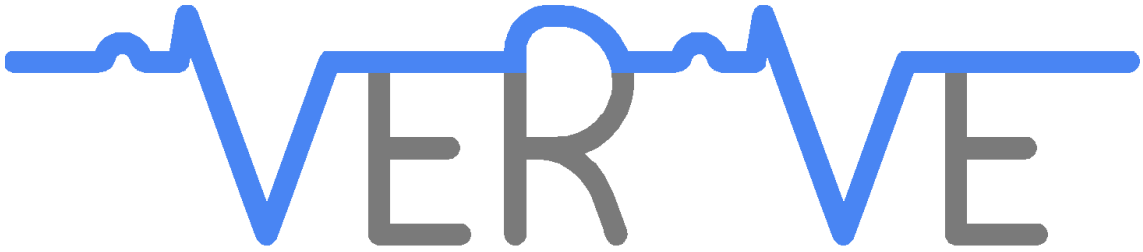

Study Protocol

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Contents

Lay summary

Introduction

There are approximately 1.5 million major operations carried out in the NHS every year. As the population ages, and surgical technique becomes more advanced, more patients are undergoing operations which carry a high risk of complications. Currently, doctors predict this risk by asking patients about their history of medical problems and how these impact on how active they are able to be. Investigations such as a heart scan or breathing tests can give further information. If an operation is very high risk, a patient may undergo cardiopulmonary exercise testing (CPET) where the patient rides an exercise bike to maximum effort (exhaustion) whilst their heart and lung function is monitored. This gives the doctor specific numbers which can be discussed with the patient about the risk of complications after surgery. By using a portable heart rate monitor placed on the skin we aim to produce a new measure of a patient's fitness for surgery which can be easily performed at clinic without needing to exercise to maximum effort (submaximal). This measure looks at how quickly heart rate slows again after submaximal exercise, called heart rate recovery (HRR).

Aim

To assess whether HRR is a valid measure of a patient's risk of post-operative complications.

Method

With their consent, patients undergoing intermediate/high risk non-cardiac surgery will be asked routine questions and blood tests will be taken. Patients will then be asked to perform a HRR assessment. To do this, a small external device will be placed on the patient's chest and their heart rate recorded. This will be done sitting at rest and performing a step test until approximately two-thirds of their predicted maximum heart rate is reached. The patient will step on and off a low box for a further minute and then rest for five minutes. Additionally, some patients will undergo pre-operative CPET as part of their routine care. After the operation, blood tests indicating whether the patient's heart has been under strain will be taken on days one and two and the presence of post-operative complications will be recorded. Patients will also complete questionnaires to describe the quality of their recovery and quality of life. Data regarding their length of hospital stay and, if applicable in rare cases, death will also be collected. This data will be analysed to see how well HRR predicts post-operative complications and how well it agrees with the predictive measures doctors currently use.

Expected outcome and implications

HRR tests will predict post-operative complications in intermediate/high risk surgical patients and will prove a valid measure compared to current practice. HRR could be used as part of a doctor's toolkit to predict the operative risk of surgical patients. Future studies will investigate whether HRR can be improved with exercise, so could be targeted to improve patients' fitness for surgery. Patients identified as high risk could be offered interventions to reduce their risk and therefore improve patient outcomes after surgery.

1. Background and rationale

1.1 Introduction

There are approximately 1.5 million major operations performed in the UK annually[1], with the majority of these surgeries carrying an intermediate (1-5%) or high (>5%) mortality risk[2, 3]. The number of operations performed annually is increasing[4] concurrent with an increase in population age[5] and therefore the prevalence of co-morbidities. Despite this, surgical mortality is reducing. In 2017 all major NHS surgery was found to have a 30-day mortality of 1.1%[1]. A planned sub-analysis of the ENIGMA-II study demonstrated that 15.7% of patients with increased peri-operative cardiovascular risk undergoing non-cardiac surgery developed a major post-operative complication. This was associated with a 1-year disability-free survival of 87.5% and a 1 year mortality of 7.4%[6]. As well as increasing the risk of mortality and further morbidity, post-operative complications have been shown to cause detriment to an individual's quality of life[7]. Post-operative complications also affect wider society by adding a financial burden on limited NHS resources, and reducing the ability of patients and their families to contribute towards the economy[8]. One of the main ways to mitigate post-operative complications is via effective pre-operative risk stratification.

