Cardiovascular risk factors for perioperative myocardial injury

A thesis submitted in partial fulfilment of the requirements of the degree of Doctor of Philosophy

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Declaration

I, Thomas Abbott, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by, others that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

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Details of collaborations and publications

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Short abstract

Background: Myocardial injury affects up to one in three patients undergoing non-cardiac surgery. However, very little is known about the underlying pathophysiology. In the general population, patients with elevated resting heart rate are at increased risk of cardiac events, mortality, heart failure and autonomic dysfunction, while hypertension is a well described risk factor for cardiovascular disease. I hypothesised that common abnormalities of heart rate or blood pressure were associated with myocardial injury after non-cardiac surgery.

Methods: This thesis comprises a series of secondary analyses of data from five prospective multi-centre epidemiological studies of surgical patients. The main outcome of interest was myocardial injury, defined using objective measurement of cardiac troponin. I used logistic regression analysis to test for association between exposures and outcomes.

Results: In a large international cohort, patients with high preoperative heart rate had increased risk of myocardial injury and patients with very low preoperative heart rate had reduced risk of myocardial injury. Patients with elevated preoperative pulse pressure had increased risk of myocardial injury, independent of existing hypertension or systolic blood pressure. High heart rate, or high or low systolic blood pressure during surgery, was associated with increased risk of myocardial injury. In a separate study, elevated preoperative heart rate was associated with cardiopulmonary and autonomic dysfunction, and reduced left ventricular stroke volume, suggestive of heart failure. Finally,

autonomic dysfunction, identified using cardiopulmonary exercise testing, was associated with elevated preoperative heart rate, elevated plasma NT-Pro-BNP (indicative of heart failure) and postoperative myocardial injury.

Conclusions: Elevated preoperative heart rate, autonomic dysfunction and subclinical heart failure may be part of a common phenotype associated with perioperative myocardial injury. Further research is needed to characterise the pathological processes responsible for myocardial injury, and to identify potential therapeutic targets.

Scientific summary

Background

Myocardial injury affects up to one in three patients undergoing non-cardiac surgery. It is predominantly asymptomatic and without ischaemic features, and is strongly associated with death. However, very little is known about predisposing risk factors for myocardial injury and the underlying pathophysiological mechanism. In the general population, patients with elevated heart rate, blood pressure and/or pulse pressure are at greater risk of cardiovascular complications and death. Elevated heart rate is associated with development of heart failure, which is a risk factor for perioperative morbidity and mortality, and with autonomic dysfunction, which occurs in one third of surgical patients. Blood pressure is routinely checked before surgery, but there is uncertainty among anaesthetists and surgeons regarding the management of hypertension before surgery, which may result in cancelled procedures. The aim of this thesis was to investigate, using epidemiological methods, whether abnormalities of heart rate and blood pressure commonly seen in the general population were risk factors for perioperative myocardial injury, thus generating hypotheses for further translational and interventional research.

Preoperative heart rate

The first part of this thesis uses data from the international, multi-centre, VISION cohort study, which first described perioperative myocardial injury. The analysis described in chapter three found that very high preoperative heart rate was associated with increased risk of myocardial injury and very low preoperative heart rate was associated with reduced risk of myocardial injury.

These findings were independent of potential confounding factors such as urgency of surgery, age or diagnosis of ischaemic heart disease.

Preoperative blood pressure

The analysis described in chapter four used data from the VISION study to identify an association between preoperative pulse pressure and perioperative myocardial injury, independent of previous history of hypertension and preoperative systolic blood pressure.

Intraoperative heart rate and systolic blood pressure

The analysis described in chapter five used data from the VISION study to identify that patients with very high heart rate, or very high or low systolic blood pressure during surgery were at greater risk of myocardial injury, compared to those without heart rate or blood pressure abnormality. Conversely, patients with a very low heart rate during surgery were at lower risk of myocardial injury. These findings are consistent with the hypothesis that elevated heart rate promotes myocardial injury through imbalance between myocardial oxygen supply and demand. However, it is also plausible that that elevated heart rate is a marker of another pathophysiological mechanism causing myocardial injury.

Sub-clinical heart failure

In chapter six, I used cardiopulmonary exercise testing to identify cardiopulmonary and autonomic impairment in patients in the POM-HR study who underwent high-risk non-cardiac surgery. However, only a small proportion of these patients had a clinical diagnosis of heart failure. Elevated preoperative heart rate was associated with impaired cardiopulmonary and autonomic

function, suggestive of heart failure. In a separate cohort of high-risk patients from the OPTIMISE and POM-O trials who underwent major abdominal surgery, elevated preoperative heart rate was associated with reduced left ventricular stroke volume. These findings suggest that elevated preoperative heart rate is a marker of subclinical or undiagnosed heart failure.

Parasympathetic dysfunction

In chapter seven, I used cardiopulmonary exercise testing to identify impaired parasympathetic autonomic function in patients in the METS study, a prospective international observational cohort study. Parasympathetic dysfunction, characterised by impaired heart rate recovery after preoperative exercise, was associated with postoperative myocardial injury, elevated resting heart rate and elevated preoperative plasma NT pro-BNP, indicative of heart failure. These findings suggest that elevated resting heart rate, autonomic dysfunction and subclinical heart failure may be part of the same preoperative clinical phenotype.

Summary

Elevated heart rate before and during surgery, elevated preoperative pulse pressure, high and low systolic blood pressure during surgery, and impaired heart rate recovery after preoperative exercise are associated with increased risk of perioperative myocardial injury. However, the preoperative phenotype of patients at risk of myocardial injury is complex. Elevated preoperative heart rate, impaired parasympathetic function and subclinical heart failure are likely to be part of the same preoperative phenotype, which may be present in approximately 15% of patients undergoing in-patient non-cardiac surgical

procedures. Further research is needed to describe the pathological processes responsible for myocardial injury, which may include heart failure and autonomic dysfunction, and to help target novel therapeutic strategies to those patients most at risk. This will require a variety of methodological approaches, from hypothesis-generating epidemiology to translational laboratory science and interventional studies of clinical treatments.

Lay summary

Introduction

Each year in the UK approximately 40,000 people die within three months after major surgery. The most common causes of death involve the heart, including heart attack and heart failure. Several studies since 2012, using simple blood tests, have shown that at least one in every ten surgical patients suffer damage to their heart muscle (myocardial injury) and are more likely to die after surgery. However, we do not understand how or why myocardial injury occurs. In the general population, people with elevated heart rate or blood pressure are more likely to suffer from heart conditions or die. The aim of my research was to investigate whether, in surgical patients, there are relationships between abnormal heart rate or blood pressure and myocardial injury after surgery.

Heart rate before surgery

The first part of my PhD uses data from the VISION study, an observational study of 15,000 surgical patients, from eight countries, between 2007 and 2011. The research described in chapter three found that very high heart rate (more than 96 beats per minute) just before surgery was associated with increased risk of myocardial injury, and very low heart rate (less than 60 beats per minute) was associated with reduced risk of myocardial injury.

Blood pressure before surgery

There is uncertainty among both anaesthetists and surgeons about how to manage high blood pressure before surgery. This may result in cancelled operations, even for patients with a normal blood pressure reading in clinic

before surgery. Pulse pressure is measured with every standard blood pressure measurement. In the general population high pulse pressure is associated with increased risk of heart attacks and strokes. In chapter four, using data from the VISION study, I identified that elevated pulse pressure before surgery was associated with approximately 20% increased risk of myocardial injury. This was not influenced by a previous diagnosis of high blood pressure. Therefore, patients with elevated pulse pressure may benefit from additional tests before surgery, or additional time in the recovery unit after surgery.

Heart rate and blood pressure during surgery

In chapter five, using data from the same study, I found that patients with very high heart rate, or very high or low blood pressure during surgery were at greater risk of myocardial injury, compared to patients with normal heart rate or normal blood pressure. Patients with very low heart rates during surgery were at lower risk of myocardial injury. These findings from the VISION study suggest that a high heart rate might cause myocardial injury, perhaps by increased requirement for oxygen above that which can be supplied to the heart. However, this is unlikely because medications that lower heart rate do not reduce the risk of cardiac complications after surgery. Therefore, other, as yet unknown, factors are likely to be involved.

Undiagnosed heart failure in surgical patients

In the general population, elevated heart rate is linked to the development of heart failure in later life, which is also a risk factor for complications after surgery. In chapter six I used exercise testing to identify impaired function of the heart, of breathing (cardiopulmonary function) and of nerves from the brain

(autonomic function) in surgical patients. I used data from the POM-HR study, an observational study of 1250 surgical patients from Plymouth and London. I found that elevated heart rate before surgery was associated with impaired cardiopulmonary and autonomic function, which suggests the presence of un-diagnosed heart failure. This was corroborated by detailed measurements of heart function in a separate group of 181 surgical patients from the OPTIMISE and POM-O studies. These results suggest that, in people who are going to have surgery, elevated heart rate is a marker of undiagnosed heart failure.

Impaired autonomic function

Data from a previous study of 250 patients suggests that one in three surgical patients have impaired autonomic function. In the general population this is linked to elevated resting heart rate. In chapter seven, I used exercise testing before surgery to identify patients with impaired autonomic function in 1325 patients from the METS study, an international observational study of surgical patients conducted between 2012 and 2016. I found that impaired autonomic function was associated with myocardial injury, elevated resting heart rate and a blood test suggestive of heart failure. Therefore these preoperative factors may be linked and part of the same disease process.

Summary

I used data from five studies of surgical patients to identify risk factors for myocardial injury after surgery. While I could identify risk factors for myocardial injury, like elevated heart rate or pulse pressure, the relationship between these factors is complex. My results suggests that elevated heart rate, impaired autonomic function and undiagnosed heart failure are all part of the same

disease process, which occurs in one in six patients having surgery in hospital. In other words, out of the 1.5 million major surgical procedures that occur in the UK every year, approximately 225,000 patients are at risk of this disease process, and neither patient, nor doctor would be aware of it. However, the biological mechanisms that might link these factors are uncertain. Therefore, further research is needed to describe the biological processes causing myocardial injury, which may include heart failure and/or impaired autonomic function. This may help identify new treatments or ways to target treatments at particular groups of patients at risk of myocardial injury.

Statement of contribution

This thesis uses epidemiological methods to analyse five large data sets, derived from multi-centre, and predominantly international, research collaborations. I was responsible for prospectively designing each analysis, cleaning and preparing the data, performing the statistical analyses and writing up the results. This required formal training in epidemiological and statistical methods, through the London School of Hygiene and Tropical Medicine. I was actively involved in the data collection for the METS and VISION studies.

Over a four-year period I was the UK coordinator for the METS study. Locally, at the Royal London Hospital, I was responsible for patient recruitment and data collection. I screened and recruited ~250 surgical patients attending the preoperative assessment clinic for two and a half years, which included conducting cardiopulmonary exercise tests and coordinating patient follow-up within our research team. As the UK coordinator I liaised with the five other UK sites on a day-to-day basis, including: answering queries and providing advice about the study protocol and procedures, collating weekly screening logs, liaising with the central laboratory and maintaining the trial master file. At the start of the study I worked with the Sponsor's representative (QMUL) to set-up the UK sites, including: organising contracts, local research and development department approvals and conducting site initiation visits. I was responsible for submitting protocol amendments to the research ethics committee, preparing the annual progress reports, organising shipments of frozen laboratory samples, conducting on-site monitoring and chasing up data queries. At an international level I was a member of the Trial Steering Committee, which involved attending regular teleconference meetings with my supervisor, during

which I often provided an update on the study progress in the UK. I was part of the writing committee for the published report of study protocol.[1]

I contributed to the VISION study as a local investigator at the Royal London Hospital over a four-year period. This included: screening patients for eligibility, obtaining written informed consent, obtaining preoperative and postoperative blood samples, collecting data before, during and after surgery both directly from patients and from their medical record, completing the paper case report forms and conducting telephone follow-up interviews. I liaised with other UK sites regarding data collection and blood samples, and with the international study team regarding the UK and international study databases.

