductance and strength of both atrial and ventricular contraction[76]. The sino-atrial node acts as the cardiac pacemaker, with pacemaker cells automatically discharging at a rate of approximately 60-70 bpm due to gradual depolarisation. Vagal stimulation of nodal tissue leads to the cell membrane becoming hyperpolarised, resulting in a decreased firing rate and slowing the intrinsic heart rate and conduction through the atrio-ventricular node. Vagal efferent fibres also act directly on the myocardium to reduce contractility[77]. In health, there is a delicate balance between cardiac sympathetic and parasympathetic tone to maintain both cardiac output and homeostasis. Very broadly, in disease states such as myocardial ischaemia, hypertension and type 2 diabetes, imbalance between the SNS and PNS develops, with loss of vagal tone and increased sympathetic excitability. The resulting tachycardia, increased myocardial contractility and loss of endothelial function can contribute to progression of cardiac disease[75]. Type 2 diabetes can lead to autonomic neuropathy i.e. damage to sympathetic and parasympathetic fibres contributing towards orthostatic hypotension, loss of heart rate variability, myocardial ischaemia and exercise intolerance[78].

1.3.3 Cardiovascular response to exercise

During exercise, cardiac output increases linearly to meet the metabolic demands of contracting skeletal muscle. Heart rate increases and there is an associated rise in stroke volume and systolic blood pressure to increase oxygen delivery to working muscles. This heart rate increase occurs primarily due to initial withdrawal of vagal stimulation, with sympathetic activation at moderate work rates increasing as exercise intensity increases, although the extent of this autonomic “imbalance” is debated[79], with a recent review suggesting that vagal tone is maintained during exercise but that SNS activation increases[79]. The balance between the two ANS systems during exercise appears dependent on

exercise intensity with sympathetic activity dominating cardiac control when the heart rate is over 140 bpm. During intense exercise, approximately 80% of heart rate control is due to SNS activity, but continued vagal activity modulates cardiac function to maintain activity[80]. This has recently been confirmed in a sheep model, with vagal activity during exercise associated with maintained coronary blood flow[81]. The relationship of cardiac vagal tone and the ability to exercise appears reciprocal. Vagal activity causally determines the ability to exercise, but regular activity or exercise is also associated with increased cardiac vagal tone. The complexities behind this "chicken or egg" situation is beyond the remit of this thesis, but there is some evidence that up to 60% of vagal tone is determined genetically[82]. Multiple studies (both clinical and translational) have demonstrated that exercise capacity is regulated by vagal activity[79]. For example, in rat studies, reduced activity of the dorsal vagal preganglionic neurons reversibly reduced exercise capacity (measured by work done) by approximately 80% whilst stimulation of the vagal neurones prolonged exercise endurance[83]. Markers of vagal tone such as heart rate variability, baroreflex sensitivity (Section 1.3.4) and heart rate recovery (Section 1.4) are consistently associated with cardiorespiratory fitness both in healthy participants/athletes[84,85] and in patients[86]; and that fitness training improves these markers further[86,87].

At exercise cessation, heart rate initially drops rapidly due to reactivation of the parasympathetic system followed by a slower reduction due to withdrawal of sympathetic stimulation. This is supported by evidence that plasma noradrenaline concentration remains high for up to one minute after exercise cessation, but despite this, heart rate drops rapidly[88].The extent of vagal reactivation appears to be dependent on exercise intensity, with a more rapid HRR after lower exercise intensity compared to maximal due to less SNS activation (Figure 8)[89].

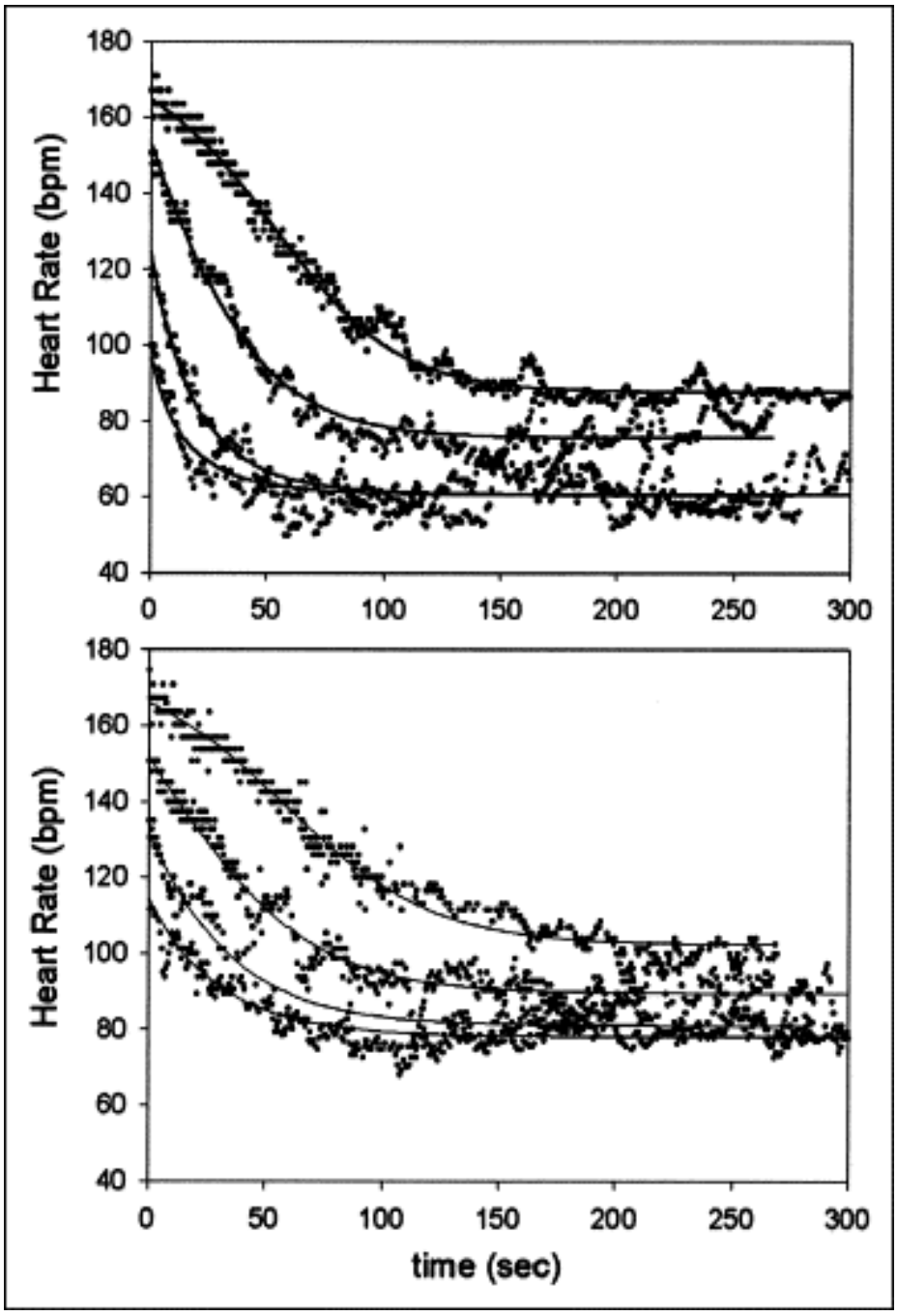


Figure 8 Heart rate recovery curves with raw data (dots) and fit curves (solid lines) at different exercise intensities (indicated by peak heart rate at end of exercise) in two individuals. Taken from Pierpoint et al[89].

During the initial recovery phase after aerobic exercise in healthy individuals, vagal activation contributes towards skeletal muscle vasodilation and arterial baroreflex resetting. Effective cardiovascular recovery allows oxygen and glucose delivery to recovering tissues and maintenance of blood volume via fluid retention amongst others[90]. Vagal modulation therefore is an important component in the attainment of oxygen delivery, consumption and recovery

during exercise. Later in the recovery phase, heart rate reflects a more complex picture including not just SNS tone but also metabolite clearance[91]. In disease states such as those described above, where there is chronic sympathetic activation and loss of vagal tone, the cardiovascular response to exercise is blunted leading to exercise intolerance (clearly respiratory and skeletal muscle inefficiency also contributes). An exaggerated early tachycardia during exercise due to high sympathetic tone is associated with myocardial ischaemia, inferior cardiac performance during exercise and prolonged hospital stay after major elective surgery[92]. Recovery from exercise is also impaired including reduction in heart rate[84]; the implications and perioperative associations of which are discussed in Chapter 2 (Systematic review and meta-analysis).

1.3.4 Impaired PNS and postoperative outcomes

In the general medical population, maintenance or restoration of vagal activity has been shown to limit systemic inflammation[93], atrial arrhythmias[94], postoperative ileus[95], ventilator-induced lung injury[96] and pain[97]. In vitro loss of cardiac vagal tone exacerbates myocardial cellular damage after inflammation[98], haemorrhage[99] and ischaemia[100]. There is emerging data to suggest that vagal nerve stimulation improves both clinical outcomes and quality of life in patients with heart failure[101], and limits myocardial injury after acute MI[102]. Conversely, SNS activation is associated with increased systemic inflammation worsening acute lung injury models[103], hepatic dysfunction and sepsis in critical care[104]. Catecholamine inotropes have been demonstrated to increase bacterial proliferation, particularly staphylococcus epidermidis[105]. Ackland et al. studied both laboratory rodent subjects and clinical human subjects (in a re-analysis of the COMPETE-C trial[106]) to investigate the molecular mechanisms linking autonomic dysfunction with critical illness[107]. This study demonstrated that baroreflex dysfunction was associated with cardiac impairment via upregulation of GRK-2 in cardiac myocytes by activation of NADPH-oxidase. Baroreflex dysfunction in patients (measured via spontaneous baroreflex sensitivity) was associated with other measures of parasympathetic dysfunction, including impaired HRR_1. Patients with PNS dysfunction who failed to achieve optimal haemodynamic performance in the COMPETE-C trial had a higher risk of postoperative complications, sepsis, use of critical care resources and prolonged hospital stay. By neatly linking the potential molecular signalling mechanisms

behind cardiac impairment and parasympathetic dysfunction, the authors describe a potential phenotype at higher risk of generalised postoperative complications, albeit in a small, single specialty cohort in a re-analysis of a previous study.

In the perioperative population, impaired vagal tone, measured predominantly by heart rate variability (HRV), is associated with poor postoperative outcomes, including postoperative complications in hip fracture patients[108] and all-cause mortality after one year in patients undergoing noncardiac surgery at risk of coronary artery disease[109]. Heart rate variability is the difference in R-R intervals between consecutive heart beats with reduced variability associated with reduced vagal tone[110]. In a systematic review, Frandsen et al. found that impaired preoperative HRV was associated with intraoperative hypotension and development of postoperative atrial fibrillation[111]. However, they also acknowledged that there was high heterogeneity within the studies identified, predominantly due to timing and method of HRV measurement. Niu et al. measured intraoperative HRV in >5000 patients undergoing non-cardiac surgery, and compared the predictive value of HRV models created by machine learning with baseline models based on clinical information. Addition of HRV to the baseline models improved the predictive value (AUROC) from 0.79 to 0.83 for postoperative ICU stay and from 0.58 to 0.70 for in-hospital mortality (confidence intervals not reported). However, in this study, HRV was not able to be determined from the ECG of over 400 patients reflecting the difficulty in reliably measuring HRV. Impaired baroreflex function (a marker of vagal tone) has also been associated with postoperative morbidity and delayed hospital stay[112], and the development of critical illness and mortality in surgical patients[107]. Heart rate recovery after exercise is a marker of cardiac vagal tone (Section 1.3.3) and is potentially an easier parameter to measure than HRV or baroreflex function warranting further investigation.

1.4 Heart rate recovery

Heart rate recovery was first described as an exponential deceleration dependent on autonomic tone by Savin et al. in 1982[113]. Six healthy individuals performed a series of treadmill tests after either parasympathetic blockade, sympathetic blockade, double blockade (PNS and SNS) or no drugs (Figure 9).

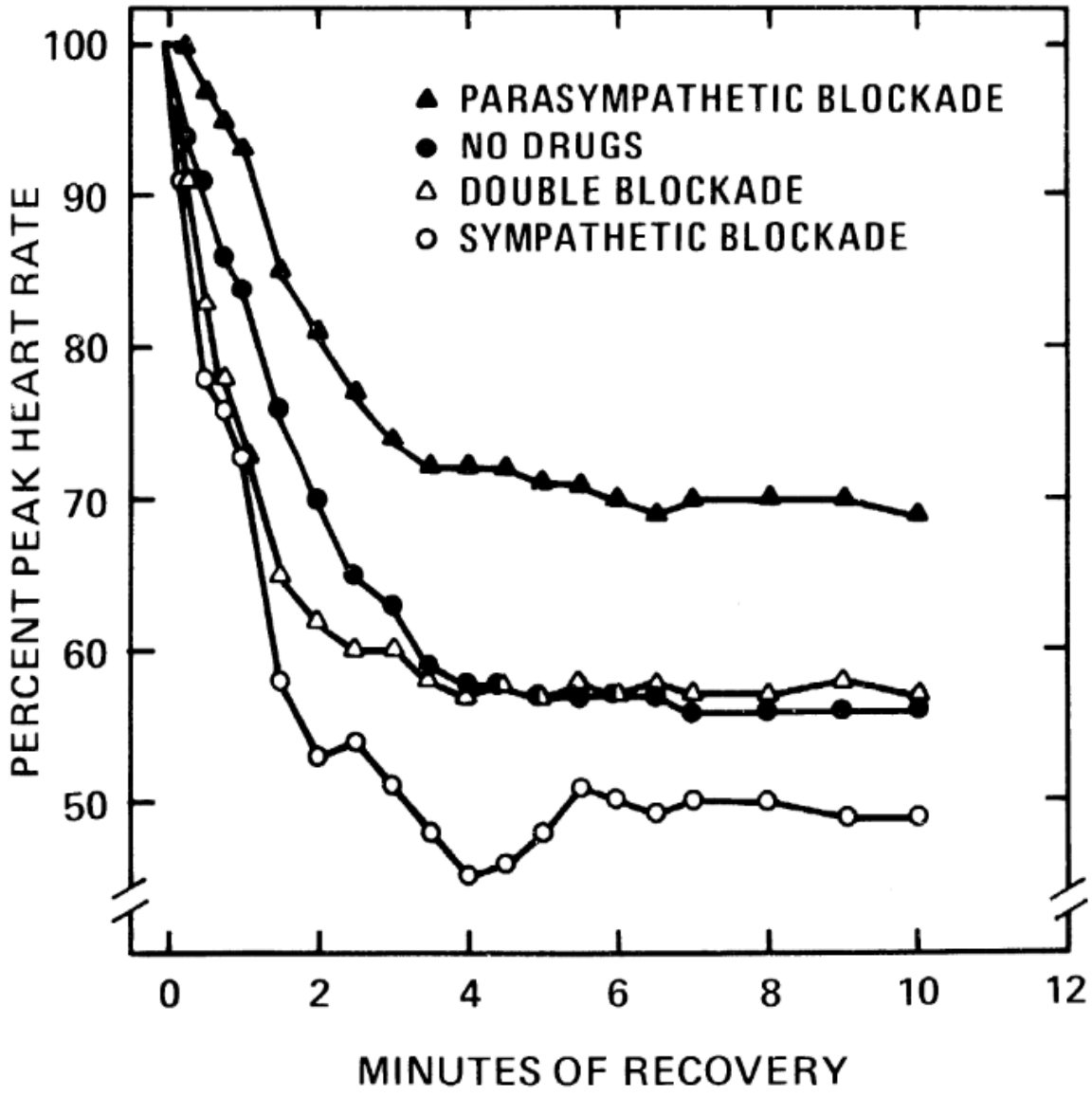


Figure 9 Mean heart rates as a percentage of peak heart rate reached. Taken from Savin et al[113].

Exponential deceleration was demonstrated for each condition, but the rate of decay was slower in individuals with PNS blockade and faster in individuals with sympathetic blockade. Imai et al. demonstrated this further in an experiment where atropine was administered to healthy volunteers leading to slowing of heart rate recovery, whereas HRR was unaffected after administration of propranolol (sympathetic blockade) [84]. Imai et al. then compared HRR in athletes and patients with heart failure and found that athletes exhibited accelerated HRR and heart failure patients a blunted response. Cole et al. subsequently defined impaired HRR_1 to be a fall of less than 12 beats per minute after the cessation of exercise, with all-cause mortality associated with an impaired HRR_1

in 2428 patients undergoing maximal treadmill stress tests[114]. Subsequent studies, primarily in cardiovascular disease[115-117] and healthy volunteers[118-121] have demonstrated HRR to be a prognostic marker for outcomes including all-cause mortality and cardiovascular events. The majority of studies investigating the prognostic application of HRR measure HRR_1 (reduction in heart rate one minute after exercise cessation) after maximal exercise. HRR_1 ≤12 bpm after symptom-limited maximal exercise is a strong predictor of mortality in patients with coronary artery disease[114]. Heart rate recovery after two minutes (HRR_2) of ≤42 bpm after submaximal exercise cessation predicted all-cause mortality in healthy individuals[118]. Association between HRR and postoperative complications is discussed further in Chapter 2 (Systematic review and meta-analysis).

1.4.1 Measurement of heart rate recovery

There is still some uncertainty regarding the most appropriate way in which to measure heart rate. Considerations include whether to measure absolute or derived values, and how exercise intensity may affect its reproducibility. Heart rate recovery has been described as absolute drop in heart rate from exercise cessation to certain timepoints[84,118], the rate of decrease over time via regression slope[122], the time constant of the first 30 seconds (T_{30})[123], mono-exponential decay functions[89] and second-order decay functions[124].

Arduini et al. investigated the reliability of different HRR measurements at different exercise intensities[91]. Twenty-one healthy individuals performed a maximal cycle ergometry test followed by submaximal tests at 80% age-predicted maximum heart rate (HR_{max}) and 65% age-predicted HR_{max}, with a variety of HRR methods measured (monoexponential decay, slope of decay, and absolute drop in heart rate). For all methods, test-retest reliability was greater at the higher exercise intensity (intra-class coefficient (ICC) ≥0.749), although absolute HRR_1 demonstrated test-retest reliability with an ICC of 0.808 at the lower intensity[91]. Intra-individual reproducibility of heart rate dynamics during and after submaximal cycle ergometry (≤75% HR_{max}) was investigated in over 800 UK Biobank participants over a period of three years[125]. The intra-individual correlation for the shape of the heart rate profile was very similar even if baseline heart rate varied (ρ = 0.95 (0.92 – 0.97)). Heart rate recovery after one minute also demonstrated good intra-individual correlation (ρ = 0.71), especially

compared to that of resting heart rate ($\rho = 0.64$)[125]. In a recent systematic review investigating the reproducibility of HRR, HRR_1 demonstrated the highest reproducibility (ICC 0.77 – 0.99) across 15 studies, whereas HRR indices based on mathematical models were less reproducible[126]. The authors postulated that this may be due to the complexity in deriving these measures from heart rate profiles. The authors also found that overall agreement of measures was higher after maximal exercise intensity (coefficient of variation (CV) ≤ 23.3%) compared to submaximal exercise (CV ≤34.9%)[126]. Overall, it appears that HRR_1 may be the most reproducible method of measuring HRR. Exercise intensity does affect the reproducibility of HRR measures, with higher intensities demonstrating higher reproducibility and reliability. However, this needs to be balanced in clinical populations with the ability of patients to reach higher exercise intensities. Further work is required to assess the methodology and reproducibility of submaximal heart rate recovery, particularly in patient populations.

1.5 Assessing the clinical usefulness of a novel measure

Submaximal heart rate recovery as described in this investigation is purported as a novel measure for perioperative risk prediction. The clinical usefulness of any new measure or diagnostic test can be scrutinised by considering eight criteria described by Sackett et al.[127]:

1. Has there been an independent, “blind” comparison with a “gold-standard” of diagnosis?

2. Has the diagnostic test been evaluated in a patient sample that included an appropriate spectrum of mild and severe, treated and untreated, disease?

3. Was the setting for this evaluation, as well as the filter through which study patient passed, adequately described?

4. Have the reproducibility of the test result (precision) and its interpretation (observer variation) been determined?

5. Has the term “normal” been defined sensibly as it applies to this test?

6. If the test is advocated as part of a cluster or sequence of tests, has its individual contribution to the overall validity of the cluster or sequence been determined?

7. Have the tactics for carrying out the test been described in sufficient detail to permit their exact replication?

8. Has the utility of the test been determined?

Accordingly, this study focusses particularly on the validity (criterion one and six) of submaximal HRR as a perioperative risk measure. The design of the study also considered the patient group and setting most appropriate for validation of the test (criteria two and three), with appropriate description of the test (criterion seven) and how this can pragmatically be applied in the real-life clinical scenario. Consideration of the other criteria, where appropriate, was attempted throughout the study. The methodology of ascribing validity to a novel measure is described in Section 3.2. An important aspect of study design is the selection of an appropriate primary outcome. Postoperative myocardial injury (PMI) was chosen for this study due to its association with impaired cardiac vagal tone; its importance as a marker of poor long term postoperative outcomes and its relative ease of measurement.

1.6 Postoperative myocardial injury

This section reviews the definitions, mechanisms and outcomes of PMI providing insight into this choice of outcome for the predictive validity of submaximal HRR. Postoperative myocardial injury is a recognised cardiovascular complication of non-cardiac surgery associated with poor postoperative outcomes. Myocardial injury is diagnosed by a change in cardiac troponin (cTn) levels indicating cardiomyocyte damage.

Despite recent attempts to determine a standardised definition, many different methods of identification exist with differing pathophysiological foundations. Furthermore, the underlying mechanisms driving PMI are not completely understood but thought to incorporate impaired cardiac vagal tone.

1.6.1 Definitions

Whilst consistently described by perioperative escalation of cTn, the definition of perioperative myocardial injury varies throughout the literature. The two most common definitions are 'myocardial injury after non-cardiac surgery' (MINS)[128,129] and 'post/perioperative myocardial injury' (PMI), however even within these definitions, the specific assays, cut-offs and measurement timepoints vary alongside differing underlying assumptions concerning the pathophysiology.

1.6.1.1 Myocardial injury after non-cardiac surgery as per VISION group

One of the earliest and largest studies to investigate postoperative cTn elevation and define MINS was the Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) trial, an international prospective cohort study of over 40000 patients aged 45 years and over investigating major complications after non-cardiac surgery. The initial VISION report on the first 15000 patients demonstrated peak cTnT in the first 72 hours after surgery was an independent predictor of 30-day mortality[130] but there was no comment on potential underlying mechanism. This definition of MINS was further updated by the VISION investigators in 2017 and defined as myocardial injury judged due to ischaemia occurring within three days of surgery and identified by a high-sensitivity TnT (hsTnT) assay >20ng/L[129]. By this definition, to diagnose MINS, myocardial ischaemia does not necessarily need to be demonstrated but there must be "no evidence of a non-ischaemic cause" for the elevated troponin. Non-ischaemic causes of troponin elevation were described as including rapid atrial fibrillation, pulmonary embolus or sepsis.

1.6.1.2 American Heart Association

The American Heart Association (AHA) released a scientific statement in 2021 with their definition of MINS including both myocardial *infarction* and myocardial injury that does not fulfil all criteria for the 4th Universal definition of myocardial infarction i.e. a troponin rise without ischaemic symptoms, ECG changes or imaging evidence of myocardial ischaemia or thrombus[131,132]. Therefore, MINS as defined by the AHA includes a postoperative cTn (T or I) over the 99th percentile upper reference limit (URL) with an acute change occurring

in the first 30-days (but typically within 72 hours) of surgery, and attributable to a presumed ischaemic mechanism in the *absence* of an overt non-ischaemic cause. Clinical signs of ischaemia are not required as they may be masked by sedation or postoperative analgesia as described by the AHA. The main difference from the VISION definition is the requirement for a baseline cTn measurement to differentiate between acute and chronic troponin elevation.

1.6.1.3 Fourth Universal Definition of Myocardial Infarction

The Fourth Universal Definition of Myocardial Infarction published in 2018 provides a different definition of PMI, distinct from myocardial infarction, namely that PMI can have any cause, including extra-cardiac. Myocardial injury is defined as an elevated troponin with at least one value above the 99th percentile URL and is considered acute if there is a rise or fall in cTn of ≥20% from baseline. To distinguish myocardial injury from myocardial infarction, the absence of myocardial ischaemia needs to be demonstrated. If one or more ischaemic features are identified alongside a perioperative troponin rise e.g. chest pain or ischaemic ECG changes then the 4th universal definition for MI is fulfilled[132] and the patient is judged to have suffered infarction rather than injury.

1.6.1.4 BASEL-PMI definition

Puelacher et al[133] characterised postoperative myocardial injury after non-cardiac surgery in 2018 as part of the BASEL-PMI study, a prospective diagnostic study in 2018 consecutive patients undergoing non-cardiac surgery with a planned postoperative stay over one day and at increased cardiovascular risk. Differing from the other definitions, they define PMI as an absolute rise in hs-TnT of ≥14ng/L above baseline within seven days of surgery without the need for consideration of the mechanism i.e. injury could be diagnosed regardless of whether the mechanism was perceived to be ischaemic or non-ischaemic.

1.6.1.5 Standardized Endpoints in Perioperative Medicine

The Standardized Endpoints in Perioperative Medicine – Core Outcome Measures in Perioperative and Anaesthetic Care initiative (StEP-COMPAC)[134] advocate the use of the term perioperative myocardial injury (PMI) to describe a troponin rise

in excess of the 99th percentile URL (in the absence of *overt* ischaemia) regardless of mechanism. This delineates between recognising infarction and injury which is recognised to be a marker of higher postoperative risk but without proven treatment options. Arguably, this is a more pragmatic view as it does not require evidence either ruling out non-cardiac causes of cTn rise or the pursuit of subclinical cardiac ischaemia.

Figure 10 shows the different definitions of PMI based firstly on whether the troponin elevation is purely higher than the reference limit or includes a change from baseline, and then by presumed cause.

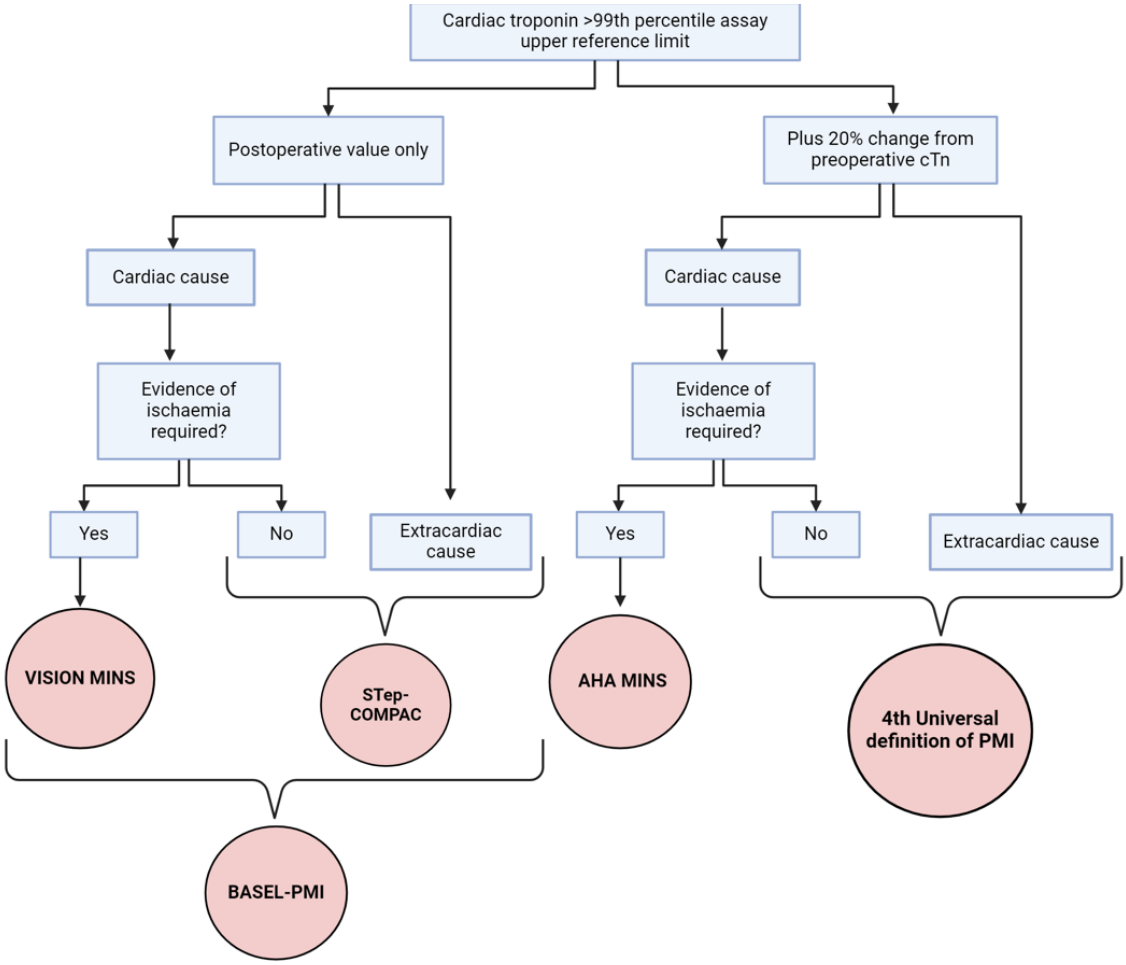


Figure 10 Flowchart indicating different criteria for the definitions of PMI/MINS. The difference in definitions whereby some mandate the demonstration of ischaemia whereas others mandate the exclusion of ischaemia reflects the variation within the literature where depending on definition, potentially different mechanisms of elevated cTn are being investigated

Throughout this section, PMI will be used as an umbrella term for elevated cTn within the perioperative period. Specific definition terms will be used where applicable and as described within the literature reported.

1.6.2 Incidence of PMI

The original VISION study defining MINS demonstrated an incidence of 8% (95%CI 7.5-8.4%) in patients aged 45 years or over undergoing a range of non-cardiac surgeries[128]. As the definition of PMI has become broader without the need to either demonstrate myocardial ischaemia (as with MINS) or exclude cases where there is evidence of extra-cardiac causes of cTn elevation, the incidence of PMI in the perioperative literature has increased, although with significant variability depending on the population and surgical risk studied. A recent systematic review and meta-analysis by Smilowitz et al. investigating MINS as defined by the AHA demonstrated a pooled incidence of 17.9% (95%CI 16.2 – 19.6%) in 530,867 surgeries in 169 reports[135]. Forty-four of these reports were high quality, prospective studies with systematic cTn measurement. The pooled incidence of MINS in this high-quality cohort was 19.5% (95%CI 17.8 – 21.3%).

Ackland et al. found that the majority of postoperative troponin elevation occurred within the first two days of surgery with early (within 24 hours) elevation associated with morbidity as defined by the postoperative morbidity survey within 72 hours of surgery[136].

1.6.2.1 Troponin assay

High-sensitivity assays measure cTn blood levels some five to ten times lower than non high-sensitivity assays, so can detect myocardial injury at lower troponin concentrations, and also allow for identification of the 99th percentile URL[137]. The type of cTn measured appears to alter the incidence of MINS. In the systematic review by Smilowitz et al., the authors found that the pooled incidence of MINS when hs-TnT was measured was 24.7% (95%CI 19.7 – 29.9%, n=10) compared to 17.4% (95%CI 14.9-20.0%, n=40) and 20.1% (95%CI 16.8 – 23.6, n=79) when (non high-sensitivity) TnT or TnI were measured, respectively[135].

The difference in incidence between TnT and TnI was further investigated by Gualandro et al. (as part of BASEL-PMI) who found that the incidence of

postoperative myocardial injury was 6.1% (95%CI 5.3-6.9%) when measured using hs-TnI (99th URL of 26ng/L) but again higher when measured using hs-TnT (11.3%, 95%CI 10.2 – 12.4%) with a 99th URL of 14ng/L[138]. All patients had both hs-TnI and hs-TnT measured pre- and postoperatively, however, there was no prognostic difference between the two cTn types.

Care also needs to be taken when describing the troponin assay used as the 99th URL for each may vary depending on the manufacturer's reference. For example, in the METS study (described in Section 1.2.4) different assays were used at different centres. Across the centres, eight different assays were utilised with hs-TnT cut-offs varying from >14ng/L to >29ng/L.

1.6.2.2 Risk factors

The systematic review by Smilowitz et al. demonstrated that the demographics of patients with MINS, when compared to patients without were older, male and more likely to have hypertension, coronary artery disease, prior myocardial infarction, heart failure and kidney disease; thereby exhibiting typical cardiovascular risk factors. Patients undergoing emergency surgery were more likely to experience MINS (RR 1.74 (95%CI 1.35–2.25)). There was also variation in the incidence of MINS in patients undergoing different surgical specialties: general surgical patients had the highest incidence (25.9% (95%CI 15.1 – 38.4%)) with orthopaedics the lowest (18.0% (95%CI 12.1 – 24.7%)).

1.6.3 Mechanism

1.6.3.1 Release of cardiac troponin

For cTn to be detectable within blood, there needs to have been a degree of cardiomyocyte damage or stress, leading to its release. There are different pathways through which this may occur and is not necessarily pathological. Troponin elevation can occur after exercise[139,140] and in healthy patients undergoing straightforward surgery without any repercussions[141], indicating a potentially benign process. Cardiomyocyte necrosis due to either type 1 (atherothrombotic coronary artery disease, usually precipitated by atherosclerotic plaque disruption leading to reduced blood supply to the myocardium) or type 2 MI mismatch between the oxygen supply and demand of

the myocardium) leads to the release of large covalent cTn complexes as there is complete disruption of the sarcolemma. However, non-necrotic pathways such as intracellular proteolysis or increased sarcolemma permeability cause smaller cTn fragments to be present in the blood. Intracellular proteolysis has been demonstrated in laboratory studies in physiological conditions, after ischaemic-reperfusion injury, mechanical stress and rapid pacing. Inflammation is also a proposed mechanism for intracellular proteolysis of cTn complexes. Increased sarcolemma permeability, either through increased expression of transmembrane proteins or via extracellular vesicles have been demonstrated in cases of cardiomyocyte stress and inflammation via TNF-α pathways. Current cTn assays cannot distinguish between large covalent troponin complexes released following cell necrosis and the smaller cTn fragments. However, there is potential in the future to ascertain the underlying mechanism via the identification of the size and type of cTn released[142].

1.6.3.2 Ischaemic mechanisms

Myocardial injury after non-cardiac surgery as defined by VISION and the AHA is presumed due to an ischaemic cause with no evidence of an overt non-ischaemic cause. The potential ischaemic causes of myocardial injury are the same as for perioperative MI with the majority attributed to a type 2 mechanism. Similar rates of coronary artery disease have been demonstrated in patients with and without MINS who underwent cardiac computed tomography within one month of discharge after major non-cardiac surgery[143]. Also, trials investigating potential therapies for PMI using conventional ACS management, such as aspirin[144] or statins[135], have not demonstrated improvements in outcome, which might have been anticipated if coronary artery disease were the underlying cause.

Type 2 ischaemia as the main mechanism behind PMI is being challenged however, with recent studies demonstrating the robustness of coronary artery autoregulation and myocardial perfusion-contraction coupling[142]. For type 2 ischaemia to occur, these compensatory mechanisms need to fail, something which is only likely to occur after prolonged or severe hypotension, hypoxia or tachycardia, or occur in vulnerable hearts. This is certainly a risk in the perioperative period but Pinto and Ackland suggest a more complex, systemic

process involving a combination of autonomic dysfunction, cardiac mechanical stress and systemic inflammation as the underlying driver for PMI[142].

1.6.3.3 Non-ischaemic mechanisms

There are multiple mechanisms through which cardiomyocytes may release cTn in the absence of ischaemia. Via the cTn release pathways described above, the non-ischaemic causes can be classified into systemic inflammation, haemodynamic strain and autonomic dysfunction, with interaction between these mechanisms (Figure 11).

There is increasing interest in the role of systemic inflammation in the perioperative period, and its subsequent effects on autonomic stress and postoperative cardiovascular complications. Ackland et al., demonstrated an association between elevated preoperative neutrophil-lymphocyte ratio (a marker of established systemic inflammation) and PMI (OR 2.56 (1.92-3.41)) in over 1600 patients undergoing elective non-cardiac surgery[23]. This demonstrated that patients with systemic inflammation preoperatively were at higher risk of PMI. In addition to preoperative inflammation, the surgical stress response elicits a state of hyper-catabolism and pro-inflammation via sympathetic stimulation. May et al., performed two nested case control studies, measuring microRNAs associated with acute coronary syndrome in the postoperative period in matched patients with and without PMI. The first investigation (n=48) found microRNAs associated with myocardial ischaemia were elevated postoperatively in all, but this was independent of troponin concentration, suggesting there is a generalised cardiac stress response to surgery seen in all patients, but which does not necessarily lead to troponin release. The second, exploratory study using next-generation microRNA sequencing reinforced this hypothesis as the top two biological processes associated with PMI were adrenergic stress and calcium dysregulation. The inference from this study was that PMI is a consequence of deficient cardioprotective mechanisms in the face of catecholamine release in the perioperative period[145].

Other mechanisms which may cause elevated cTn in the absence of oxygen deficit include increased mechanical stress on the heart e.g. both increased preload and afterload. Increased preload e.g. intraoperative fluid administration

causes myocardial stretch, and, as already described, acute heart failure is associated with PMI[146]. Increased left ventricular afterload may be caused by catecholamine release secondary to the surgical stress response. Pulmonary embolus, increasing right ventricular afterload, is a common perioperative complication found in 33% of patients with postoperative MI and 20% of patients without postoperative MI[147]. A review of the cardiovascular pathophysiological changes following lung resection surgery noted that postoperative troponin elevation is associated with the volume of lung resected in a dose-dependent manner and that postoperative troponin elevation is associated with right ventricle ejection fraction but not the left[148].

Autonomic dysfunction has detrimental effects on coronary microvascular tone, worsens baroreflex function, causes tachycardia and is proinflammatory; all of which can lead to cardiomyocyte stress. There is increasing evidence that ANS dysfunction is associated with PMI[149,150], with suggestions that preserving or restoring vagal function can limit myocardial injury (in rat models)[151].

Overall, the mechanisms behind PMI are complex and likely to incorporate both the systemic effects of surgical stress e.g. autonomic dysfunction and inflammation, and local cardiac effects such as increased mechanical stress and a degree of oxygen supply-demand mismatch. All these interlinking mechanisms (Figure 11) are likely to have a detrimental effect on patients predisposed to PMI either via existing coronary artery disease, or potentially more likely via existing inflammation and autonomic dysfunction.

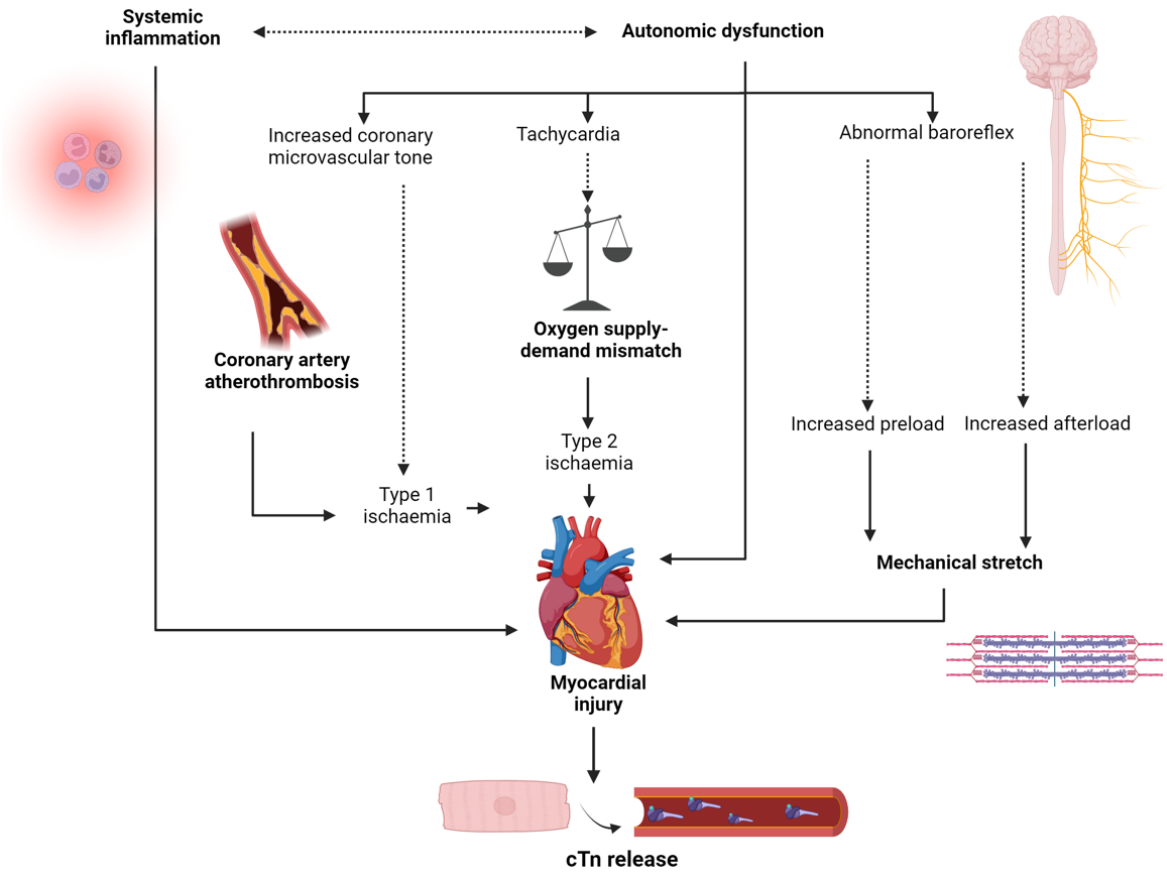


Figure 11 Proposed mechanisms of myocardial injury. Dashed lines indicate additional detrimental effects. Figure created using BioRender®.

1.6.4 Outcomes

Postoperative myocardial injury has been consistently demonstrated to be associated with poor postoperative outcomes, regardless of mechanism. The systematic review performed by Smilowitz et al., found that in-hospital mortality reported in 25 studies was 8.1% (4.4-12.7%) in patients with MINS versus 0.4% (0.2-0.7%) in patients without (p<0.001). Thirty-day and 1 year mortality were also significantly higher in patients with MINS than without (8.5% (6.2-11.0%) versus 1.2% (0.9-1.6%, p<0.001)), and 20.6% (15.9-25.7%) versus 5.1% (3.2-7.4%, p<0.001), respectively)[135]. Longer term data is lacking, but pooled mortality incidence from 11 studies ranging from 2-7 year follow-up demonstrated mortality of 42.7% (33.8-51.8%) among patients with MINS versus 19.7% (10.6-30.9%) in patients without MINS (p<0.001)[135].

A prospective cohort study in 2021 in 2455 patients undergoing non-cardiac surgery found that PMI was an independent predictor of 30-day all-cause

mortality (aHR 2.8 (1.4-5.5)) and was comparable to the 30-day mortality for patients in the same group with demonstratable perioperative myocardial *infarct* (adjusted hazard ratio of 2.5 (1.1-6.0))[138]. The risk of mortality was increased in both the infarct group at one year (aHR 2.0 (1.2-3.3)) and the injury group (aHR 1.8 (1.2–2.7)) although remained relatively similar. Although not to the extent seen in the infarction group, PMI was also associated with an increased risk of MACE (aHR 2.2 (1.3-3.8) at 30-days and 1.7 (1.1-2.5) at one year)[138]. The BASEL-PMI study is an ongoing programme of active PMI surveillance for high-risk patients undergoing major non-cardiac surgery. Over a one year period, recruiting 2018 patients undergoing non-cardiac surgery, they found that 9.8% (6.8-14.0%) of patients with PMI died 30-days after surgery compared with 1.6% (1.1-2.4%) who did not develop PMI ($p<0.001$). At one year, 22.5% (17.9-27.8%) of patients who developed PMI had died compared to 9.3% (8.0 – 10.8%, $p<0.001$) of patients who did not.

There is clear evidence that PMI is associated with poor postoperative outcomes with mortality effects continuing long into the postoperative period. The morbidity burden and reduced disability-free survival will have implications not just on patient quality of life but also health economics. Overall, despite differences in definition within the literature, PMI is a relatively easy to measure postoperative outcome which reflects cardiac vagal tone and is associated with worse postoperative outcomes.

1.7 Conclusion

The number and complexity of patients presenting for surgery is increasing, with the development of postoperative complications placing considerable burden on the health service, as well as negatively impacting patients' quality and length of life. Effective preoperative risk stratification aims to assess the likelihood of poor postoperative outcomes, thereby guiding shared-decision making and the consent process; intraoperative conduct; and the level of postoperative care required. Current risk stratification modalities include risk scores, biomarkers and exercise testing. However, taken individually, the predictive value of these modalities is variable, depending on the patient population and outcome measured, with varying uptake and recommendations in international guidelines. Cardiopulmonary exercise testing is considered the gold-standard exercise test

to assess cardiorespiratory fitness as it provides objective measures of cardiorespiratory and skeletal muscle function. However, the translation of CPET-derived measures as a predictive perioperative tool is less clear-cut. Cardiopulmonary exercise testing is also resource-intensive and not available to all patients.

Assessment of cardiac vagal tone presents an opportunity to measure cardiorespiratory fitness but also underlying comorbidity and systemic inflammation, and has been demonstrated to be associated with postoperative complications. Heart rate recovery is a marker of cardiac vagal tone, which can be measured after submaximal exercise, therefore potentially less resource-intensive and more acceptable to patients than CPET. Submaximal HRR in the perioperative population is a novel measure which requires determination of its clinical usefulness. Postoperative myocardial injury is a relatively easy-to-measure endpoint which reflects autonomic dysfunction and the surgical stress response. Therefore, this thesis aims to assess the predictive value of submaximal HRR as a preoperative risk measure with PMI as the primary outcome.

Chapter 2 Systematic review and meta-analysis

Heart rate recovery has been extensively investigated as a prognostic measure in cardiology and in population-based health studies (Section 1.4). However, the use of HRR, particularly after submaximal exercise, has been investigated very little within the perioperative setting. The purpose of this systematic review and meta-analysis is to collate the available literature and summarise evidence for this potentially useful metric in the surgical population to guide this investigation.

2.1 Methods

2.1.1 Registration

This systematic review was prospectively registered on 3rd November 2021 on the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021286416, available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021286416.

2.1.2 Search strategy

Scoping searches were performed by the author, and formal systematic search strategies specific to each database were created by the author with the guidance of a medical librarian. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed throughout[152]. A systematic search of OVID MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) were performed on 15th November 2021, and OVID EMBASE on 16th November 2021. Controlled terms such as MeSH and text words were used. A combination of heart rate recovery terms, exercise terms and terms for post-operative complications were searched for. Limits applied were for English language articles only. The following search strategy was used for Ovid Medline® 1946 to November week one 2021:

Number	Search term	Result
1	(heart rate adj3 recover*).tw	1616
2	(HR adj2 recover*).tw	922
3	((heart rate OR HR OR heart beat OR heartbeat OR beat* per min* OR bpm) adj5 (post-exer* OR postexer* OR exer* cessation OR ((after OR post OR following) adj2 (exer* OR effort OR recovery)))).tw	1628
4	((drop OR decreas* OR decline OR fall OR decay*) adj4 (heart rate* OR beat OR bpm OR HR OR heart rat*) AND (post-exer* OR postexer* OR exer* cessation OR (after OR post OR following) adj2 (exer* OR effort OR recover*))).tw	584
5	(HRR OR HRR1 OR HRR2 OR HRR3 OR HRR60).tw	1932
6	(HR OR heart rate*) adj2 (profile* OR respons*).tw	8774
7	Heart Rate/ AND Recovery of Function/	824
8	OR/1-7 [HRR]	14114
9	Exercise Test/ OR Exercise/ OR Walk Test/	183414
10	(cardiopulmon* OR cardiopulmonary exer*).tw	66746
11	(walk* adj3 (test* OR six min* OR 6 min* OR 6-min* OR shuttle)).tw	17084
12	(tread* OR treadmill OR Bruce protocol OR ramp).tw	38535
13	(6MWT OR 6-MWT OR 6MWD OR 6-MWD or CPET or CPEX).tw	5838
14	OR/9-13 [Exercise]	277201
15	Treatment Outcome/ OR Postoperative Complications/	1378294
16	((Complicat* OR outcome* OR morbid* OR mortalit* OR risk) adj3 (Post-operat* OR postop* OR pre-operat* OR preop* OR peri-op* OR periop* OR surg*)).tw	275575
17	OR/15-16 [Outcomes]	1501251
18	8 AND 14 [HRR and exercise]	3713
19	17 AND 18 [HRR after exercise and perioperative outcome]	206
20	Exp Adults/	7638268
21	Humans/	19874316
22	19 AND 20 AND 21	177
23	22 limited to English Language	175

Search strategies specific to EMBASE and CENTRAL followed similar search language (Appendix 1).

2.1.3 Inclusion and exclusion criteria

The inclusion criteria were adults (aged 18 years and over) undergoing non-cardiac surgery who had heart rate recovery measured after preoperative exercise testing.

Exclusion criteria were:

- aged less than 18 years
- cardiac surgery or non-operative procedures e.g. percutaneous coronary angioplasty
- patients with cardiac pacemakers
- studies involving the administration of drugs with the purpose of altering heart rate e.g. dobutamine stress tests.

The main aims of the exclusion criteria were to exclude studies where heart rate recovery was measured as part of an outcome or intervention rather than an observational finding. Non-cardiac surgery was chosen as postoperative outcomes in cardiac surgery are not generalisable to the wider surgical population.

Study design was not part of the inclusion or exclusion criteria. We expected eligible studies to be prospective or retrospective observational cohort studies reporting on the relationship of HRR and postoperative complications, including mortality. However, we did not rule out randomised controlled trials at the screening stage to ensure data was not missed.

2.1.4 Article selection

Two investigators, the author and Hassan Ismahel (HI), a BSc Intercalating medical student, independently screened all abstracts. Any indecision was resolved by consensus with a third investigator, Prof. Ben Shelley (BS). After initial screening, all potentially eligible studies were reviewed in full text.

Citation lists of each article were reviewed to screen for any additional papers not identified using the database search strategy.

2.1.5 Risk of bias

All studies identified were observational cohort studies, therefore the Quality in Prognostic Studies (QUIPS) tool was used[153]. The QUIPS tool is based on six domains: study participants; study attrition; prognostic factor measurement; outcome measurement; study confounding and statistical analysis and reporting. Each domain was rated as high, moderate or low-risk of bias with an overall rating then given to each article based on the number and distribution of risk of bias by consensus agreement between the author and HI. As per article selection, any disagreements were arbitrated by BS.

2.1.6 Data extraction

Data extraction was performed individually by the author, HI and an elective medical student, Catriona MacKenzie (CM) using modified Cochrane data collection forms[154] and a Microsoft Excel spreadsheet. Any indecision was resolved by consensus with investigator BS. Data collected on the data collection forms included title, author and date of publication; population and setting; methods; participants; outcomes; results and applicability. Information was then transferred to an Excel spreadsheet with the following information retrieved: country of study population; number of participants; study design; length of follow-up/ primary outcome; reported patient demographics; reported co-morbidities; mean resting heart rate; type of exercise test; level of intensity of exercise test (submaximal or maximal); quantification of exercise intensity; recovery period length and whether active or passive; type of heart rate recovery measurement; statistical model; raw outcome data and associated measure (e.g. odds ratio) and whether a multivariable prediction model was developed.

The primary outcomes extracted were: postoperative morbidity score; incidence of cardiopulmonary complications; postoperative myocardial injury and hospital length of stay. Secondary outcomes extracted were hospital length of stay and mortality.

2.1.7 Statistical handling

Data are presented as mean (SD) or median (IQR) appropriate to distribution. A p-value <0.05 was considered statistically significant.

Where regression models were used, results were extracted as odds ratio or hazard ratio. For the purpose of meta-analysis, raw data (events versus non-events) were used when able. Random effects meta-analysis was performed where able to generate pooled incidence of postoperative complications and hospital length of stay. Due to the small number of studies and high levels of heterogeneity, sub-study analysis could not be performed. Meta-analysis was performed using "Comprehensive Meta-Analysis" software (Version 4), BioStat, Englewood, New Jersey (www.meta-analysis.com).

Heterogeneity was assessed via the Chi-squared test and the I^2 statistic. A p-value of less than 0.05 and I^2 statistic of over 75% were deemed to demonstrate significant heterogeneity[155]. If heterogeneity was significant, no combined effect of HRR on outcome would be estimated. If heterogeneity allowed, pooled estimates were generated and forest plots used to visualise the variation of odds/hazard ratio across included studies.

2.2 Results

2.2.1 Studies

In total, after removing duplicates, the abstracts of 475 reports were screened. Thirty studies were selected to retrieve the full text articles. One eligible paper was identified by reviewing the citation lists of the full text articles. In total, four reports met the inclusion criteria and were included in the systematic review. Figure 12 shows the PRISMA flow diagram for this systematic review

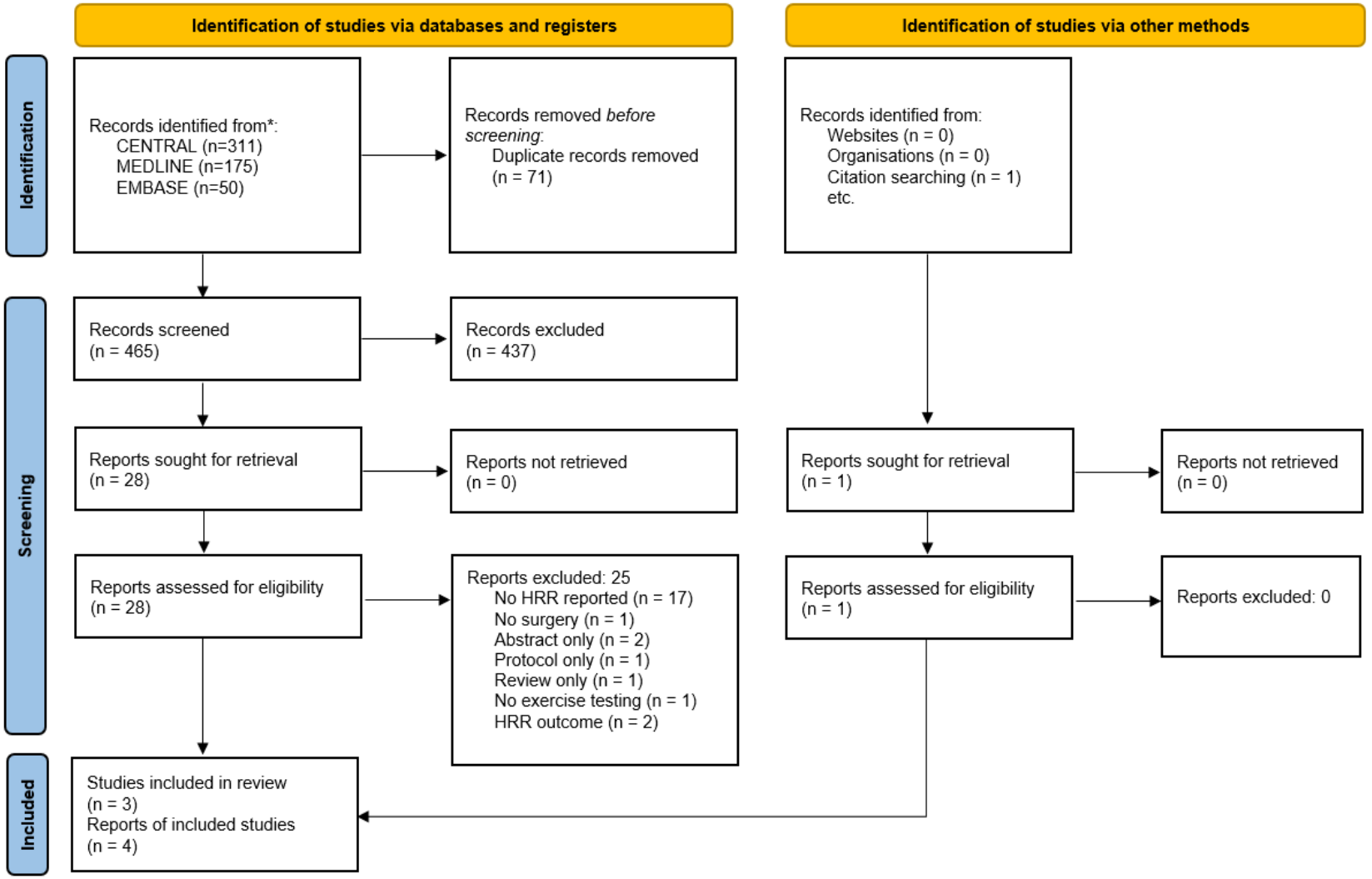


Figure 12 PRISMA Flow chart. HRR: heart rate recovery.

The characteristics of the studies included in the analysis are shown in Table 3. Two reports were planned secondary analyses of the same study (the Measurement of Exercise Tolerance before Surgery (METS) study[38]); both are described below but only one was used for the meta-analysis. A total number of 3538 patients were included across the four reports. All four were observational studies measuring the association between preoperative heart rate recovery and postoperative outcomes. Primary outcomes were reported as postoperative complications, a composite of death or myocardial injury and length of hospital stay.

Table 3 Characteristics of included studies. HRR: heart rate recovery; CPET: cardiopulmonary exercise testing; bpm: beats per minute. POMS: postoperative morbidity survey

Report (year)	Corresponding study	Study type	Country	Type of surgery	Exercise test	HRR_1 impairment threshold	HRR_1 start time	Type of cooldown	Total number of participants	Impaired HRR1 incidence	Primary outcome	Secondary outcomes
Abbott et al. (2019)[150]	METS[38]	Observational; prospective cohort study	Canada UK Australia New Zealand	Elective non-cardiac surgery	CPET	≤ 12 bpm	End of exercise	Active	1326	548 (41.3%)	Postoperative myocardial injury, defined by serum troponin concentration within 72 h after surgery	-
Ackland et al. (2016)[107]	COMPETE-C[106]	Double-blind stratified RCT	UK	Open or laparoscopic colorectal surgery	CPET	≤ 10 bpm	Peak exercise	Unclear	175	61 (34.9%)	Length of hospital stay	Severe (>grade 3 Clavien-Dindo) complications Postoperative sepsis Critical care requirement
Ackland et al. (2019)[156]	METS[38]	Observational; prospective	Canada UK Australia New Zealand	Elective non-cardiac surgery	CPET	≤ 12 bpm	Peak exercise	Active	1301	538 (41.4%)	Death or myocardial infarction within 30-days after surgery	Complications after surgery, as defined by POMS and Clavien-Dindo grading.
	POM-HR[157]	Observational; prospective	UK	Any lasting > 2 hours	CPET	≤ 12 bpm	Peak exercise	Active	640	284 (44.4%)	Any postoperative complication defined by the POMS within five days of surgery	-
	Trials combined	-	-	-	-	-	-	-	1941	822 (42.3%)	All-cause postoperative morbidity, assessed using the POMS	Type of morbidity (as defined by POMS) Time to become morbidity-free Length of hospital stay
Ha et al. (2015)[158]	-	Observational; retrospective	Canada	Lung resection for lung cancer	6MWT	≤ 12 bpm	End of exercise	Unclear	96	31 (32.3%)	Cardiopulmonary complications within 30-days after surgery	30-day mortality

The four reports varied predominantly in their method of HRR measurement and primary outcome. Hence an exploratory meta-analysis was performed. In total, across the four reports, postoperative outcomes were recorded in 3538 patients who had preoperative heart rate recovery measured. Ackland et al. (2019)[156] and Abbott et al.[150] both reported patients enrolled in the METS study[38]. Ackland et al. (2019) reported 1301 patients and Abbott et al. reported 1326 patients. Reviewing the flow charts and study protocols it is unclear why there is a difference of 25 patients with HRR data available. However, there is likely to be overlap between patients in the same study but different reports (i.e. a patient may have undergone preoperative HRR measurement and had both postoperative myocardial injury and perioperative morbidity score recorded). To avoid duplication, only one paper (Ackland et al. (2019)[156]) was included in the meta-analysis. This was because the primary outcome (PostOperative Morbidity Score (POMS) five days within surgery) allowed comparison with another study (Ha et al.[158]).

2.2.2 Risk of bias

Two studies were assessed to be at moderate risk of bias; one at low-moderate risk and one low-risk (Table 4). Meta-analysis was deemed useful to perform, dependent on statistical heterogeneity analysis, with the caveat that some of the studies reported were at risk of moderate bias. The small number of reports precluded funnel plot analysis of publication bias.

Table 4 Risk of bias according to the QUIPS tool. Green: low-risk; orange: moderate risk; red: high-risk; grey: not applicable

Report	Study participants	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall risk bias
Abbott et al. (2019)[150]							
Ackland et al. (2016)[107]							
Ackland et al. (2019)[156]							
Ha et al. (2015)[158]							

2.2.3 Patient and study demographics

Table 5 shows the baseline characteristics of the study populations. Demographics were similar between studies with mean age, BMI and sex comparable between all four reports. Measures of cardiovascular fitness, medication use, biomarkers and patient comorbidities were reported inconsistently. Two reports included patients aged over 40 years undergoing noncardiac elective surgery, one report was only in colorectal surgical patients and one only included patients undergoing lung resection. Three reports described beta-blocker use, ranging from 16.2% to 25.3%; two reports considered the potential effect of beta-blockers on outcome. Three reports presented resting heart rate: Ackland et al. (2019) and Abbott et al. were comparable but Ha et al. demonstrated a higher resting heart rate.

Table 5 Baseline characteristics of patient cohorts. Data reported as mean±SD, median (IQR) or n(%) as appropriate. BMI: body mass index; bpm: beats per minute; ASA: American Society of Anaesthesiologists; COPD: chronic obstructive pulmonary disease; NR: not reported

Report (year)	Age (years)	Male	BMI	Resting heart rate (bpm)	Anaerobic threshold (ml/kg/min)	ASA status (1/2/3/4)	Pre-existing atrial arrhythmia	COPD	Malignancy	Beta-blockers	Calcium channel blockers	Creatinine (mmol/L)	Haemoglobin (g/dl)
Abbott et al. (2019)[150]	64.2±10.3	816 (61.5%)	NR	77±14.1	12.7±4.1	99/780/427/18	50 (3.8%)	155 (11.7%)	NR	215 (16.2%)	26 (2.0%)	NR	NR
Ackland et al. (2016)[107]	66.5±14.7	125 (71.4%)	28.0±4.3	NR	NR	NR	NR	NR	130 (74.3%)	NR	NR	NR	NR
Ackland et al. (2019)[156]	65.7±10.8	1230 (63.4%)	28.4±6.0	78.4±14.8	12.4±3.9	NR	NR	NR	NR	357 (18.4%)	169 (8.7%)	77 (67-90)	13.8±1.6
Ha et al. (2015)[158]	65.5±9.6	50 (52.1%)	27.8±5.2	84.8±16.1	NR	0/4/68/24	6 (6.3%)	41 (42.7%)	96 (100%)	24 (25.3%)	NR	80±27	13.3±1.4

Table 6 Statistical analysis and summary results of reports. Risk measures reported as ratio (confidence intervals). RCRI: revised cardiac risk index; PMI: postoperative myocardial injury; POMS: postoperative morbidity survey; NR: not reported.

Report (year)	Statistical analysis	Risk measurement	Unadjusted	Adjusted	Primary Outcome
Abbott et al. (2019)[150]	Univariable/multivariable logistic regression	Odds ratio	1.54 (1.11 – 2.13)	1.50 (1.08 – 2.08) (RCRI)	PMI within 72 hours of surgery
Ackland et al. (2016)[107]	Cox proportional hazard	Hazard ratio	1.59 (1.13 – 2.24)	NR	Length of hospital stay
Ackland et al. (2019)[156]	Fishers exact test	Odds ratio	1.38 (1.14 – 1.67)	NR	All-cause POMS within five days of surgery
Ha et al. (2015)[158]	Univariable/multivariable logistic regression	Odds ratio	3.43 (1.40 – 8.42)	4.97 (1.79 – 13.8)	Cardiopulmonary complications within 30-days of surgery

2.2.4 Heart rate recovery measurement

Exercise test conduct and method of HRR measurement is detailed in Table 3. All studies measured heart rate recovery one minute after exercise cessation (HRR_1) but the methods of measurement were inconsistent between studies. Three studies measured heart rate recovery one minute after maximal cardiopulmonary exercise testing[107,150,156]; the other reported heart rate recovery one minute after a six-minute walk test (6MWT, submaximal exercise)[158]. Heart rate recovery after CPET however is seldom reported clinically, with other variables preferred (Section 1.2.10).

Three studies used a cut-off of a reduction in heart rate of 12 bpm to demonstrate poor aerobic capacity. A HRR1 ≤12 bpm was first described by Cole et al.[114] as a predictor of mortality in healthy participants and is the typical method of stratifying risk after maximal exercise. One of the studies measuring HRR_1 after CPET used the cut-off of ≤10 bpm as a discriminator of impaired vagal tone[107]. This was following stratification of patients by spontaneous baroreflex sensitivity (measured via preoperative intra-arterial pressure recordings). The authors found that a HRR ≤10 bpm was a more sensitive measure of autonomic dysfunction in their population.

The described point at which HRR_1 measurement began also varied between studies with three reporting it at peak exercise (during maximal exercise) and two at the end of exercise. In theory this will be the same point if patients reached maximal effort at the same time as test termination, however different papers described these timepoints differently. Similarly, the type of cool down (active or static) varied. CPET protocols describe an active recovery (workload of 20W for five minutes as per POETTS[57]), and where reported this was the type of recovery used. Ha et al. describe a static recovery, sitting on a chair as per the ATS guidelines for the 6MWT[70].

The incidence of impaired HRR_1 was fairly similar across reports, ranging from 32.3% to 44.4%. Ackland et al. (2016) and Ha et al. had the lower rates of impaired HRR_1 (34.9% and 32.3% respectively). In the case of Ackland et al. (2016) this could be because they used a lower cut-off to define impaired HRR_1

(≤10 bpm), and in the case of Ha et al., because they measured HRR_1 after submaximal exercise but used a cut-off defined from maximal testing.

2.2.5 Primary outcomes reported

Primary outcome measures varied between reports but all reported a significantly increased risk of primary outcome when HRR_1 was impaired (Table 6). Ackland et al. (2019)[156] and Ha et al.[158] both measured the incidence of postoperative complications (postoperative complications as defined by the POMS and cardiopulmonary complications, respectively) and so these results were combined for initial heterogeneity testing.

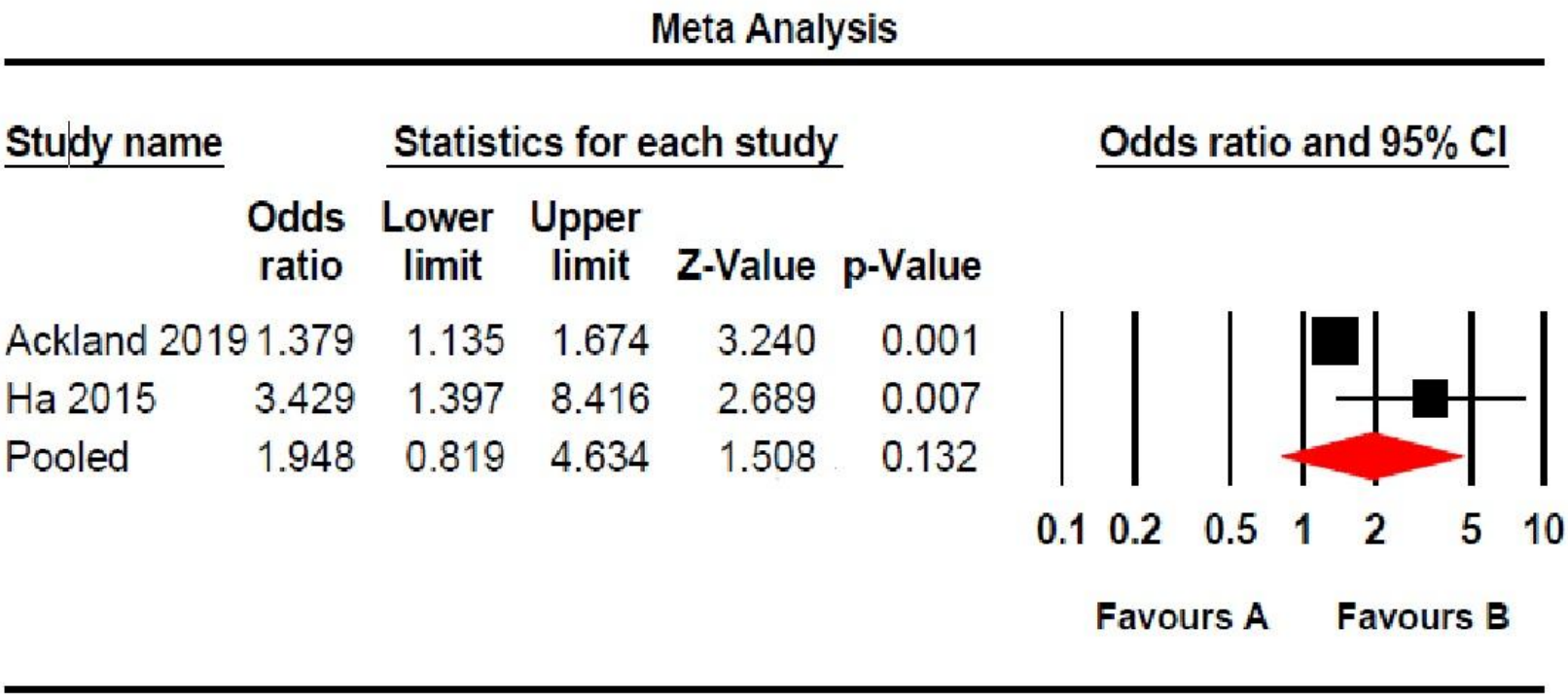
Three studies reported unadjusted odds ratio for impaired versus non-impaired HRR_1 with two reporting adjusted odds ratios. Ackland et al. (2016) reported a hazard ratio of 1.59 (95%CI 1.13-2.24) for length of hospital stay. When Abbott et al. adjusted the odds ratio for Revised Cardiac Risk Index (RCRI) score and individual components of the score, impaired HRR remained independently associated with PMI. Ha et al. adjusted for multiple individual risk factors for cardiopulmonary complications, and found impaired HRR_1 remained independently associated with cardiopulmonary outcomes. Using this multivariable logistic regression model, they found an optimal cut-off for HRR_1 of 13 bpm.