1.2 Pre-operative risk assessment

Pre-operative risk assessment is primarily based on patients' functional capacity. This encompasses an assessment of how co-morbidity and physiological fitness impacts on patients' daily life and indicates the level of cardiopulmonary reserve available for undergoing the physiological insult of surgery. Current modalities for pre-operative risk stratification range from subjective assessments and validated physiological scoring systems such as the Surgical Outcome Risk Tool (SORT)[9], to measurement of biomarkers such as brain natriuretic peptide (BNP), and to cardiopulmonary exercise testing (CPET), an objective measure of cardiopulmonary function. Subjective assessment of patients' functional capacity conducted via pre-operative interview has been shown to be unreliable[10]. Validated scoring systems combine multiple risk indices to stratify post-operative risk. Activity scales such as the Duke Activity Index Score (DASI)[11] however still rely on the patient's subjective view of their ability to perform daily tasks, whilst physiology scores such as P-POSSUM[12] do not include functional domains. Biomarkers are increasingly proposed as part of peri-operative risk stratification. Brain natriuretic peptide (BNP) is a hormone released by cardiac myocytes in response to stress. BNP and corresponding N-terminal proBNP (NT-proBNP) are recommended by the European Society of Cardiology for cardiac risk stratification in high risk patients[2]. The gold-standard exercise test for measuring functional capacity is CPET. CPET comprises incremental workload increases during cycle ergometry until exhaustion and peak oxygen consumption (VO_{2peak}) is reached. Analysis of measured variables including oxygen consumption at anaerobic threshold and VO_{2peak} determine the patient's risk threshold for post-operative morbidity and mortality[13]. 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 its availability varies extensively. Submaximal exercise tests are advocated as predictive tests because they are better tolerated for patients and are less resource-intensive than maximal exercise testing[14]. Defined cut-offs for risk however are limited, as measurements are effort-dependent i.e. HRR may be relative to the peak heart rate reached during the submaximal test. Different methods of HRR analysis can take this into account, and analysis of the whole HRR curve may give further information. Previous work by our group has identified novel objective submaximal heart rate recovery (HRR) analyses to account for effort by HRR and utilising the whole HRR curve profile. As an intermediary (enabling high risk patients to be triaged to formal CPET) or alternative objective measure of physiological fitness we suggest HRR measured after submaximal exertional effort as a simple, lower-cost alternative.

1.3 Exercise physiology and functional capacity

During exercise, cardiac output increases linearly to meet the metabolic demands of contracting skeletal muscle. Heart rate (HR) increases and there is an associated rise in systolic blood pressure and stroke volume to increase oxygen delivery to working muscles in order to match oxygen consumption (VO_2, the product of cardiac output and arterio-venous oxygen content difference). This HR 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[15]. 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. Vagal modulation therefore is a very important component in the attainment of oxygen delivery, consumption and recovery during exercise.

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. Resting heart rate is indicative of vagal activity as the vagus reduces the intrinsic rate of cardiac pacemaker cells. It has long been assumed that vagal activity is a marker of aerobic fitness but recent evidence also suggests that cardiac vagal activity also determines the ability to exercise[15]. Therefore, measures of vagal tone can indicate both the aerobic capacity of an individual, but also their potential to respond to exercise and training.

In Anaesthesia, the term functional capacity is used to describe the ability of the body to increase and maintain tissue oxygen delivery and consumption[16] in response to the physiological stress and increased oxygen demand that surgery places on the body. Although the mechanisms are different to exercise, the surgical stress response results in an increase in VO_2, primarily via entering a catabolic state which can continue for several days post-operatively. Inability to compensate for this increased oxygen demand increases the risk of post-operative complications including delayed wound healing, impaired immune function and organ failure[17]. Therefore, an individual with a higher functional capacity is likely to be able to maintain oxygen delivery to the tissues under surgical stress better than an unfit individual. This forms the fundamental pretext underlining the majority of pre-operative assessment and risk stratification for patients. On this basis, a patient's capacity to exercise is a surrogate marker for how their body will cope with the increased oxygen demand of surgery. It follows that vagal tone can be used as a measure of functional capacity in surgical patients.

1.4 Markers of vagal parasympathetic activity

There are three relatively simple in-vivo methods to indicate vagal activity measured via electrocardiograph: heart rate variability (HRV), resting heart rate and heart rate recovery. Heart rate variability describes the oscillation between R-R intervals. There are many indices incorporated within HRV measurement but overall, high HRV indicates high vagal tone[18]. HRV however, is dependent on resting heart rate and respiration, and recent evidence suggests that it may not be a reliable measure[19]. A low resting heart rate indicates high vagal activity as the vagus inhibits activity of the cardiac pacemaker cells in the sino-atrial node which have an intrinsic rate of approximately 100-110bpm. There is also some evidence that in trained athletes, a low resting heart rate also reflects a reduced intrinsic pacemaker cell rate[20]. In patients with subclinical cardiac failure a higher resting heart rate is associated with increased post-operative mortality[21], and in healthy individuals associated with an increased risk of developing cardiac failure over a 15 year period[22]. Although reflective of vagal tone, the

parameters of resting heart rate which increase peri-operative risk have not been defined. Heart rate recovery presents a measure combining both heart rate evaluation and exercise testing.

