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Study protocol for IMPRoVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery

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ABSTRACT

Introduction Perioperative myocardial injury evidenced by elevated cardiac biomarkers (both natriuretic peptides and troponin) is common after major non-cardiac surgery. However, it is unclear if the rise in cardiac biomarkers represents global or more localised cardiac injury. We have previously shown isolated right ventricular (RV) dysfunction in patients following lung resection surgery, with no change in left ventricular (LV) function. Given that perioperative RV dysfunction (RVD) can manifest insidiously, we hypothesise there may be a substantial burden of covert yet clinically important perioperative RVD in other major non-cardiac surgical groups. The Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction (IMPRoVE) study has been designed to address this knowledge gap.

Methods and analysis A multicentre prospective observational cohort study across four centres in the West of Scotland and London. One hundred and seventy-five patients will be recruited from five surgical specialties: thoracic, upper gastrointestinal, vascular, colorectal and orthopaedic surgery (35 patients from each group). All patients will undergo preoperative and postoperative (day 2–4) echocardiography, with contemporaneous cardiac biomarker testing. Ten patients from each surgical specialty (50 patients in total) will undergo T1-cardiovascular magnetic resonance (CMR) imaging preoperatively and postoperatively. The coprimary outcomes are the incidence of perioperative RVD (diagnosed by RV speckle tracking echocardiography) and the effect that RVD has on days alive and at home at 30 days postoperatively. Secondary outcomes include LV dysfunction and clinical outcomes informed by Standardised Endpoints in Perioperative Medicine consensus definitions. T1 CMR will be used to investigate for imaging correlates of myocardial inflammation as a possible mechanism driving perioperative RVD.

Ethics and dissemination Approval was gained from Oxford C Research Ethics Committee (REC reference 22/SC/0442). Findings will be disseminated by various methods including social media, international presentations and publication in peer-reviewed journals.

Trial registration number NCT05827315.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to investigate the incidence of perioperative right ventricular dysfunction (RVD) after major non-cardiac surgery, and the association between RVD and patient outcomes in this group.

⇒ T1-cardiovascular MR substudy to investigate whether inflammation is a mechanism underlying perioperative RVD.

⇒ A large prospective multicentre study with appropriate statistical power analysis.

⇒ It is difficult to predict the incidence of perioperative RVD in surgical groups other than lung resection since there are such limited data.

INTRODUCTION

Perioperative myocardial injury (PMI) is common after major non-cardiac surgery, with a recent large international observational study demonstrating an elevated postoperative high-sensitivity troponin level in 19.7% of patients undergoing major non-cardiac surgery.[1] Perioperative PMI has also been shown to be associated with poor cardiovascular outcomes in patients undergoing non-cardiac surgery.[2] Similarly, natriuretic peptides increase following surgery, and this is associated with an increased risk of cardiovascular complications and mortality.[3] Our group has demonstrated that peak postoperative brain natriuretic peptide is associated with postoperative complications and length of hospital stay after thoracic surgery.[4] Although

an increase in cardiac biomarkers after major non-cardiac is well described, there has been little research to investigate the location of the myocardial injury (although it is frequently attributed to injury of the left ventricle with little evidence to substantiate this assertion). A study in a mixed surgical population requiring 'rescue' echocardiography demonstrated that postoperative right ventricular (RV) dysfunction (RVD) was as prevalent as left ventricular (LV) dysfunction (LVD), occurring in 24.1% of patients.[5] Postoperative RVD is difficult to diagnose, manifesting with subtle clinical signs; it is therefore unsurprising that its importance may have been overlooked.[6] In addition to postoperative RVD, it has been shown that there may be a considerable burden of preoperative RVD in patients undergoing non-cardiac surgery. A study in patients undergoing major vascular surgery found a prevalence of preoperative RVD of 10%, and this was associated with postoperative major cardiac complications.[7] The incidence and significance of perioperative RVD in other non-cardiac surgical populations has been poorly described. We have previously shown that patients undergoing lung resection experience significant impairment of RV function postoperatively with no change in LV function.[8] Further research is needed to investigate the incidence and impact of perioperative RVD on patient outcomes in other non-cardiac surgery groups. Additionally, the mechanisms underlying perioperative RVD require elucidation to allow effective preventative and treatment strategies to be devised. The Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction (IMPRoVE) study has been conceived to address this gap in our understanding of perioperative RVD.