2.3 Meta-analysis

2.3.1 Postoperative complications

Prior to performing the systematic review, it was acknowledged there were likely to be little consistent data, and a pragmatic plan was made that if sufficient data were available, meta-analysis would be performed. The four studies measured different outcomes; however, Ackland et al. (2019) and Ha et al. both measure postoperative complications as their primary outcome. Therefore, the results were combined for initial heterogeneity testing. The I^2 statistic for the data was 73% ($p = 0.05$) which met the prespecified criteria to perform random effects meta-analysis. The pooled odds ratio for patients with postoperative complications with a HRR_1 ≤12 bpm was 1.95 (95%CI 0.82 – 4.63), demonstrating, within the limitations of this meta-analysis, HRR_1 is not

associated with postoperative complications in the published literature (Figure 13). Due to the small number of reports and high levels of heterogeneity, sub-study analysis could not be performed.



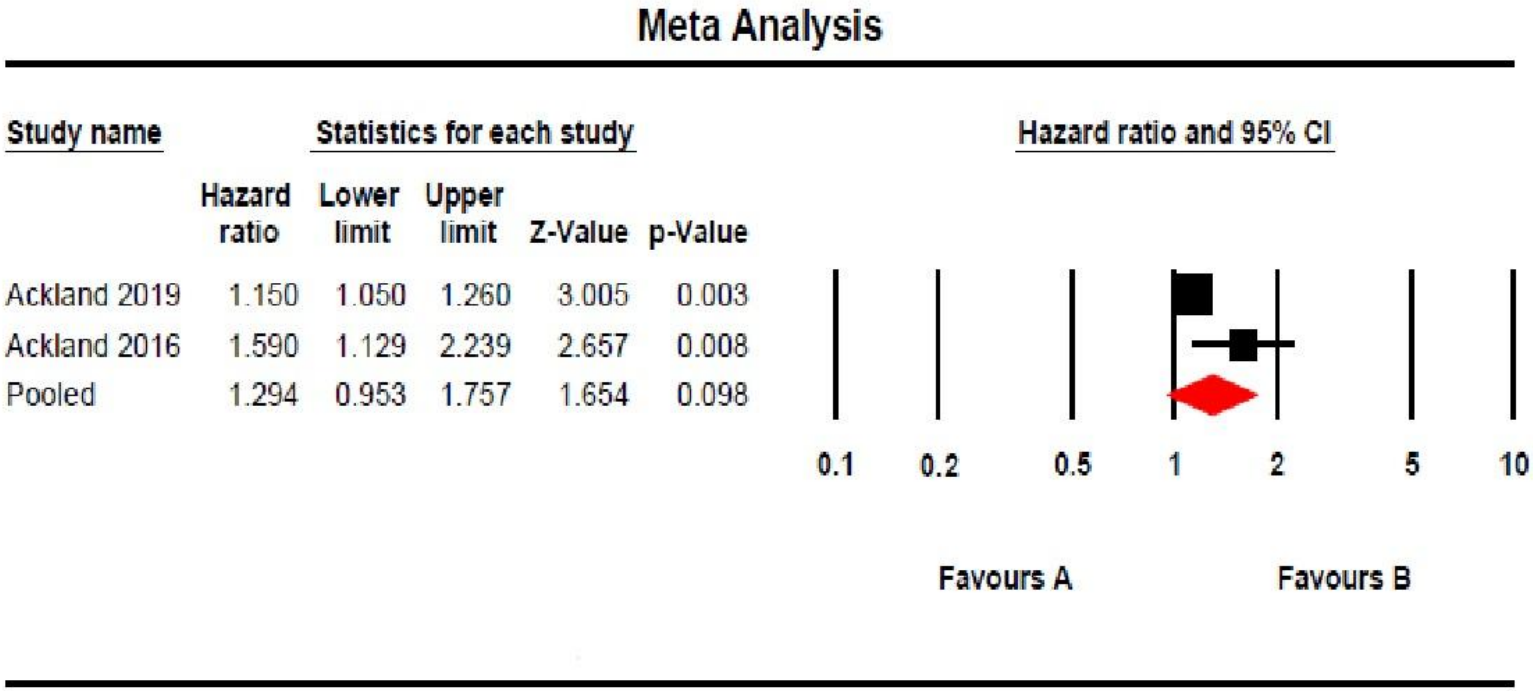
Meta Analysis

Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	2	1.436	1.188	1.736	3.736	0.000	3.778	1	0.052	73.530	0.305	0.587	0.345	0.552
Random	2	1.948	0.819	4.634	1.508	0.132								

Figure 13 Forest plot of postoperative complications reported in Ackland et al (2019)[156] and Ha et al.[158]. A: non-impaired HRR_1; B: impaired HRR_1

2.3.2 Length of hospital stay

Two studies reported length of hospital stay in association with HRR_1; Ackland et al. (2016)[107] as the primary outcome and Ackland et al. (2019)[156] as a secondary outcome. Initial heterogeneity testing determined I^2 = 68.9% (p = 0.07), meeting the prespecified criteria for random effects meta-analysis (Figure 14). The pooled hazard ratio for hospital length of stay was 1.29 (95%CI 0.95 – 1.76) demonstrating that preoperative maximal HRR_1 is not associated with hospital length of stay, within the limitations of this analysis (Figure 14).



Meta Analysis

Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	2	1.175	1.076	1.283	3.588	0.000	3.216	1	0.073	68.907	0.036	0.074	0.006	0.190
Random	2	1.294	0.953	1.757	1.654	0.098								

Figure 14 Forest plot of length of hospital stay reported in Ackland et al (2019) and Ackland et al. (2016). A: non-impaired HRR_1; B: impaired HRR_1

2.4 Discussion

This systematic review and meta-analysis found four reports measuring heart rate recovery after preoperative exercise testing in a total of 3538 patients. There was variation in the mode and exertion level of the exercise tests and primary outcomes reported. All reports individually demonstrated a significant association between impaired HRR_1 and poor postoperative outcome. Meta-analyses of the data, however, did not demonstrate association between HRR_1 and postoperative complications or hospital length of stay.

Two of the reports adjusted the primary outcomes for potential confounders. Ha et al. adjusted for beta-blocker therapy, nodal clinical stage, predicted postoperative forced expiratory volume in one second, and change in blood pressure during the test finding impaired HRR remained independently associated with postoperative cardiopulmonary complications (OR 4.97 (1.79 – 13.80))[158]. The authors created a predictive model including beta-blocker therapy, change in SBP and impaired HRR_1 with a AUROC of 0.73 (confidence interval not reported). Using this model, in their patient cohort, the optimal cut-off for HRR in predicting cardiopulmonary complications (CPCs) was ≤13 bpm. Sensitivity analysis excluding patients with atrial fibrillation (n = 6 (6%)) did not alter the association between impaired HRR_1 and CPCs. In this study, Ha et al. also measured submaximal HRR in a cohort of 49 patients with early-stage lung cancer who were deemed too high-risk for surgical resection based on traditional measures of cardiopulmonary fitness and therefore underwent stereotactic body radiation therapy instead. There was a higher rate of impaired HRR_1 in this cohort compared to the group who underwent surgical resection (65.0% versus 32.3%). This demonstrates the face validity (Section 3.2.5) of impaired HRR as patients deemed too high-risk via clinician opinion also had a significantly higher rate of impaired HRR. After adjusting for baseline cardiovascular risk via the RCRI score and its separate components, Abbott et al. found the association between impaired HRR_1 and PMI remained (OR 1.50 (1.08 – 2.08))[150]. Two reports adjusted for beta-blocker use and found administration made no difference to the impact of HRR_1 on outcome. This is consistent with the literature examining heart rate recovery in patients with cardiovascular disease[159] and corroborates results of early physiological studies which suggest initial fall in heart rate after exercise is due to vagal reactivation (and therefore not affected by sympathetic

blockade) with the sympathetic component occurring later after exercise[84] (Section 1.3.3).

Heart rate, whether resting heart rate, or HRR, is reflective of cardiac vagal tone (Section 1.3.3). There is laboratory evidence that cardiac vagal tone is protective on a cellular level, as murine in-vitro loss of cardiac vagal tone exacerbates myocardial cellular damage after inflammation[98], haemorrhage[99] and ischaemia[100], providing a clear mechanistic rationale for the prognostic effect of HRR for cardiovascular outcomes. The Revised Cardiac Risk Index (RCRI)[40] is a validated tool estimating the risk of postoperative cardiac complications. Abbott et al. stratified patients into three risk groups based on their RCRI score and found that mean HRR declined as RCRI score increased. Heart rate recovery also showed a similar pattern with preoperative NT-ProBNP, a marker of cardiac myocyte stress, with the proportion of patients with impaired HRR increasing with increasing concentrations of NT-ProBNP. This supports the construct validity (Section 3.2.4) of cardiac vagal dysfunction (as demonstrated by impaired HRR_1) and postoperative cardiac injury.

The assessment of functional capacity before major non-cardiac surgery (METS) study was a large, international, prospective cohort study comparing different methods of assessing functional capacity for predicting death or myocardial infarction (MI) within 30-days of surgery[38] in 1404 patients. Only the Duke Activity Status Index was associated with prediction of death or MI albeit weakly (adjusted OR 0.96 (0.83 - 0.99, p = 0.03). Both the Abbott et al. and Ackland et al. (2019) reports were pre-planned analyses of data from the METS study and both demonstrated a stronger association with HRR_1 and postoperative complications than the association between DASI and death or complications after major elective noncardiac surgery. Although comparing slightly different outcomes, this is an indication that HRR_1 could be as useful in predicting perioperative risk as currently used functional capacity assessment.

2.4.1 Meta-analyses

The first meta-analysis combines data from two reports including 2037 patients who underwent preoperative exercise testing with postoperative complications as the primary outcome. However, the methods of exercise testing were

different; one was after maximal CPET and the second after 6MWT, a submaximal test. Taken separately, both reported an association with HRR_1 and the incidence of postoperative complications. Pooled analysis did not demonstrate this effect however. The odds ratio in Ha et al. was 3.25 (95%CI 1.40 – 8.42)[158] compared to 1.38 (95%CI 1.14 – 1.67) in the Ackland et al. (2019) paper[156]. The Ha et al. report was in a much smaller and more comorbid population with more severe systemic disease, demonstrated by a higher mean resting heart rate and worse ASA Physical Status. These patients were more likely to have COPD and malignancy due to their inclusion criteria of only measuring HRR_1 in patients undergoing lung resection for lung cancer. There was also heterogeneity within the reporting of the postoperative outcomes: Ha et al. reported the incidence of cardiopulmonary postoperative complications within 30-days whereas Ackland et al. (2019) reported postoperative complications as defined by the POMS within 5 days of surgery, possibly explaining the stronger signal of association in the Ha et al. paper. However, Ha et al. also measured submaximal heart rate recovery which could be less robust than HRR_1 after maximal exercise. HRR_1 is an absolute measure which is usually reported after maximal exercise testing. HRR_1 after submaximal testing could be relative to the peak heart rate reached during the exercise test and is an unvalidated measure in a perioperative population. Both reports presented postoperative complications by body system. Ackland et al. (2019) presented number of complications whereas Ha et al. presented number of patients with a complication. The corresponding author of one study was contacted for the breakdown of the number of patients with complications but did not respond, so further analysis of this parameter was not possible.

The second meta-analysis did not demonstrate association between maximal preoperative HRR_1 and hospital length of stay, pooling data from 2116 patients from two reports. Although meeting the prespecified heterogeneity criteria for analysis, there was variation in the method of dichotomisation of HRR_1 and in the measurement of hospital length of stay. Both studies dichotomised patients by HRR_1, however, as previously discussed, Ackland et al (2016)[107] used a cut-off of ≤10 bpm to identify patients with autonomic dysfunction as opposed to the standard HRR_1 ≤12 bpm used in the Ackland et al. (2019) paper[156]. The Ackland et al. (2016) paper also followed patients up for a much longer, with the longest

hospital stay of approximately 180 days. The Ackland et al. (2019) patient cohort follow-up lasted 30-days in comparison. Both differences may explain why there was a stronger association between HRR_1 and hospital length of stay in the Ackland et al. (2016) report. The Ackland et al. (2019) paper also only reports the unadjusted hazard ratio for hospital length of stay, so there is potential for confounders such as comorbidity to influence this outcome. Ackland et al. (2016) reported relative risk of length of hospital stay when patients are dichotomised into those with or without autonomic dysfunction ($HRR_1 \leq 10$ bpm and $HRR_1 > 10$ bpm, respectively).

2.4.2 Limitations

The small number, and observational nature of the reports limit the conclusions that can be drawn from this systematic review and meta-analysis. Heterogeneity, although meeting the prespecified criteria for meta-analysis, was high between each pooled study in both meta-analyses. These can be viewed as exploratory meta-analyses but not particularly robust findings. Between all four reports there were differences in the workload of the exercise tests, methodology for HRR measurement and primary outcomes. Three of the reports measure HRR_1 after maximal exercise testing. However, Ha et al. measured HRR_1 after submaximal exercise testing via 6MWT, where, by definition, maximal heart rate is not reached. Whereas HRR_1 after maximal exercise is a valid and reproducible measure[125,159], HRR_1 after submaximal exercise has been less extensively investigated. Cole et al. (2000) demonstrated in 5234 healthy volunteers that a HRR two minutes after exercise cessation of ≤42 bpm was associated with all-cause mortality over a 12 year follow-up period[118]. Orini et al. demonstrated the intra-individual reproducibility of the whole heart rate profile, including heart rate recovery, in healthy individuals who underwent two exercise tests at 50% and 35% their predicted maximum workload three years apart[125]. Ha et al. add to this data by revealing that defining impaired HRR_1 as an absolute drop of ≤12 bpm without correcting for predicted maximum heart rate is associated with postoperative CPCs in their specific patient cohort.

Despite the small number of reports, the number of patients for whom an outcome associated with HRR_1 was measured was 3538, although there may be overlap in patient populations between the two pre-planned analyses of the

METS study. The observational design limits the mechanistic value of the studies and increases the risk of potential confounding factors. Only two of the reports adjusted the risk ratio for known risk factors for postoperative complications. Despite these inconsistencies, there appears to a be demonstratable, consistent association between impaired HRR_1 and poor postoperative outcomes, including when controlling for other measures known to increase this risk amongst the individual reports identified by this systematic review.

These studies all reported postoperative outcomes or length of hospital stay as primary outcomes. Patient-centred outcomes such as days alive and out of hospital, or postoperative pain analyses could be more meaningful, when considering patient expectations. The widespread effects of parasympathetic dysfunction, not just on organ systems but on pain and inflammation could be better relayed via a patient-centred outcome.

2.4.3 Future work

Future studies could focus on the validity of submaximal heart rate recovery in larger patient cohorts. Although Ha et al. found a positive association by measuring HRR_1, there may be more appropriate measures of heart rate recovery after submaximal exercise which consider the proportion of maximal workload exerted by the patient. The timepoint after exercise cessation could also be investigated; it may be that earlier measurement after exercise cessation could be a more sensitive marker of vagal tone, better reflecting the initial vagal withdrawal. Submaximal heart rate recovery warrants further investigation as a perioperative risk measure as it is feasible to measure at preoperative assessment clinics and requires less resource than maximal heart rate recovery methods (CPET, treadmill tests). One of the main limitations of this systematic review and meta-analysis is variation in measurement of HRR. To meaningfully understand the role of HRR measurement in perioperative risk stratification however, consistency in the conduct of heart rate recovery measurement is required.

2.5 Conclusion

Although exploratory meta-analyses did not demonstrate association between HRR_1 and either postoperative complications or hospital length of stay, the few individual reports identified by systematic review appear to demonstrate an encouraging association between impaired preoperative HRR_1 and a higher incidence of postoperative complications. The reports identified also offer feasible mechanistic proposals regarding the role of impaired vagal tone (measured via HRR) and increased incidence of postoperative complications. Though there is very little perioperative literature examining HRR, this technique has the potential to improve perioperative risk stratification in the future and is worthy of further exploration.

2.6 Addendum

Since the systematic review was completed and during the recruitment period for this study, our group also undertook a separate investigation assessing the association of submaximal HRR parameters with postoperative cardiopulmonary complications in a separate patient group. This study would meet the inclusion criteria for this systematic review, and so is described within this addendum. The study was a planned secondary analysis of the BNP for prediction of outcomes following lung resection surgery (PROFILES) study[160]. A subgroup of 36 patients performed 6MWTs during preoperative assessment with HRR recorded at 30 second intervals over a six-minute recovery period using a portable ECG monitor (Avant 4000, Nonin Medical, Plymouth, MN, USA). Submaximal HRR_1 and area under the heart rate recovery curve after six-minutes from exercise cessation (AUC_6, y axis lower limit of minimum heart rate during recovery period) were available for 29 patients. Significant association was demonstrated between AUC_6 and cardiopulmonary complications (CPC) within 30-days following lung resection ($p = 0.048$). There was no association demonstrated between HRR_1 and cardiopulmonary complications ($p = 0.937$). Submaximal AUC_6 also demonstrated fair predictive value for CPCs with an AUROC of 0.72 (95% CI 0.52 – 0.90); HRR_1 showed no predictive value for CPCs (AUROC 0.53 (95% CI 0.30 – 0.76))[161].

This was a small, exploratory, retrospective secondary analysis. It shares similarities with the Ha et al.[158] paper in that it involved patients undergoing lung resection only with the same primary outcome of CPCs within 30-days of surgery. In contrast to this study, there was no association between HRR_1 and CPCs, however. This was the first study to report area under the heart rate recovery curve in a patient population and so, although a positive finding in a small population, further exploration of this measure is required.

Chapter 3 Hypothesis and aims

The population presenting for surgery is increasingly co-morbid, is older and is undergoing more complex procedures, as previously described. Chronic disease is related to worse postoperative outcomes whereas improved functional capacity is associated with improved postoperative outcome. Currently, preoperative functional capacity assessment predominantly involves subjective reporting of activity levels by patients allowing clinicians to approximate the patient's metabolic equivalents; completion of the DASI score; or more rarely, objective measurement by CPET, which is costly and resource intensive. Heart rate recovery after submaximal exercise testing may offer a widely available and economical additional method to identify high-risk patients to discuss risk and to allocate resources correctly e.g. elective post-operative critical care. Previous work has examined the reproducibility of submaximal HRR in a healthy population. This is the first study seeking to validate submaximal HRR in an intermediate/high-risk noncardiac surgical population.

3.1 Determination of submaximal heart rate recovery parameters measured

There is only one paper reporting submaximal HRR and association with postoperative outcomes in the perioperative population (Section 2.2.1) These investigators used HRR one minute after exercise cessation following a six-minute walk test with a cut-off of <12 bpm indicating impaired HRR[158]. As discussed previously, the cut-off of 12 bpm is derived from maximal exercise test data, with no reported cut-offs for submaximal HRR_1. Maximal HRR_1 has been demonstrated to be a marker of cardiac vagal tone (Section 1.3.3) and subsequently associated with postoperative outcomes (Section 2.2.5). The submaximal nature of exercise in this study however, requires consideration of the best way to measure heart rate recovery where the signal may not be as robust and is potentially effort-dependent.

3.1.1 Previous work

Previous volunteer studies by our group have developed novel methods for submaximal exercise HRR assessment utilising all the data contained within the

HRR curve, including non-linear mixed-effects modelling[162] and determination of the area under the HRR curve[163].

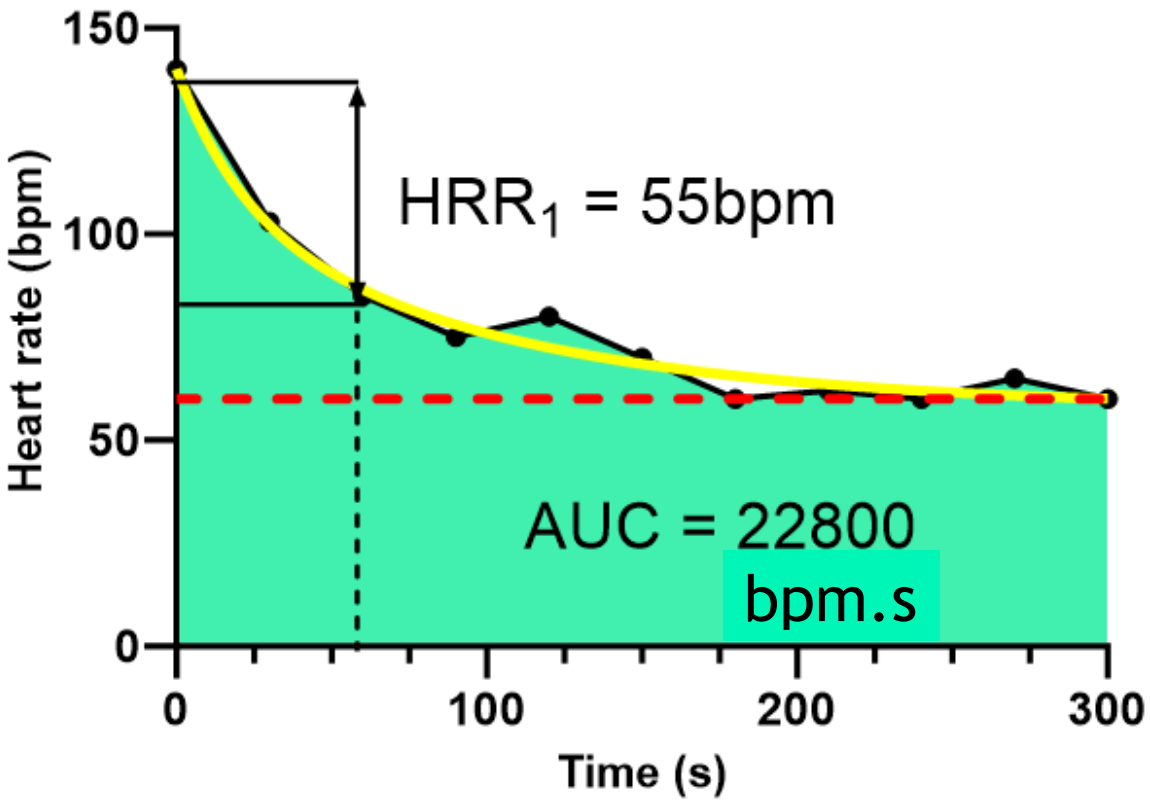


Figure 15 Schematic of heart rate recovery profile curve : (heart rate (beats per minute)) versus time (seconds (s)) after cessation of exercise. HRR_1: heart rate recovery one minute after exercise cessation. AUC: area under the heart rate recovery curve after six-minutes. Red dashed line: baseline heart rate. Yellow curve: non-linear mixed-effects modelling curve from which rate constant can be obtained.

The reproducibility of HRR parameters between workloads and different exercise intensities has been investigated plus the effect of effort-correction on reproducibility. The investigations have formed a series of studies within our research group, entitled "Adding objectivity to submaximal exercise testing by assessment of heart rate recovery (SEARCH)". Results and findings from the SEARCH studies described below informed the rationale and design of this study.

The reproducibility of submaximal HRR_1, HRR_2 and AUC_6 (the area under the whole HRR curve from end of exercise to six-minutes post exercise) was investigated after cycle ergometry at different workloads (40% and 60% maximum predicted workload) in 34 healthy volunteers (SEARCH-I)[163]. Reproducibility was poor for the absolute measures (ICC 0.15 (-0.12 – 0.43), r

0.22 and ICC 0.35 (-0.1 – 0.68), r 0.62 for HRR_1 and HRR_2, respectively) but better for AUC_6 (ICC 0.58, r 0.68, Figure 16).

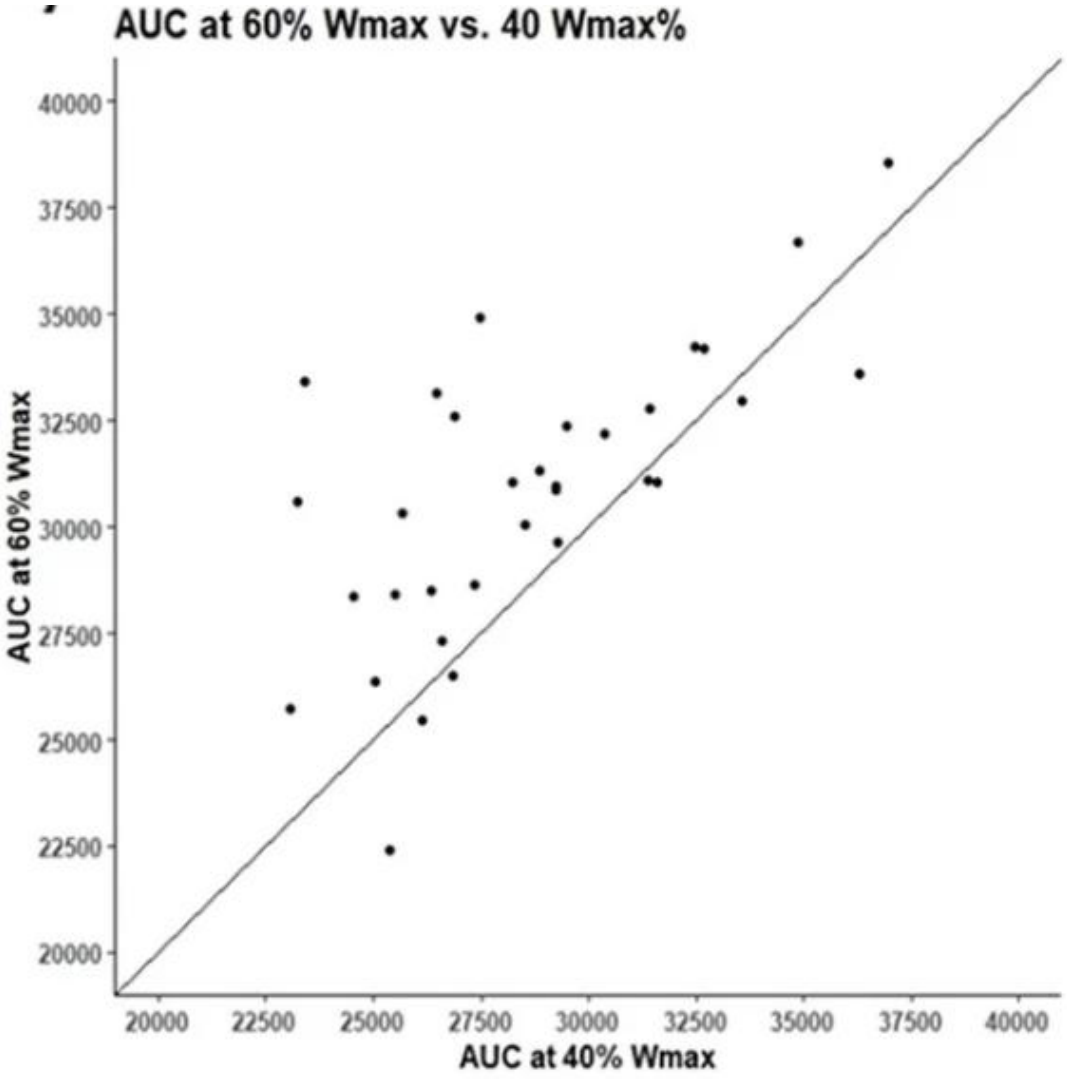


Figure 16 Association of AUC_6 after exercise at 60% predicted maximum workload and AUC_6 at 40% predicted maximum workload via cycle ergometry. Taken from Minhas et al[163]. Line represents line of equality. AUC_5: area under the heart rate recovery profile curve six-minutes after exercise cessation. Pearson's correlation coefficient = 0.68, p <0.001, n = 33.

These results suggested that the kinetics of individual HRR varies depending on effort, and therefore that effort-correction may be required to improve the reproducibility of submaximal measures[163]. Within the same participant group, non-linear effects modelling was investigated as a novel method for assessment of rate of heart rate fall post-exercise. The model demonstrated good fit, independent of workload[162], however is not an intuitive measure to calculate.

The effect of exercise modality on submaximal HRR reproducibility was investigated in a second healthy participant study. Thirty-one volunteers performed a submaximal (50 – 85% age-predicted HR_{max}) cycle ergometry test, step test and shuttle walk test. Submaximal HRR_1, HRR_2 and AUC_6 were compared between tests. The absolute HRR parameters were poorly reproducible across tests; HRR_1 demonstrated the highest ICC of 0.45 (0.10 – 0.70, r 0.53, Figure 17a) between cycle ergometry and the step test. The AUC_6 demonstrated better reproducibility with the higher ICC of 0.81 (0.63 – 0.90, r 0.84) between the step test and shuttle walk (Figure 17b)[163].

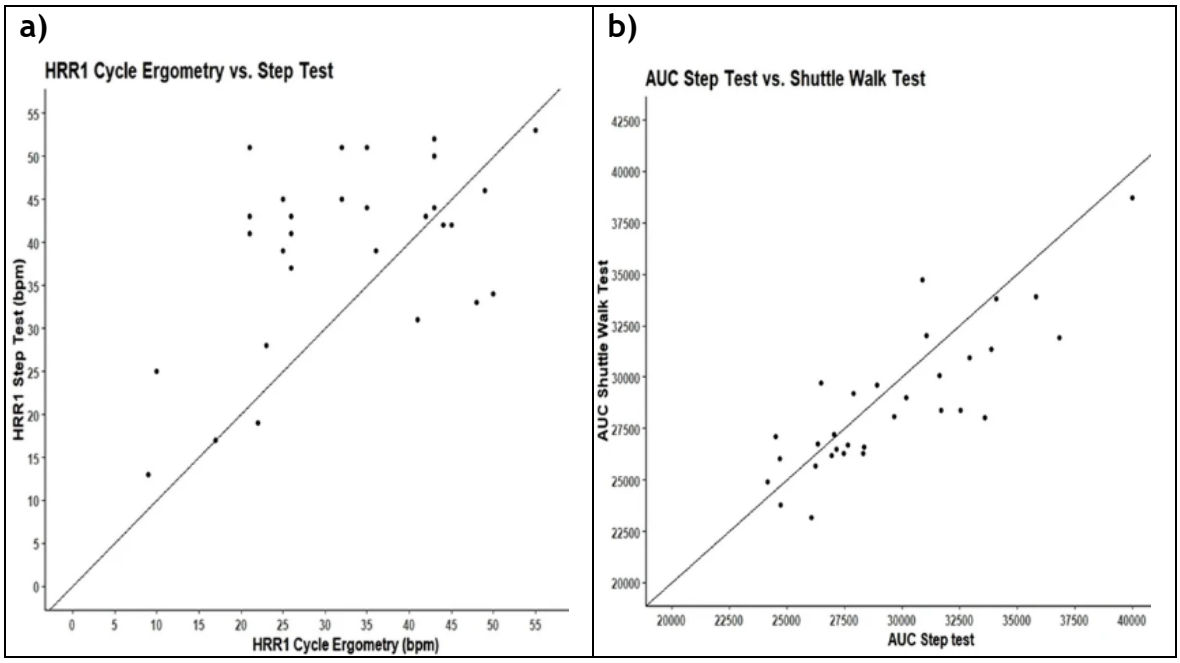


Figure 17a) Association of HRR_1 after submaximal step test and HRR_1 after submaximal cycle ergometry. Pearsons correlation coefficient r = 0.53, p = 0.003, n = 30**. b) Association of AUC_6 after submaximal shuttle walk test and AUC_6 after submaximal step test.** r = 0.84, p <0.001, n = 31. Taken from Minhas et al. HRR_1: heart rate recovery one minute after exercise cessation; AUC_6: area under the heart rate recovery curve six-minutes after exercise cessation (units: beats per minute*seconds); bpm: beats per minute**.**

There may be two reasons for these results. Heart rate recovery is more reproducible when exercise intensity is standardised with higher workloads associated with improved reliability of HRR measures (Section 1.4.1)[91]. During this study, effort as assessed by percentage of age-predicted HR_{max} reached was very variable between participants. During the step test, healthy participants reached a median (IQR) of 64% (95% CI 62 - 72%) age-predicted HR_{max}. Furthermore, subsequent (unpublished) analysis calculating AUC_6 with the y axis minimum being the lowest heart rate during recovery (rather than 0 bpm)

eliminated the reproducibility of AUC_6 between exercise modalities with the best ICC becoming 0.32 between the step test and shuttle walk. Further (unpublished) analysis of this study examined the effect of effort-correction of the submaximal HRR parameters to age-predicted $HR_{max.}$ Effort-correction improved the reproducibility of both HRR parameters (HRR_1 and HRR_2) across all exercise modalities but did not significantly affect AUC_6. After effort-correction, the most reproducible measure was effort-corrected HRR_1 (ICC 0.58 (95% CI 0.15 – 0.80), r 0.68 (95% CI 0.43 – 0.84)). Despite the wide confidence intervals, these findings indicate that correcting submaximal HRR values to an approximation of values after maximal exertion may be more reproducible across modalities.

The initial fall in heart rate after exercise cessation is predominantly due to vagal reactivation (Section 1.3.3) A post-hoc analysis of the SEARCH-I study sought to evaluate the test-retest reproducibility of the gradient of HRR within the first 30 seconds, compared to HRR_1 with both values also effort-corrected to age-predicted HR_{max}. The HRR gradient at 30 seconds was calculated by dividing the HRR at 30 seconds by 30. Data from eight volunteers who participated in SEARCH-I and undertook the cycle ergometry on two separate occasions was available for analysis. The HRR gradient at 30 seconds demonstrated moderate test-retest reproducibility at both 40% maximum (ICC 0.56 (95% CI -0.12 – 0.90)) and 60% maximum workload (ICC 0.62 (95% CI -0.04 – 0.92)). Effort-correction to age-predicted HR_{max} did not meaningfully improve reproducibility. Albeit in a very small cohort with wide confidence intervals, these findings suggest that submaximal HRR recorded earlier in recovery may be a reproducible measure with potential beneficial effect from effort-correction.

The third SEARCH study aimed to ascertain the minimal exercise intensity required to generate reliable HRR quantification[164]. Thirty-six healthy volunteers performed submaximal cycle ergometry at both 60% age-predicted HR_{max} and 70% age-predicted HR_{max}. Submaximal HRR_1, HRR_2 and AUC_6 were measured, with effort-corrected HRR parameters also calculated. Effort-corrected HRR_1 demonstrated the best reproducibility (ICC 0.58 (95% CI 0.32 - 9.76), r 0.64 (Figure 18)).

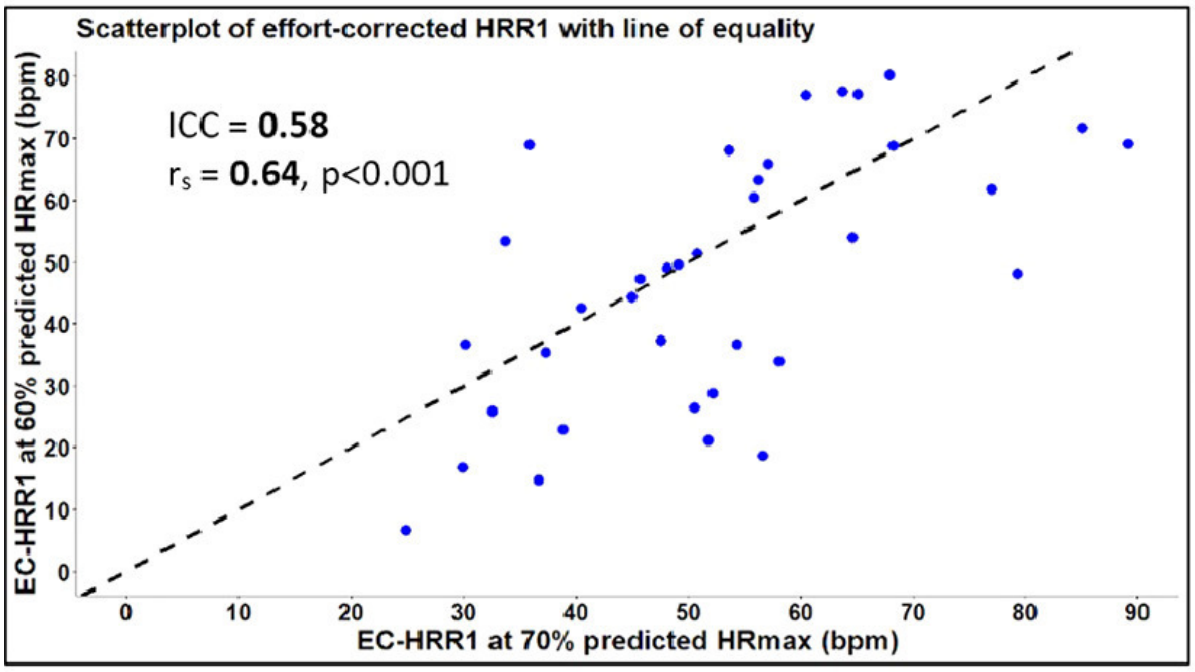


Figure 18 Association of effort-corrected heart rate recovery one minute after exercise cessation (EC-HRR$_1$) at 60% age-predicted maximum heart rate (HR$_{max}$) and EC-HRR$_1$ at 70% age-predicted maximum heart rate. Taken from Ismahel et al.[164] Spearman's rank correlation coefficient (r_s) = 0.64, p <0.001, n = 36. Bpm: beats per minute, ICC: intraclass coefficient

The reproducibility of AUC$_6$ improved after effort-correction (ICC 0.56, confidence intervals not reported) but HRR$_2$ demonstrated poor reproducibility which did improve after effort-correction but remained poor. Within this study, there was a cohort of patients whose resting heart rate was very close to, or at, the 60% age-predicted HR$_{max}$ target and so required minimal exertion on the cycle ergometer. Sensitivity analysis removing these "non-responders" demonstrated improved reproducibility of the HRR parameters.

The final SEARCH study investigated the feasibility, acceptability and reproducibility of submaximal HRR parameters measured via wearable technology in the community[165]. Thirteen healthy participants performed a laboratory-based submaximal cycle ergometry test and HRR was recorded over six-minutes. The participants then performed multiple submaximal exercise tests in the community in their own time via chest-worn heart rate monitor (Vivalink, California, USA). Community HRR data were available for twelve patients, with accelerometery confirming exercise cessation. Submaximal HRR$_1$ demonstrated good reproducibility (ICC 0.68, p = 0.03) with strong association between the laboratory and community tests (r 0.70, p = 0.01). Submaximal AUC$_6$

demonstrated low reproducibility (ICC 0.34, p = 0.12). A survey revealed that all volunteers found both the heart rate monitor and community exercise tests to be acceptable[165].

Overall, the SEARCH studies indicate that HRR parameters are more reproducible at higher exercise intensities and that effort-correction appears to improve reproducibility. There were not any significant differences in reproducibility between exercise modalities with HRR_1 demonstrating moderate association between cycle ergometry and the step test. Furthermore, these studies demonstrate the usefulness of exploring the whole heart rate recovery profile curve including timepoints earlier than usually measured (<1 minute after exercise cessation) and the area under the heart rate recovery curve. Therefore, it was hypothesised that using more of the HRR profile curve rather than just the fall in heart rate over time may provide more information and potentially a more robust measure of vagal reactivation post-exercise. The area under the HRR curve will incorporate the fall in heart rate to the minimum heart rate at the measured post-exercise time point. Therefore, in this thesis, the HRR parameters measured will be:

- Absolute fall in heart rate from end of exercise to 10 seconds, 20 seconds, 30 seconds, one minute and two minutes post-exercise

- The area under the HRR profile curve from end of exercise to 30 seconds, one minute, two minutes and five minutes post-exercise.

The absolute values will be recorded but effort-correction will also be applied. Effort-correction aims to correct the HRR parameter value to that if the patient was able to complete a maximal test. Two methods of effort-correction will be applied in this study: effort-correction to proportion of age-predicted HR_{max} reached and effort-correction to proportion of predicted maximum power output reached during exercise.

It is already known that less fit patients have slower heart rate recovery (Section 1.3.3), and so it is hypothesised that in this study, patients with worse postoperative outcomes, including PMI, will have slower absolute heart rate recovery. It is hypothesised that effort-correction will enhance predictive value.

Slower HRR will lead to a larger area under the heart rate recovery curve, and so it is hypothesised that a larger area under the curve will be associated with poorer postoperative outcomes. Again, it is hypothesised that effort-correction will enhance this effect. Figure 19 provides a schematic of the submaximal heart rate recovery profile for two patients; Figure 19a shows the heart rate recovery profile of a fitter patient, with a larger HRR_1 and smaller AUC; Figure 19b shows the heart rate recovery profile of an unfit patient demonstrating an impaired HRR_1 and larger AUC. The lower limit of the y axis for calculation of the AUC is the minimum heart rate reached during the recovery period measured; this ensures that the AUC signal reflects the HRR rather than “empty” space below.

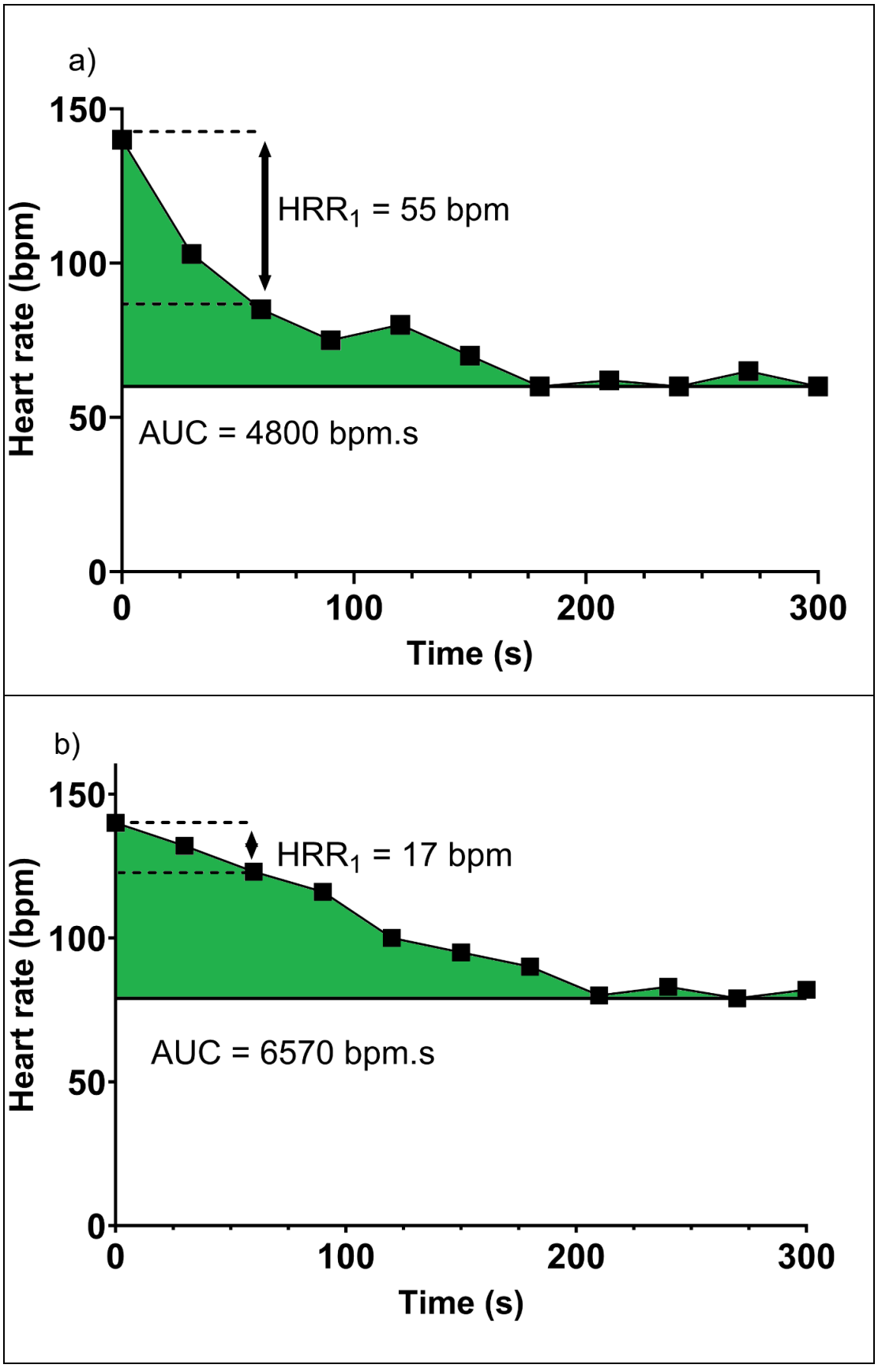


Figure 19 Schematic of heart rate recovery profiles. a) Fit patient. b) unfit patient. Top dashed line: heart rate at end of exercise (time 0 seconds). Bottom dashed line: heart rate one minute after exercise cessation; bottom full line: minimum heart rate during recovery period. Green shaded area: area under the heart rate recovery curve. HRR_1: heart rate recovery one minute after exercise cessation. AUC: area under the curve for the whole recovery period.

3.2 Validity

For submaximal heart rate recovery to be used in the wider clinical arena as a perioperative risk measure, clinical validity needs to be ascertained. Clinical validity is defined as "the extent to which a clinical sign or test is a true indicator of the disease being tested"[166]. Clearly, with perioperative risk prediction, the "disease" is a postoperative complication which the patient may or may not develop. Furthermore, validity in this sense requires a test to be compared to a "gold-standard" which represents the most accurate measure currently used. For perioperative risk prediction, which can incorporate many different preoperative markers and postoperative outcomes, there is currently no gold-standard measure with which to compare submaximal HRR to. Therefore, assessment of the validation of a novel perioperative risk measure should incorporate different types of validity to best assess its place within the gamut of perioperative risk prediction tools currently in place. There are several types of validity which can be applied to a clinical test which are discussed in detail, with relevance to the study, below and summarised in Table 7 .

3.2.1 Criterion validity

Criterion validity is defined as

"the extent to which the measurement correlates with an external criterion of the phenomenon under study; ideally *a gold standard"*[167].

As discussed above, this is dependent on firstly there being an external criterion and the accuracy of this criterion. In the case of perioperative risk prediction, there is not a gold standard measure. However, CPET is considered the gold standard of cardiovascular fitness testing providing the most accurate information on a person's cardiovascular, respiratory and neuromuscular response to exercise. This is due to it being a maximal test with comprehensive physiological information collected during the test (Section 1.2.10)[66]. Criterion validity in this investigation will therefore be assessed by assessing the association between submaximal HRR parameters and CPET variables. Criterion validity is further divided into predictive validity and concurrent validity.

3.2.2 Predictive validity

Predictive validity is observed when the measurement identifies patients who go on to develop a specific outcome i.e the test is able in reality to predict an outcome it theoretically is able to predict[167]. Therefore, the measure and the outcome are separated by time. The predictive validity of submaximal HRR will be assessed by how well the HRR parameters predict PMI, the primary outcome of the investigation.

3.2.3 Concurrent validity

Concurrent validity is where both measurements are taken "at the same point in time"[167]. Concurrent validity also reflects ability of the measurement to distinguish between different groups of patients, for example, between patients at high or low-risk of complications. Concurrent validity in this investigation will be assessed by the association between submaximal HRR and patients when dichotomised into high and low-risk groups by the CPET variables.

3.2.4 Construct validity

Construct validity is defined as

> *"the extent to which the measurement corresponds to theoretical concepts (constructs) concerning the phenomenon under study"[167],*

and therefore is particularly useful where there is no gold standard for comparison. The constructs should be measures which align with what the test in question is purporting to measure. For example, in this investigation, construct validity will be assessed by the association between submaximal HRR and a selection of currently used perioperative risk prediction measures incorporating biomarkers (NT-ProBNP), functional capacity assessment (DASI) and surgical risk prediction tools (e.g. SORT) amongst others (Section 1.2).

3.2.5 Face validity

Face validity is where the theoretical basis behind the measurement is scientifically sound and so taken at "face-value" it superficially represents what

it purports to measure[167]. Face validity, although the least scientific of the types of validity, is important to warrant clinician buy-in for a novel measure. In this investigation, face validity will be assessed by the association between submaximal HRR and postoperative complications. If “worse” submaximal HRR is associated with worse postoperative outcomes, face validity will be demonstrated.

Table 7. Types of validity and how these will be applied to submaximal HRR measurement. Modified from Ferguson et al[168].

Validity Measure	Explanation	Example as applied to this investigation
Criterion validity	Test corresponds to a gold standard measure	HRR is associated with cardiopulmonary exercise testing derived indices – anaerobic threshold (AT), peak oxygen consumption (VO_{2peak}) and the ventilatory equivalent of carbon dioxide at AT.
Concurrent validity	Test is able to distinguish between groups that theoretically it should be able to distinguish between	High risk patients as determined by CPET (Section 1.2.10)[59]: • **AT <11ml/kg/min** • **VO_{2peak} < 15ml/kg/min** • **VE/VCO_2 at AT <34**
Predictive validity	Test is able to predict something it theoretically should be able to predict	Identifies patients who go on to develop postoperative myocardial injury
Construct validity	Extent to which the test corresponds to other measurements that theoretically support the concept (or construct) being measured	Association observed between HRR and clinically used preoperative risk predictors e.g. Duke Activity Status Index, Revised cardiac risk index and NT-ProBNP etc
Face validity	The theoretical basis behind the test is scientifically sound	Association observed between submaximal HRR and postoperative outcomes

3.3 Validation of submaximal heart rate recovery

The aim of this thesis is to validate submaximal HRR as a perioperative risk measure using methods of validation described above. The first investigation (Chapter 6 (Heart rate recovery and postoperative myocardial injury (predictive validity))) assesses the association between, and predictive value of, all measured heart rate recovery parameters for PMI. Postoperative myocardial injury is an objective cardiovascular complication which is associated with impaired maximal HRR_1^{150}, with pathophysiology related to impaired vagal tone (Section 1.6.3), hence its choice as the primary outcome for this study. It is hypothesised that all HRR parameters will be associated with PMI; with lower absolute HRR and larger area under the heart rate recovery profile curve associated with PMI incidence. The area under the curve parameters are novel measures for the prediction of PMI but it is hypothesised that AUC will be predictive for PMI with effort-corrected parameters demonstrating stronger predictive value. The HRR parameters which demonstrate the best predictive value for PMI will be taken forward for further validity testing in subsequent chapters.

The second investigation (Chapter 7 (Heart rate recovery and postoperative complications (face validity)) will explore the face validity of the best-performing (for prediction of PMI) submaximal HRR parameters. Secondary outcomes incorporating clinical postoperative complications, clinical indicators and patient-reported outcome measures will be recorded. It is hypothesised that impaired submaximal HRR will be associated with poorer secondary outcomes in a similar manner to which they are hypothesised to be associated with PMI, thereby demonstrating face validity.

The third investigation (Chapter 8 (Heart rate recovery and preoperative risk scores (construct validity))) will assess construct validity of the best-performing HRR parameters. The risk prediction measures currently in use described in Section 1.2 form the constructs for which association between HRR parameters will be measured. It is hypothesised that association will be demonstrated between the constructs and the HRR parameters, although this association will not be perfect as the constructs and HRR parameters measure different aspects of perioperative risk.

The final validation investigation (Chapter 9 (Heart rate recovery and cardiopulmonary exercise testing variables (criterion and concurrent validity))) will explore both criterion and concurrent validity of the best-performing HRR parameters. A subset of patients will undergo CPET as part of their routine preoperative assessment. As discussed in Section 1.2.10, CPET is the gold-standard exercise test for determining cardiorespiratory fitness. Criterion validity will be assessed by the association between the submaximal HRR parameters and anaerobic threshold, peak oxygen consumption and ventilatory equivalent of carbon dioxide at anaerobic threshold as determined by CPET. It is hypothesised that submaximal HRR (as a marker of functional capacity) will demonstrate association with the CPET variables. Concurrent validity will be assessed by dichotomising patients into high and low-risk group by established CPET thresholds (Section 1.2.10). It is hypothesised the high-risk patient group will have impaired submaximal HRR.

One of the hypothesised benefits of submaximal HRR over CPET is that it is a more comfortable and acceptable test for patients due to the submaximal nature. The final investigation (Chapter 10 (Acceptability of the exercise test modalities for patients)) will describe the results of a questionnaire which was completed by participants who completed both the submaximal exercise test and CPET, comparing their experience of the two.

Chapter 4 Generic methods

This chapter details methods common to the validity investigations presented in this thesis. These investigations form the basis of the "Validation of hEart Rate recoVery as a periopErative risk measure (VERVE)" study (NCT05561608).

4.1 Ethical Approval

The study received ethical approval from the Wales Research Ethics Committee (REC Ref: 21/WA/0207) on 28th July 2021. NHS Research Scotland Generic Review approval was obtained on 7th January 2022. Unfortunately, there was a delay due to administrative reasons from both the sponsor and research and development. Non-substantial amendments to the consent form and patient information leaflets were also required to obtain generic review approval.

4.2 Patient, Carer and Public Involvement and Engagement (PCPIE)

The study was designed during the Covid-19 pandemic meaning the local Patient and Public Involvement group could not be approached for input. However, the National Institute of Academic Anaesthesia Health Services Research Centre provide a Patient, Carer and Public Involvement and Engagement (PCPIE) working group which delivers patient, carer and public input to researchers regarding

"research topic importance, consent issues and the participant experience"[169].

The PCPIE working group were contacted via email to provide an opinion on study design from a public perspective. Overall, the PCPIE group felt the study had a number of strengths, including the potential for reducing

"time and costs involved [in perioperative care] and overall benefit to patient care and healthcare costs".

They recommended further clarification in the patient information leaflet regarding what the step test and blood test would involve for patients; the importance of a face-to-face discussion with a research team member;

clarification of the procedure in the event of grossly abnormal blood test results; and input regarding the language used in the patient-facing correspondence. These changes were executed and helped develop the following methods.

4.3 Study Setting

This was a multi-centre study performed at three hospitals in the West of Scotland: Golden Jubilee National Hospital, Clydebank (GJNH); University Hospital Crosshouse, Kilmarnock (UHC); and University Hospital Hairmyres, East Kilbride (UHH). The centres comprise a mixture of a tertiary referral centre and district general hospitals.

4.4 Study Summary

Intermediate and high-risk surgical patients were identified via screening of theatre lists or at anaesthetic pre-assessment clinic. All patients had baseline demographics, subjective functional capacity and risk scores recorded preoperatively (Table 8). Preoperative NT-ProBNP and high-sensitivity troponin T (hsTnT) blood samples were taken. Cardiopulmonary exercise testing was performed if indicated as part of routine care. Patients performed a submaximal step test prior to their operation with continuous electrocardiogram measurement allowing for measurement of heart rate during exercise and recovery. Patients underwent their operation as standard with clinicians blinded to the HRR result. The primary outcome was postoperative myocardial injury as defined by a cardiac troponin level above the 99th percentile upper reference limit and a 20% change (increase or decrease) from baseline[132]. Secondary outcomes include clinical indicator outcomes and postoperative complications measured within 30-days of surgery (Table 8). The predictive, face, construct and criterion validity of heart rate recovery parameters were investigated.

Table 8 Timeline of preoperative and postoperative data collection. Hs-TNT: high-sensitivity troponin T; DASI: Duke Activity Status Index; CFS: Clinical Frailty Score; RCRI: Revised Cardiac Risk Index; SORT: Surgical Outcome Risk Tool; POSSUM: Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; 4AT: 4 A's Test for delirium; QoR-15: quality of recovery 15 score; DaOH: days alive and out of hospital; AKI: acute kidney injury; MAKE: major adverse kidney events; CVS: cardiovascular system; MACE = major adverse cardiac events; ICU: intensive care unit

Measurement	Preoperative	POD1	POD2	POD7	POD14	POD30
NT-ProBNP	✓					
Hs-TnT	✓	✓	✓			
DASI	✓					
CFS	✓					
RCRI	✓					
SORT	✓					
P/V-POSSUM	✓					
4AT	✓			✓		
QoR-15			✓			
DaOH						✓
Renal complications				✓		
MAKE						✓
Infective complications				✓		
CVS complications				✓		
MACE						✓
Pulmonary complications				✓		
Length of hospital stay						✓
Admission to ICU					✓	
Readmission to hospital						✓
Mortality						✓

4.5 Patient Population

Any patient over the age of 50 years undergoing non-cardiac surgery deemed to be intermediate/high-risk surgery and able to walk unaided was eligible to be screened. Intermediate/high-risk of surgery was defined as per the European Society of Cardiology/European Society of Anaesthesiology guidelines where

intermediate risk surgery carries a 1-4% risk, and high-risk surgery carries a risk of ≥5% of cardiovascular death or myocardial infarction[3]. Exclusion criteria were: pregnancy; ongoing participation in another study which may undermine the scientific basis of this study; previous intermediate/high-risk surgery within the last three months; previous participation in this study; presence of any of the American Thoracic Society/American College of Chest Physician's contraindications to CPET (Appendix 2)[66];unable to walk unaided and presence of a cardiac pacemaker or implantable cardioverter-defibrillator.

4.5.1 Justification of inclusion/exclusion criteria

Aging is a risk factor for cardiovascular disease. Previous perioperative risk assessment studies have identified patients >65 years at increased risk of postoperative cardiovascular events[38,170]. This increased risk is demonstrated in lower age groups (≥40 years) if the patient also has an additional risk factor for postoperative cardiovascular complications e.g. arterial hypertension. Internationally, the majority of patients undergoing high-risk surgery are aged over 59 years[2]. Considering these factors, an age cut-off of over 50 years was deemed appropriate: old enough to ensure a cohort at increased risk of PMI whilst also young enough to allow generalisability within non-cardiac surgery patients.

The submaximal exercise test used in this study relied on patients being able to step up and down on a low step to generate a heart rate response of approximately 60% age-predicted HR_{max}. Therefore, to complete the step test effectively and safely, only patients who were able to walk unaided were eligible for the study. All patients were screened for any contraindications to exercise testing to ensure patient safety (Appendix 2)[66].

The presence of a cardiac pacemaker may alter the heart response to exercise and recovery, thereby not reflecting the patient's underlying physiology and cardiovascular risk. Although a very low risk, implantable cardioverter-defibrillators may discharge if a patient's heart rate exceeds set levels.

The prevalence of PMI after low-risk surgery is low, and so may be a difficult signal to identify. Low-risk surgery is often performed as day-case and so

postoperative monitoring is difficult in this cohort. In order to facilitate generalisability of the measure, patients undergoing intermediate/high-risk surgery as defined by the ESC/ESA (Section 4.5) were recruited (Table 9)[171]. Identifying patients by surgical risk rather than individual patient risk aimed to allow a wide variety and degree of comorbidity.

Table 9 ESC/ESA risk of cardiovascular death or myocardial infarction within 30-days of operation[171]

Low-risk: < 1%	Intermediate-risk: 1–5%	High-risk: > 5%
• Superficial surgery • Breast • Dental • Endocrine: thyroid • Eye • Reconstructive • Carotid asymptomatic (CEA or CAS) • Gynaecology: minor • Orthopaedic: minor (meniscectomy) • Urological: minor (transurethral resection of the prostate)	• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopaedic: major (hip and spine surgery) • Urological or gynaecological: major • Renal transplant • Intra-thoracic: non-major	• Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolectomy • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumonectomy • Pulmonary or liver transplant

4.6 Participant Recruitment

Patient screening and recruitment differed between sites, predominantly due to the differing preassessment pathways in each hospital, as detailed below.

4.6.1 Golden Jubilee National Hospital Patient Pathway

Elective thoracic surgery lists were screened and patients meeting inclusion criteria were sent a patient information leaflet and cover letter by post, along with their procedure information. Patients were then contacted by telephone by a member of the research team to discuss the study and answer any questions the patient information leaflet may have created. Thoracic patients at the GJNH are admitted to the hospital the day before surgery, where they were approached and screened for inclusion and exclusion criteria. Consent was then discussed and those patients providing informed consent entered the study.

4.6.2 University Hospital Crosshouse Patient Pathway

Preoperative assessment clinic lists (general surgery, gynaecology, orthopaedic, ENT and maxillofacial surgery) were screened and patients meeting inclusion criteria, and with an expected clinic appointment when an investigator was available, were sent a patient information leaflet and cover letter by post with

their appointment letter. Patients were then contacted by telephone by a member of the research team to discuss the study and answer any questions. Patients were then approached at the preoperative assessment clinic and screened for inclusion and exclusion criteria. Consent was discussed and patients providing informed consent entered the study.

4.6.3 University Hospital Hairmyres Patient Pathway

Vascular and major colorectal preoperative assessment clinic lists were screened, with patients meeting inclusion criteria sent the Patient Information Sheet and cover letter with their preoperative assessment clinic appointment letter by post. Patients were then contacted by telephone by a member of the research team to discuss the study and answer any questions. Patients were subsequently approached at the preoperative assessment clinic and screened for inclusion and exclusion criteria. Consent was discussed and patients providing informed consent entered the study.

4.7 Step test protocol

4.7.1 Heart rate measurement

A device was required to accurately measure the ECG whilst the patient was performing the step test. Excessive noise (signal interference) can be a problem when recording the ECG during exercise particularly at higher work intensities[172]. The investigation also required a device which indicated the participant's heart rate in real time to allow the investigator to determine the point at which 60% age-predicted HR_{max} was reached. The Actiheart 5 BT monitor (Actiheart, CamNTech, Cambridge, UK) was trialled and chosen as it's features included: single-lead ECG with accurate trace at high workload intensities; live Bluetooth transmission to the Actiheart software on a laptop showing both the ECG trace and heart rate; accelerometery data which was helpful to accurately confirm the timings of the step test; the ability to record and analyse full tests and the ability to review the ECG trace and confirm R wave position. The Actiheart monitor has been extensively used in physiological research. Heart rate measurement and accelerometery data has been validated in the laboratory and free-living conditions[173,174].

4.7.2 Patient preparation

Step tests were performed in the patient's individual room on the Thoracic ward at GJNH and in the pre-assessment clinic at UHC and UHH. All step tests were performed in a clinical setting with Advanced Life Support trained personnel and cardiac arrest trolleys available. Prior to attaching the ECG electrodes, the skin was prepared using 70% alcohol swabs. Two Ag/AgCl ECG electrodes (Dormo, Telic Group, Barcelona, Spain) were placed on the skin at the level of T5 in the midline and mid-clavicular line (Figure 20)

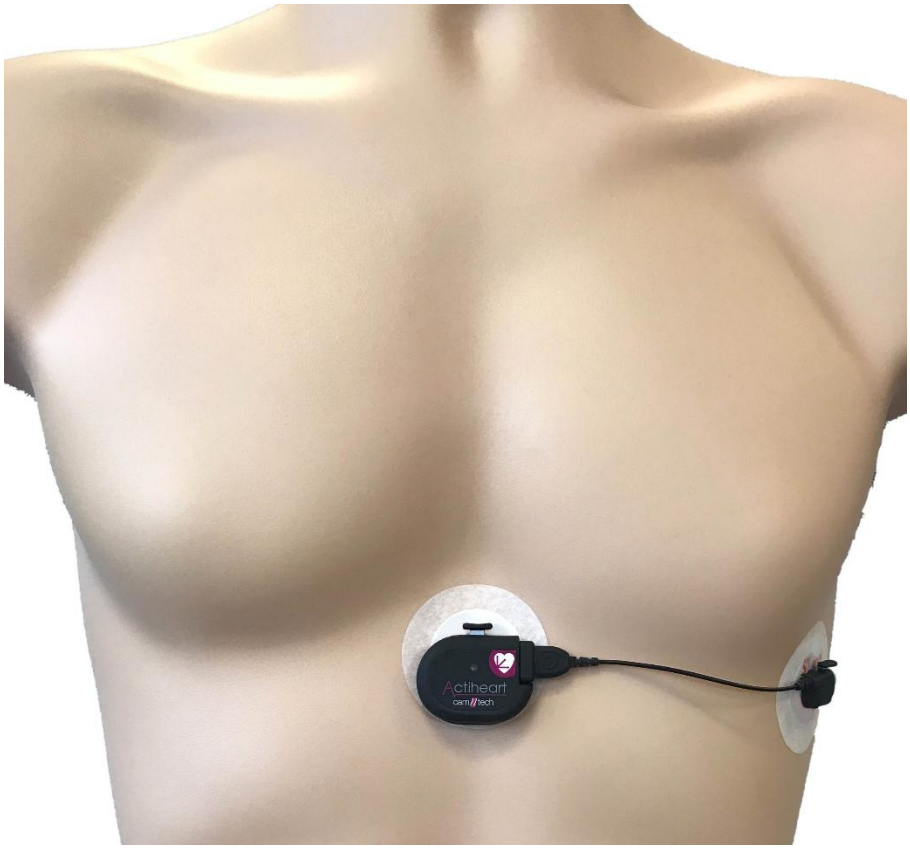


Figure 20 Position of Actiheart 5 BT monitor (reproduced from https://www.camntech.com/actiheart-wearing-the-actiheart/, accessed 13/08/2024)

The Actiheart 5 BT monitor (Actiheart, CamNTech, Cambridge, UK) was connected, having been set up via the Actiheart software (V5.1.24) (see section 4.9.1) by inputting the patient's demographics (date of birth, sex, height and weight). The patient's age-predicted maximum heart rate was calculated using the Tanaka formula:

$$\text{Age-predicted } HR_{max} = 208-(0.7 \times \text{age})^{175}$$

Target heart rate parameters of 60% HR_{max} +/- 5% were calculated for each individual patient prior to commencing the test.

The height of the step could be altered between three different heights (9.5 cm, 14.5 cm and 19.5 cm). The height of the step was chosen by the investigator based on the participant's functional and clinical history to allow the participant to be able to perform the test comfortably.

Prior to the step test, the patient was asked to score breathlessness at rest using a Modified Borg score (Figure 21)[176].

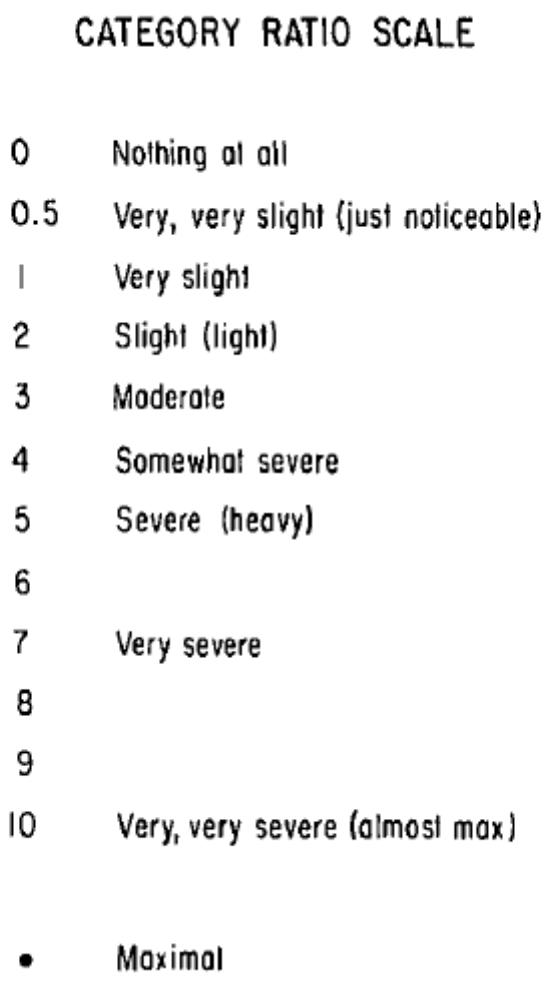


Figure 21 Modified Borg score , taken from Mahler et al[176].

4.7.3 Performance of the exercise test

The patient's heart rate was monitored via Bluetooth on a secure University laptop throughout the test. The Actiheart 5 BT monitor has a sampling frequency of 256Hz for ECG. Patients began at rest sitting on a chair. Baseline heart rate was recorded for five minutes with the patient sitting still, without talking. After five minutes the patient was asked to promptly stand and remain standing for three minutes. This provided data for a potential investigation into orthostatic heart rate recovery, which will not be addressed within this thesis. The patient returned to sitting until their heart rate returned to baseline (for at least one minute). They were then asked to commence the step test. This consisted of the patient repeatedly stepping onto a low step one foot, then another until they are standing on the step and then stepping down one foot at a time. Initially this was at the patient's own pace; if the heart rate needed to increase to reach target, the patient was encouraged to step faster. Once the heart rate encroached 60% age-predicted maximum, the patient was asked to maintain a steady pace for a further minute. If the heart rate became higher than 65% age-predicted maximum, they were asked to slow down. After one minute of maintaining the heart rate at approximately 60% age-predicted maximum, the patient promptly returned to sitting in the chair. Recovery heart rate was measured for five minutes with the patients sitting still without talking. The test was then terminated.

The patient was asked to report a modified Borg score for breathlessness as an indication of their perceived workload[176] immediately after the step test.

The total number of steps and length of time of the test were collected by reviewing the accelerometery data on the Actiheart software (Section 4.9.1, Figure 22).

4.7.4 Quantifying effort

A variety of heart rate recovery parameters were investigated (as discussed below). The submaximal nature of the test means that HRR parameters may potentially be more accurate if corrected to the amount of effort generated by the patient (as a proportion of maximum predicted effort). Therefore, both the percentage of age-predicted HR_{max} and the power generated during the exercise

test were calculated. This created two methods of effort-correction to compare during validity testing.

An estimation of work done was calculated using the following formula:

Work done (J) = mass (kg) x height of step (m) x 9.8 (gravity) x total number of step cycles[177]

Multiplying work done by the length of time of the step test in seconds gives the total power (Watts) generated by the patient.

Predicted maximum power output was calculated using the following formula:

$$W_{max} = 1.08^{*} \left(\frac{20.4(\text{height(cm)}) - 8.74(\text{age (years)}) - 288(\text{sex}) - 1909\text{kpm/min}}{6.116}\right)$$

where male sex = 0 and female sex = 1, as described by Jones et al.[178].

4.8 Data Collection

Data were collected by the author, research staff and clinical development fellows during the patients' hospital admissions and via telephone consultations 30-days postoperatively. All anonymised data were collated and stored in a secure password-protected database created by the author (REDCap, Vanderbilt University, Tennessee, USA). Site initiation visits were completed at each site prior to recruitment. These featured a presentation on the study protocol, blood testing and data to be collected, and the use of the case report forms (CRFs) and REDCap, with the opportunity to ask the author and site principal investigator questions.

4.8.1 Baseline demographic data

Patient demographics were collected prospectively at the time of recruitment. Data were extracted from the patients' medical records and from face-to-face interview. Information was recorded on dedicated paper case report forms.