1.5 Heart rate recovery

HRR after exercise is mediated by rapid re-activation of the parasympathetic nervous system[23] and has been shown to be independent of resting heart rate and respiration[24], but correlates with other markers of vagal tone[25]. Greater initial HRR is considered to indicate greater aerobic fitness (Figure 1). HRR has been described as a prognostic marker in heart failure[26], after non-cardiac surgery[27, 28] and in healthy individuals[29]. The majority of studies investigating the prognostic application of HRR measure HRR_1 (reduction in HR one minute after exercise cessation after maximal exercise). HRR_1 ≤12bpm after symptom-limited maximal exercise is a strong predictor of mortality in patients with coronary artery disease[30]. A study by Ha et al[27] investigated HRR_1 after six minute walk test (submaximal) and found that post-operative cardiopulmonary complications were increased in patients undergoing lung resection with HRR_1<12bpm. HRR_1 however is effort-dependent[31], so may not be the most appropriate measure for submaximal exercise testing. HRR after two minutes (HRR_2) ≤42bpm after exercise cessation predicted all-cause mortality in healthy individuals[32]. Further analyses of submaximal HRR as a peri-operative risk measure are absent, so it is an area requiring further investigation.

1.6 Previous HRR work

Previous volunteer studies by our group have developed novel methods for HRR assessment utilising all the data contained within the HRR curve, including non-linear mixed-effects modelling and determination of the area under the curve (Figure 1)[33], and have demonstrated their reproducibility following submaximal exercise across differing workloads and exercise modalities.

The exercise protocol for the submaximal test used in this investigation (detailed below) is based on these previous study findings. Specifically, this prior work reveals that in a healthy population, resting heart rate is approximately 40% predicted maximum heart rate (HR_{max}). Reproducibility across differing exercise modalities was demonstrated. Participants walked on a flat surface, performed a ramped protocol on an exercise bike, and repeatedly stepped on and off a low box. During the step test, participants reached a median (IQR) of 64%(62-72%) predicted HR_{max}. All of our previous work has examined HRR over a recovery time of six minutes. However, during the six minutes heart rate does not return to baseline, even when exercising at low levels (e.g. 20% predicted maximum power). In general, the heart rate curve plateaus after approximately four minutes after cessation of exercise (Figure 1).

The natural next step of our group's work therefore is the validation of effort-corrected submaximal HRR in a clinical population (Table 1).

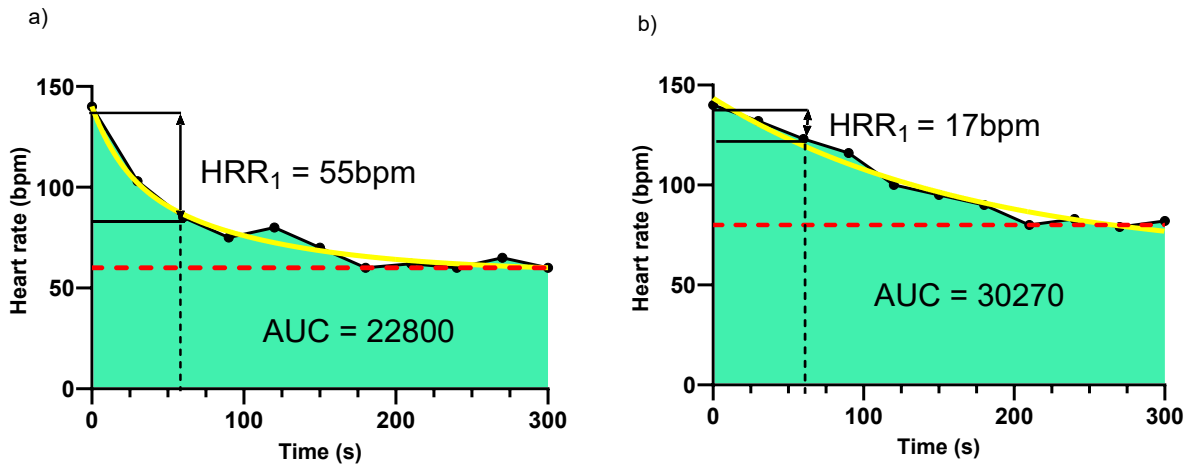

Figure 1 Graphs demonstrating HRR curves after cessation of exercise. a) typical curve of fitter participant with high HRR1 and smaller AUC, incorporating lower resting HR. b) typical curve of less fit participant for comparison. Red dashed line = baseline HR. Yellow line = non-linear mixed-effects modelling curve from which rate constant can be obtained. AUC can be effort-corrected by dividing AUC by effort ratio (cessation HR/age-corrected maximal HR).

1.7 Validation of clinical tests

In order for submaximal heart rate recovery to be used as a peri-operative risk measure, we need to demonstrate scientific validity. There are several types of validity which can be applied to a clinical test[34]. Face validity is where the theoretical basis behind the measurement is scientifically sound and so taken at "face-value" represents what it purports to measure. Criterion validity is where the test is compared to a "gold-standard" criterion. Concurrent validity is where both measurements are taken concurrently and the test has the ability to distinguish between different groups of patients, for example, between patients at high or low risk of complications. Predictive validity is observed when the measurement identifies patients who develop a specific outcome. Construct validity is comparison of the measure against "constructs" used in place of the gold-standard. Table 1 details the types of validity and their application in the validation of submaximal heart rate recovery as a peri-operative risk stratification tool.