Potential mechanisms of perioperative RVD

The mechanisms of postoperative RVD likely reflect a complex interplay between pre-existing RVD, patient susceptibility, surgical risk and a multitude of potential perioperative insults.

As described above,[7] RVD may predate surgery. In the general population, RVD is more prevalent in the elderly, and in people with hypertension, diabetes mellitus, ischaemic heart disease and lung disease[9]; risk factors which are over-represented in the surgical population. As anticipated, in our previous thoracic surgery cohort we found a high prevalence of pre-existing RVD of 50%.[8]

The perioperative period exposes patients to many insults that may contribute to RVD. Excess preload may occur in the form of injudicious intravenous fluid administration, resulting in RV distension and tricuspid regurgitation.[6 10] Impaired contractility may occur due to myocardial ischaemia. RV afterload may increase by many mechanisms, including:

► Pulmonary thromboembolism: Occurring subclinically in up to 28% of patients undergoing elective intermediate to high-risk non-cardiac surgery.[11]
► Lung injury and inflammation: Due to pre-existing lung disease and the combined deleterious effects of ventilator induced lung injury, systemic inflammation and fluid overload.[6]
► Positive-pressure mechanical ventilation: Especially one-lung ventilation (OLV).[6]
► Lung resection: Recently, we have demonstrated the pulsatile component of RV afterload significantly increases after lung resection.[12]

Inflammation and PMI

Although it is widely hypothesised that PMI results predominantly from ischaemia secondary to myocardial oxygen supply/demand imbalance, this hypothesis remains unproven and is challenged by important observations; in excess of 90% of patients with PMI have no ischaemic symptoms to support a diagnosis of myocardial infarction,[1] and the extent and severity of coronary artery disease does not correlate closely with the occurrence of PMI.[13]

The inflammatory response is an important contributor to the myocardial injury seen after myocardial infarction and cardiac surgery, but the extent to which systemic inflammation is involved in the pathogenesis of PMI after non-cardiac surgery is not known. Ackland *et al* recently demonstrated that PMI was associated with an elevated neutrophil-to-lymphocyte ratio, suggesting systemic inflammation may predispose patients to PMI.[14] Using T1-weighted cardiovascular magnetic resonance (T1-CMR) imaging, our group has described the presence of imaging correlates of perioperative RV (but not LV) myocardial inflammation in patients following lung resection.[15]

In summary, with greater understanding of the incidence, impact and underlying mechanisms of perioperative RVD provided through this investigation, preventative interventions targeted at patients at greatest risk may offer a unique therapeutic opportunity to provide a personalised approach to perioperative management and improve patient outcomes across a wide range of surgical populations.

Hypotheses

► RVD after major non-cardiac surgery is a common covert contributor to perioperative morbidity.
► Inflammatory injury to the RV is a significant contributing factor to PMI.

METHODS AND ANALYSIS

Summary: A multicentre prospective observational cohort study in patients undergoing major non-cardiac surgery in five surgical specialties. Main study: 175 patients to undergo transthoracic echocardiography (TTE) preoperatively and postoperatively (figure 1). Substudy: 50 patients to undergo T1-CMR preoperatively and postoperatively.