4.8.2 Preoperative risk scores

A variety of preoperative risk scores were completed by the research team (if not completed as part of routine preoperative assessment) using both the patient's medical records and information from face-to-face questioning. The scores recorded were: Duke Activity Scale Index (DASI)[38], Revised Cardiac Risk Index (RCRI)[40], Surgical Outcome Risk Tool (SORT)[25], the American College of Surgeon's Surgical Risk Calculator (ACS NSQIP SRC)[31] and P-POSSUM[44]/V-POSSUM[179] (Section 1.2). All preoperative risk scores were completed by study investigators and recorded on the dedicated case report form and REDCap database. Risk scores performed by the research team were not available to the clinical team. Clinical teams however were free to use risk scores as per their usual practice. If risk scores had been performed as routine pre-assessment, these were recorded rather than being repeated by the research team.

4.8.3 Patient-reported outcome measures

The quality of recovery 15 question score (QoR-15) is a validated postoperative questionnaire assessing the quality of a patient's recovery from surgery from the patient's perspective[180]. It covers five dimensions of health: patient support in hospital, comfort, emotions, physical independence and pain. Each question is answered via an 11-point numerical rating scale with a maximum score across the whole questionnaire of 150 indicating excellent quality of recovery (Appendix 3). In this study, research personnel completed the questionnaire with patients in the hospital on postoperative day two with the total score out of 150 recorded.

Days alive and out of hospital (DaOH)[181] is a validated patient-centred outcome that reflects mortality, length of hospital stay, readmissions and discharge to another health facility. It is recommended as a Step-COMPAC outcome for "life-impact" of surgery[29]. Patients or their care-giver were telephoned at approximately 30-days postoperatively and asked how many days since their operation they had spent at home, at a family/friend's house or at a care facility following a standardised script (Appendix 4). Days alive and out of hospital was then calculated as 30 minus days in hospital/care facility.

4.8.4 Intraoperative clinical data

The method of recording intraoperative clinical data varied between the hospitals. At the GJNH, anaesthetic data is recorded automatically and continuously by the "RECALL Anaesthetic Intraoperative Management System electronic charting system (Informatics Clinical Information Systems Limited, Glasgow). At UHC and UHH intraoperative parameters are charted by hand, usually at five-minute intervals on a paper chart. The beginning of anaesthesia was taken as the commencement of the end-tidal carbon dioxide trace ($etCO_2$) on the RECALL charts. On paper charts, the beginning of anaesthesia was noted to be the timing of induction agent administration, as $etCO_2$ is only recorded at 15-minute intervals on paper charts and patients may be anaesthetised in anaesthetic rooms without recorded $etCO_2$. The end of anaesthesia was taken to be either the disappearance of $etCO_2$ on the RECALL charts, which correlates to extubation; or cessation of recording of cardiovascular parameters on the paper charts prior to the recording of post-operative care unit (PACU)/recovery charting.

4.8.5 Postoperative clinical data

Postoperative clinical data encompassing any postoperative morbidity and hospital stay were recorded. The patients' medical notes were reviewed up to seven days postoperatively to ascertain whether any postoperative complications occurred, as defined by StEP-COMPAC[134,182-184] which were graded for severity using the Clavien-Dindo scale[185] (Appendix 5). Major adverse kidney events (MAKE)[186] and major adverse cardiac events (MACE)[134] were screened for via the patients' medical notes at postoperative day 30.

Admission or re-admission to the Intensive Care Unit (ICU) was recorded up to postoperative day 14. For the purposes of this thesis, intensive care denoted admission to the physical ICU and therefore potentially both level three and level two care[187], and both expected and unexpected admission. Length of hospital stay was calculated as postoperative hospital stay commencing from the day of surgery (day zero) onwards and recorded in whole days. This was because different hospitals have different preoperative admission pathways. Mortality was recorded at 30-days.

4.8.6 Laboratory sampling

Blood sampling was performed preoperatively either at the pre-assessment clinic or on the ward the day before surgery, and on the first and second days postoperatively by research team members. An NT-ProBNP sample was taken prior to surgery. High-sensitivity troponins (hsTnT) were taken preoperatively and on postoperative days one and two. Where possible, bloods were sampled along with bloods required for routine care. All preoperative blood sampling required venepuncture; where patients had an arterial cannula postoperatively, this was used for blood sampling to maintain patient comfort. Blood samples were anonymised, with only the participant's study identification number, date and time of sample, and whether pre- or post-op recorded on the collection bottle and laboratory form. The study team were blinded to the laboratory results until the final patient completed postoperative day one and day two data collection at each site. Only the author had access to the test results when released; the other data collectors remained blinded. Blood sample analysis varied between hospitals.

4.8.6.1 Golden Jubilee National Hospital Sample Handling

Blood was collected using BD Vacutainer® blood collection tubes: hs-TnT in gold topped tubes (ml) and NT-ProBNP in 1x4ml EDTA (purple top) tubes. At the GJNH, both NT-ProBNP and hs-TnT samples were analysed on site. NT-ProBNP samples were initially spun down and separated from red cells. The serum was then stored at -40℃ until the next batch run. High-sensitive-TnT were spun down and analysed as soon as they were received by the laboratory. All samples were analysed on a Roche Cobas 6000e module (Roche, Basel, Switzerland).

4.8.6.2 University Hospital Crosshouse Sample Handling

Blood was collected using S-Monovette® blood collection tubes: hs-TnT in Lithium heparin gel+ (orange cap) 4.9ml tube and NT-ProBNP in K3 EDTA (violet cap) 4ml tubes. NT-ProBNP samples were stored at -20℃ until recruitment was complete. The batch was then transferred to and analysed at the Queen Elizabeth University Hospital laboratory in Glasgow using the Alere NT-ProBNP for ARCHITECT assay (Alere, Stockport, UK). High-sensitive-TnT samples were

analysed at the UHC laboratory on a Roche Cobas e801 immunoassay module (Roche, Basel, Switzerland) as a batch after being frozen at -20℃. Prior to analysis, they were thawed and centrifuged at 3000rpm for five minutes.

4.8.6.3 University Hospital Hairmyres Sample Handling

Blood was collected using BD Vacutainer® Plus blood collection tubes, both hs-TnT and NT-ProBNP were analysed from 5ml plastic serum tubes (Gold BD Hemogard™ closure). The samples were transferred via taxi to the laboratory at University Hospital Wishaw where they were analysed. Prior to analysis, they were centrifuged at 3000rpm for five minutes. Both hs-TnT and NT-ProBNP analysis was carried out on the e601 modules of the Roche Cobas 6000 (Roche, Basel, Switzerland).

4.9 Data synthesis and statistics

4.9.1 Heart rate data extraction

Electrocardiographic data was recorded using the Full Waveform Analysis (FWA) package provided by Actiheart Software. The Full Waveform package produces an output of the raw ECG data, accelerometer data displayed via x, y and z axes (g), heart rate (bpm), interbeat interval (IBI, ms) derived from the raw ECG and information on participant movement and position based on the accelerometer data (Figure 22).

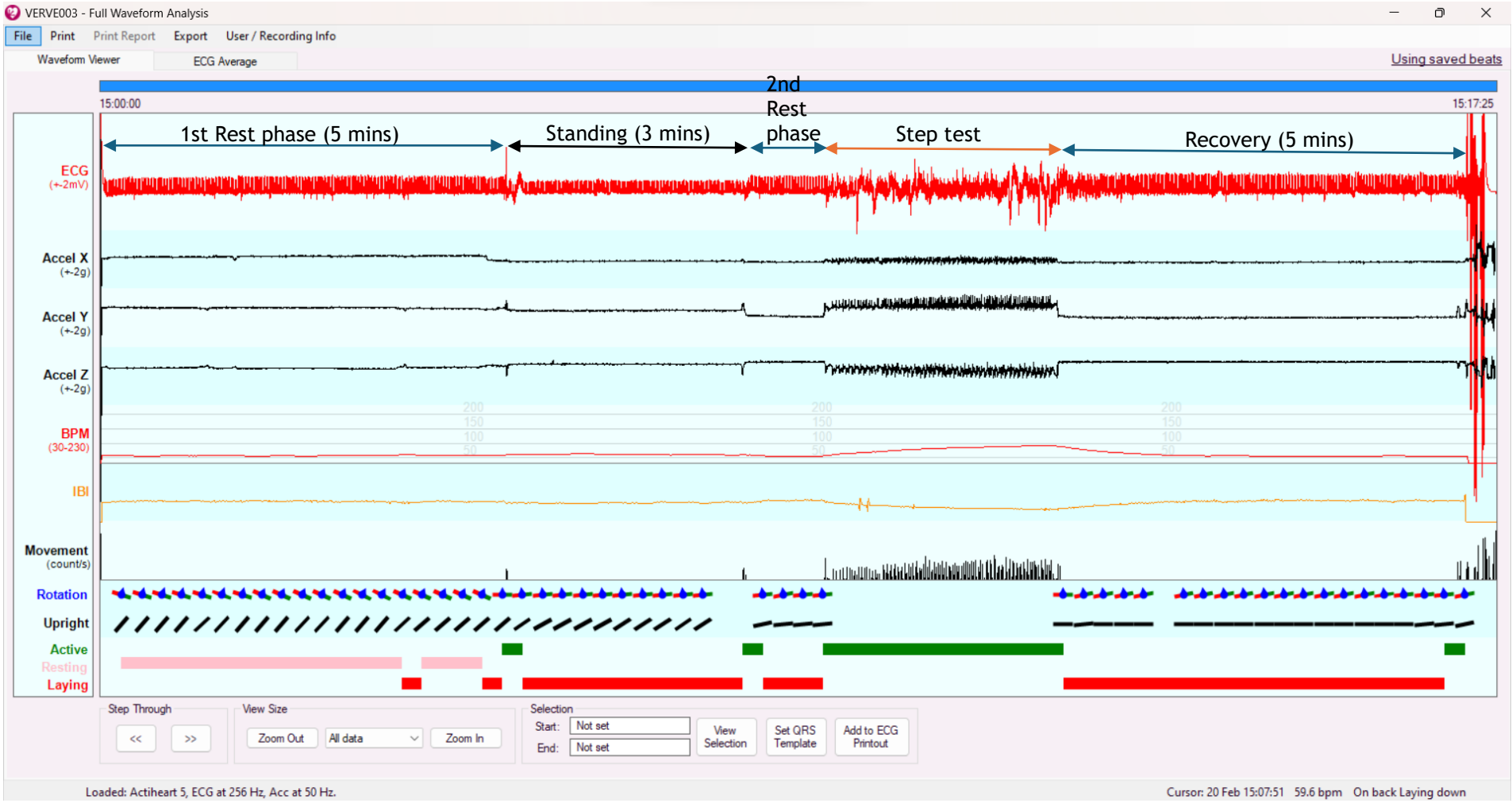


Figure 22 Printout of Full Waveform Analysis for Participant 003 of whole ECG recording, lasting 17minutes 25 seconds, with different phases of recording described. Top red line is single lead ECG. Accel X, Y and Z represent accelerometery data: X being lateral movement, Y being vertical (upward inflection = upward movement), Z being vertical (downward inflection = upward movement). BPM: beats per minute (heart rate); IBI: interval beat analysis (R-R wave interval). The movement, rotation, upright, active, resting and laying are indications of patient position from accelerometery data analysed by Actiheart software.

The Actiheart software recognises QRS complexes of the ECG and records IBI from the R-R interval. From this software, the full IBI data was exported into an Excel spreadsheet. Prior to data extraction, the IBI data was manually checked to ensure that the software had correctly identified R waves and to identify any periods of missing data. The software delineates QRS complexes using a vertical light blue line. This allowed an initial indication of the quality of the ECG recording. The "Edit Beats" function of the FWA package allowed manual removal or addition of R waves where required. All R waves were recorded including ectopics (Figure 23).

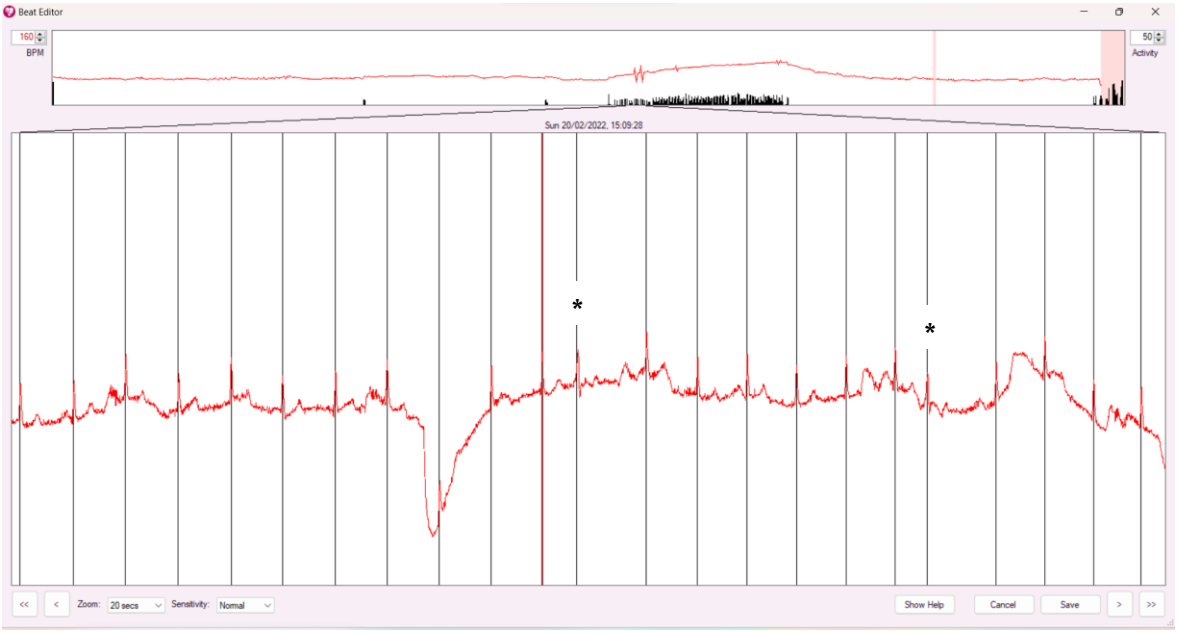
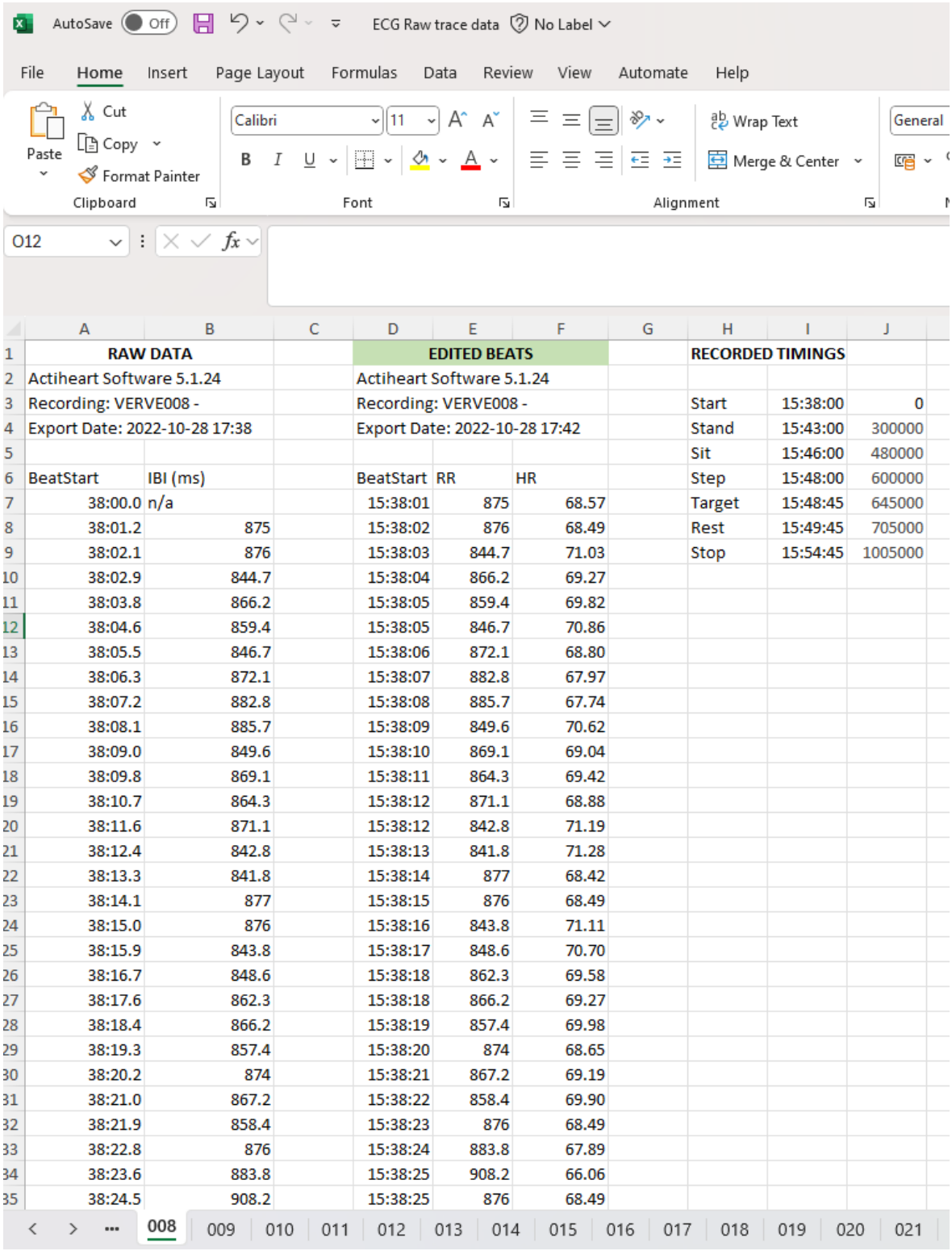


Figure 23 Partial ECG trace of participant 003 during step test. Top box shows the heart rate (bpm, red line) during the whole test plus movement indication (black lines at base of box). Bottom, larger box: single-lead ECG trace (red), black lines indicate R waves after manual R wave detection. Ectopics are marked with *.

Where data were missing, R-R intervals were estimated based on the adjacent R-R intervals. All time periods of missing data were recorded. Heart rate recovery profiles were analysed after study recruitment had finished to ensure investigator blinding. Only two full HRR profiles were unable to be analysed due to missing data. All IBI data plus timestamps were exported to a Microsoft Excel spreadsheet with a sheet per participant (Figure 24).



	A	B	C	D	E	F	G	H	I	J
1	RAW DATA			EDITED BEATS				RECORDED TIMINGS		
2	Actiheart Software 5.1.24			Actiheart Software 5.1.24						
3	Recording: VERVE008 -			Recording: VERVE008 -				Start	15:38:00	0
4	Export Date: 2022-10-28 17:38			Export Date: 2022-10-28 17:42				Stand	15:43:00	300000
5								Sit	15:46:00	480000
6	BeatStart	IBI (ms)		BeatStart	RR	HR		Step	15:48:00	600000
7	38:00.0	n/a		15:38:01	875	68.57		Target	15:48:45	645000
8	38:01.2	875		15:38:02	876	68.49		Rest	15:49:45	705000
9	38:02.1	876		15:38:03	844.7	71.03		Stop	15:54:45	1005000
10	38:02.9	844.7		15:38:04	866.2	69.27				
11	38:03.8	866.2		15:38:05	859.4	69.82				
12	38:04.6	859.4		15:38:05	846.7	70.86				
13	38:05.5	846.7		15:38:06	872.1	68.80				
14	38:06.3	872.1		15:38:07	882.8	67.97				
15	38:07.2	882.8		15:38:08	885.7	67.74				
16	38:08.1	885.7		15:38:09	849.6	70.62				
17	38:09.0	849.6		15:38:10	869.1	69.04				
18	38:09.8	869.1		15:38:11	864.3	69.42				
19	38:10.7	864.3		15:38:12	871.1	68.88				
20	38:11.6	871.1		15:38:12	842.8	71.19				
21	38:12.4	842.8		15:38:13	841.8	71.28				
22	38:13.3	841.8		15:38:14	877	68.42				
23	38:14.1	877		15:38:15	876	68.49				
24	38:15.0	876		15:38:16	843.8	71.11				
25	38:15.9	843.8		15:38:17	848.6	70.70				
26	38:16.7	848.6		15:38:18	862.3	69.58				
27	38:17.6	862.3		15:38:18	866.2	69.27				
28	38:18.4	866.2		15:38:19	857.4	69.98				
29	38:19.3	857.4		15:38:20	874	68.65				
30	38:20.2	874		15:38:21	867.2	69.19				
31	38:21.0	867.2		15:38:22	858.4	69.90				
32	38:21.9	858.4		15:38:23	876	68.49				
33	38:22.8	876		15:38:24	883.8	67.89				
34	38:23.6	883.8		15:38:25	908.2	66.06				
35	38:24.5	908.2		15:38:25	876	68.49				

Figure 24 Screenshot of Microsoft Excel spreadsheet of ECG data. Raw data columns: data directly transferred from Actiheart software. Edited beats columns: data directly transferred from Actiheart software after manual confirmation of R waves. BeatStart changed to 24 hour clock from Raw BeatStart; RR is IBI; HR calculated as 60000/RR. Recorded timings were based on timing recorded during the step test and also corroborated with accelerometery data from individual patients' Full Waveform Analysis (**Figure 22**). Column J: how many milliseconds have passed from Start (0ms) of test (using formula (I4-I3)*(24*60*60*1000). Start = start of 1st rest period (5 minutes); Stand = patient stands from seated; Sit = patient sits (after 3 mins of standing); Step = patient starts step test; Target = point at which 60% HR_{max} reached; Rest = patient sits, beginning of recovery period (5 minutes); Stop = cessation of test and removal of Actiheart monitor.

An original R Studio programme was created by the author and Dr. Adam Glass to generate the HRR parameters (absolute values and area under the curve) from the exported IBI data (Appendix 6). Due to variation in the timings of each participant's total ECG recording, each trace needed to be analysed individually.

For each participant, a graph of heart rate (bpm) against time was created via R (Figure 25). Time was cumulative from start point (0 mins).

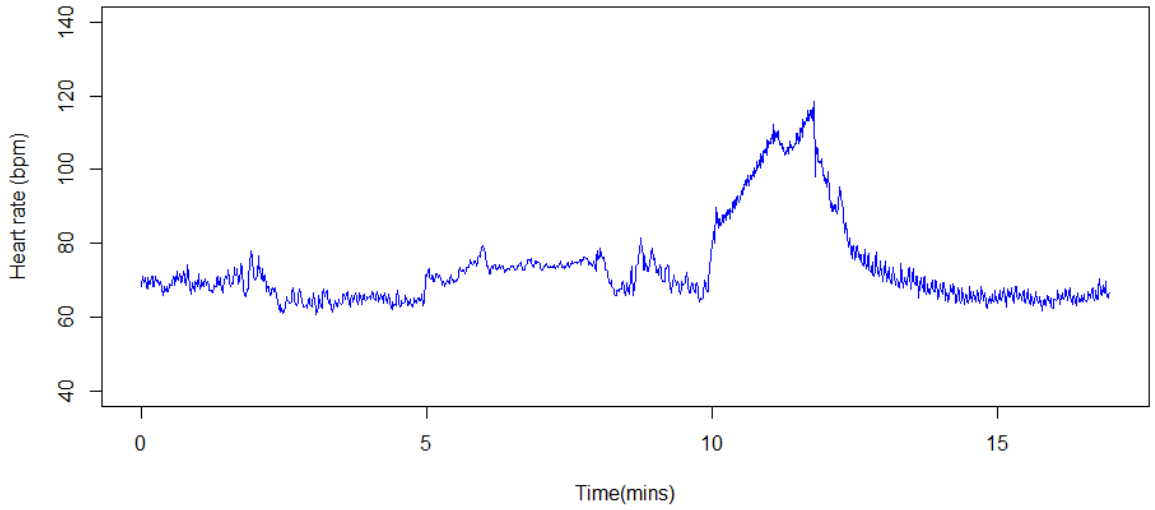
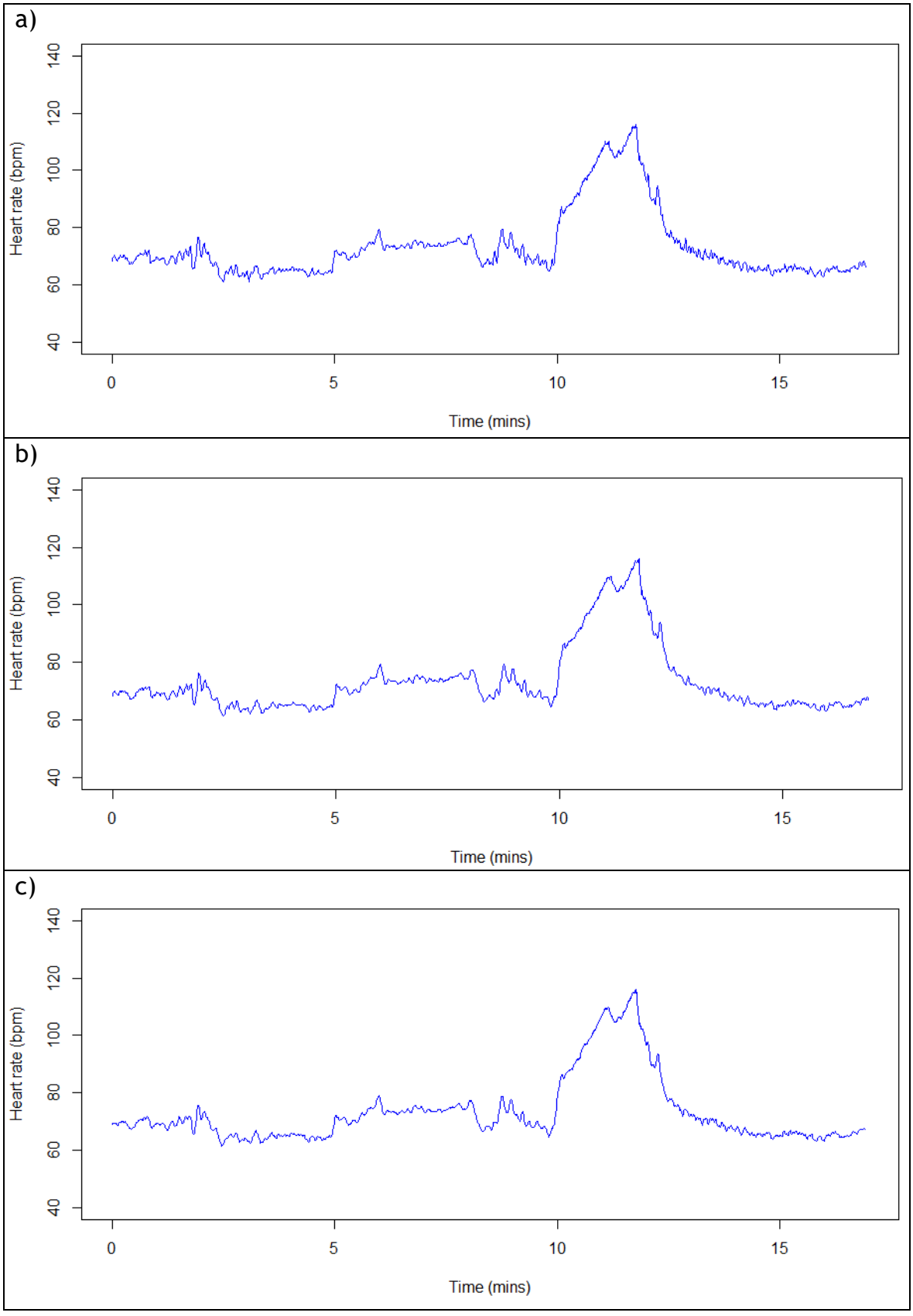


Figure 25 Heart rate versus time graph for whole heart rate recording of participant 008, created in R and derived from Actiheart IBI data.

4.9.1.1 Savitzky-Golay filter

The presence of ectopic beats and ECG noise (particularly during the step test) necessitated the use of a "smoothing filter" to minimise potential error in recorded heart rate. Smoothing was performed using a Savitsky-Golay filter[188] with a polynomial filter order of 2 and filter length of 11. The filter length was decided by running a variety of filter lengths on the first few heart rate traces (filter lengths of 7, 9, 11, 13, 15 and 17, Figure 26). A combination of visual inspection of the plots (as is usual convention) and appraisal of the maximum and minimum heart rate after the filter was applied determined the optimum filter length of 11. This was decided by the author and MD supervisor (Prof. Shelley) A filter length of 11 allowed conservation of the heart rate signal whilst removing appropriate noise e.g an abnormally high heart rate of 160 bpm due to

a single ectopic beat. Higher window sizes resulted in reduction in peak heart rate therefore potentially introducing error when calculating HRR.



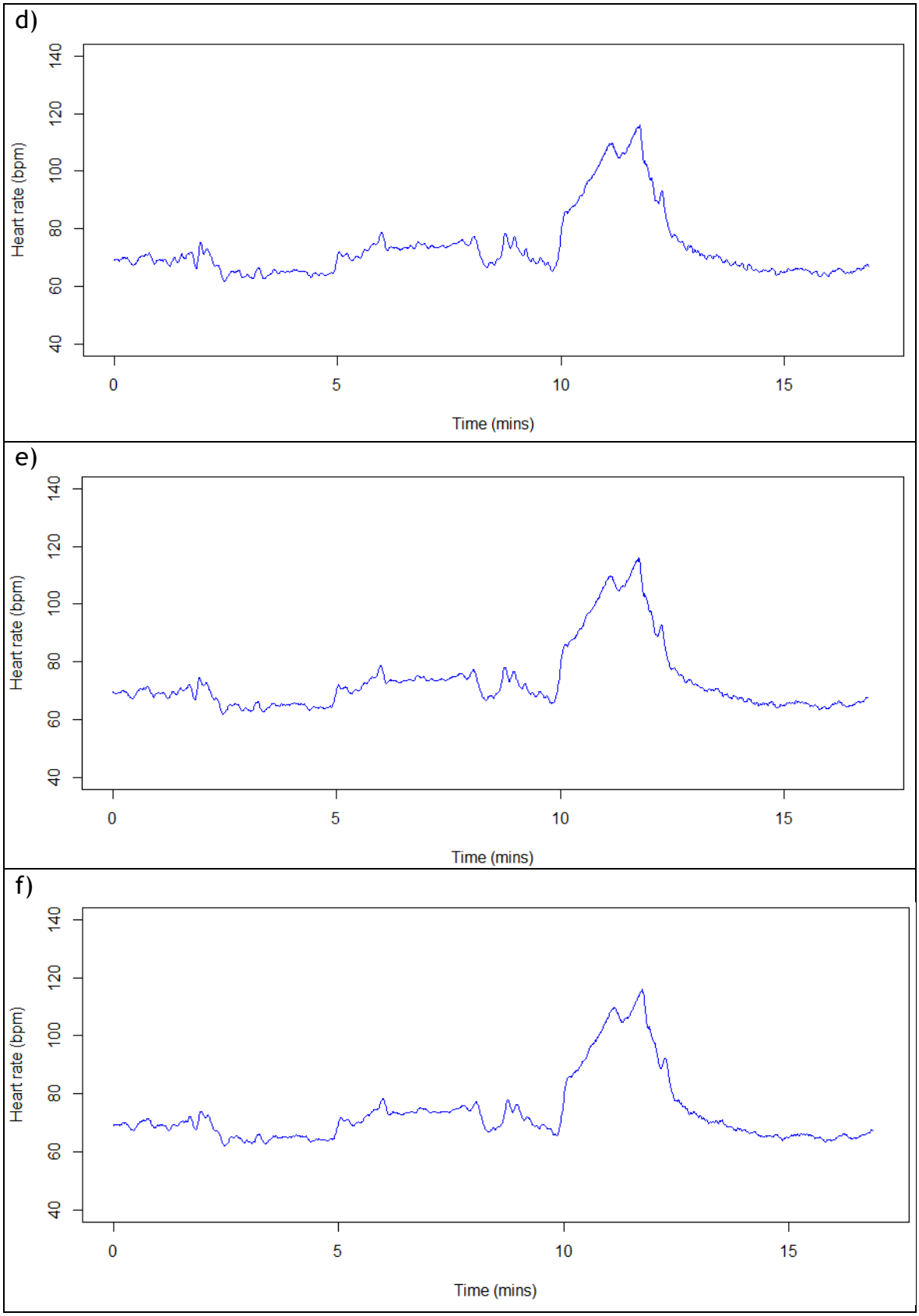


Figure 26 Examples of different Savitzky-Golay filter lengths applied to the heart rate versus time graph of participant 008 . a) SG filter length of 7. b) SG filter length of 9. c) SG filter length of 11. d) SG filter length of 13. e) SG filter length of 15. f) SG filter length of 17. All have polynomial filter order of 2.

4.9.1.2 Heart rate recovery parameters

The timepoint at which recovery after the step test began (hereafter termed "Rest") was identified in cell J8 (Figure 24) for each participant, with the corresponding HR at end of exercise recognised. From this point, the heart rate at each subsequent recovery timepoint could be identified e.g. "Rest" + 10000ms gave HRR at 10 seconds post exercise cessation. Heart rate recovery being the difference between heart rate at exercise cessation (Rest) and the heart rate at the specific timepoint. The R Studio programme produced a graphical representation of each filtered heart rate profile with vertical lines at Rest and the different heart rate recovery timepoints (10 seconds, 20 seconds, 30 seconds, one minute, two minutes and five minutes). Each graph was manually checked to ensure that the timings of the end of exercise and time points were correct (Figure 27).

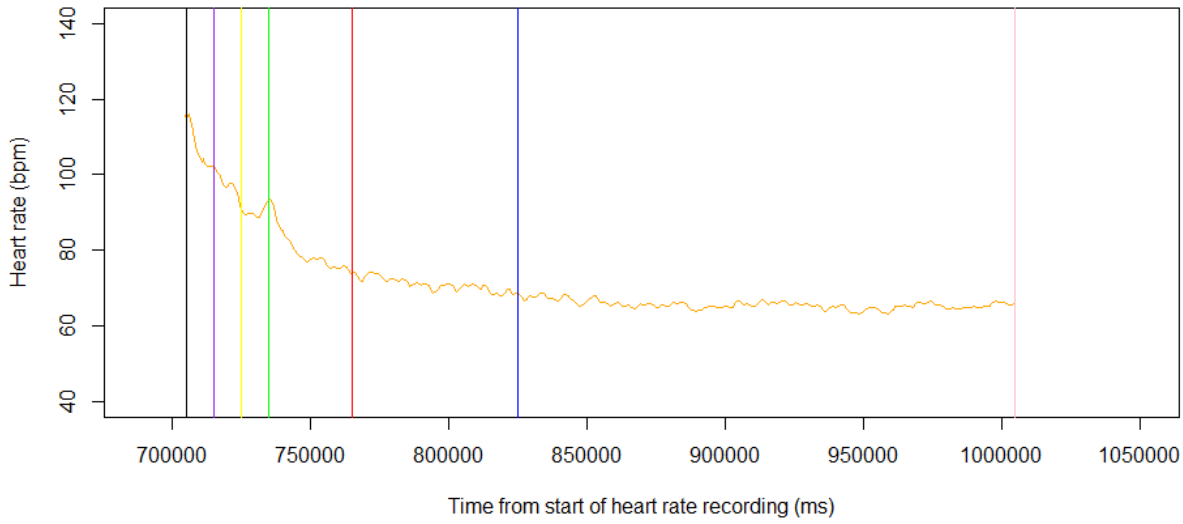


Figure 27 Heart rate versus time plot of participant 008 recovery period demonstrating HRR timepoints. Orange line: heart rate after SG filter applied. Black line: end of exercise ("Rest"). Purple line: 10s after Rest. Yellow line: 20s after Rest. Green line: 30s after Rest. Red line: 1 minute after Rest. Blue line: 2 minutes after Rest. Pink line: 5 minutes after Rest.

Absolute HRR was calculated by subtracting the heart rate at each time point (10 seconds, 20 seconds, 30 seconds, one minute and two minutes) from the heart rate at Rest. The area under the curve was calculated from Rest to the appropriate time point (30 seconds, one minute, two minutes and five minutes) limited vertically by the maximum and minimum heart rate during the recovery period (Figure 28). Using the minimum heart rate during the whole recovery

period as the lower border normalised the AUC to an approximation of the patient's resting heart rate.

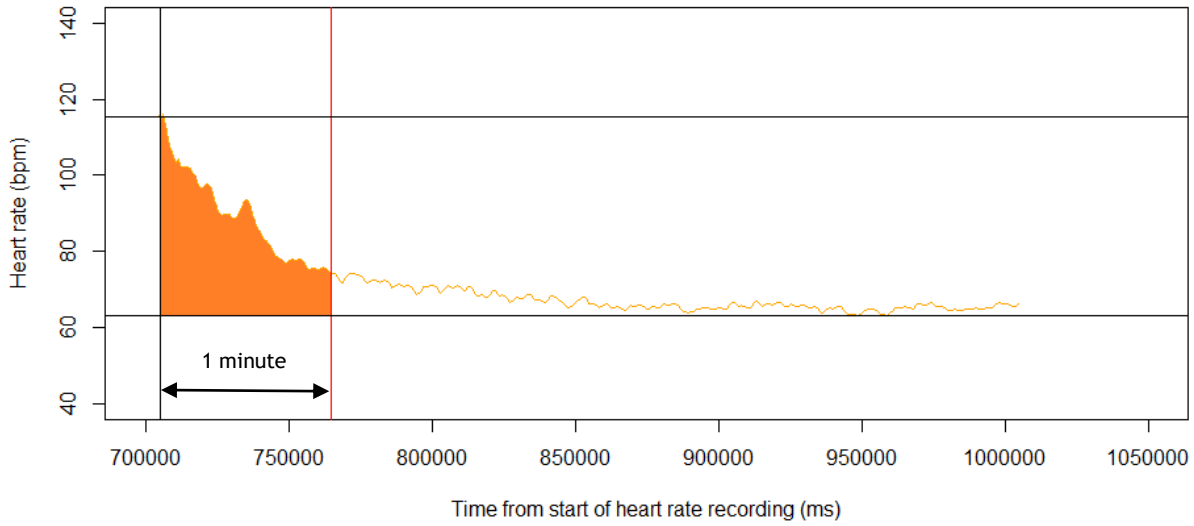


Figure 28 Heart rate versus time plot of participant 008 recovery period demonstrating AUC_1. Black vertical line: end of exercise (Rest). Red line: 1 minute after exercise cessation. Black horizontal lines: maximum and minimum heart rates during recovery period. Orange area: area under the curve.

All values were subsequently effort-corrected to standardise the parameters as a proportion of the patients' predicted maximal effort. Effort-correction was via the patient's age-predicted HR_{max} and maximum predicted power output. To calculate the proportion of maximum predicted heart rate the patient reached, the heart rate at Rest was divided by the patient's calculated age-predicted HR_{max} via the Tanaka formula (Section 4.7.2). To calculate the proportion of maximum predicted power output, the calculated power output during the whole step test was divided by the patient's maximum predicted power output (Section 4.7.4). The absolute HRR over each time interval and the area under the curve between Rest and each timepoint were then divided by the calculated effort-proportion to give effort-corrected values for each parameter at each timepoint. Table 10 and Table 11 show all parameters generated for validity testing with associated abbreviations used henceforth.

Table 10 All heart rate recovery outputs generated for validity testing.

Heart rate recovery outputs generated		
Absolute HRR	Effort-corrected to proportion of age-predicted maximum heart rate reached (ECHR)	Effort-corrected to proportion of predicted maximum power output reached (ECW)
HRR after 10 seconds (HRR_{10})	HRR_{10}-ECHR	HRR_{10}-ECW
HRR after 20 seconds (HRR_{20})	HRR_{20}-ECHR	HRR_{20}-ECW
HRR after 30 seconds (HRR_{30})	HRR_{30}-ECHR	HRR_{30}-ECW
HRR after 1 minute (HRR_{1})	HRR_{1}-ECHR	HRR_{1}-ECW
HRR after 2 minutes (HRR_{2})	HRR_{2}-ECHR	HRR_{2}-ECW

Heart rate recovery was measured earlier in the recovery period than AUC as it is likely that the stronger HRR signal is earlier in recovery whereas AUC might demonstrate a stronger signal later in the recovery period as it incorporates more of the curve. This decision was made to rationalise the total number of parameters assessed for predictive validity (27 in total).

Table 11 All area under the heart rate recovery curve outputs generated for validity testing

Area under the heart rate recovery curve outputs generated		
Absolute AUC	Effort-corrected to proportion of age-predicted maximum heart rate reached (ECHR)	Effort-corrected to proportion of predicted maximum power output reached (ECW)
AUC after 30 seconds (AUC_{30})	AUC_{30}-ECHR	AUC_{30}-ECW
AUC after 1 minute (AUC_1)	AUC_1-ECHR	AUC_1-ECW
AUC after 2 minutes (AUC_2)	AUC_2-ECHR	AUC_2-ECW
AUC after 5 minutes (AUC_5)	AUC_5-ECHR	AUC_5-ECW

4.9.2 Statistical handling

Data are presented as mean (SD) or median (IQR) appropriate to distribution. Normality was assessed with visual inspection and the Shapiro-Wilk test ($p > 0.05$). All statistical analysis was performed in R Statistical Software (V4.3.2; R Core Team 2023). A p value <0.05 was considered statistically significant. The statistical handling specific to each type of validity is included in each relevant Chapter.

Chapter 5 Generic results

The results described here apply to all patients recruited who underwent the preoperative exercise test. Specific results for the validation of the HRR parameters plus secondary outcomes are detailed in each Chapter.

5.1 Patient recruitment

From February 2022 to January 2023 84 patients were recruited to the study by the author (Figure 29).

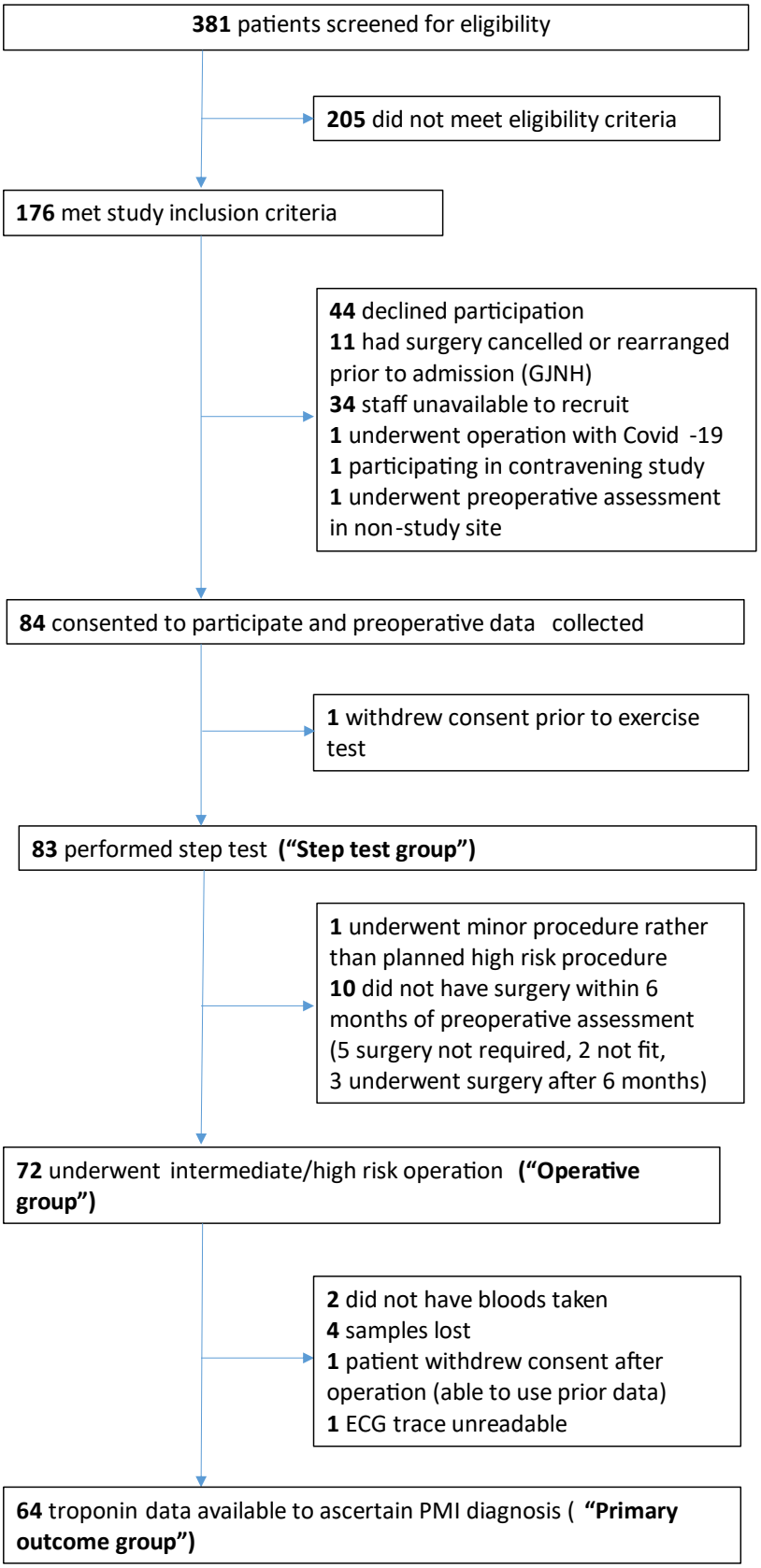


Figure 29 Study recruitment CONSORT diagram. Step test group included participants who did not undergo surgery but had data e.g. NT-ProBNP/risk scores and step test data available for construct validity testing. Operative group included patients who did not have troponin data available for PMI determination but had undergone both exercise test and surgery. Groups are referred to by this nomenclature throughout the thesis. GJNH: Golden Jubilee National Hospital; PMI: postoperative myocardial injury.

Twelve of the recruited patients did not undergo either the exercise test or their operation. One patient withdrew consent after recruitment and preoperative blood sampling, but before the exercise test; one patient was scheduled for a video-assisted thoracoscopy and lung resection but during the operation it was decided to take a biopsy only and so their surgery was downgraded from intermediate to low-risk. A further ten patients did not undergo their planned operation within six months of pre-assessment and recruitment to the study. Two of these were deemed not clinically fit to undergo their procedure; for five patients it was subsequently decided that they did not require or want their surgery; and three patients did have their operation but more than six months after recruitment and so were withdrawn from the study. Recruitment to the study was undertaken whilst the NHS was recovering from the Covid-19 pandemic with a large elective surgery backlog and both pre-assessment and surgical services not running at full capacity.

5.2 Patient characteristics

Baseline demographic data for the patients recruited to the study who performed the step test (hereafter known as the "Step Test" group, n = 83) are presented in Table 12.

Table 12 Participant demographics, comorbidities, preoperative blood results and medications in Step Test group. n = 83 unless stated otherwise. Values are number (percentage), mean±SD and median (IQR) [range]. BMI: body mass index; ASA: American Society of Anaesthesiologists Physical Status; COPD: chronic obstructive pulmonary disease; hsTnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme.

Characteristic	Descriptive Statistics
Age (years)	66.6±8.2
Female sex	42 (51%)
BMI (kg/m^2)	27.4 (24.2 – 31.2) [17.4 – 47.5]
Ethnicity: White British	 83 (100%)
Smoking status: Current smoker Ex-smoker Never smoked	 17 (20%) 35 (42%) 31 (38%)
Clinical Frailty Scale: 1 2 3 4 5 >5	 4 (5%) 23 (28%) 30 (36%) 19 (23%) 7 (8%) 0
ASA score:	

1 2 3 4 *Missing data*	0 26 (31%) 26 (31%) 3 (4%) *28*
Duke Activity Status Index (points)	39.0 (24.6 - 50.7) [10.7 - 58.2]
Comorbidities	
None	5 (6%)
History of cancer	32 (39%)
Asthma	5 (6%)
COPD	16 (19%)
Arterial hypertension	35 (42%)
Ischaemic heart disease	15 (18%)
Cardiac failure	1 (1%)
Atrial fibrillation	3 (4%)
Peripheral vascular disease	9 (11%)
Stroke	2 (2%)
Type 1 Diabetes mellitus	2 (2%)
Type 2 Diabetes mellitus	12 (14%)
Previous covid infection Long covid	32 (39%) 1 (1%)
Preoperative blood results	
NT-ProBNP (pg/ml) *Missing data*	90 (47 – 196) [12 – 13751] *1*
hsTnT (ng/L) *Missing data*	7 (5 – 11) [3 – 130] *3*
Haemoglobin (g/L) *Missing data*	13.9 (12.9 - 15.0) [8.9 - 18.1]
Creatinine (µmol/L) *Missing data*	77 (65 - 89) [45 - 537]
Preoperative renal function eGFR >59 (ml/min) eGFR 30-59 (ml/min) eGFR <30 (ml/min) *Missing data*	 71 (86%) 10 (12%) 1 (1%) *1*
Medications	
No regular medication	7 (8%)
Beta-blocker	16 (19%)
Calcium channel blocker	23 (28%)
ACE-inhibitor	18 (22%)
Diuretics	9 (11%)
Antiarrhythmic	0
Beta-agonist	12 (14%)
Steroids: Inhaled Oral	 9 (11%) 1 (1%)

5.3 Preoperative risk scores

The preoperative risk scores of the Step Test group are described in Table 13.

Table 13 Preoperative risk scores of Step Test group. n=83 unless stated otherwise. Values are number (percentage), or median (IQR) [range]. Bpm: beats per minute P/V-POSSUM: Portsmouth/Vascular-Physiologic and Operative Severity Score for the study of Mortality and Morbidity; ACS NSQIP SRC: American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; SORT: Surgical Outcome Risk Tool; RCRI: Revised Cardiac Risk Index.

Preoperative risk score	Descriptive Statistics
P/V-POSSUM 30-day morbidity (%)	28.9 (19.0 – 41.2) [8.8 – 81.5]
P/V-POSSUM 30-day mortality (%)	1.5 (0.8 – 2.6) [0.4 – 11.6]
ACS NSQIP SRC any complication risk (%)	9.3 (6.3 – 16.8) [2.2 – 39.3]
ACS NSQIP SRC length of hospital stay (days) *(n=82)*	3.5 (2.5 – 5.5) [0.5 – 8.0]
SORT 30-day mortality (%)	0.79 (0.28 – 1.56) [0.06 – 4.81]
RCRI (risk of postoperative cardiovascular complications): Class I 3.9% Class II 6.0% Class III 10.1% Class IV 15.0%	 7 (8%) 58 (70%) 14 (17%) 4 (5%)

5.4 Step test parameters

The step test parameters for all patients who completed the exercise test (Step Test group) are described in Table 14. Unfortunately, the ECG trace during the exercise test was unreadable for two patients, hence the missing data for proportion of age-predicted HR_{max} reached and heart rate at end of exercise.

Table 14 Step test parameters for Step test group. n = 83 unless stated otherwise. Values are number (percentage), mean±SD or median (IQR [range]. Bpm: beats per minute

Step test parameter	Descriptive statistics
Height of step: 19.5cm 14.5cm 9.5cm	 56 (68%) 26 (31%) 1 (1%)
Length of time taken (seconds)	92 (80 – 119) [63 – 240]
Proportion of age-predicted maximum heart rate reached *Missing data*	0.67 (0.62 – 0.71) [0.44 – 1.01] *2*
Heart rate at end of exercise (bpm) *Missing data*	108.0±14.2 *2*
Power output (Watts)	41.4±14.8
Proportion of maximum predicted power reached	0.29 (0.22 – 0.45) [0.12 – 1.63)
Modified Borg score	4.0 (2.0 – 5.5) [0.0 – 10.0]
Wearing a facemask	48 (58%)

5.5 Intraoperative parameters

Seventy-two patients underwent the exercise test and their operation (hereafter referred to as "Operative group"). Patients were recruited from a variety of surgical specialities to assess the generalisability of heart rate recovery as a measure. Surgical speciality and intraoperative parameters for the Operative group are detailed in Table 15.

Table 15 Intraoperative parameters for Operative group. n = 72 unless stated otherwise. Values are number (percentage), mean±SD or median (IQR) [range]. PACU: post-anaesthesia care unit

Surgical Specialty	**Descriptive statistics**
Thoracic	23 (46%)
Colorectal	13 (18%)
Upper Gastrointestinal	4 (6%)
Vascular	11 (15%)
Gynaecology	7 (10%)
Orthopaedic	1 (1%)
ENT/Max-fax	3 (4%)
Intraoperative parameter	
Duration of surgery (mins)	214 (140 – 316) [50 – 660]
Type of anaesthetic: General anaesthetic Regional General anaesthetic and regional combined	 50 (69%) 0 22 (31%)
Anaesthesia maintenance: Inhalational Intravenous	 43 (60%) 29 (40%)
Arterial monitoring	47 (65%)
Bispectral index monitoring *Missing data*	38 (54%) *2*
Lowest systolic blood pressure (mmHg) Missing data	84.8±12.4 2
Lowest mean arterial pressure (mmHg) *Missing data*	57.3±9.25 *44*
Vasopressor administration: Yes No	 40 (56%) 32 (44%)
Hypotension requiring treatment in recovery/PACU *Missing data*	13 (18%) *1*
Intraoperative complication (major haemorrhage)	7 (10%)

5.6 Discussion

This study recruited 84 patients to assess the validity of submaximal HRR as a perioperative risk measure. The protocol was well-tolerated with only one patient withdrawing consent for the exercise test and one withdrawing consent for postoperative blood sampling. However, the total number of patient data

available for validity testing was limited primarily by patients not undergoing their planned procedure and problems with the collection or processing of hsTnT for determination of PMI.

5.6.1 Participant characteristics

Participant demographics demonstrated variety in the age of participants; an equal sex distribution and variety of physical fitness and comorbidity. However, there is no ethnic diversity within the study population with 100% participants being White British. This reflects the West of Scotland population but is a limitation in the potential generalisability of the results. One of the main inclusion criteria of the study was age >50 years to recruit a population at increased risk of PMI. The mean age of participants was 66.6±8.2 years so just over the 65 year threshold for increased perioperative cardiovascular risk. Body mass index was varied; the largest BMI was 47.5 kg/m^2 and this patient completed the step test. Sixty-two percent of participants were either current or ex-smokers. This is higher than the 2022 average for adults in Scotland (13.9% and 25.1% respectively)[189] and likely reflects both the increased age of the participants and the large thoracic and vascular surgery cohort. Most patients fulfilled the criteria for a clinical frailty scale between 2 and 4, being well but not fit through to vulnerable with symptoms limiting abilities. The ASA physiological status was also split between ASA 2 and 3 reflecting a degree of symptom impact on life. Compared to UK-wide data where 49% of operative patients were ASA 2 and 23% were ASA 3[7], the study cohort included a higher proportion of ASA 3 patients (31%). The median DASI was 39.0, with wide variety within the cohort. A DASI score of less than 34 has been identified as a cut-off for increased risk of cardiovascular and respiratory complications[39]. Compared to a secondary analysis of the METS study investigating maximal heart rate recovery and PMI[150], this patient cohort was of a similar age, had a more equal sex distribution, a similar proportion of ASA 3 patients, and a similar proportion of patients on beta-blockers.

Only 6% of patients did not have any co-morbidity. The most prevalent co-morbidities were arterial hypertension (42%), a history of cancer (39%) and COPD (19%). Three patients had atrial fibrillation. Thirty-nine percent of patients had also received a positive diagnosis of Covid-19 at some point prior to study

recruitment. However, only one patient had a suspected diagnosis of Long Covid syndrome. The most common medications were those for arterial hypertension and ischaemic heart disease, being calcium channel blockers (28%), ACE-inhibitors (22%) and beta-blockers (19%). A sensitivity analysis for beta-blocker and calcium channel therapy was performed for the primary outcome investigation (Section 6.2.8).

5.6.2 Preoperative risk scores

There was variety in perioperative risk demonstrated within the study population by the preoperative risk scores. Median predicted 30-day mortality was 0.79% by SORT score and 1.5% by P/V-POSSUM score, both of which incorporate surgical factors. The surgical inclusion criteria for this study were any operation deemed to have over 1% risk of cardiovascular death or MI within 30-days, regardless of patient risk. Although not perfectly equitable parameters, the SORT and P/V-POSSUM scores indicate that the operations undertaken were of appropriate risk for the purposes of the study.

Compared to the METS study[38], there was a higher proportion of patients with an RCRI score of ≥3 in this investigation (22% versus 10%) indicating high cardiovascular risk. The median DASI in a nested cohort analysis of METs was 42.7[39], so indicating a higher median functional capacity in the METs cohort. The patients in METS were slightly younger (inclusion criteria ≥40 years) which may explain these differences, but these findings may indicate that the patient cohort in this investigation demonstrated slightly higher cardiovascular risk and were less fit than the METS cohort.

Overall, the patient demographics, comorbidities, functional capacity and preoperative risk scores indicate that the patient cohort recruited fulfilled the aims of the inclusion and exclusion criteria. There is sufficient variation in the demographics, apart from ethnicity, to ensure the generalisability of the results, but there is also evidence of higher cardiovascular risk and reduced functional capacity, improving the likelihood of a signal for PMI.

5.6.3 Step test

The step test itself was well-tolerated, taking less than five minutes with tolerable levels of dyspnoea. On average, patient exertion was slightly higher than the aim of 60% age-predicted maximum heart rate and so a lower aim could potentially be utilised. Whether this target was high enough to generate a valid HRR response will be explored in the following chapters. The step test was well-tolerated (Chapter 10 for more information), taking just over one and a half minutes on average with patients reporting a median Modified Borg Score[176] of four at cessation of exercise. This equates to "somewhat severe" dyspnoea. The longest step test took four minutes, in a patient on beta-blockers whose heart rate took longer than usual to reach 60% age-predicted maximum.

The protocol worked well with the median percentage of age-predicted heart rate reached being 67% with a relatively tight interquartile range. Three patients did not reach the target heart rate; all three were on beta-blockers and continued the test for at least a minute after their heart rate appeared to reach a plateau. The patient who only reached 44% age-predicted HR_{max} was subsequently deemed unfit for their procedure by their clinical team, who were blinded to the exercise test results. A patient who reached 51% age-predicted HR_{max} did not undergo their planned operation as it was deemed not required after further discussion with the surgeons. The other patient who did not reach target heart rate did undergo their operation.

The proportion of predicted maximum power output was much more variable than the proportion of age-predicted HR_{max} reached. Clearly one aspect to this will be the fact that a specific target heart rate was aimed for during the test, ensuring tight control around this. Maximum heart rate is also predominantly dependent on age only where effort is corrected for (aside from rate-limiting medications)[175], whereas power output is dependent on patient weight, age, sex and both the height of the step and the time length of the exercise test[178], thereby incorporating more parameters to introduce variability. Heart rate is potentially a more accurate measure of the bodies response to exercise (particularly influenced by the autonomic system as discussed in Section 1.3.3). Power output however, is a measure of effort, indicating how much the patient is able do to. This is both dependent on cardiorespiratory function but also

neuromuscular function and strength and therefore overall fitness. Measurement of power output has the potential to provide a method of effort-correction, where less fit patients may have a reduced heart rate recovery for a lower power output. Therefore, the variability demonstrated in the step test parameters indicates that the power output may have more effect in effort-correction than the tightly controlled proportion of HR_{max} reached.

Wearing a facemask was mandatory in hospitals unless clinically exempt at the beginning of the study. The rules changed during the study and latterly it was down to patient preference to wear a face mask. Most patients did wear a facemask during the exercise test. At the time of writing (2024), surgical face mask use is no longer a requirement in UK hospitals. The effect of wearing a surgical face mask during exercise, particularly on heart rate is uncertain. Wearing a surgical face mask during steady state exercise significantly increased peak heart rate in fourteen healthy men compared to exercising without a mask but rating of perceived exertion (RPE) was similar[190]. However, two subsequent studies found conflicting results. There was no difference in heart rate in older adults performing a 6MWT with and without a surgical face mask[191], although again, RPE was significantly increased. However, peak heart rate was actually lower in participants wearing masks and performing maximal exercise tests, again with a significantly higher RPE[192]. It may be that wearing a surgical face mask is uncomfortable and increases the sensation of exertion[G], thereby limiting maximal performance. Although limited, the evidence suggests that wearing a face mask does not affect heart rate during submaximal exercise and so will pose no limitation to the generalisability of these results.

5.6.4 Intraoperative parameters

Ten patients did not undergo surgery within six months of recruitment and one underwent a “low-risk” operation (lung biopsy) rather than the expected intermediate risk operation of a video-assisted thoracoscopic wedge resection. Therefore, intraoperative and postoperative data is available for 72 patients (identified as Operative group). Patients underwent a broad range of surgery split between seven specialties, although nearly half underwent thoracic

[G] In these studies, RPE measured either by Borg, or modified Borg score (Section 4.7.2)

surgery. The median length of operative time (including anaesthetic time) was just over 3.5 hours. Three operations were less than one hour (50 and 55 minutes); these were all major gynaecology cases which, despite the relatively short operative time, all required hospital stays of two to four days. The intraoperative parameters indicate that surgical selection fulfilled the inclusion criteria of intermediate/high-risk operations. Sixty-five percent of patients had intraoperative arterial monitoring with 56% requiring vasopressor administration during the operation and nearly a fifth requiring ongoing blood pressure support in PACU. Over half of the patients did not have data for the lowest intraoperative mean arterial blood pressure (MAP); this is predominantly due to the use of paper anaesthetic charts in two of the three hospitals meaning MAP is not usually recorded. The mean lowest recorded intraoperative systolic blood pressure (SBP) was 84.8±12.4 mmHg. Intraoperative blood pressure targets are a contentious subject within anaesthesia but it is generally recommended to maintain a SBP >100 mmHg, with evidence that an SBP <100mg mmHg increases the risk of perioperative myocardial injury and death[193]. Although this risk is dependent on the severity and duration of hypotension; length of intraoperative hypotension was not recorded in this study. The relatively low mean intraoperative SBP demonstrated within the Operative group of this study will be multifactorial in its cause but could be a result of the increased age and relatively comorbid and frail status of the patients, plus a high percentage of patients taking antihypertensives. It is also likely a reflection of the surgical severity of the cohort as mentioned above. Ten percent of patients also experienced a major haemorrhage (defined as blood loss over 1000ml intraoperatively, or leading to administration of packed red cells). Five of these patients were undergoing vascular operations and one underwent a thoracic operation.

The intraoperative parameters reinforce that the surgical selection for the study fulfilled the criteria of intermediate/high-risk operations with a significant level of invasive monitoring, intraoperative hypotension and major complications.

5.7 Conclusion

This chapter details the generic results for all patients recruited to the study. The step test and study protocol were generally well-tolerated with operative

data missing for twelve patients primarily because they did not undergo their planned procedure. Primary outcome data was available for 64 patients, with issues with troponin sampling or processing the main reason for lack of determination of PMI in this cohort.

These results demonstrate that this was a generalisable sample undergoing intermediate/high-risk surgery as planned. The demographics, comorbidities, preoperative risk scores and intraoperative parameters all confirm that patient selection and recruitment to the study fulfilled the aims of the inclusion/exclusion criteria in selecting a sample of patients across a broad range of demographics and surgical specialities whilst also ensuring a level of cardiovascular risk for postoperative myocardial injury. The results detailed in this chapter form the basis for the validity of the heart rate recovery measures detailed in the following chapters.

Chapter 6 Heart rate recovery and postoperative myocardial injury (predictive validity)

This Chapter explores the predictive value of the measured HRR parameters (as described in Section 4.9.1.2) for PMI. This investigation will first evaluate association between absolute and effort-corrected HRR parameters, and PMI. Secondly, the predictive value for PMI of a variety of HRR parameters including absolute values, effort-corrected values and the area under the heart rate recovery curve (AUC) will be assessed. Finally, the potential for HRR parameters to improve the discrimination of currently-used risk prediction measures will be assessed. The most successful HRR measures will subsequently undergo further validity testing (face, construct, criterion and concurrent).

6.1 Specific Methods

Patient recruitment, the exercise test protocol, extraction of heart rate recovery parameters and laboratory sampling are described in Chapter 4 (Generic methods). The specific methods pertaining to the assessment of predictive validity of the submaximal HRR parameters are described here.

6.1.1 Postoperative myocardial injury determination

All patients had baseline preoperative hs-Troponin T (hsTnT) measured, either on the ward on the day before surgery or at the pre-assessment clinic. Postoperative myocardial injury was deemed to be present if the postoperative hs-TnT was ≥14ng/L AND there was an increase of ≥20% from baseline. Where possible, patients had two postoperative hs-Troponin T samples taken; one on the first calendar day after surgery and one on the second calendar day. If a patient was well enough to be discharged on day two, before blood sampling, and their day one troponin result did not fulfil the criteria for PMI, they were deemed to be negative for PMI. Absence of acute myocardial ischaemia was judged via ECG review where available, or lack of clinical concern or documentation within the postoperative notes review.

6.1.2 Specific statistical handling

Comparisons of non-parametrically distributed heart rate recovery parameters between PMI and non-PMI groups were made using Wilcoxon rank sum exact test. Sensitivity analyses were performed to assess the potential effect of heart rate-limiting medications (beta-blockade and calcium channel blockade) on the predictive value of the HRR parameters. No adjustments were made for multiple comparisons as this was an exploratory study investigating the potential for many different methods of measuring submaximal HRR.

6.1.3 Determining predictive validity of heart rate recovery parameters

6.1.3.1 Area under the receiver operating curve

Due to the very limited data available for the use of perioperative submaximal HRR in the literature (Chapter 2 Systematic review and meta-analysis), several parameters were investigated to optimise the potential of the HRR curve. Absolute values were heart rate recovery after 10 seconds (HRR_{10}), HRR after 20 seconds (HRR_{20}), HRR after 30 seconds (HRR_{30}), HRR after one minute (HRR_1) and HRR after two minutes (HRR_2) from cessation of exercise. Four area under the curve values were assessed: AUC at 30 seconds (AUC_{30}), AUC at one minute (AUC_1), AUC at two minutes (AUC_2) and AUC after five minutes of recovery (AUC_5), as described in Section 4.9.1.2. Each parameter was subsequently effort-corrected to the proportion of age-predicted HR_{max} reached and the proportion of maximum predicted power output reached, given 27 HRR parameters in total.

The predictive value of the HRR parameters for PMI was determined via receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUROC). No adjustments were made for multiple comparisons. Area under the ROC curve and 95% confidence intervals are presented using the Delong method. The area under the curves were interpreted as per Mandrekar et al.[194] (Table 16):

Table 16 Interpretation of area under the receiver operating curve. Reproduced from Mandrekar et al.[194]

Area under the receiver operating curve	Interpretation
1.0	Perfect
0.90 – 0.99	Excellent predictive value
0.80 – 0.89	Good predictive value
0.70 – 0.79	Fair predictive value
0.60 – 0.69	Poor predictive value
0.50 – 0.59	No predictive value

If there were multiple HRR parameters which demonstrated predictive value for PMI, only the five with the highest AUROC would be taken forward for further analysis to ascertain the parameter for best clinical use.

6.1.3.2 Determining thresholds for identification of low and high-risk patients using the HRR parameters

Cut-offs to indicate high-risk and low-risk for the HRR parameters were determined via two methods: the threshold at Youden's index and weighted 2:1 sensitivity: specificity. Youden's index is the classical method of obtaining the optimum threshold where the sum of the sensitivity and specificity are maximal and is predominantly used within clinical literature for diagnostic testing[195]. When evaluating screening tests, however, which HRR as a risk prediction tool is more similar to, it is generally recommended to focus more on sensitivity i.e. the test is more likely to identify those patients at risk and for whom further investigation is necessary, whereas the implication for a false positive patient is fairly minimal with further investigations likely to give a more accurate measure of the actual risk[196,197]. Sinclair et al. used a 2:1 sensitivity:specificity weighting when determining the cut-offs for 6MWT distance in predicting the preoperative anaerobic threshold[198].

6.1.3.3 Effect of submaximal heart rate recovery on risk prediction measures currently in use

Logistic regression was performed to assess the potential additive effect of HRR parameters to currently-used risk prediction methods. Univariate logistic regression models for four current risk prediction modalities were created using data from this patient cohort (preoperative NT-ProBNP, RCRI, DASI and SORT score). Bivariate models were then created for each risk prediction modality

with the addition of the best-performing HRR parameter to assess whether it improved the predictive value of each independent variable. The extent of improvement was measured via the change in the AUROC and net reclassification index (NRI)[199].

Net reclassification provides a more granular assessment of how well predictive models work compared to AUROC. A new predictive model which works well should increase the predicted risk for the event and reduce the predicted risk for non-events compared to an older, inferior model. NRI assesses how many patients are correctly and incorrectly reclassified between different predictive models by adding the proportion of patients correctly reclassified with those incorrectly reclassified:

$$NRI = NRI_e + NRI_{ne}, \text{ where}$$

$$NRI_e = P(up|event) + P(down|event), \text{ and}$$

$$NRI_{ne} = P(down|nonevent) - P(up|nonevent)^H.$$

In a continuous ("category-free") NRI calculation, as used in this investigation, "up" means any upward movement in risk prediction and "down" means any downward movement in risk prediction. "Events" are cases, so patients with PMI in this investigation and "non-events" are controls i.e. patients who did not develop PMI. Patients who are correctly reclassified by the new model are assigned +1 and patients who are incorrectly reclassified assigned -1. Patients who are not reclassified by the new model are assigned 0. These assigned values are then counted together in each group and divided by the total number of patients in that group to give a proportion. The overall NRI is the sum of these two values and is itself a unitless statistic as it is the sum of two proportions with different denominators. The maximum value of NRI is 2; but what constitutes a "large" or "small" value is currently undefined[200]. For each risk prediction measure, the baseline model and model with HRR_1 were assessed using continuous net reclassification for risk difference[201]. This is because these

[H] P (|) denotes probability of direction of change AND either event or nonevent.

are exploratory, naïve models in a small patient cohort with no defined cut-offs for high/low-risk determination.

6.1.4 Sample size calculation

Postoperative myocardial injury was the primary outcome for the VERVE study and so a power calculation was performed based on the hypothesis that submaximal HRR will improve the AUROC for the prediction of PMI from 0.5 (null hypothesis) to 0.7. Based on a prior incidence of PMI of 24.5%[156] after non-cardiac surgery in patients at higher risk of cardiovascular complications, 90 patients were required, with a type 1 error of 0.05 and power of 80%. This incidence was chosen for the power calculation as Ackland et al. investigated PMI in a similar patient population to this study[156]. Adding an expected 5% dropout rate, a final sample size of 95 patients was required between the three study sites. MedCalc Statistical Software V19.7.2 (MedCalc Software Ltd., Ostend, Belgium) was used to calculate the sample size.