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Table of Contents

List of figures

List of tables

List of abbreviations

AF	Arial fibrillation
AT	Anaerobic threshold
BP	Blood pressure
BPM	Beats per minute
BP	Blood pressure
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HR	Heart rate
Kg	Kilogram
Min	Minute
MINS	Myocardial injury after non-cardiac surgery
MmHg	Millimetres of mercury
ML	Millilitres
NT pro-BNP	N-terminal pro-B-type natriuretic peptide
OR	Odds ratio
PP	Pulse pressure
RCRI	Revised cardiac risk index
SBP	Systolic blood pressure
TnI	Troponin-I
TnT	Troponin-T
VE/VCO_2	Ventilatory equivalent for carbon dioxide
VE/VO_2	Ventilatory equivalent for oxygen
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption

Chapter One

Introduction

1.1 Perioperative morbidity and mortality

Demand for surgical treatments is increasing.[2, 3] Perhaps due to growing global population, or as a result of an increasingly inclusive approach to selection of candidates, surgical treatments are now routinely offered to patients who, at the end of the 20th Century, may have been considered too high-risk for surgery.[4-6] This may be due to improvements in surgical or anaesthetic technique, increased healthcare capacity, or evolving views about which patients might benefit from surgery. However, the result is a shifting demographic of the surgical population toward patients with multiple pre-existing conditions.

1.1.1 The global burden of surgery is increasing

More than 300 million surgical procedures are performed worldwide each year.[2] This is larger than the global prevalence of malaria (~200 million cases) and represents over 4% of total world population.[3, 7] However, the incidence of morbidity and mortality after surgery is unclear. In developed nations death is thought to occur after 0.5-2.0% of surgical procedures.[3, 8-14] A recent cohort study of 44,000 patients from 27 high/middle/low income countries, found that 0.5% of elective surgical patients died before hospital discharge. The most common causes of postoperative death are cardiovascular in origin, followed by multi-organ failure and sepsis.[14] Death is more common after emergency surgery, compared to elective surgery.[10] Estimates of the proportion of patients with complications following surgery vary widely between 3-20% of procedures

(table 1.1).[9, 14-16] Complications range from surgical site infection to myocardial infarction, acute kidney injury or pneumonia.[17] The presence of any postoperative complication is associated with reduced long-term survival.[18]

Complication	Incidence (%)
All complications	15%
Infectious complications	
Sepsis	5%
Superficial surgical site	3%
Pneumonia	2%
Urinary tract	2%
Deep surgical site	1%
Body cavity	<1%
Cardiovascular complications	
Myocardial injury	8%
Myocardial infarction	3%
Arrhythmia	3%
Heart failure	2%
Pulmonary embolism	<1%
Stroke	<1%
Cardiac arrest	<1%
Other complications	
Postoperative bleed	3%
Acute kidney injury	2%
Acute Respiratory Distress Syndrome	<1%
Gastro-intestinal bleed	<1%

Table 1.1. Approximate incidence of complications after elective surgery. Stratified by type of complication: infectious, cardiovascular and other.[9, 14-16]

Until very recently the number of surgical procedures performed in the United Kingdom (UK) was unknown. Estimates of procedure frequency from the Royal College of Surgeons of England and the NHS Confederation vary widely, from between 5.6 million to 11 million procedures per year (personal correspondence). There are few reliable epidemiological data describing the surgical population in the UK, which makes it difficult to understand the total population at risk of postoperative complications. In a recent time-trend ecological study, we used Hospital Episode Statistics to describe the total number of hospital procedures performed in the UK each year and the

associated postoperative mortality rates. Over the five-year period from 2009 to 2014, ~40 million hospital procedures were performed, representing ~8 million procedures per year, of which 1.5 million procedures would be classed as 'major surgery' by most anaesthetists or surgeons. The crude postoperative mortality rate associated with these procedures was 1.5% within 30 days of surgery, rising to 2.8% within 90 days of surgery.[19]

1.1.2 Perioperative cardiovascular complications

The most common causes of early postoperative mortality are widely held to be cardiovascular in origin (table 1.2).[8] The incidence of symptomatic myocardial infarctions after non-cardiac surgery is ~1% in previously healthy patients having elective procedures, rising to ~5% in patients with a pre-existing cardiovascular disease.[15, 16, 20, 21] Symptomatic perioperative myocardial infarction results in death in one out of five cases.[14] However, death and symptomatic cardiac events represent only a small proportion of total cardiac pathology, since the majority of perioperative cardiac complications are asymptomatic. In a large surgical cohort, only ~35% of patients with confirmed myocardial infarction reported symptoms of myocardial ischaemia.[22] But, the reasons for this asymptomatic or 'silent' aetiology remain unclear. There is growing evidence that asymptomatic myocardial injury, identified by elevation in blood concentration of specific biomarkers of cardiac muscle damage (e.g. cardiac troponin), is much more common than overt myocardial ischaemia or infarction. Furthermore, it is strongly associated with all-cause mortality, regardless of the presence or absence of ischaemic symptoms, or the presence of electrocardiographic or echocardiographic evidence of myocardial ischaemia or infarction.[16, 23]

Cause of death	Number of deaths	Proportion of deaths (%)
Cardiovascular causes	435	34
Mesenteric ischaemia	264	20
Multi-organ failure	255	20
Septicaemia	239	18
Respiratory causes	165	13

Table 1.2. Causes of postoperative deaths. Illustrating the five most common causes of death (taken from death certificates) within 48 hours of surgery, among 1299 postoperative deaths recorded by the Scottish audit of surgical mortality.[8] Percentages rounded to the nearest whole number.

1.1.3 Some patients are at high-risk of perioperative complications

Four out of five postoperative deaths occur in a small group (~15%) of 'high-risk' patients,[24] who are typically elderly, have pre-existing conditions and/or require emergency surgery.[24] The physiological phenotype of patients at risk of perioperative morbidity and/or mortality has not yet been characterised in detail. The current paradigm judges perioperative risk according to patient and procedure factors.[25, 26] Procedure factors include: intraoperative complications, for example, blood loss; procedure length; and surgical or anaesthetic technique; all of which may be more significant during emergency surgery.[26] Patient factors comprise pre-existing conditions (co-morbidity), and general physical health and/or ability (functional capacity/reserve). The inter-relation of these factors is complex,[25, 26] with overlap between functional capacity and co-morbidity since physical illness affects cardiorespiratory fitness, while surgical or anaesthetic technique is often influenced by the presence of pre-existing conditions.[27] Limitation in any of these domains may impact the degree to which a patient can tolerate surgery.[25, 26, 28, 29]

1.1.4 Preoperative assessment clinics aim to identify high-risk patients

Preoperative assessment clinics are present in most UK hospitals, visited by at least four out of five patients before elective surgery.[30] Their introduction was driven in part by the findings of the National Confidential Enquiry into Perioperative Deaths, which advocates evaluation of all patients before surgery in a preoperative clinic,[30] the guidelines for the provision of anaesthetic services (Royal College of Anaesthetists) and the National Institute for Health and Care Excellence (NICE) guidelines for routine preoperative testing.[31, 32] The purpose of preoperative assessment clinics is to provide opportunities to optimise pre-existing conditions, assess functional capacity and plan perioperative care.[31] Visits usually include a medical history, clinical examination, electrocardiogram and routine blood tests with additional investigations arranged on a case-by-case basis.[33] Risk assessment uses a variety of methods, including: clinical (subjective) assessment; risk scores or stratification tools; objective clinical measures, for example cardiopulmonary exercise testing; or prognostic biomarkers, for example brain natriuretic peptide (BNP).[87] Observational evidence suggests that patients attending a preoperative assessment clinic tend to have a shorter stay in hospital, lower risk of critical care unit admission and lower risk of death.[30, 33-37] However, there are no interventional studies to support the use of preoperative assessment clinics and evidence for specific preoperative tests is generally weak (as assessed by NICE).[38]

1.1.5 'Fitness' for surgery and cardiopulmonary exercise testing

Since Paul Older identified a plausible link between preoperative cardiorespiratory capacity and postoperative outcomes in the 1990s,[39-44] there has been much interest in preoperative 'fitness' and how this might be

optimised.[29, 45] Small studies, most often focused on abdominal surgery, have identified association between cardiorespiratory capacity and postoperative complications, suggesting that patients with better preoperative 'fitness' tend to suffer fewer complications.[46-50] The widely accepted explanation for this observation centres around tissue oxygen delivery[51] that patients with poor preoperative oxygen consumption are less able to deliver oxygen to respiring tissues during periods of physiological stress (like during surgery or the immediate postoperative period).[47, 52] However, the physiology of this proposed mechanism is unclear and it remains uncertain whether preoperative exercise training can improve postoperative clinical outcomes.[53-56]

Cardiopulmonary exercise testing (CPET) is used to objectively measure preoperative functional capacity at ~40% of UK hospitals.[57] First described in the perioperative context in the 1980s, the most common set-up consists of a cycle ergometer using an incremental ramp protocol, where the workload steadily increases throughout the test. Continuous non-invasive measurement of respiratory and cardiovascular function allows multiple parameters to be derived. The two most widely used CPET variables are peak oxygen consumption (VO_2peak) and oxygen consumption at the anaerobic threshold (VO_2AT), the point where the metabolism switches from predominantly aerobic respiration to predominantly anaerobic respiration.[48] A number of studies have identified associations between preoperative VO_2AT,[41, 43, 58-65] VO_2peak,[59, 61, 65-67] and postoperative clinical outcomes. However, it is unclear which variable is superior for predicting postoperative clinical outcomes. Other CPET-derived cardiopulmonary and autonomic variables known to be associated with postoperative clinical outcomes or cardiovascular morbidity in the general

population include: pulse pressure, heart rate recovery and ventilatory equivalent for carbon dioxide (V_E/VCO_2). The original papers detailing the prognostic value of these variables are listed in table 1.3. However, the majority of studies used to justify preoperative CPET were conducted in single centres and in specific groups of patients, which limits their external validity.[68] [46]

CPET variable	References
Oxygen consumption at the anaerobic threshold <11 $ml.kg^{-1}min^{-1}$	Hennis et al 2011[46], Older et al 1999[41], Older et al 1993[43], Wilson et al 2010[58].
Peak oxygen consumption ≤14 $ml.kg^{-1}min^{-1}$	James et al 2014[69], Myers 2008[70].
$\dot{V}_E/\dot{V}CO_2$ ratio at anaerobic threshold ≥34	Myers et al 2008[70], Myers et al 2013[71], Wilson et al 2010[58].
Heart rate recovery <12 bpm	Myers et al 2008[70].
Pulse pressure >53 mmHg	Jackson et al 2015[72].

Table 1.3. Binary CPET variable thresholds and references.

1.1.6 Summary

Cardiovascular complications represent a prominent component of overall postoperative morbidity and contribute to the total burden of postoperative mortality. It is therefore important to seek ways to identify patients at risk of, and subsequently prevent, perioperative cardiovascular morbidity and mortality. However, first we must understand the underlying pathophysiology mechanisms, which are currently unclear.

1.2 Relevant cardiac and autonomic physiology

Here, I briefly describe the sympathetic and parasympathetic divisions of the autonomic nervous system, and the involuntary neural control of heart rate, restricted to detail pertinent to this thesis.

1.2.1 The autonomic nervous system

The autonomic nervous system (ANS) is part of the peripheral nervous system, which innervates organs and smooth muscle that are not under voluntary control, for example the heart and endocrine glands.[73, 74] It comprises parasympathetic and sympathetic divisions.[73, 74] Broadly speaking, the sympathetic system regulates the stress response, for example by increasing blood flow to aerobic muscles through increased rate and force of cardiac contraction, and constriction of the splanchnic circulation, diverting blood away from the digestive tract. Conversely, the parasympathetic division regulates the resting state, for example by diverting blood to the digestive system and stimulating urination/defecation. Acetylcholine is the main neurotransmitter in the parasympathetic nervous system, whereas the predominant neurotransmitter in sympathetic postganglionic neurons is noradrenaline, an endogenous catecholamine[75] containing a catechol moiety attached to an amine side-chain, which is synthesised from the amino acid tyrosine.[76] In comparison, adrenaline is synthesised in the adrenal medulla and secreted directly into the circulation.[77] Sympathetic catecholamines stimulate adrenoceptors (adreno-receptors),[77] which are G-protein-coupled receptors and can be divided into alpha- and beta-subtypes.[76, 77] They are widely distributed throughout and trigger various responses when stimulated (table 1.4).[76, 78] The heart contains Beta-1 receptors that increase the rate and force of cardiac contraction, and therefore cardiac output, when stimulated.