Centres: Three hospitals in the West of Scotland (Golden Jubilee National Hospital (GJNH), Queen Elizabeth University Hospital and Glasgow Royal Infirmary) and one London hospital (Royal London Hospital).
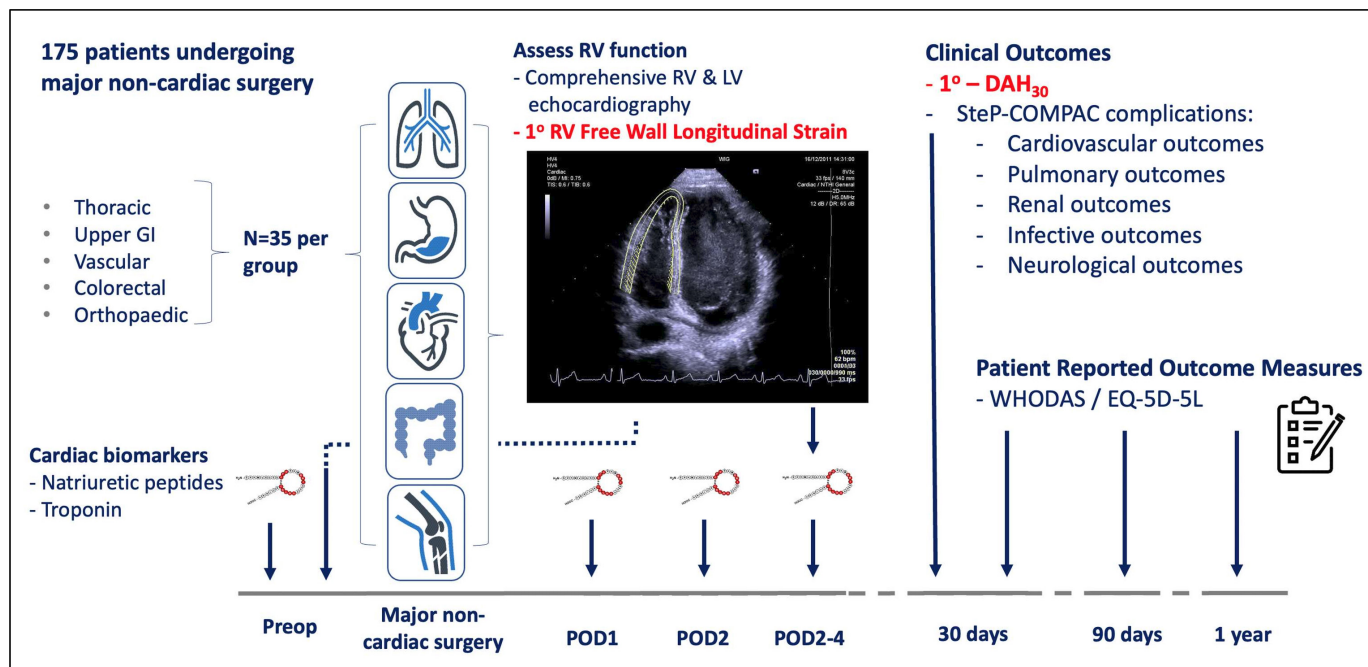
Figure 1 Overview of IMPRoVE Main Study. One hundred and seventy-five patients (35 from each surgical group) will undergo echocardiography and cardiac biomarker testing preoperatively and postoperatively. Coprimary outcomes are the incidence of RV dysfunction, diagnosed by RV free wall longitudinal strain, and DAH_{30} (shown in red). DAH_{30}, days alive and at home at 30 days postoperatively; EQ-5D-5L, EuroQol-5 Dimension-5 Level; GI, gastrointestinal; IMPRoVE, Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction; LV, left ventricular; POD, postoperative day; RV, right ventricular; StEP-COMPAC, Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care; WHODAS, WHO Disability Assessment Schedule 2.0.

Study status: Grant funding was secured on 12th February 2021, with ethical approval on 12th January 2023 (REC reference 22/SC/0442). Recruitment commenced in May 2023 with an anticipated study duration of 36 months.

Selection of study subjects
Inclusion criteria
► Patient aged >18 years.
► Patient undergoing planned elective primary hip or knee joint replacement under spinal anaesthesia, major colorectal, major vascular surgery or major surgery requiring OLV with or without lung resection.
► Provision of informed consent.