Table 1. Types of validity and how these will be applied to HRR measurement. Modified from Ferguson et al[35].

Validity Measure	Explanation	Example as applied to HRR
Criterion validity	Test corresponds to a gold standard measure	HRR is associated with cardiopulmonary exercise testing derived indices – anaerobic threshold (AT) and peak VO_2 (VO_{2peak})
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[13]: • **AT <10ml/kg/min** • **VO_{2peak} < 20ml/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 with poor post-operative outcomes e.g. 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 pre-operative risk predictors e.g. METs score, DASI, Clinical frailty score, Revised cardiac risk index, P-POSSUM and NT-ProBNP

1.8 Rationale

Effective pre-operative functional capacity testing is part of the evolving peri-operative care pathway which aims to involve patients and their families in integrated and shared decision making to improve patient experience and outcome, and also cost-effectiveness of the surgical pathway within the NHS. Heart rate recovery after submaximal exercise testing offers a widely available and economical additional way to identify high risk patients in order to discuss risk with patients and to allocate resources correctly e.g. elective post-operative critical care[36]. This is the first study seeking to validate submaximal HRR in an intermediate/high risk surgical population.

1.9 Aim and Hypotheses

- To assess predictive, criterion and construct validity of submaximal heart rate recovery as a peri-operative risk measure in patients undergoing intermediate/high risk surgery
- Heart rate recovery following submaximal exercise is a valid predictor of post-operative myocardial injury in patients undergoing intermediate/high risk surgery and when compared to current peri-operative risk measures, HRR fulfils both criterion and construct validity.

2. Study Plan

2.1 Study Design

Multi-centre prospective observational cohort study of 95 patients presenting for intermediate/high risk elective surgery.

2.2 Study Setting

Multi-centre study led by the Golden Jubilee National Hospital (GJNH). The other collaborating centres are the Queen Elizabeth University Hospital (QEUH), University Hospital Hairmyres (UHH) and University Hospital Crosshouse (UHC). The centres comprise a mixture of tertiary referral centres and district general hospitals in the West of Scotland.

2.3 Study Summary

Intermediate/high risk surgical patients will be identified at surgical multi-disciplinary meetings, clinics or at anaesthetic pre-assessment clinic. All patients will have baseline demographics, subjective functional capacity and risk scores recorded pre-operatively (Table 1). NT-proBNP and troponin samples will be taken. A cohort of patients at UHH and UHC will undergo CPET testing as per their routine pre-operative care. A sub-study of the CPET patients will compare submaximal heart rate recovery with maximal heart rate recovery, and also patients' perceptions of the two different tests.

Submaximal HRR will be measured and recorded at pre-assessment clinic or on admission to hospital if prior to the day of surgery. Patients will undergo their operation as standard with clinicians blinded to the HRR result.

The primary outcome is myocardial injury as defined by a troponin level above the 99th centile upper reference limit and a 20% change (increase or decrease)[37], therefore troponin levels will be measured at baseline and on post-operative days 1 and 2. Secondary outcomes will include quality of life questionnaires, clinical indicator outcomes and post-operative complications measured up to 1 year post-operatively (Table 2).

Table 2 Indication of timeline for both pre-operatitve measures and post-operative measures. METS = metabolic equivalents; 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; QoR = quality of recovery score; DaOH = days alive and out of hospital; AKI = acute kidney injury; MAKE = major adverse kidney events; CVS = cardiovascular complications; MACE = major adverse cardiac events; PPC = post-operative pulmonary complications

Test	Preop	D1	D2	D7	D14	D30	M3	1 year
NT-proBNP	X							
Troponin	X	X	X					
METs	X							
DASI	X							
CFS	X							
RCRI	X							
SORT	X							
P/V-POSSUM	X							
QoR-15	X		X					
EQ-5D-5L	X						X	X
DaOH						X		
4AT				X				
AKI				X				
MAKE						X		
Infective				X				
CVS				X				
MACE						X	X	X
PPC				X				
Mortality						X	X	X
Admission to ICU					X			
Readmission to hospital						X		
LOS (+/- inhosp mortality)								

3. Objectives and outcomes measures

3.1 Primary outcome measures

Post-operative myocardial injury as defined by the 4th Universal definition of Myocardial Infarction[37], with troponins measured pre-operatively and on days one and two post-operatively.

3.1.1 Rationale for primary outcome

Post-operative myocardial injury is a well-recognised and widely used outcome measure of the cardiovascular effects of surgery and anaesthesia. It is independently associated with an increased risk of post-operative death in the absence of myocardial infarction[6]. Troponin assays are a relatively cost-effective test to add to the peri-operative blood tests the majority of patients will undergo as part of their routine care. Recent studies have demonstrated that approximately 90% of troponin elevation occurs within the first two days post-operatively[39, 40].