	Receptor sub-types			
Characteristics	**alpha-1**	**alpha-2**	**beta-1**	**beta-2**
Blood vessels	Constrict	Constrict/dilate	-	Dilate
Bronchi	Constrict	-	-	Dilate
GI tract	Relax	Relax	-	Relax
Cardiac contraction	-	-	Increase	-
Salivary gland	K+ release	-	Amylase secretion	-

Table 1.4 - Summary of distribution and effects of adrenoceptor subclasses, taken from *Rang, Dale, Ritter and Moore 2003*.[76]

Endogenous catecholamines are non-selective agonists, acting on all adrenoceptor sub-types, whereas synthetic agonists/anatagonists can act at a range of receptor sub-types (table 1.5). For example, beta-antagonists block the beta-receptor, hence 'beta-blockers'. In this thesis I use the terms beta-blocker and beta-antagonist interchangeably. Antagonism of beta-1 receptors in the heart reduces rate and force of contraction, thus lowering cardiac output and myocardial oxygen demand. However, side effects are not uncommon, including: bronchoconstriction;[79-81] exacerbation of *uncontrolled* heart failure;[80, 81] bradycardia;[80, 81] intermittent claudication;[80] and complete heart block.[82]

Agonist or antagonist	**Receptor sub-types**			
	alpha-1	**alpha-2**	**beta-1**	**beta-2**
Selective agonist	Phenylephrine	Clonidine	Dobutamine	Salbutamol
Selective antagonist	Doxazosin	Yohimbine	Atenolol, metoprolol, bisoprolol	Butoxamine
Non-selective antagonist	Phenoxybenzamine, phentolamine		Propanolol	
	Carvedilol, labetolol			

Table 1.5 - Examples of adrenoceptor agonists and antagonists, taken from *Rang, Dale, Ritter and Moore 2003*.[76]

1.2.2 Autonomic control of heart rate

Cardiac contraction is initiated by the sinoatrial node and a spreading wave of depolarisation across the myocardium.[75, 83] The heart is innervated by both noradrenergic sympathetic nerves from the cervical ganglia of the sympathetic chain and cholinergic parasympathetic nerve fibres from the vagus nerve.[75] Contractile rate (chronotropy) and force (inotropy) are modulated by the autonomic nervous system.[75] Over fifty years ago Jose and colleagues investigated the intrinsic rate of contraction of the human heart by injecting healthy volunteers with propranolol (beta-antagonist) and atropine (anti-

cholinergic) to obliterate sympathetic and parasympathetic cardiovascular control.[84, 85] They observed that in the presence of these drugs, heart rate increased, and that the intrinsic rate of cardiac contraction was higher than resting heart rate under normal circumstances.[85] Later experiments in humans and animals showed that at rest, the predominant autonomic action was parasympathetic, thereby lowering intrinsic heart rate and demonstrating that resting heart rate can be marker of parasympathetic activity.[86-88] Therefore elevated resting heart rate may be the result of autonomic dysfunction: either parasympathetic under-activity or sympathetic over-activity.

1.2.3 Parasympathetic autonomic dysfunction

In the general population, an increasing body of evidence suggests that parasympathetic dysfunction is present in approximately one in four people and is associated with clinical outcomes. Parasympathetic dysfunction can be identified by the degree of reduction in heart rate immediately after the end of exercise,[85] since in the first few minutes after exercise this is mediated by parasympathetic stimulation and thereafter by sympathetic withdrawal.[89] Thus early heart rate recovery is a measure of parasympathetic function.[89] Typically heart rate is measured at specific time points after maximal exercise and 'heart rate recovery' in beats per minute calculated. A study of ~2,500 apparently healthy men and women identified that impaired heart rate recovery within the first minute after exercise was associated with increased risk of mortality.[90] Similarly, in 9,000 men and women without existing cardiovascular disease, prolonged heart rate recovery (≤ 12 beats in the first minute after exercise) was associated with increased risk of subsequent mortality.[91] These results are replicated in longitudinal population cohorts, with average follow-up durations

between 14 and 20 years, suggesting that this may represent an as yet un-recognised chronic underlying pathology.[92, 93]

1.3 Perioperative myocardial injury

1.3.1 The universal definition of myocardial infarction

The widely accepted framework for identifying and classifying acute myocardial pathology centres on the universal definition of myocardial infarction, derived by expert consensus.[94] The third iteration defines myocardial infarction as "evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia".[94] In the absence of interventional radiology or post-mortem evidence of coronary artery occlusion, myocardial infarction is most commonly diagnosed by elevation in a cardiac biomarker >99th centile in addition to one or more of the following findings: symptoms of ischaemia; electrocardiographic evidence of new ST segment abnormalities, new left bundle branch block or new Q waves; or imaging (typically echocardiographic) evidence of regional wall motion abnormality or loss of myocardium.[94] However, the application of the universal definition of myocardial infarction to perioperative patients is not straightforward, since the majority of patients with perioperative myocardial infarction are asymptomatic. This is further complicated by the high incidence (~10%) of perioperative cardiac biomarker elevation in the absence of symptoms (~90%) or objective evidence of ischaemia/infarction (~75%).[95] Therefore, asymptomatic perioperative cardiac biomarker elevation is likely to be a distinct pathophysiological entity from traditional paradigm of acute myocardial infarction.

1.3.2 The pathophysiology of myocardial injury

The pathophysiology of perioperative cardiac biomarker elevation (myocardial injury) is poorly understood. Landesberg and colleagues describe two separate models of perioperative myocardial injury and infarction. Firstly, the occlusive model of acute coronary syndrome, characterised by the rupture of unstable coronary atherosclerotic plaques with subsequent thrombosis, leading to partial or total occlusion of the coronary artery and distal myocardial ischaemia and/or infarction (type I). Secondly, prolonged ST-segment depression myocardial ischaemia due to oxygen-supply-demand-imbalance in patients with critical, but stable, coronary stenosis (type II).[96] It is plausible that damage or death of cardiac myocytes, and consequent troponin release, could occur as a result of both mechanisms.[96-98] However, 'type I' plaque rupture and thrombosis is unlikely to be the predominant biological mechanism underlying perioperative myocardial injury for two reasons.[99] Firstly, only 4% of patients with postoperative troponin elevation show evidence of ST-elevation, Q waves or left bundle branch block on electrocardiogram.[95] Secondly, standard treatments for acute coronary syndrome do not reduce the incidence of perioperative cardiac complications when given prophylactically. For example, in the POISE-2 trial, prophylactic aspirin did not reduce the incidence of postoperative death or myocardial infarction compared to placebo,[100] and in the CARP trial, prophylactic coronary revascularisation did not reduce the incidence postoperative myocardial infarction in patients undergoing vascular surgery.[101] Thus, the aetiology and pathophysiology underlying perioperative myocardial injury remains unclear.

1.3.3 Risk factors for perioperative cardiac complications

Lee and colleagues undertook a study of risk factors for perioperative cardiac complications in 1999.[20] In a single-centre observational cohort of ~4000 patients having elective non-cardiac surgery, they identified six preoperative risk factors for postoperative cardiac complications, including: high-risk surgery (intraperitoneal, intrathoracic or suprainguinal vascular procedures), history of ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes and preoperative serum creatinine >2.0mg/dL.[20] Subsequently, the VISION study investigators identified additional preoperative risk factors for myocardial injury after non-cardiac surgery (defined by serum troponin), including: age ≥75 years, male gender, history of atrial fibrillation, history of diabetes (not limited to insulin therapy), history of peripheral vascular disease, estimated glomerular filtration rate ≤60 ml/min/1.73m^2 and emergency surgery. [95]

1.3.4 Biomarkers of myocardial injury

A systematic review of 15 studies identified creatinine kinase brain and muscle isoenzyme (CK-MB), troponin-I (TnI) and troponin-T (TnT) as the three most commonly used perioperative biomarkers of myocardial injury.[102] Elevation in any cardiac biomarker within 3 days of surgery is independently associated with 30-day postoperative mortality.[16, 102] In the context of surgery or trauma, where CK-MB is likely to be elevated due to skeletal muscle damage, troponin is a more specific biomarker for myocardial injury.[102] The majority of subsequent studies use troponin assays to detect perioperative myocardial injury.[16, 95, 103-106]

Troponin (Tn) is a calcium binding protein consisting of three subunits (I, T and C) found in both skeletal and cardiac muscle and is closely associated with other muscle proteins: tropomyosin, actin and myosin.[83] There are separate isoforms of the I and T subunits, which are specific to cardiac muscle (cTnI and cTnT).[107, 108] In this thesis, further discussion of troponin will relate to cardiac troponin unless otherwise stated. The function of troponin is to regulate muscle contraction in response to intracellular calcium release, specifically the positioning of tropomyosin in relation to actin, and thus the interaction between actin and myosin (muscle contraction).[83] Troponin is an intracellular protein, where ~90% is bound to structural proteins and ~10% is un-bound in the cytoplasm.[98] Therefore, if troponin is detectable in serum or plasma, it implies the release of the cellular contents of cardiac myocytes into the bloodstream.[98, 108] The pathophysiology of troponin release is still under investigation, and while the predominant cause of troponin release is thought to be myocyte necrosis, several other mechanisms have been suggested, including apoptosis, increased cell membrane permeability and release of cellular vesicles containing troponin.[98] In healthy volunteers, cardiac troponin is not usually detectable in blood plasma, therefore measureable concentrations of cTnI/T represent sensitive and specific markers of injury to heart muscle (myocardial injury).[98, 108, 109] Thus, cardiac troponins are routinely used in the identification and diagnosis of acute coronary syndromes, including myocardial infarction.[110, 111] However, emerging research using high-sensitivity troponin assays suggest that there may be chronic leak of troponin from cardiac myocytes in patients with cardiovascular disease, for example undiagnosed hypertension,[112] which may represent on-going chronic sub-clinical myocardial injury.

1.3.5 Myocardial injury after non-cardiac surgery

'Myocardial injury after non-cardiac surgery' (MINS) was first defined by the Vascular events In non-cardiac Surgery cohort evaluatION (VISION) study[16] and has subsequently been adopted by consensus guidelines on perioperative outcome measures. MINS is defined as:[113]

> *"A peak troponin T (TnT) ≥ 0.03ng ml^{-1} judged due to myocardial ischaemia (i.e. no evidence of a non-ischaemic aetiology causing the TnT elevation)."*

This definition uses a fourth generation Troponin-T assay, with a reported incidence of postoperative myocardial injury between 8% and 15%,[95, 104] although rates of greater than 40% have been reported in high-risk patient groups.[103, 114, 115] While the Roche Diagnostics TnT assay is very common, not all hospitals use it, opting instead for either Troponin-T assays from other manufacturers or Troponin-I assays. Therefore the definition may not be applicable to all clinical settings. In addition, highly sensitive '5th generation' troponin assays are now available, which are increasingly adopted by many hospitals.[115] In the first published cohort of VISION study - the largest epidemiological study of its type, which defined MINS - myocardial injury was detected after one in ten non-cardiac procedures.[95] On this basis, approximately 150,000 cases of postoperative myocardial injury will occur in the UK every year, assuming an annual procedure frequency of 1.5 million.[19, 24, 95, 116] Importantly, the majority of these patients will be asymptomatic, yet at much higher risk of death compared to patients without myocardial injury. Despite this, the clinical significance of myocardial injury remains controversial for four principal reasons; firstly, the pathophysiology is poorly understood; secondly,

the long-term impact on cardiac function is unclear; thirdly, troponin assays are not standardised and a wide variety are used in clinical practice; and fourthly, the incidence of myocardial injury in the general (non-surgical) population is unknown. Therefore, treatments have not yet been developed, leaving clinicians unclear about how best to manage a patient with myocardial injury.[117] Research is urgently needed to understand postoperative myocardial injury and develop new treatments.[16, 95, 102, 104]

1.4 Pathophysiology of heart disease in the wider population

The single leading cause of death worldwide is ischaemic heart disease, with deaths from cardiovascular diseases accounting for ~13% of deaths among men and ~11% of deaths among women.[118] In the United Kingdom, cancers and cardiovascular diseases account for 28% and 26% of all deaths respectively.[119] In men aged 50 years or older, ischaemic heart disease is the leading cause of death.[120]

1.4.1 Ischaemic heart disease

The aetiology of ischaemic heart disease is complex. The principal underlying pathophysiological mechanism is atherosclerosis leading to coronary artery stenosis, impaired myocardial blood supply and myocardial ischaemia, which clinically manifests as angina. Rupture of atherosclerotic plaques and thrombosis results in sudden partial or complete coronary artery occlusion, which presents as an acute coronary syndrome of unstable angina or myocardial infarction.[94] The seminal epidemiological study in this field is the Framingham Heart study; an observational cohort study of ~5000 men and

women from Framingham, Massachusetts, which started in the late 1940s and continues today.[121] [122] Analyses of the Framingham cohort identified key risk factors for ischaemic heart disease,[123] including: hypertension,[124-126] diabetes mellitus,[127, 128] hypercholesterolaemia,[129, 130] and cigarette smoking.[131, 132]