Main study exclusion criteria
► Pregnancy.
► Ongoing participation in any investigational research which could undermine the scientific basis of the study.
► Major surgery within previous 3 months.
► Previous participation in the IMPRoVE study.
► Inadequate comprehension of English resulting in inability to comply with instructions while undergoing interventions required for main study and substudy.

Risk factors for RVD are likely to be over-represented in patients presenting for surgery and participants with pre-existing RVD could represent an important population that may face greater consequences of acute perioperative insults to the RV. For this reason, although not a specific inclusion or exclusion criteria, patients with pre-existing RVD, including when identified on preoperative echocardiography will be included in the study.

T1-CMR substudy exclusion criteria
► Contraindication to T1-CMR (see online supplemental material).
► Atrial fibrillation at baseline.
► Acute or chronic kidney disease.
► Allergy to intravenous contrast.

Study conduct
Recruitment
Patients will be identified from hospital waiting lists. Patients will be informed of the study, offered a patient information sheet and invited to participate at the earliest possible opportunity after they have been informed of their decision for surgery. Following appropriate time to consider participation, informed consent will be obtained by a member of the research team.

Consent
Written informed consent will be obtained, following a face-to-face discussion about the study by a member of the study team. Signing of consent form and preoperative blood sampling and imaging may take place at any time in the 30 days prior to surgery or on the day of surgery.

Table 1 Schedule of assessments for all patients enrolled into IMPRoVE study

Visit window	Preoperative	Day of surgery (day 0)	POD1	POD2	Day of echocardiography (POD 2–4)	Discharge	30 days	3 months	12 months
Informed consent	x								
Inclusion/exclusion criteria	x								
Baseline demographics and risk scoring	x								
BNP/HsTn	x		x	x	x				
NT-proBNP	x								
Immediate perioperative data		x							
Laboratory data	x		x	x	x				
Echocardiography	x				x				
T1-CMR*	x				x				
QoR-15	x				x				
Organ-specific complications (Clavien-Dindo ≥2)			x	x	x	x	x		
Unplanned ICU admission			x	x	x	x			
Length of hospital stay						x			
Length of ICU/HDU stay					x	x			
Mortality					x	x	x	x	x
DAH$_{30}$							x		
Hospital readmission							x		
EQ-5D-5L	x						x	x	x
WHODAS 2.0	x						x	x	x

*Ten patients from each of the five surgical groups (50 in total).
BNP, brain natriuretic peptide; DAH$_{30}$, days alive and at home at 30 days; EQ-5D-5L, EuroQol-5 Dimension-5 Level; HDU, high-dependency unit; HsTn, high sensitivity troponin; ICU, intensive care unit; IMPRoVE, Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction; NT-proBNP, N-terminal prohormone of BNP; POD, Post operative day; QoR-15, quality of recovery-15 score; T1-CMR, T1 cardiovascular magnetic resonance; WHODAS 2.0, WHO Disability Assessment Schedule 2.0.

Medical management

Medical management will be according to the standard of care at each treating site and is not influenced by this study protocol.

Study interventions

Table 1 shows the general schedule of assessments/study interventions that patients will undergo.

Echocardiography conduct and analysis

TTE will be performed on all 175 patients by a British Society of Echocardiography (BSE) accredited echocardiographers preoperatively and between postoperative days 2 and 4. Echocardiography will acquire the minimum BSE image dataset.[16] In addition to this minimum image dataset, we will acquire an RV focused apical four chamber view for RV free-wall peak longitudinal strain (FWLS) analysis (optimising feasibility as per consensus guidelines).[17][18] All echocardiography study images will be sent centrally for offline analysis: anonymised images will be transferred via routine clinical imaging systems to the GJNH.

A full echocardiography data set will be used to assess for RVD (the primary outcome) and LVD. Offline RV and LV two-dimensional (2D) speckle tracking strain analysis will be performed using Tomtec 2D Cardiac Performance Analysis software. Twenty echocardiography scans will be randomly selected and re-reported by the same reporter a minimum of 2 weeks after initial reporting, and reported by a second reporter, to allow assessment of intraobserver and interobserver agreement. Reproducibility will be assessed by intraclass correlation coefficient using two-way mixed effects with absolute agreement and Bland-Altmann plots.