3.2 Secondary outcome measures

- Post-operative complications at day 7 based on and including StEP-COMPAC cardiovascular complications[38], post-operative pulmonary complications[41], infection[42], cognitive dysfunction, and acute kidney injury[43].
- Composite outcomes: major adverse cardiac events (MACE) and major adverse kidney events (MAKE) at days 7 and 30

- Patient-centred outcomes[44]: quality of recovery scale 15 (QoR-15), EQ-5D-5L score, days alive and out of hospital (DAOH) at day 30 and after 1 year
- Clinical indicators[45]: mortality at day 30 and after 1 year, admission to ICU at day 14, readmission to hospital at day 30 and length of hospital stay (with/without in-hospital mortality)
- CPET sub-study: comparison of maximal and submaximal heart rate recovery, plus HRR versus CPET derived indices (AT, VO_{2peak}, and VE/VCO_2 at AT). We will also examine patients' perceptions of both tests.

3.2.1 Rationale for secondary outcomes

Poor functional capacity has been associated with post-operative morbidity[10]. StEP-COMPAC aims to standardise and clearly define a set group of outcomes to facilitate comparison between studies[46]. Therefore, all secondary outcomes reflect criteria within the current StEP-COMPAC endpoints, with outcomes of relevance to clinicians but also to patients.

4. Selection and withdrawal of study participants

4.1 Inclusion criteria

1. Provision of informed consent
2. Age >50 years
3. Able to walk unaided
4. Planned elective intermediate/high risk surgery as defined by European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) guidelines [3] (Table 3)

Table 3 Reproduced from ESC/ESA non-cardiac surgery guidelines[2]

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

4.2 Exclusion criteria

1. Pregnancy
2. On-going participation in any investigational research which could undermine the scientific basis of the study
3. Presence of any of the American Thoracic Society's contraindications to exercise testing (Appendix 1)
4. Previous intermediate/high risk surgery within three months prior to recruitment
5. Previous participation in the VERVE study at any time
6. Presence of cardiac pacemaker or implantable cardioverter-defibrillator.

4.2.1 Rationale for inclusion/exclusion criteria

Aging is a cardiovascular risk factor. Previous studies have identified patients over 65 years or age over 40-45 years with one peri-operative risk factor[6, 10] as at increased risk of post-operative cardiovascular events. Proportionally, the majority of patients undergoing high risk surgery are aged over 59 years[1] so including patients over 50 years of age should allow for a

cohort at increased risk of peri-operative myocardial injury whilst ensuring a degree of generalisability within non-cardiac surgery patients.

Although incorporating orthostatic heart rate recovery[47] into the protocol, our main intervention relies on patient's being able to step well enough to generate a heart rate response of approximately 60% predicted maximum heart rate (HR_{max}). This criterion will also therefore exclude a proportion of patients whose mobility may be limited by musculoskeletal problems rather than impaired cardiovascular fitness. The presence of a cardiac pacemaker may alter the heart response to exercise and recovery; an implantable cardioverter-defibrillator (ICD) may be stimulated if the patient heart rate exceeds that which is expected.

The prevalence of post-operative myocardial injury 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 post-operative 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 i.e. >1% risk of cardiovascular death or myocardial infarction will be recruited[2]. Identifying patients by surgical risk rather than individual patient risk should allow a wide variety and degree of co-morbidity.

4.3 Withdrawals and exclusions

A patient may request withdrawal from the study at any time without it affecting their clinical care. The patient will not have to give a reason for their decision to withdraw.

Participants will be made aware from the beginning of their participation in the study that they can freely withdraw (discontinue participation) from the study (or part of) at any time. The sample size calculation allows for participant withdrawal of approximately 5%, so it is not anticipated that it will be necessary to replace participants who withdraw. The situation will be monitored throughout the study by the Chief Investigator.

Types of withdrawal will be collected on a "Change of Status Form" defined as:

- The participant would like to withdraw from the study but is willing to be remotely followed up in accordance with the schedule of assessments (i.e. the participant has agreed that data from medical notes can be collected and used in the study analysis but they do not want to be contacted via telephone for questionnaires from that point onwards).
- The participant would like to withdraw from the study and is not willing to be followed up in any way for the purposes of the study and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the study analysis).
- The participant wishes to withdraw completely from the study and all study follow up, and is not willing to have any of their data, including that already collected, to be used in any future analysis.

The details of withdrawal (date, reason and type of withdrawal) will be clearly documented in the source data and on the "Change of Status Form".

All patients will be consented pre-operatively, but can withdraw consent at any time. Patients undergoing some high risk procedures e.g. elective AAA repair may be admitted to Intensive Care post-operatively, and may be sedated for longer than one post-operative day. This will be explicitly clarified with the patient pre-operatively, and confirmed that troponin levels and post-operative complication data will still be collected and recorded if they are unconscious. However, the day 2 QoR-15 scale will not be performed. If sedation is required for longer, the

patient-centred secondary outcomes may not be completed but we envisage this will be a minority of patients. All other post-operative complication and clinical indicator data will be collected from notes reviews.