1.4.2 Heart failure

Heart failure is a clinical syndrome of signs and symptoms including: paroxysmal nocturnal dyspnoea, cardiomegaly, central venous congestion and neck vein distension, basal crepitations on auscultation of the chest, peripheral oedema, shortness of breath on exertion, hepatomegaly and pleural effusion.[133] Clinical heart failure syndrome is strongly associated with death; in the Framingham cohort the median survival from diagnosis was 3.2 years for women and 1.7 years for men.[134] Despite improvements in the identification, treatment and prevention of ischaemic heart disease, the prevalence of heart failure has stayed relatively stable.[135] In the USA, the annual incidence of clinical heart failure syndrome is 1% in people aged over 65 years,[136] which increases with increasing age.[137] The pathophysiological mechanisms underlying heart failure are poorly understood. There are common risk factors with ischaemic heart disease (e.g. hypertension and diabetes mellitus). However, the dissociation between decreasing mortality from ischaemic heart disease and stable mortality from heart failure suggests two separate aetiologies.[135, 136] This is complicated by the clinically subjective nature of the predominant definition/classification of heart failure (New York Heart Association classification),[138] which is based on exercise tolerance and does not take into account emerging functional sub-types of heart failure, for

example, heart failure with reduced ejection fraction, versus heart failure with preserved ejection fraction.[135]

1.4.3 Hypertension

Hypertension, typically defined as systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg, is a modifiable risk factor for cardiovascular diseases in the general population, including ischaemic heart disease, heart failure and stroke.[139, 140] In the UK, clinical management of hypertension is based on measured blood pressure, age, ethnicity and predicted ten-year risk of cardiovascular complications.[139] Treatment includes lifestyle interventions (diet and exercise) and pharmacological therapy to a target blood pressure of ≤140/90mmHg.[139] However, new evidence suggests that a target of systolic blood pressure ≤120mmHg is associated with reduced incidence of cardiovascular morbidity and mortality.[141, 142]

Components of blood pressure change with normal ageing; for example, elevated mean arterial pressure[A] appears more common in younger men, while elevated pulse pressure[B] is more common in older women.[143] Pulse pressure is the arithmetic difference between systolic and diastolic blood pressure, which reflects the compliance of large arteries (stiffness), arterial resistance, myocardial contractility and left ventricular filling.[144-146] Elevations in systolic, diastolic, mean arterial and pulse pressures are differentially associated with various cardiovascular diseases;[140] arterial pulse pressure may be a superior predictor of cardiovascular disease than systolic or diastolic blood pressures alone. In the prospective PROCAM study of >5,000 healthy men, pulse

[A] Mean arterial pressure (MAP) = Diastolic blood pressure + ⅓ systolic blood pressure
[B] Pulse pressure = systolic blood pressure – diastolic blood pressure

pressure was more strongly associated with ischaemic heart disease than systolic or diastolic blood pressure, independently of hypertension status.[147] Similarly, elevated pulse pressure was associated with increased incidences of cardiovascular events and mortality in a registry study of ~45,000 patients with atherosclerosis,[148] a cohort study of ~120,000 men and a systematic review and meta-analysis.[149-151]

1.4.4 Resting heart rate

Elevated resting heart rate is associated with early mortality in both hypertensive and non-hypertensive cohorts, independently of gender or pre-existing cardiovascular disease.[152, 153] In a Portuguese study of patients with acute coronary syndrome, heart rate >82 beats per minute was associated with reduced survival to hospital discharge,[154] and elevated heart rate was associated with other cardiovascular risk factors in a large Italian cohort of hypertensive patients.[155] This relationship is not limited to patients with pre-existing cardiovascular disease. In a Finish cohort of ~22,000 healthy men and women, elevated resting heart rate was independently associated with increased risk of subsequent cardiovascular disease.[156] While a similar study in Denmark identified a relationship between elevated resting heart rate and mortality, independent of physical fitness.[157]

Elevated resting heart rate is also independently associated with the development of clinical heart failure syndrome. In the EPIC-Norfolk cohort study of ~22,000 men and women without pre-existing disease, increasing risk of heart failure was strongly associated with increasing heart rate.[158] This relationship was also observed in a smaller study of ~5,000 men and women

from Rotterdam, where each 10 beat per minute increase in resting heart rate was associated with a 16% increase in the risk of developing heart failure.[159]

1.5 Heart rate in the perioperative period

It is plausible that tachycardia could cause myocardial injury via a mechanism of myocardial oxygen supply-demand imbalance.[96, 97, 102, 160] However, there is little clinical evidence to support this hypothesis. Here, I consider the evidence to support or refute potential associations between perioperative heart rate and clinical outcomes. This includes studies of heart rate before and during surgery, studies of cardiac and non-cardiac surgery and studies of heart rate during and after preoperative exercise testing.

1.5.1 Heart rate before surgery

Heart rate before cardiac surgery is associated with postoperative morbidity and mortality. In two observational cohorts of patients undergoing coronary artery bypass grafting (CABG), preoperative tachycardia, defined as either heart rate >130 or >80 beats per minute respectively, was associated with postoperative mortality.[161, 162] The difference in heart rate threshold could be due to variation in sample size or the unadjusted influence of confounding factors. In a different cohort, resting heart rate at hospital admission as a continuous variable was associated with postoperative myocardial infarction, and stroke, corrected for potentially confounding factors.[163] Patients with a complication had a mean heart rate that was five beats per minute higher than those patients without a complication ($p<0.0001$). However, a specific heart rate threshold was not defined.

In patients undergoing non-cardiac surgery there is less evidence to support a relationship between preoperative heart rate and postoperative outcomes. Preoperative heart rate is reported in only a small proportion of the trials of perioperative beta-blockade and, where it is reported, is subject to confounding by drug therapy. Evidence from two small trials suggests that heart rates lower than 65 or 70 beats per minute are associated with improved clinical outcome.[39, 44] Similarly, a retrospective study reported that patients treated with beta-blockers who later died had higher preoperative heart rate compared to those that survived. However, it is impossible disentangle the confounding effect of beta-blocker therapy, since patients without treatment were not described.[40] Furthermore, there is insufficient data to determine the degree of beta-receptor antagonism for individual patients receiving beta-blockers, which could confound an observed relationship between heart rate and clinical outcome.[39, 40, 44]

Only three studies have described resting heart rate before non-cardiac surgery in the absence of beta-blockade. In 172 patients with ischaemic heart disease, increasing preoperative heart rate was associated with increasing risk of postoperative mortality and cardiovascular morbidity.[164] In contrast, in a separate cohort of 181 patients undergoing vascular or orthopaedic surgery, elevated preoperative heart rate was not associated with increased risk of myocardial infarction.[165] These studies were similar in size and patient group. However, the contradictory results leave uncertainty about whether elevated preoperative heart rate is associated with postoperative clinical outcome. The largest study to examine preoperative heart rate is a secondary analysis of ~4,000 placebo group patients in the POISE trial. The investigators found that

each 10 beats per minute increase in preoperative heart rate was associated with a 29% increase in the risk of postoperative myocardial infarction.[22] However, there were several limitations of this analysis. Firstly, it is not clear when heart rate was measured, for example in the preoperative assessment clinic or in the anaesthetic room before the induction of anaesthesia.[22, 166, 167] Secondly, the analysis does not test whether there is a particular heart rate threshold above or below which patients are at greater risk of postoperative morbidity. Thirdly, the outcome measures were subjective and clinically defined, which has the potential to introduce observer bias and measurement error. Biochemical myocardial injury has not been investigated in this context.

1.5.2 Heart rate during surgery

Early studies reported association between intraoperative tachycardia and myocardial ischaemia, but did not define 'tachycardia'.[168-170] Subsequently, three cohort studies identified association between heart rates >100 beats per minute during non-cardiac surgery and postoperative morbidity and mortality.[171-173] However, these used *a priori* heart rate thresholds and non-comparable composite outcome measures, including: mortality, intensive care unit admission or prolonged hospital stay;[171] "negative surgical outcome", consisting of postoperative hospital stay >10 days or death;[173] and "cardiovascular complications", consisting of ischaemic symptoms, myocardial infarction, cardiac dysrhythmia or new heart failure.[172] In contrast, an observational study of the surgical APGAR score did not identify a relationship between intraoperative tachycardia and the development of any one of 17 postoperative complications or mortality.[174] On balance, it is likely that intraoperative tachycardia is associated with postoperative complications. However, there is

insufficient evidence of association between tachycardia and specific outcome measures, for example myocardial infarction or myocardial injury. Furthermore, it is unclear how to numerically define 'tachycardia' and whether there are specific heart rate thresholds at which the risk of morbidity is increased.

1.5.3 Heart rate recovery after preoperative exercise

Exercise testing is increasingly used to assess appropriateness for surgery. However, research has focused on biomarkers of ventilation or gas exchange. Few studies have investigated heart rate or blood pressure during preoperative exercise testing. In a study of 177 elderly patients, the risk of postoperative morbidity was greater for those unable to raise their heart rate over 99 beats per minute during preoperative exercise, compared to controls.[175] Similarly, evidence from a small study (n=32) suggests that the magnitude of change in heart rate from rest to maximum may predict postoperative morbidity.[60]

The cardiac response to exercise is affected by increased sympathetic activity and decreased parasympathetic activity. Thus recovery of heart rate after exercise can be used to evaluate the autonomic nervous system, where prolonged heart rate recovery in the first minute after exercise suggests parasympathetic dysfunction. However, heart rate recovery after preoperative exercise has been subject to only limited investigation. In two small studies delayed heart rate recovery was associated with increased risk of mortality after paediatric heart transplantation, and intraoperative hypotension in intermediate-risk adults.[176, 177] New evidence suggests that parasympathetic dysfunction, reflected by impaired baroreflex sensitivity, is associated with clinically defined cardiovascular and infectious complications after major surgery.[178]

In the context of autonomic control of heart rate and potential association between abnormal heart rate and cardiovascular morbidity, autonomic nervous system dysfunction may form part of the mechanism of perioperative myocardial injury. Parasympathetic autonomic dysfunction is associated with multiple risk factors for cardiovascular disease, including: diabetes mellitus,[179] ischaemic heart disease,[180] cardiac failure,[181] renal impairment[182] and stroke.[183, 184] Parasympathetic dysfunction has been implicated in the development of cardiovascular disease in the general population, due to the loss of cardio-protective vagal activity which is known to increase production of nitric oxide and anti-inflammatory cytokines, inhibit the renin-angiotensin axis and inhibit cardiac dysrhythmia formation.[185] In the perioperative setting, two out of five high-risk surgical patients have parasympathetic impairment.[178, 186] However, further research is needed to determine whether parasympathetic dysfunction is associated with biochemical myocardial injury after surgery.

1.6 Arterial pressure in the perioperative period

It is widely believed that changes in blood pressure during the perioperative period could cause or contribute to cardiovascular morbidity, through either oxygen supply-demand imbalance secondary to hypotension and low myocardial perfusion pressure, or as a result of existing cardiovascular disease and left ventricular strain in response to hypertension. However, the clinical blood pressure thresholds associated with organ injury remain unclear. This is important, given the apparent disconnect between haemodynamic variables and blood pressure, where in healthy volunteers, more than 25% of circulating blood volume must be lost before measureable changes in blood pressure

become apparent.[187] The majority of existing research into perioperative blood pressure is limited to observational studies of intraoperative hypotension, using subjective clinical outcome measures, rather than objective biomarkers of organ injury. Few studies have investigated blood pressure before surgery, as highlighted in recent consensus guidelines.[188] Here, I discuss the current evidence for association between perioperative blood pressure and postoperative morbidity and mortality.