T1-CMR conduct

A subcohort of 50 patients (10 from each surgical group) will undergo a preoperative T1-CMR scan and a single postoperative scan (between postoperative days 2–4). Replicating our previous protocol,[8] CMR will be undertaken on a 1.5 or 3.0 Tesla scanner, by band 7 Health and Care Professions Council accredited radiographers. T1-weighted scans will be performed preintravenous and postintravenous gadolinium administration.

Postprocessing will be protocolised and dual reported by blinded observers.

Laboratory sampling

Where possible samples will be drawn contemporaneously with routine clinical blood tests. Cardiac biomarkers will be batch analysed at University of Glasgow Laboratories.

DAH_{30} conduct

Days alive and at home at 30 days postoperatively (DAH_{30}) will be assessed by telephone on postoperative day 30 (up to +5 days). A script will be used to ensure that DAH_{30} is reliably and consistently recorded.

Data collection will be performed by the local study team on case report forms (CRFs), which will be filed and securely stored at participating sites. The data will be anonymised at site and a unique numeric study number allocated. Completed CRFs will be entered onto a secure online database in a linked anonymised form. Electronic data will be stored in an encrypted and anonymised format for 15 years following the completion of the trial. At the end of this period, the dataset will be destroyed according to DoD 5220.22-M standards. All data will be held in accordance with the General Data Protection Regulation (2018).

Laboratory data

Laboratory data (full blood count, urea and electrolytes, liver function tests and C reactive protein) will be obtained from the local biochemistry and haematology laboratory reporting systems perioperatively, on the day of echocardiography and if clinically indicated, at follow-up.

Clinical data

Baseline demographic information will be collected including chronic comorbidities. We will specifically gather information on sleep apnoea status and previous COVID-19 infection since these may affect baseline RV function. Preoperative data will include previous pulmonary function tests, cardiopulmonary exercise testing, CT thorax imaging (for coronary artery calcium scoring), American College of Surgeons National Surgical Quality Improvement Programme risk scoring, and baseline questionnaires (Duke Activity Status Index, quality of recovery-15, EuroQol-5 Dimension-5 Level (EQ-5D-5L) and WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)). Immediate perioperative data will include the operation performed, duration of surgery and anaesthesia, duration of OLV (if applicable), and use of vasopressor/inotropic support.

Study outcomes
Coprimary outcomes
Incidence of postoperative RVD
RVD defined as:

▶ 2D-speckle tracking derived RV free wall longitudinal strain (RVFWLS) less negative than −20%.[17 19]
▶ (When RVFWLS is not available) two of tricuspid annular plane systolic excursion <16 mm, S' wave velocity at the tricuspid annulus <10 cm/s or tissue doppler RV index of myocardial performance >0.55.[20]

Clinical impact of postoperative RVD
Days alive and at home at 30 days postoperatively (DAH_{30}). DAH_{30} is a continuous number between 0 and 30 which reflects, out of the 30 days following surgery, the total number of those days that a patient spends alive and at home. If a patient dies within those 30 days, their value is set to 0.

Justification for coprimary outcomes
Incidence of postoperative RVD
There is currently no consensus on how best to measure RV function in the context of clinical trials.[21] However, recent work (by our group and others) has demonstrated the superiority and increased reproducibility of RVFWLS in identifying RVD compared with 'conventional indices'.[22–24] A recent American Thoracic Society Research Statement has advocated the use of RVFWLS due to its ability to assess RVD at an early stage and to detect differences when other traditional measurements fail to do so.[21]

Clinical impact of perioperative RV
Days alive and at home at 30 days postoperatively (DAH_{30}) is a novel, well-validated clinical endpoint describing all facets of the perioperative experience and has been recommended as a patient-centred outcome by the Standardising Endpoints in Perioperative (StEP) Medicine initiative. DAH_{30} is sensitive to prolonged stay due to complications, discharge to a rehabilitation or nursing care facility, readmission to hospital after discharge and mortality thus integrating efficacy, quality and safety.[25 26]

Exploratory outcomes
Exploratory outcomes that we will investigate are shown in table 2.