5. Study Conduct

5.1 Recruitment

Each recruiting hospital and surgical specialty has its own referral pathway from surgical outpatient clinic and diagnosis through to pre-assessment and admission for surgery. Therefore each pathway will vary, but in general we will aim to identify patients as early as possible in their pathway either via surgical referral or pre-assessment clinic. Eligible patients will ideally speak with a member of the research team face to face and take the Participant Information Sheet home to consider and discuss with others. Due to the rapid turnaround of surgical referrals to surgery however, some patients may receive a cover letter and Patient Information sheet in the post with the paperwork about their procedure. This will allow for telephone discussion prior to consent. We will aim to consent and collect all pre-operative data, including performing the submaximal exercise test at pre-assessment clinic or on the ward if the patient is admitted prior to the day of surgery. Exercise testing will not be performed on the day of surgery.

5.2 Consent

Written informed consent will be obtained following a face-to-face discussion about the study. Prior to obtaining consent, patients will have received a Patient Information Sheet and allowed at least 24 hourscontemplation time before consenting to participate and performance of the exercise test. The research team will endeavour to ensure understanding including study procedures, risks, benefits and the patient's right to withdraw.

5.3 Data collection

Data collection involves:

- Baseline demographic data
- Laboratory sampling
- Pre-operative questionnaires
- Pre-operative risk scores
- Post-operative clinical data
- Post-operative questionnaires

All clinical data will be collected locally and case report forms (CRFs) completed by study staff. The data will be anonymised at site and a unique alphanumeric study number allocated. The study will adhere to data protection regulations. Patients' identities will be protected and their information held securely.

5.3.1 Baseline demographic data

Case note review and routine pre-operative investigations:

- Age
- Sex
- Ethnicity
- Height and weight
- Operation
- Indication for operation
- Alcohol consumption (units/week)
- Smoking history (current and pack years; time since abstinence if applicable)
- Metabolic equivalents

- American Society of Anaesthesiology score
- Clinical Frailty Score
- Co-morbidity (including history of Covid-19 infection)
- Drug history, including medication taken on day of test
- Routine observations (blood pressure, oxygen saturations, respiratory rate)
- Pre-operative ECG finding
- Consultant Anaesthetist caring for the patient on the day of surgery's perception of peri-operative risk as per their routine risk assessment

5.3.2 Laboratory sampling

- Pre-operative NT-proBNP
- High-sensitivity troponin assay (as per the NHS clinical laboratory of each recruiting centre): pre-operatively and days one and two post-operatively. These will be drawn contemporaneously with routine bloods**.**

5.3.3 Pre-operative questionnaires (Full details in Appendix 2)

- Quality of Recovery-15 scale (QoR-15)[48]: a validated evaluation of the quality of post-operative recovery. It will be performed pre-operatively for baseline score.
- EQ-5D-5L[49]: EuroQol health-related quality of life scale
- Patient perception of submaximal versus maximal exercise testing in CPET cohort

5.3.4 Pre-operative risk scores

- Duke Activity Scale Index[11]: brief self-reported functional capacity scale (Appendix 2).
- Revised Cardiac Risk Index[50]: commonly used risk score for cardiovascular complications after major elective noncardiac surgery.
- Surgical Outcome Risk Tool[51]: commonly used risk stratification tool predicting 30 day mortality after non-cardiac surgery.
- P-POSSUM[12]/V-POSSUM[52]: pre-operative risk scores incorporating physiology and surgical domains, predicting post-operative morbidity and mortality.
- All pre-operative risk scores will be completed by study investigators, blinded to clinical team. It is permissable for clinical teams to use risk scores as per their usual practice.

5.3.5 Post-operative clinical data (Full details in Appendix 3)

- Acute Kidney Injury (AKI) as defined by KDIGO consensus[53] at day 7. If urine output is no longer recorded (as not perceived to be clinically necessary), AKI will be scored by serum creatinine only.
- Major Adverse Kidney Events (MAKE)[54] at day 30. MAKE is a composite of ≥30% decline in eGFR at baseline, renal replacement therapy of any duration and renal mortality.
- Infective complications at day 7. These will include presence of fever >38.5°C more than 24 hours following surgery; non-prophylactic antibiotic use and documentation of suspected site (chest/urinary/blood/wound/other). Adapted from StEP-COMPAC outcomes for infection and sepsis[42].
- Cardiovascular complications at day 7. As per StEP-COMPAC, these include myocardial infarction, cardiovascular death, non-fatal cardiac arrest, coronary revascularisation, PE/DVT and new-onset of atrial fibrillation[38].
- Major adverse Cardiac Events (MACE)[38] at day 30, day 90 and at 1 year. MACE is a composite of myocardial infarction, non-fatal cardiac arrest, coronary revascularisation and cardiac death.

- Pulmonary complications at day 7, encompassing atelectasis, pneumonia, acute respiratory distress syndrome (ARDS, as defined by Berlin criteria[35]) and pulmonary aspiration[41].
- Neurological complications at day 7 including 4AT[55] score, and use of anti-delirium medications.
- Admission to ICU at day 14 (or re-admission)
- Days alive and out of hospital[56] at day 30: validated patient-centred outcome that reflects mortality, length of hospital stay, readmissions and discharge to another health facility other than the patient's home.
- All-cause mortality at day 30, 90 and 1 year
- Length of hospital stay +/- in-hospital mortality

5.3.6 Post-operative questionnaires

- QoR-15 at day 2.
- EQ-5D-5L at day 90 and 1 year.