1.6.1 Arterial pressure before surgery

As many as half of all patients undergoing high-risk non-cardiac surgery have pre-existing hypertension.[16] Evidence from two large cohort studies and a meta-analysis suggests that pre-existing hypertension is associated with increased risk of morbidity and mortality after non-cardiac surgery (table 1.6). However, hypertension is most often defined according to an existing diagnosis, rather than objective measurement of blood pressure before surgery. Therefore, the risk associated with elevated blood pressure on the day of surgery remains unclear, and it is not uncommon for surgery to be postponed or cancelled due to uncertainty about how to manage elevated preoperative blood pressure.[189, 190] Recent consensus guidelines suggest that surgery can proceed safely if the blood pressure is below 180/110mmHg in the preoperative assessment clinic, or less than 160/100mmHg in general practice.[188, 191] However, this guidance varies internationally[192] and is mainly derived from expert opinion, since there are only a limited number of small studies in this field, all of which use subjective clinically-defined outcome measures.[193, 194]

Study	Sample size	Key findings
Howell et al 1996[195]	152	Retrospective case-control study. Pre-existing hypertension was strongly associated with postoperative cardiovascular death within 30 days of surgery. However, the absolute value of systolic of diastolic blood pressure was not associated with outcome.
Howell et al 1997[196]	183	Prospective observational cohort study. Pre-existing hypertension was associated with increased risk of postoperative silent myocardial ischaemia.
Howell et al 1998[197]	230	Case-control study. Pre-existing hypertension was associated with cardiovascular death within 30 days of elective surgery.
Howell et al 1999[198]	146	Case-control study. Pre-existing hypertension was not associated with cardiovascular death within 30 days of urgent or emergency surgery.
Basali et al 2000[199]	207	Matched case-control study of intracranial haemorrhage after craniotomy. Preoperative hypertension was not associated with postoperative intracranial haemorrhage.
Howell et al 2004[200]	13671	Meta-analysis of 30 studies between 1971 and 2001. Hypertensive disease was associated with postoperative cardiovascular complications.
Sanders et al 2012[201]	429509	Retrospective cohort study using hospital episode statistics. Existing diagnosis of hypertension was associated with mortality following total knee replacement but not AAA repair.
Mathis et al 2013[202]	244397	Retrospective cohort study. Existing diagnosis of hypertension was associated with a composite outcome of mortality and morbidity with 72 hours of day case surgery.

Table 1.6. Summary of previous studies of preoperative hypertension. Two large retrospective cohort studies suggest that a diagnosis of hypertension is associated with mortality after day-case total knee replacement surgery. A meta-analysis of 30 small studies suggests that hypertension is associated with postoperative mortality and morbidity. Five smaller studies show weaker and inconsistent evidence of an association between hypertension and postoperative outcome.

1.6.2 Arterial pressure during surgery

The incidence of intraoperative hypotension is unknown, largely due to the absence of a consistent definition. *Bijker et al* reviewed 130 studies of intraoperative hypotension and identified 140 different definitions.[203] When

these were applied to an observational cohort of ~15,000 patients, the incidence of hypotension was between 5% and 99% of the sample, depending of the definition used.[203] However, numerous studies have identified association between intraoperative hypotension and perioperative mortality. One of the largest studies found that intraoperative hypotension was among the commonest cited factors contributing to deaths related to anaesthesia.[204] In the POISE trial, "clinically significant hypotension" was independently associated with perioperative mortality and stroke,[166] while numerous other studies have identified systolic hypotension and low mean arterial pressure as risk factors for perioperative mortality.[205-207] Similarly, several studies have identified association between intraoperative hypotension and cardiovascular complications after surgery.[208, 209] However, these use subjective clinically defined outcome measures, rather than objective biomarkers of organ injury.

Intraoperative hypertension is comparatively under-researched. The majority of published articles are case reports/series of patients undergoing endocrine or vascular surgery. In two observational cohort studies of cataract surgery and thyroid surgery the incidence of hypertension was between 10% and 60%.[210, 211] However, whether intraoperative hypertension is associated with adverse postoperative outcomes is unclear. Further research is needed to understand intraoperative hypertension and the potential association with postoperative morbidity and mortality.

1.6.3 Arterial pulse pressure before surgery

In the general population arterial pulse pressure is associated with cardiovascular morbidity, independent of existing hypertension.[147, 148, 212, 213]

Data from the Framingham heart study suggests that as age increases, pulse pressure becomes the main blood pressure related risk factor for incident cardiovascular events.[143] This finding is replicated in other longitudinal cohorts.[147] It seems intuitive that pulse pressure should be a more instructive physiological biomarker than systolic or diastolic pressures alone. Blood pressure is regulated by feedback from baroreceptors in the carotid sinus, aortic arch and atrial wall.[75] Baroreceptors are stretch receptors and the degree of arterial stretch is dictated by pulse pressure. Elevated pulse pressure is associated with increased aortic wall stiffness,[214] which influences sympathetic baroreflex sensitivity in elderly men and women.[215] Impaired baroreflex sensitivity is associated with cardiovascular morbidity after major surgery.[178] Alternatively, pulse pressure could combine pathophysiological processes usually associated with either elevated systolic pressure or reduced diastolic pressure, for example left ventricular hypertrophy secondary to systolic hypertension, leading to end-systolic myocardial stress,[216, 217] or poor coronary perfusion as a result of low diastolic pressure relative to left ventricular end-diastolic pressure, causing myocardial ischaemia.[218]

In this context, preoperative pulse pressure may be a superior predictor of perioperative cardiovascular outcomes compared to systolic blood pressure or pre-existing diagnoses of hypertension. However, the majority of existing studies of preoperative pulse pressure are restricted to patients undergoing cardiac surgery (table 1.7). Two observational studies identified association between preoperative pulse pressure >70-80mmHg and cardiovascular morbidity and mortality of patients undergoing coronary artery bypass grafting (CABG).[163, 219] These findings were replicated in a separate retrospective

cohort.[220] In contrast, only two retrospective studies have investigated pulse pressure before non-cardiac surgery (table 1.8), neither of which identified association between pulse pressure and postoperative outcomes.[221, 222] However, these studies have several limitations. They were retrospective in design and had small sample sizes, which limits the statistical power. In keeping with the majority of research in this field, they used subjective clinical outcome measures.

Study	Sample size	Key findings
Benjo et al 2007[223]	703	Retrospective cohort study of patients having coronary artery bypass grafting. Preoperative pulse pressure was associated with postoperative stroke.
Aboyans et al 2008[163]	1022	Prospective cohort study of patients undergoing coronary artery bypass grafting. Preoperative pulse pressure >70mmHg was associated with mortality, myocardial infarction, stroke or TIA with 30 days of surgery.
Fontes et al 2008[219]	4801	Prospective cohort study of patients undergoing coronary artery bypass surgery. Preoperative pulse pressure >80mmHg was associated with cardiac complications and death from a cardiac cause.
Nikolov et al 2010[220]	973	Retrospective cohort study of patients undergoing coronary artery bypass grafting. Elevated preoperative pulse pressure was associated with reduced long-term survival (mean follow-up 7.3 years).
Mazzeffi et al 2012[222]	556	Retrospective cohort study of patients having infrainguinal arterial bypass surgery. No association between preoperative pulse pressure and 30-day or 1-year mortality.
Asopa et al 2012[221]	412	Retrospective cohort study of patients undergoing lower extremity bypass surgery. Preoperative pulse pressure is not associated with postoperative cardiovascular events.

Table 1.7. Summary of previous studies of preoperative pulse pressure. Four studies demonstrate association between preoperative pulse pressure and postoperative outcomes in patients undergoing cardiac surgery. The remaining two retrospective cohort studies did not identify association between preoperative pulse pressure and postoperative mortality or cardiovascular events inpatients undergoing vascular surgical procedures.

Thus there is evidence of association between preoperative pulse pressure and postoperative morbidity and mortality after cardiac surgery, but it is unclear if this is the same for non-cardiac surgery. Furthermore, it is unclear if preoperative pulse pressure is associated with perioperative myocardial injury defined using cardiac biomarkers, or if there is a pulse pressure threshold above or below which the risk of morbidity or mortality increases. Further research is needed to evaluate these unanswered questions.

1.7 Perioperative beta-blockade

Until recently, beta-blockers were widely used to reduce cardiovascular complications after surgery. However, growing evidence over the past decade suggests that the clinical benefit of perioperative beta-blocker therapy may be outweighed by harmful side effects.[224] Despite over thirty years of research in this area,[145, 146, 156, 157, 165, 166, 169-174] very little is known about the pathophysiology of perioperative myocardial infarction and myocardial injury,[166, 225-235] or how beta-blockade might exert a cardio-protective effect.[236] The presumed mechanism of action is that beta-blockers reduce tachycardia, which could plausibly contribute to myocardial injury via a mechanism of myocardial oxygen supply-demand imbalance.[96, 97, 102, 160] However, there is little evidence to support this. Thus it remains controversial whether there is any place for perioperative beta-blockers in contemporary anaesthetic practice.

If tachycardia does contribute to perioperative myocardial injury then it is plausible that other negatively chronotropic agents, for example non-dihydropyridine calcium channel antagonists or ivabradine, may prevent

perioperative cardiovascular complications.[237, 238] However, since beta-blockade has been the prevailing focus of research and clinical activity in this field for over thirty years, I have restricted my analysis to beta-blockade.

1.7.1 Beta-blocker therapy for cardiovascular disease

Given the observation that elevated heart rate is associated with the development of heart failure in the general population, it seems intuitive that beta-adrenoceptor antagonists (beta-blockers) are used to treat heart failure, in addition to the negative inotropic benefits. Two randomised controlled trials by the Carvedilol Heart Failure Study Group in the late 1990s, found that compared to placebo, treatment with Carvedilol was associated with reduced mortality in patients with mild/moderate or severe heart failure.[239, 240] One trial was stopped early after the independent data monitoring committee found the risk of mortality was 65% lower in the beta-blocker group at the interim analysis.[239] Another randomised trial by the same group of investigators identified a reduction in both symptoms and the number and duration of hospital admissions for heart failure associated with beta-blocker treatment in patients with severe heart failure.[241] Other clinical trials have shown that beta-blocker therapy can reduce the risk of death after acute myocardial infarction,[242] and the subsequent risk of re-infarction.[243]

1.7.2 Perioperative beta-blockade: early evidence of clinical benefit

Until recently beta-blockers were commonly used to prevent perioperative morbidity and mortality.[244, 245] The American Heart Association recommended beta-blocker treatment for several patient groups, largely based on the results of the DECREASE I trial,[228, 229] including: vascular surgery patients with

preoperative myocardial ischaemia; patients with a history of ischaemic heart disease; or with risk factors for ischaemic heart disease or hypertension.[246] However, the evidence supporting perioperative beta-blockade became increasingly conflicted. In 2005 two meta-analyses were published, which supported beta-blockade to differing degrees (table 1.8).

Author & year of publication	Number of cases	Formulation of beta-blocker	Outcome measures	Included in meta-analysis?
Stone 1988[169]	128	Labetolol, atenolol or oxprenolol	Myocardial ischaemia	McGory
Mangano 1996[228]	200	Atenolol	Mortality and composite of: myocardial infarction, unstable angina, heart failure, coronary revascularisation and mortality	McGory
Jakobsen 1997[247]	36	Metoprolol	Myocardial infarction	Devereaux
Wallace 1998[248] §	-	-	-	Devereaux
Bayliff 1999[249]	99	Propanolol	Myocardial ischaemia	Devereaux
Poldermans 1999[229]	112	Bisoprolol	Cardiac death, non-fatal myocardial infarction	McGory & Devereaux
Raby 1999[250]	26	Esmolol	Myocardial ischaemia	McGory & Devereaux
Zaugg 1999[251]	63	Atenolol	Myocardial infarction, myocardial ischaemia	McGory & Devereaux
Urban 2000[252]	107	Esmolol & Metoprolol	Myocardial infarction, myocardial ischaemia	McGory & Devereaux
Yang 2004[253] Ψ	496	Metoprolol	Composite of cardiac death, atrial fibrillation or ventricular arrhythmia, heart failure, unstable angina and non-fatal myocardial infarction	Devereaux

Table 1.8. Summary of trials included in meta-analyses by *McGory* and *Devereaux*.[226, 244]

§ *Wallace* 1998 used the same dataset as *Mangano* 1996. Ψ *Yang et al.* initially published this analysis as a supplement in the Canadian Journal of Anesthesia in 2004, and subsequently re-published in 2006 in the American Heart Journal.