6.2 Results

Eighty-four patients were recruited to the study over a one-year period by the author. Study recruitment was finished early due to a combination of factors: site opening was delayed due to the slow restart of perioperative research approval following the COVID-19 pandemic; the manufacture of the Actiheart 5 BT monitor was delayed due to a global microchip shortage; laboratories were understandably reticent to agree to cTn assay measurement due to a global shortage of blood collection bottles; only the author was available to recruit patients whilst also undertaking clinical work plus due to the demands of an MD by research only had one year to complete recruitment after a six month delay due to slow site approval.

Primary outcome analysis was not possible for 20 patients: one patient withdrew consent before the step test and one after their surgery, ten patients did not undergo their planned surgery within six months of the step test, one patient unexpectedly underwent a minor procedure, six patients' hs-TnT samples were either not taken or processed and one was found to have an unreadable HRR trace (Figure 29). Therefore, 64 patients underwent their expected surgery and

had both preoperative and postoperative hs-TnT results available for PMI determination.

6.2.1 Incidence of postoperative myocardial injury

The overall incidence of PMI was 35.9% (23/64). The distribution of hs-TnT between patients with and without PMI is shown in Table 17 and Figure 30.

Table 17 Median (IQR) high-sensitivity Troponin T at baseline, postoperative day 1 and day 2 split between patients with or without PMI.

Timepoint	High-sensitivity Troponin T (ng/L)	
	No PMI Median (IQR) *Number of patients*	**PMI** Median (IQR) *Number of patients*
Baseline	6 (5 – 8) *21*	9 (8 - 16) *41*
Postoperative day 1	8 (6 – 10) *21*	23 (14 – 33) *40*
Postoperative day 2	7 (6 – 9) *11*	23 (15 – 32) *38*

Patients with PMI had significantly higher hs-TnT postoperatively but with similar values between postoperative day one and day two. This correlates with the findings of Ackland et al. who demonstrated that the majority of PMI occurs within the first 24 hours post surgery[136].

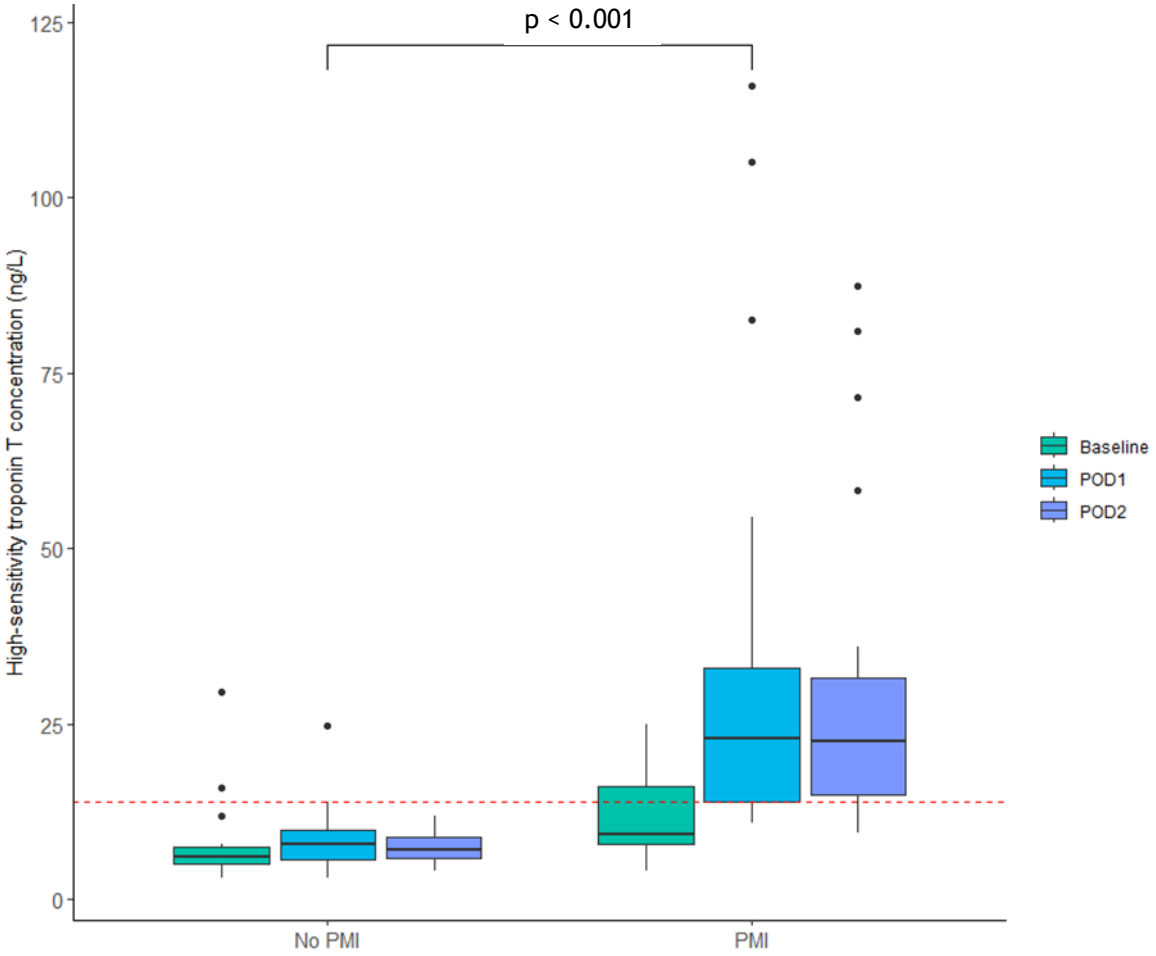


Figure 30 Grouped boxplot displaying high-sensitivity Troponin T (hs-TnT) at baseline, postoperative day 1 and postoperative day 2 split between patients with and without PMI. Red dashed line: hs-TnT 14ng/L, the 99th percentile upper reference limit. Wilcoxon rank sum test.

Determination of PMI was not only by an absolute value of >14ng/L but also a 20% change from baseline. Figure 31 shows that patients with PMI had a larger change in hs-TnT compared to patients without PMI (median (IQR) 11 (8 – 24) ng/L versus 1 (0 – 3) ng/L, respectively).

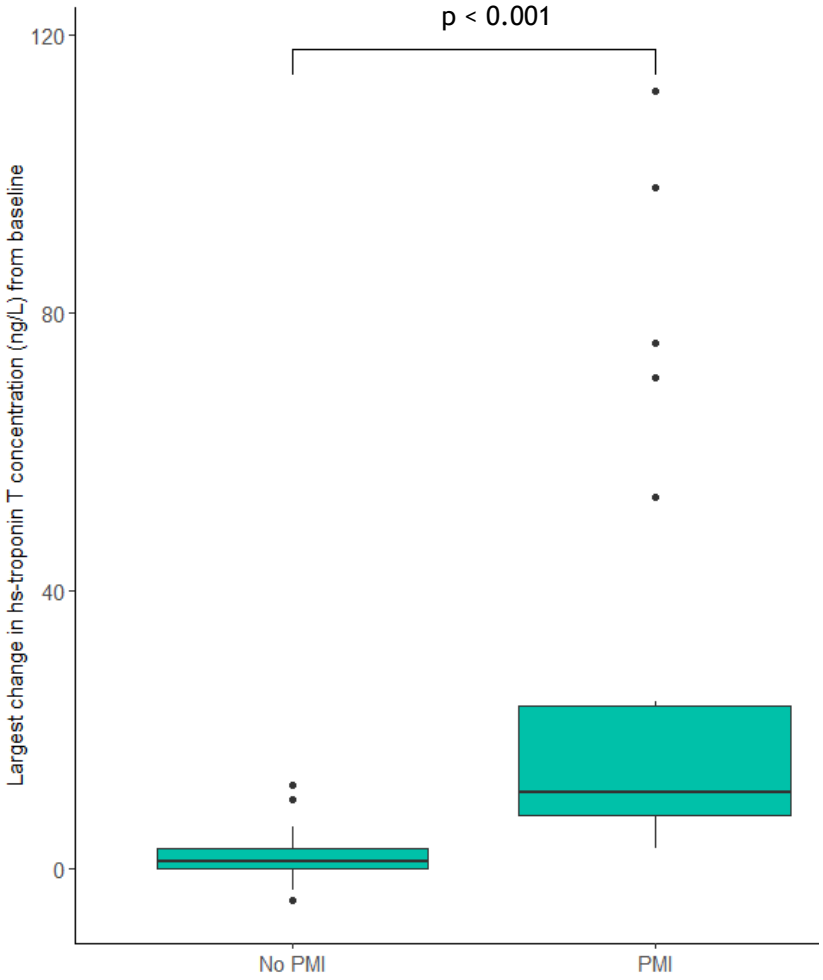


Figure 31 Largest change in high-sensitivity Troponin T between baseline and either postoperative day 1 or day 2 split between patients with and without PMI. Wilcoxon rank sum test. n = 64

6.2.2 Patient characteristics

Patient demographic data for patients with PMI and those without is displayed in Table 18.

Table 18 Participant demographics, comorbidities, preoperative blood results and medications in patients with postoperative myocardial injury (PMI). Values are number (percentage), mean±SD and median (IQR) [range]. BMI: body mass index; ASA: American Society of Anaesthesiologists Physical Status; COPD: chronic obstructive pulmonary disease; hs-TnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme. *unless stated otherwise. Unpaired t-test for parametric data, Mann-Witney test for nonparametric data, chi-squared test for dichotomous data. P vales in bold are significant (<0.05).

Characteristic	PMI (n = 23*)	No PMI (n = 41*)	p value
Age (years)	69.3±7.9	64.1±7.1	**0.009**
Female sex	5 (22%)	25 (61%)	**0.03**
BMI (kg/m^2)	27.5 (23.6 – 30.6) [18.7 – 47.5]	27.7 (24.9 – 30.9) [18.2 – 46.1]	0.80
Ethnicity: White British	23 (100%)	41 (100%)	1.00
Smoking status:			

Current smoker	2 (9%)	8 (20%)	0.29
Ex-smoker	15 (65%)	17 (41%)	0.20
Never smoked	6 (26%)	16 (39%)	0.40
Clinical Frailty Score:			
1	0	3 (7%)	0.20
2	7 (30%)	12 (29%)	0.94
3	6 (26%)	17 (41%)	0.33
4	6 (26%)	7 (17%)	0.44
5	4 (17%)	2 (5%)	0.12
>5	0	0	
ASA:			
1	0	0	
2	5 (22%)	16 (39%)	0.25
3	12 (52%)	13 (32%)	0.21
4	0	3 (7%)	0.20
Missing data	*6*	*9*	
Duke Activity Status Index (points)	34.7 (23.4 – 46.2) [10.7 – 58.2]	39.4 (24.2 – 50.7) [10.7 – 58.2]	0.30
Comorbidities			
None	1 (4%)	3 (7%)	0.65
History of cancer	9 (39%)	18 (44%)	0.78
Asthma	1 (4%)	3 (7%)	0.65
COPD	5 (22%)	9 (22%)	0.99
Arterial hypertension	14 (61%)	10 (24%)	**0.02**
IHD	4 (17%)	4 (10%)	0.41
Cardiac failure	0	1 (2%)	0.45
AF	0	1 (2%)	0.45
PVD	5 (22%)	2 (5%)	0.05
Stroke	0	1 (2%)	0.45
T1DM	0	1 (2%)	0.45
T2DM	5 (22%)	4 (10%)	0.22
Previous covid infection	9 (39%)	18 (44%)	0.78
Long covid	1 (4%)	0	0.04
Preoperative blood results			
NT-ProBNP	114 (62 – 280) [20 – 1250]	71 (43 - 124) [12 – 1611]	0.05
hs-TnT (ng/L)	9 (8 - 16) [4 – 25]	6 (5 – 8) [3 – 30)	**<0.001**
Missing data	*0*	*2*	
Haemoglobin (g/L)	14.1 (13.0 – 15.3) [9.6 – 18.1]	13.7 (12.8 – 14.6) [12.0 – 16.6]	0.55
Missing data	*1*	*0*	
Creatinine (µmol/L)	91 (73 – 106) [60 - 182]	69 (62 – 82) [45 – 100]	**<0.001**
Preoperative renal function:			
eGFR >59 (ml/min)	17 (74%)	39 (95%)	0.38
eGFR 30-59 (ml/min)	6 (26%)	2 (5%)	**0.02**
eGFR <30 (ml/min)	0	0	
Medications			
No regular medication	1 (4%)	5 (12%)	0.33
Beta-blocker	3 (13%)	7 (17%)	0.70
Ca channel blocker	7 (30%)	9 (22%)	0.52
ACE-inhibitor	10 (43%)	4 (10%)	**0.01**
Diuretics	3 (13%)	3 (7%)	0.47
Antiarrhythmic	0	0	
Beta-agonist	3 (13%)	9 (22%)	0.43
Steroids:			

Inhaled	1 (4%)	7 (17%)	0.17
Oral	0	1 (2%)	0.45

Patients with PMI were older, male and had a higher proportion of arterial hypertension and renal impairment. Patients who went on to develop PMI had higher preoperative hs-TnT and creatinine. The higher rate of ACE-I reflects the higher incidence of arterial hypertension and peripheral vascular disease in the PMI patients. These findings conform with known risk factors for PMI (Section 1.6.2.2).

6.2.3 Preoperative risk scores

Preoperative risk scores for the PMI and no PMI groups are shown in Table 19.

Table 19 Preoperative risk scores of patients with PMI and without PMI. Values are number (percentage) and median (IQR) [range]. P/V-POSSUM: Portsmouth/Vascular-Physiologic and Operative Severity Score for the study of Mortality and Morbidity; ACS NSQIP SRC: American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; SORT: Surgical Outcome Risk Tool; RCRI: Revised Cardiac Risk Index. Mann-Witney test for nonparametric data, chi-squared test for dichotomous data. P vales in bold are significant (<0.05).

Preoperative risk score	PMI (n = 23)	No PMI (n = 41)	p value
P/V-POSSUM 30-day morbidity (%)	40.9 (35.4 – 46.3) [18.5 – 77.4]	19.5 (16.2 – 31.9) [8.8 – 55.0]	**<0.001**
P/V-POSSUM 30-day mortality (%)	2.5 (1.7 – 3.1) [0.8 -10.4]	0.8 (0.7 – 1.5) [0.4 – 9.3]	**<0.001**
ACS NSQIP SRC any complication risk (%)	15.0 (8.8 – 19.6) [2.7 – 29.3]	8.1 (6.1 – 14.9) [2.2 – 25.6]	**0.02**
ACS NSQIP SRC length of hospital stay (days)	5.0 (2.8 – 6.3) [0.5 – 7.0]	3.5 (2.5 – 4.5) [0.5 – 8.0]	**0.04**
SORT 30-day mortality (%)	0.79 (0.59 – 2.19) [0.13 – 3.17]	0.54 (0.25 – 1.14) [0.06 – 4.81]	**0.04**
RCRI (risk of postoperative cardiovascular complications):			
Class I 3.9%	2 (9%)	4 (10%)	0.89
Class II 6.0%	17 (74%)	31 (76%)	0.94
Class III 10.1%	3 (13%)	5 (12%)	0.93
Class IV 15.0%	1 (4%)	1 (2%)	0.68

Predicted mortality, morbidity and hospital length of stay were higher in patients who subsequently developed PMI for the majority of risk measures. There was minimal difference in the distribution of RCRI risk however, indicating that RCRI did not perform well as a risk prediction measure in this cohort of patients.

6.2.4 Step test parameters

Any difference in step test performance between patients who subsequently went on to develop PMI versus those who did not are shown in Table 20.

Table 20 Step test parameters for patients with PMI and without PMI. Values are number (percentage), mean±SD or median (IQR [range]. Bpm: beats per minute. Unpaired t-test for parametric data, Mann-Witney test for nonparametric data, chi-squared test for dichotomous data. P vales in bold are significant (<0.05).

Step test parameter	PMI (n = 23)	No PMI (n = 41)	p value
Height of step: 19.5 cm 14.5 cm 9.5 cm	 13 (57%) 10 (43%) 0	 30 (73%) 11 (27%) 0	 0.44 0.27
Duration of step test (seconds)	88 (80 – 112) [63 – 176]	98 (82 – 121) [63 – 208]	0.36
Proportion of age-predicted maximum heart rate reached	0.67±0.09	0.67±0.07	0.98
Heart rate at end of exercise (bpm)	107.0±12.4	109.6±11.7	0.37
Power output (Watts)	40.4±13.0	44.5±15.4	0.28
Proportion of maximum predicted power reached	0.25 (0.19 – 0.33) [0.12 – 1.63]	0.33 (0.24 – 0.46) [0.15 – 0.76]	**0.01**
Modified Borg score at end of exercise	5.0 (3.5 – 6.0) [1.0 – 8.0]	4.0 (2.0 – 5.0) [1.0 – 10.0]	0.12
Wearing a facemask	14 (61%)	22 (54%)	0.71

Performance of the step test (in terms of duration and step height) were similar between groups as were heart rate parameters (heart rate at end of exercise and proportion of age-predicted HR_{max} reached). Although there was no difference in power output between groups, proportion of maximum predicted power output reached was lower in patients who developed PMI. Therefore, these patients had a higher heart rate response for less activity, indicating reduced fitness. Despite this, patients with PMI were able to reach the target heart rate and were not significantly more breathless (as per modified Borg score) demonstrating the feasibility of this test in less fit, high-risk patients.

6.2.5 Intraoperative parameters

Difference in surgical specialty distribution and intraoperative parameters between patients with and without PMI are shown in Table 21.

Table 21 Intraoperative parameters for patients with PMI and without PMI. Values are percentage (number), mean±SD or median (IQR) [range]. PACU: post-anaesthesia care unit. *unless stated otherwise. Unpaired t-test for parametric data, Mann-Witney test for nonparametric data, chi-squared test for dichotomous data. P vales in bold are significant (<0.05).

Surgical Specialty	PMI (n = 23*)	No PMI (n = 41*)	p value
Thoracic	10 (44%)	21 (51%)	0.67
Colorectal	4 (17%)	6 (15%)	0.79
Upper Gastrointestinal	1 (4%)	3 (7%)	0.65
Vascular	7 (30%)	4 (10%)	0.06
Gynaecology	0	4 (10%)	0.13
Orthopaedic	0	1 (2%)	0.45
Ear Nose Throat/Maxillo-facial	1 (4%)	2 (5%)	0.93
Intraoperative parameter			
Duration of surgery (minutes)	260 (222 – 365) [140 – 660]	198 (120 – 250) [50 – 570]	**<0.001**
Type of anaesthetic: General anaesthetic Regional General anaesthetic and regional combined	 15 (65%) 0 8 (35%)	 31 (76%) 0 10 (24%)	 0.64 0.45
Anaesthesia maintenance: Inhalational Intravenous	 8 (35%) 15 (65%)	 17 (41%) 24 (59%)	 0.68 0.74
Arterial monitoring	18 (78%)	26 (63%)	0.49
Bispectral index monitoring *Missing data*	14 (15%) *0*	19 (46%) *2*	0.53
Lowest systolic blood pressure (mmHg) *Missing data*	87.0±14.7 *2*	83.5±11.8 *0*	0.30
Lowest mean arterial pressure (mmHg) *Missing data*	55.9±8.8 *15*	57.6±9.9 *23*	0.67
Required intraoperative vasopressor administration	13 (57%)	23 (56%)	0.98
Hypotension requiring treatment in recovery/PACU *Missing data*	7 (30%) *1*	6 (15%) *0*	0.15
Intraoperative complication (major haemorrhage)	4 (17%)	3 (7%)	0.24

The intraoperative parameters when split between PMI groups indicate potential differences confirming the known surgical risk factors for PMI (Section 1.6.2.2) although the only clear difference was length of surgery. There appears to be little difference in intraoperative blood pressure between the two groups, however, the PMI patients were twice as likely to develop postoperative hypotension requiring either fluid bolus or vasopressor therapy.

6.2.6 Difference in HRR parameters between patients with and without PMI

The difference in different HRR parameters between patients with and without PMI was investigated, including between the two different methods of effort-correction[I]. Table 22 presents the median absolute HRR for patients without and with PMI. There was no difference in submaximal HRR_{10}, HRR_{20} or HRR_2 between patients who did and did not develop PMI. Heart rate recovery after 30 seconds demonstrated a difference approaching significance, with higher values in patients who did not develop PMI.

Table 22 Difference between absolute heart rate recovery parameters in patients without and with postoperative myocardial injury. Wilcoxon rank sum test. p values <0.05 highlighted in bold.

Absolute HRR parameter	No PMI	PMI	p value
	Median (IQR) [range] (bpm) *Number of patients*		
HRR_{10}	4.2 (1.8 – 8.9) [-3.2 – 30.1] *40*	3.0 (1.6 – 6.3) [-3.8 – 8.8] *23*	0.38
HRR_{20}	9.0 (5.1 – 14.3) [0.0 – 40.1] *40*	6.5 (3.9 – 12.0) [-1.4 – 17.0] *22*	0.20
HRR_{30}	13.4 (7.2 – 19.8) [1.8 – 42.1] *40*	9.4 (5.1 – 15.2) [-1.3 – 30.6] *22*	0.06
HRR_1	23.5 (15.1 – 30.7) [7.2 – 55.6) *41*	15.2 (10.3 – 22.8) [0.7 – 45.2) *23*	**0.01**
HRR_2	26.2 (20.1 – 35.0) [6.4 – 64.4] *41*	21.0 (16.0 – 29.5) [6.3 – 49.3] *23*	0.10

[I] Effort-correction to age-predicted HR_{max} and predicted maximum power output.

Submaximal HRR_1 was higher in patients who did not develop PMI (23.5 bpm versus 15.2 bpm, p = 0.01, Figure 32).

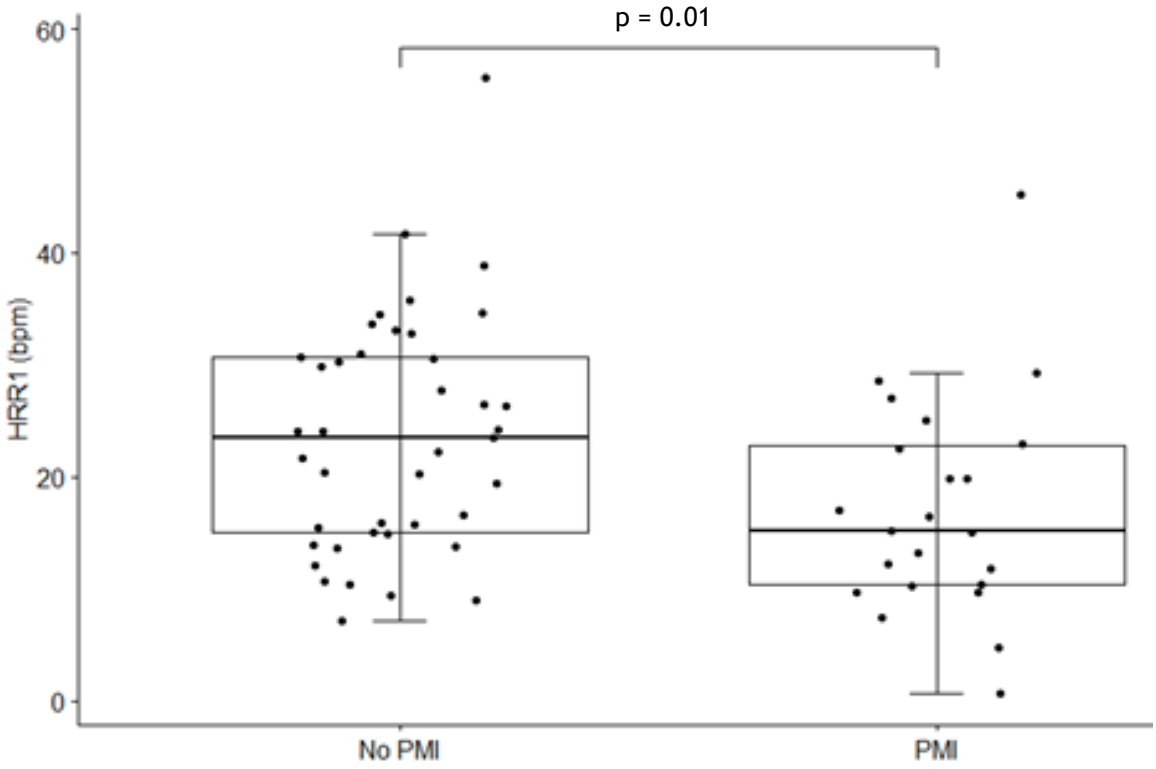


Figure 32 Difference in absolute heart rate recovery one minute after exercise cessation between patients without and with PMI. Wilcoxon rank-sum exact test. n=64.

Table 23 presents the median absolute AUC[J] for patients without and with PMI.

[J] Area under the heart rate recovery curve to 30 seconds (AUC_{30}), one minute (AUC_1), two minutes (AUC_2) and five minutes (AUC_5) after exercise cessation

Table 23 Difference between absolute area under the heart rate recovery curve parameters in patients without and with postoperative myocardial injury. Wilcoxon rank sum test. p values <0.05 highlighted in bold.

Absolute AUC parameter	No PMI	PMI	p value
	Median (IQR) [range] (bpm.s) *Number of patients*		
AUC_{30}	939 (763 – 1078) [409 – 1243] *40*	731 (630 – 935) [498 – 1243] *22*	**0.02**
AUC_{1}	1544 (1229 – 1748) [602 – 2500] *40*	1335 (1029 – 1561) [870 – 1921] *22*	0.10
AUC_{2}	2038 (1649 – 2703) [867 – 4030] *40*	2108 (1679 – 2368) [1240 – 2722] *22*	0.47
AUC_{5}	3208 (2472 – 4301) [1561 – 7653] *37*	3295 (2736 – 4243) [1784 – 5512] *21*	0.76

The only AUC parameter to demonstrate a difference between the two groups was AUC_{30}; patients without PMI had a larger area under the heart rate recovery curve at 30 seconds post exercise (939 bpm.s versus 730 bpm.s, p = 0.02, Figure 33). Although a significant difference, it is in the opposite direction to that expected (Chapter 3 Hypothesis and aims). This is further explored in Section 6.3.3.3.

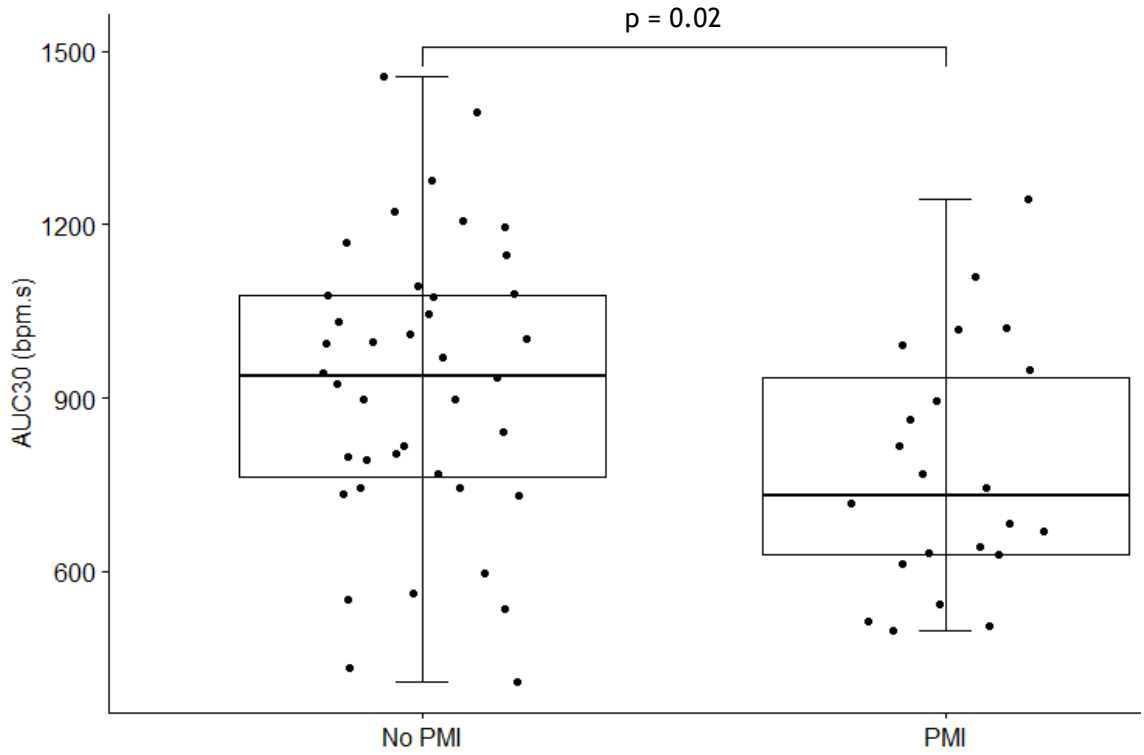


Figure 33 Difference in area under the heart rate recovery curve up to 30 seconds after exercise cessation between patients with and without PMI. Wilcoxon rank-sum exact test. n=62.

Each parameter was subsequently effort-corrected to the proportion of age-predicted HR_{max} reached. Table 24 presents the median HRR effort-corrected to proportion of age-predicted HR_{max} for patients both without and with PMI at the different timepoints post exercise cessation. The notation for effort-correction to age-predicted HR_{max} for the remainder of this thesis is "-ECHR".

Table 24 Difference between heart rate recovery parameters corrected to proportion of age-predicted maximum heart rate reached in patients without and with postoperative myocardial injury. Wilcoxon rank sum test. p values <0.05 highlighted in bold.

HRR parameter effort-corrected to proportion of age-predicted maximum heart rate reached (ECHR)	No PMI	PMI	p value
	Median (IQR) [range] (bpm) *Number of patients*		
HRR_{10}	6.3 (2.7 – 13.6) [-4.3 – 44.3] *40*	4.7 (2.4 – 9.4) [-5.5 – 15.0] *23*	0.41
HRR_{20}	14.1 (7.9 – 21.9) [0.0 – 59.1] *40*	9.9 (6.4 – 17.6) [-2.2 – 24.4] *22*	0.27
HRR_{30}	20.6 (11.8 – 29.2) [2.9 – 62.1] *40*	15.5 (8.2 – 22.1) [-2.1 – 39.2] *22*	0.12
HRR_{1}	34.5 (22.3 – 44.6) [10.8 – 81.9] *41*	24.0 (16.8 – 30.3) [1.0 – 57.9] *23*	**0.01**
HRR_{2}	36.5 (30.1 – 52.6) [10.0 – 94.9] *41*	32.7 (25.1 – 41.9) [9.0 – 63.3] *23*	0.12

Again, only HRR_1 demonstrated a significant difference between PMI groups with HRR_1-ECHR significantly higher in patients who did not develop PMI (Figure 34).

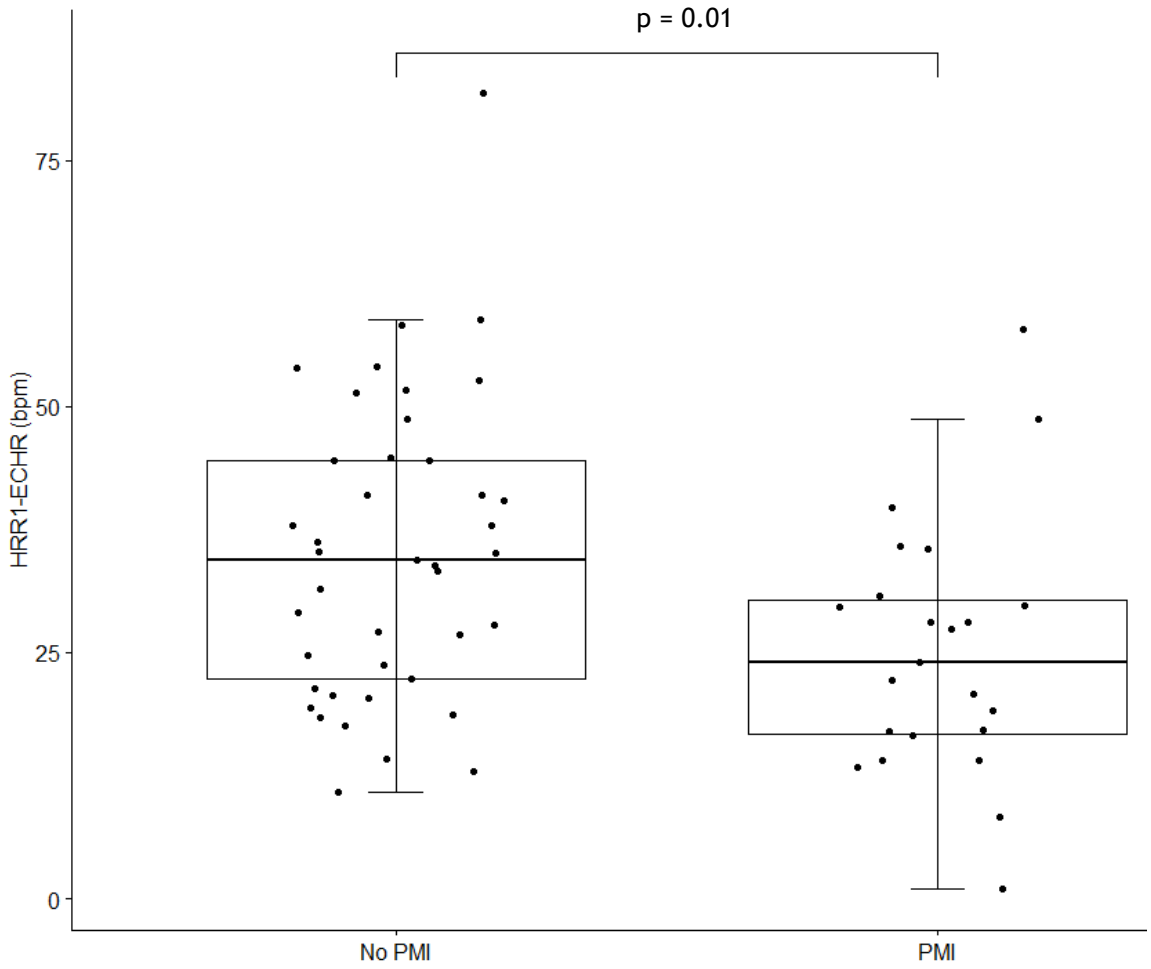


Figure 34 Difference in heart rate recovery one minute after exercise cessation after effort-correction to proportion of age-predicted maximum heart rate reached between patients without and with PMI. Wilcoxon rank-sum exact test. n=64.

Table 25 presents the difference between AUC parameters between PMI groups after effort-correction to proportion of age-predicted HR_{max} reached.

Table 25 Difference between area under the heart rate recovery curve parameters after effort-correction to proportion of age-predicted maximum heart rate reached in patients without and with postoperative myocardial injury. Wilcoxon rank sum test. p values <0.05 highlighted in bold.

AUC parameter effort-corrected to proportion of age-predicted maximum heart rate reached	No PMI	PMI	p value
	Median (IQR) [range] (bpm.s) *Number of patients*		
AUC_{30}	1428 (1117 – 1640) [585 – 2412] *40*	1137 (950 – 1345) [706 – 1765] *22*	**0.02**
AUC_{1}	2274 (1820 – 2659) [861 – 3818] *40*	2026 (1707 -2247) [1194 – 3018] *22*	0.13
AUC_{2}	3085 (2427 – 3834) [1240 – 5722] *40*	3062 (2661 – 3507) [1706 – 4101] *22*	0.83
AUC_{5}	4981 (3695 – 6612) [2558 – 10333] *37*	5319 (3800 – 6423) [2593 – 7824] *21*	0.72

The parameters demonstrate the same pattern as without effort-correction to age-predicted HR_{max} with only AUC_{30}-ECHR demonstrating a significant difference between groups, with a larger AUC in patients without PMI (Figure 35).

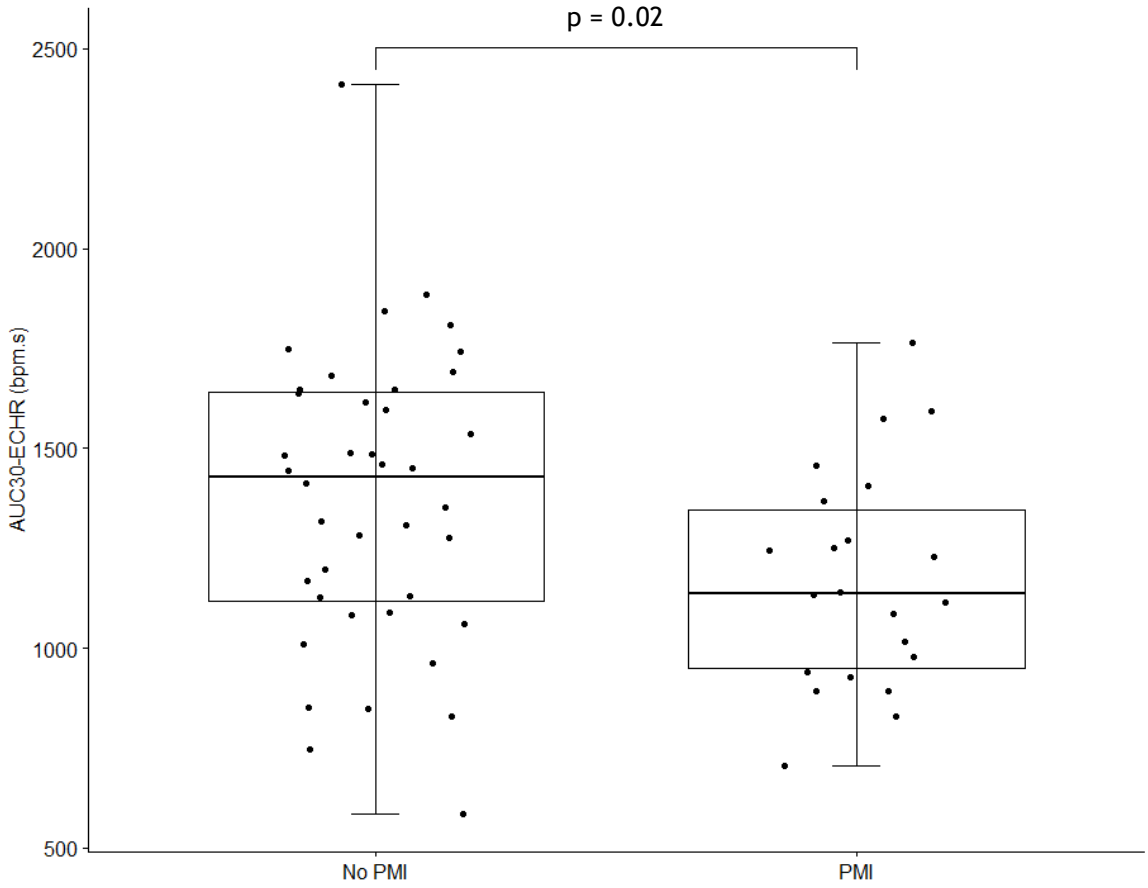


Figure 35 Difference in area under the heart rate recovery curve up to 30 seconds after exercise cessation after effort-correction to proportion of age-predicted maximum heart rate reached between patients with and without PMI. Wilcoxon rank-sum exact test. n=62.

The heart rate parameters were also effort-corrected to proportion of maximum predicted power output reached. Effort-correction to predicted maximum power output removed any differences in HRR parameters between patients without and with PMI (Table 26). The notation for effort-correction to predicted maximum power output (Watts) for the remainder of this thesis is "-ECW".

Table 26 Difference between heart rate recovery parameters corrected to proportion of predicted maximum power output reached in patients without and with postoperative myocardial injury. Wilcoxon rank sum test. p values <0.05 highlighted in bold.

HRR parameter effort-corrected to proportion of maximum predicted power output reached (-ECW)	No PMI	PMI	p value
	Median (IQR) [range] (bpm) *Number of patients*		
HRR_{10}	10.2 (5.8 – 25.0) [-14.7 – 114.0] *40*	11.3 (6.2 – 24.9) [-10.2 – 65.3] *23*	0.82
HRR_{20}	20.0 (16.5 – 41.0) [0.1 – 133.0] *40*	29.5 (12.0 – 38.5) [-6.3 – 111.0] *22*	0.57
HRR_{30}	40.2 (24.7 – 53.6) [7.2 – 140.0] *40*	43.6 (18.7 – 56.2) [-5.9 – 125.0] *22*	0.77
HRR_{1}	63.3 (46.7 – 87.0) [14.1 – 184.0] *41*	56.7 (37.1 – 96.7) [2.4 – 184.0] *23*	0.68
HRR_{2}	77.1 (47.9 – 104.0) [23.4 – 215.0] *41*	76.6 (59.4 – 115.0) [21.5 – 207.0] *23*	0.57

However, effort-corrected to proportion of predicted maximum power output completely changed the difference between AUC parameters between patients without and with PMI (Table 27)

Table 27 Difference between area under the heart rate recovery curve parameters after effort-correction to proportion of predicted maximum power output reached in patients without and with postoperative myocardial injury. Wilcoxon rank sum test. p values <0.05 highlighted in bold.

AUC parameter effort-corrected to proportion of maximum predicted power output reached (-ECW)	No PMI	PMI	p value
	Median (IQR) [range] (bpm.s) *Number of patients*		
AUC_{30}	2560 (1844 – 3678) [1153 – 7012] *40*	2825 (2365 – 4751) [1465 – 6082] *22*	0.23
AUC_{1}	4086 (2878 – 6107) [1563 – 11441] *40*	4899 (4304 – 7946) [2289 – 10056] *22*	0.10
AUC_{2}	5525 (4206 – 9189) [1996 – 18445] *40*	7723 (6267 – 11451) [2963 – 16073] *22*	0.06
AUC_{5}	8682 (6607 – 14436) [3101 – 35026] *37*	14165 (9535 – 17035) [4260 – 29101] *21*	**0.02**

There was no longer any difference between groups for AUC_{30} but there was a significant difference between PMI groups for AUC_{5} with a smaller AUC_{5} in patients who did not develop PMI (Figure 36); the expected pattern (Chapter 3 (Hypothesis and aims)).

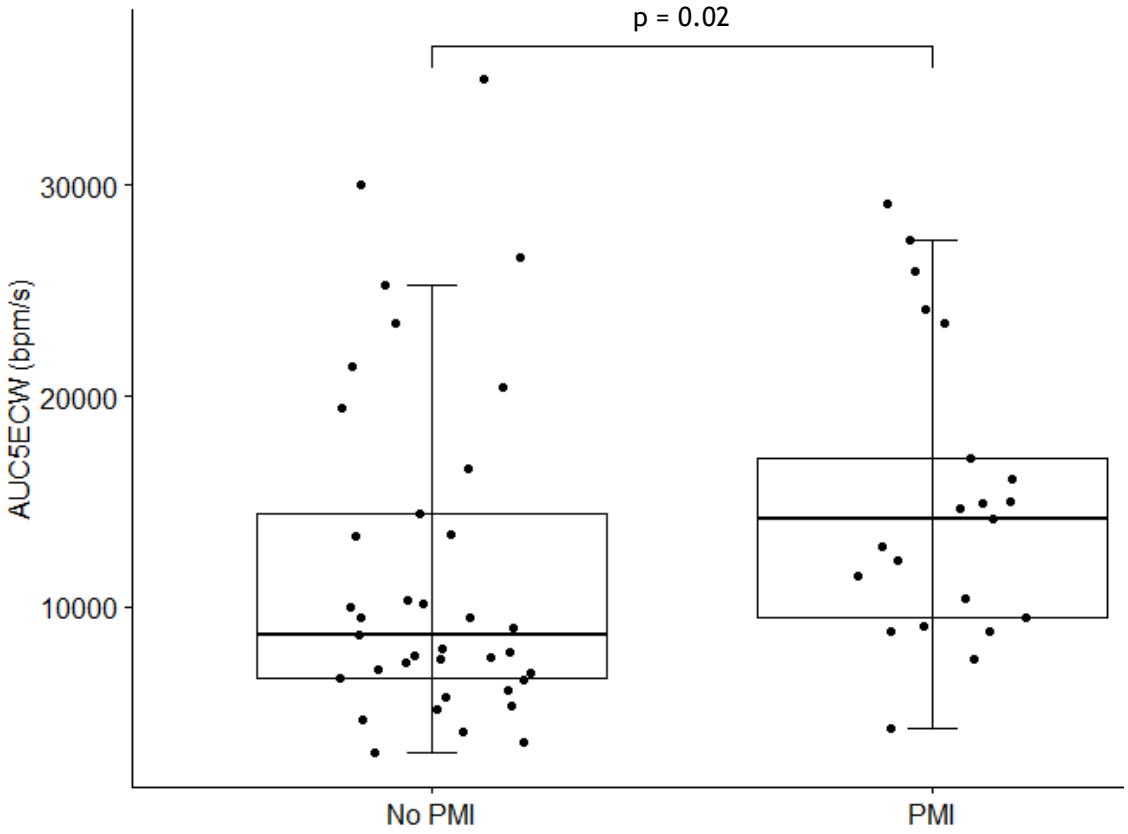


Figure 36 Difference in area under the heart rate recovery curve effort-corrected to proportion of predicted maximum power output reached between patients with and without PMI. Wilcoxon rank-sum exact test. n=58.

In summary (Table 28), of the absolute parameters only HRR_1 and AUC_{30} demonstrated difference between patients who did and did not develop PMI. Effort-correction to proportion of age-predicted HR_{max} reached did not change these differences. Heart rate recovery one minute after exercise cessation was lower in patients who developed PMI, which was the hypothesised pattern; AUC_{30} however was also lower in patients who developed PMI; the opposite to that hypothesised. Effort-correction to maximum predicted power output negated any difference between PMI groups demonstrated by the absolute HRR parameters and by AUC_{30}. Conversely, AUC_5 when effort-corrected to predicted maximum power output reached was higher in patients who developed PMI compared to those that did not.

Table 28 Heart rate recovery parameters with difference between patients who did and not develop postoperative myocardial injury (PMI). Values displayed are median.

Parameter	No PMI group	PMI group	p value
HRR_1	23.5 bpm	15.2 bpm	0.01
AUC_{30}	939 bpm.s	731 bpm.s	0.02
HRR_1-ECHR	34.5 bpm	24.0 bpm	0.01
AUC_{30}-ECHR	1428 bpm.s	1137 bpm.s	0.02
AUC_5-ECW	8682 bpm.s	14165 bpm.s	0.02

6.2.7 Predictive validity of submaximal heart rate recovery for postoperative myocardial injury (primary outcome)

The predictive value for PMI of all the measured absolute HRR (Table 29) and area under the curve (Table 30) parameters was investigated.

Table 29 Predictive value of the absolute HRR parameters for PMI demonstrated by area under the receiver operating curve. Highlighted in bold are those with statistically significant 95% confidence intervals (CI) i.e. which do not cross 0.5, the point at which no predictive value is demonstrated.

Absolute HRR parameter	Number of patients (no PMI/PMI)	AUROC	95% CI
HRR_{10}	63 (40/23)	0.57	0.42 – 0.71
HRR_{20}	62 (40/22)	0.60	0.45 – 0.75
HRR_{30}	62 (40/22)	0.64	0.50 – 0.79
HRR_1	**64 (41/23)**	**0.69**	**0.55 - 0.82**
HRR_2	64 (41/23)	0.63	0.48 – 0.78

Table 30 Predictive value of the absolute AUC parameters for PMI demonstrated by area under the receiver operating curve. Highlighted in bold are those with statistically significant 95% confidence intervals (CI) i.e. which do not cross 0.5, the point at which no predictive value is demonstrated.

Area under the HRR curve parameter	Number of patients (no PMI/PMI)	AUROC	95% CI
AUC_{30}	**62 (40/22)**	**0.68**	**0.54 - 0.82**
AUC_1	62 (40/22)	0.63	0.49 – 0.77
AUC_2	62 (40/22)	0.44	0.30 – 0.59
AUC_5	58 (37/21)	0.53	0.37 – 0.68

The only absolute parameters to demonstrate predictive value for PMI were HRR_1 and AUC_{30}; each demonstrating poor to fair predictive value. Each parameter was subsequently effort-corrected to the proportion of age-predicted maximum heart rate reached (Table 31, Table 32) as it was hypothesised that this may improve predictive value.

Table 31 Predictive value of the HRR parameters corrected to proportion age-predicted maximum heart rate reached. Highlighted in bold are those with statistically significant 95% confidence intervals (CI) i.e. which do not cross 0.5, the point at which no predictive value is demonstrated. -ECHR: effort-corrected to age-predicted maximum heart rate

Absolute HRR parameters corrected to proportion of age-predicted maximum heart rate	Number of patients (no PMI/PMI)	AUROC	95% CI
HRR_{10}-ECHR	63 (40/23)	0.56	0.41 – 0.71
HRR_{20}-ECHR	62 (40/22)	0.59	0.44 – 0.74
HRR_{30}-ECHR	62 (40/22)	0.62	0.47 – 0.77
HRR_{1}-ECHR	**64 (41/23)**	**0.69**	**0.55 – 0.83**
HRR_{2}-ECHR	64 (41/23)	0.62	0.47 – 0.76

Table 32 Predictive value of the AUC parameters corrected to proportion age-predicted maximum heart rate reached. Highlighted in bold are those with statistically significant 95% confidence intervals (CI) i.e. which do not cross 0.5, the point at which no predictive value is demonstrated. -ECHR: effort-corrected to age-predicted maximum heart rate

Area under the HRR curve parameter corrected to proportion of age-predicted maximum heart rate	Number of patients (no PMI/PMI)	AUROC	95% CI
AUC_{30}-ECHR	**62 (40/22)**	**0.68**	**0.54 – 0.81**
AUC_{1}-ECHR	62 (40/22)	0.62	0.48 – 0.76
AUC_{2}-ECHR	62 (40/22)	0.52	0.37 – 0.66
AUC_{5}-ECHR	58 (37/21)	0.53	0.37 – 0.69

Again, the only parameters to demonstrate predictive value for PMI were HRR_1 and AUC_{30}. Effort-correction to age-predicted HR_{max} reached made no difference to predictive value. This may be due to the tight heart rate control during the step test with no difference in proportion age-predicted HR_{max} reached between patients who developed PMI and those who did not (Table 20).

The heart rate parameters were also effort-corrected to proportion of maximum predicted power output reached (Table 33, Table 34).

Table 33 Predictive value of the HRR parameters corrected to proportion predicted maximum power output reached. Highlighted in bold are those with statistically significant 95% confidence intervals (CI) i.e. which do not cross 0.5, the point at which no predictive value is demonstrated. -ECW: effort-corrected to maximum power output reached

Absolute HRR parameters corrected to proportion predicted maximum power output	Number of patients (no PMI/PMI)	AUROC	95% CI
HRR_{10}-ECW	63 (40/23)	0.52	0.37 – 0.67
HRR_{20}-ECW	62 (40/22)	0.54	0.38 – 0.71
HRR_{30}-ECW	62 (40/22)	0.52	0.36 – 0.68
HRR_{1}-ECW	64	0.53	0.37 – 0.69
HRR_{2}-ECW	64	0.46	0.31 – 0.61

Table 34 Predictive value of the AUC parameters corrected to proportion predicted maximum power output reached. Highlighted in bold are those with statistically significant 95% confidence intervals (CI) i.e. which do not cross 0.5, the point at which no predictive value is demonstrated. -ECW: effort-corrected to maximum power output reached

Area under the HRR curve parameter corrected to % predicted maximum power output	Number of patients (no PMI/PMI)	AUROC	95% CI
AUC_{30}-ECW	62 (40/22)	0.59	0.45 – 0.74
AUC_{1}-ECW	62 (40/22)	0.63	0.49 – 0.77
AUC_{2}-ECW	**62 (40/22)**	**0.64**	**0.51 - 0.78**
AUC_{5}-ECW	**58 (37/21)**	**0.69**	**0.55 - 0.83**

Effort-corrected to maximum power output reached worsened the predictive value of HRR_1 to the extent that it was not predictive for PMI. None of the other absolute HRR parameters demonstrated predictive value when effort-corrected to maximum power output. The AUC_{30} also lost predictive value when effort-corrected to maximum power output. However, this type of effort-correction improved the predictive value of both AUC_2 (poor predictive value) and AUC_5 (poor to fair predictive value).

A summary of the HRR parameters which demonstrated predictive value for PMI is shown in Table 35; all parameters demonstrated poor, or poor to fair predictive value (as per Table 16). This is comparable with other risk prediction scores currently in use (Section 1.2).

Table 35 Heart rate recovery parameters with predictive value for postoperative myocardial injury. AUROC: area under the receiver operator curve; CI: confidence interval

Parameter	AUROC	95% CI
AUC_5-ECW	0.69	0.55 - 0.83
HRR_1-ECHR	0.69	0.55 - 0.83
HRR_1	0.69	0.55 - 0.82
AUC_{30}	0.68	0.54 - 0.82
AUC_{30}-ECHR	0.68	0.54 - 0.81
AUC_2-ECW	0.64	0.51 - 0.78

Figure 37 demonstrates the receiver operating curves for the predictive HRR measures from Table 35.

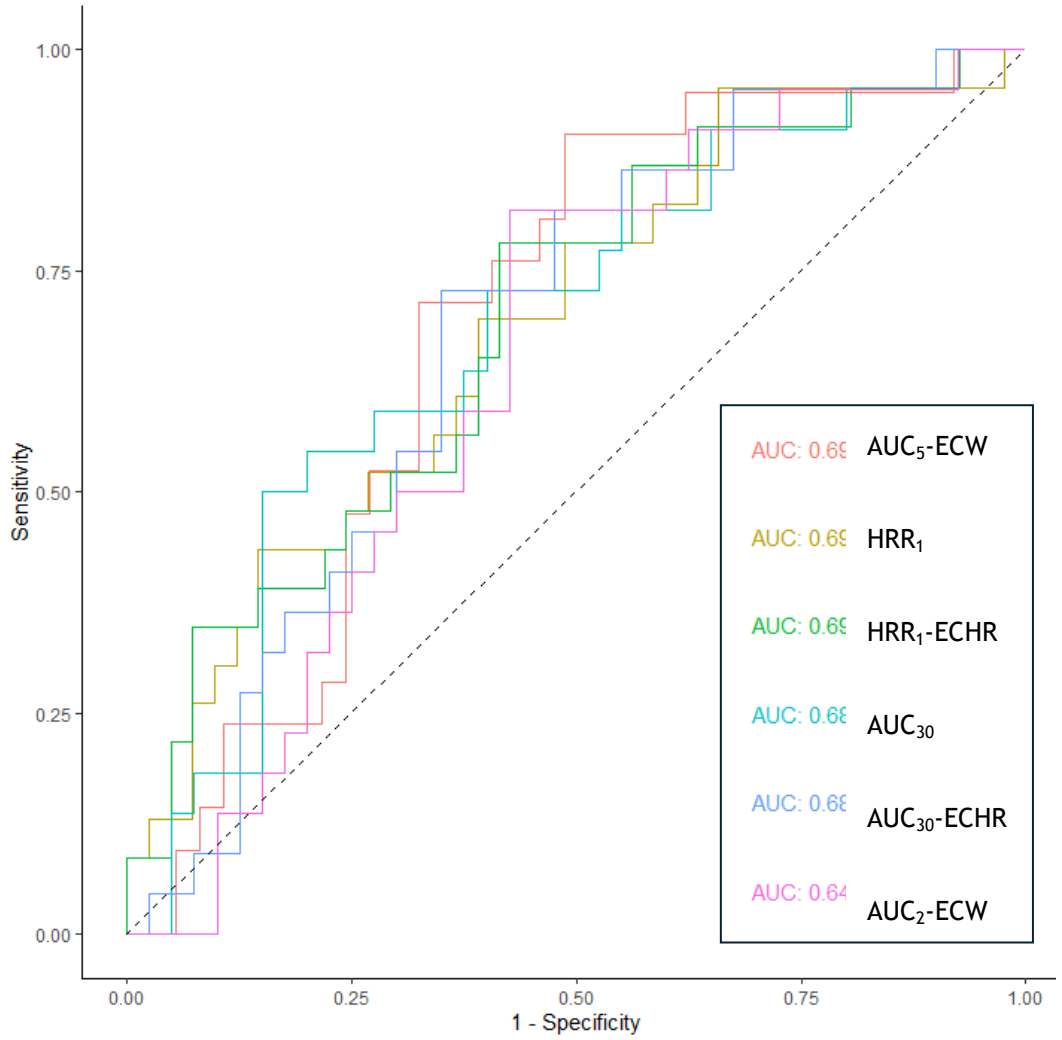


Figure 37 Receiver operating curves for the six best-performing HRR parameters. Orange line: AUC_5-ECW (95%CI 0.55 - 0.83); yellow line: HRR_1 (95% CI 0.55 – 0.82); green line: HRR_1-ECHR (95%CI 0.55 – 0.83); turquoise line: AUC_{30} (95%CI 0.54 – 0.82); blue line: AUC_{30}-ECHR (95%CI 0.54 – 0.81), pink line: AUC_2-ECW (95%CI 0.51 - 0.78). Dashed line: line of equality.

Per the data analysis plan, only the five best-performing HRR parameters were taken forward for further analysis and discussion: AUC_5-ECW, HRR_1, HRR_1-ECHR, AUC_{30} and AUC_{30}-ECHR.

6.2.8 Sensitivity analysis

Sensitivity analyses were performed to assess the potential effect of rate-limiting medications on the predictive validity of the five best-performing heart rate recovery parameters. The first sensitivity analysis excluded ten patients with primary outcome data available on beta-blockade and the second excluded three patients on rate-limiting calcium channel blockers (Diltiazem or Verapamil). No patients were on both a beta-blocker and rate-limiting calcium channel blocker. The incidence of PMI in the cohort excluding beta-blocked patients was 37.0% (20/54). Table 36 shows the predictive value of the parameters excluding these patients.

Table 36 Sensitivity analysis of predictive value of the five best-performing HRR parameters, excluding patients on beta-blockade. AUROC: area under the receiver operating curve; CI: confidence interval; n: number of patients.

Heart rate recovery parameter	**Excluding beta-blockade** AUROC (95% CI) *n (without PMI/with PMI)*	**Whole cohort** AUROC (95%CI) *n (without PMI/with PMI)*
AUC_5-ECW	0.65 (0.50 – 0.81) *49 (31/18)*	0.69 (0.55 – 0.83) *58 (37/21)*
HRR_1	0.65 (0.50 – 0.80) *54 (34/20)*	0.69 (0.55 – 0.82) *64 (41/23)*
HRR_1-ECHR	0.65 (0.50 – 0.81) *54 (34/20)*	0.69 (0.55 – 0.83) *64 (41/23)*
AUC_{30}	0.69 (0.54 – 0.84) *53 (34/19)*	0.68 (0.54 – 0.82) *62 (40/22)*
AUC_{30}-ECHR	0.69 (0.55 – 0.83) *53 (34/19)*	0.68 (0.54 – 0.81) *62 (40/22)*

There was little change in the predictive value of the five best-performing HRR parameters when patients on beta-blockade were excluded from the analysis. The 95% confidence intervals for AUC_5-ECW, HRR_1 and HRR_1-ECHR cross 0.5 (null hypothesis) but this is likely due to the reduced number of patients.

The incidence of PMI in the cohort excluding rate-limiting CCBs was 36.1% (22/61) so no different to the whole cohort incidence. Table 37 demonstrates the effect of excluding these patients on the predictive value of the HRR parameters.

Table 37 Sensitivity analysis of predictive value of the five best-performing HRR parameters, excluding patients on calcium channel blockers. AUROC: area under the receiver operating curve; CI: confidence interval; n: number of patients.

Heart rate recovery parameter	**Excluding calcium channel blockade** AUROC (95%CI) *n (without PMI/with PMI)*	**Whole cohort** AUROC (95% CI) *n (without PMI/with PMI)*
AUC_5-ECW	0.68 (0.53 – 0.82) *55 (35/20)*	0.69 (0.55 – 0.83) *58 (37/21)*
HRR_1	0.70 (0.56 – 0.84) *61 (39/22)*	0.69 (0.55 – 0.82) *64 (41/23)*
HRR_1-ECHR	0.70 (0.56 – 0.84) *61 (39/22)*	0.69 (0.55 – 0.83) *64 (41/23)*
AUC_{30}	0.70 (0.56 – 0.84) *59 (38/21)*	0.68 (0.54 – 0.82) *62 (40/22)*
AUC_{30}-ECHR	0.69 (0.55 – 0.83) *59 (38/21)*	0.68 (0.54– 0.81) *62 (40/22)*

Excluding the patients on beta-blockers or CCBs did not meaningfully change the predictive value of the HRR parameters. Therefore, throughout the rest of this thesis whole cohort data is used.

6.2.9 Optimum sensitivity and specificity cut-offs

Table 38 demonstrates the optimum cut-offs for each HRR parameter as ascertained using Youden's index, the method most frequently used for determining cut-offs in diagnostic testing, and a 2:1 sensitivity:specificity weighted index to better reflect the screening aspect of preoperative HRR measurement. These show the cut-offs to delineate high and low-risk patients using these HRR parameters and the associated sensitivity and specificity. The higher cut-offs (aside from AUC_5-ECW) for the weighted index means that more patients would be identified as high-risk (i.e. more patients would be expected to have a HRR_1 <29.6 bpm than <20 bpm) agreeing with the concept that this weighting system is more appropriate for a screening tool. Both HRR_1 (Figure 32) and AUC_{30} (Figure 33) were higher in patients who did not develop PMI (including when effort-corrected to age-predicted HR_{max}), therefore a value lower than the cut-off described would indicate high-risk. Conversely, AUC_5-ECW was higher in patients who did develop PMI so a value higher than the cut-off would indicate high-risk (Figure 36).

Table 38 Optimum cut-off as determined by Youden's index and 2:1 sensitivity:specificity weighted Youden's index for each HRR parameter with associated sensitivity and specificity for PMI.

HRR Parameter	Youden's index			2:1 weighted Youden's index		
	Cut-off	Sensitivity	Specificity	Cut-off	Sensitivity	Specificity
AUC_5-ECW	8748 bpm.s	0.91	0.51	8748 bpm.s	0.91	0.51
HRR_1	20.1 bpm	0.70	0.61	29.6 bpm	0.96	0.34
HRR_1-ECHR	31.2 bpm	0.78	0.59	40.0 bpm	0.91	0.37
AUC_{30}	724 bpm.s	0.50	0.85	1027 bpm.s	0.91	0.35
AUC_{30}-ECHR	1274 bpm.s	0.73	0.65	1595 bpm.s	0.95	0.33

6.2.10 Effect of submaximal HRR_1 on current perioperative risk predictors

In this investigation, submaximal HRR_1 is one of the best-performing parameters for prediction of PMI. Heart rate recovery after one minute is also one of most intuitive to understand and calculate, and there is evidence, albeit minimal, within the wider literature that it may have perioperative prognostic relevance (Chapter 2 Systematic review and meta-analysis)[158]. For these reasons, HRR1 was used in this exploratory analysis investigating whether the addition of submaximal HRR improves the predictive value of currently-used risk prediction measures. Univariate logistic regression models for four current risk prediction tools were created (NT-ProBNP, RCRI, DASI and SORT score). Bivariate models were then created for each risk prediction modality with the addition of submaximal HRR_1 to assess if HRR_1 improved the predictive value of each independent variable. This potential effect of improvement was measured via change in the AUROC and net reclassification index.

6.2.10.1 NT-ProBNP

NT-ProBNP is a prognostic cardiac biomarker used in heart failure. It is also increasingly used in the preoperative setting as a screening tool to guide further investigation e.g. echocardiography in patients identified as high-risk (>300 pg/ml) (Section 1.2.7). Univariate logistic regression demonstrated NT-ProBNP was not predictive for PMI in this cohort, but the bivariate model indicated that HRR_1 showed a significant association with PMI though NT-ProBNP made a non-significant contribution to this model (Table 39).

Table 39 Univariate and bivariate logistic regression models for NT-ProBNP and NT-ProBNP plus HRR1.

Model	Model predictor	Intercept	Beta - coefficient (p value)	Odds ratio	95% CI
Univariate	NT-ProBNP	-0.83	0.001 (0.17)	1.00	1.00 – 1.00
Bivariate	NT-ProBNP	0.50	0.001 (0.39)	1.00	1.00 – 1.00
	HRR_1		-0.06 (0.05)	0.94	0.88 – 1.00

Addition of HRR_1 to the logistic regression model of NT-ProBNP for PMI improved the AUROC from 0.65 (0.51 – 0.80) to 0.70 (0.57 – 0.84) (Figure 38).

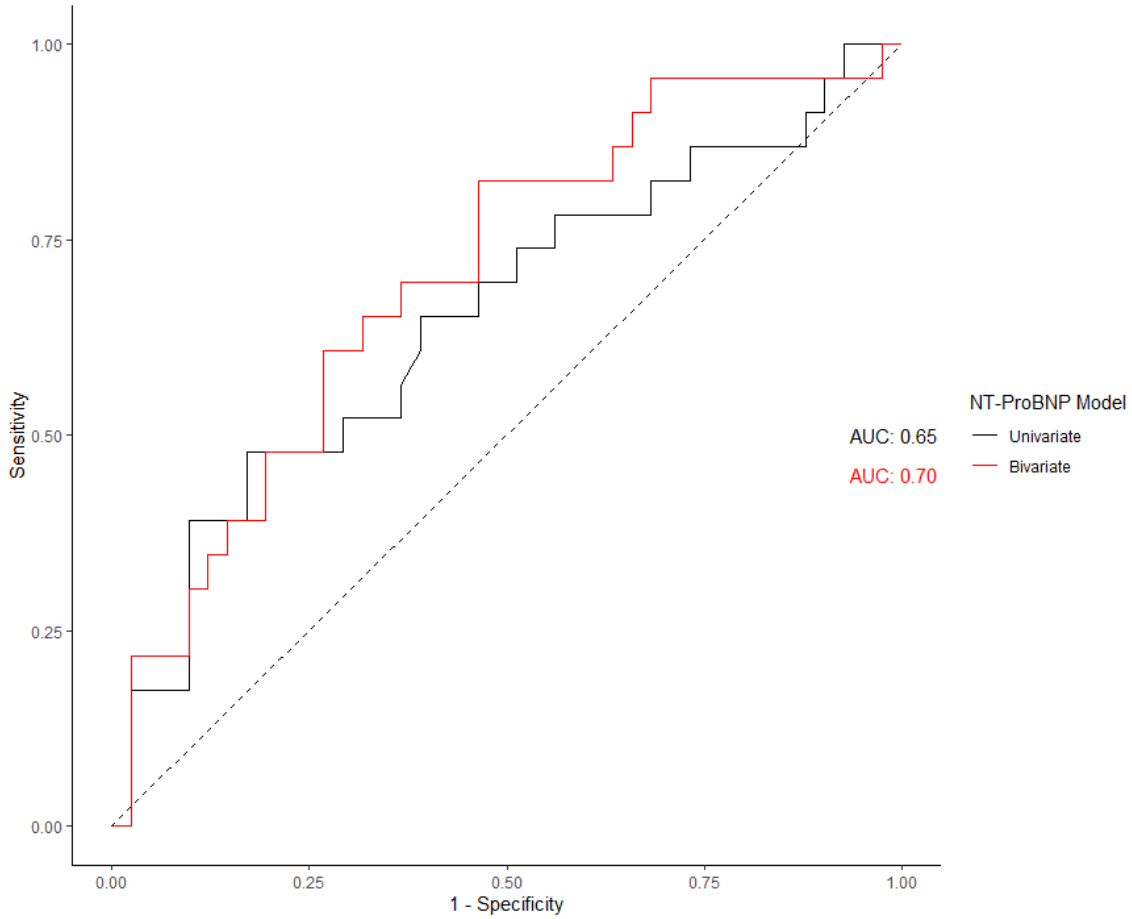


Figure 38 Receiver operating curves for NT-ProBNP as a predictive measure of PMI (univariate model) and the logistic regression model of NT-ProBNP plus HRR_1 as a predictive measure of PMI (bivariate model). Black line: univariate model (95%CI 0.51 – 0.80); red line: bivariate model (95%CI 0.57 – 0.84).

6.2.10.2 Duke Activity Status Index

The DASI score is a subjective measure of a patient's activity levels and can be correlated with their metabolic equivalents (Section 1.2.4). Univariate logistic regression demonstrated that DASI was not predictive for PMI in this cohort, but the bivariate model indicated that HRR_1 showed a significant adjusted association with PMI (Table 40).

Table 40 Univariate and bivariate logistic regression models for Duke Activity Status Index and DASI plus HRR_1.

Model	Model predictor	Intercept	Beta-coefficient (p value)	Odds ratio	95% CI
Univariate	DASI	0.10	-0.02 (0.32)	0.98	0.95 – 1.02
Bivariate	DASI	0.91	-0.00 (0.83)	1.00	0.96 – 1.04
	HRR_1		-0.07 (0.04)	0.94	0.88 – 0.99

The DASI did not demonstrate predictive value for PMI in this cohort (AUROC 0.58 (0.43 – 0.73)). Addition of HRR_1 via logistic regression improved the predictive value (AUROC 0.69 (0.55 – 0.83)) (Figure 39).