Statistical considerations
All statistical analyses will be performed in conjunction with the Robertson Centre for Biostatistics at the University of Glasgow.

Analysis of coprimary outcomes
Incidence of perioperative RVD
The identified incidence of postoperative RVD will be compared with the null hypothesis that the incidence equals zero using a one-sample binomial test; 95% CIs for the incidence will be defined using the Clopper-Pearson method. In addition, we will perform sensitivity analyses to identify the incidence of patients that develop new postoperative RVD, and identify the incidence of those that have pre-existing RVD maintained through to the postoperative period. Subgroup analyses will estimate the incidence rate of postoperative LVD and RVD within surgical subgroups and compare the incidence in patients with chronic obstructive pulmonary disease (COPD) versus no COPD, in operations involving mechanical

Table 2 Exploratory outcomes

Left ventricular dysfunction	Defined by two-dimensional echocardiography derived biplane ejection fraction
Cardiac biomarkers	NT-proBNP, BNP, hsTn
Clinical outcomes informed by StEP trials consensus definitions:	
Cardiovascular outcomes[27]	Myocardial infarction Myocardial injury Cardiac death Non-fatal cardiac arrest Coronary revascularisation Major adverse cardiac event
Pulmonary outcomes[28]	Pneumonia Atelectasis Acute respiratory distress syndrome Pulmonary aspiration
Renal outcomes[29]	Acute kidney injury Need for renal replacement therapy
Infection outcomes[30]	Fever Clinical suspicion of infection
Neurological outcomes[31]	Delirium Stroke
Major complications	Sequential Organ Failure Assessment Score
Clinical indicators	Need for unplanned HDU or ICU admission Requirement for new invasive or non-invasive ventilation Length of postoperative critical care and hospital stay Mortality at 30 days
Patient quality of recovery	QoR-15
Patient-centred outcomes	EQ-5D-5L WHODAS 2.0 (assessed at 30 days, 3 months and 12 months postoperatively)
T1-CMR	Preoperative and postoperative T1-CMR. T1 weighted CMR preintravenous and postintravenous gadolinium to calculate T1 signal and extracellular volume (imaging correlates of myocardial inflammation)

BNP, brain natriuretic peptide; EQ-5D-5L, EuroQol-5 Dimension-5 Level; HDU, high-dependency unit; HsTn, high sensitivity troponin; ICU, intensive care unit; NT-proBNP, N-terminal prohormone of BNP; QoR-15, quality of recovery-15; StEP, Standardised Endpoints in Perioperative; WHODAS 2.0, WHO Disability Assessment Schedule 2.0.

ventilation and no mechanical ventilation (orthopaedic surgery under spinal anaesthesia), OLV versus no OLV, in videoscopic versus open surgeries, and in patients with

ischaemic heart disease (IHD) versus no IHD. Secondary analyses will explore the association between preoperative and postoperative cardiac biomarker levels and perioperative LVD and RVD.

With a one sample binomial test at a one-sided significance level of 5% with 80% power, 31 patients would be required to confidently identify an incidence of postoperative RVD of 5% as different from zero in any individual surgical subgroup. As such, recruiting 35 patients per group provides a 10% margin for lost to follow-up and withdrawals. This results in a total sample size of 175.

Clinical impact of perioperative RVD

Assuming the incidence of RVD is proven to be different from zero in any group (highly likely given our previous findings[8]), then additional analyses will be performed in pooled data across all surgical groups to assess the clinical impact of postoperative LVD or RVD. Sensitivity analyses will be performed to assess the clinical impact of RVD on patients that develop new postoperative RVD, compared with the clinical impact of pre-existing RVD, which is maintained through to the postoperative period.