One meta-analysis by *McGory* et al included data from six randomised controlled trials and supported beta-blockade, citing reductions in mortality and

cardiovascular complications associated with treatment.[169, 228, 229, 250-252] However, the other much larger meta-analysis by *Devereaux et al* found that beta-blockade was only associated with reduced risk of a composite outcome of myocardial infarction, non-fatal cardiac arrest or death, but that the results were not replicated when each outcome was considered individually.[229, 247-253] An accompanying power calculation suggested that a definitive clinical trial would need at least 6,000 participants, compared to the majority of existing studies, which had sample sizes of less than 100 participants.[225]

1.7.3 The influence of bias and research misconduct

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) studies had a prominent influence on guidelines and clinical practice in favour of perioperative beta-blocker use.[229, 254] [224, 246, 255] However, it later emerged that the principal investigator was responsible for several breaches of academic integrity, described as 'negligent conduct', including: fabricating data and methods, pretending to use adjudication committees and failing to obtain informed consent.[256-258] Given the concerns about the integrity of the DECREASE studies and the methods and sample sizes of the early beta-blocker trials, the influence of bias on the evidence in support of beta-blockers is likely to be high.[259, 260] One meta-analysis concluded that the majority (21/34) of available trials were at a high-risk of bias.[225] When these were excluded, the previously observed cardio-protective effect of beta-blockade was diminished (table 1.9).[225] *Bouri et al.* performed a meta-analysis of 'secure trials', excluding data from the high-bias trials like DECREASE, which found that beta-blockade was associated with cardiovascular benefit at the expense of harm from strokes and death.[258]

Outcome	Low bias trials [OR (95% CI)]	High bias trials [OR (95% CI)]	Low & high bias trials [OR (95% CI)]
Myocardial Infarction	0.72 (0.59 – 0.87)	0.19 (0.19 – 0.39)	0.65 (0.54 – 0.79)
Myocardial Ischaemia	0.42 (0.27 – 0.65)	0.31 (0.20 – 0.49)	0.36 (0.26 – 0.50)

Table 1.9. The effect of peri-operative beta-blockade on post-operative cardiac outcomes. Shown as odds ratios stratified according to the estimated bias of the data sources.[225]

1.7.4 The POISE trial

The Peri-operative Ischaemia Evaluation (POISE) trial is the largest trial of peri-operative beta-blockade.[227] Over 8,000 patients were randomised to receive either metoprolol succinate or placebo at 190 hospitals in 23 countries over five years. Treatment with metoprolol was associated with a lower risk of myocardial infarction, non-fatal cardiac arrest (hazard ratio 0.84, 95% CI: 0.7 to 0.99) within 30 days of surgery. However, metoprolol was also associated with an increased risk of death (hazard ratio 1.33, 95% CI: 1.03 to 1.74) and stroke (hazard ratio 2.17, 95% CI: 1.26 to 3.74).[166] Thus, the beneficial effect of beta-blockade was outweighed by greater risk of harm.[225] Mortality in the beta-blocker group was associated with hypotension. Therefore, it is possible that stroke and death could be caused by reduced cardiac output, secondary to beta-blockade, manifest as hypotension.[166] The trial used a fixed dose of metoprolol for all patients, irrespective of age or co-morbidity, which was withheld only if the blood pressure or heart rate were very low.[227] Recent guidelines suggest titrating beta-blocker dose to a heart rate between 60-80 beats per minute. However, there is little evidence to support targeting specific heart rates and it is unclear whether elevated heart rate is associated with clinical outcomes.

1.7.5 Summary of perioperative beta-blockade

Current evidence suggests that perioperative beta-blockade is associated with reduced risk of perioperative myocardial infarction, but increased risk of stroke and death. Consequently, the routine use of beta-blockers in patients undergoing surgery is no longer recommended.[261] The pathophysiological mechanism by which beta-blockers might confer benefit or cause harm is poorly understood. Chiefly, there is little evidence of association between perioperative heart rate (or specific values of heart rate) and postoperative cardiovascular complications.[236] Further research is needed to resolve this.

1.8 Summary

The most common causes of postoperative mortality are cardiovascular in origin. However, symptomatic cardiac events represent only a small proportion of postoperative cardiovascular morbidity. Myocardial injury, identified by a transient rise in cardiac biomarkers, is predominantly asymptomatic and occurs after one in ten non-cardiac surgical procedures. It is strongly associated with mortality, but the pathophysiological mechanism(s) for this relationship is unclear. The majority of existing research uses clinical outcome measures, but these are subjectively defined and at risk of bias. In contrast, myocardial injury is an objective, biomarker-defined outcome measure at lower risk of bias.

Beta-blocker therapy reduces the risk of perioperative myocardial infarction. One potential explanation is that lower heart rate prevents myocardial injury by reducing rate-related myocardial ischaemia. This treatment was routinely used until the results of the POISE trial suggested that perioperative beta-blockade

may be harmful due to the increased risk of stroke and death. However, this trial used a standard dosage regime for all patients and did not titrate drug dosage to heart rate, which may have resulted in inappropriate dosing for some patients, potentially explaining some of the observed harm. Currently, there is a lack of evidence to support association between perioperative heart rate and cardiac complications. Thus, evidence-based heart rate thresholds, which could be used to target rate-controlling therapy, are not available.

Several observational studies identified that intraoperative tachycardia was associated with clinically defined cardiac complications after surgery. However, these studies did not quantitatively define ‘tachycardia’. Other observational studies have identified association between preoperative heart rate and cardiac complications after both cardiac and non-cardiac surgery, but not biochemical myocardial injury. The largest study was a secondary analysis of the POISE trial. However, again, quantitative heart rate thresholds that could be used clinically were not identified. Limited data from pilot studies suggest that impaired heart rate recovery after preoperative exercise, a marker of parasympathetic autonomic dysfunction, may be associated with postoperative clinical outcome. While evidence from the general population suggests that elevated resting heart rate is a poor prognostic indicator in patients with heart failure. However, this has not been investigated in surgical patients.

Elevated blood pressure is an accepted risk factor for cardiovascular disease in the general population. Growing evidence suggests that, particularly in elderly patients, pulse pressure may be more strongly associated with clinical outcomes than systolic or diastolic pressure. It is plausible that very high or very

low blood pressure in the perioperative period could cause myocardial injury, as a result of oxygen supply-demand imbalance. However, the majority of perioperative blood pressure research has focused on intraoperative hypotension, rather than preoperative blood pressure or intraoperative hypertension. As a result, many clinicians are uncertain about how to deal with elevated blood pressure on the day of surgery, leading to postponed or cancelled surgical procedures. Research is needed to determine whether abnormal blood pressure before or during surgery is a risk factor for myocardial injury.

1.9 Research aims

1. To investigate the relationship between preoperative heart rate and myocardial injury after non-cardiac surgery.

2. To investigate the relationship between preoperative pulse pressure and myocardial injury after non-cardiac surgery.

3. To investigate the relationship between intraoperative heart rate and blood pressure, and myocardial injury after non-cardiac surgery.

4. To investigate the relationship between preoperative heart rate and cardiopulmonary and autonomic function.

5. To investigate the relationship between parasympathetic autonomic dysfunction, identified by impaired heart rate recovery after preoperative exercise, and myocardial injury after non-cardiac surgery.

Chapter two

Methods

2.1 Methodology

In this thesis I use epidemiological methods to identify cardiovascular risk factors for perioperative myocardial injury. Epidemiology is the study of the frequency, distribution and causes of disease.[262] Its origins date back to the 19th Century when William Farr systematically recorded causes of death in England in 1839 and when John Snow identified contaminated water as a vector for cholera transmission in London in 1854.[262, 263] The epidemiological paradigm is based on two core assumptions, that disease "does not occur at random" and "has causal and preventative factors".[262] Epidemiology relies on the observation and measurement of association between exposures and outcomes, to identify risk factors for disease and build evidence of causal mechanism, in samples of subjects from defined populations. Health Services Research (HSR) encompasses clinical research drawing on a range of disciplines, which involve patients and the health services and systems that serve them.[265-267]

2.1.1 Research using existing data

Health Services Research falls into two broad categories according to the data source: research using primary data and secondary analyses of existing data.[268] Research using existing data is increasingly common in critical care, and perioperative medicine,[269] and provision for data sharing to *bona fide* researchers is often a mandatory condition of research council or charity funded research grants in the UK.[270] The main advantage is that secondary analyses maximise the utility of the data and at a much lower cost than collecting a

similar data set *de novo*. For large data sets, which are often required for complex statistics, or where a long follow-up period is needed, secondary analyses may be the most financially and logistically efficient way to answer a research question, compared to a new, multi-centre study.[269]

2.1.2 Strategies for analysis

The purpose of analytic epidemiology is to identify association between exposures and outcomes, in order to identify causal risk factors for (and thus prevent) disease. There are two broad strategies for analysing observational data: explanatory ('causal') and predictive ('data-driven') modelling, where 'modelling' means to define a mathematical relationship between exposure(s) and outcome(s).[271] Predictive modelling seeks to identify variables within a data set that are associated with an outcome, which often develops into a prediction rule or scoring system where constituent factors are weighted according to association with the outcome. These models include a large number of variables and it is common practice to examine the data before planning the analysis.[268] In contrast, explanatory modelling aims to identify association according to *a priori* hypotheses, which usually include adjustment for potential confounding. The number of variables included in an explanatory model is usually less than for a predictive model. The ultimate aim of explanatory modelling is to identify factors that could cause disease. However, association between variables in a statistical model does not necessarily imply a causative relationship.

2.1.3 Methodological approach and rationale for this thesis

The overarching aim of this thesis is to investigate potential cardiovascular risk factors for perioperative myocardial injury. Specifically, whether extremes of heart rate or blood pressure are associated with perioperative myocardial injury in patients undergoing non-cardiac surgery. I used explanatory modelling to analyse five existing data sets to answer a series of linked research questions. Data from three studies that were already complete were supplemented with data from two further studies where I was actively involved in data collection. I played a leading role in one study as the UK national co-ordinator, in addition to recruiting patients and collecting data at my own hospital over four years. This approach has several benefits. Firstly, using data from large studies provided a sufficiently large number of cases to make adjustments for potential confounding factors. This provided an important opportunity for training in epidemiological methods and statistical analysis of large data sets, which would not otherwise be possible. Secondly, using data from three studies that were already completed reduced the risk of non-completion through lack of data. Thirdly, playing a central role in an international multi-centre observational cohort study was a unique opportunity to manage a large multi-centre research project, including consenting and recruiting patients.

2.1.4 Data sources and data collection

The data for this thesis is derived from five epidemiological studies. Two international cohort studies: the '**V**ascular events **I**n non-cardiac **S**urgery pat**I**ents c**O**hort evaluatio**N**' (VISION) and the '**M**easurement of **E**xercise **T**olerance for **S**urgery' (METS) studies; one UK cohort study: the '**P**eri-**O**perative **M**orbidity – **H**eart **R**ate' (POM-HR); and two multi-centre randomised

controlled trials: the '**O**pimisation of periopera**T**ive card**I**ovascular **M**anagement to **I**mprove **S**urgical outcom**E**' (OPTIMISE) and the '**P**ost **O**perative **M**orbidity - **O**xygen' (POMO) trial. In all studies, surgical patients were enrolled according to clearly defined eligibility criteria and data were collected using standardised case report forms, with clear definitions exposure and outcomes, which were compatible between studies. I describe each study in further detail below.

2.2 The Measurement of Exercise Tolerance before Surgery (METS) study

I performed secondary analyses of the METS study as described in chapter seven. The methods of the study have been published previously.[1]

2.2.1 Primary aim of the METS study

Cardiopulmonary fitness is thought to be an important risk factor for morbidity and mortality after surgery. The METS study aimed to compare preoperative cardiopulmonary exercise testing, a standardised questionnaire (Duke Activity Status Index) and physician judgement for predicting cardiovascular morbidity and mortality after non-cardiac surgery.[1]

2.2.2 Study design

International, multi-centre, prospective, observational cohort study in 23 hospitals in the United Kingdom, Canada, Australia and New Zealand. I was the study coordinator for the United Kingdom and led recruitment at The Royal London Hospital.

2.2.3 Participants

Participants were aged 40 years or older, undergoing elective non-cardiac surgery, with an anticipated overnight stay in hospital and at least one of the following risk factors: coronary artery disease, heart failure, cerebrovascular disease, diabetes mellitus, estimated glomerular filtration rate <60ml/min/1.73m^2, peripheral arterial disease, hypertension, smoking within the previous one year, age of 70 years or more, or intermediate- or high-risk surgery. Patients were excluded if there was: inadequate time to feasibly complete cardiopulmonary exercise testing at least 24 hours in advance of surgery, planned use of cardiopulmonary exercise testing for preoperative risk stratification independent of the METS study, planned surgery performed exclusively using an endovascular technique, presence of an automated implantable cardio-defibrillator, known or suspected pregnancy, previous enrolment in the METS study, active cardiac conditions,[224] absolute contraindications to cardiopulmonary exercise testing (American Thoracic Society and American College of Chest Physicians guidelines)[272] or conditions expected to preclude cardiopulmonary exercise testing (e.g. lower limb amputation), or systolic blood pressure of 180mmHg or more or diastolic blood pressure of 100mmHg or more at the time of study recruitment.