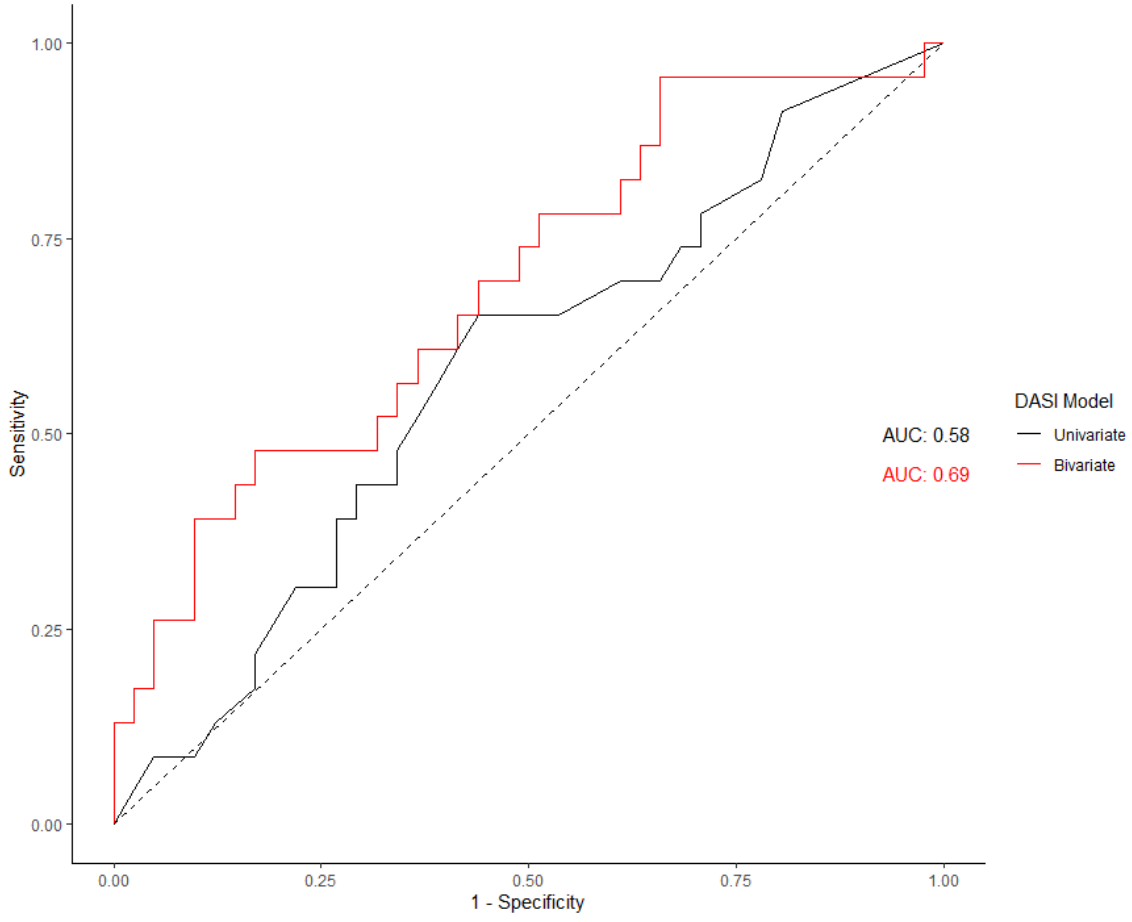


Figure 39 Receiver operating curves for DASI as a predictive measure of PMI (univariate model) and the logistic regression model of DASI plus HRR_1 as a predictive measure of PMI (bivariate model). Black line: univariate model (95%CI 0.43 – 0.73); red line: bivariate model (95%CI 0.55 – 0.83).

6.2.10.3 Revised Cardiac Risk Index

The RCRI is a risk score used for predicting perioperative cardiac risk based on six preoperative risk factors with a score of three or over typically indicating high-risk (Section 1.2.5). Only two patients in the cohort had an RCRI score of three or over, so risk categories were split into zero risk factors, one risk factor and two or more risk factors. Ordinal logistic regression demonstrated that RCRI was not predictive for PMI in this cohort, but addition of submaximal HRR_1 showed a significant adjusted association with PMI (Table 41).

Table 41 Ordinal univariate and bivariate logistic regression models for the Revised Cardiac Risk Index (categorised as ≥2 as high-risk) and RCRI plus HRR_1.

Model	Model predictor	Intercept	Beta-coefficient (p value)	Odds ratio	95% CI
Univariate	RCRI = 1	-0.69	0.06 (0.95)	1.06	0.19 – 8.23
	RCRI ≥ 2		0.47 (0.67)	1.60	0.19 – 16.31
Bivariate	RCRI = 1	0.54	0.29 (0.76)	1.34	0.22 – 10.83
	RCRI ≥ 2		0.33 (0.77)	1.39	0.16 – 14.78
	HRR_1		-0.07 (0.03)	0.93	0.87 – 0.99

The receiver operating curve also showed that RCRI did not demonstrate predictive value for PMI in this cohort (AUROC 0.53 (0.42 – 0.64)). However, the logistic regression model of RCRI plus HRR1 improved the predictive value: AUROC 0.69 (0.55 – 0.82) (Figure 40).

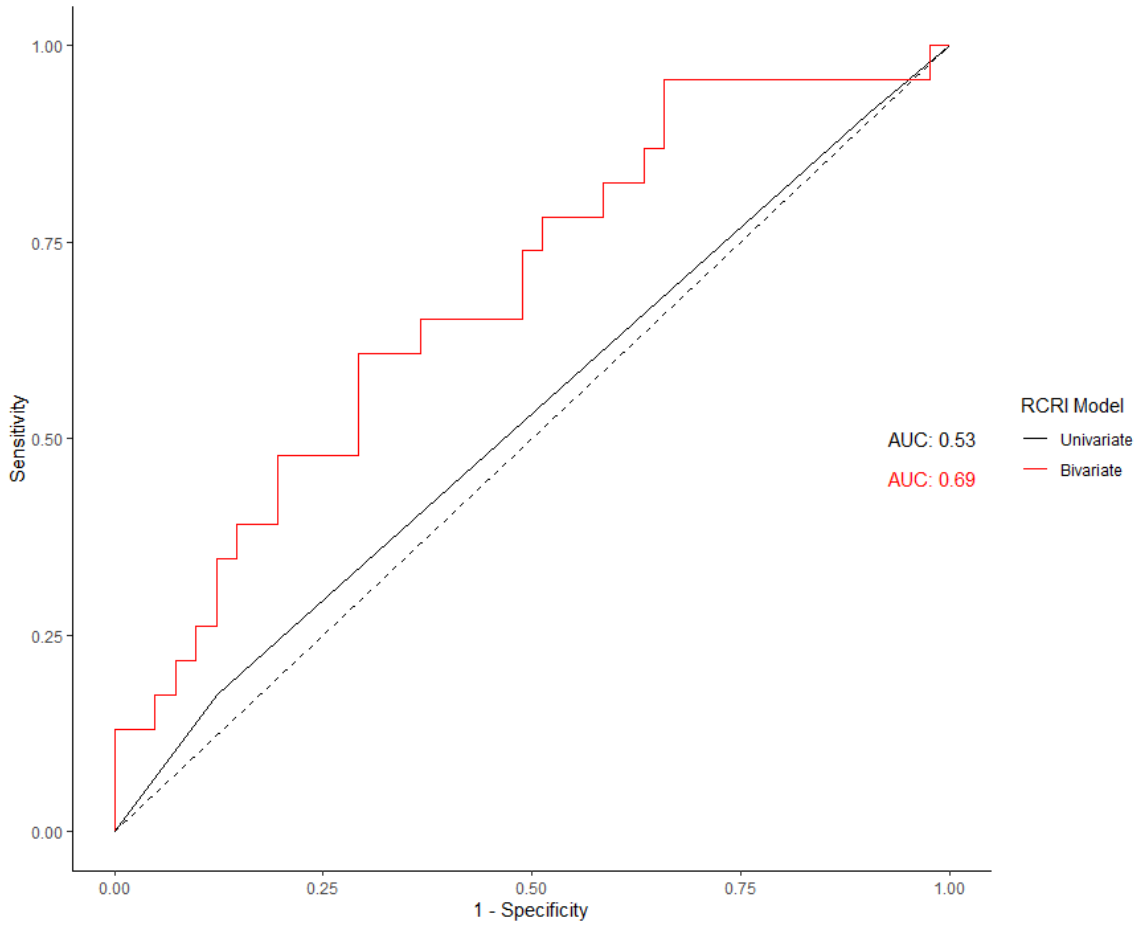


Figure 40 Receiver operating curves for RCRI as a predictive measure of PMI (ordinal univariate model) and the logistic regression model of RCRI plus HRR_1 as a predictive measure of PMI (ordinal bivariate model). Black line: univariate model (95%CI 0.42 – 0.64); red line: bivariate model (95%CI 0.55 – 0.82).

6.2.10.4 Surgical Outcome Risk Tool

The SORT score is a preoperative risk assessment model used to predict 30-day mortality risk. It includes both patient and surgical factors (Section 1.2.2). Univariate logistic regression demonstrated that SORT was predictive for PMI in this cohort. However, the bivariate model indicated that HRR_1 showed a significant association with PMI but SORT did not (Table 42)

Table 42 Univariate and bivariate logistic regression models for Surgical Outcome Risk Tool and SORT plus HRR_1.

Model	Model predictor	Intercept	Beta-coefficient (p value)	Odds ratio	95% CI
Univariate	SORT	-1.19	0.561 (0.05)	1.75	1.03 – 3.19
Bivariate	SORT	0.11	0.49 (0.10)	1.64	0.93 – 3.06
	HRR_1		-0.06 (0.04)	0.94	0.88 – 1.00

In this cohort the SORT score demonstrated equivalent predictive value (AUROC of 0.66 (0.52 – 0.80)) to the best-performing HRR parameters. The bivariate logistic regression model improved the predictive value to an AUROC of 0.74 (0.62 – 0.86); the best performing model (Figure 41) with fair (rather than poor to fair as with the other models) predictive value for PMI. The SORT model combines the surgical and patient comorbid risk factors measured by SORT plus the patient's functional capacity as indicated by HRR_1.

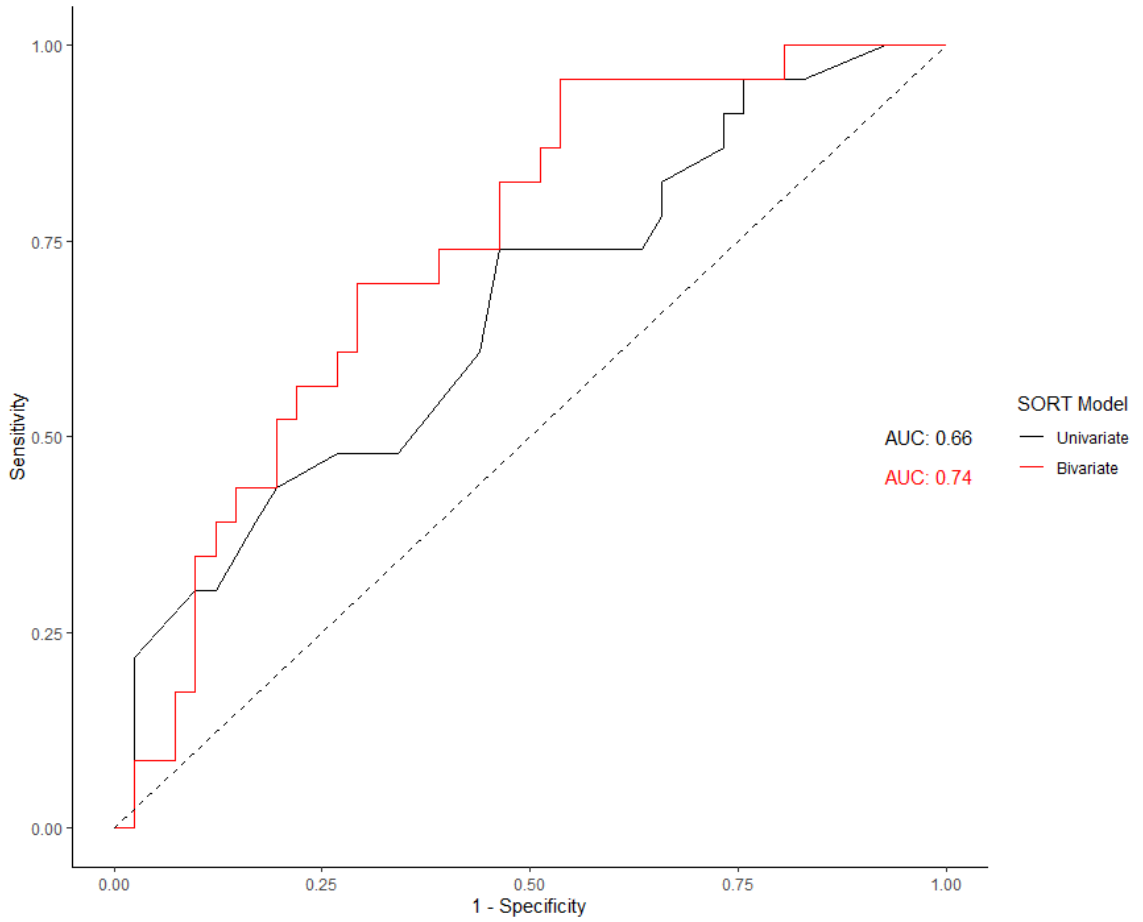


Figure 41 Receiver operating curves for SORT as a predictive measure of PMI (univariate model) and the logistic regression model of SORT plus HRR as a predictive measure of PMI (bivariate model). Black line: univariate model (95%CI 0.52 – 0.80); red line: bivariate model (95%CI 0.62 – 0.86).

6.2.10.5 Net reclassification improvement

Net reclassification is a measure of how a model may reclassify patients either correctly or incorrectly, first described by Pencina[199] (Section 6.1.3.3). Table 43 details the overall NRI, NRI for events and NRI for non-events for each risk prediction measure bivariate model when compared to the univariate model.

Table 43 Overall net reclassification index, NRI for events and NRI for non-events for each bivariate model comprising the risk prediction measure plus HRR_1 when compared to the univariate model. DASI: Duke Activity Status Index; RCRI: Revised Cardiac Risk Index; SORT: Surgical Outcome Risk Tool

	Risk predictor bivariate model (+ HRR_1)			
	NT-ProBNP	DASI	RCRI	SORT
NRI (95% CI)	0.48 (-0.04 – 0.96)	0.38 (-0.11 – 0.92)	0.48 (-0.01 – 0.99)	0.51 (0.01 – 1.01)
NRI event	0.30	0.30	0.30	0.39
NRI non-event	0.17	0.07	0.17	0.12

Net reclassification improvement analysis demonstrates that the bivariate model of SORT plus HRR_1 model reclassified the most patients correctly (NRI 0.51); this is in agreement with the improvement in AUROC between both SORT models. Overall, the bivariate models improved reclassification when compared to the risk prediction measures singularly. The two subsets of NRI, NRIevent and NRInon-event, show the proportion of patients who were correctly reclassified as higher risk (NRIevent) and correctly reclassified as lower risk (NRInon-event), respectively and are presented as proportions. All bivariate models correctly reclassified approximately one third of patients with PMI to an appropriate higher risk classification; the SORT plus HRR_1 model performed best in this measure, correctly reclassifying nearly 40% of patients compared to the univariate SORT model. Reclassification of patients who did not develop PMI into lower risk classification was both more variable and occurred to a lesser extent with all bivariate models. The lower proportions of NRInon-event indicate that the bivariate models reclassified less patients who did not develop PMI as low-risk. However, as discussed previously (Section 6.1.3.2), risk prediction measures pose more clinical utility if they are more likely to identify those truly at risk (reflected in this investigation by NRI event).

Table 44 provides a summary of predictive value improvement between the univariate and bivariate models for each risk prediction measure. Overall, HRR_1 demonstrated significant, or close to significant, prediction of PMI in each

bivariate logistic regression model. All bivariate models improved predictive value determined by AUROC and NRI. The bivariate model incorporating both SORT score and HRR_1 demonstrated the best predictive value.

Table 44 Summary of improvement measures for logistic regression model predictive value. CI: confidence intervals; AUROC: area under the receiver operating curve: NRI: net reclassification index; HRR_1: submaximal heart rate recovery one minute after exercise cessation; DASI: Duke Activity Status Index; RCRI: Revised Cardiac Risk Index; SORT: Surgical Outcome Risk Tool.

Logistic regression model variates	Unadjusted odds ratio (95%CI)	AUROC	NRI overall (95% CI)	NRI events	NRI non - events
NT-ProBNP	1.00 (1.00 – 1.00)	0.65			
+ HRR_1	0.94 (0.88 – 1.00)	0.70	0.48 (-0.04 – 0.96)	0.30	0.17
DASI	0.98 (0.95 – 1.02)	0.58			
+ HRR_1	0.94 (0.87 – 0.99)	0.69	0.38 (-0.11 – 0.92)	0.30	0.07
RCRI	1.60 (0.19 – 16.31) (RCRI ≥2)	0.53			
+ HRR_1	0.93 (0.87 – 0.99)	0.69	0.48 (-0.01 – 0.99)	0.30	0.17
SORT	1.75 (1.03 – 3.19)	0.66			
+ HRR_1	0.94 (0.88 – 1.00)	0.74	0.51 (0.01 – 1.01)	0.39	0.12

6.3 Discussion

The aim of this investigation was to determine the predictive validity of a range of different submaximal HRR parameters for PMI. Six of the HRR parameters demonstrated predictive value for PMI with AUROCs between 0.64 – 0.69. These six parameters included absolute HRR values and area under the heart rate recovery profiles, with different methods of effort-correction. The investigation also identified potential cut-offs for dichotomising patients into high and low-risk groups for the five best-performing HRR parameters. Finally, this investigation demonstrated that addition of submaximal HRR_1 into current risk prediction tools improved the predictive value for PMI in this cohort.

6.3.1 Incidence of PMI

The incidence of PMI was relatively high in this patient cohort (35.9%). This may reflect the older population compared to the larger studies described previously (most studies included patients aged ≥45 years)[150], but also the West of Scotland population and the surgical specialties represented (predominantly thoracic, colorectal and vascular surgery) which are recognised to be high-risk populations[135]. Sixty-four percent (7/11) of patients undergoing vascular surgery developed PMI. This incidence is high, especially considering that only elective cases were included (i.e. elective abdominal aortic aneurysm repairs or aorto-bifemoral grafts). The incidence of PMI/MINS in the literature in vascular surgical patients ranges from 20 to 30%[135,202,203]. A recent snapshot audit of preoperative assessment services in the West of Scotland demonstrated patients undergoing elective surgery in the West of Scotland tended to have a higher ASA physical status than the UK population,[204] reflecting a potentially more comorbid group. There is also increasing evidence that the UK patient population is becoming more comorbid following the COVID-19 pandemic[7].

6.3.2 Patient characteristics

Patients who developed PMI were older, male, with a higher rate of arterial hypertension and renal impairment and underwent longer operations. The cohort of patients with PMI therefore show equivalent baseline risk factors and intraoperative findings to risk factors common to the PMI literature (Section 1.6.2.2). The lower proportion of maximum predicted power reached during the step test indicates poor fitness in the PMI group. All preoperative risk scores (apart from RCRI, discussed later (Section 6.3.3.5)) were higher in the PMI group. These findings provide reassurance that the study population is reflective of PMI populations previously described in the literature supporting the robustness of the predictive validity results.

6.3.3 Predictive value of HRR parameters

Interestingly, the heart rate recovery parameters with the best predictive value encompassed a variety of different measures including absolute values (HRR_1), area under the HRR curve (AUC_{30}) and both effort-correction to the proportion of

age-predicted HR_{max} reached (HRR_1-ECHR, AUC_{30}-ECHR) and proportion of maximum predicted power output reached (AUC_5-ECW).

6.3.3.1 HRR_1

Submaximal HRR_1 showed significant difference between patients without and with PMI (23.5 bpm versus 15.2 bpm, p = 0.01, Figure 32) and demonstrated one of the best AUROC values for prediction of PMI (0.69 (0.55 – 0.82), Figure 37). It was the only absolute measure to demonstrate difference between those with and without PMI, and predictive value for PMI. The results of this study indicate that HRR_1 shows promise as a perioperative cardiovascular predictive measure despite the submaximal nature of the exercise testing, consistent with the perioperative HRR literature (Chapter 2 (Systematic review and meta-analysis)). In this study, participants aimed to reach a heart rate of 60% age-predicted HR_{max}. The median (IQR) age-predicted maximum reached was 67% (62-71%). This study has demonstrated that an objectively submaximal test i.e defined by a peak target heart rate of 60% age-predicted HR_{max} rather than patient perception produces a heart rate response and recovery robust enough to generate predictive HRR values for PMI. The only other perioperative submaximal HRR study by Ha et al measured HRR_1 after the patients performed a 6MWT[158], so although the tests were submaximal by definition, there was no standardisation of effort.

Two methods were used to identify potential thresholds for high and low-risk for PMI. For HRR_1 the cut-offs were 20 bpm and 30 bpm using Youden's index and a weighted 2:1 sensitivity:specificity Youden's index, respectively. Both of these cut-offs are much higher than the 12 bpm described in the literature, originating from Cole et al (1999)[114] and used widely since[150]. Heart rate recovery is faster after submaximal exercise as there is less activation of the sympathetic nervous system with less circulating catecholamines and so reactivation of the parasympathetic nervous system is more rapid, allowing the heart rate to fall to recovery faster than after maximal exercise[205] (Section 1.3.3). Therefore, these cut-offs make physiological sense but larger trials would be needed to clarify their clinical use.

Absolute submaximal HRR_1 was subsequently the only measure taken forward for exploratory analysis examining the effect of adding HRR_1 to perioperative risk measures in current use via change in AUROC value and net reclassification improvement. Heart rate recovery in one minute was chosen as it demonstrated one of the best predictive values for PMI, plus it is easy and intuitive to measure and is a familiar measure used in the literature. Addition of HRR_1 improved the predictive value and correct reclassification of patients for all of the currently used risk measures assessed. In bivariate logistic regression analysis, HRR_1 was the only variable significantly associated with PMI; the other risk predictors were not, suggesting that HRR_1 was the prime factor behind prediction improvement. The bivariate logistic regression model comprising SORT score and HRR_1 demonstrated a predictive value for PMI (AUROC 0.74 (0.62 – 0.86)) which is comparable or better than many of the currently-used risk prediction measures in the literature (discussed further in Section 6.3.3.5).

The other absolute HRR parameters did not demonstrate a difference between PMI groups or predictive value for PMI, although all reported a higher median value for patients without PMI than those with PMI. It may be that the study was underpowered to find these differences. Only HRR_1 has been investigated in the perioperative setting, however HRR at other timepoints have been investigated in other settings. Van de Vegte et al. investigated HRR in 40727 UK Biobank participants at 10, 20, 30, 40 and 50 seconds after maximal exercise testing and found that HRR after 10 seconds was predictive of all-cause and cardiovascular mortality after six years[206]. Earlier HRR can be postulated to be a better measure of initial parasympathetic reactivation and therefore potentially a better measure of aerobic fitness. However, there is a higher risk of noise so soon after exercise cessation plus difficulty in accurately identifying the exact point of cessation, affecting the accuracy of HRR earlier in recovery. The prognostic value of earlier HRR measures has not been definitively confirmed in the literature, nor in this study.

6.3.3.2 Effort-correction by heart rate

Effort-correction by heart rate was performed to “correct” the HRR parameters as if the patient had performed a maximal test. Effort-correction of HRR_1 and AUC_{30} did not meaningfully improve the predictive value of these measures, but

as described above, the patients' effort as measured by heart rate response was tightly controlled between patients. Therefore, it is unsurprising that heart rate effort-correction did not equate to a meaningful improvement in predictive value in this study with a specific target heart rate. However, the utility of effort-correction to heart rate remains unknown in circumstances where submaximal exercise testing is undertaken without specific heart rate targets. Ha et al. measured submaximal HRR after performance of a 6MWT[158]. The 6MWT measurements they report indicate very little difference in both peak heart rate and overall heart rate increase during exercise between patient groups who went on to develop cardiopulmonary complications after lung resection and those who did not. However, the group who developed CPC complications appeared to walk a smaller distance than the group without complications although this was not statistically significant; the difference between groups in percentage predicted 6MWT distance reached however was statistically significant (81.9±15.8% versus 76.4±16.6%, p=0.045, n=96). The mean age of all patients in the Ha et al study was 65.5±9.6 years and mean peak heart rate reached was 107.4±13.9 bpm[158]; very similar to the mean age and peak heart rate in this investigation, and indicating that the mean age-predicted HR_{max} reached was approximately 66%. There is not enough data available from the Ha et al. study to ascertain if variation in peak heart rate during the 6MWT would support effort-correction to age-predicted HR_{max}. However, both the relatively narrow spread around the medians and similarity between the age and heart rate parameters between the Ha et al. study and this investigation potentially indicate this would not be of particular use in their cohort. Where there was difference in percent-predicted 6MWT distance could indicate that effort-correction to markers of test performance (such as distance walked or power output in this investigation) may demonstrate more value.

6.3.3.3 AUC_{30}

The area under the heart rate recovery profile curve at 30 seconds after exercise cessation was the only AUC parameter to demonstrate a significant difference between patients with and without PMI (730 bpm.s and 939 bpm.s, respectively, p=0.02, Figure 33a). The AUC_1 appeared smaller in patients who developed PMI but this difference was not statistically significant, and there was large variation in AUC_1, particularly in the "no PMI" group (Figure 33b). There

was no difference between groups for both AUC_2 and AUC_5. These findings were unexpected and in contrast to the hypothesised pattern for the AUC, which was that less fit patients at higher risk of PMI would have a slower heart rate recovery equating to a larger AUC (Figure 19). The HRR differences, at least at 30 seconds and one minute after exercise cessation, indicate that the heart rate fall after exercise did follow the expected pattern (i.e. slower HRR in patients who developed PMI) but the AUC did not reflect this. However, AUC_{30} was the only absolute AUC parameter which demonstrated predictive value for PMI (AUROC 0.68 (0.54 – 0.82)). As with HRR_1, effort-correction to heart rate for AUC_{30} demonstrated predictive value but with very minimal improvement, and therefore will not be further discussed. The positive predictive value result for AUC_{30} warrants further exploration as to why it appears predictive for PMI but in the 'opposite direction' to that expected.

Firstly, this result might reflect a type I error in that the null hypothesis has been falsely rejected. The significance level set in this investigation is 0.05, therefore there is a 5% chance of incorrectly rejecting the null hypothesis. The p value for the difference in AUC_{30} between PMI groups was 0.02, indicating a potential 2% risk of type 1 error. For the predictive value of AUC_{30}, the 95% CI are broad (0.54 – 0.82) with the lower end close to the point of accepting the null hypothesis. This could be a spurious result with the investigation cohort not representative of the population, particularly as the sample size available for analysis of AUC_{30} results was 62 patients. This is a novel measurement and many different HRR parameters have been explored, increasing the risk of type I error. However, it is also possible that this result is correct but that the one-tailed alternative hypothesis put forward for the AUC parameters (that AUC will be larger in patients at risk of PMI) was flawed, as discussed below.

Secondly, AUC_{30} was the only AUC parameter to show a significant difference between PMI groups and predictive value for PMI. Thirty seconds after exercise cessation was the earliest point at which area under the HRR curve was measured. The x limits of the AUC were from the point of exercise cessation to the defined timepoint after exercise; the y limits were the heart rate at end of exercise (maximum) and the lowest heart rate during the whole five minute recovery period (minimum) (Figure 15). Potentially, 30 seconds after exercise

cessation may not be a long enough time period to optimise the proposed utility of AUC and so this result could be a reflection that AUC measured early in the HRR curve is actually a marker of another HRR parameter rather than the area, such as total fall in heart rate during the recovery period. Subsequent analysis showed that the total fall in heart rate over the five minute recovery period showed predictive value for PMI (AUROC 0.70 (0.56 – 0.83), n=64, Figure 42), comparable with the best-performing original HRR parameters, and slightly better than AUC_{30}.

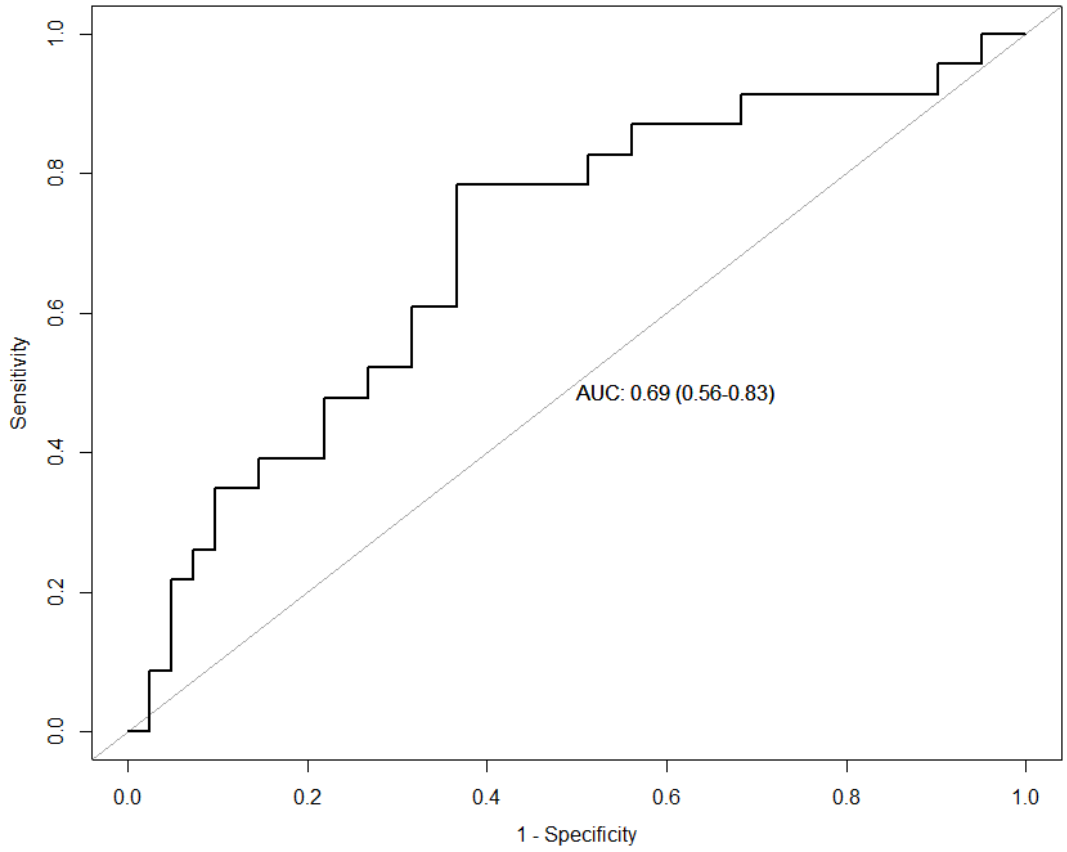


Figure 42 Receiver operating curve for the total heart rate recovery (within five minutes of exercise cessation) as a predictive measure of postoperative myocardial injury. n= 64.

The total fall in heart rate over five minutes also showed statistically significant difference between no PMI and PMI groups (total HRR_5 39.9 bpm v 30.8bpm respectively, p = 0.01, n=64, Figure 43).

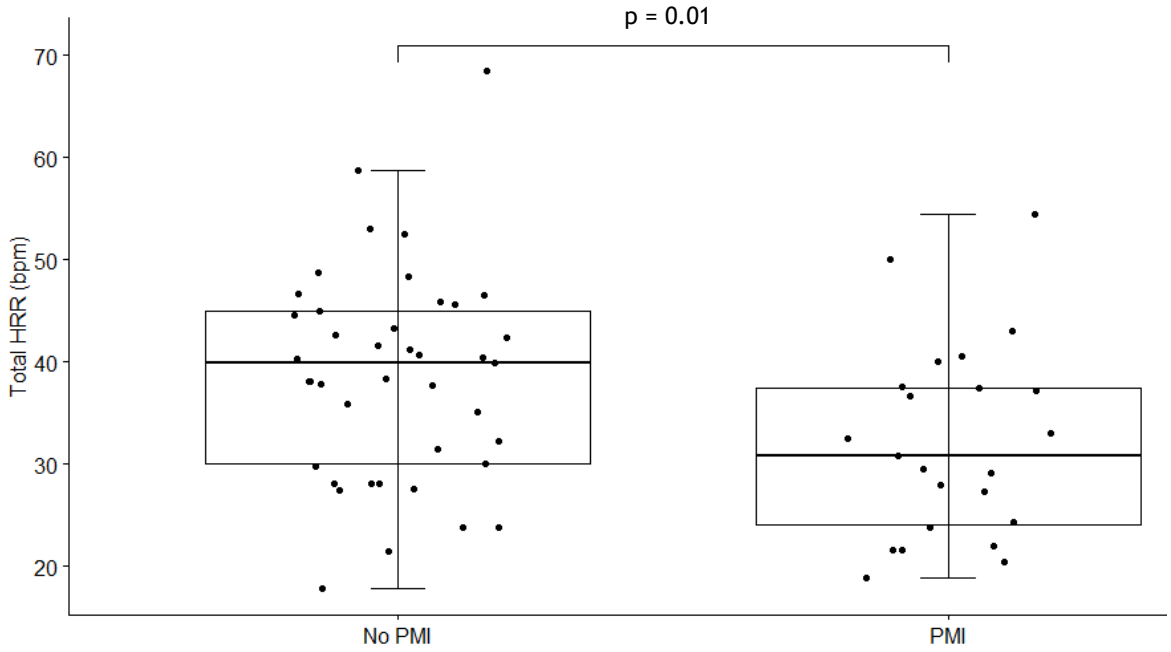


Figure 43 Difference in total heart rate recovery in five minutes between patients with and without PMI. Wilcoxon rank-sum exact test, n=64.

The total HRR results are similar to the HRR_1 results. It would be expected that the majority of HRR occurs early in recovery, particularly in fitter patients due to rapid reactivation of the cardiac vagal tone (Section 1.3.3). In this investigation, HRR_1 and the total HRR in five minutes demonstrated strong positive correlation (Spearman's rho = 0.73, p <0.001, Figure 44).

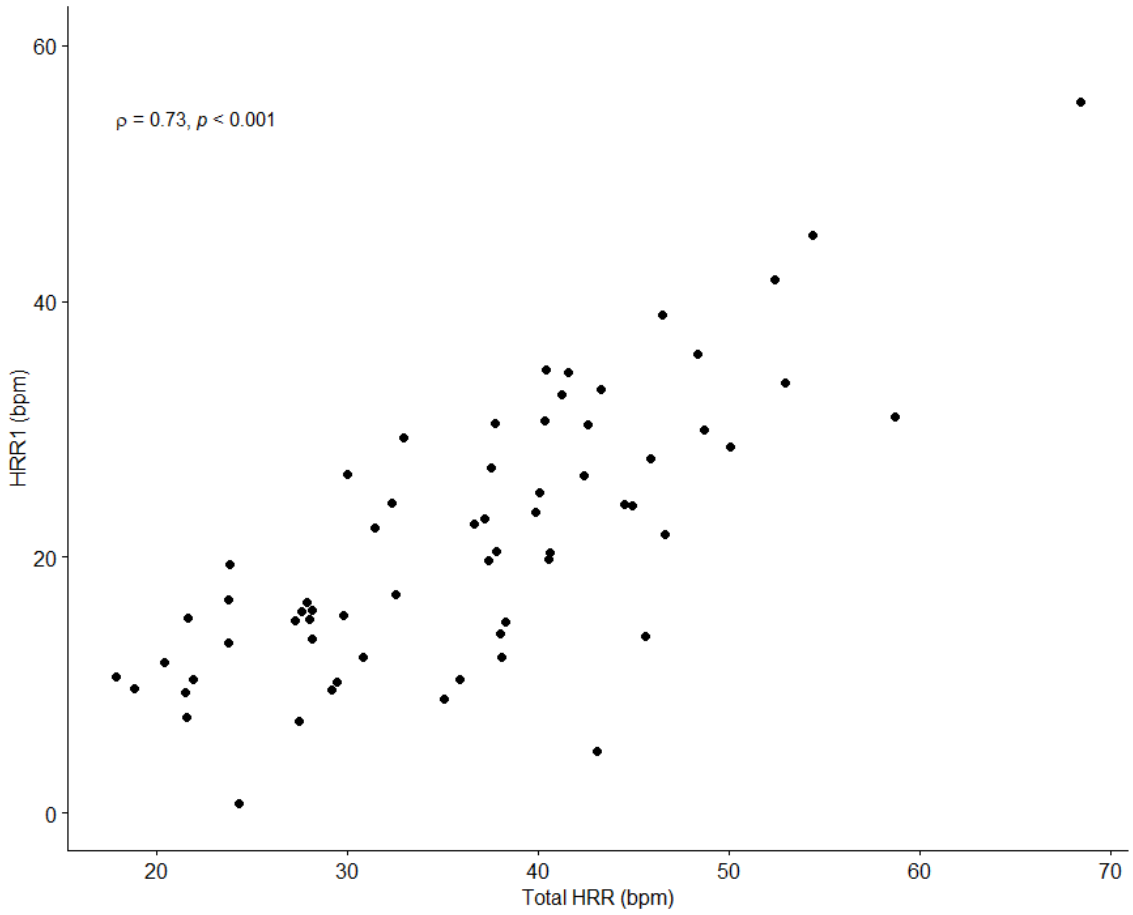


Figure 44 Correlation between heart rate recovery one minute after exercise cessation and the total heart rate recovery after five minutes in all patients with PMI data available.
Spearman's rank correlation, n=64. Bpm: beats per minute.

Heart rate recovery two minutes after exercise cessation was also strongly associated with total HRR in five minutes (Spearman's rho = 0.80, p <0.001). These results indicate that the majority of HRR occurs within the first minute or two after cessation of exercise. Therefore, the AUC_{30} result may indicate that AUC_{30}, when measured using the methods described above, more accurately reflects the total fall in heart rate which is very similar to HRR_1 hence providing one explanation for why AUC_{30} was larger in patients who did not develop PMI and displayed a similar predictive value to HRR_1.

Finally, it is feasible that the method of identification of the area under the HRR profile does not actually encompass the additional "useful" information that was hypothesised. By using the lowest heart rate during recovery as the minimum y-axis limit, the additional information on vagal tone that approximation to resting heart rate gives is lost. The rationale for using the lowest heart rate during

recovery as the y-axis limit was to exclude the large "empty" area below this limit which could dilute the potential signal from the heart rate recovery profile (Figure 15). However, this may have inadvertently lost the additional information that resting heart rate provided, and explains why the AUC_{30} and AUC_{1} results appeared "opposite" to what was hypothesised. A worked example using the heart rate recovery profiles of the patients with the smallest and largest HRR_{30} is described below to highlight how incorporating the whole y-axis gives a more expected picture.

Figure 45 shows the AUC_{30} for the patient with the "worst" HRR after 30 seconds (participant 077); their heart rate actually increased by 1.3 bpm after 30 seconds. This patient did develop PMI. Figure 45a shows the AUC_{30} using the minimum recovery heart rate as the lower y-axis limit. This patient's heart rate remained high for the whole recovery period, and so the AUC_{30} is relatively small (630 bpm.s). However, if the lower y-axis limit is removed and so the AUC incorporates the whole y-axis, the AUC_{30} is much higher (3120 bpm.s, Figure 45b) as this measurement now reflects the fact that the recovery heart rate remains high.

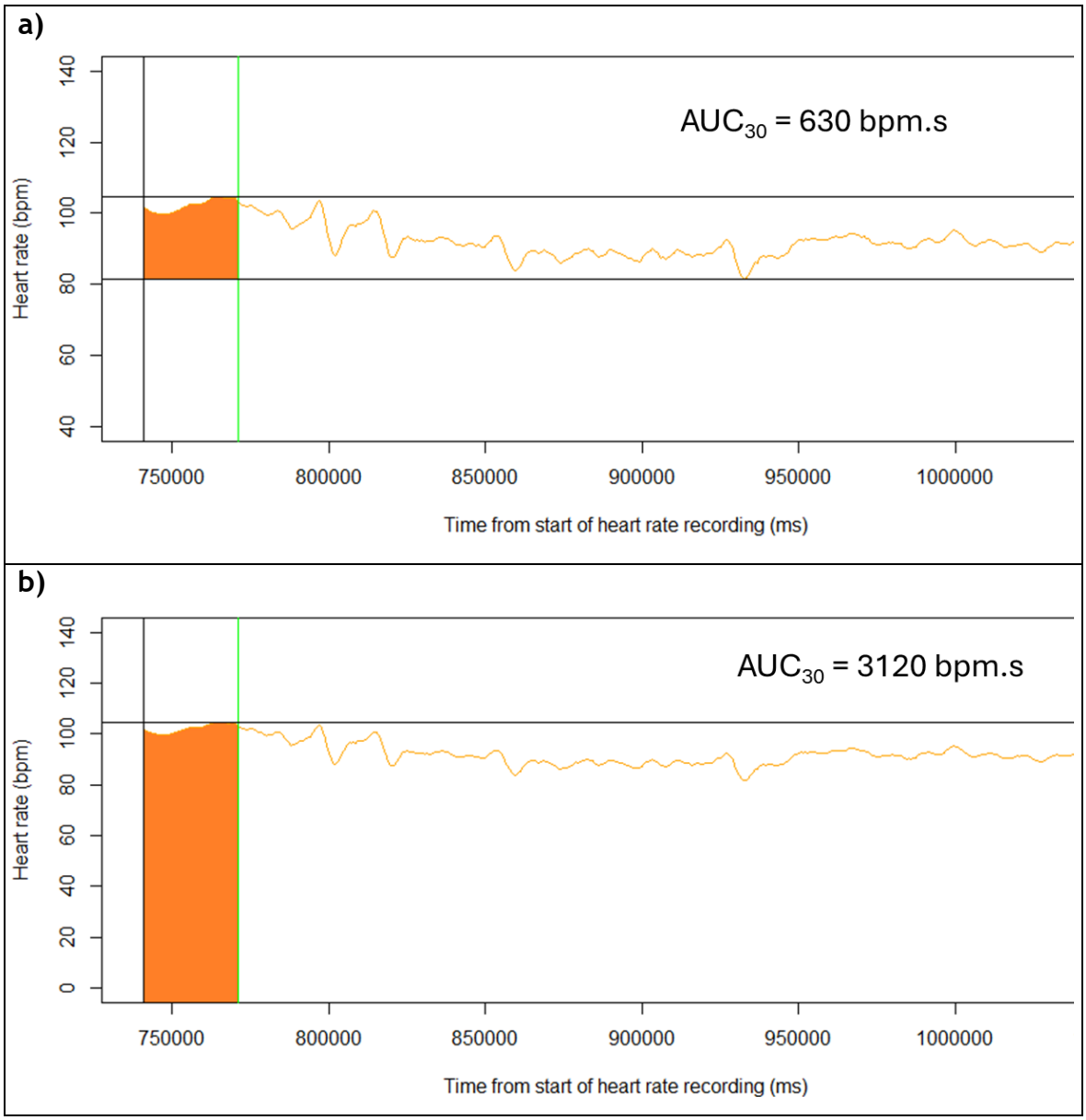


Figure 45 Heart rate versus time plot of participant 077 recovery period demonstrating AUC_{30}. a) AUC30 as calculated in this investigation. **b)** AUC if no lower y-axis limit. Black vertical line: end of exercise (Rest). Green line: 30 seconds after exercise cessation. Black horizontal lines: maximum and minimum heart rates during recovery period. Orange area: area under the curve.

Compare this to the AUC_{30} of the patient who had the fastest HRR_{30} of 42 seconds (participant 041); this patient did not develop PMI (Figure 46). Figure 46a shows the AUC_{30} as measured in this investigation (1149 bpm.s); because of the rapid fall to a low heart rate (both indications of cardiac vagal tone) the AUC_{30} is larger than that of the other patient despite the rapid HRR. Figure 46b shows the AUC_{30} if the whole y-axis is counted. Compared to the "unfit" patient with PMI (participant 077, Figure 45), the AUC_{30} is now smaller (2527 bpm.s) because this measure now incorporates the fact that the heart rate fell to a lower level.

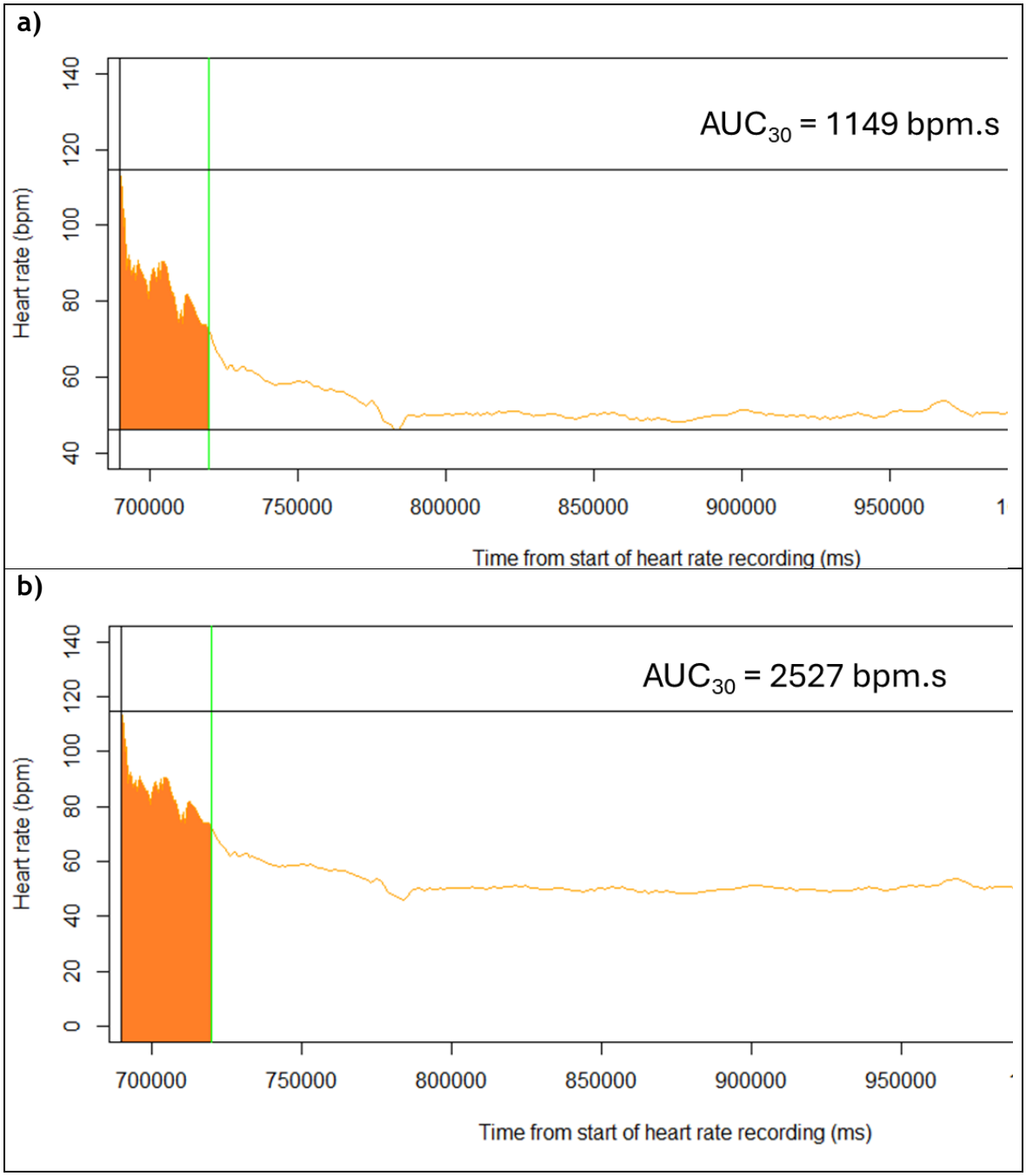


Figure 46 Heart rate versus time plot of participant 041 recovery period demonstrating AUC_{30}. a) AUC_{30} as calculated in this investigation. **b)** AUC_{30} if no lower y-axis limit. Black vertical line: end of exercise (Rest). Green line: 30 seconds after exercise cessation. Black horizontal lines: maximum and minimum heart rates during recovery period. Orange area: area under the curve.

Although just an example using two individual patients, the above working offers an explanation as to why the AUC_{30} (and AUC_1) results were unexpected.

Overall, the author believes it is unlikely that the unexpected AUC_{30} result is spurious. The findings have highlighted that the AUC parameters, as measured in this investigation, may actually represent different aspects of the HRR profile than originally hypothesised. The AUC_{30} as measured may be more a reflection of

the extent of the total fall in heart rate which itself is an approximation of HRR_1, a more intuitive marker which performs better as a predictive measure for PMI in this cohort.

6.3.3.4 AUC_5 and effort-correction by power output

The "raw" AUC_5 did not demonstrate any difference between PMI groups or predictive value for PMI at all; however, when effort-corrected to the proportion of predicted maximum power output reached, it demonstrated significant difference between PMI groups (Figure 36) and one of the best predictive values for PMI (AUROC 0.69 (0.55 – 0.83)). Unlike AUC_{30}, AUC_5-ECW did follow the expected pattern being that patients with PMI had a larger AUC_5-ECW (14165 bpm.s versus 8682 bpm.s, p = 0.02). However, this effect was not demonstrated by the uncorrected AUC parameters, with very little difference between PMI groups for both AUC_2 and AUC_5 (Table 23). In terms of the uncorrected AUCs (excluding AUC_{30}), it could be that the study was underpowered to detect a difference in these measures; or that area under the HRR curve is not sensitive enough to discriminate differences between aerobic fitness in patients when measured after submaximal exercise; or, as discussed above, there could be more effective way to measure this area.

There is also the possibility that effort-correction to power output is a more effective measure of effort-correction than proportion of age-predicted HR_{max} reached and improved the small difference in AUC_5 to become a significant predictor for PMI. A similar pattern was also seen with AUC_2 where there was minimal difference between patients with and without PMI, no predictive value for PMI for the absolute values, but it did demonstrate predictive value for PMI when effort-corrected to proportion of maximum power output reached, indicating this was unlikely to be a spurious result. Power output encompasses whole body effort combining cardiorespiratory and neuromuscular function. Predicted power output incorporates patient age, height and sex, therefore yielding much more variation between patients in our cohort (than age-predicted HR_{max}), with the median (IQR [range]) proportion of maximum predicted power output reached being 0.29 (0.22 – 0.45 [0.12 – 1.63], n=83). In comparison, the median proportion of age-predicted HR_{max} reached during the exercise test was 0.67 (0.62 – 0.71 [0.44 – 1.01], n = 83). There was also a

difference in median (IQR) proportion of maximum power output reached between patients with and without PMI, it being lower in patients who went on to develop PMI (median (IQR) 0.25 (0.19 – 0.33), versus 0.33 (0.24 – 0.46)). Therefore, there is potential there was a larger AUC in patients who developed PMI and the study was underpowered to demonstrate this effect, but the addition of effort-correction to power output uncovered the true signal. However, only AUC_2 and AUC_5 improved with effort-correction to power output. Effort-correction to proportion of maximum power output reached worsened the AUROCs for all HRR parameters. This inconsistency raises uncertainty about the utility of effort-correction to power output.

The area under the HRR profile curve is a novel measure which was hypothesised to give more information on HRR than just the absolute drop in heart rate after exercise cessation, with the expectation that the AUC would be larger in patients who develop PMI. The AUC results reported in this Chapter present a very mixed picture. The earlier AUCs (30 seconds and one minute after exercise cessation) were both larger in patients (the opposite of that hypothesised) who did not develop PMI (although this result was only significant for AUC_{30}). The later AUCs (two and five minutes after exercise cessation) do appear to demonstrate the expected pattern (larger in patients who did develop PMI) but this result is not significant and arguably minimal for AUC_5. The only uncorrected AUC to demonstrate predictive value for PMI was AUC_{30} (AUROC 0.68) with minimal improvement when effort-corrected to proportion of age-predicted HR_{max} reached. There may be a number of reasons for this finding, as described above, including a spurious result, AUC_{30} being representative of total fall in heart rate or reconsideration of the method of AUC measurement required. The later AUCs do suggest the expected pattern (larger in patients who develop PMI) potentially as the longer time period of measurement may better reflect the slower rate of fall in heart rate after exercise cessation. However, these only demonstrated predictive value for PMI after effort-correction to proportion of maximum predicted power output reached. Either these are both spurious results or the variability between patients in power output (particularly between PMI and no PMI groups) unmasked a difference in these measures. These results warrant further investigation of the measurement and utility of area under the

heart rate recovery profile curve and potential fine-tuning of this novel measure.

6.3.3.5 Comparison of submaximal heart rate recovery with current risk prediction measures in clinical use

Within this patient population, the current risk measures in use (NT-ProBNP, DASI, RCRI and SORT score) performed poorly, with only SORT demonstrating a weak association with PMI (Section 6.2.10). Both NT-ProBNP and SORT score demonstrated poor predictive value for PMI (AUROC 0.65 and 0.66, respectively), a worse performance than the five best-performing HRR parameters. Neither DASI nor RCRI demonstrated predictive value for PMI in this patient cohort. Within the perioperative risk prediction literature, performance of these measures is variable and comparable with the results in this study, although there are few directly comparable studies investigating PMI as a primary outcome.

In the METS study (Section 1.2.4), the only measure to demonstrate a significant association with the primary outcome[K] was DASI, which also improved the predictive value of the baseline model (RCRI only) from an AUROC of 0.59 to 0.67. Secondary outcomes included a composite of death or myocardial injury (defined as postoperative troponin concentrations exceeding the 99th percentile of the normal reference population and the threshold at which the assay coefficient of variation was 10%) within 30-days of surgery. Within their population, a baseline model comprising age, sex and RCRI demonstrated a predictive value (AUROC) of 0.70 for the composite of death and PMI within 30-days. For this outcome, only NT-ProBNP showed significant adjusted association (aOR 1.78, 95%CI 1.21 – 2.62, p = 0.003), with an improvement in AUROC from 0.70 to 0.71. Net reclassification was 0.20 (NRI_{events} 0.07, $NRI_{nonevents}$ 0.13). NT-ProBNP was also the only parameter to demonstrate association and improvement in predictive value for one year mortality. Neither of the CPET variables (AT or VO_{2peak}) demonstrated either association or predictive value with the primary outcome or PMI outcome. However, VO_{2peak} demonstrated significant association with in-hospital moderate or severe outcomes and

[K] Death or myocardial infarction within 30-days of surgery

improved the predictive value of the baseline model (age, sex, high-risk surgery) from 0.72 to 0.74[38]. Note that within this large study all measures only demonstrated poor to fair predictive value for the different outcomes. In the current study, neither DASI nor RCRI performed well, not demonstrating association or predictive value for PMI. Based on the METS study (including data on association between DASI and functional capacity as reported by CPET), the European Society of Cardiology guidelines recommend DASI as a measure of functional capacity (Class IIa recommendation)[52].

The predictive value of NT-ProBNP for PMI in this cohort is comparable or slightly poorer to that described in the literature for cardiovascular and postoperative morbidity outcomes. Duceppe et al. found that NT-ProBNP demonstrated fair predictive value for vascular death and myocardial injury within 30-days of noncardiac surgery in over 10000 patients aged 45 years or over (AUROC 0.70). Addition of RCRI improved the predictive value to an AUROC of 0.73[50]. AS described in Section 1.2.7, NT-ProBNP demonstrated a predictive value for a composite endpoint of postoperative morbidity (AUROC 0.68 (95%CI 0.60 - 0.77)) when dichotomised by a threshold of 433 pg/ml[51]. A study comparing the predictive value of preoperative NT-ProBNP, RCRI and echocardiogram in 1923 patients undergoing noncardiac surgery found AUROCs of 0.74, 0.59 and 0.58, respectively for a composite outcome of postoperative cardiovascular complications[207]. NT-ProBNP is recommended for preoperative cardiac risk stratification in selected higher risk patients is some jurisdictions based on the evidence described above[42,52].

The SORT is only validated as a risk stratification tool for 30-day mortality following noncardiac surgery[25]. It has consistently demonstrated excellent predictive value for 30-day mortality in a range of very large validation trials with AUROCs ranging from 0.88 in a cohort of high-risk patients[25] to 0.92 in Australasian retrospective study in over 44000 patients undergoing noncardiac surgery[27]. However, its use as a risk stratification measure for other postoperative complications has not been investigated and so there is no data available to compare its use as a risk measure for postoperative cardiovascular outcomes. In this study (VERVE), the SORT score was the best-performing currently-used risk score but still demonstrated only poor or equivalent

predictive value for PMI compared to the HRR parameters. This is with the caveat that this outcome is not what SORT is designed to predict.

Currently, the RCRI is the measure that has been most extensively validated in surgical patients for preoperative cardiac risk stratification and as such is commonly used as the comparator for the performance of newer risk prediction measures (as above). As described in Section 1.2.5, a systematic review of cohort studies in 2010 showed that RCRI demonstrated a poor to fair predictive value for postoperative cardiovascular complications (variable timeframes) and all-cause mortality (median AUROC 0.69 (IQR 0.62 - 0.75) and 0.62 (IQR 0.54 – 0.78), respectively) in patients undergoing noncardiac surgery. The RCRI performs less well in patients undergoing vascular surgery with predictive value (AUROC) of 0.60 (0.54 – 0.65) for 30-day major cardiovascular complications (cardiac death, nonfatal MI, nonfatal cardiac arrest)[208]. The authors attribute the poor performance of the RCRI in this cohort to underestimation of MI, due to both the higher prevalence of postoperative MI in vascular patients and that the RCRI was derived over 20 years ago with very different diagnostic criteria for MI than is now used[208]. Risk estimates for all noncardiac surgery patient groups have subsequently been revised, with the Canadian Cardiovascular Society recommending RCRI as the primary risk stratification tool for perioperative cardiovascular risk[42]. In the current study, RCRI showed no association with PMI and no predictive value for PMI when divided into risk categories. The prevalence of vascular patients in this cohort may have contributed to this poor performance. Despite its poor performance as a perioperative risk measure of cardiovascular complications, it is extensively utilised both clinically and as a comparator in performance for validation studies of other risk prediction measures (as demonstrated above). The five best-performing HRR parameters all demonstrated comparable or better predictive value for PMI than the poor discriminative value extensively reported in the literature for RCRI.

The predictive value of both CPET and the 6MWT for postoperative outcomes are described in Sections 1.2.10 and 1.2.11. Again, the five best-performing HRR parameters demonstrated similar predictive value for PMI as CPET, with AT demonstrating predictive value (AUROCs) between 0.57 and 0.83 for postoperative cardiorespiratory complications[62]. Similarly, 6MWT distance

demonstrated predictive value (AUROC) of 0.70 for 30-day mortality or MI[38]. Overall therefore, submaximal HRR parameter appear equivalent in postoperative risk prediction to measures currently in use.

6.3.4 Sensitivity analyses

A sensitivity analysis was performed to evaluate the potential effect of beta-blockade and calcium-channel blockade on HRR parameters. Both beta-blockers and non-dihydropyridine calcium-channel blockers (Diltiazem and Verapamil) slow heart rate. Both drugs are in common use for cardiovascular disease and therefore a sensitivity analysis was performed to assess if the negative chronotropic effects of these drugs could affect the predictive value of the HRR parameters.

The incidence of PMI was slightly higher in patients without beta-blockade than the whole cohort (37% versus 36%) and a higher proportion of patients were on beta-blockade in the no PMI group than those who developed PMI (17% versus 13%, respectively.) The sensitivity analysis findings match those in the literature where beta-blockade made no difference to the association between HRR_1 and postoperative outcome in both perioperative and cardiovascular studies[150,156,159]. This stands to reason as the main mechanism behind HRR, at least initially, is vagal reactivation. Where beta-blockade may have an effect is on the maximum heart rate reached during exercise, however the submaximal nature of this test potentially limits this effect.

Administration of rate-limiting calcium-channel blockers also did not appear to affect heart rate recovery. Similarly to beta-blockade, they reduce the potential maximum heart rate during exercise but do not appear to affect the rate of slowing after exercise[209]. Again, this result agrees with sensitivity analyses in the literature on maximal HRR and postoperative outcomes[150,156].

The sensitivity analysis is reassuring and demonstrates the generalisability of submaximal HRR as a measure. Many surgical patients are on either beta-blockade, calcium-channel blockers or both. A larger study is needed to confirm these findings but the HRR literature also indicates that these patients do not need to be excluded from the measure. This supports the use of submaximal HRR

as a risk predictor in patients at risk of postoperative cardiovascular complications on beta- or calcium-channel blockade.

6.4 Conclusion

The VERVE study is the first to demonstrate the predictive validity of a range of submaximal HRR parameters (HRR_1, HRR_1-ECHR, AUC_{30}, AUC_{30}-ECHR and AUC_5-ECW) for PMI, including novel area under the heart rate recovery curve and effort-correction measures. The predictive value for PMI for each parameter was poor to fair but this is comparable with current risk prediction measures in predicting postoperative cardiovascular complications. Effort-correction to age-predicted HR_{max} did not change the predictive value of HRR parameters, although this may be due to tight heart rate control during the step test. Effort-correction to proportion of maximum predicted power output reached worsened absolute HRR parameters but improved the performance of the AUC parameters at longer timepoints. Overall, these results support the underlying hypothesis that heart rate recovery is a measure of cardiac vagal dysfunction and that submaximal exercise (targeting a heart rate of 60% age-predicted maximum) generates a sufficient HRR response to identify patients at increased risk of PMI. Thresholds for dichotomising risk were identified for each predictive submaximal HRR parameter using two different methods to reflect their potential usefulness as risk stratification tools. Submaximal HRR_1 demonstrated better association with PMI than currently used risk prediction measures in this cohort. Addition of submaximal HRR_1 to logistic regression models improved the predictive value for currently-used perioperative risk tools as measured by both area under the receiver operating curve and net reclassification index.

Although six HRR parameters demonstrated predictive value for PMI, only the five best-performing (AUC_5-ECW, HRR_1, HRR_1-ECHR, AUC_{30} and AUC_{30}-ECHR) were taken forward for further validity testing, as per the pre-planned data analysis plan. It so happened that these five measures demonstrated poor-to-fair predictive value for PMI with AUROCs 0.68-0.69, whereas the parameter not taken forward (AUC_2-ECW) demonstrated poor predictive value (AUROC 0.64, Table 35).

Validation of the five best-performing predictive submaximal HRR parameters for PMI are investigated in the following chapters by assessment of face validity (postoperative complications), construct validity (association between currently-used perioperative risk tools and submaximal HRR) and criterion validity (association between cardiopulmonary exercise test variables and submaximal HRR).

Chapter 7 Heart rate recovery and postoperative complications (face validity)

This Chapter assesses the face validity of the five best-performing submaximal HRR parameters for PMI. Association between the submaximal HRR parameters and secondary outcomes was assessed. These outcomes encompassed postoperative complications at seven and 30-days, clinical outcome measures and patient-reported outcomes measures. Face validity would be demonstrated if there is association between the HRR parameters and postoperative outcomes (Section 3.2.5).

7.1 Specific statistical handling

Data collection for the secondary outcome measures are described in Chapter 4 (Generic methods). Comparisons of non-parametrically distributed HRR parameters between groups were made using Wilcoxon rank sum exact test. Correlation between HRR parameters and continuous data was assessed using Spearman's rank correlation. Assessment of the degree of linear association was made via visual inspection of the plots and indicative cut-offs described in Table 45[210]. No adjustments were made for multiple comparisons due to the exploratory nature of the investigation.

Table 45 Interpretation of Spearman's correlation coefficient as per Schober et al[210].

Spearman's correlation coefficient (ρ)	Interpretation
0.00 - 0.10	Negligible correlation
0.10 – 0.39	Weak correlation
0.40 – 0.69	Moderate correlation
0.70 – 0.89	Strong correlation
0.90 – 1.00	Very strong correlation

7.2 Results

7.2.1 Participant characteristics

The baseline demographics for the Operative group (n = 72) are described in Table 12. Intraoperative parameters for this group are described in Section 5.5.

Table 46 Participant demographics, comorbidities, preoperative blood results and medications in Operative group. n = 72 unless stated otherwise. Values are number (percentage), mean±SD and median (IQR)[range]. BMI: body mass index; ASA: American Society of Anaesthesiologists Physical Status; COPD: chronic obstructive pulmonary disease; hsTnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme.

Characteristic	Descriptive Statistics
Age (years)	65.7±7.9
Female sex	36 (50%)
BMI (kg/m^2)	27.6 (24.2-30.5) [17.4-47.5]
Ethnicity: White British	 72 (100%)
Smoking status: Current smoker Ex-smoker Never smoked	 14 (19%) 33 (46%) 25 (35%)
Clinical Frailty Score: 1 2 3 4 5 >5	 4 (6%) 21 (29%) 28 (39%) 13 (18%) 6 (8%) 0
ASA score: 1 2 3 4 *Missing data*	 0 26 (36%) 26 (36%) 3 (4%) *17*
Duke Activity Status Index (points)	39.2 (24.2 - 50.7) [10.7 – 58.2]
Comorbidities	
None	5 (7%)
History of cancer	29 (36%)
Asthma	4 (6%)
COPD	14 (19%)
Arterial hypertension	27 (38%)
Ischaemic heart disease	9 (13%)
Cardiac failure	1 (1%)
Atrial fibrillation	1 (1%)
Peripheral vascular disease	8 (11%)
Stroke	2 (3%)
Type 1 Diabetes mellitus	2 (3%)
Type 2 Diabetes mellitus	10 (14%)
Previous covid infection Long covid	29 (40%) 1 (1%)
Preoperative blood results	
NT-ProBNP *Missing data*	80 (45-167) [12 – 1611] *1*
hsTnT (ng/L) *Missing data*	7 (5-9) [3 – 30] *3*
Haemoglobin (g/L) *Missing data*	14.0±1.54 *2*
Creatinine (µmol/L) *Missing data*	76.0 (64.5-89.0) [45.0 – 182.0) *1*
Preoperative renal function eGFR >59 (ml/min) eGFR 30-59 (ml/min)	 63 (88%) 8 (11%)

eGFR <30 (ml/min) *Missing data*	0 *2*
Medications	
No regular medication	7 (10%)
Beta-blocker	11 (15%)
Calcium channel blocker	19 (26%)
ACE-inhibitor	14 (19%)
Diuretics	6 (8%)
Antiarrhythmic	0
Beta-agonist	12 (17%)
Steroids: Inhaled Oral	 8 (11%) 1 (1%)

Preoperative risk scores of the Operative group are described in Table 47.

Table 47 Preoperative risk scores for Operative group (n = 72). Values are number (percentage) or median (IQR) [range]. P/V-POSSUM: Portsmouth/Vascular-Physiologic and Operative Severity Score for the study of Mortality and Morbidity; ACS NSQIP SRC: American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; SORT: Surgical Outcome Risk Tool; RCRI: Revised Cardiac Risk Index.

Preoperative risk score	Descriptive Statistics
POSSUM morbidity (%)	27.0 (18.9 – 38.8) [8.8 – 77.4]
POSSUM mortality (%)	1.25 (0.8 – 2.52) [0.4 – 17.4]
ACS NS QIP any complication risk (%)	9.2 (6.2 – 16.7) [2.2 – 29.3]
ACS NS QIP length of hospital stay (days)	3.5 (2.5 – 5.5) [0.5 – 8]
SORT score (%)	0.77 (0.28 – 1.23) [0.06 – 4.81]
RCRI: Class I 3.9% Class II 6.0% Class III 10.1% Class IV 15.0%	 7 (10%) 53 (74%) 10 (14%) 2 (3%)

7.2.2 Incidence of postoperative complications

Out of the 72 patients who underwent both the exercise test and their operation, 36 (50%) developed at least one postoperative complication (as per Appendix 5) within seven days of their operation. The incidence of postoperative complications by system at both seven and 30-days of surgery is detailed in Table 48.

Table 48 Incidence of postoperative complications within seven days of surgery for Operative group (n = 72, unless stated otherwise). Values are number (percentage).

Postoperative complications within seven days of surgery	Descriptive Statistics
Any cardiovascular complication	4 (6%)
Myocardial infarction	0
Non-fatal cardiac arrest	0
Cardiac death	0
Pulmonary embolism	0
Deep veined thrombosis	0
New-onset atrial fibrillation	4 (6%)
Acute kidney injury	7 (10%)
Stage:	
1	4 (6%)
2	1 (1%)
3	1 (1%)
Missing data to determine stage	*1*
Infection	19 (26%)
Neurological complications	
4AT score ≥ 4	0
Missing data	*30*
Use of anti-delirium medication	1 (1%)
Stroke	0
Any pulmonary complication	30 (42%)
Atelectasis	28 (39%)
Pneumonia	5 (7%)
Acute respiratory distress syndrome	2 (3%)
Pulmonary aspiration	1 (1%)
30-day composite outcomes	
Major adverse kidney event	4 (6%)
Major adverse cardiac event	2 (3%)

Only two patients developed complications graded as severe (Clavien-Dindo grade III or above). One patient developed acute respiratory distress syndrome following pulmonary aspiration within seven days of a transverse colectomy, requiring intensive care admission. The other patient developed a bowel perforation within seven days of a gynaecological procedure, which lead to multi-organ failure requiring intensive care admission.

Two patients (3%) died within thirty days with no further deaths at 90 days postoperatively. Nine patients (13%) were admitted to the intensive care unit within 14 days of surgery. Median (IQR) hospital stay was 5 (3-9) days, with three patients (4%) being readmitted to hospital within 30-days.

7.2.3 Postoperative complications within seven days

Although 72 patients completed both the exercise test and underwent surgery, HRR data was not available for all (Figure 29). Two patients did not have HRR_1 data, four patients did not have AUC_{30} data and nine patients did not have AUC_5-ECW data available hence the variable numbers described in the results below.

There was no statistically significant difference in any of the five best-performing HRR parameters between patients with and without any postoperative complication within seven days of surgery (Table 49).

Table 49 Difference in HRR parameters between patients with and without postoperative complications within seven days of surgery. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	No postoperative complication *Number of patients*	Postoperative complication *Number of patients*	p value
HRR_1 (bpm)	22.0 (15.2 – 29.1) *34*	20.1 (12.2 – 29.6) *36*	0.64
HRR_1-ECHR (bpm)	31.2 (22.4 – 43.5) *34*	29.7 (19.3 – 41.0) *36*	0.85
AUC_{30} (bpm.s)	897 (734 – 1051) *32*	937 (709 – 1042) *36*	0.80
AUC_{30}-ECHR (bpm.s)	1290 (1086 – 1557) *32*	1388 (1099 – 1606) *36*	0.51
AUC_5-ECW (bpm.s)	9839 (7534 – 16911) *29*	10371 (7654 – 16078) *34*	0.71

Only two patients developed complications graded as severe (Clavien-Dindo grade III and above) therefore association between the HRR parameters and complication severity was not performed.

The only cardiovascular complication to occur within seven days of surgery was new-onset atrial fibrillation in four (6%) patients, therefore just meeting the criteria for Wilcoxon rank sum test analysis[211]. There was no difference between patients who did and did not develop new-onset AF for any of the HRR parameters (Table 50).

Table 50 Difference in HRR parameters between patients with and without postoperative new-onset atrial fibrillation within seven days of surgery. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	No postoperative cardiovascular complication *Number of patients*	Postoperative cardiovascular complication *Number of patients*	p value
HRR_1 (bpm)	21.1 (13.9 – 29.8) *66*	19.5 (14.2 – 22.7) *4*	0.41
HRR_1-ECHR (bpm)	31.2 (20.6 – 43.6) *66*	28.9 (24.5 – 31.3) *4*	0.52
AUC_{30} (bpm.s)	911 (734 – 1070) *64*	703 (532 – 884) *4*	0.14
AUC_{30}-ECHR (bpm.s)	1334 (1088 – 1594) *64*	1085 (937 – 1264) *4*	0.18
AUC_5-ECW (bpm.s)	10033 (7547 – 16787) *59*	14481 (12716 – 18096) *4*	0.17

There was no difference between patients who did and did not develop any postoperative pulmonary complication for any of the HRR parameters (Table 51).