DAH_{30} postoperatively will be compared between the groups with and without postoperative RVD using negative binomial regression analysis adjusting for age and other known predictors of DAH_{30}.[25 26] It will also be explored how adjustment for further variables (including cardiac biomarker profile) affects results. We will conduct the same DAH_{30} analysis on the sensitivity analysis groups described above.

Performing power analysis for this comparison is challenging given the large number of unknowns in terms of the incidence of RVD, and the potential effect size. As such, an indicative power analysis was performed exploring sample sizes from 50 to 200 patients, an incidence of RVD 15%–50% and for a difference in DAH_{30} of 2 or 3 days. The anticipated power is in excess of 0.8 in all simulations containing over 125 patients suggesting that in the 175-patient sample should have sufficient power in most conceivable scenarios (figure 2).

Exploratory outcomes

LVD will be analysed analogously to RVD as a secondary analysis.

Secondary outcomes from the postoperative period will be used to compare their incidence in patients with and without the primary outcome (RVD). We will assess for association between RVD and PMI (via cardiac biomarkers), cardiovascular complications, major complications, patient recovery, length of intensive care unit and hospital stay. Analysis of intraoperative data will be used with the aim to identify mechanisms by which RVD may have arisen. Where appropriate, multivariate analysis will be used.

We will use 30-day mortality as our primary survival end point and will assess for association with RVD via appropriate survival analyses.
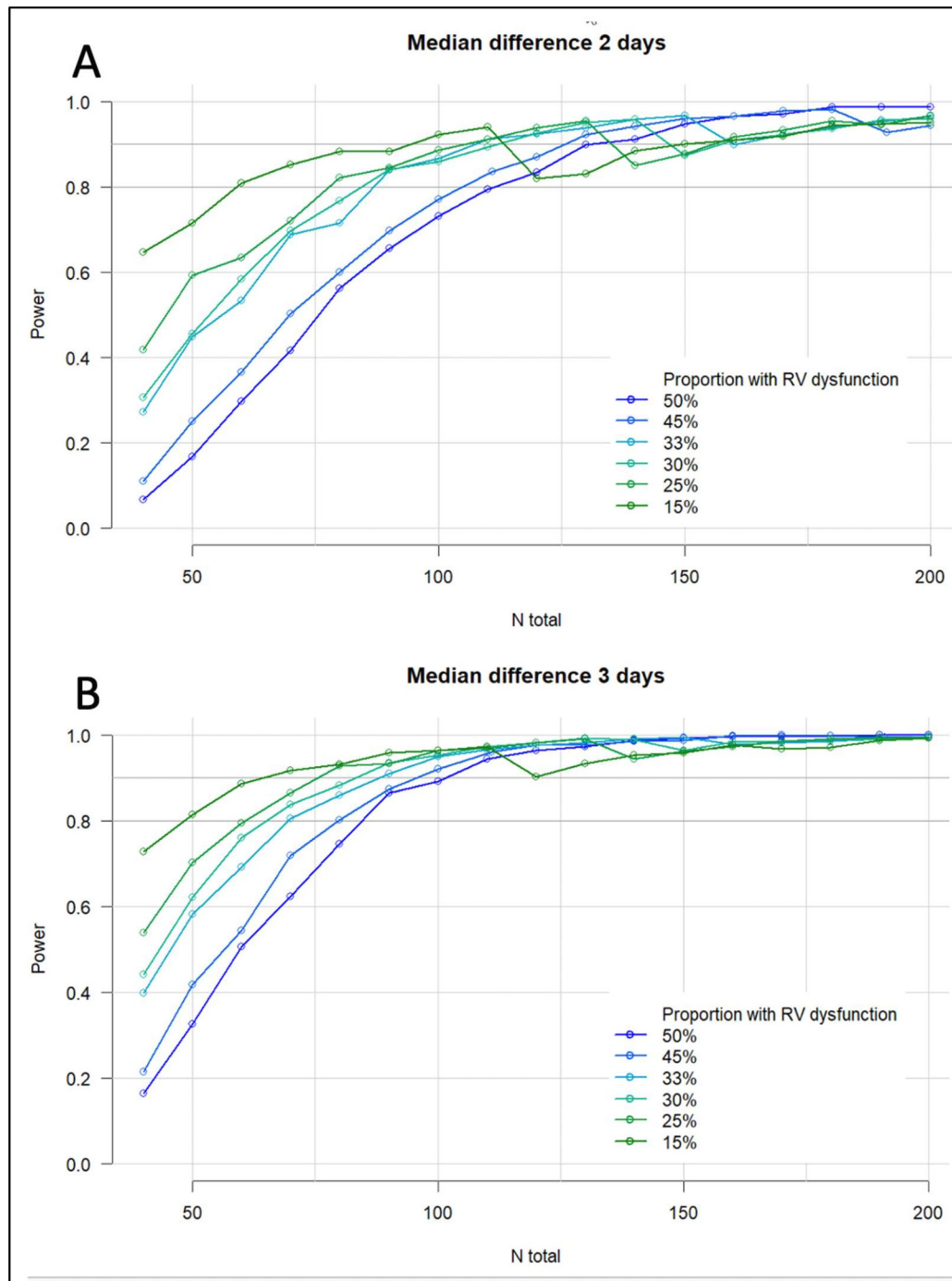
Figure 2 Simulated power analysis for impact of RVD on days alive and at home at 30 days. Assuming for 1% of the patients $DAH_{30}=0$, for the remainder DAH_{30} follows a negative binomial distribution with parameters chosen such that the median DAH_{30} is 24/25 in one group and 27 in the other group and the shape of the distribution is similar to that seen in the validation cohorts. The simulated DAH_{30} was then compared between groups using negative binomial regression (repeated) in 1000 samples. The figures show the resulting estimated power for incidences of postoperative RVD from 15% to 50%[#], and for a clinical effect size of 2 (A) or 3 (B) days difference in DAH_{30}[*]. [#]In our previous work the incidence of postoperative RVD was 50% in thoracic surgical patients but may be significantly less in, for example, an orthopaedic population. [*]In Chou *et al*'s study preoperative RV dysfunction prolonged hospital length of stay by over 50%, but this cohort was a very high-risk vascular surgical population.[7] DAH_{30}, days alive and at home at 30 days postoperatively; RVD, right ventricular dysfunction.