2.2.4 Study conduct and data collection

All patients enrolled in the study underwent preoperative cardiopulmonary exercise testing, between February 2013 and March 2016. Researchers at each site collected data from patients and their medical record before, during and after surgery using a standardised case report form, with standardised definitions. These data were entered on to a secure web-based data entry platform. All patients underwent a preoperative symptom-limited

cardiopulmonary exercise test, the protocol for which is explained below. Blood samples and electrocardiograms were collected before surgery and on the first, second and third postoperative days. In the United Kingdom, blood samples were centrifuged and serum extracted for freezing, to facilitate analysis at the central laboratory. The laboratory measured preoperative and postoperative troponin I (TnI). At 30 days and one year after surgery, researchers contacted participants on the telephone to conduct a short interview using a standardised questionnaire.

2.2.5 Research ethics approval and sponsorship

Research ethics committee/board approval for the METS study was obtained for each hospital before starting the study. Ethics approval for the UK was granted by the South East Coast (Surrey) Research ethics committee (reference: 13/LO/0135). The study was sponsored by St. Michael's Hospital, Toronto, Canada, with Queen Mary University of London acting as the Sponsor's representative in the United Kingdom. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Research Governance Framework.

2.3 The Vascular events In non-cardiac Surgery patIent cOhort evaluatioN (VISION) study

I performed secondary analyses of the prospective international observational cohort study, the Vascular Events in Non-cardiac Surgery Cohort Evaluation (VISION) study as described in chapters three, four and five.[16] The methods of the study have been published previously.[16, 273-275]

2.3.1 Primary aim of the VISION study

The VISION study aimed to determine whether postoperative cardiac troponin T (TnT) release was associated with mortality within 30 days after non-cardiac surgery.[16, 276]

2.3.2 Study design

International, multi-centre, prospective, observational cohort study of patients undergoing non-cardiac surgery.

2.3.3 Participants

Participants were aged 45 years or older, undergoing non-cardiac surgery using a general or regional anaesthetic technique and were anticipated to require at least an overnight hospital admission after surgery. Patients were excluded if they had previously been enrolled in the study. All participants or their designates provided written informed consent to take part in the study. Eight hospitals used deferred consent for patients who were unable to provide consent and had no next of kin available. Where it was not possible to approach the patient before surgery (e.g. emergency surgery), they were approached for written consent within 24 hours after the procedure.

2.3.4 Data collection

The data included in this thesis is derived from the first cohort of ~15,000 patients, recruited from 12 hospitals in eight countries in Asia, Australia, Europe and North/South America between 6th August 2007 and 11th January 2011. Researchers at each hospital collected data from patients and their medical record before, during and up to one year after surgery. Data were collected

using a standardised and detailed case report form, with standardised definitions of exposures and outcomes. At 30 days after surgery, researchers contacted participants on the telephone to conduct a short interview regarding postoperative complications.

2.3.5 Outcome measures

The VISION study defined myocardial injury after non-cardiac surgery (MINS) as: serum Troponin T (TnT) ≥0.03ng/mL within 30 days after surgery, adjudicated as due to an ischaemic pathology.[95, 113] Blood samples were obtained before surgery, 6-12 hours after the end of surgery and then on postoperative days one, two and three. In addition, investigators were encouraged to take additional blood samples if participants experienced an ischaemic symptom within the 30-day postoperative period. Serum was tested for troponin T using a Roche 4th generation Roche Elecsys^{TM} assay. For patients with postoperative troponin ≥0.04ng/mL, the accepted laboratory threshold at the start of the study, an electrocardiogram was performed and subsequently an echocardiogram in the absence of dynamic electrocardiographic changes. For each TnT measurement ≥0.03ng/mL, one of 15 independent adjudicators reviewed the clinical information, including the medical record, electrocardiograms and echocardiograms, and decided if there was evidence of a non-ischaemic cause of the TnT elevation (e.g. pulmonary embolus, sepsis, renal failure etc.). Patients with a serum troponin elevation <0.04ng/mL were not investigated for evidence of myocardial ischaemia.

The VISION study defined myocardial infarction using the third universal definition; serum troponin elevation in the presence of at least one of: ischaemic

symptoms; the development of new or presumed new Q waves, ST segment or T wave changes, or left bundle branch block on the electrocardiogram; or the finding of a new or presumed new regional wall motion abnormality on echocardiography.[94]

2.3.6 Research ethics approval and sponsorship

Research ethics committee/board approval for the VISION study was obtained for each hospital before starting the study. Ethics approval for UK hospitals was granted by North Wales Research ethics committee (reference: 10/WN/0325). The research was conducted in accordance with the Declaration of Helsinki and the Research Governance Framework. The study was sponsored by McMaster University, Hamilton, Canada, with Queen Mary University of London acting as the Sponsor's representative in the United Kingdom. The study was registered with clinicaltrials.gov (NCT00512109).

2.4 The Post Operative Morbidity-Heart Rate (POM-HR) study

I performed secondary analyses of POM-HR study as described in chapter six. The methods of study have been published previously.[277, 278]

2.4.1 Primary aim of the POM-HR study

The POM-HR study aimed to demonstrate that parasympathetic autonomic dysfunction (as reflected by heart rate response to exercise) was associated with postoperative morbidity and hospital length of stay.[277, 278]

2.4.2 Study design

Prospective observational cohort study of patients undergoing major surgery, who were referred for preoperative cardiopulmonary exercise testing in five UK hospitals.

2.4.3 Participants

Participants were aged 45 years or more, scheduled for major surgery predicted to last for more than two hours, and were referred for cardiopulmonary exercise testing (CPET) as part of their routine preoperative assessment. Patients provided written informed consent before taking part in the study (prior to exercise testing). Patients were excluded if there was: a history exercise induced angioedema, pregnancy, or any contraindication to cardiopulmonary exercise testing.[272] These criteria are very similar to the eligibility criteria for the VISION study.[16]

2.4.4 Study conduct

The POM-HR study included 1,572 patients undergoing major non-cardiac surgery at five UK centres between March 2013 and March 2015. All participants underwent cardiopulmonary exercise testing as part of their routine preoperative assessment. Researchers at each site collected data before, during and after surgery using a standardised case report form.

2.4.5 Research ethics approval and sponsorship

The study was approved by the National Research Ethics Committee London (Camden & Islington; 12/LO/0453) and registered with Controlled Trials (ISRCTN88456378). The study was sponsored by University College London Hospitals NHS Foundation Trust.

2.5 The Optimisation of perioperaTive cardIovascular management to Improve Surgical outcomE (OPTIMISE) trial

I performed secondary analyses of OPTIMISE trial as described in chapter six. The methods of study have been published previously.[279]

2.5.1 Primary aim of the OPTIMISE trial

The OPTIMISE trial aimed to determine whether cardiac output monitor guided (goal directed) intravenous fluid therapy and inotropes according to a standardised treatment algorithm was superior to usual clinical care.[279]

2.5.2 Study design

Multi-centre randomised controlled trial of perioperative cardiac output-guided haemodynamic therapy according to a standard treatment algorithm for intravenous fluid therapy and dopexamine (inotrope) infusion during surgery and for six hours after surgery, compared to usual clinical care in patients undergoing major gastrointestinal surgery.

2.5.3 Participants

Adults undergoing major gastrointestinal surgery with expected duration greater than 90 minutes that also satisfied the following criteria: aged 65 years or over, or; aged 50-64 years, and one of the following: non-elective surgery, acute or chronic renal impairment defined as serum creatinine ≥130μmol/l, diabetes mellitus or the presence of a risk factor for cardiac or respiratory disease.[280] Patients were excluded if they: refused to provide informed consent, received palliative treatment only (likely to die within 30 days), had acute myocardial ischaemia (within the 30 days prior to randomisation), had acute pulmonary oedema (within 7 days prior to randomisation), had septic shock, had

thrombocytopenia (platelet count <50 x 10^9/l), received monoamine oxidase inhibitors, had a phaeochromocytoma, had severe left ventricular outlet obstruction e.g. due to hypertrophic obstructive cardiomyopathy or aortic stenosis, had hypersensitivity to dopexamine hydrochloride or disodium edelate, were participating in another randomised controlled trial, or were pregnant at the time of enrolment.

2.5.4 Study conduct

The OPTIMISE trial included 734 patients undergoing major gastrointestinal surgery at 17 UK hospitals, between June 2010 and November 2012. Participants in the intervention group were commenced on the treatment algorithm at the induction of anaesthesia and continued until six hours after surgery. Cardiac output monitoring was conducted using LidCo Rapid (Lidco, London, UK) cardiac output monitors (see section 2.10). Researchers at each site collected data before, during and after surgery using a standardised case report form. Researchers collecting outcome data were blinded to treatment group allocation where possible.

2.5.5 Research ethics approval and sponsorship

Research ethics approval was granted by the East London and City Research Ethics Committee (09/H0703/23). The trial was approved by the Medical and Healthcare Products Regulatory Agency. The trial was sponsored by Queen Mary University of London. The study was coordinated by the Intensive Care National Audit and Research Centre Clinicial Trials Unit (ICNARC CTU).

2.6 The Post Operative Morbidity-Oxygen (POMO) trial

I performed secondary analyses of POM-O trial as described in chapter six. The methods of study have been published previously.[281]

2.6.1 Primary aim of the POM-O trial

The POM-O trial aimed to determine whether oxygen-delivery targeted haemodynamic therapy would reduce postoperative morbidity in high-risk surgical patients.[281]

2.6.2 Study design

Multi-centre, randomised, double-blinded controlled trial of an intravenous fluid protocol with or without dobutamine, targeted to achieve individual preoperative oxygen delivery, compared to standard perioperative care in adults undergoing major elective surgery.

2.6.3 Participants

Eligible patients were those undergoing major surgical procedures (abdominal or oesophageal or hepatic or gynaecological or urological reconstructive) with a high risk of postoperative morbidity and who met the following criteria:[282] American Society of Anesthesiologists risk score 3 or 4, age greater than 50 years, and more than three cardiovascular risk factors according to the Revised Cardiac Risk Index.[20] The exclusion criteria were:[282] current lithium therapy, acute myocardial ischaemia, acute cardiac arrhythmia, pregnancy or palliative treatment.

2.6.4 Study conduct

The POM-O trial recruited 204 patients from four UK hospitals between 20th May 2010 and 12th February 2014. Participants were allocated to treatment groups using a concealed envelope system, with the allocation sequence generated using STATA (Statacorp, USA). Participants in the intervention group were commenced on treatment alogorithm once they reached the critical care unit after surgery. Cardiac output monitoring was conducted throughout the surgical procedure using a LidcoPlus (Lidco, London, UK) cardiac output monitor (see section 2.10), which required the insertion of a radial artery catheter before the induction of anaesthesia. The intervention continued until six hours after the completion of surgery. Participants in the control group received usual postoperative care. Researchers collected detailed data before, during and after surgery using a standardised case report form until hospital discharge.

2.6.5 Research ethics approval and sponsorship

Research ethics approval was granted by the South London Research Ethics Committee (09/H0805/58). The trial was sponsored by University College London NHS Foundation Trust. The trial was registered with ISRCTN (76894700).

2.7 Literature review

As part of the preliminary work for this thesis I conducted a review of the existing literature. I searched the following databases: MEDLINE; EMBASE; and Web of Science. I used the following search terms: heart rate; non-cardiac

surgery; pre-operative heart rate; resting heart rate; baseline heart rate; peri-operative mortality; post-operative mortality; surgical mortality; surgical outcome; morbidity; surgery; pulse-pressure; pre-operative pulse-pressure; pre-operative arterial pulse-pressure; cardiopulmonary exercise test; CPET; CPX; CPEX; pre-operative cardiopulmonary exercise test; pre-operative beta blockade; peri-operative beta-blockade; pre-operative beta-blocker; peri-operative beta-blocker; beta-blocker; perioperative myocardial injury; MINS; perioperative myocardial infarction. I reviewed the reference lists of the relevant journal articles to generate further papers to review. I collated and managed journal articles using Papers version 2.8.3 (BV Mekentosj, Dordrecht, The Netherlands). I managed references using Endnote™ version X6 (Thomson Reuters, New York, USA).

2.8 Patient and public involvement

The patient representative for this research was David Hepworth, who reviewed the scientific content of this thesis and provided advice during the writing of the lay summary. During the preliminary stages of planning this project, the Patient and Public Involvement (PPI) Group of the Royal College of Anaesthetists Health Services Research Centre (HSRC) reviewed and provided feedback on the initial project proposal. They felt that there was clear potential for patient benefit from this and subsequent research. Their feedback helped me to improve the proposal during various funding applications.