Table 51 Difference in HRR parameters between patients with and without any postoperative pulmonary complication within seven days of surgery. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	No postoperative pulmonary complication *Number of patients*	Postoperative pulmonary complication *Number of patients*	p value
HRR_1 (bpm)	21.1 (15.0 – 28.8) *40*	21.4 (12.5 – 29.8) *30*	0.81
HRR_1-ECHR (bpm)	30.0 (22.0 – 41.8) *40*	32.1 (19.7 – 40.8) *30*	1.00
AUC_{30} (bpm.s)	857 (686 – 1039) *38*	960 (751 – 1063) *30*	0.37
AUC_{30}-ECHR (bpm.s)	1220 (1066 – 1538) *38*	1421 (1206 – 1627) *30*	0.17
AUC_5-ECW (bpm.s)	10248 (7560 – 19668) *34*	10348 (7625 – 14969) *29*	0.81

There was no difference between patients who did and did not develop postoperative infection for any of the HRR parameters (Table 52).

Table 52 Difference in HRR parameters between patients with and without postoperative infection within seven days of surgery. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	No postoperative infective complication *Number of patients*	Postoperative infective complication *Number of patients*	p value
HRR_1 (bpm)	21.7 (14.9 – 29.6) *51*	20.3 (12.0 – 28.3) *19*	0.74
HRR_1-ECHR (bpm)	29.8 (21.8 – 40.8) *51*	34.5 (18.3 – 44.8) *19*	0.97
AUC_{30} (bpm.s)	897 (717 – 1068) *49*	862 (757 – 1008) *19*	0.90
AUC_{30}-ECHR (bpm.s)	1309 (1083 – 1558) *49*	1370 (1130 – 1595) *19*	0.67
AUC_5-ECW (bpm.s)	9535 (7521 – 16540) *45*	12817 (8226 – 19406) *18*	0.30

There was no difference between patients who did and did not develop postoperative acute kidney injury for any of the HRR parameters (Table 53).

Table 53 Difference in HRR parameters between patients with and without postoperative acute kidney injury within seven days of surgery. Wilcoxon rank sum test. Values are median (IQR). AKI: acute kidney injury

HRR parameter	No postoperative AKI	Postoperative AKI	p value
HRR_1 (bpm)	22.3 (15.0 – 29.7) *63*	13.6 (11.0 – 20.5) *7*	0.14
HRR_1-ECHR (bpm)	31.5 (22.2 – 42.7) *63*	20.6 (17.8 – 29.4) *7*	0.17
AUC_{30} (bpm.s)	925 (734 – 1068) *61*	745 (664 – 872) *7*	0.30
AUC_{30}-ECHR (bpm.s)	1351 (1089 – 1594) *61*	1127 (998 – 1340) *7*	0.32
AUC_5-ECW (bpm.s)	10033 (7521 – 16540) *57*	14548 (11319 – 19386) *6*	0.18

No patients developed any neurological complications with only one requiring the use of anti-delirium medication postoperatively therefore, statistical analysis was not performed.

7.2.4 30-day composite outcomes

Only two patients developed major adverse cardiovascular events (MACE) so the association between the HRR parameters and MACE was not assessed; both of these patients also developed MAKE.

Four patients developed major adverse kidney events (MAKE), meaning the assumptions for Wilcoxon rank sum test were just met for analysis[211]. Despite these low numbers of major adverse kidney events, HRR_1 and AUC_5-ECW were associated with the development of MAKE (Table 54, Figure 47).

Table 54 Difference in HRR parameters between patients with and without major adverse kidney event within thirty days of surgery. Wilcoxon rank sum test. Values are median (IQR). MAKE: major adverse kidney event.

HRR parameter	No MAKE *Number of patients*	MAKE *Number of patients*	p value
HRR_1 (bpm)	22.4 (14.9 – 29.8) *66*	11.9 (10.1 – 14.3) *4*	0.04
HRR_1-ECHR (bpm)	32.4 (21.5 – 43.6) *66*	18.6 (16.0 – 22.5) *4*	0.05
AUC_{30} (bpm.s)	930 (728 – 1070) 64	745 (694 – 751) *4*	0.09
AUC_{30}-ECHR (bpm.s)	1360 (1087 – 1594) *64*	1107 (1047 – 1158) *4*	0.13
AUC_5-ECW (bpm.s)	10088 (7560 – 15276) *60*	24151 (20593 – 25777) *3*	0.03

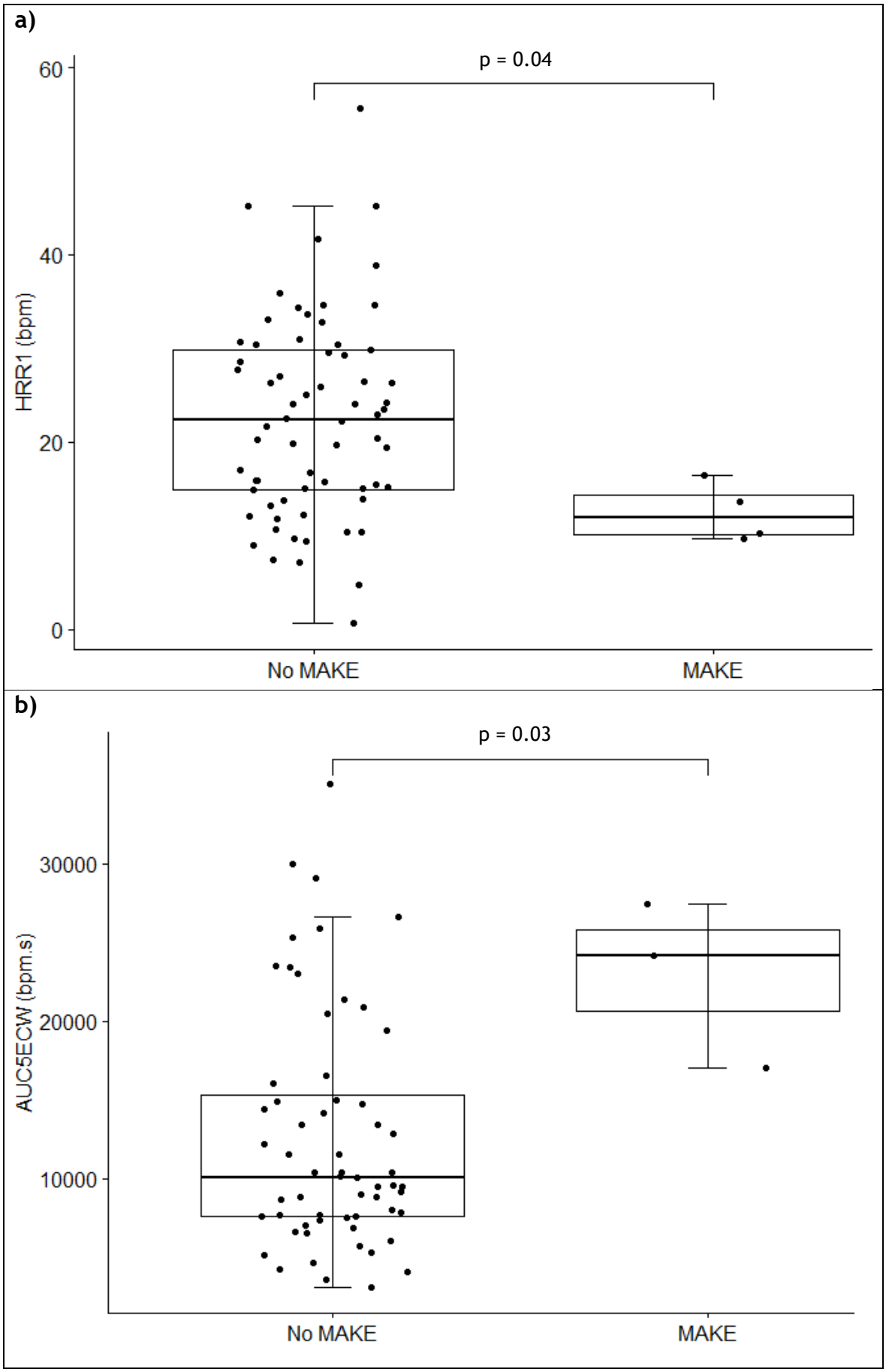


Figure 47 Difference in absolute heart rate recovery parameters between patients who did and did not develop a major adverse kidney event (MAKE) within thirty days of surgery. Wilcoxon rank-sum exact test. a) HRR_1, n = 70. b) AUC_5-ECW, n = 63.

7.2.5 Postoperative clinical outcomes

Two patients died within 30-days of their operation with no further deaths within 90 days. One patient had PMI and one did not. The patient who did not died of multiorgan failure secondary to an unexpected surgical complication. Due to the low number of patients, association between mortality and HRR parameters was not performed.

Three patients were readmitted to hospital within 30-days of their operation so association between readmission and HRR parameters was not investigated. None of the HRR parameters were associated with hospital length of stay (Table 55).

Table 55 Correlation between HRR parameters and length of hospital stay. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 70	-0.19	0.11
HRR_1-ECHR n = 70	-0.16	0.17
AUC_{30} n = 68	-0.08	0.50
AUC_{30}-ECHR n = 68	-0.06	0.64
AUC_5-ECW n = 63	0.22	0.09

All HRR parameters were significantly associated with postoperative intensive care admission (including level 2/3, planned and unplanned) except AUC_5-ECW although this was approaching significance (Table 56).

Table 56 Difference in HRR parameters between patients who did and did not require ICU admission within fourteen days of surgery. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	No ICU admission *Number of patients*	ICU admission *Number of patients*	p value
HRR_1 (bpm)	23.0 (15.1 – 30.3) *61*	13.6 (10.2 – 16.4) *9*	0.01
HRR_1-ECHR (bpm)	33.3 (22.3 – 44.6) *61*	20.6 (16.5 – 28.0) *9*	0.02
AUC_{30} (bpm.s)	949 (739 – 1075) *59*	744 (643 – 769) *9*	0.02
AUC_{30}-ECHR (bpm.s)	1413 (1114 – 1605) *59*	1087 (979 – 1251) *9*	0.02
AUC_5-ECW (bpm.s)	9535 (7454 – 16309) *55*	14548 (11753 – 18814) *8*	0.06

Figure 48 shows the boxplots for the difference in submaximal HRR_1 and submaximal AUC_{30} between patients admitted to ICU and those not admitted to ICU postoperatively. These results are discussed further in Section 7.2.7.2 (exploratory analyses).

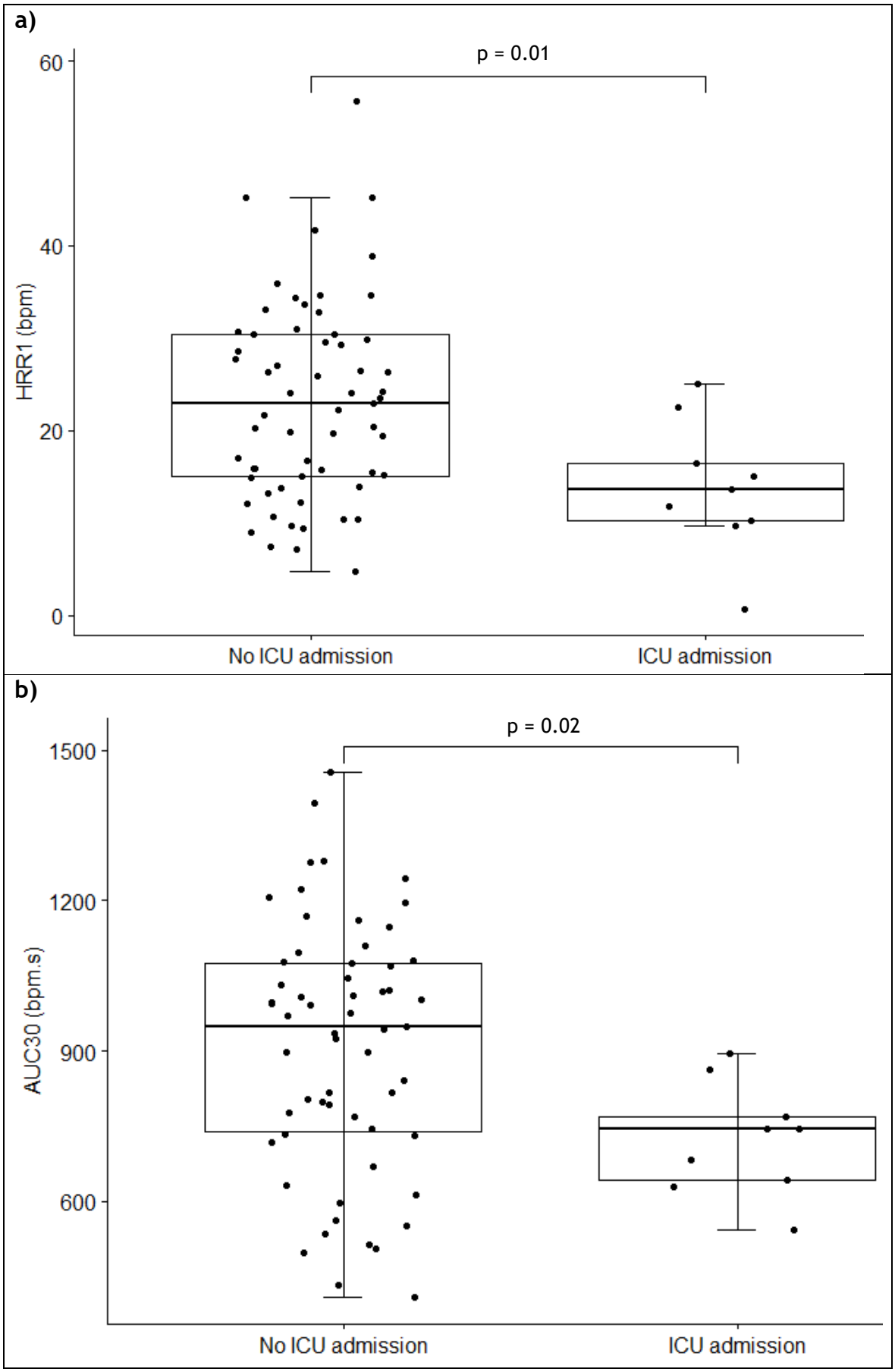


Figure 48 Difference in absolute heart rate recovery parameters between patients who did and did not require postoperative intensive care admission within fourteen days of surgery. Wilcoxon rank-sum exact test. a) HRR_1, n = 70. b) AUC_5-ECW, n = 63.

7.2.6 Patient-reported outcome measures

Median (IQR [range]) Quality of Recovery (QoR-15) on postoperative day two was 105 (86 – 116 [26 – 146], n=48). There was no association between any of the HRR parameters and postoperative quality of recovery (Table 57).

Table 57 Correlation between HRR parameters and quality of recovery-15 score at postoperative day two. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 48	0.19	0.20
HRR_1-ECHR n = 48	0.18	0.23
AUC_{30} n = 46	0.17	0.25
AUC_{30}-ECHR n = 46	0.21	0.17
AUC_5-ECW n = 45	0.06	0.69

Sixty-four patients were contacted after thirty days postoperatively to record days alive and out of hospital. Median (IQR [range]) $DaOH_{30}$ was 22 days (13 – 25 [0 – 29], n=64). Days alive and out of hospital at 30-days demonstrated no association with the HRR parameters (Table 58).

Table 58 Correlation between HRR parameters and number of days alive and out of hospital within 30-days of surgery. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 63	-0.03	0.83
HRR_1-ECHR n = 63	-0.01	0.93
AUC_{30} n = 63	-0.09	0.50
AUC_{30}-ECHR n = 63	-0.04	0.78
AUC_5-ECW n = 58	-0.05	0.71

7.2.7 Exploratory analyses

7.2.7.1 Change in postoperative creatinine

Major adverse kidney events demonstrated association with HRR_1 and AUC_5-ECW. However, there was no association demonstrated between any of the HRR parameters and development of AKI within seven days. The AKI data nonetheless displayed the expected pattern between AKI and no AKI groups; namely that the median HRR_1, HRR_1-ECHR, AUC_{30} and AUC_{30}-ECHR were larger in the patient group that did not develop AKI with AUC_5-ECW exhibiting the opposite pattern. Therefore, there is the potential that the study was underpowered to detect this association where it may exist. As part of the determination of diagnosis of AKI, the highest measured creatinine within seven days of surgery was recorded. An exploratory analysis of change in creatinine was performed to gain further insight into the potential face validity of the HRR parameters for postoperative renal function.

The highest postoperative creatinine within seven days of surgery was available for 68 patients with a median (IQR) of 82 (66 -105) μmol/L. The change in creatinine from preoperative level to the highest within seven days postoperatively demonstrated weak negative correlation with HRR_1 and HRR_1-ECHR. However, the AUC measures were not associated with change in creatinine (Table 59).

Table 59 Correlation between HRR parameters and change in creatinine from preoperative measurement to within seven days of surgery. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 65	-0.31	0.01
HRR_1-ECHR n = 65	-0.30	0.01
AUC_{30} n = 64	-0.20	0.12
AUC_{30}-ECHR n = 64	-0.16	0.22
AUC_5-ECW n = 59	0.14	0.28

Figure 49 shows the weak positive correlation between submaximal HRR_1 and highest change in creatinine from baseline within seven days of surgery. A

sensitivity analysis removing the two patients with the largest change in creatinine (79 µmol/L and 127 µmol/L) did not meaningfully change the correlation demonstrated between HRR_1 and change in creatinine (ρ = -0.27, p = 0.03).

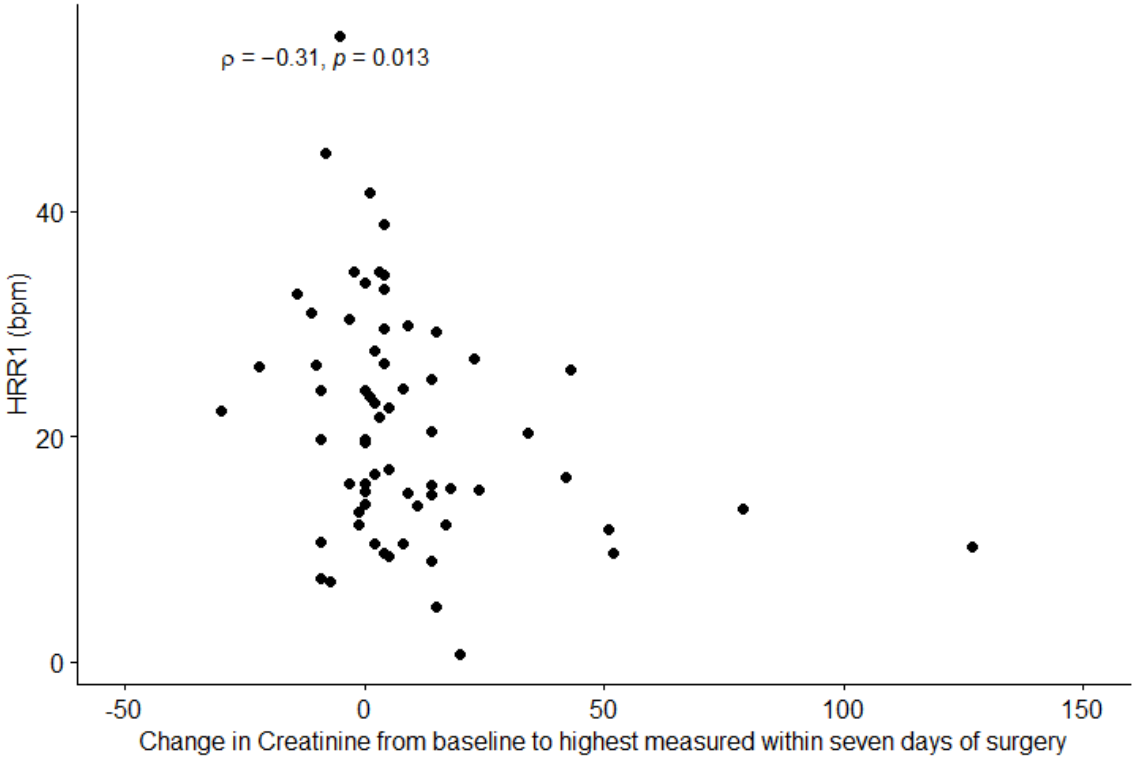


Figure 49 Correlation between HRR1 and change in creatinine between baseline and highest measured within seven days of surgery. Spearman's rank correlation. n = 70

7.2.7.2 Intensive care admission

Association was demonstrated between both HRR_1 and AUC_{30} parameters and intensive care admission. However, as detailed in Section 4.8.5, ICU admission was a broad criterion including both planned and unplanned admission, and both level two and three care. This association may be a demonstration of the face validity of the HRR parameters in that patients identified as high-risk are pre-emptively booked to ICU without necessarily requiring critical care interventions. Therefore, exploratory analysis investigating the more granular details of ICU admission was performed.

Nine patients were admitted to ICU within 14 days of their operation. Four were planned (i.e. after elective major vascular surgery), the rest were unplanned

admissions. All of the planned admissions required level two care; the five remaining unplanned admissions all required level three care. When only unplanned admissions were assessed, association between the HRR parameters and ICU admission was lost (Table 60).

Table 60 Difference in HRR parameters between patients who did and did not require unplanned ICU admission within fourteen days of surgery. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	Patients who did not require unplanned ICU admission *Number of patients*	Patients who did require unplanned ICU admission *Number of patients*	p value
HRR_1 (bpm)	21.7 (14.0 – 29.9) *65*	16.4 (13.6 – 22.6) *5*	0.33
HRR_1-ECHR (bpm)	30.8 (20.8 – 44.5) *65*	28.0 (20.6 – 35.5) *5*	0.44
AUC_{30} (bpm.s)	935 (724 – 1071) *63*	745 (744 – 862) *5*	0.17
AUC_{30}-ECHR (bpm.s)	1351 (1086 – 1595) *63*	1127 (1087 – 1271) *5*	0.20
AUC_5-ECW (bpm.s)	10144 (7547 – 16309) *59*	14624 (11443 – 18814) *4*	0.28

7.3 Discussion

The secondary outcomes measured encompassed postoperative complications, clinical outcome indicators (mortality, length of stay etc) and patient-reported outcome measures. Face validity was assessed by analysing the association between the five best-performing HRR parameters for PMI with the secondary outcomes. Association was demonstrated between most of the HRR parameters and ICU admission, and between both HRR_1 and AUC_5-ECW with MAKE at 30-days. There was no association between the HRR parameters and incidence of any postoperative complication, pulmonary complications or $DaOH_{30}$. None of the other outcomes demonstrated a significant relationship with the HRR parameters; however, did follow a similar pattern to the association with PMI

(i.e. higher median HRR_1 and AUC_{30}, lower median AUC_5-ECW in patients who did not develop the complication, or correlation in the expected direction). For example, the expected pattern of medians was demonstrated between patients who did and did not develop AKI within seven days of surgery, and further exploration showed significant correlation between the HRR_1 parameters and change in creatinine postoperatively. Further exploration of ICU admission as an outcome, however, demonstrated that the association demonstrated between HRR_1, HRR_1-ECHR, AUC_{30} and AUC_{30}-ECHR was lost when only *unplanned* ICU admissions were included in the analysis.

7.3.1 Incidence of postoperative complications

The overall incidence of postoperative complications was comparable to that in the literature investigating postoperative morbidity in similar patient populations within seven days of surgery[156,212-214]. The incidence of severe postoperative complications (as defined by Clavien-Dindo grade of III or above) was relatively low (3% (2/72)). In the METS study, the incidence of moderate-severe postoperative complications was 14% (194/1399)[38] and in a substudy of VISION, the incidence of severe postoperative complications was 11% (486/4335). Both of these studies recorded postoperative complications in similar patient populations to this study but up to 30-days after surgery which may explain the larger percentage of severe complications. The incidence of specific organ system complications is very variable within the literature, predominantly due to variation in the definitions used and timeframes measured. Specific organ system complications in this study and comparison with the literature are discussed below.

7.3.2 Face validity of the HRR parameters

There was no association between any of the HRR parameters and development of any postoperative complication within seven days of surgery, and therefore face validity for poor postoperative outcome was not demonstrated. This is in contrast to Ackland et al., where impaired maximal HRR_1 was associated with all-cause morbidity, as measured by the PostOperative Morbidity Survey, within five days of surgery (OR 1.29 (1.06-1.58))[156]. This difference may be explained by the imbalance in postoperative outcomes in the current study with few

cardiovascular outcomes and a relatively large number of pulmonary complications, as discussed below.

7.3.2.1 Cardiovascular complications

Aside from PMI, only 6% of patients developed cardiovascular complications as defined by StEP-COMPAC[134] within seven days of surgery, with new-onset atrial fibrillation being the only complication. In the paper by Ackland et al., assessing the association between maximal HRR_1 and postoperative morbidity in a similar patient population, the incidence of CVS complications was much higher (67%). However, postoperative hypotension was included in their definition of postoperative CVS complications which may have skewed the incidence[156]. Conversely, a validation study of the SORT using POMS-defined morbidity found an incidence of CVS complications within five days of surgery of 3.5%[214]. There was no association between any of the HRR parameters and new-onset AF within seven days in the current study. However, patients who did not develop new-onset AF did have larger median HRR_1 and AUC_{30} parameters and smaller median AUC_5-ECW, with this effect more pronounced in the AUC measures. Only two patients developed MACE and so association between HRR parameters and MACE could not be assessed. It is surprising that the HRR parameters chosen because of their association with PMI did not demonstrate association with another postoperative CVS complications. Postoperative AF has a multitude of potential causes including cardiac autonomic dysfunction and myocardial ischaemia but also extra-cardiac causes such as electrolyte disturbance and infection[215]. It is also particularly common after thoracic surgery, with perioperative right ventricular dysfunction a potential cause[148]. Of the patients who developed AF, 50% (2/4) underwent thoracic surgery so the incidence of AF in this cohort may be related to the surgery as well as patient cardiovascular risk.

7.3.2.2 Pulmonary and infective complications

There was no association between the HRR parameters and development of pulmonary or infective complications. The incidence of pulmonary complications was relatively high at 42%. The incidence of pulmonary complications in the study by Ackland et al. investigating maximal HRR_1 and postoperative morbidity was 22%[156]. The relatively high incidence in the current study may reflect the

large thoracic cohort, particularly as atelectasis is included within the StEP-COMPAC definition of pulmonary complications[184]. Impaired HRR_1 has been associated with postoperative pulmonary complications in the literature, both when measured after maximal exercise (RR 1.31 (1.05 – 1.62))[156] and after submaximal exercise (OR 3.43 (1.40 – 8.42)) although this was for a combination of cardiopulmonary complications in patients undergoing lung resection[158].

The incidence of postoperative infective complications in this study (VERVE) seems comparable with that reported in the literature. Within similar populations, and with a similar definition, the incidence of postoperative infection was 20% and 11% in papers described above by Ackland et al.[156] and Wong et al.[214], compared to 26% in this patient cohort. Akin to pulmonary complications, there was no association demonstrated between the HRR parameters and postoperative infection within seven days. However, Ackland et al. did demonstrate association between impaired HRR_1 and postoperative infection within five days of surgery (RR 1.38 (1.10 – 1.72)).

It may be that submaximal HRR measures which best predict PMI reflect cardiac vagal tone rather than the wider PNS and cardiorespiratory fitness. Therefore, face validity for organ system complications that are not directly connected to cardiovascular complications such as pulmonary or immunological systems is not demonstrated. However, association between impaired maximal HRR_1 and both pulmonary and infective postoperative complications was demonstrated in a larger study investigating impaired maximal HRR_1 and postoperative morbidity within five days[156]. Submaximal HRR parameters may not exhibit a strong enough signal to identify those at risk of extra-cardiac complications or it could also be that the incidence of these complications was relatively low, in a small cohort and so the study was underpowered to find associations where they exist.

7.3.2.3 Renal complications

The only postoperative complications which demonstrated association between the HRR parameters were renal complications, both change in creatinine within seven days of surgery and MAKE within 30-days of surgery. However, none of the HRR parameters demonstrated an association with development of AKI within seven days of surgery, although the expected pattern between medians was

indicated for each parameter. The lack of association may have been due to low numbers (incidence of AKI was 10%), particularly as urine output was frequently not recorded. It is reassuring that the association found at seven days between four of the HRR parameters for highest change in creatinine level is maintained for HRR_1 and AUC_5-ECW with MAKE at day 30 implying that this is a robust finding. Multiple comparisons have been made and so the potential for type I error is high but the combination of association with different measures of renal function make this unlikely. The five best performing HRR parameters were chosen on their ability to predict PMI. The development of postoperative acute kidney injury may have similar underlying pathological mechanisms to PMI (i.e. hypotension, inflammation and autonomic dysfunction)[216] and similarly to PMI, AKI can be a sign of recoverable renal stress rather than renal cell damage. Therefore, it is conceivable that the same HRR parameters that are predictive for PMI are associated with AKI. Intraoperative hypotension demonstrates a dose-dependent association with PMI and AKI, with increasing rates of both as the length of intraoperative time with MAP <60 mmHg increases[217]. In this study, intraoperative hypotension was similar between groups, but postoperative hypotension appeared more common in the PMI group (Table 21). Ackland et al. found association between maximal HRR_1 and renal complications (OR 1.91(1.30-2.79)) within five days of surgery in 1941 patients[156]. It is the Author's opinion that there is enough of a signal with the change in postoperative creatinine; the association of both submaximal HRR_1 and AUC_5-ECW and MAKE; the trend of medians for all HRR parameters and AKI; and the pathophysiological similarity between development of PMI and AKI, that the lack of association is predominantly due to a relatively low rate of AKI and small study population.

7.3.2.4 Clinical outcome indicators

The association between the HRR parameters and 30-day mortality and hospital readmission could not be assessed due to very low numbers. There was no association between any of the HRR parameters and hospital length of stay. Median (IQR) length of stay was 5 (3 – 9) days. Only nine patients (13%) had a hospital length of stay over 14 days. Ackland et al. demonstrated that in 1941 patients undergoing noncardiac surgery, a maximal HRR_1 >12 bpm was associated with reduced hospital length of stay (RR 0.80 (0.72-0.90))[156]. It may be that submaximal HRR parameters are not sensitive enough to be associated with

hospital length of stay, or that the combination of low numbers of patients and skew towards shorter hospital admissions indicates that the study did not have power to demonstrate this association.

Postoperative intensive care admission was significantly associated with HRR_1, HRR1-ECHR, AUC_{30} and AUC_{30}-ECHR. The loss of association when only unplanned admissions (also all required level three care) are counted may be indicative of the face validity of the HRR parameters, where it would be expected that patients identified preoperatively as high-risk and therefore electively admitted to ICU postoperatively have impaired HRR. The four patients who were electively admitted to ICU were all vascular patients identified as high-risk at preoperative assessment. The author is not aware of any literature exploring the direct association of HRR and postoperative critical care admission.

7.3.2.5 Patient-reported outcome measures

This is the first study to examine preoperative HRR parameters and patient-reported outcome measures. Neither postoperative QoR-15 score or $DaOH_{30}$ were associated with any of the five best-performing submaximal HRR parameters. Forty-eight out of 72 patients completed the QoR15. The spread in QoR-15 was wide (IQR 86 – 116) indicating conceivable variability within the data to demonstrate a difference between HRR parameters where it exists. All submaximal HRR parameters except AUC_5-ECW showed weak positive correlation with QoR-15 but this was not significant. It was hypothesised that quality of recovery and the HRR parameters would demonstrate association as quality of recovery is related to the surgical severity, length of surgery and co-morbidity[180]; all of which were higher in the PMI group. The relatively low percentage of patients completing the QoR-15 may reflect that some patients were discharged before the end of postoperative day two and that patients may not have wanted to complete a questionnaire so soon after their operation.

Data for $DaOH_{30}$ was available for up to 64 patients. Median (IQR) $DaOH_{30}$ was 22 (13 – 25) days. The majority of patients had a $DaOH_{30}$ of over 20 days so there may not have been enough variability within the data to reveal any potential association between the submaximal HRR parameters and $DaOH_{30}$. Days alive and out of hospital is also a patient-reported outcome measure which is related to a

patient's postoperative clinical course but also their social situation. For example, a patient who lives with supportive family or friends may be discharged earlier than someone in the same clinical situation but who lives alone. Therefore, although an important measure for patients, $DaOH_{30}$ may be too broad a measure to demonstrate association with a specific measure of cardiac vagal tone.

7.4 Conclusion

Face validity was not demonstrated by the HRR parameters for most of the postoperative complications. However, HRR_1 and HRR_1-ECHR did display face validity for renal complications demonstrating association with change in creatinine and association with MAKE at 30-days. Although not reaching significance, the HRR parameters did show the expected pattern in patients who did, and did not, develop AKI, supporting this result.

Overall, the assessment of face validity for the five-best performing HRR parameters was limited by a low incidence of complications, potential type II error due to a small sample size and multiple comparisons increasing the risk of type I error where positive results did occur. However, submaximal HRR_1 particularly did demonstrate face validity for postoperative renal complications further reinforcing its position as the best parameter for further investigation.

Chapter 8 Heart rate recovery and preoperative risk scores (construct validity)

This Chapter explores the construct validity of the five best-performing submaximal HRR parameters elucidated in Chapter 6 (Heart rate recovery and postoperative myocardial injury (predictive validity)). Construct validity is the comparison of the performance of a new measure against the measures currently in use (Section 3.2.4). Within the perioperative maximal HRR literature, HRR_1 is associated with both RCRI and NT-ProBNP, both of which are independent predictors of postoperative cardiovascular complications, conferring construct validity[150]. This investigation will investigate the association of the five best-performing submaximal HRR parameters in our cohort with perioperative risk measures currently in use. These incorporate biomarkers (NT-ProBNP), perioperative risk tools (Surgical Outcome Risk Tool (SORT), POSSUM, ACS-NSQIP), and functional status assessments (Duke Activity Status Index (DASI), Section 1.2). Construct validity will be determined if association is demonstrated between the HRR parameters and these measures.

Effective preoperative risk estimation is complex and involves consideration of surgical factors and patient factors including comorbidity, functional capacity and biomarker measurement. The constructs used in this investigation (NT-ProBNP, SORT, POSSUM, ACS-NSQIP and DASI) reflect the different risk stratification tools used internationally. There is not a "gold-standard" perioperative risk tool with which to compare submaximal HRR. Therefore, by comparing submaximal HRR with constructs recommended in international guidelines and incorporating functional capacity; risk tools incorporating surgical and patient factors; and biomarkers, this investigation aims to assess the place of submaximal HRR in this gamut of perioperative risk prediction tools.

8.1 Specific Methods

Preoperative NT-ProBNP collection and handling and preoperative risk score data collection are described in Chapter 4 (Generic methods). For this investigation, the patients did not require to undergo their surgery or have postoperative data collected, increasing the sample size available for this investigation from 64 in the Primary outcome group to 83 in the Step test group (Figure 29).

8.1.1 Specific statistical handling

Comparisons were made using t-tests or Wilcoxon rank sum test where appropriate. Correlation was assessed using Spearman's rank correlation for continuous data and Kendall's rank correlation for ordinal data. Assessment of the degree of linear association was made via visual inspection of the plots and indicative cut-offs in Table 45 for Spearman's correlation and Table 61 for Kendall's correlation[210,218]:

Table 61 Interpretation of Kendall's correlation coefficient as per Gilpin et al[218].

Kendall's correlation coefficient (τ)	Interpretation
0.00 – 0.06	Negligible correlation
0.07 – 0.26	Weak correlation
0.27 – 0.49	Moderate correlation
0.50 – 0.71	Strong correlation
0.72 – 1.00	Very strong correlation

No adjustments were made for multiple comparisons due to the exploratory nature of the investigation.

8.2 Results

Eighty-three patients underwent the step test and had preoperative data, including NT-ProBNP and data for risk score calculation collected. The ECG trace was unreadable for two patients meaning no HRR parameters could be measured, leaving 81 patients for analysis of construct validity.

8.2.1 Patient demographics

Baseline demographic data for these 81 patients are shown in Table 62.

Table 62 Construct validity participant demographics, comorbidities, preoperative blood results and medications. n=81 unless stated otherwise. Values are number (percentage), mean±SD and median (IQR) [range]. BMI: body mass index; ASA: American Society of Anaesthesiologists Physical Status; COPD: chronic obstructive pulmonary disease; hsTnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme.

Characteristic	Descriptive Statistics
Age (years)	66.9±8.2
Female sex	40 (49%)
BMI (kg/m^2)	27.4 (24.1 – 30.9) [17.4 – 47.5]
Ethnicity: White British	 81 (100%)

Smoking status: Current smoker Ex-smoker Never smoked	 16 (20%) 35 (43%) 30 (37%)
Clinical Frailty Score: 1 2 3 4 5 >5	 4 (5%) 22 (27%) 29 (36%) 19 (23%) 7 (9%) 0
ASA: 1 2 3 4 *Missing data*	 0 25 (31%) 25 (31%) 3 (4%) *28*
Duke Activity Status Index (points)	39.0 (24.2 – 50.7) [10.7 – 58.2]
Comorbidities	
None	5 (6%)
History of cancer	32 (40%)
Asthma	5 (6%)
COPD	16 (20%)
Arterial hypertension	35 (43%)
IHD	15 (19%)
Cardiac failure	1 (1%)
AF	3 (4%)
PVD	9 (11%)
Stroke	2 (2%)
T1DM	1 (1%)
T2DM	11 (14%)
Previous covid infection Long covid	32 (40%) 1 (1%)
Preoperative blood results	
NT-ProBNP (pg/ml) *Missing data*	91 (46 - 203) [12 - 13751] *1*
hsTnT (ng/L) *Missing data*	7 (5 - 12) [3 - 130] *3*
Haemoglobin (g/L) *Missing data*	13.9 (12.9 – 15.0) [8.9 – 18.1] *2*
Creatinine (µmol/L) *Missing data*	77 (65 – 90) [45 – 537] *1*
Preoperative renal function eGFR >59 (ml/min) eGFR 30-59 (ml/min) eGFR <30 (ml/min) *Missing data*	 69 (85%) 10 (12%) 1 (1%) 1 (1%)
Medications	
No regular medication	7 (9%)
Beta-blocker	16 (20%)
Ca channel blocker	23 (28%)
ACE-inhibitor	18 (22%)
Diuretics	9 (11%)
Antiarrhythmic	0
Beta-agonist	12 (15%)
Steroids:	

Inhaled	9 (11%)
Oral	1 (1%)

8.2.2 Preoperative risk scores

Preoperative risk scores for these 81 patients are described in Table 63.

Table 63 Preoperative risk scores of construct validity group. Values are number (percentage) and median (IQR) [range] n=81 unless stated otherwise. P/V-POSSUM: Portsmouth/Vascular-Physiologic and Operative Severity Score for the study of Mortality and Morbidity; ACS NSQIP SRC: American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; SORT: Surgical Outcome Risk Tool; RCRI: Revised Cardiac Risk Index.

Preoperative risk score	Descriptive Statistics
POSSUM morbidity (%)	28.9 (19.0 – 41.6) [8.8 – 81.5]
POSSUM mortality (%)	1.5 (0.8 – 2.6) [0.4 – 11.6]
ACS-NSQIP SRC any complication risk (%)	9.4 (6.2 – 17.0) [2.2 – 39.3]
ACS-NSQIP SRC length of hospital stay (days) *Missing data*	3.5 (2.5 – 5.6) [0.5 – 8.0] *1*
SORT score (%)	0.79 (0.28 – 1.65) [0.06 – 4.81]
RCRI: Class I 3.9% Class II 6.0% Class III 10.1% Class IV 15.0%	 7 (9%) 56 (69%) 14 (17%) 4 (5%)

As discussed in more detail in Section 5.6.2, the preoperative risk scores demonstrate that the predicted surgical risk met with the inclusion criteria of intermediate/high-risk surgery. Cardiovascular comorbidity and functional capacity assessment indicated that patients in this investigation were more comorbid and less fit than those in the METS study[38].

8.2.3 Association of constructs with HRR parameters

8.2.3.1 Preoperative NT-ProBNP

Histogram of the preoperative NT-ProBNP data revealed two significant outliers (13751 pg/ml and 6755 pg/ml) (Figure 50). One patient had chronic renal disease and one had heart failure; neither underwent their operation. For the purposes of the construct validity investigation, these outliers were removed from the analysis. One NT-proBNP sample was also not processed. Therefore, the total number of patients for whom HRR_1 data was available was 78. A further two

patients did not have AUC_{30} data available and a further five did not have AUC_5-ECW data available hence the variable numbers described in the results below.

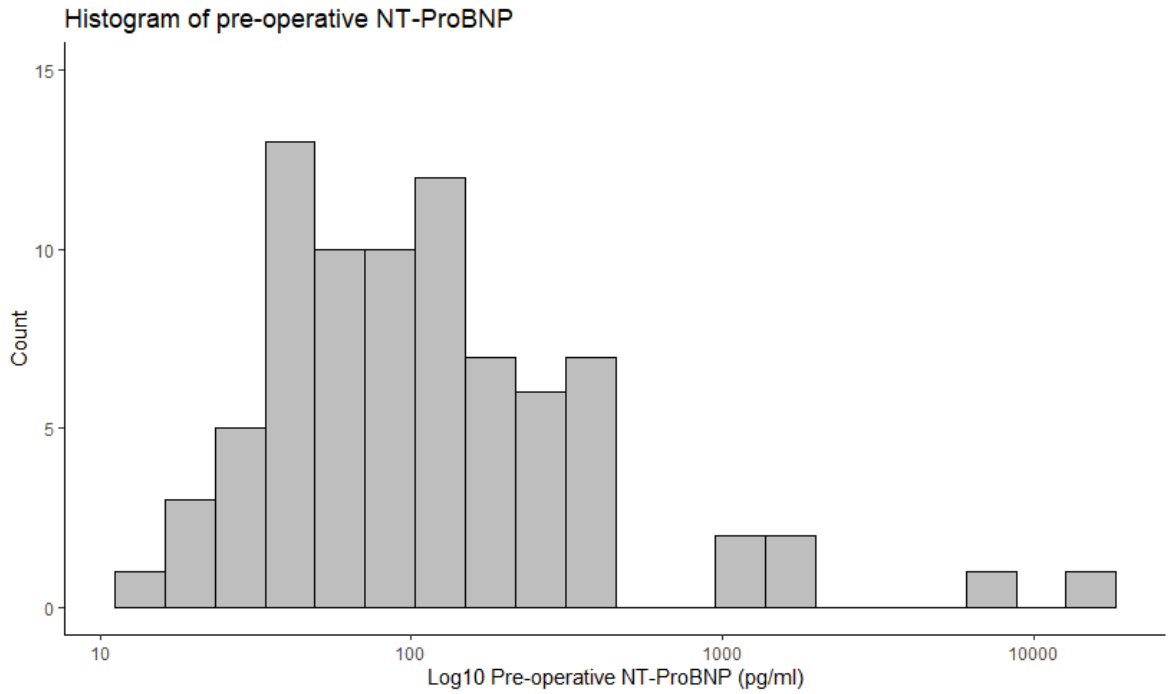


Figure 50 Histogram of preoperative NT-ProBNP with log_{10} transformation (n = 81).

Spearman's rank correlation of preoperative NT-ProBNP and the five best-performing HRR parameters is shown in Table 62.

Table 64 Correlation between HRR parameters and preoperative NT-ProBNP. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 78	-0.14	0.21
HRR_1-ECHR n = 78	-0.12	0.29
AUC_{30} n = 76	0.14	0.23
AUC_{30}-ECHR n = 76	0.16	0.16
AUC_5-ECW n = 71	0.36	<0.01

The only submaximal HRR parameter to demonstrate statistically significant weak positive correlation was AUC_5-ECW (Figure 51).

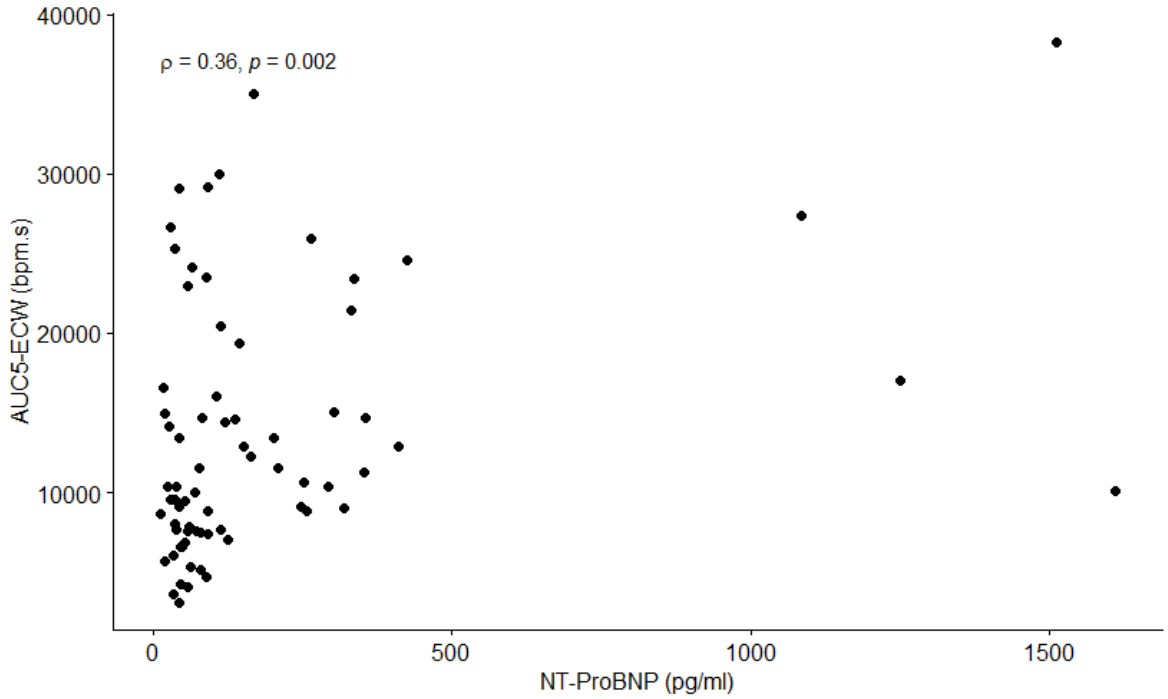


Figure 51 Correlation of preoperative NT-ProBNP with AUC_5-ECW (n = 71). Spearman's rank correlation

NT-ProBNP was dichotomised into low and high-risk via the threshold of 300 pg/ml as per current Canadian guidelines[42] (Section 1.2.8). Twelve patients (15%) were categorised as high-risk using this measure. The difference in the submaximal HRR parameters between low and high-risk patients as per preoperative NT-ProBNP is shown in Table 65.

Table 65 Difference in HRR parameters between patients identified as high-risk (>300 pg/ml) and low-risk (≤ 300 pg/ml) by preoperative NT-ProBNP. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	Preoperative NT-ProBNP ≤300pg/ml *Number of patients*	Preoperative NT-ProBNP >300pg/ml *Number of patients*	p value
HRR_1 (bpm)	22.4 (15.0 – 29.5) *66*	18.1 (10.1 – 34.5) *12*	0.79
HRR_1-ECHR (bpm)	31.6 (22.2 – 42.3) *66*	27.6 (16.0 – 53.0) *12*	0.82
AUC_{30} (bpm.s)	967 (754 – 1132) *64*	1111 (992 – 1294) *12*	0.06
AUC_{30}-ECHR (bpm.s)	1419 (1153 – 1694) *64*	1681 (1517 – 1746) *12*	0.05
AUC_5-ECW (bpm.s)	10033 (7547 – 14812) *59*	16022 (12486 – 23732) *12*	0.009

The only HRR parameter which displayed a significant difference between low and high NT-ProBNP was AUC_5-ECW, with high-risk patients demonstrating a higher median AUC_5-ECW, as expected (Figure 52).

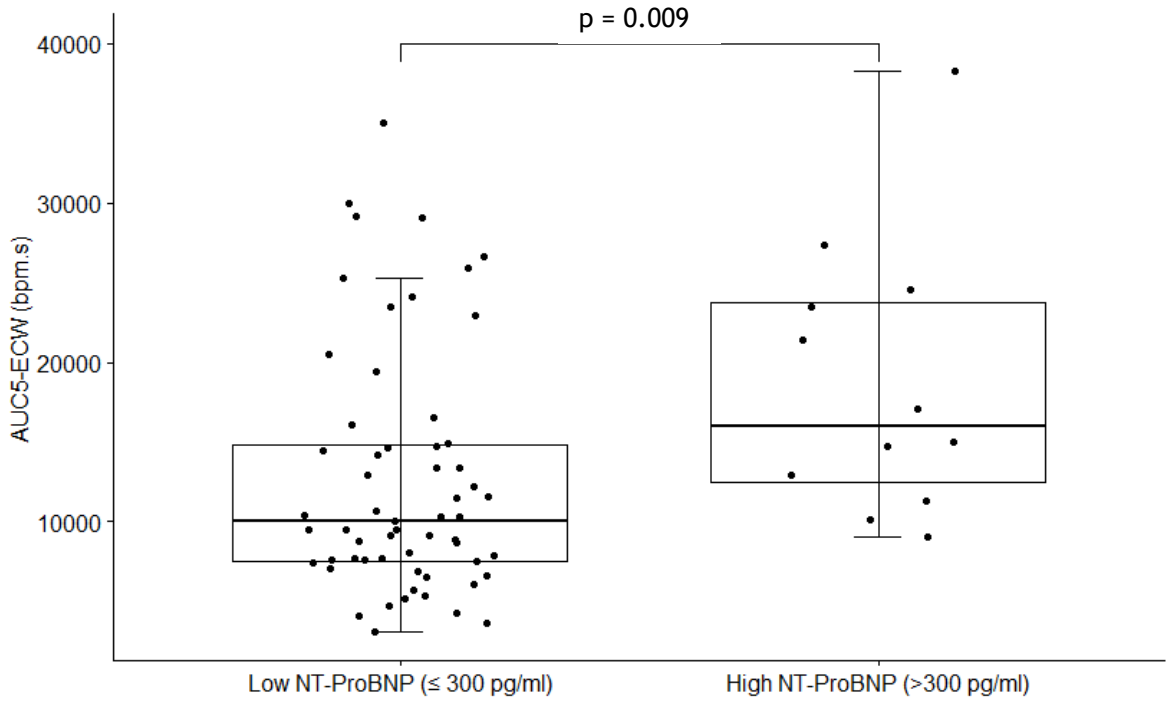


Figure 52 Difference in AUC_5-ECW between patients identified as low-risk and high-risk via preoperative NT-ProBNP. Wilcoxon rank-sum exact test. n=73

8.2.3.2 SORT

Correlation of SORT-predicted 30-day mortality (%) and the five best-performing submaximal HRR parameters is shown in Table 66.

Table 66 Correlation between HRR parameters and Surgical Outcome Risk Tool predicted 30-day mortality. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 81	-0.32	0.003
HRR_1-ECHR n = 81	-0.36	0.001
AUC_{30} n = 79	-0.14	0.21
AUC_{30}-ECHR n = 79	-0.13	0.23
AUC_5-ECW n = 74	0.18	0.13

Both submaximal HRR_1 and HRR_1-ECHR demonstrated weak to moderate negative correlation with SORT-predicted 30-day mortality (Figure 53).

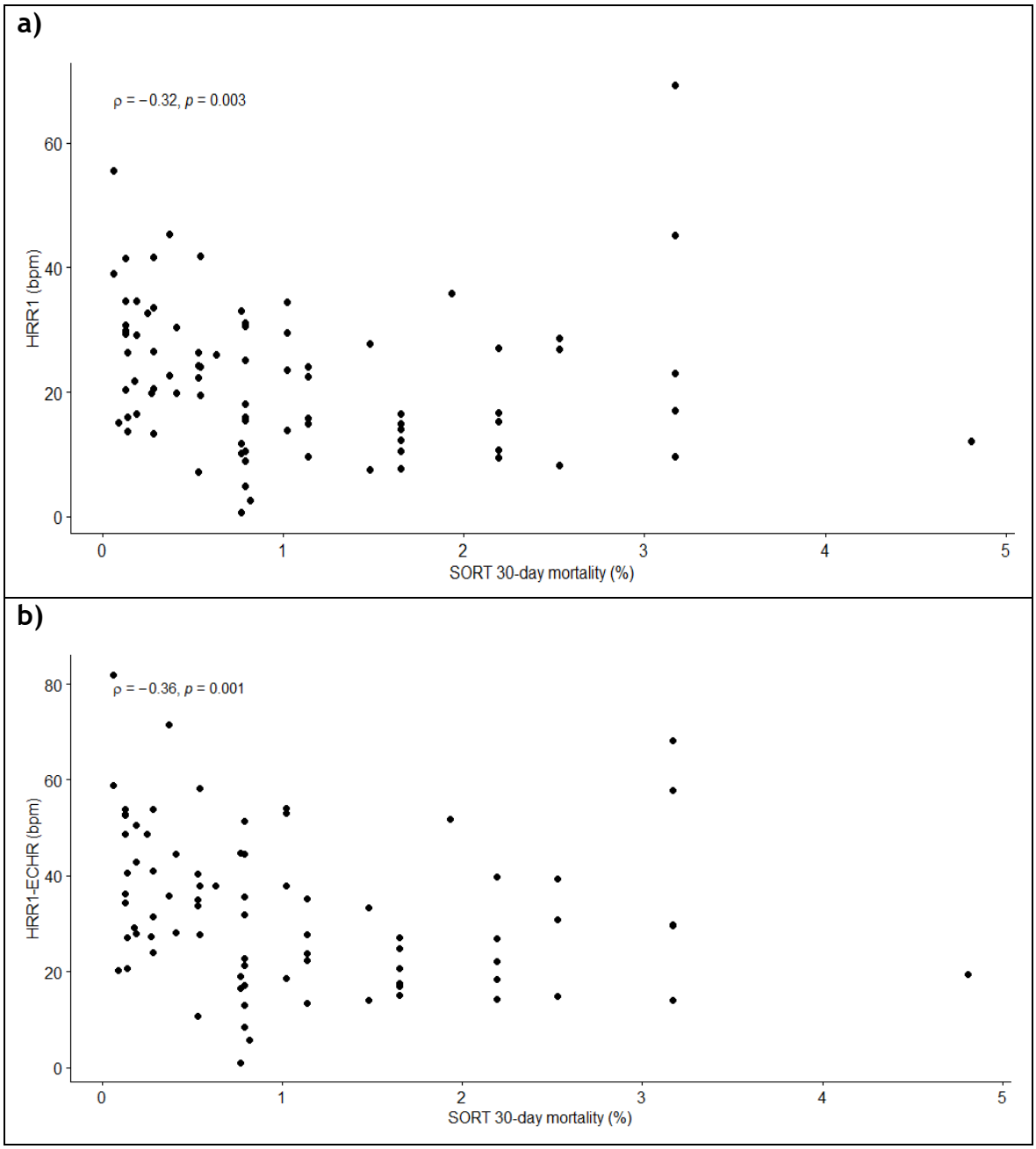


Figure 53 Correlation between submaximal HRR_1 parameters and predicted 30-day mortality (%) calculated by the Surgical Outcome Risk Tool (SORT). n = 81. Spearman's correlation. a) HRR_1. b) HRR_1-ECHR.

8.2.3.3 ACS NSQIP Surgical Risk Calculator

The correlation of the ACS NSQIP Surgical Risk Calculator for any postoperative complication (percentage risk) is shown in Table 67.

Table 67 Correlation between HRR parameters and ACS NSQIP Surgical Risk Calculator any postoperative complication risk (%). Spearman's rank correlation.

HRR parameter	Spearman's rho	p-value
HRR_1 n = 81	-0.39	<0.001
HRR_1-ECHR n = 81	-0.40	<0.001
AUC_{30} n = 79	-0.12	0.30
AUC_{30}-ECHR n = 79	-0.08	0.46
AUC_5-ECW n = 74	0.22	0.06

The only HRR parameters to demonstrate association with the ACS NSQIP Surgical Risk Calculator risk of any postoperative complications were HRR_1 and HRR_1-ECHR, both displaying weak to moderate negative correlation, as expected (Figure 54).

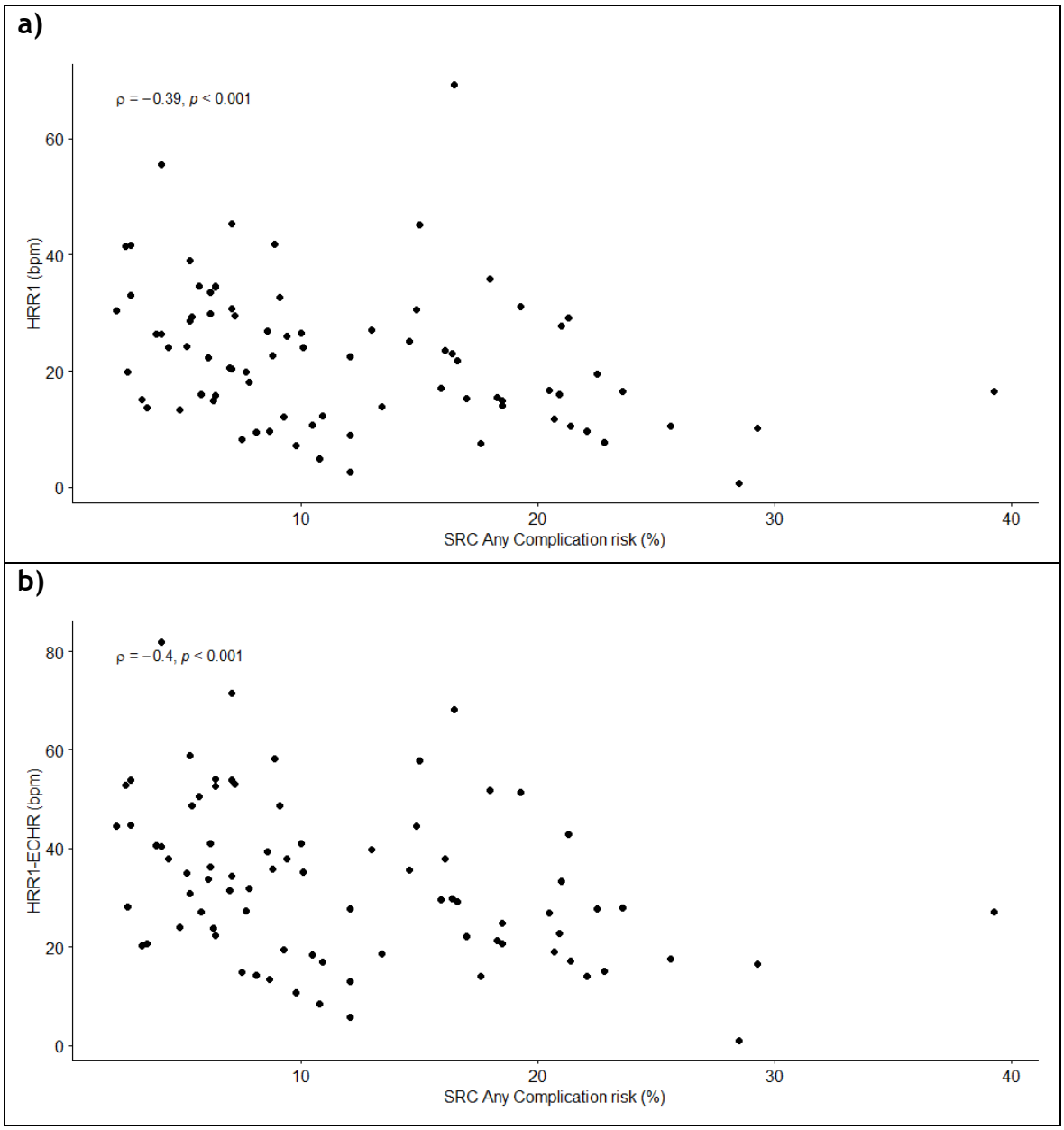


Figure 54 Correlation between submaximal HRR_1 parameters and any postoperative complication risk (%) calculated by the ACS NS-QIP Surgical Risk Calculator (SRC). n = 81. Spearman's correlation. a) HRR_1. b) HRR_1-ECHR.

8.2.3.4 ACS NSQIP Surgical Risk Calculator Length of stay

The correlation between ACS NSQIP estimated length of hospital stay and the five best-performing HRR parameters are detailed in Table 68. One patient was missing length of hospital stay data.

Table 68 Correlation between HRR parameters and ACS NSQIP Surgical Risk Calculator length of hospital stay(days). Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 80	-0.26	0.02
HRR_1-ECHR n = 80	-0.026	0.02
AUC_{30} n = 78	-0.042	0.72
AUC_{30}-ECHR n = 78	-0.008	0.95
AUC_5-ECW n = 73	0.18	0.14

The only HRR parameters to demonstrate association with estimated length of hospital stay were HRR_1 and HRR_1-ECHR, both of which exhibited weak negative correlation (Figure 55).

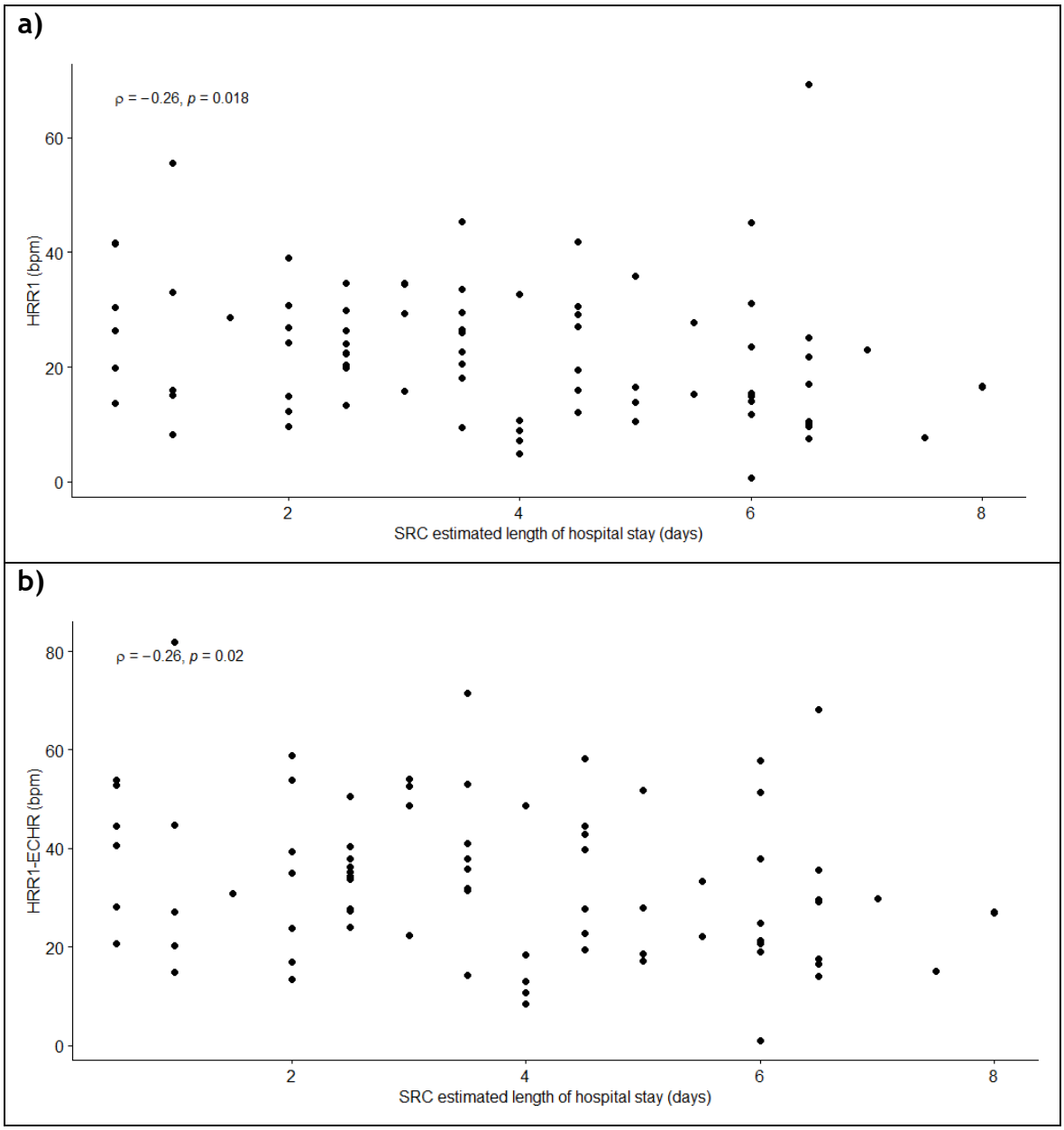


Figure 55 Correlation between submaximal HRR_1 parameters and length of hospital stay (days) calculated by the ACS NS-QIP Surgical Risk Calculator (SRC). n = 80. Spearman's correlation. a) HRR_1. b) HRR_1-ECHR.

8.2.3.5 Duke Activity Status Index

The correlation between DASI score and the five best-performing HRR parameters are detailed in Table 69.

Table 69 Correlation between HRR parameters and Duke Activity Status Index score.
Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 81	0.32	0.004
HRR_1-ECHR n = 81	0.34	0.002
AUC_{30} n = 79	0.10	0.39
AUC_{30}-ECHR n = 79	0.07	0.54
AUC_5-ECW n = 74	-0.11	0.35

Only HRR_1 and HRR_1-ECHR demonstrated correlation with DASI score, both demonstrating fair positive correlation (Figure 56).

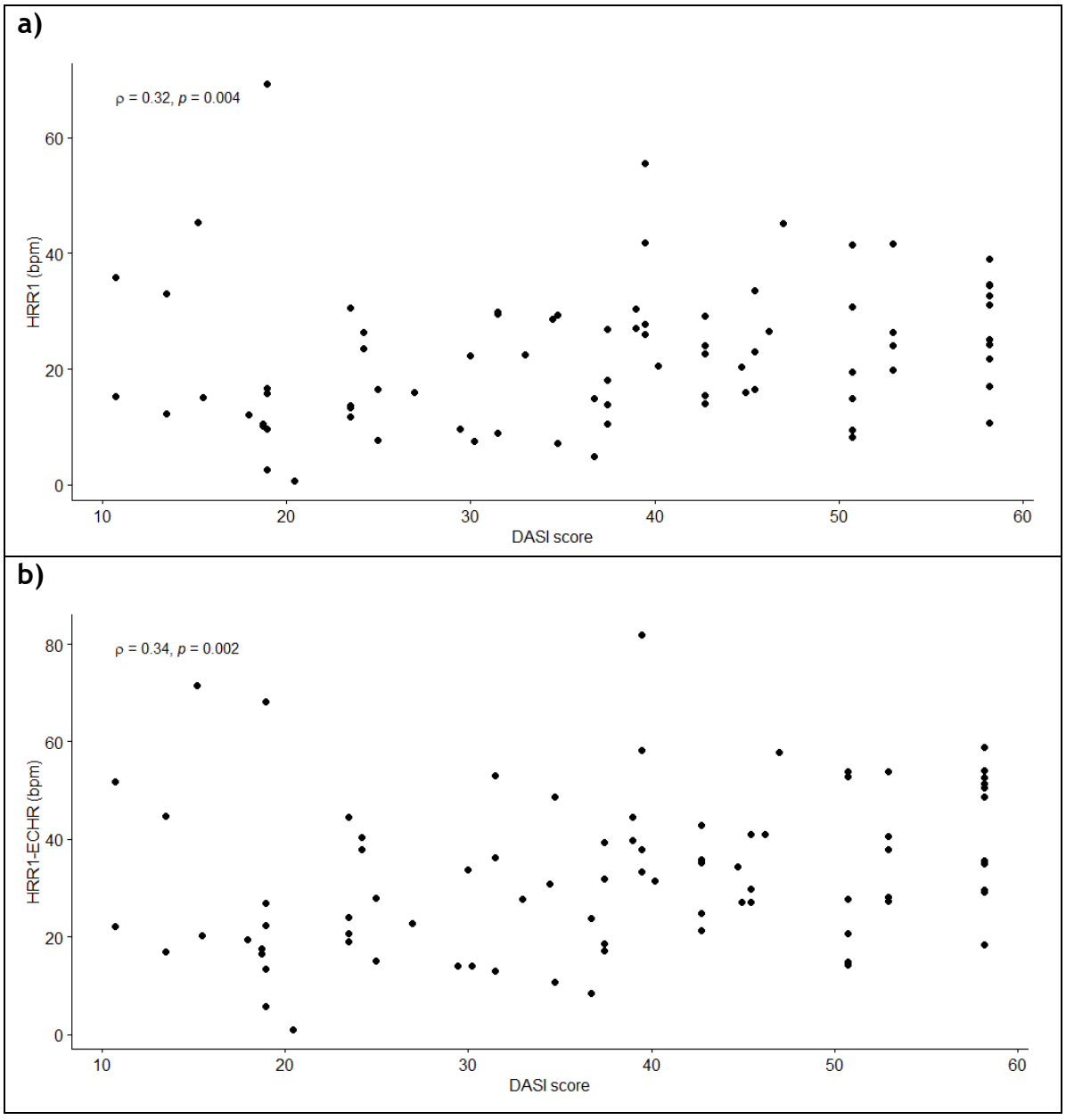


Figure 56 Correlation between submaximal HRR_1 parameters and Duke Activity Status Index. n = 81. Spearman's correlation. a) HRR_1. b) HRR_1-ECHR.

DASI score was dichotomised into high and low-risk via the cut-off of 34 described by Wijeysundera et al, with a DASI of ≤34 associated with worse postoperative morbidity.[39] Thirty-one patients were identified as high-risk by DASI score (≤34). The difference in submaximal HRR parameters between patients with high and low DASI scores is shown in Table 70.

Table 70 Difference in HRR parameters between patients identified as high-risk (≤34) and low-risk (>34) by Duke Activity Status Index. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	DASI score ≤34 *Number of patients*	DASI score >34 *Number of patients*	p value
HRR_1 (bpm)	15.2 (10.3 – 24.9) *31*	24.2 (16.6 – 30.6) *50*	0.009
HRR_1-ECHR (bpm)	22.3 (16.8 – 37.0) *31*	35.1 (27.2 – 47.6) *50*	0.007
AUC_{30} (bpm.s)	962 (716 – 1105) *31*	993 (812 – 1172) *48*	0.37
AUC_{30}-ECHR (bpm.s)	1379 (1137 – 1656) *31*	1459 (1264 – 1750) *48*	0.38
AUC_5-ECW (bpm.s)	12883 (7715 – 21392) *29*	10033 (7654 – 15009) *45*	0.28

Only HRR_1 and HRR_1-ECHR demonstrated difference when split between patients deemed high and low-risk by DASI score, in the expected direction, with patients with a worse DASI score having a smaller HRR (Figure 57).