5.4 Exercise Protocol

Patients will begin at rest, sitting on a chair. Heart rate will be recorded via one-lead ECG (Actiheart, CamNTech, Cambridge, UK). The ECG leads will remain in situ throughout the test and HR monitored by the investigator throughout. The participant will not be able to see their HR. To ensure baseline heart rate is accurate patients will sit still, without talking, for 5 minutes. Baseline HR will be noted.

5.4.1 Orthostatic HRR

The initial test will be orthostatic heart rate recovery. Patients will be asked to stand promptly, remain standing for three minutes and then to sit back down, until their heart rate is back to baseline[57].

5.4.2 Step test

Prior to the exercise, the patients' age-predicted maximum heart rate will be calculated:

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

The aim of the test will be for the patient to repetitively step onto and off a low box until they reach 60% predicted HR_{max} +/- 5% or the point of subjective limitation. Participants will be encouraged throughout to place alternate feet onto the top of the box, stand erect at the top of the box and place both feet fully on the ground at the end of the stepping "cycle"[14]. Standard phrases of encouragement will be used in a neutral tone[58]. Once the HR is approximately 60% predicted HR_{max}, the patients will maintain the effort for a further minute. At the end of the minute, patients will sit and rest. Heart rate will continue to be monitored for a further 5 minutes. A modified Borg score[59] will be assessed at the beginning and end of the test as an indication of perceived workload. The step test also allows an estimate of work done to be calculated:

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

During the test, patients will be asked not to speak as this has been demonstrated to raise heart rate[60].

5.5 Medical Management and Safety Reporting

Medical management will be according to the standard of care at each treating site and is not part of this research protocol. The investigator performing the submaximal exercise test will not be involved in the anaesthetic or surgical management for the patient's procedure. If, either when interviewing the patient or during the submaximal exercise test, the investigator has concerns about the peri-operative fitness of the patient, the clinical team will be informed. Aside from this, the clinical team will not be aware of the HRR test results, or pre-operative risk scores unless performed separately by the attending anaesthetist as per their usual care.

The submaximal exercise test will be terminated early if the patient demonstrates chest pain, intolerable dyspnoea, dizziness etc as per the ATS statement on the six minute walk test (6MWT)[58]. The exercise test will be performed in clinical areas, all of which are equipped with oxygen points and cardiac arrest trolleys, with clinical staff presence. All investigators will be trained in basic life support.

Troponins and NT-proBNP will be blinded to the clinical teams. Blood tests will be linked-anonymised and analysed at the local NHS laboratory. They will be processed in real time and screened by the team for grossly abnormal results. If abnormal results are identified, the study team will discuss the result with the patient and arrange further medical follow-up if required.

5.6 Covid-19 Considerations

We expect the Covid-19 pandemic will be abating by August 2021 when data collection is planned to start. However, there may still be potential for ongoing effects of the pandemic to affect the deliverability and validity of this study.

5.6.1 Deliverability

The NIHR have published guidance concerning commencement of non-Covid research. This study has been designed with the NIHR framework in mind particularly concerning viability, capacity and safety. Locally this study has been risk assessed at level 3a (lowest risk): where patient attend hospital for clinically required interventions and follow-up is done remotely.

At present, all four centres' infection control policy requires the wearing of a surgical face-mask when in the hospital, unless there is a medical exemption. Therefore, all patients and investigators will wear face-masks for the duration of interview and exercise test, unless exempt. The wearing of a surgical face mask may affect heart rate[61], however as this measure is likely to be in place for the foreseeable future it aids to the generalisability of the study moving forward. This will not affect the scientific validity of the test as we are looking at HRR relative to resting and submaximal heart rate. Submaximal exercise testing does not fulfil the criteria of aerosol-generating procedure (private correspondence, Health Protection Scotland) and therefore no further infection control measures need to be taken apart from ongoing good infection control hygiene and the above.

5.6.2 Scientific validity

Evidence continues to emerge on the multi-system effects of Covid-19 disease, particularly in regards to the increasing prevalence of "Long-Covid". It is plausible that recent Covid-19 infection, or development of "Long-Covid" syndrome after infection could be a confounder in this study. To mitigate against confounding, previous Covid-19 infection will be specifically investigated at patient interview with data recorded on date and severity of infection, along with co-morbidity relating to "Long-Covid".

6. Data Management

6.1 Data collection

Patient data will be collected locally via case report forms (CRFs) by one of the investigators or an appropriately trained research nurse. This data will be submitted electronically to a protected online database (Research Electronic Data Capture (REDCap), Vanderbilt University, Tennessee, USA) in linked-anonymised form with a unique alphanumeric study number allocated. The study will adhere to all data protection regulations. Patients' identities will be protected and their information held securely.