We will also assess the intermediate-term and long-term impact of RVD on patients by assessing association between RVD and health-related quality of life (via EQ-5D-5L) and functional status (via WHODAS 2.0) at 30-day, 3-month and 1-year postoperatively.

Preoperative and postoperative T1-CMR will explore for association between imaging correlates of myocardial inflammation (T1 and extracellular volume) and both RVD and PMI. This substudy will also aim to confirm our previous findings of elevated

postoperative T1/extracellular volume in patients after thoracic surgery,[15] and replicate this in other surgical groups.

Patient and public involvement

Our programme of work was presented to the Society of Cardiothoracic Surgeons 'RESOLVES' Patient and Public Involvement (PPI) group with very positive feedback. This PPI group was unanimously in favour of our research and its obvious benefits to patients.

Ethics and dissemination

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the Good Clinical Practice Guidelines. UK wide ethical approval was obtained from the South Central- Oxford C Research Ethics Committee (REC reference 22/SC/0442) and will comply with all applicable UK legislation. Local research and development approval was obtained from each participating site. All local site Standardised Operating Procedures (SOPs) will be followed.

All publications and presentations relating to this study will be authorised by the trial chief investigator (BS). Authorship will be determined according to the international committee of medical journal editors' recommendations. The results of the study will be first reported to study collaborators. Subsequently, we will communicate our results by reporting them to the funder and presentation at national meetings, with publication in appropriate peer-reviewed journals. Further details about the trial results and final report will be available on request to the scientific community in a timely manner.

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