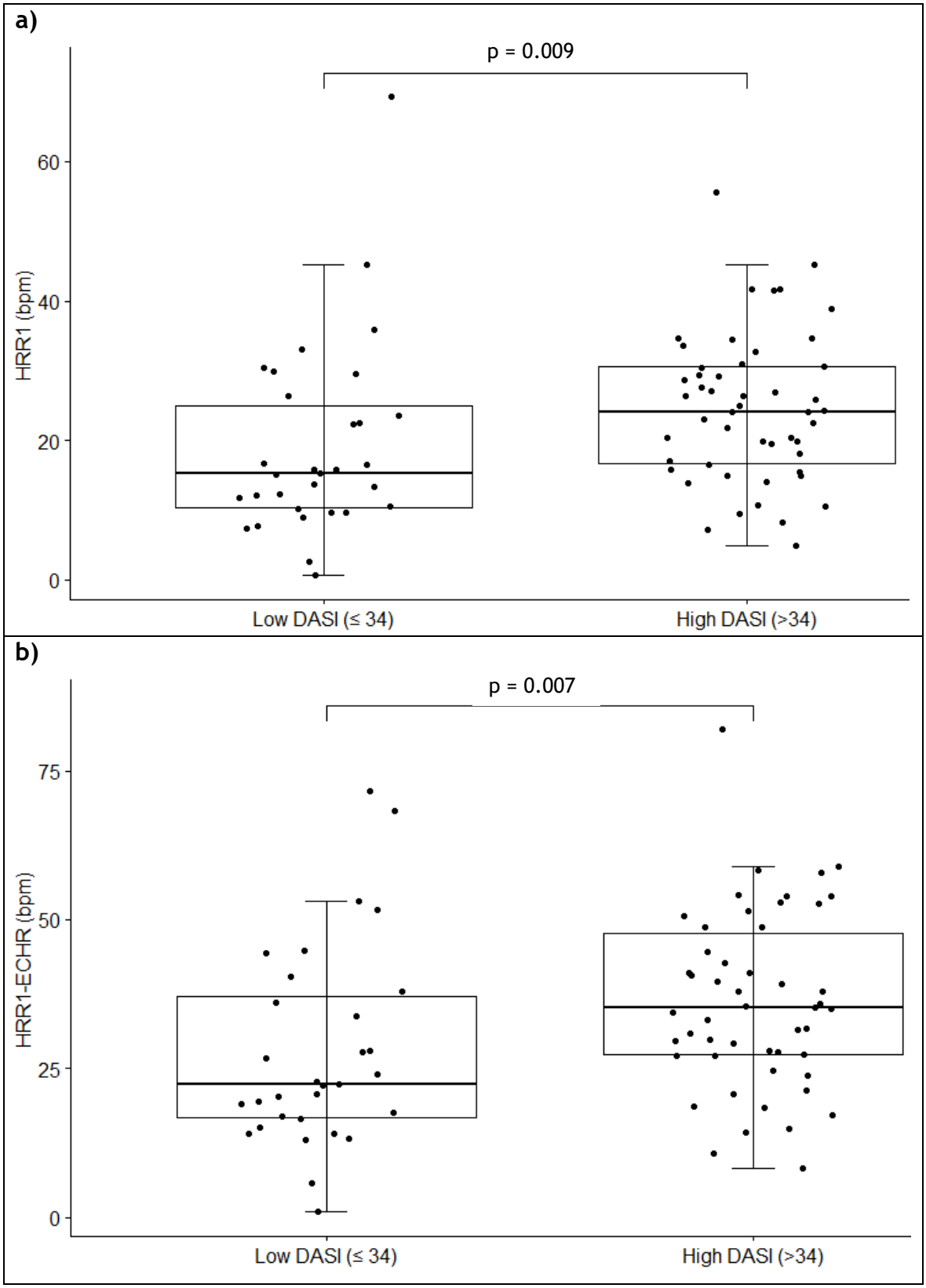


Figure 57 Difference in submaximal HRR_1 between patients identified as low-risk (>34) and high-risk (≤34) via Duke Activity Status Index. Wilcoxon rank-sum exact test. n=81. a) HRR_1. b) HRR_1-ECHR

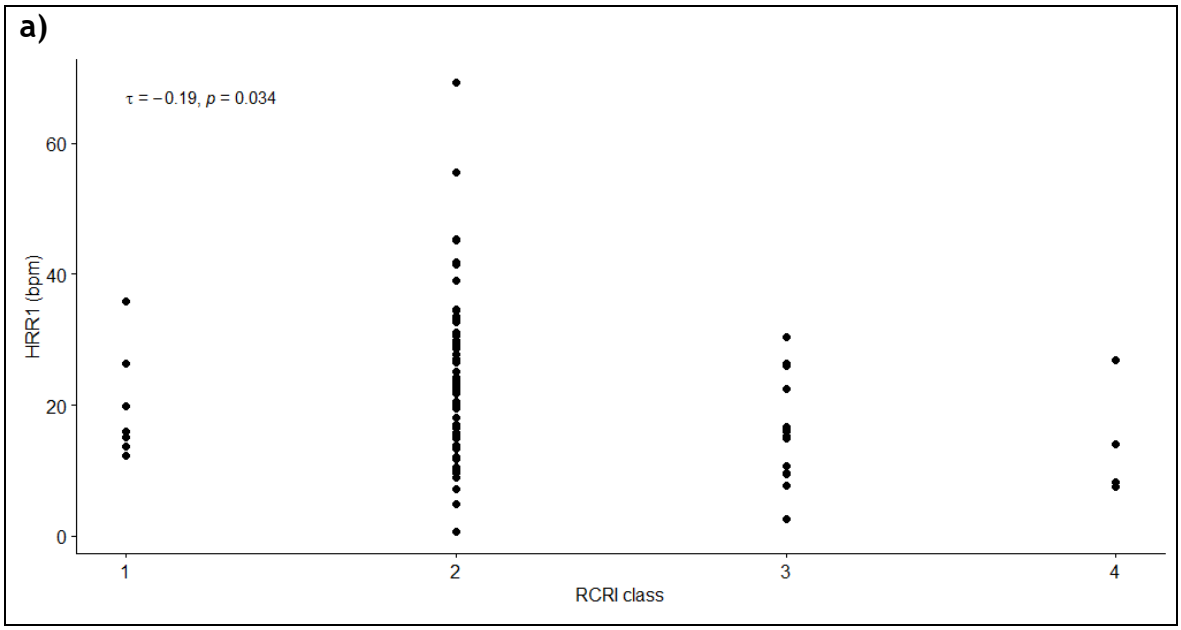
8.2.3.6 Revised Cardiac Risk Index

Correlation between the RCRI and the five best-performing HRR parameters are shown in Table 71.

Table 71 Correlation between HRR parameters and Revised Cardiac Risk Index risk of major postoperative cardiovascular complications (%). Kendall's correlation (tau).

HRR parameter	Kendall's τ	p value
HRR_1 n = 81	-0.19	0.03
HRR_1-ECHR n = 81	-0.17	0.05
AUC_{30} n = 79	-0.26	0.003
AUC_{30}-ECHR n = 79	-0.22	0.02
AUC_5-ECW n = 74	-0.14	0.12

In contrast to the other constructs, AUC_{30} and AUC_{30}-ECHR demonstrated the highest correlation with RCRI (Figure 58b,c). HRR_1 also demonstrated correlation with RCRI class (Figure 58a), although all correlations demonstrated are weak.



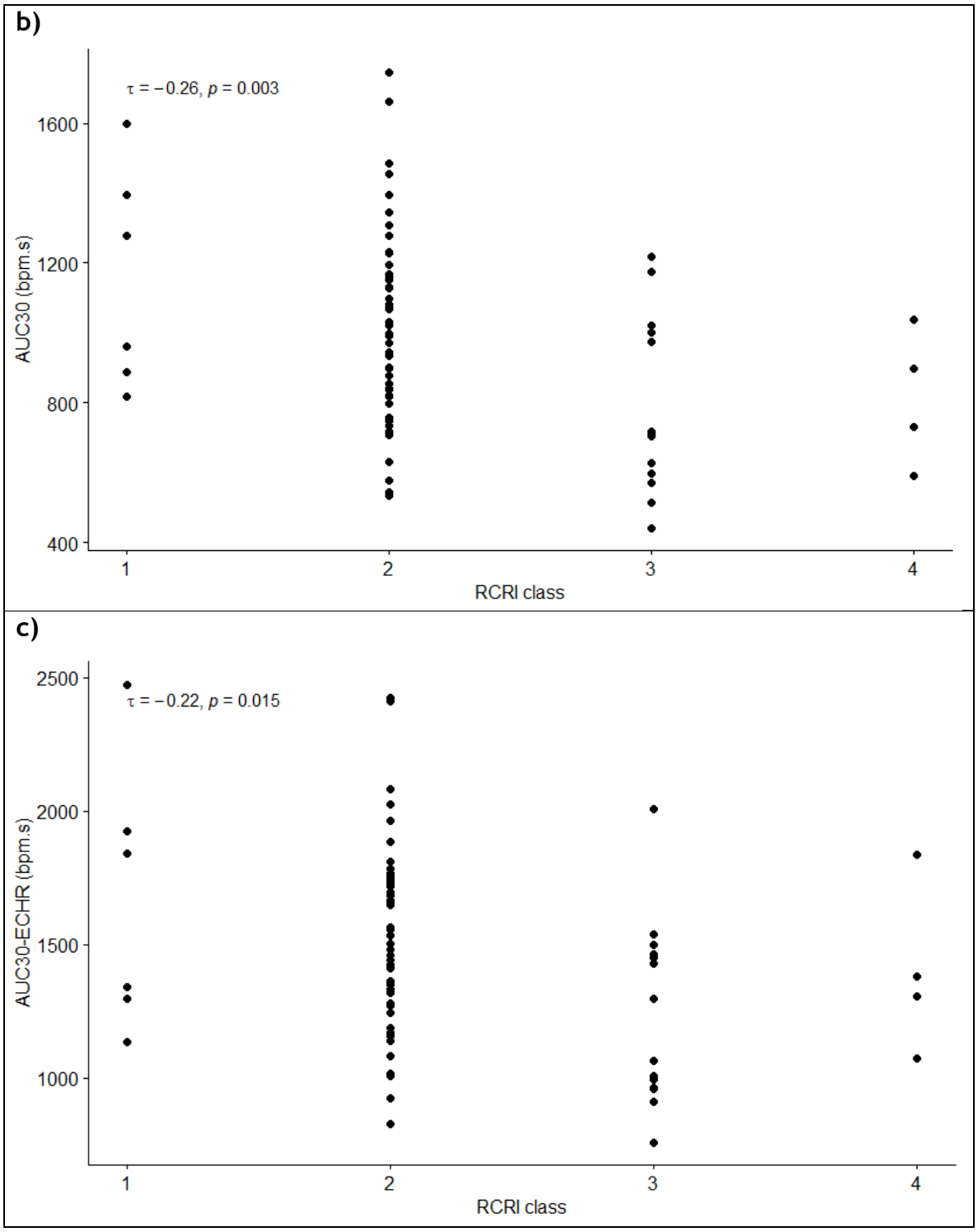
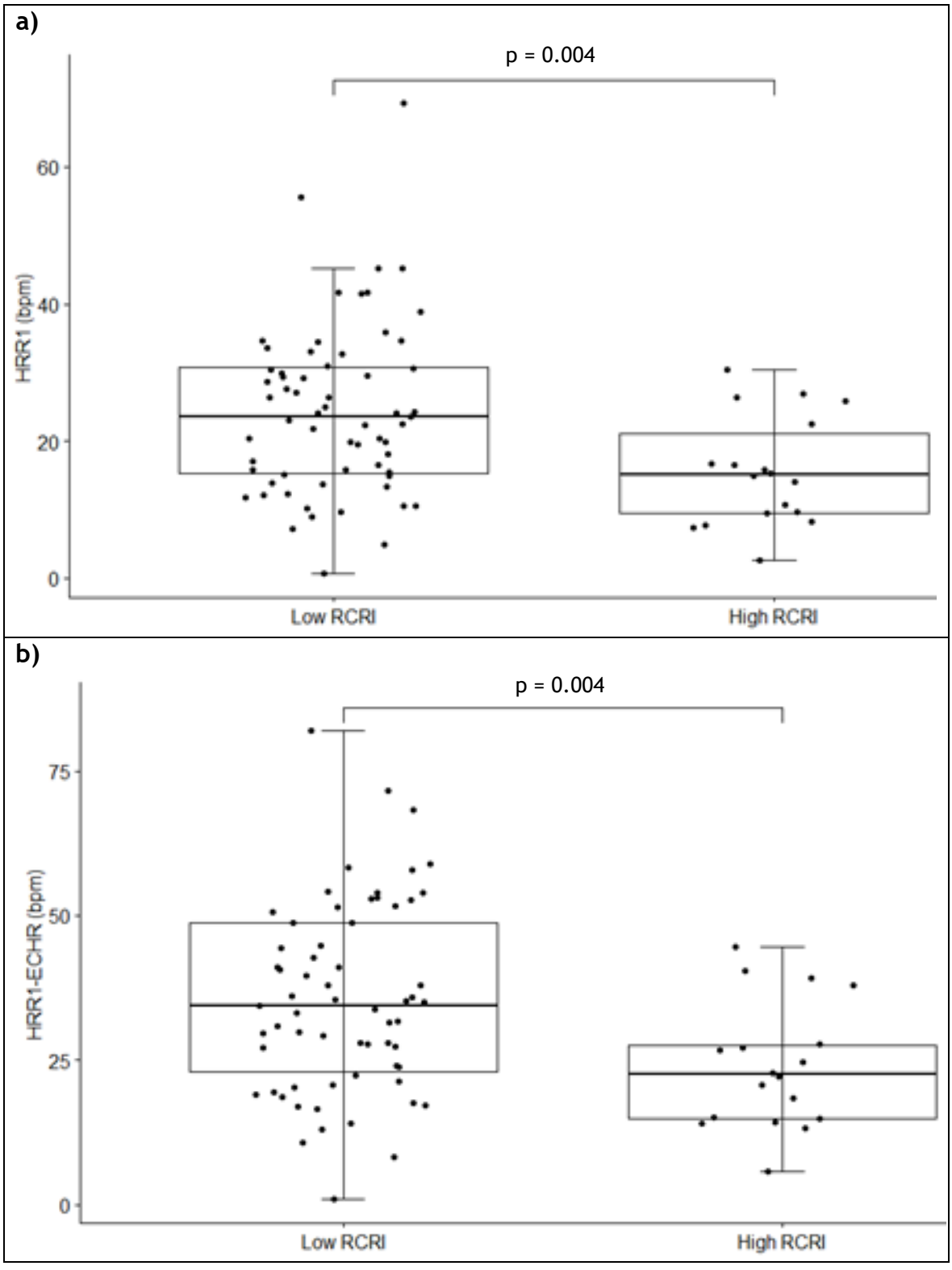


Figure 58 Correlation between submaximal HRR parameters and Revised Cardiac Risk Index. Kendall's correlation. a) HRR_1, n = 81. b) AUC_{30}, n = .79 c) AUC_{30}-ECHR, n = 79.

RCRI was dichotomised into high (≥3) and low-risk (<3) and all HRR parameters, other than AUC_5-ECW were different between these groups (Figure 59).


a)
p = 0.004
HRR1 (bpm)
60
40
20
0
Low RCRI
High RCRI
b)
p = 0.004
HRR1-ECHR (bpm)
75
50
25
0
Low RCRI
High RCRI

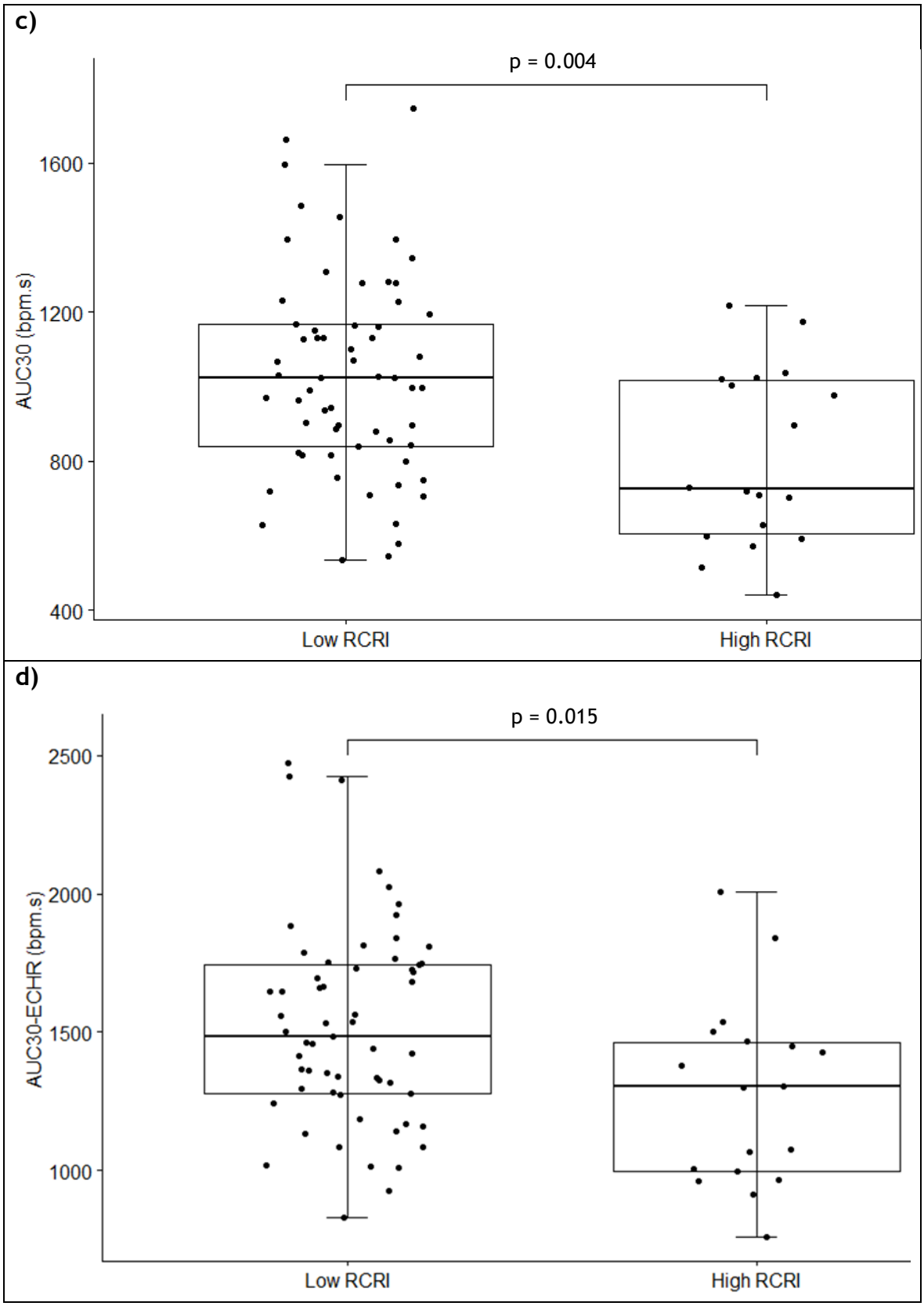


Figure 59 Difference in submaximal HRR parameters between patients identified as low-risk (<3) and high-risk (≤3) via Revised Cardiac Risk Index. Wilcoxon rank-sum exact test. a) HRR_1, n = 81. b) HRR_1-ECHR, n = 81. c) AUC_{30}, n = 79. d) AUC_{30}-ECHR, n = 79.

8.2.3.7 P/V-POSSUM Morbidity Score

The correlation between P/V-POSSUM morbidity risk percentage and the five best-performing HRR parameters was examined (Table 72).

Table 72 Correlation between HRR parameters and P/V-POSSUM risk of postoperative morbidity (%). Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 81	-0.32	0.004
HRR_1-ECHR n = 81	-0.35	0.002
AUC_{30} n = 79	-0.07	0.53
AUC_{30}-ECHR n = 79	-0.06	0.59
AUC_5-ECW n = 74	0.23	0.05

Both HRR_1 and HRR_1-ECHR demonstrated weak negative correlation with P/V POSSUM morbidity (Figure 60), with a lower HRR associated with a higher predicted risk of postoperative morbidity, as expected.

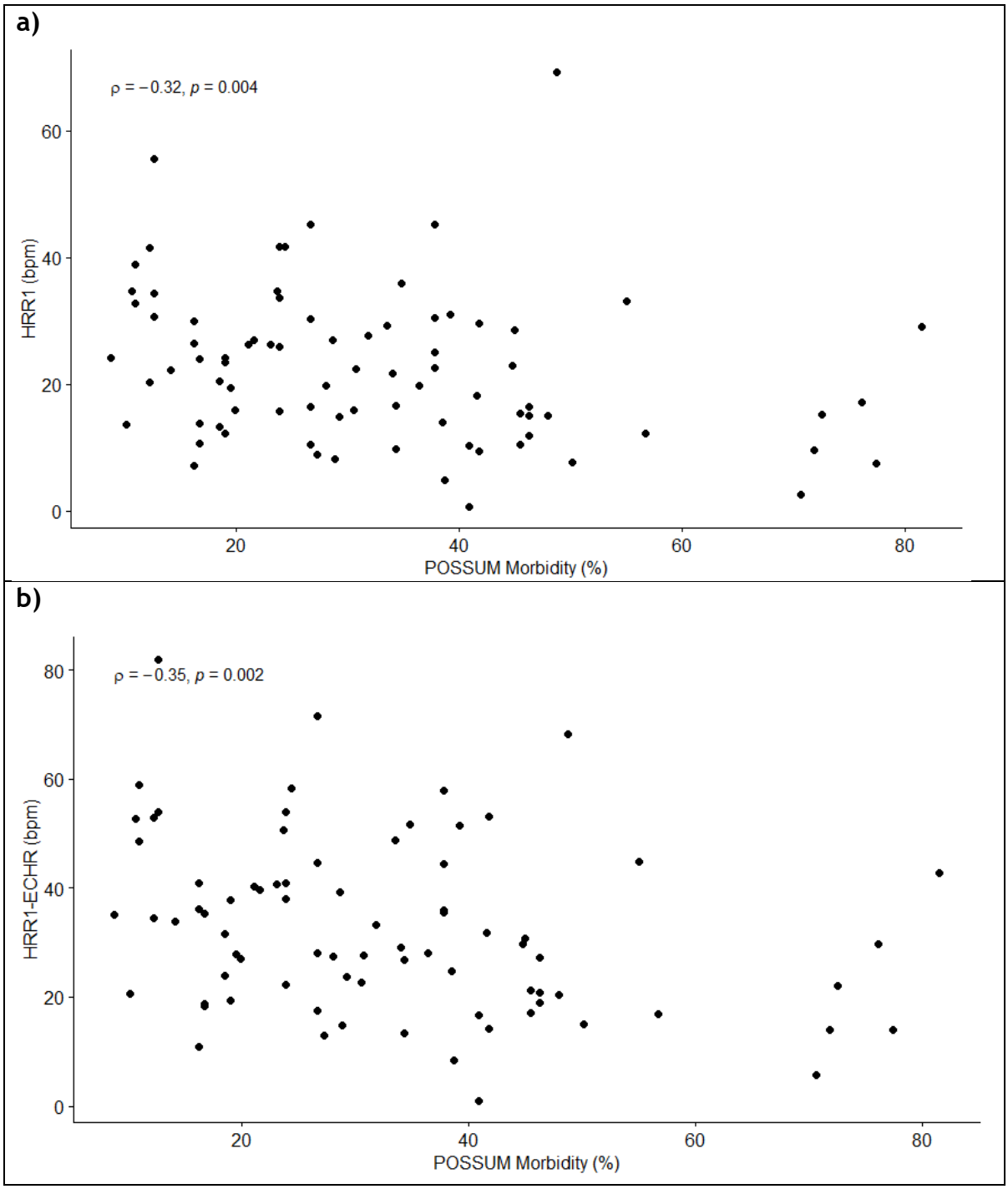


Figure 60 Correlation between submaximal HRR_1 parameters and P/V-POSSUM risk of postoperative morbidity (%). n = 81. Spearman's correlation. a) HRR_1. b) HRR_1-ECHR.

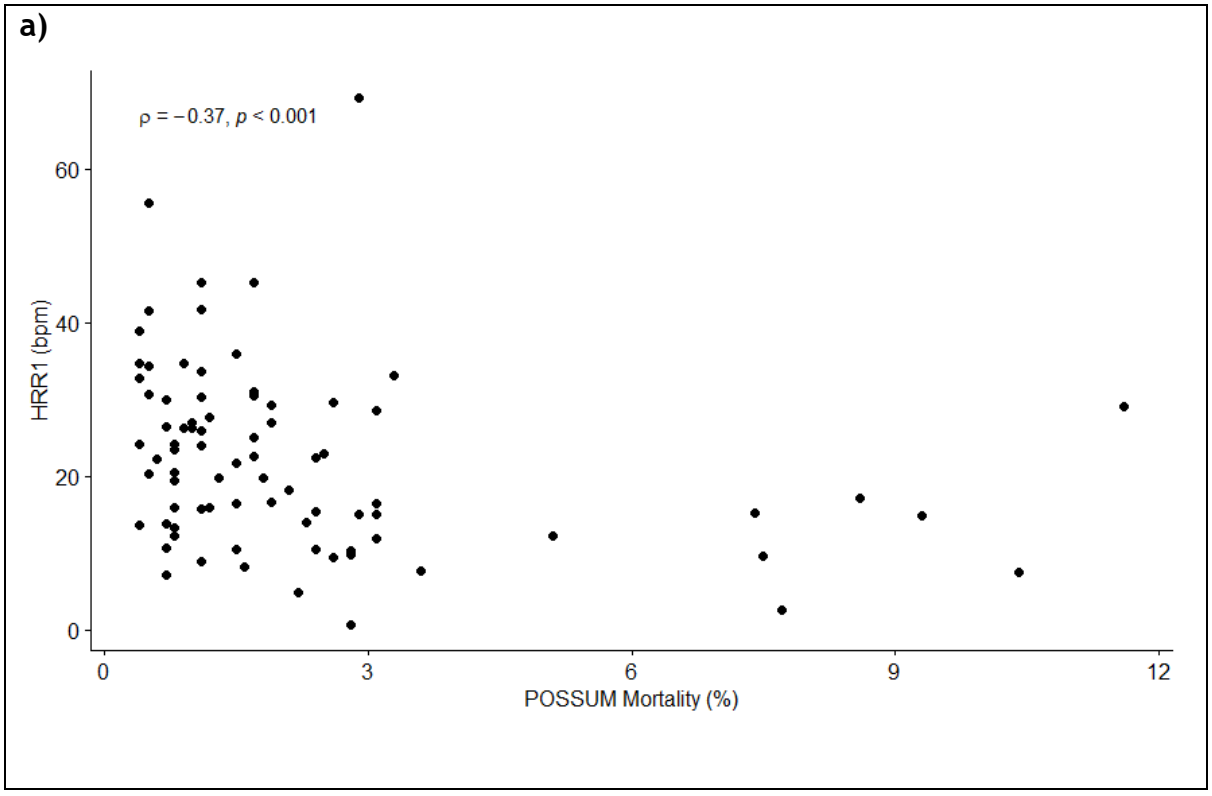
8.2.3.8 P/V-POSSUM Mortality Score

The correlation between P/V-POSSUM mortality risk percentage and the five best-performing HRR parameters was examined Table 73.

Table 73 Correlation between HRR parameters and P/V-POSSUM risk of postoperative mortality (%). Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1 n = 81	-0.37	<0.001
HRR_1-ECHR n = 81	-0.39	<0.001
AUC_{30} n = 79	-0.11	0.34
AUC_{30}-ECHR n = 79	-0.09	0.41
AUC_5-ECW n = 74	0.26	0.02

Both HRR_1 parameters and AUC_5-ECW demonstrated correlation with POSSUM mortality risk. The HRR_1 parameters demonstrated weak to moderate negative correlation and AUC_5-ECW demonstrated weak positive correlation (Figure 61). Lower HRR_1 and higher AUC_5 were associated with a higher predicted mortality risk, as expected.



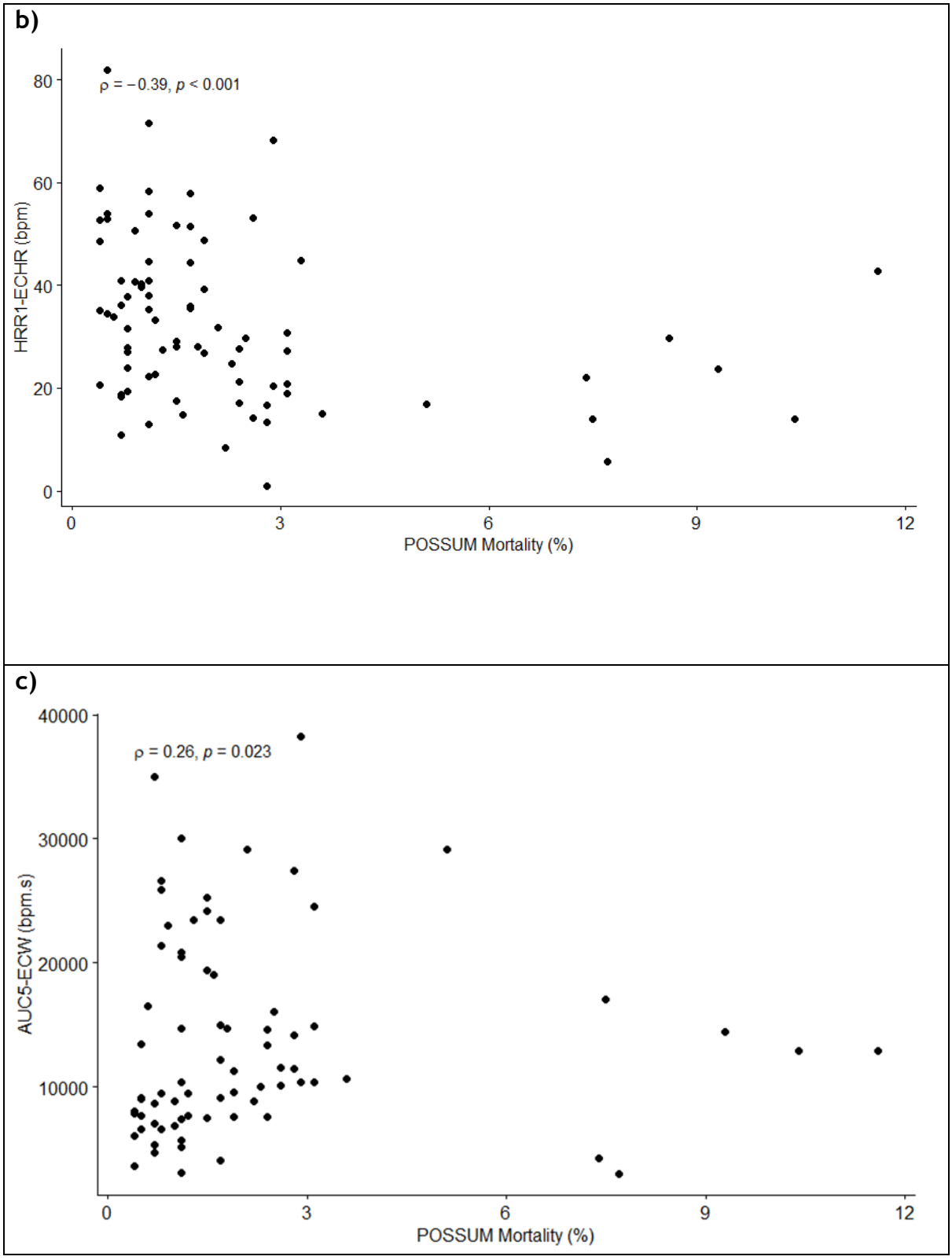


Figure 61 Correlation between submaximal HRR parameters and P/V-POSSUM risk of postoperative mortality (%). Spearman's correlation. a) HRR_1, n = 81 b) HRR_1-ECHR, n = 81. c) AUC_5-ECW, n = 74.

8.2.3.9 Results summary

A summary of the correlation between constructs and submaximal HRR parameters are shown in Table 74.

Table 74 Summary of the correlation between constructs and HRR parameters. Values are correlation coefficient. *RCRI Kendall's tau; Spearman's rho for all others. Values in bold signify associations with significant p values.

Construct	HRR_1	HRR_1-ECHR	AUC_{30}	AUC_{30}-ECHR	AUC_5-ECW
NT-ProBNP	-0.14	-0.12	0.14	0.16	**0.36**
SORT	**-0.32**	**-0.36**	-0.14	-0.13	0.18
ACS NSQIP SRC Any complications	**-0.39**	**-0.40**	-0.12	-0.08	0.22
ACS NSQIP SRC Length of stay	**-0.26**	**-0.26**	-0.04	-0.01	0.18
DASI	**0.32**	**0.34**	0.10	0.07	-0.11
RCRI*	**-0.19**	-0.17	**-0.26**	**-0.22**	-0.14
P/V-POSSUM morbidity	**-0.32**	**-0.35**	-0.07	-0.06	-0.23
P/V-POSSUM mortality	**-0.37**	**-0.39**	-0.11	-0.09	**0.26**

8.3 Discussion

The aim of this investigation was to examine the construct validity of the five HRR parameters with the best predictive value for PMI. Heart rate recovery after one minute, both the absolute values and effort-corrected to heart rate, demonstrated weak to moderate correlation with all constructs, other than NT-ProBNP, thereby exhibiting construct validity. Of the other submaximal HRR parameters, AUC_{30} and AUC_{30}-ECHR demonstrated weak to moderate correlation with RCRI only, and AUC_5-ECW demonstrated weak to moderate correlation with POSSUM mortality only. When the constructs were dichotomised into high and low-risk groups, the HRR_1 parameters demonstrated association with DASI and RCRI; AUC_{30} and AUC_{30}-ECHR only with RCRI and AUC_5-ECW only with NT-ProBNP.

8.3.1 HRR_1 parameters

Submaximal HRR_1 and HRR_1-ECHR demonstrated construct validity for all constructs apart from NT-ProBNP. The constructs investigated encompassed a variety of measures for perioperative risk; only DASI score is a gauge of functional capacity, and in accordance with this, there was a weak to moderate positive association between HRR_1 and HRR_1-ECHR and DASI. This relationship was further supported by association of both HRR_1 parameters with high and low DASI scores.

Both HRR_1 parameters demonstrated weak to moderate negative correlation with the constructs which predict postoperative complications based on patient and surgical risk factors (SORT, ACS-NSQIP SRC, POSSUM, RCRI) and in the expected direction (i.e. lower HRR_1 and worse predicted outcomes). It would be expected that submaximal HRR_1, as a proposed measure of functional capacity, would demonstrate association with patient factors known to increase risk of postoperative complications, as functional capacity is limited not just by aerobic capacity but also presence and severity of comorbidity. All of the surgical risk parameters also include surgical factors in risk calculation and clearly, HRR parameters do not incorporate surgical risk. Therefore, it is encouraging that the HRR_1 parameters show some association with the surgical risk constructs. It would not be expected that any of the HRR parameters demonstrate perfect correlation as they all measure different aspects of perioperative risk.

The RCRI predicts risk of death, MI or cardiac arrest based on five patient factors and one surgical risk factor (Section 1.2.5). The HRR_1 parameters demonstrated the best predictive value for PMI, a cardiovascular outcome most similar to that predicted by the RCRI. The association between the HRR_1 parameters and RCRI was weaker than the other constructs, which may be due to its ordinal nature. When RCRI was dichotomised into high and low-risk, the HRR_1 parameters demonstrated association.

There was no correlation between the HRR_1 parameters and NT-ProBNP and no difference between HRR_1 parameters when patients were dichotomised into high and low-risk by preoperative NT-ProBNP. This is surprising as NT-ProBNP is a cardiovascular risk measure. These results (RCRI and NT-ProBNP) suggest that

submaximal HRR_1 may provide a better reflection of "whole-body" risk rather than purely cardiovascular risk. However, this suggestion contrasts with the lack of association between HRR parameters and actual postoperative cardiovascular complications in this patient cohort (Section 7.3.2.1).

For all constructs, effort-correcting HRR_1 to heart rate slightly improved the association. As discussed in Section 6.3.3.2, by controlling the effort exerted by patients to 60% age-predicted maximum heart rate, the overall impact of effort-correction to heart rate in the study presented is likely to be low, and potentially unnecessary in this cohort, however may be beneficial where heart rate control is less robust.

8.3.2 AUC_{30} parameters

Both AUC_{30} and AUC_{30}-ECHR demonstrated weak negative correlation with RCRI. This association was stronger for RCRI than the HRR_1 parameters. The negative correlation indicates that patients deemed less risk via the RCRI have a larger AUC_{30} and AUC_{30}-ECHR, which, as discussed in Section 6.3.3.3, is opposite to the original hypothesis regarding the area under heart rate recovery profile. As described previously, AUC_{30} may reflect the total fall in heart rate during recovery, and therefore HRR_1, explaining the similarity in direction, although it does not explain the lack of association with the other constructs.

Construct validity for the AUC_{30} parameters was not demonstrated. The lack of association of the AUC_{30} parameters and the other constructs may reflect that submaximal AUC_{30} is a weaker perioperative measure than HRR_1 or that the sample size was too small to detect association. There is potential that the correlation between the AUC_{30} parameters and RCRI is due to type I error from multiple comparisons, especially due to the lack of association with the other constructs.

8.3.3 AUC_5-ECW

The area under the curve at five minutes corrected to power output demonstrated positive moderate correlation with both NT-ProBNP and P/V-POSSUM mortality score. It was the only parameter to demonstrate correlation

with NT-ProBNP. Conversely to the AUC_{30} parameters, positive correlation is the expected "direction" i.e patients with larger AUC_5-ECW had higher NT-ProBNP values and higher predicted mortality risk via POSSUM score. The AUC_5-ECW reflects the total fall back to resting heart rate over the longest period of recovery time measured. A few patients would not have returned to resting heart rate even after five minutes of recovery; these patients would be expected to have high NT-ProBNP. It could be that only AUC_5-ECW and NT-ProBNP demonstrated weak/moderate positive correlation because AUC_5-ECW most accurately reflects only the most unfit patients.

Construct validity has not been demonstrated for AUC_5-ECW. The lack of association of the AUC_5-ECW and the other constructs may reflect that submaximal AUC_5-ECW is a weaker measure than HRR_1 or that the sample size was too small to detect association. Again, there is a risk that the positive results for NT-ProBNP and POSSUM mortality are due to a type I error due to multiple comparisons.

8.3.4 Construct validity of perioperative heart rate recovery in the literature

There have been no studies specifically investigating the construct validity of either submaximal or maximal heart rate recovery in the perioperative setting. The association of maximal HRR_1 with NT-ProBNP and RCRI was investigated by Abbott et al. in a substudy of the METs trial involving 1326 patients[150]. Patients with ≥3 RCRI risk factors were more likely to have impaired preoperative HRR_1 (≤12 bpm) than those who had no RCRI risk factors (OR 3.92 (95%CI 1.84-8.34), $p<0.001$). Similarly, impaired maximal HRR_1 was associated with elevated preoperative NT-ProBNP (>300 pg/ml) (OR 2.58 (95% CI 1.82-3.64), $p<0.001$). The authors of this paper suggest that underlying cardiac vagal dysfunction is one of the reasons that the preoperative risk factors as defined by the RCRI are linked to PMI. In comparison to this paper, there was no association between NT-ProBNP and the submaximal HRR_1 parameters, both for continuous data and when dichotomised by risk. The weakest association was demonstrated between RCRI and submaximal HRR_1 and HRR_1-ECHR in this investigation, despite showing predictive value for PMI. This could be due to the effect of submaximal exercise

weakening the strength of the HRR signal or it could be because of the small sample size.

8.4 Conclusion

The associations observed strongly suggest construct validity for submaximal heart rate recovery after one minute, both the absolute value and effort-corrected to age-predicted maximum heart rate reached. These findings reinforce the results from Chapter 6 and Chapter 7 where submaximal HRR_1 had the best predictive value for PMI and strongest association with renal complications. All the submaximal HRR parameters investigated were associated with at least one construct but with variety demonstrated between constructs. This could be an indication that different measurements from the HRR profile reflect different pathophysiological processes, or could be spurious results due to type I error after multiple comparisons. Overall, these findings reinforce the results from the predictive validity investigation with submaximal HRR_1 demonstrating predictive, face and construct validity as a perioperative risk measure.

Chapter 9 Heart rate recovery and cardiopulmonary exercise testing variables (criterion and concurrent validity)

This Chapter explores the criterion and concurrent validity of the five best-performing HRR parameters compared to CPET findings in a small subset of patients. Criterion validity is the assessment of a measurement against the "gold-standard" measure (Section 3.2.1). Concurrent validity is a type of criterion validity which determines if the measure in question can distinguish between groups (e.g. high and low-risk) as classified by the "gold-standard" measure (Section 3.2.3). Criterion validity will be investigated by assessing the association between submaximal HRR parameters and CPET parameters (peak oxygen consumption (VO_{2peak}), anaerobic threshold (AT) and ventilatory equivalent for carbon dioxide at anaerobic threshold (VE/VCO_2)). Concurrent validity will be assessed by comparing the submaximal HRR when patients were dichotomised into high and low-risk groups via the same CPET parameters.

9.1 Specific methods

The submaximal exercise test and extraction of submaximal HRR parameters are discussed in Chapter 4 (Generic methods). For this investigation, the patients did not require to undergo their surgery or have postoperative data collected.

9.1.1 Patient identification

9.1.1.1 University Hospital Crosshouse

Patients at UHC were referred for CPET at the discretion of either the lead consultant surgeon or the anaesthetist who reviewed the patient at preoperative assessment clinic. As per local guidelines, A DASI score of ≤34 was used as a guide to identify patients who may benefit from preoperative CPET for either risk prediction enhancement, or potential optimisation prior to surgery[39].

9.1.1.2 University Hospital Hairmyres

All patients undergoing major elective aortic surgery at UHH undergo specific vascular preassessment. This includes discussion at a vascular multidisciplinary

meeting, a face-to-face clinic appointment with a vascular nurse specialist and the planned list anaesthetist. Through the initial pre-assessment process, a decision is made about whether the patient is fit to proceed for further assessment. All patients with aneurysmal disease who “pass” this process are subsequently referred for CPET. Patients with occlusive disease may be considered depending on their function but clearly due to the symptoms of occlusive aortic disease are unlikely to be able to fully complete CPET.

9.1.2 CPET Protocol

Both centres perform CPET as a standardised ramped incremental test per the Perioperative Exercise Testing and Training Society (POETTS) guidelines (Section 1.2.10)[57]. At UHC, POETTS accredited anaesthetists conduct and interpret the test, whereas at UHH at respiratory physiologist conducts and interprets the test. Gas and flow-volume calibration occurs before each test. Both centres use cycle ergometry as the exercise modality and a “rapid ramp” exercise protocol. The ramp slope is determined by computer software which calculates the patients predicted peak load based on height, weight, age and sex[219]. The ramp is the peak load divided by ten e.g. a predicted peak load of 210W gives a slope of 20W over 10 minutes. The first stage of the CPET is rest, where the patient sits on the bike at rest for a minimum of three minutes with the parameters above measured. The second stage is unloaded cycling which aims to acclimatise the patient to exercise and the face mask and lasts approximately three minutes. The ramp phase consists of a progressive increase in work rate by increasing the cycle resistance. The patients are encouraged to pedal at a cadence of between 55-75 rpm for as long as possible until they cannot maintain this cadence despite encouragement. Recovery is the final stage where the load is removed and the patient is encouraged to pedal unloaded, with monitoring continuing until ECG changes and blood pressure have returned to baseline and heart rate has fallen to within 10 bpm of resting value. Indications for premature termination of CPET are described in Appendix 7.

9.1.3 CPET interpretation

At UHC, test results are interpreted by the anaesthetist conducting the test at UHH, by the respiratory physiologist. Tabular and graphical CPET data is

reported in the standardised way with a nine-plot graph as per POETTS[57]. Both centres also report whether there were any signs of cardiac ischaemia and any patient symptoms. The test results are discussed with patients by an anaesthetist and used as a teachable moment prior to surgery where appropriate.

The CPET variables investigated were anaerobic threshold, peak oxygen consumption and the ventilatory equivalent for carbon dioxide at anaerobic threshold, all determined via processes described in Section 1.2.10. There is no overall consensus on high-risk cut-offs for these variables, with variation depending on the patient population and surgical speciality being investigated. Neither centre uses cut-offs to predict risk, rather the combination of objective and subjective findings during the test to give an indication of functional capacity. However, for the purpose of determining concurrent validity, this investigation used cut-offs based on studies with the largest numbers, most commonly reported in the literature and most relevant to the patient population studied[57].

High risk cut-offs used in this investigation:

- AT <11ml/kg/min
- VO_{2peak} <15ml/kg/min
- VE/VCO_2 at AT >34.

9.1.4 Specific statistical handling

Comparisons were made using t-tests or Wilcoxon rank sum test where appropriate. Correlation was assessed using Spearman's rank correlation coefficient. No adjustments were made for multiple comparisons as this was an exploratory analysis.

9.2 Results

Twelve patients underwent CPET as part of their routine pre-assessment.

9.2.1 Patient Demographics

Baseline data for these 12 patients is shown in Table 75. Two patients were planned for colorectal surgery and the remainder were being assessed for vascular surgery. Four of the patients being assessed for vascular surgery did not undergo their operation: one was deemed not fit for surgery, one did not require the procedure and two underwent surgery more than six months after pre-assessment.

Table 75 Participant demographics, comorbidities, preoperative blood results and medications for cardiopulmonary exercise test group. n = 12 unless otherwise stated. Values are number (percentage) and median (IQR) [range]. BMI: body mass index; ASA: American Society of Anaesthesiologists Physical Status; COPD: chronic obstructive pulmonary disease; hs-TnT: high sensitivity Troponin T; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme.

Characteristic	Descriptive Statistics
Age (years)	72 (67 – 75) [60 - 80]
Female sex	0%
BMI (kg/m^2)	27.2 (25.1 – 30.8) [21.6 – 36.9]
Ethnicity: White British	 12 (100%)
Smoking status: Current smoker Ex-smoker Never smoked	 4 (33%) 5 (42%) 3 (25%)
Clinical Frailty Score: 1 2 3 4 5 >5	 0 2 (17%) 4 (33%) 5 (42%) 1 (8%) 0
ASA: 1 2 3 4 *Missing data*	 0 3 (25%) 3 (24%) 0 *6*
Duke Activity Status Index (points)	37.1 (28.3 – 42.7) [19.0 – 50.7]
Comorbidities	
None	0
History of cancer	4 (33%)
Asthma	0
COPD	4 (33%)
Arterial hypertension	7 (57%)
IHD	7 (57%)
Cardiac failure	0
AF	1 (8%)
PVD	3 (25%)
Stroke	0
T1DM	0
T2DM	3 (25%)

Previous covid infection Long covid	6 (50%) 1 (8%)
Preoperative blood results	
NT-ProBNP (pg/ml)	128 (76 – 308) [20 -1250]
hsTnT (ng/L)	8 (7 – 17) [5 – 30]
Haemoglobin (g/L)	14.6 (14.5 – 15.4) [13.7 – 16.8]
Creatinine (µmol/L)	84 (79 – 105) [59 – 134]
Preoperative renal function eGFR >59 (ml/min) eGFR 30-59 (ml/min) eGFR <30 (ml/min)	 10 (83%) 2 (17%) 0
Medications	
No regular medication	0
Beta-blocker	4 (33%)
Calcium channel blocker	3 (25%)
ACE-inhibitor	6 (50%)
Diuretics	2 (17%)
Antiarrhythmic	0
Beta-agonist	1 (8%)
Steroids: Inhaled Oral	 1 (8%) 0

When compared to the baseline demographics of the whole cohort (n = 83, Table 12), the patients in this investigation were older, all male, with a higher proportion of smokers. Their functional status was slightly worse with a higher percentage of patients at clinical frailty scale of four and reduced DASI score. There was a higher level of cardiovascular comorbidity, with increased preoperative NT-ProBNP, and consequently a higher proportion of patients were taking cardiovascular medication. Renal function appeared similar between groups.

9.2.2 Preoperative risk scores

Preoperative risk scores for the twelve patients in this investigation are described in Table 76.

Table 76 Preoperative risk scores of patients who underwent cardiopulmonary exercise testing , n = 12. Values are number (percentage) and median (IQR) [range]. P/V-POSSUM: Portsmouth/Vascular-Physiologic and Operative Severity Score for the study of Mortality and Morbidity; ACS NSQIP SRC: American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; SORT: Surgical Outcome Risk Tool; RCRI: Revised Cardiac Risk Index.

Preoperative risk score	Descriptive Statistics
POSSUM morbidity (%)	36.4 (30.4 – 46.3) [16.7 – 71.9]
POSSUM mortality (%)	3.0 (2.2 – 3.2) [1.1 – 9.3]
ACS NSQIP SRC any complication risk (%)	18.5 (9.8 – 21.3) [6.3 – 39.3]
ACS NSQIP SRC length of hospital stay (days)	5.8 (2.4 – 6.1) [2.0 – 8.0]
SORT score (%)	1.56 (1.14 – 1.65) [0.77 – 3.17]
RCRI: Class I 3.9% Class II 6.0% Class III 10.1% Class IV 15.0%	 0 5 (42%) 5 (42%) 2 (17%)

The median for each perioperative risk score in the CPET patient group was higher in all categories than the whole cohort (n = 83, Table 13), including both physiological scores and surgical scores. These results are to be expected, as the CPET group was composed predominantly of patients undergoing major vascular procedures, and, in the UHC cohort, patients undergoing major colorectal surgery with limited functional capacity. However, the median DASI for the CPET group (37.1), although lower than the whole cohort median (39.0) was higher than the recommended cut-off for identification of high perioperative risk (DASI ≤34)[220].

9.2.3 Step test parameters

The step test parameters for the twelve patients in this investigation are described in Table 77.

Table 77 Step test parameters for patients who also underwent cardiopulmonary exercise testing , n = 12. Values are number (percentage) or median (IQR) [range]. Bpm: beats per minute

Step test parameter	Descriptive statistics
Height of step: 19.5cm 14.5cm 9.5cm	 9 (75%) 2 (25%) 0
Duration of step test (seconds)	83 (79 – 111) [73 – 152]
Proportion of age-predicted maximum heart rate reached	0.68 (0.62 – 0.72) [0.51 – 0.83]
Heart rate at end of exercise (bpm)	105 (98 – 114) [79 – 138]
Power output (Watts)	42 (35 – 46) [27 – 82]
Proportion of maximum predicted power reached	0.25 (0.22 – 0.28) [0.16 – 0.36]
Modified Borg score at end of exercise	5 (2-5) [0 – 7]
Wearing a facemask	10 (83%)

In terms of the step test parameters between the CPET group (n = 12) and the whole cohort(n = 83, Table 14), there was very little difference. Overall, in the CPET group, a larger proportion of patients performed the test on a higher step but had shorter tests indicating that they reached 60% age-predicted HR_{max} quicker. All other parameters, including heart rates, power and median Borg score were broadly similar. This is indicative that, even in a more comorbid population, a submaximal step test is feasible and, likely due to its submaximal nature, does not exert these patients to a subjective point of discomfort as shown by the similar median Borg scores.

9.2.4 Cardiopulmonary exercise test variables

All twelve patients completed the CPET with none demonstrating signs of cardiac ischaemia. The CPET variables including heart rate parameters are shown in Table 78. Maximal HRR_1 was not available for one patient because their ECG signal was too poor during exercise to ascertain their heart rate.

Table 78 Cardiopulmonary exercise test variables. n = 12 unless otherwise stated. Values are median (IQR) [range]. Bpm: beats per minute

Cardiopulmonary exercise test variable	Descriptive statistics
Anaerobic threshold (ml/kg/min)	12.0 (11.0 – 13.6) [9.0 – 17.1]
Peak oxygen consumption (ml/kg/min)	17.1 (14.8 – 20.5) [13.0 – 24.7]
VE/VCO_2 (ml/kg/min)	34.6 (27.3 – 40.7) [22.9 – 59.4]
Heart rate at anaerobic threshold (bpm)	100 (85 – 117) [75 – 140]
Heart rate at peak oxygen consumption (bpm)	130 (112 – 148) [100 – 175]
Proportion of age-predicted maximum heart rate reached at peak oxygen consumption (bpm)	0.82 (0.69 – 0.92) [0.64 – 1.10]
Heart rate recovery at one minute (bpm) *Missing data = 1*	11 (7 – 16) [4 – 41]

9.2.5 Criterion validity

9.2.5.1 Anaerobic threshold

There was no correlation between the submaximal HRR parameters and the anaerobic threshold reported via CPET (Table 79).

Table 79 Correlation between submaximal HRR parameters and anaerobic threshold , n = 12. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1	0.20	0.54
HRR_1-ECHR	0.42	0.18
AUC_{30}	-0.07	0.83
AUC_{30}-ECHR	0.06	0.87
AUC_5-ECW	-0.41	0.19

For illustration, Figure 62 shows the distribution of HRR_1 against anaerobic threshold.

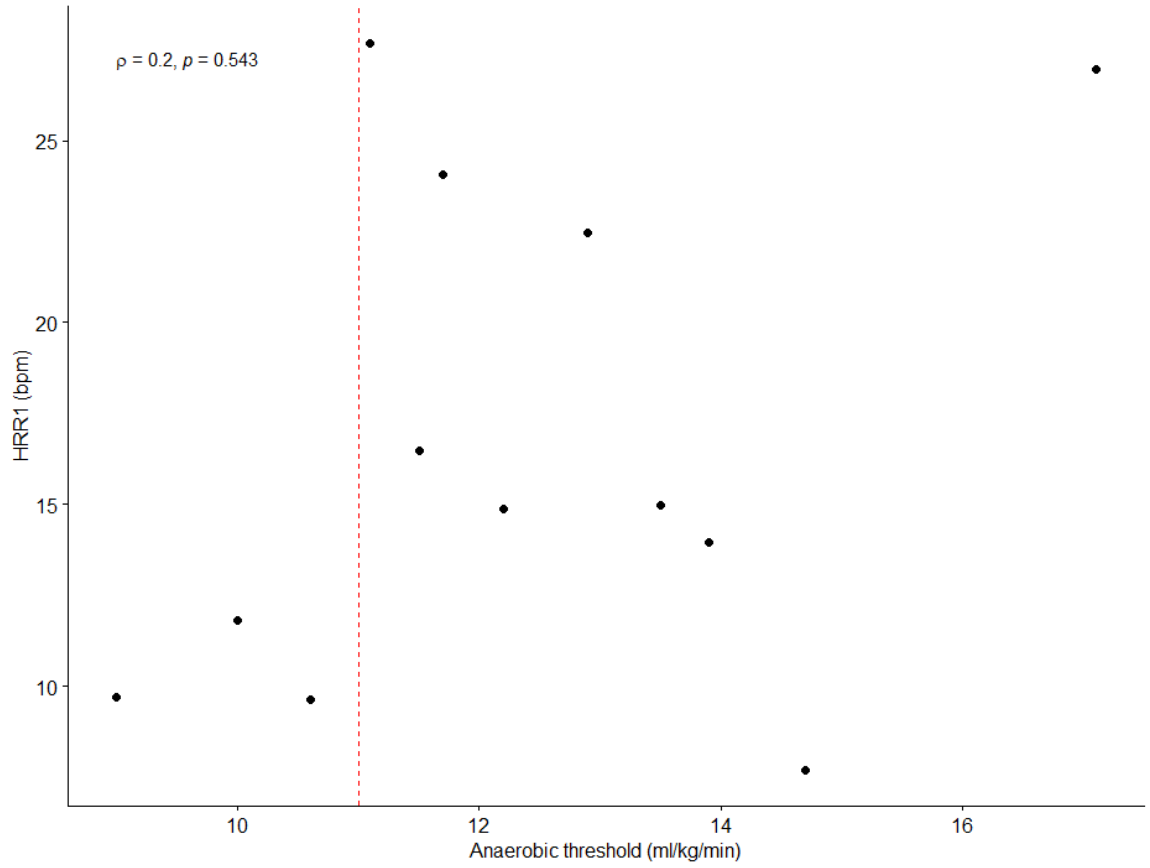


Figure 62 Scatterplot of HRR1 and anaerobic threshold. n = 12. Spearman's rank correlation. Red dashed line = 11 ml/kg/min, the threshold used in this study for high/low-risk.

9.2.5.2 Peak oxygen consumption

There was no correlation between the HRR parameters and the peak oxygen consumption reported via CPET was assessed (Table 80).

Table 80 Correlation between submaximal HRR parameters and peak oxygen consumption , n = 12. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1	0.23	0.47
HRR_1-ECHR	0.29	0.35
AUC_{30}	0.42	0.17
AUC_{30}-ECHR	0.48	0.11
AUC_5-ECW	-0.04	0.90

9.2.5.3 Ventilatory equivalent of carbon dioxide at anaerobic threshold

There was no correlation between the submaximal HRR parameters and the ventilatory equivalent for carbon dioxide at anaerobic threshold reported via CPET was assessed (Table 81).

Table 81 Correlation between submaximal HRR parameters and ventilatory equivalent for carbon dioxide at anaerobic threshold , n = 12. Spearman's rank correlation.

HRR parameter	Spearman's rho	p value
HRR_1	-0.07	0.83
HRR_1-ECHR	-0.04	0.90
AUC_{30}	-0.06	0.85
AUC_{30}-ECHR	-0.16	0.62
AUC_5-ECW	0.52	0.09

9.2.6 Concurrent validity

9.2.6.1 Anaerobic threshold

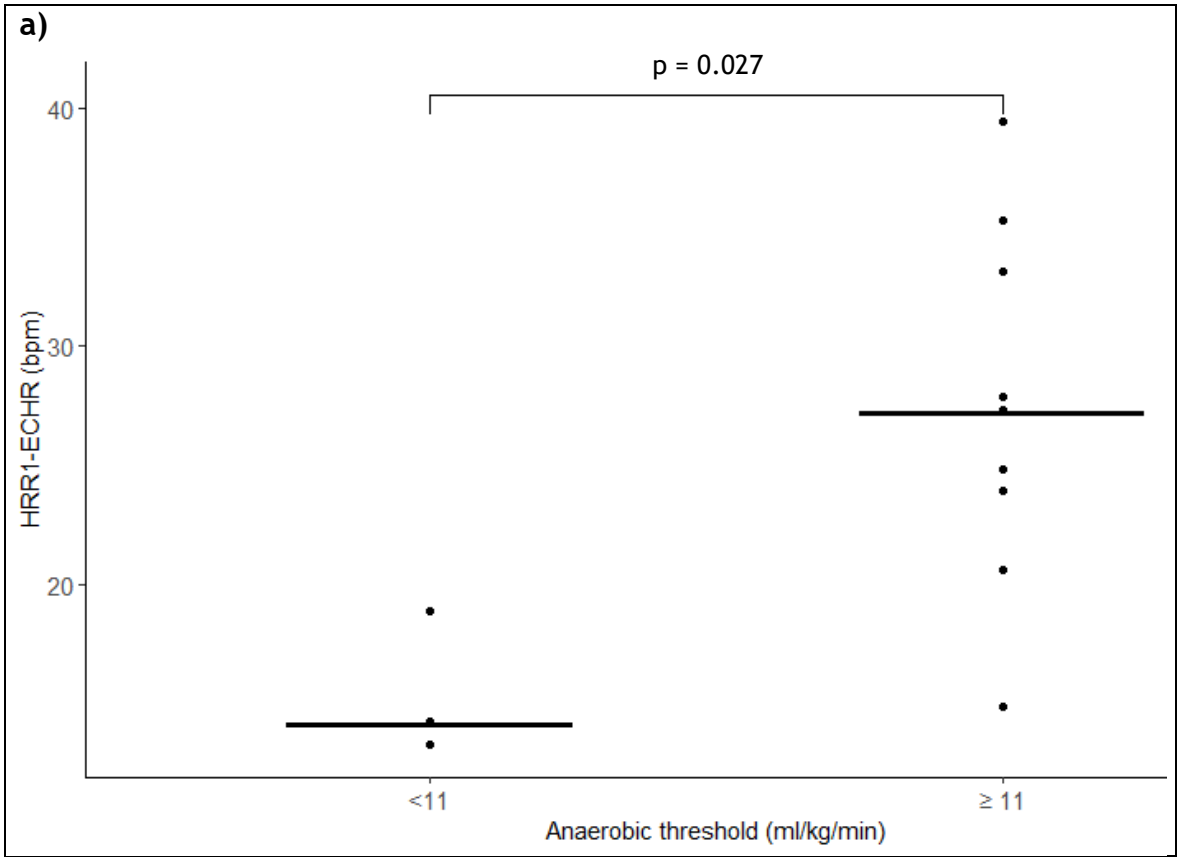
Patients were grouped into low and high-risk via an anaerobic threshold cut-off of <11 ml/kg/min equating to high-risk. Each of the five best-performing submaximal HRR parameters were then compared between groups (Table 82).

Table 82 Difference in HRR parameters between patients dichotomised into high and low-risk by anaerobic threshold. n = 12. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	Anaerobic threshold <11 ml/kg/min *n = 3*	Anaerobic threshold ≥11 ml/kg/min *n = 9*	p value
HRR_1 (bpm)	9.7 (9.7 – 10.8)	16.5 (14.9 – 24.1)	0.06
HRR_1-ECHR (bpm)	14.1 (13.7 – 16.6)	27.2 23.8 – 33.3	0.03
AUC_{30} (bpm.s)	703 (666 – 887)	1038 (799 – 1216)	0.28
AUC_{30}-ECHR (bpm.s)	1016 (991 – 1290)	1450 (1170 1838)	0.28
AUC_5-ECW (bpm.s)	14930 (13216 – 15982)	11296 (10371 – 14634)	0.37

Submaximal HRR_1-ECHR was the only HRR parameter to demonstrate difference between the two groups (Figure 63a), although HRR_1 was approaching

significance. Due to the difference between the two groups for HRR_1-ECHR, the relationship between the two parameters is shown in Figure 63b.



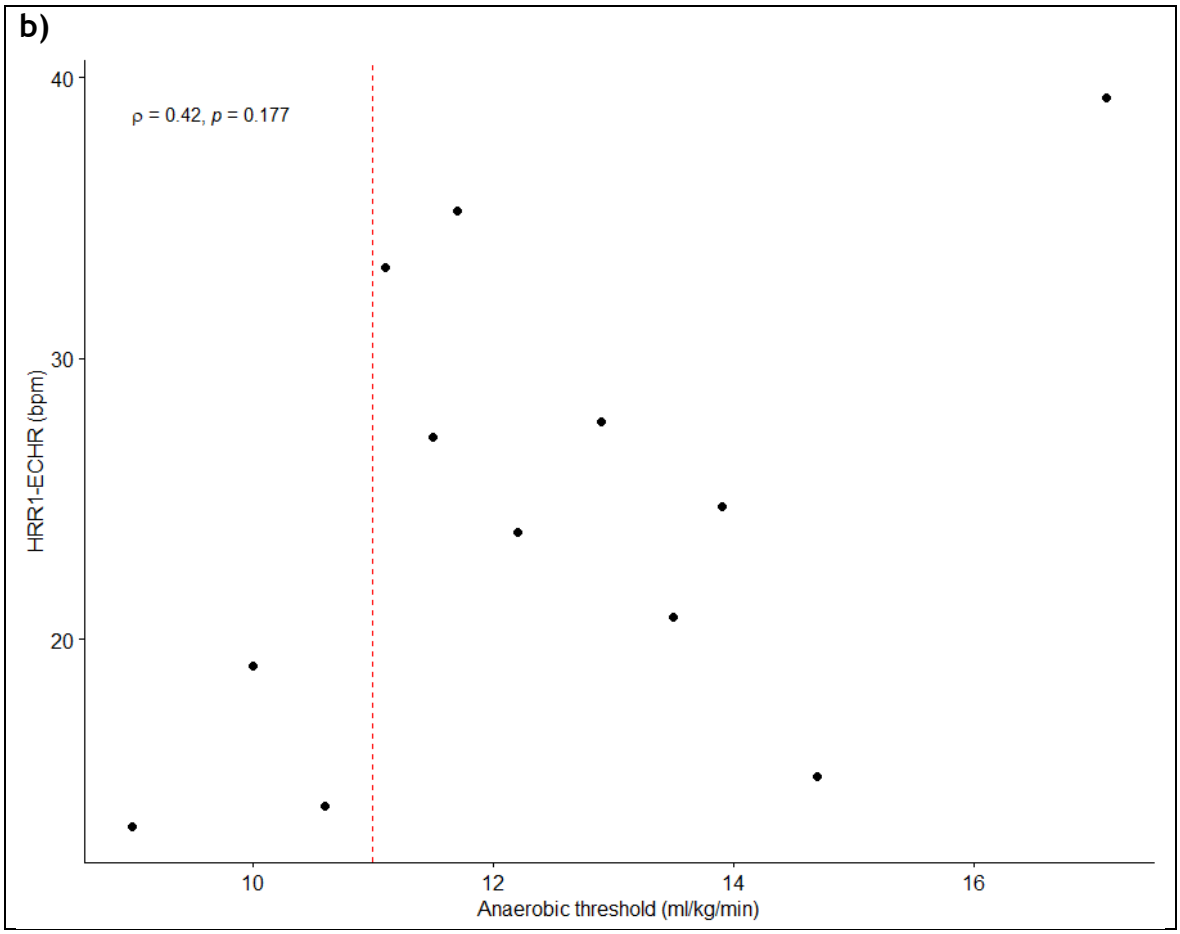


Figure 63a) Difference in heart rate recovery after one minute effort-corrected to proportion of age-predicted maximum heart rate reached (HRR_1-ECHR) between patients identified as high-risk or low-risk by anaerobic threshold. High risk: anaerobic threshold <11 ml/kg/min. n = 12. Wilcoxon rank sum test. Horizontal lines: median for each group. **b) Scatterplot of HRR_1-ECHR and anaerobic threshold.** Red dashed line: 11 ml/kg/min threshold.

9.2.6.2 Peak oxygen consumption

There was no difference in the submaximal HRR parameters between patients identified as low and high-risk by VO_{2peak} (Table 83). However, for each parameter the expected pattern was displayed.

Table 83 Difference in HRR parameters between patients dichotomised into high and low-risk by peak oxygen consumption. n = 12. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	Peak oxygen consumption <15 ml/kg/min *n = 3*	Peak oxygen consumption ≥15 ml/kg/min *n = 9*	p value
HRR_1 (bpm)	11.8 (10.8 – 17.9)	15.0 (14.0 – 22.4)	0.73
HRR_1-ECHR (bpm)	19.0 (16.2 – 27.1)	24.7 (20.8 – 27.7)	0.60
AUC_{30} (bpm.s)	703 (666 – 751)	1070 (896 – 1216)	0.10
AUC_{30}-ECHR (bpm.s)	1016 (991 – 1093)	1563 (1306 – 1838)	0.10
AUC_5-ECW (bpm.s)	14930 (13216 – 22466)	11296 (10371 – 14634)	0.21

9.2.6.3 Ventilatory equivalent for carbon dioxide at anaerobic threshold

There was no difference in the submaximal HRR parameters between patients identified as low and high-risk by VE/VCO_2 (Table 84).

Table 84 Difference in HRR parameters between patients dichotomised into high and low-risk by ventilatory equivalent for carbon dioxide at anaerobic threshold (VE/VCO_2). n = 12. Wilcoxon rank sum test. Values are median (IQR).

HRR parameter	VE/VCO_2 <34 *n = 6*	VE/VCO_2 ≥34 *n = 6*	p value
HRR_1 (bpm)	14.9 (14.2 – 16.1)	16.1 (9.7 – 23.7)	0.81
HRR_1-ECHR (bpm)	24.3 (21.5 – 26.6)	21.4 (14.3 – 31.9)	0.69
AUC_{30} (bpm.s)	967 (763 – 1172)	934 (727 – 1147)	0.94
AUC_{30}-ECHR (bpm.s)	1572 (1089 – 1931)	1310 (1047 – 1535)	0.38
AUC_5-ECW (bpm.s)	12866 (10602 – 14806)	13068 (10854 – 16434)	0.81

9.3 Discussion

The aim of this investigation was to determine the concurrent and criterion validity of the five best-performing submaximal HRR parameters identified in Chapter 6 (Heart rate recovery and postoperative myocardial injury (predictive validity)). Construct validity was not demonstrated for any of the submaximal

HRR parameters. Only HRR_1-ECHR demonstrated criterion validity with a significant difference between high and low-risk groups as identified by anaerobic threshold. Strong conclusions cannot be made due to the small sample size, and the potential for type I error due to multiple comparisons, thereby limiting this weak difference between groups. However, criterion validity was not demonstrated for the HRR parameters as assessed by VO_{2peak} or VE/VCO_2.

9.3.1 Cardiopulmonary exercise test parameters

Cardiopulmonary exercise testing is a resource-intensive modality which is offered in only a few centres within the West of Scotland and consequently only 12 of the patients recruited to the VERVE study underwent CPET (14%). In both centres in this study (UHH and UHC), referral to the CPET service requires careful patient selection and enough time within the preoperative journey to allow for slot allocation and interpretation of results. As described in Section 6.2recruitment to the study, particularly of patients undergoing vascular surgery from UHH, was limited by the post-pandemic landscape and slow site approvals. All patients with aortic aneurysmal disease undergo CPET at UHC when able, but in the limited time available, only ten of these patients were recruited. At UHC, it is predominantly major colorectal patients with limited subjective functional capacity who are referred to preoperative CPET and only were recruited within the study period. The study was designed to only include patients who were having preoperative CPET as part of their routine clinical care, as the resources (research funding, CPET availability) were not available to offer it for every patient. Unfortunately, this limited the investigation of concurrent and criterion validity for submaximal HRR and is a limitation to the interpretation of these results.