6.2 Data storage

Anonymised patient data will be stored on password protected university and NHS hospital computers. A patient identifier list will be kept in a secure location within the Research Department of the hospital the patient was recruited from.

The data from each patient will be sent in an anonymised format to either NHS or University computers where analysis will be carried out. The research teams will not have access to the patient details from the other centres. If a patient needs to be contacted for any reason, contact will be made via the local recruitment team.

6.3 Archiving

Study data will be archived for ten years after the completion of the trial. It will be filed and stored securely as per each local site's guidelines. At the end of ten years, the dataset will be destroyed to DoD 5220.22-M standards. All data will be held in accordance with General Data Protection Regulations (2018).

7. Statistical Considerations

Our group has developed novel indices for measuring heart rate recovery including area under the curve and non-linear mixed effects modelling[33]. This study is part of a higher degree programme (MD by research; Cara Hughes) which will encompass statistical methodology as an iterative process. The primary method of measuring HRR will be effort-corrected area under the curve (EC-AUC)[62] but our other methods will also be examined. A formal statistical analysis plan will be written and agreed between the principal investigator (CH) and chief investigator (BS) prior to any data analysis.

All statistical analysis will be carried out using R-studio.

7.1 Power calculation

A power calculation was performed based on the hypothesis that submaximal heart rate recovery will improve the AURROC for the prediction of post-operative myocardial injury from 0.5 (null hypothesis) to 0.7. Based on prior incidence of PMI of 24.5%[28] after non-cardiac surgery in patients at higher risk of cardiovascular complications, 90 patients will be required, with a type 1 error of 0.05 and power of 80%. Adding an expected 5% dropout rate, a sample size of 95 patients will be recruited between the four recruiting centres. MedCalc V19.7.2 was used to calculate the sample size.

7.2 Primary Outcome

Predictive ability of heart rate recovery of post-operative myocardial injury will be quantified by determination of area under the receiver operative characteristic curve.

7.3 Secondary Outcomes

Secondary outcomes such as post-operative complications, patient-reported outcome measures, clinical indicators and CPET substudy will be analysed using appropriate statistical methods.

Paired secondary outcomes will be assessed for normality. Comparison will be made using a paired t-test or Wilcoxon signed ranks test. ANOVA or Friedmann's test will be used to assess differences between variables repeated over time. Association will be sought between HRR and appropriate variables using Pearson correlation coefficient or Spearman's rank correlation coefficient as appropriate.

8. Study Organisation

8.1 Sponsor

This study will be sponsored by the National Waiting Times Centre Board (Golden Jubilee National Hospital).

8.2 Administration

All routine clinical and non-clinical co-ordinations of the study will be the responsibility of the Principal Investigator (CH) in conjunction with the research team staff at each site. The Chief Investigator (BS) will assume responsibility for the overall management and conduct of the study.

8.3 Indemnity

The NHS research indemnity scheme will apply.

8.4 Monitoring

This study will be sponsored by the National Waiting Times Centre Board (Golden Jubilee National Hospital). As such, the Research and Development department will monitor this research in line with the Research Governance Framework for Health and Community Care (Scotland).

8.5 Funding

NIAA/VASGBI Trainee Research Development Awarded December 2020.

9. Ethics and regulatory approval

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. The study will be submitted to a Research Ethics Committee for approval.

10. Protocol amendments

Any substantial amendments to the final protocol will be clearly documented and forwarded to the Research Ethics Committee for approval prior to the implementations via the IRAS process of Notification of Substantial Amendment.

11. Dissemination

The results of the study will be reported first to study collaborators.

Subsequently, we plan to communicate our results by reporting them to the funder and presentation at national meetings with publication in appropriate peer reviewed journals.

At the end of the study, all participants will be thanked in writing for their participation in the study and will be provided with a short summary of the trial findings. Further details about the trial results and final report will be available on request.

12. Projected study timetable

The anticipated duration is 24 months. Set up will take six months from February 2021 and all centres will aim to start recruiting from August 2021, for one year. Follow-up questionnaires will be completed via telephone at three months post-operatively and at one year. We therefore anticipate the dataset for the primary outcome (post-operative myocardial injury) to be complete by August 2022.

Appendix 1 – ATS Contraindications to exercise testing

Table 4 Reproduced from ATS Cardiopulmonary Exercise Testing guidelines[63]

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

Appendix 2 – Pre-operative Questionnaires

Quality of Recovery scale – 15[48]

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

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

EQ-5D-5L[49]

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

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

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

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 3 – Secondary outcome definitions (alphabetical)

1. Acute Kidney Injury (AKI)

According to the KDIGO consensus definition of AKI[53]:

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$^{\circ C}$ 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[64]. A snapshot 4AT test will be performed at day 7 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[65]:

- 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$^{\circ C}$) 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)[35]:

- Within one week ofa known clinical insult or new worsening respiratory symtoms
- AND bilateral infiltrates onchest 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

All reported postoperative complications will be graded on severity by using the Clavien-Dindo scale[66]:

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

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