9.3.2 Criterion validity

There was no correlation between the five best-performing HRR parameters and each of anaerobic threshold, peak oxygen consumption and ventilatory equivalent at anaerobic threshold meaning criterion validity was not demonstrated. Aside from the low number of patients, there are other considerations which may have affected these results. Firstly, the twelve patients who underwent CPET were all quite similar with little variation in CPET

parameters (Table 78). This is likely due to the narrow indications for CPET clinically as described above meaning the spread of data may not have been enough to demonstrate correlation where it exists. Secondly, as discussed in Section 1.2.10, the CPET variables reported in this investigation and submaximal HRR measure different aspects of physiological fitness and so are not directly comparable. Both anaerobic threshold and peak oxygen consumption are measures of the ability of the body to deliver oxygen to working muscles, thereby incorporating respiratory, cardiovascular and muscle function. The ventilatory equivalent of carbon dioxide at AT is a measure of gas exchange efficiency incorporating both cardiovascular and respiratory function. Submaximal HRR is a measure of cardiac vagal tone which although reflecting overall aerobic capacity is more cardio-specific than the CPET variables. The five submaximal HRR parameters used were chosen based on their predictive value for PMI, and most of the evidence for the CPET variables is for postoperative mortality and combined cardiorespiratory complications, with very few studies investigating purely cardiovascular complications[62]. In the METS study, neither VO_{2peak} nor AT were associated with postoperative myocardial infarction or injury[38]. Therefore, although CPET is currently the "gold-standard" exercise modality for prediction of perioperative risk, the measures may be too dissimilar to demonstrate correlation with PMI in this limited patient cohort.

9.3.3 Concurrent validity

The three CPET variables were split into high and low-risk groups based on thresholds described in the literature. Three patients met the high-risk criteria for AT and three patients met the high-risk criteria for VO_{2peak}; two of these were the same patients. Concurrent validity was only demonstrated for HRR_1-ECHR as there was a difference in HRR_1-ECHR for patients dichotomised into low and high perioperative risk by AT ($p = 0.03$). There was no difference between groups in any of the other HRR parameters for AT, but the groups did display the expected pattern (e.g. low HRR_1 with low AT). When dichotomised by VO_{2peak}, concurrent validity was not demonstrated for any of the submaximal HRR parameters but again the expected pattern was demonstrated for all. This was an exploratory investigation in a very small cohort of patients and so there is potential for type II error.

Due to multiple comparisons, there is an increased risk that the positive result for HRR_1-ECHR is due to type I error. However, the other HRR parameters do show the expected pattern when dichotomised by AT, although criterion validity was not demonstrated (Table 79). Potentially, by dichotomising patients by risk, the effect of the lack of variety between patients as described above is reduced.

Another limitation of the criterion validity investigation is that the cut-offs for interpretation of the CPET variables are not established within the literature, with variation depending on type of surgery, sex and patient population. The cut-offs used in this investigation were chosen carefully, however may be fairly arbitrary in accurately predicting risk. It is out with the remit of this investigation to determine more accurate CPET variable cut-offs for this patient cohort.

There were six patients identified as high-risk as per VE/VCO_2 at AT and compared to the low-risk group, there was no difference in any of the HRR parameters. The HRR parameters did not demonstrate concurrent validity with VE/VCO_2 likely because VE/VCO_2 is more a marker of respiratory rather than cardiovascular function (although clearly both are related and interdependent in the response to exercise).

9.3.4 Criterion and concurrent validity of perioperative heart rate recovery in the literature

There are no studies specifically investigating the criterion validity of submaximal HRR in a perioperative population. The association between maximal HRR and VO_{2peak} is moderate in cardiology patients undergoing maximal treadmill tests. A retrospective study of 296 patients with chronic congestive heart failure (defined as left ventricular ejection fraction <50%) found moderate correlation (Pearson's correlation coefficient 0.47, $p < 0.001$) and this effect was independent of beta-blocker use[221]. In 388 patients with stable coronary artery disease undergoing maximal treadmill test, HRR and VO_{2peak} also demonstrated mild correlation ($r = 0.35$, $p < 0.001$)[222].

In the perioperative population, there is indication that maximal HRR and peak VO_2 are related. Although not part of the analysis, two substudies of the METS

trial reported CPET variables as part of baseline demographics when the study population was dichotomised by maximal HRR_1, with HRR_1 ≤12 bpm defined as high-risk and HRR_1 >12 bpm low-risk of postoperative complications. Abbott et al., reported mean±SD VO_{2peak} 17.1±5.6 ml/kg/min in high-risk patients and 20.8±6.5 ml/kg/min in low-risk patients (p <0.001); and mean±SD AT 11.6±3.4 ml/kg/min in high-risk patients versus 13.4±4.4 ml/kg/min in low-risk patients (p <0.001)[150]. Similarly, Ackland et al., reported mean±SD AT of 11.5±3.3 ml/kg/min in high-risk patients (per maximal HRR_1) and 13.0±4.1 ml/kg/min in low-risk patients (p <0.001)[156]. Both studies dichotomised patients by the established maximal HRR_1 cut-off of 12 bpm, rather than the less established CPET variables thresholds as used in this investigation. The submaximal HRR parameters are novel measures without established risk cut-offs.

Association between orthostatic HRR_1 and VO_{2peak} has been investigated recently as a secondary outcome in a study looking at correlation between orthostatic HRR and maximal HRR after CPET in 87 older patients. The investigators found slower orthostatic HRR (defined as a HRR one minute after peak standing heart rate reached of ≤1 bpm) was associated with a lower VO_{2peak} (mean difference 3.7 ml/kg/min (95%CI 0.7 – 6.8), p = 0.04)[223]. The cut-off of 1 bpm was determined by dichotomising patients based on their maximal HRR_1.

There are no studies investigating the relationship between HRR and ventilatory equivalents in the perioperative population. Although there is limited data within the literature (and within different patient populations), there appears to be moderate association between HRR and VO_{2peak}, and to a lesser extent, anaerobic threshold. This is to be expected as both are markers of the cardiovascular response to exercise and therefore aerobic capacity. However, this was not demonstrated in this investigation. It is perhaps unsurprising that none of the HRR parameters demonstrated association with VE/VCO_2 as this is more a measure of the ventilatory response to exercise, which although still interlinked with the ability of the body to effectively transport oxygen to working muscles, is a different system to the main determinants of HRR.

9.4 Conclusion

Criterion validity for the five best-performing submaximal HRR parameters was not demonstrated. Concurrent validity was indicated for HRR_1-ECHR with a significant difference in HRR_1-ECHR between patients identified as low and high-risk by anaerobic threshold, although the results are limited by the very small size of the cohort and construct validity cannot be confirmed as there was no correlation between the two measures. This was the only evidence of criterion validity however, with none of the other HRR parameters demonstrating a difference when dichotomised by AT, VO_{2peak} or VE/VCO_2. The results highlight the limited utilisation of CPET within the study population and the limited evidence for CPET as a predictive measure for postoperative cardiovascular complications.

Chapter 10 Acceptability of the exercise test modalities for patients

This Chapter describes the results of a questionnaire assessing the comfort and acceptability of both the step test and cardiopulmonary exercise test (CPET) for those patients who undertook both.

10.1 Specific Methods

All patients who underwent both CPET and the step test were sent a questionnaire, created by the author, via post after they had completed both tests (Figure 64). A stamped return envelope was included. The questionnaire aimed to ascertain any differences in comfort and preference between the two tests and included closed and open questions and 10-point numerical scales. The questionnaire is unvalidated but based on a patient survey performed by the European Lung Foundation to determine the acceptability of regular CPET in patients with lung disease[224]. This survey reported the most common reasons for discomfort during CPET which were then used as options in the questionnaire for this investigation. This is the first questionnaire to assess the acceptability of a submaximal step test for patients. For the questionnaire and the following results, CPET is referred to as the “bike test”.

VERVE exercise test questionnaire

Date of completion (after both bike and step test) ...../...../..... (DD/MM/YY)

Which did you prefer to complete? Please circle: Bike / Step / no preference

Section 1: Cardiopulmonary exercise testing (bike test)

1. Would you do the bike test again? Yes / no

2. Did you experience any discomfort? Yes / no
   If you answer "no" please proceed to question 5.

3. If yes, please circle as appropriate: sore legs, chest pain, difficulty breathing, dry mouth, sweat, muscle soreness, seat uncomfortable, mask uncomfortable, cough, other

   If other, please write here: _____

4. If yes, how much did this discomfort affect your ability to complete the test?

   Not at all _____ Had to stop test
   0 1 2 3 4 5 6 7 8 9 10

5. How hard do you feel you exerted yourself during the bike test?

   Not at all _____ Full exertion
   0 1 2 3 4 5 6 7 8 9 10

6. How acceptable did you find the bike test?

   Not at all acceptable _____ Very acceptable
   0 1 2 3 4 5 6 7 8 9 10

Section 2: Step test

1. Would you do the step test again? Circle as appropriate: Yes / no

2. Did you experience any discomfort? Circle as appropriate: Yes / no

   If you answer "no" please proceed to question 5.

3. If yes, please circle as appropriate: sore legs, chest pain, difficulty breathing, dry mouth, sweat, muscle soreness, difficulty in balance, cough, other

   If other, please write here: _____

4. If yes, how did this discomfort affect your ability to complete the test?

   Not at all _____ Had to stop test

   0 1 2 3 4 5 6 7 8 9 10

5. How hard do you feel you exerted yourself during the step test?

   Not at all _____ Full exertion

   0 1 2 3 4 5 6 7 8 9 10

6. How acceptable did you find the step test?

   Not at all acceptable _____ Very acceptable

   0 1 2 3 4 5 6 7 8 9 10

Figure 64 Exercise test acceptability questionnaire which was posted to patients. Bike test refers to cardiopulmonary exercise testing.

10.2 Results

Twelve patients completed both CPET and the step test (see Section 9.2.1 for demographics) and were sent the questionnaire. Seven out of the twelve patients returned the exercise test questionnaire; a response rate of 58%, although data were missing from some questions.

Preference for the exercise test modality was split with two patients preferring CPET, two preferring the step test and two patients with no preference between the two tests. One patient did not complete this question.

Willingness to perform the exercise test again was higher for the step test with five patients saying they would perform it again versus three patients for CPET. One patient did not answer this question in relation to the bike test (Figure 65).

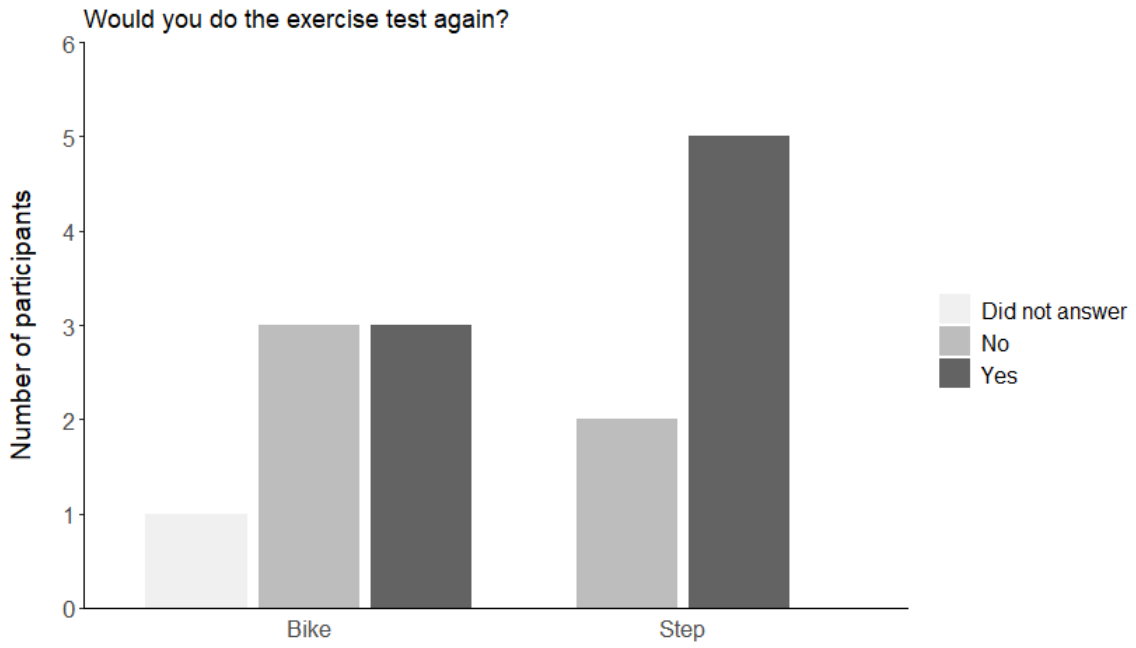


Figure 65 Patient response to "Would you do the exercise test again?" for cardiopulmonary exercise testing (bike) and the step test. n = 7. Light grey: did not answer; grey: "No"; dark grey: "Yes"

Five patients experience discomfort during CPET (one patient did not answer this question) and three during the step test. This indicates that overall, patients found the step test more comfortable than CPET, although two patients also found the step test uncomfortable (Figure 66).

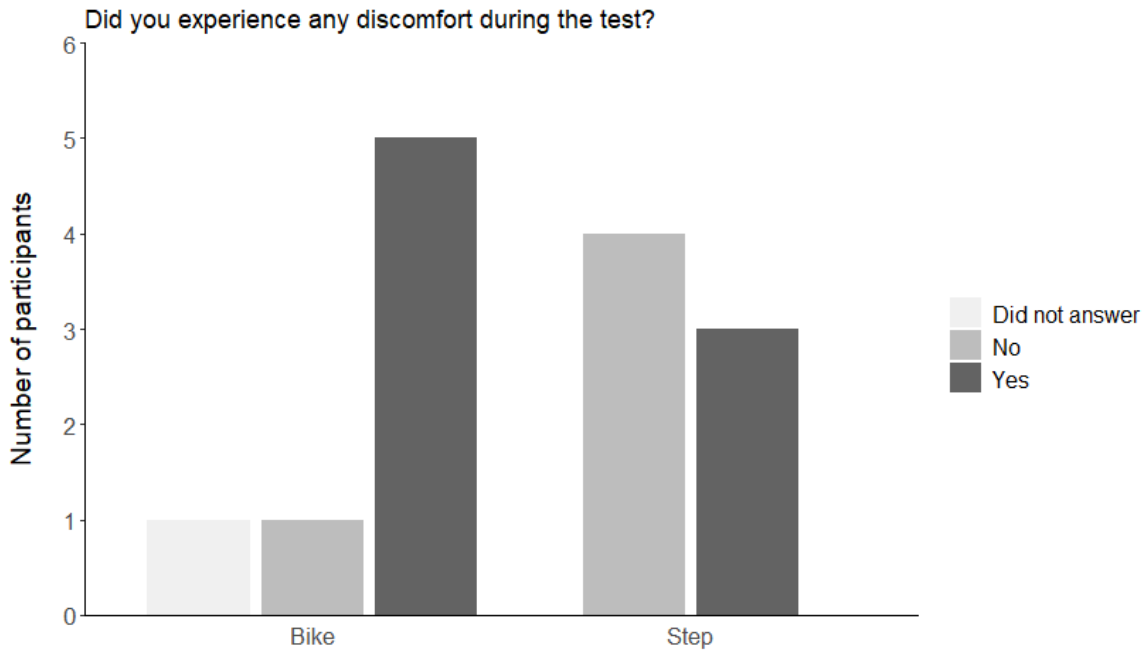


Figure 66 Patient response to "Did you experience any discomfort during the test?" for cardiopulmonary exercise testing (bike) and the step test. n = 7. Light grey: did not answer; grey: "No"; dark grey: "Yes"

Of the five patients who experienced discomfort during CPET, three experienced sore legs, two experienced mask discomfort, one experienced overall muscle soreness and one experienced difficulty in breathing (patients could circle multiple options in response to this question). Of the three patients who experienced discomfort during the step test, two experienced sore legs and one difficulty in breathing (Figure 67).

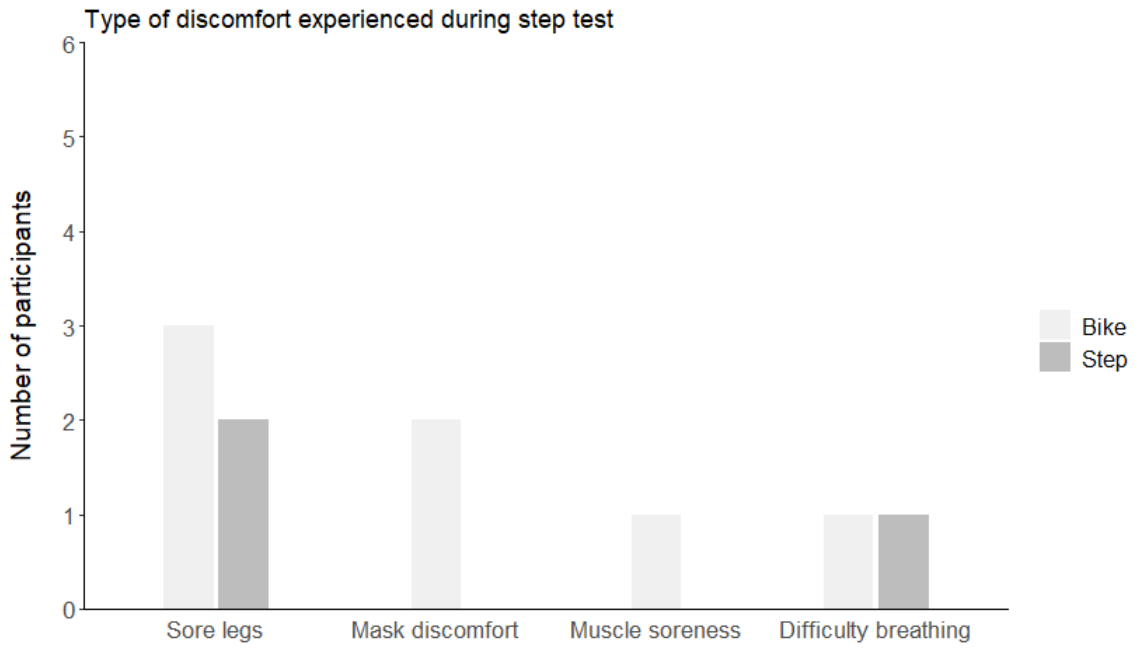


Figure 67 Type of discomfort experienced during cardiopulmonary exercise test (light grey, n = 5) and step test (grey n = 3)

The scores on the 10-point scale in response to how much did the discomfort affect the ability to complete the test is shown in Figure 68.

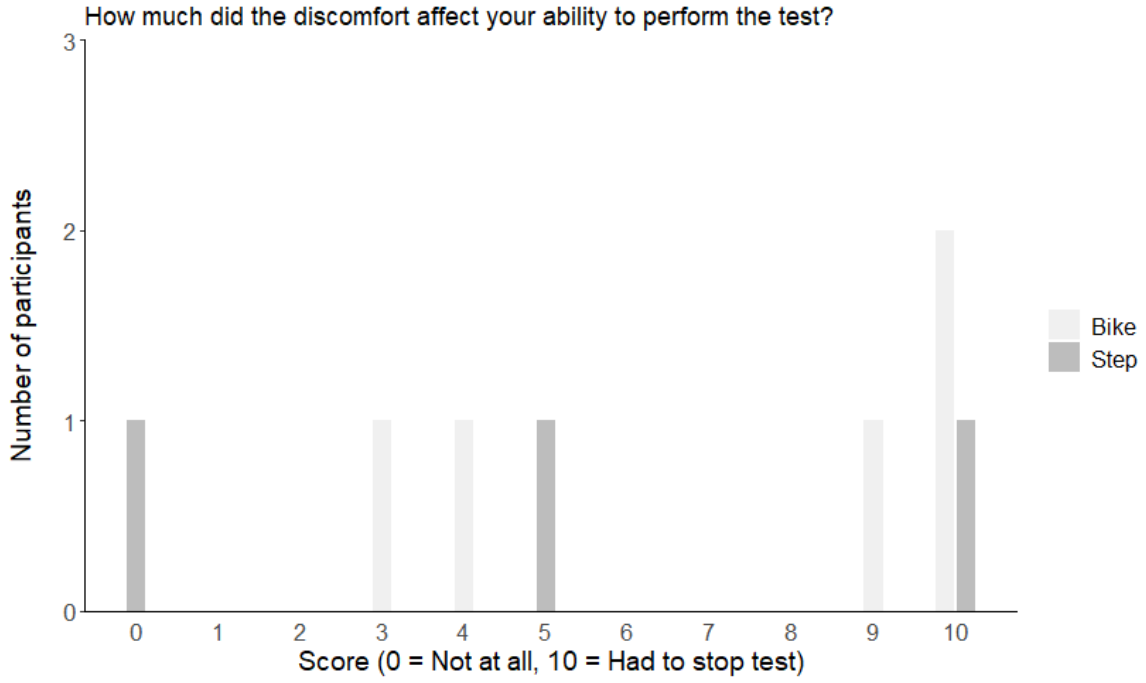


Figure 68 Amount the discomfort affected the ability to perform the cardiopulmonary exercise test (light grey, n = 5) and step test (grey, n = 3). 10-point scale where 0 = "not at all" and 10 = "Had to stop test".

There was no difference (p = 0.76) in the median (IQR) score for discomfort affecting the ability to complete the test for CPET (9.0 (4.0 – 10.0), n = 5) compared with the step test (5.0 (2.5 – 7.5) n = 3).

Subjective exertion was compared between the two exercise modalities via a 10-point scale where 0 = “Not at all” and 10 = “Full exertion” (Figure 69). There was no difference in the median (IQR) score for CPET (8.0 (5.5 – 9.8), n = 6) compared with the step test (7.0 (3.5 – 9.5), n = 7, p = 0.61).

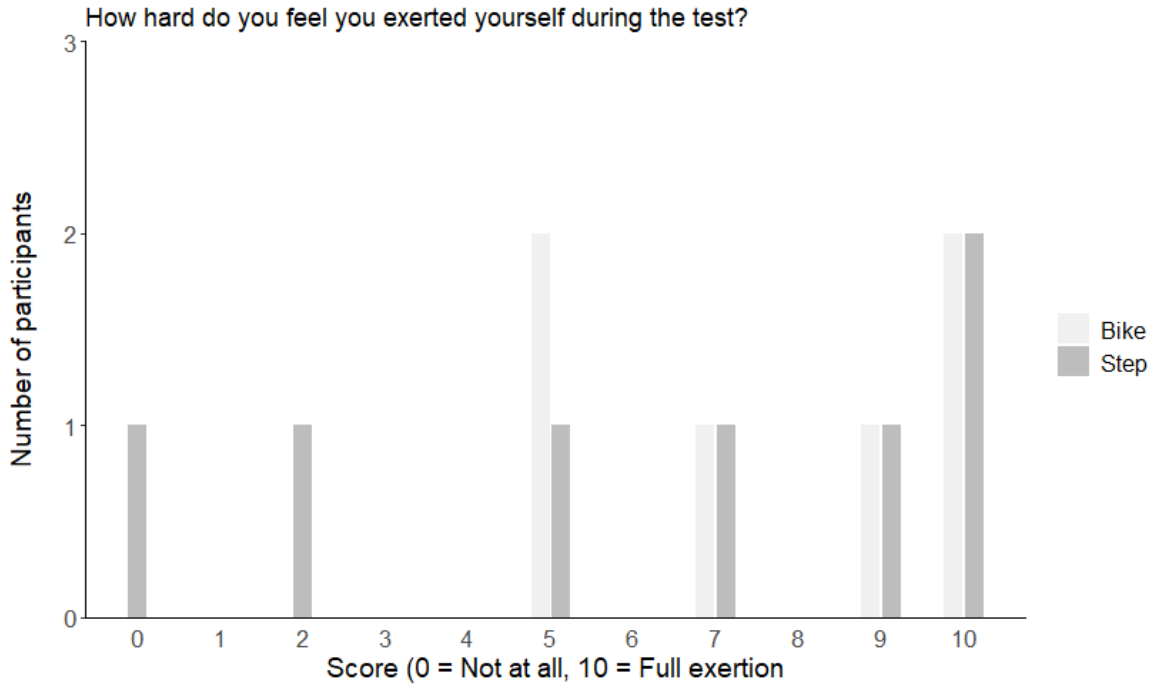


Figure 69 Subjective exertion during the cardiopulmonary exercise test (light grey, n = 6) and step test (grey, n = 7). 10-point scale where 0 = "not at all" and 10 = "Full exertion".

Finally, the acceptability of the two exercise tests to perform was compared via a 10-point scale where 0 = “Not at all acceptable” and 10 = “Very acceptable” (Figure 70). The median (IQR) score for CPET was 7.5 ((5.0 – 10.0), n = 6) and the median score for the step test was 10.0 ((9.0 – 10.0), n = 7) and there was no difference (p = 0.25).

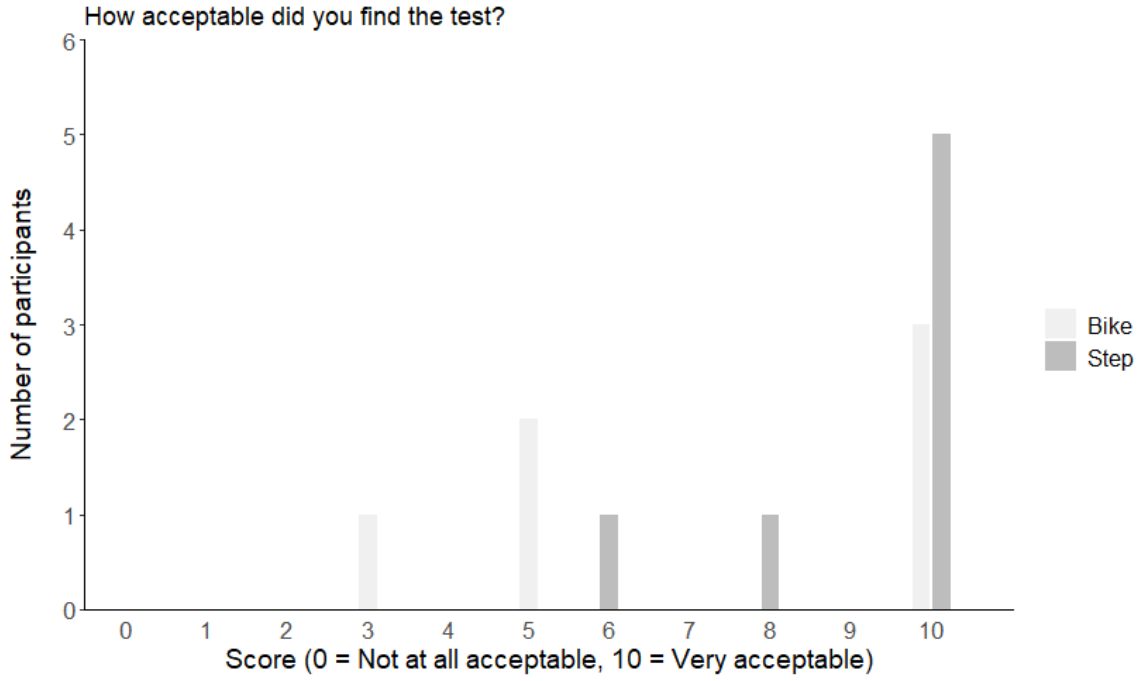


Figure 70 Acceptability of the cardiopulmonary exercise test (light grey, n = 6) and step test (grey, n = 7). 10-point scale where 0 = "not at all acceptable" and 10 = "very acceptable".

10.3 Discussion

This is the first patient questionnaire investigating comfort and acceptability of a submaximal step test for patients and comparing this with CPET, albeit within a very small cohort of patients. The questionnaire aimed to ascertain any preference between the two tests, and to explore any perceived issues with the step test, if it is to be incorporated into routine clinical use. Seven patients filled out the form but unfortunately one patient did not complete the section for CPET; this equating to a response rate of 58% which is considered good[225].

In terms of patient preference, there was no difference between the two tests, although when asked how acceptable they found the tests, the step test appeared more acceptable (Figure 70) and more patients would prefer to perform the step test again (5/7 (71%) versus 3/6 (50%)). More patients experienced discomfort during CPET (5/6 (83%) versus 3/7 (43%)). This discomfort was due to sore legs, mask discomfort, muscle soreness and difficulty breathing. Discomfort during the step test was due to sore legs and difficulty breathing; this is reinforced by the median Borg score of 4 (“somewhat severe” dyspnoea) reported at the end of exercise by all patients who completed the

step test (Table 14). The impact of this discomfort on the ability to complete the test was equivocal between the two exercise tests, although the fact that more patients experienced discomfort during CPET implies that discomfort during CPET may lead to a higher rate of failure of test completion. Patients exerted themselves more during CPET which is to be expected. The step test appeared to be more acceptable to patients than CPET, although when the median scores were compared, they were not different. One reason for this may be that patients were aware of the clinical benefit of CPET for their care and perioperative planning. Clearly in this case, the step test was performed as research and so had no measurable benefit for the individual patients aside from altruism.

There are no published patient surveys comparing attitudes towards CPET and step tests. However, Scherrenberg et al., found no difference in patient preference between the 6MWT and CPET in 98 patients with cardiovascular disease. Patients who preferred the six-minute walk test did so because they found it “easy” or “pleasant”, whereas those who preferred CPET did so because they preferred cycling as the exercise modality or because they found it gave them more information about their health status[226]. Patients reported similar considerations in a survey as part of an investigation into the feasibility of CPET in interstitial lung disease. Nineteen patients strongly rated CPET as feasible and did not find it too challenging to perform. In free text answers, patients reported preferring CPET as they felt it gave them more information than “walk tests” (either shuttle or six-minute walk tests), citing being able to push themselves and measuring more parameters as the benefits to CPET[227]. A patient survey in 2018 investigating the acceptability of CPET in 295 patients with chronic lung disease found that 80% found the duration of CPET “mostly acceptable” but that generally patients would prefer to perform its less regularly than they currently were (1-2 times/year rather than 2-5 times/year). A dry mouth, muscle soreness, discomfort from the bicycle seat, cough and the mouthpiece were rated as a “serious problem” whilst performing CPET. However, 75% patients reported that they found the increased knowledge regarding their lung disease that CPET presents as useful. The conclusions from the survey were that patients would like more information about the test and

test results, and implementation of ways to make the test more comfortable such as fans, or water availability[224].

10.4 Conclusion

Strong conclusions cannot be made due to the very small number of patients who completed the questionnaire but the results indicate that overall, both CPET and the submaximal step test were well tolerated, but the step test appeared more comfortable and potentially more acceptable to a small group of patients. Discomfort was more common with CPET, encompassing muscle pain, discomfort from the face mask and difficulty breathing. Discomfort during the step test was due to muscle soreness and difficulty breathing. Patients seemed to feel that this discomfort was more likely to affect their ability to complete their test more during CPET, although the difference between median scores was not significant. Similarly, the step test appeared more acceptable to patients, whilst comparison of median scores did not demonstrate a difference, these results are from a very small cohort of patients. Overall, the step test appears to cause less discomfort than, and was well tolerated compared to, CPET. However, this is in a very small cohort and so further work needs to be done to potentially develop the survey methodology, and to assess acceptability of the step test in a larger cohort. Despite this, the results provide reassurance that a submaximal step test appears to be acceptable for patients to perform when appropriate and clinically indicated

Chapter 11 Major findings, conclusions and future work

This thesis initially presents a review of perioperative risk and how preoperative submaximal HRR is hypothesised to be a useful measure of functional capacity and therefore may have a role in identifying patients at postoperative risk. A comprehensive assessment of the validity of submaximal HRR as a perioperative risk measure follows. A summary of the major findings of each investigation is presented here.

11.1 Major findings

11.1.1 Chapter 2 (Systematic review and meta-analysis)

This systematic review and meta-analysis found four observational studies investigating association between preoperative HRR and postoperative outcomes. Three of these studies measured HRR_1 after maximal exercise testing (CPET) and one after submaximal exercise testing (6MWT). Meta-analysis of pooled results did not demonstrate association between HRR_1 and postoperative complications or hospital length of stay, but was limited by heterogeneity in both study design and outcomes measured. Taken individually, each study did demonstrate potential association between HRR_1 and postoperative outcome, although selection bias may lead to over representation of studies which demonstrated association. Though there is very little perioperative literature examining HRR, this technique has the potential to improve perioperative risk stratification in the future and is worthy of further exploration.

11.1.2 Chapter 5 (Generic results)

The generic results demonstrate that the step test and protocol were well-tolerated but there was some dropout of participants for the primary outcome measurement, predominantly because of patients not undergoing their planned surgery or sampling issues with hs-TnT. Patient demographics, surgical specialties and intraoperative parameters confirm that patient selection met the prespecified aims of the investigation to capture a generalisable population at increased risk of postoperative cardiovascular complications.

The step test appeared to be well-tolerated, taking approximately one and half minutes on average and with tolerable levels of dyspnoea. The protocol worked well with tight target heart rate control, and all patients able to complete the step test, indicating feasibility for future use.

11.1.3 Chapter 6 (Heart rate recovery and postoperative myocardial injury (predictive validity))

The main finding from this investigation was that six of the proposed HRR parameters demonstrated predictive value (and therefore predictive validity) for postoperative myocardial injury (HRR_1, HRR_1-ECHR, AUC_{30}, AUC_{30}-ECHR, AUC_5-ECW, AUC_2-ECW). These results included both the absolute fall in heart rate after exercise cessation and the area under the HRR curve, and effort-correction to both proportion of age-predicted HR_{max} reached and proportion of predicted power output reached. The predictive value (AUROC) ranged from 0.64 – 0.69, indicating poor to fair predictive value but, importantly, comparable, and in some cases better, to perioperative risk prediction measures in clinical use.

Submaximal HRR_1 demonstrated better association with PMI than all currently-used risk measures (NT-ProBNP, DASI, RCRI, SORT) in this cohort of patients. Addition of submaximal HRR_1 to logistic regression models improved the predictive value of all these currently-used risk measures via both area under the receiver operating curve and net reclassification index.

11.1.4 Chapter 7 (Heart rate recovery and postoperative complications (face validity))

Association between the HRR parameters and postoperative complications including clinical outcomes indicators was investigated to assess face validity. Face validity was not demonstrated by the HRR parameters for most postoperative complications. However, HRR_1 and HRR_1-ECHR did demonstrate face validity for renal complications, with association with change in creatinine within seven days of surgery and MAKE at 30-days. Although not demonstrating statistical significance, all the selected HRR parameters showed the expected pattern in patients who did and did not develop AKI, supporting this result (e.g. worse HRR associated with worse outcomes). Postoperative renal stress and PMI

share similar biological mechanisms and so this result is consistent with the pathophysiological basis behind both outcomes.

There was also association between both HRR_1 parameters (absolute and effort-corrected to heart rate) and both AUC_{30} parameters (absolute and effort-corrected to heart rate) and all ICU admission, however this association lost statistical significance when only unplanned ICU admission was assessed. This may be because of low incidence of unplanned ICU admissions (five patients) or actually reinforces face validity as the patients that had planned admissions to ICU were recognised as high-risk by their perioperative clinicians.

11.1.5 Chapter 8 (Heart rate recovery and preoperative risk scores (construct validity))

Association between currently-used preoperative risk prediction measures and the five best-performing HRR parameters was investigated to assess construct validity. Construct validity was demonstrated for submaximal HRR_1 as it demonstrated significant association with SORT mortality, ACS-NSQIP SRC risk of any postoperative complication and length of stay, DASI, RCRI and both P/V-POSSUM morbidity and mortality. These associations were demonstrated for both absolute submaximal HRR_1 and submaximal HRR_1 effort-corrected to proportion age-predicted HR_{max} reached, however effort-correction to heart rate did not significantly improve the association with the constructs. Both the AUC_{30} parameters and AUC_5-ECW were associated with one or two constructs, but not consistently and so did not demonstrate construct validity.

11.1.6 Chapter 9 (Heart rate recovery and cardiopulmonary exercise testing variables (criterion and concurrent validity))

Criterion validity was assessed through association between the HRR parameters and AT, VO_{2peak} and VE/VCO_2 at AT as measured via CPET. Concurrent validity was assessed by difference between HRR parameters when patients were dichotomised into high/low-risk via the CPET variables. Criterion validity was not demonstrated for any of the five submaximal HRR parameters investigated. The only submaximal HRR parameter suggestive of concurrent validity was submaximal HRR_1-ECHR, which demonstrated a difference between patients identified as high and low-risk by anaerobic threshold. However, this difference

was not demonstrated with the other CPET variables. Only twelve patients underwent CPET and the step test and so the conclusions drawn from this investigation are limited.

11.1.7 Chapter 10 (Acceptability of the exercise test modalities for patients)

Overall, both exercise tests (submaximal step test and CPET) were well-tolerated by a small subset of patients. The questionnaire indicated that the step test appeared to be both more comfortable and more acceptable to patients, although this was in a very small cohort of patients and so requires confirmation in a larger population.

11.2 Conclusion

The main finding of this thesis is that submaximal HRR does demonstrate predictive validity for postoperative myocardial injury. Submaximal HRR_1 specifically also appears to improve the predictive value of currently used risk prediction measures for PMI. Five other submaximal HRR parameters also demonstrated predictive value for PMI, and the four best-performing were taken forward for further validity testing. Submaximal HRR_1 was most consistent in demonstrating construct validity and association with postoperative renal complications (face validity). None of the five best-performing HRR parameters demonstrated convincing criterion or concurrent validity when compared to markers of aerobic fitness as measured via cardiopulmonary exercise testing.

A range of different methods of measuring submaximal HRR were proposed, based on previous work and to ensure information from the whole HRR profile was incorporated. Effort-correction to both heart rate and power output was also used to approximate the parameters, as if a maximal test had been performed to potentially strengthen their predictive capability. As described above, the fall in heart rate one minute after end exercise (HRR_1) was one of the best-performing measures with the most consistent performance in both construct and face validity investigations. Effort-correction to proportion of age-predicted HR_{max} reached did not greatly improve its validity. Two area under the heart rate recovery curve measures also demonstrated predictive value for PMI,

however, performance for other types of validity were poor and less consistent than HRR_1.

Heart rate recovery one minute after exercise cessation is a straightforward and intuitive measure, which does not require complex mathematics to calculate and can easily be relayed to patients. There is already evidence that it is associated with postoperative outcome when measured after maximal exercise testing and one study reporting its association with cardiopulmonary complications when measured after six-minute walk test. Therefore, it is not a completely novel marker, although this is the first time submaximal HRR_1 has been measured after a step test in clinic or the ward in a perioperative population. Heart rate recovery is also becoming a more familiar term within the general population as many smartwatches now display HRR after activity.

In terms of performance of submaximal HRR_1 as a novel perioperative risk measure, the author refers back to the Sackett criteria[127] (Section 1.5):

1. *Has there been an independent, "blind" comparison with a "gold-standard" of diagnosis?*

   There is not a "gold-standard" of risk prediction to compare submaximal HRR to, however, the demonstration of predictive value for PMI and construct validity for submaximal HRR_1 is strongly suggestive that it is comparable to, if not better than, risk prediction measures in currently use.

2. *Has the diagnostic test been evaluated in a patient sample that included an appropriate spectrum of mild and severe, treated and untreated, disease?*

   Submaximal HRR was assessed in a wide variety of patients undergoing a variety of intermediate/high-risk operations for predictive and construct validity. For the criterion and concurrent validity studies, there is the potential that patient group was very narrow (i.e. all high-risk patients undergoing high-risk surgery) limiting the spread and therefore signal of

potential association between the CPET variables and the submaximal HRR parameters.

3. *Was the setting for this evaluation, as well as the filter through which study patient passed, adequately described?*

   The setting was pragmatic and routine; either in preoperative assessment or on the ward on the day prior to surgery. The step test was well-tolerated, with the acceptability questionnaire (Chapter 10) indicating that it was acceptable to patients. Submaximal HRR_1 particularly is a straightforward to measure metric.

4. *Have the reproducibility of the test result (precision) and its interpretation (observer variation) been determined?*

   Reproducibility of submaximal HRR has previously been described in healthy participants by our group[163,164] and in the wider literature[125,126]. It is also reproducible across exercise modalities. However, reproducibility within a patient group has not been investigated and should be a consideration for future studies.

5. *Has the term "normal" been defined sensibly as it applies to this test?*

   "Normal" values for submaximal HRR_1 have not been described, however in this study, two different methods for ascertaining cut-offs for high and low-risk have been described. Further validation of these thresholds is required.

6. *If the test is advocated as part of a cluster or sequence of tests, has its individual contribution to the overall validity of the cluster or sequence been determined?*

   Bivariate logistic regression models incorporating submaximal HRR_1 in addition to all currently-used risk prediction measures demonstrated improvement in prediction for PMI. In this cohort of patients, the best model was SORT + HRR_1 which demonstrated a predictive value (AUROC)

of 0.74 compared to 0.66 for SORT alone and 0.69 for HRR_1 alone. Net reclassification for all bivariate models demonstrated that the models reclassified patients who developed PMI correctly, and to a lesser extent, those who did not.

7. *Have the tactics for carrying out the test been described in sufficient detail to permit their exact replication?*

   The test is straightforward to perform, with ECG measurement of heart rate in the clinical setting and easy calculation of target heart rate based on age[175]. As described elsewhere, submaximal HRR appears reproducible across exercise modalities including walking and so step equipment may not be necessary if resources do not allow.

8. *Has the utility of the test been determined?*

   This is the first study to demonstrate the predictive and construct validity of submaximal HRR_1 in the perioperative population. Submaximal HRR_1 particularly, appears to perform as well as risk prediction measures currently in use. Therefore, the utility of the test is determined in that it provides an objective measure of functional capacity but without the need for CPET. However, how the clinician would act upon a submaximal HRR_1 result requires further investigation.

In summary, the VERVE study demonstrated the feasibility of performing a submaximal exercise test in an intermediate/high-risk surgical population within the preoperative assessment or ward environment, which is acceptable to patients. Submaximal HRR_1 has been validated in this cohort as a perioperative risk measure for PMI, with performance equivalent to, or sometimes better than, risk prediction measures currently in use. The addition of submaximal HRR_1 to univariate logistic models of currently-used risk prediction measures improves their performance for the prediction of PMI, with the caveat that none of these risk measures are validated for PMI prediction. Submaximal HRR_1 also demonstrated construct validity and face validity through its association with postoperative renal complications and ICU admission. Criterion and concurrent validity, as measured by the association between submaximal HRR parameters

and maximal measures of functional capacity as measured by cardiopulmonary exercise testing was not demonstrated. However, despite CPET being the "gold-standard" for determination of cardiorespiratory fitness, it is not the "gold-standard" for perioperative risk prediction and so lack of association between submaximal HRR and CPET variables is not necessary to determine the clinical usefulness of submaximal HRR, particularly as they measure different physiological responses to exercise. Submaximal HRR_1 is an easy to measure, objective marker of functional capacity (and likely cardiac vagal tone) which shows promise as a perioperative risk measure.

11.3 Strengths and limitations

The main strength of this study was the comprehensive design incorporating novel HRR parameters to include the whole HRR profile curve and the investigation of five different types of validity to fully assess the potential clinical usefulness of submaximal HRR. The study was an observational, pragmatic trial meaning that the exercise test and heart rate measurement could be easily incorporated into the clinical setting. Despite challenges and delays in starting the study, and a limited timeframe in which to recruit patients, eighty-four patients were recruited which is similar to the only other published study investigating submaximal HRR in the perioperative population[158], with the breadth of validation much wider in this thesis. Overall, the results conform to the physiological basis of the study, with submaximal HRR parameters demonstrating predictive value for PMI, with HRR_1 demonstrating face validity for postoperative renal complications (similar pathophysiology to PMI) and demonstrating fair association with currently-used risk measures, therefore construct validity. Heart rate recovery after one minute is also widely validated in other populations, and so the findings from this study are consistent with the literature. In particular, the investigation assessing improvement in predictive value for PMI when submaximal HRR_1 was added to logistic regression models of currently-used perioperative risk measures (NT-ProBNP, SORT, DASI, RCRI) is a strength as it demonstrates both the relatively poor performance of these measures in this cohort (for PMI) compared to HRR_1 and how submaximal HRR_1 could be utilised in the future potentially as part of a multiple logistic regression model for risk prediction. The association between HRR parameters and patient-reported outcome measures (QoR-15 and $DaOH_{30}$) was investigated,

although no association was demonstrated. Patient opinion was also sought regarding the acceptability of the step test compared to CPET, demonstrating that the impact of this submaximal HRR on patient experience was considered throughout.

The main limitation is that the sample size for the primary outcome was not met due to reasons described in Section 6.2. Primary outcome data was further limited by patients either being cancelled for their surgery after pre-assessment or not undergoing their surgery within six months of recruitment and problems with hs-TnT processing. The lower sample size clearly increases the risk of a lack statistical power for analysis but despite this, statistically significant predictive value for PMI was demonstrated for a selection of the HRR parameters. There is the potential however that other HRR parameters which were investigated were underpowered to detect predictive value where it exists.

Multiple comparisons were made in each investigation without correction, which increases the risk of a type I error. This was a pre-planned statistical decision due to the exploratory nature of the investigations, whereby a variety of novel methods of measuring HRR were assessed to account for the submaximal nature of the exercise test (Section 4.9.1.2). There is potential that some of the positive results may be false such as the predictive value of AUC_5-ECW. However, there is enough consistency in the positive results for predictive, construct and face validity for HRR_1 to give confidence that these results are unlikely to be due to type I error.

Postoperative myocardial injury is not a common outcome for perioperative risk prediction; it was specially chosen for the VERVE study as it is a common postoperative complication which confers increased cardiovascular risk with impaired cardiac vagal tone as a likely pathophysiological mechanism. Therefore, the predictive value of submaximal HRR_1 for more generic perioperative risk such as postoperative morbidity or mortality or even patient-reported outcome measures may be useful for discussing risk with patients. Equally, there is the potential that HRR parameters which did not demonstrate predictive value for PMI and therefore were not assessed for face validity may have demonstrated association with other postoperative outcomes such as mortality. To assess the predictive value of submaximal HRR_1 or other HRR

parameters for these outcomes, a much larger study would need to be undertaken.

Construct validity was demonstrated for submaximal $HRR_{1,}$ however there is some divergence between the use of constructs and the five-best performing submaximal HRR parameters as none of the constructs used are designed to predict PMI. This is also the case for CPET variables. Therefore, the associations assessed in the construct and concurrent validity investigations are comparing different potential mechanisms for postoperative complications, explaining why strong correlation was not found nor expected. However, demonstrating association between different measures is useful for potential future studies investigating the addition of submaximal HRR to perioperative risk prediction model development. The constructs used encompassed biomarker testing, surgical risk score and functional capacity. Another potentially useful construct which is not reported could have been the HRR parameters of patients who underwent their operation compared with those who were clinically assessed to be medically unfit for surgery; however, within the whole study cohort there was only one patient this applied to.

11.4 Future directions

Future work building on this thesis needs to further explore how submaximal HRR_1 is incorporated into perioperative assessment including risk cut-offs and integration into risk prediction models; whether measurement needs to remain in the clinical setting or if the evolving use of heart rate monitors could allow submaximal HRR_1 assessment within the community; and whether submaximal HRR_1 shows a training effect which could guide, or assess the efficacy of, prehabilitation.

11.4.1 External validation and incorporation of submaximal HRR into perioperative risk assessment

External validation is required in a larger cohort to confirm the study results. Risk cut-offs for submaximal HRR_1 for PMI are described in Section 6.1.3.2; these also require external validation in a larger cohort to determine their usefulness for risk prediction. As described above, consideration of other postoperative

complications such as clinical outcome indicators or patient-reported outcome measures as the primary outcome may provide more clinical usefulness to the predictive value of submaximal HRR. The effect of effort-correction also warrants further investigation. In this study, effort-correction to age-predicted HR_{max} made minimal difference to the predictive value of the HRR parameters for PMI, but this is likely due to the tight heart rate control during the step test. In situations where heart rate may not be as tightly controlled (e.g. in the community, as described below), effort-correction to heart rate may have more value. Effort-correction to power output reached improved the predictive value of AUC parameters measured later in the recovery period. Within this cohort there was much more variety within power output reached, likely reflecting that power output incorporates cardiorespiratory and neuromuscular function and strength. The author considers that effort-correction of AUC parameters to power output warrants further investigation as the combination of the whole HRR profile plus effort-correction to power output may reflect the whole body response to exercise rather than the PNS response, and could provide further information on perioperative risk.

Currently, there is not one well-established and validated perioperative risk prediction model. As discussed earlier in this thesis, current risk prediction usually involves a combination of factors including assessment of functional capacity, physiological assessment, assessment of co-morbidities and inherent surgical risk. Assessment of functional capacity is usually subjective unless CPET is performed; submaximal HRR_1 provides an objective measure with less resource use and is potentially more accessible for patients to perform. It may have use as a risk prediction measure on its own plus as a screening tool to identify patients for whom further investigation via CPET may be useful. Bivariate logistic regression models incorporating submaximal HRR_1 showed fair predictive value for PMI. Multiple logistic regression was not performed due to the relatively small sample size in this investigation. A future, larger study however could investigate how the incorporation of submaximal HRR_1 affects the predictive value of multiple logistic models for postoperative outcome for example when combined with biomarkers, surgical risk score and comorbidity.

11.4.2 Heart rate recovery in the community

Over recent years there has been growth in the general population purchasing and using heart rate monitors whether via chest straps for use during exercise, wrist-watches which measure pulse continuously or even mobile phone applications. The market for heart rate monitoring devices is expected to grow to a 10 billion dollar industry by 2036[228]. This plus the combination of the predictive value of submaximal HRR_1 may provide an opportunity for objective measurement of patients' functional capacity within the community. Measurement of physical activity within the community is already underway within other medical sectors including diabetes[229], cancer[230] and cardiac rehabilitation[231]. A recent paper by Dr. Jim Luckhurst within our research group demonstrated that a wearable accelerometer (VivaLink ECG Patch, VivaLink, California, USA) was very effective at identifying sedentary and active behaviour in healthy participants in the community[232]. This particular wearable monitor also measures and records ECG so could feasibly measure HRR after activity to provide an objective assessment of functional capacity prior to pre-assessment and without the patient needing to attend the hospital. However, more work needs to be done to assess the validity and reproducibility of heart rate measurement by such devices in the community[233]. Measurement of HRR in the community via wearable technology also raises the possibility of very large datasets of heart rate recovery profiles after varying levels of activity. This opens up the possibility for machine learning to analyse and identify aspects of the HRR profile with predictive value that we have not considered.

11.4.3 Training effect on heart rate recovery and prehabilitation

Training (repetitive exercise at increasing intensities) improves the VO_{2max}, the maximum rate at which oxygen is used during dynamic exercise. This is via adaptation of the cardiorespiratory and skeletomuscular system in a variety of ways including increased stroke volume and reduced resting heart rate, and improved skeletal muscle oxygen utilisation. Recent evidence suggests that cardiac vagal activity also determines the ability to exercise[79]. Therefore, measures of vagal tone can indicate both the aerobic capacity of an individual, but also their potential to respond to exercise and training.

Prehabilitation is a process by which patient health is optimised prior to surgery with the aim of improving their perioperative journey and reducing poor postoperative outcomes. It encompasses patient nutrition, psychological preparedness, healthier lifestyle advice (e.g. smoking/alcohol cessation) and improvement of functional capacity[234]. Improvement of functional capacity involves targeted exercise with monitoring of performance guided by subjective measurement such as 6MWT distance. A recent systematic review found that prehabilitation improved postoperative outcomes (overall and pulmonary morbidity) for patients undergoing major abdominal surgery but interestingly found no improvement in six-minute walk test distance[235]. Submaximal HRR may provide an objective measure of the need and response for exercise within prehabilitation, and may be particularly useful as a community measure as discussed above. Therefore, future studies would be needed firstly to assess whether submaximal HRR demonstrates a trainable effect i.e. it improves in line with other measures of cardiorespiratory fitness in response to exercise; and finally to assess its usefulness as a measure of improvement of functional capacity providing targets for prehabilitation with an associated improvement in postoperative outcome.

In conclusion, this prospective, observational, pragmatic study has demonstrated predictive value for submaximal HRR parameters for PMI in the perioperative population. Of the HRR parameters investigated, HRR_1 demonstrated fair predictive value for PMI, face validity in its association with postoperative renal complications and construct validity in its association with currently-used risk prediction measures. Submaximal HRR_1 performed better than current risk prediction measures for the prediction of PMI in this cohort and addition of submaximal HRR_1 to logistic regression models incorporating these measures improved their performance. Heart rate recovery was measured after a submaximal step test performed in the ward or preoperative assessment setting and appeared acceptable for patients. Moving forward, submaximal HRR_1 appears to be a valid and objective perioperative risk measure which warrants further investigation to ascertain its clinical utility in the perioperative population.

Appendices

11.5 Appendix 1

Search strategy for a systematic review (EMBASE) – 15/11/2022

Source: OVID Embase 1947 to Present
Interface: OVID SP/Wolters Kluwer
Database coverage dates: 1947 to Present (15/11/22)
Search date: 15 November 2022
Retrieved records: 56

Number	Search term	Result
1	(heart rate adj3 recover*).tw	2950
2	(HR adj2 recover*).tw	1791
3	((heart rate OR HR OR heart beat OR heartbeat OR beat* per min* OR bpm) adj5 (post-exer* OR postexer* OR exer* cessation OR ((after OR post OR following) adj2 (exer* OR effort OR recovery)))).tw	2862
4	((drop OR decreas* OR decline OR fall OR decay*) adj4 (heart rate* OR beat OR bpm OR HR OR heart rat*) AND (post-exer* OR postexer* OR exer* cessation OR (after OR post OR following) adj2 (exer* OR effort OR recover*))).tw	1002
5	(HRR OR HRR1 OR HRR2 OR HRR3 OR HRR60).tw	4333
6	(HR OR heart rate*) adj2 (profile* OR respons*).tw	13263
7	Heart Rate/ AND Recovery of Function/	697
8	OR/1-7 [HRR]	23170
9	Exercise Test/ OR Exercise/ OR Walk Test/	405561
10	(cardiopulmon* OR cardiopulmonary exer*).tw	113094
11	(walk* adj3 (test* OR six min* OR 6 min* OR 6-min* OR shuttle)).tw	41238
12	(tread* OR treadmill OR Bruce protocol OR ramp).tw	60925
13	(6MWT OR 6-MWT OR 6MWD OR 6-MWD or CPET or CPEX).tw	20784
14	OR/9-13 [Exercise]	570515
15	Treatment Outcome/ OR Postoperative Complications/	1032381
16	((Complicat* OR outcome* OR morbid* OR mortalit* OR risk) adj3 (Post-operat* OR postop* OR pre-operat* OR preop* OR peri-op* OR periop* OR surg*)).tw	527054
17	OR/15-16 [Outcomes]	1446163
18	8 AND 14 [HRR and exercise]	6731
19	17 AND 18 [HRR after exercise and perioperative outcome]	106
20	Exp Adults/	10588940
21	Humans/	19177391
22	19 AND 20 AND 21	58
23	22 limited to English Language	56

Search strategy for a systematic review (CENTRAL) – 15/11/22

Source: Cochrane Central Register of Controlled Trials (CENTRAL): Issue 10 of 12, October 2022
Interface: Cochrane Library/Wiley Interscience
Database coverage dates: not available
Search date: 15 November 2022
Retrieved records: CENTRAL subset = 316
Search Strategy:

Number	Search term	Result
1	(“heart rate” near/2 recover*):ti,ab	445
2	(HR near/1 recover*):ti,ab	132
3	((“heart rate” OR HR OR “heart beat” OR heartbeat OR beat* per min* OR bpm) near/4 (post-exer* OR postexer* OR “exer* cessation” OR ((after OR post OR following) near/1 (exer* OR effort OR recovery)))):ti,ab	2103
4	((drop OR decreas* OR decline OR fall OR decay*) near/3 (“heart rate*” OR beat OR bpm OR HR OR “heart rat*”) AND (post-exer* OR postexer* OR “exer* cessation”) OR ((after OR post OR following) AND (exer* OR effort OR recover*))):ti,ab	18175
5	(HRR OR HRR1 OR HRR2 OR HRR3 OR HRR60):ti,ab	534
6	(HR OR “heart rate*”) near/1 (profile* OR respons*):ti,ab	1266
7	MeSH descriptor: [Heart Rate] this term only	19750
8	MeSH descriptor: [Recovery of Function] this term only	5736
9	#7 and #8	151
10	#1 or #2 or #3 or #4 or #5 or #6 or #9	20119
11	MeSH descriptor: [Exercise Test] this term only	8700
12	MeSH descriptor: [Exercise] this term only	18741
13	MeSH descriptor: [Walk Test] this term only	478
14	#11 or #12 or #13	25945
15	(cardiopulmon* OR “cardiopulmonary exer*”):ti,ab	13510
16	((walk*) near/2 (test* OR “six min*” OR “6 min*” OR 6min OR “6-min*” OR shuttle)):ti,ab	11459
17	(tread* OR treadmill OR “Bruce protocol” OR ramp):ti,ab	10324
18	(6MWT OR 6MWD OR CPET OR CPEX):ti,ab	4713
19	#14 or #15 or #16 or #17 or #18	56062
20	MeSH descriptor: [Treatment Outcome] this term only	146431
21	MeSH descriptor: [Postoperative Complications] this term only	18718
22	((Complicat* OR outcome* OR morbid* OR mortalit* OR risk) near/2 (Post-operat* OR postop* OR pre-operat* OR preop* OR peri-op* OR periop* OR surg*));ti,ab	44986
23	#20 or #21 or #22	196301
24	#10 and #19	5292
25	#23 and #24	414

26	MeSH descriptor: [Adult] explode all trees	495527
27	MeSH descriptor: [Humans] explode all trees	656851
28	#25 and #26 and #27	316
29	28 limited to Clinical trials	316

11.6 Appendix 2

American Thoracic Society/American College of Chest Physicians contraindications to cardiopulmonary exercise testing[66]

Absolute	Relative
Acute myocardial infarction (3–5 days)	Left main coronary stenosis or its equivalent
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms	Severe untreated arterial hypertension at rest
or hemodynamic compromise	(> 200 mm Hg systolic, > 120 mm Hg diastolic)
Syncope	Tachyarrhythmias or bradyarrhythmias
Active endocarditis	High-degree atrioventricular block
Acute myocarditis or pericarditis	Hypertrophic cardiomyopathy
Symptomatic severe aortic stenosis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Acute pulmonary embolus or pulmonary infarction	Electrolyte abnormalities
Thrombosis of lower extremities	Orthopedic impairment that compromises exercise performance
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest ⩽ 85%*	
Respiratory failure	
Acute noncardiopulmonary disorder that may affect: exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)	
Mental impairment leading to inability to cooperate	

*Exercise patient with supplemental oxygen

11.7 Appendix 3

Quality of recovery 15 scale

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1.	Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
2.	Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
3.	Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
4.	Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
5.	Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
6.	Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
7.	Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
8.	Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9.	Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10.	Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11.	Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12.	Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
13.	Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
14.	Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
15.	Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time

11.8 Appendix 4

Days alive and out of hospital at 30-days telephone script for research personnel

"Hi…

It's … ringing from the … for some follow-up questions for the VERVE study you are participating in.

How are you getting on?

As I understand it you were discharged from the …on …?

Since you were discharged from the …, have you had to return to hospital?

And have you been admitted to hospital?

When you were discharged did you go straight home or did you stay elsewhere in order to get extra support e.g. with friends or family, or in a rehab facility?

Aside from any holidays, have there been any nights in the last month where you have stayed somewhere not your home, for health reasons?

Thanks"

11.9 Appendix 5

Postoperative complications as defined by STepCOMPAC and Clavien-Dindo scale for severity

1. **Acute Kidney Injury (AKI)**

According to the KDIGO consensus definition of AKI[236]:

Stage	Serum Creatinine	Urine output
1	1.5-1.9x baseline OR ≥0.3mg/dL (≥26.5mmol/L) increase	<0.5ml/kg/hr for 6-12 hours
2	2.0-2.9x baseline	<0.5ml/kg/hr for ≥12 hours
3	3.0x baseline OR ≥4.0mg/dL (≥353.6mmol/L) increase OR initiation of renal replacement therapy	<0.3ml/kg/hr for ≥24 hours OR no urine output for ≥12 hours

If urine output is not measured/recorded, incidence of AKI will be solely based on serum creatinine or commencement of renal replacement therapy.

2. **Cardiovascular complications**

Myocardial infarction (MI)

Acute myocardial injury (20% change in troponin with at least one value above the 99th centile upper reference limit) with clinical evidence of acute myocardial ischaemia, including at least one of:

- Symptoms of myocardial ischaemia
- New ischemic ECG changes
- Development of pathological Q waves
- Imaging evidence of new loss of viable myocardium or regional wall motion abnormality consistent with an ischaemic aetiology

- Identification of coronary thrombus by angiography or autopsy

Cardiac death

Death with a vascular cause, including deaths after an MI, cardiac arrest and cardiac revascularisation procedures. Does not include death after pulmonary embolism, haemorrhage, multi-organ failure or unknown cause of death.

Non-fatal cardiac arrest

Successfully resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy or cardiac defibrillation.

Coronary revascularisation

Percutaneous coronary intervention or coronary artery bypass graft surgery within 30-days of index surgery.

Pulmonary embolism (PE)

Requires one of the following:

- High probability ventilation/perfusion lung scan
- Intraluminal filling defect of segmental or larger artery on a helical CT scan
- Intraluminal filling defect on pulmonary angiography
- Positive diagnostic test for deep venous thrombosis (e.g. positive compression ultrasound) plus one of:
    - Non-diagnostic ventilation/perfusion lung scan

- Non-diagnostic helical CT scan

Deep venous thrombosis

Requires one of the following:

- Persistent intraluminal filling defect on contrast venography
- Non-compressibility of one or more venous segments on B-mode compression ultrasonography
- Clearly defined intraluminal filling defect on contrast enhanced CT

Atrial fibrillation

New onset of irregularly irregular heart rate in the absence of P waves lasting for at least 30 seconds or for the duration of the ECG recording (if <30s).

3. Infective complications

Fever

Core body temperature over 38.5°C more than 24 hours following surgery with two readings in a 12 hour period.

Clinical suspicion of infection

Use of non-prophylactic antibiotics PLUS documentation of suspected site (respiratory/urinary/blood/wound/other).

4. Major adverse cardiac events (MACE)

Composite outcome that includes:

- Cardiac death

- Myocardial infarction
- Non-fatal cardiac arrest
- Coronary revascularisation

Measured at a pre-specified time e.g. 30-days after the index operation

5. Major adverse kidney events (MAKE)

Composite outcome that includes:

- Renal mortality
- Renal replacement therapy of any duration
- ≥30% decline in eGFR from baseline

Measured at a pre-specified time e.g. 30-days after the index operation

6. Neurological complications

Delirium screening

Post-operative delirium is defined as delirium that occurs up to one week post-operatively or up until discharge if earlier than 7 days[237]. A snapshot 4AT test will be performed at day 2 if the patient remains in hospital. A score ≥4 is indicative of delirium.

Use of anti-delirium medication

Documentation of any anti-delirium medications given within 7 days postoperatively, including medication and dose given.

Stroke

New neurological signs (weakness, expressive/receptive difficulties) lasting over 24 hours or cerebral infarction or intracerebral haemorrhage on computed tomography or magnetic resonance imaging scan.

7. Pulmonary complications

Composite of atelectasis, pneumonia, ARDS and pulmonary aspiration as described below:

Atelectasis

Diagnosed on chest radiograph or computed tomography

Pneumonia

Diagnosed using the US Center for Disease control criteria[238]:

Two or more serial chest radiographs with at least one following feature:

- New or progressive and persistent infiltrate
- Consolidation
- Cavitation
- (One radiograph is sufficient for patients with no underlying pulmonary/cardiac disease)

AND at least one of:

- Fever (>38.0°C) with no other recognised cause
- Leukopaenia (<4x10^9/L) or leucocytosis (>12x10^9/L)
- Altered mental state with no other cause in adults >70 years old

AND at least two of:

- New onset of purulent sputum/change in character of sputum/increased respiratory secretions/increased suctioning requirements

- New onset/worsening cough, dyspnoea or tachypnoea

- Rales or bronchial breath sounds

- Worsening gas exchange (hypoxia/increased oxygen requirement/increased ventilator demand)

Acute respiratory distress syndrome (ARDS)

As defined by the Berlin Consensus criteria (2012)[168]:

Within one week of a known clinical insult or new worsening respiratory symptoms

AND bilateral infiltrates on chest imaging, not fully explained by effusions, lobar/lung collapse or nodules

AND respiratory failure not explained by cardiac fluid/fluid overload (requires objective assessment)

AND supplemental oxygenation:

Mild = PaO_2:FiO_2 26.7-40.0kPa with PEEP or CPAP ≥5cmH_2O

Moderate = PaO_2:FiO_2 13.3-26.6kPa with PEEP ≥5cmH_2O

Severe = PaO_2:FiO_2 ≤13.3kPa with PEEP ≥5cmH_2O

Pulmonary aspiration

Diagnosed by clear clinical history AND radiological evidence.

Clavien-Dindo scale grading[185]:

Grade I Any deviation from the normal post-operative course not requiring pharmacological treatment or surgical, endoscopic or radiological intervention. This does not include drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy.

Grade II Requiring pharmacological treatment with drugs other than those described in Grade I. Includes blood transfusions and parenteral nutrition.

Grade III Requires surgical, endoscopic or radiological intervention

Grade IIIa Intervention not under general anaesthesia

Grade IIIb Intervention under general anaesthesia

Grade IV Life-threatening complication requiring critical care admission

Grade IVa Single organ dysfunction (not including dialysis)

Grade IVb Multi-organ dysfunction

Grade V Death

11.10 Appendix 6

R Studio programme for identification of HRR parameters from individual heart rate recovery profiles

```
dat1<-read_excel("/Users/carah/OneDrive/Desktop/VERVE Data/ECG Raw trace data.xlsx", sheet = "[]", range = "E6:F2100", col_names = TRUE)
# as.numeric changes the data to be recognised as a number
dat1$HR<-as.numeric(dat1$HR)
# Detects missing data, must be removed for checked before filtration
which(is.na(dat1$HR))
#Import exercise test timings as ms from start
HRR<-read_excel("/Users/carah/OneDrive/Desktop/VERVE Data/ECG Raw trace data.xlsx", sheet = "[]", range = "J8:J8", col_names = FALSE)
Rest<-as.numeric(HRR[1,1])
HRR10<-Rest+10000
HRR20<-Rest+20000
HRR30<-Rest+30000
HRR1<-Rest+60000
HRR2<-Rest+120000
HRR5<-Rest+300000
# this function will add the RR values to in theory give you a running time total in ms, will only work without missing data
# 0 added to have first value as 0
dat1$Time.s<-c(0,(cumsum(dat1$RR)[-length(dat1$RR)]))
plot(dat1$Time.s, dat1$HRsg11, typ="l", ylim = c(40,140), col="black", ylab = "Heart rate (bpm)", xlab = "Time (mins)")
#Apply SG filter
dat1<-transform(dat1,HRsg11=(signal::sgolayfilt(x = dat1$HR,p = 2,n = 11)))
#Find the row number CLOSEST to Time(in ms)
Restvalue<-which.min(abs(dat1$Time.s-Rest))
HRR10value<-which.min(abs(dat1$Time.s-HRR10))
HRR20value<-which.min(abs(dat1$Time.s-HRR20))
HRR30value<-which.min(abs(dat1$Time.s-HRR30))
HRR1value<-which.min(abs(dat1$Time.s-HRR1))
HRR2value<-which.min(abs(dat1$Time.s-HRR2))
HRR5value<-which.min(abs(dat1$Time.s-HRR5))
#Isolate recovery period
Recoverydata <- dat1[Restvalue:HRR5value,]
view(Recoverydata)
#Plot and check
plot(dat1$Time.s,dat1$HRsg11, typ="l",xlim=c(0000, 1050000), ylim = c(40,170), col="orange", ylab = "Heart rate (bpm)", xlab = "Time(ms)", )
plot(Recoverydata$Time.s,Recoverydata$HRsg11, typ = "l", xlim=c(740000, 1050000), ylim =c(0,140), col = "orange", ylab = "Heart rate (bpm)", xlab = "Time from start of heart rate recording (ms)")

abline(v=Rest)
abline(v=HRR10, col = "purple")
abline(v=HRR20, col = "yellow")
abline(v=HRR30, col = "green")
```

```
abline(v=HRR1, col="red")
abline(v=HRR2, col="blue")
abline(v=HRR5, col = "pink")
abline(h=max(Recoverydata$HRsg11))
abline(h=min(Recoverydata$HRsg11))
#HRR values
HRR10actual<-dat1$HRsg11[Restvalue] - dat1$HRsg11[HRR10value]
HRR20actual<-dat1$HRsg11[Restvalue] - dat1$HRsg11[HRR20value]
HRR30actual<-dat1$HRsg11[Restvalue] - dat1$HRsg11[HRR30value]
HRR1actual<-dat1$HRsg11[Restvalue] - dat1$HRsg11[HRR1value]
HRR2actual<-dat1$HRsg11[Restvalue] - dat1$HRsg11[HRR2value]
HRR5actual<-dat1$HRsg11[Restvalue] - dat1$HRsg11[HRR5value]
maxend<-dat1$HRsg11[Restvalue]

#AUC values
HRR30AUC<-AUC(x=Recoverydata$Time.s, y=(Recoverydata$HRsg11 -
min(Recoverydata$HRsg11, na.rm = TRUE)), from =
min(dat1$Time.s[Restvalue]), to = max(dat1$Time.s[HRR30value]))
HRR1AUC<-AUC(x=Recoverydata$Time.s, y=(Recoverydata$HRsg11 -
min(Recoverydata$HRsg11, na.rm = TRUE)), from =
min(dat1$Time.s[Restvalue]), to = max(dat1$Time.s[HRR1value]))
HRR2AUC<-AUC(x=Recoverydata$Time.s, y=(Recoverydata$HRsg11 -
min(Recoverydata$HRsg11, na.rm = TRUE)), from =
min(dat1$Time.s[Restvalue]), to = max(dat1$Time.s[HRR2value]))
HRR5AUC<-AUC(x=Recoverydata$Time.s, y=(Recoverydata$HRsg11 -
min(Recoverydata$HRsg11, na.rm = TRUE)), from =
min(dat1$Time.s[Restvalue]), to = max(dat1$Time.s[HRR5value]))
```

11.11 Appendix 7

American Thoracic Society/American College of Chest Physicians indications for premature exercise test cessation[66]

Chest pain suggestive of ischaemia
Ischaemic electrocardiographic changes
Complex ectopy
Second or third degree heart block
Fall in systolic pressure >3=20 mmHg from the highest value during the test
Hypertension (>250 mmHg systolic; >120 mmHg diastolic)
Severe desaturation: arterial oxygen saturation (as indicated by pulse oximetry)$_2$ ≤80 % when accompanied by symptoms and signs of severe hypoxaemia
Sudden pallor
Loss of coordination
Mental confusion
Dizziness or faintness
Signs of respiratory failure

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