2.9 Cardiopulmonary exercise testing (CPET)

I used cardiopulmonary exercise test (CPET) data from the POM-HR and METS studies. Here I provide an overview of preoperative CPET with specific details of the experimental approaches used in the METS and POM-HR studies.

2.9.1 Overview of preoperative CPET

Physiologists have measured cardiopulmonary responses to exercise for over a century.[283] There are many methods for evaluating cardiovascular performance. However, the cardiopulmonary exercise test is the only method for simultaneous assessment of cardiovascular and respiratory performance, particularly the quantitative measurement of oxygen consumption.[284, 285] Treadmill exercise tests, developed by Bruce[286] and Ellestad,[287] are routinely used to detect exercise-induced myocardial ischaemia.[284] However, these protocols only utilise electrocardiogram and blood pressure monitoring and do not measure ventilatory parameters. Multiple other tests can be employed to evaluate cardiovascular fitness,[284] including: the Harvard Step Test,[288] the 600-yard Run-Walk,[284] the 12-minute field test,[289] the 12-minute walk test[290] and six-minute walk test.[291] However, these tests estimate cardiovascular fitness by measuring function (e.g. distance walked) rather than a quantitative physiological variable.

Cardiopulmonary exercise testing is most often performed using a cycle ergometer and continuously measures the electrocardiogram, heart rate, pulse-oximetry, minute ventilation, oxygen uptake and carbon dioxide production, as well as intermittent non-invasive measurement of arterial blood pressure.[292] CPETs most commonly follow an incremental ramp protocol, where the

workload increases gradually throughout the test.[284] Cardiopulmonary exercise testing was not used as part of preoperative assessment until after Older and Smith's work of the 1990s, which identified a link between measurable cardiopulmonary performance, namely anaerobic threshold, and clinical outcome after surgery.[41-43] At the Royal London Hospital, CPET is routinely used as part of preoperative assessment for high-risk patients undergoing vascular, hepatobiliary and some colorectal surgery.

CPETs for the METS and POM-HR studies were conducted in accordance with the American Thoracic Society and American College of Chest Physicians (ATS/ACCP) guidelines on exercise testing and the individual study protocols.[272, 278, 293]

2.9.2 Laboratory environment and equipment

CPETs were conducted in an appropriate clinical area, with ready access to resuscitation equipment.[292] At the Royal London Hospital this was in the preoperative assessment clinic. Participants underwent incremental ramp protocol symptom-limited CPET using an electromagnetically-braked cycle ergometer, which allowed the precise control of work rate.[272] Researchers at each hospital used commercially available CPET machines, typically consisting of an airflow or volume transducer, a gas analyser with a high sampling rate for breath by breath oxygen and carbon dioxide measurement, pulse-oximeter, electrocardiogram, non-invasive arterial blood pressure measurement and a computer.[272] Software for analysing and presenting CPET data varies between manufacturers. Equipment was checked and calibrated before each test and decontaminated after each test.

At the Royal London Hospital, the CPET equipment was provided and serviced by NSpire Health (Hertford, UK) and consisted of a pneumotachometer airflow transducer, a gas analyser consisting of a 'fuel cell' oxygen analyser and an infrared carbon dioxide analyser, and a 12-lead electrocardiogram (figures 2.1 and 2.2). The analysis software was 'Zan' (NSpire Health, Hertford, UK), using 30-second data averaging.[272] Before each test, the gas analyser was calibrated using calibration gas containing known concentrations of oxygen, carbon dioxide and nitrogen. The airflow sensor was calibrated with a cylinder of known volume, using both high and low flows. Calibrations were corrected for barometric pressure, temperature and relative humidity. The equipment was regularly serviced by the manufacturer, including testing the oxygen fuel cell. Emergency equipment was available in the preoperative assessment clinic and an independent oxygen supply with a selection of masks was available in the CPET laboratory.

Figure 2.1 – Photograph of CPET equipment showing cycle ergometer, computer, gas analyser and cyclinder of calibration gas (rear).

Figure 2.2 – Photograph of CPET equipment showing cycle ergometer display, blood pressure cuff, flow sensor and electrocardiogram wires.

2.9.3 Protocol for CPET using an incremental ramp

The majority of preoperative CPETs follow the same standard protocol; thus the conduct of CPETs for POM-HR and METS study were very similar. I will briefly describe the CPET protocol for the METS study.

Before starting the test, informed consent and patient suitability was confirmed. Patients were asked to attend the clinic wearing appropriate loose clothing, not to drink caffeinated drinks on the day of the test and not to undertake vigorous exercise in the 24 hours before the test. Electrocardiogram (ECG) electrodes were placed on the patient's chest. At the Royal London we used 12-lead ECG monitoring. An appropriately sized blood pressure cuff was placed on the upper

arm at the level of the heart and a pulse-oximeter probe on a finger of the opposite hand. A tight-fitting facemask, or a mouthpiece with a bite block and nose clip, was fitted. The airflow meter was fitted to the mask or mouthpiece. In the seated position, resting heart rate, blood pressure and pulse-oximetry was measured. Lung function tests, including forced inspiration, expiration and spirometry was performed. If FEV_1 was less than 30% of age and gender predicted values then testing was discontinued.[272] The cycle ergometer was adjusted to the patient, including seat height, handlebar height and handlebar angle, and that participant was seated comfortably on the bike.

The exercise test proper consisted of five phases: rest, unloaded cycling (warm up), incremental workload exercise, recovery and rest. Before starting exercise, baseline measurements of ventilation, gas exchange, heart rate and blood pressure were taken during three minutes of rest. Next, the patient was instructed to start pedalling, aiming to meet a target pedal rate of 60 revolutions per minute (RPM). During this phase the resistance to pedalling was set at 0 watts.[C] After three minutes of unloaded cycling, the workload was progressively increased in an incremental fashion at a constant rate according to a pre-determined 'ramp'.[272] The participant was encouraged to continue pedalling at 60RPM for as long as they were able to continue. At the end of loaded pedalling, the workload was reduced to 20 watts and pedalling continued for five minutes at 60RPM. This helped to reduce the incidence of dizziness or syncope due to abrupt cessation of high intensity exercise.[284] During this period

[C] Depending on the manufacturer of the CPET equipment, some centres may not have been able to set the resistance to 0 watts. Where this was the case they set the resistance to the lowest setting possible during warm-up.

the full set of respiratory and cardiovascular variables was recorded. At the end of the recovery period, the participant dismounted from the ergometer and monitoring equipment was removed. The participant was invited sit in the laboratory and rest until they felt ready to leave the clinic. During this time a brief interview was conducted in order to identify any adverse symptoms that may have occurred during exercise and to complete fatigue and dyspnoea ratings according to the BORG scale.[1]

The aim of the incremental rate of workload increase (ramp) is for the participant to reach peak exercise capacity after eight to twelve minutes of incremental exercise.[272, 284] The recommended method for determining the ramp is based on the expected maximal oxygen consumption (VO_2), calculated as follows:[294]

1. Predicted VO_2 unloaded (ml/min) = 150 + (6 x weight [kg])
2. Predicted peak VO_2 (ml/min) = height (cm) – age (years) x constant[D]
3. Work rate increment (W/min) = Predicted peak VO_2 – predicted unloaded VO_2 / 100

For the METS study, which was a pragmatic study the clinical effectiveness of preoperative CPET, the rate of workload increase (ramp) was selected according to the subjective judgement of the investigator: 10W/minute in untrained individuals, 20-30W/minute in trained participants or those who regularly undertook physical activity.[295] Contraindications to CPET, reasons for stopping a test, and adverse events are listed in the appendix.

[D] Constant = 20 for men and 14 for women

2.9.4 Interpreting a cardiopulmonary exercise test

After the CPET is complete, the test is interpreted and a report compiled. This includes a global assessment of all cardiovascular and respiratory data as well as detailed assessment of specific parameters, including oxygen consumption/work rate relationship, anaerobic threshold, peak oxygen consumption, oxygen pulse, ventilatory equivalents for carbon dioxide and oxygen, and heart rate and blood pressure responses to exercise.[296] Typically, interpretation of a CPET will start with the inspection of summary screen displaying a 'nine panel plot' (figure 2.3),[297, 298] before moving to inspect specific plots in more detail, as well as reviewing the raw cardiorespiratory data in numerical format. The typical interpretation strategy for preoperative CPET has historically centred around two key variables: anaerobic threshold and peak oxygen consumption.

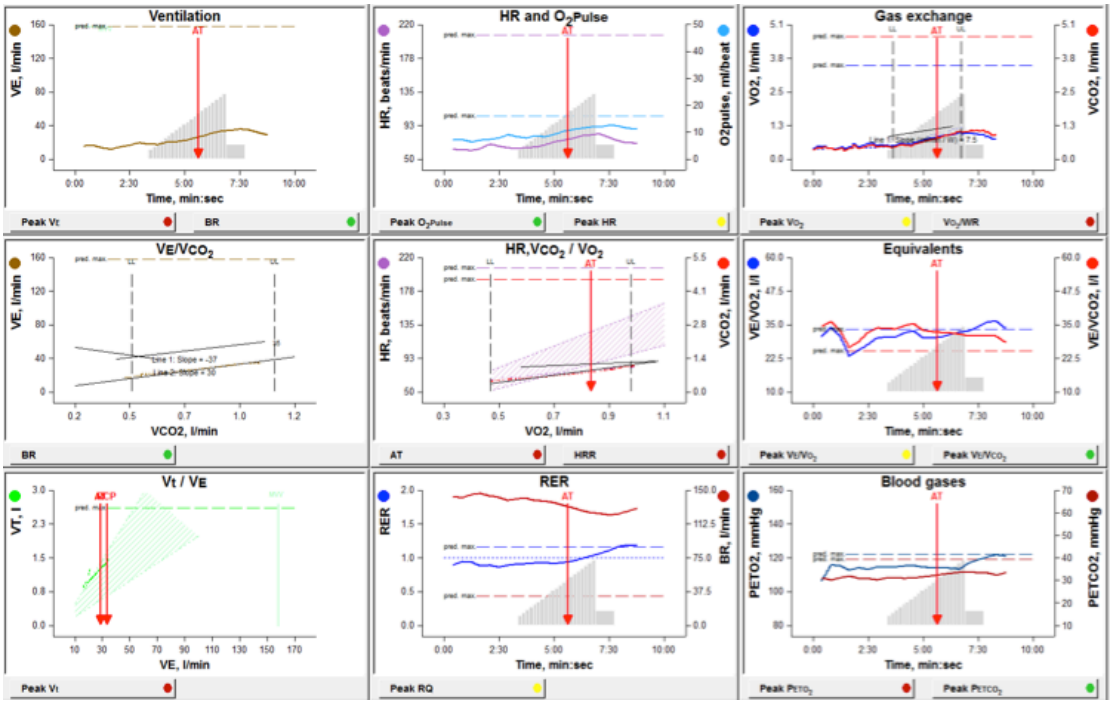


Figure 2.3 – Example nine panel plot

2.9.5 Anaerobic threshold

Anaerobic threshold and ventilatory threshold are broadly equivalent and the terms are often used interchangeably.[285] Anaerobic threshold is the value of oxygen consumption or work rate at which the concentration of blood lactate begins to increase during incremental exercise (lactate threshold), theoretically signalling a conversion from a predominantly aerobic cellular metabolism to a predominantly anaerobic cellular metabolism, via anaerobic glycolysis.[299, 300] Since it is impractical to obtain serial blood gas samples to measure changing concentrations of blood lactate, non-invasive estimation of the lactate threshold, using ventilatory gas analysis, is common.[301] The principle of the ventilatory threshold is that during aerobic metabolism carbon dioxide production is equivalent to oxygen consumption. However, during anaerobic metabolism carbon dioxide production exceeds oxygen consumption due to the shift in respiratory substrate. The relative changes in carbon dioxide production and oxygen consumption can be used to infer a specific ventilatory threshold, which is broadly equivalent to anaerobic threshold, which is in turn, broadly equivalent to lactate threshold.[301] The standardised approach to identifying the anaerobic threshold in the METS study, adapted from Gaskill and colleagues,[302] was threefold:[303]

1. Modified V-Slope method. On a plot of VCO_2 against VO_2 the anaerobic threshold is the point at which the gradient of the line increases to >1.[304] (figure 2.4)

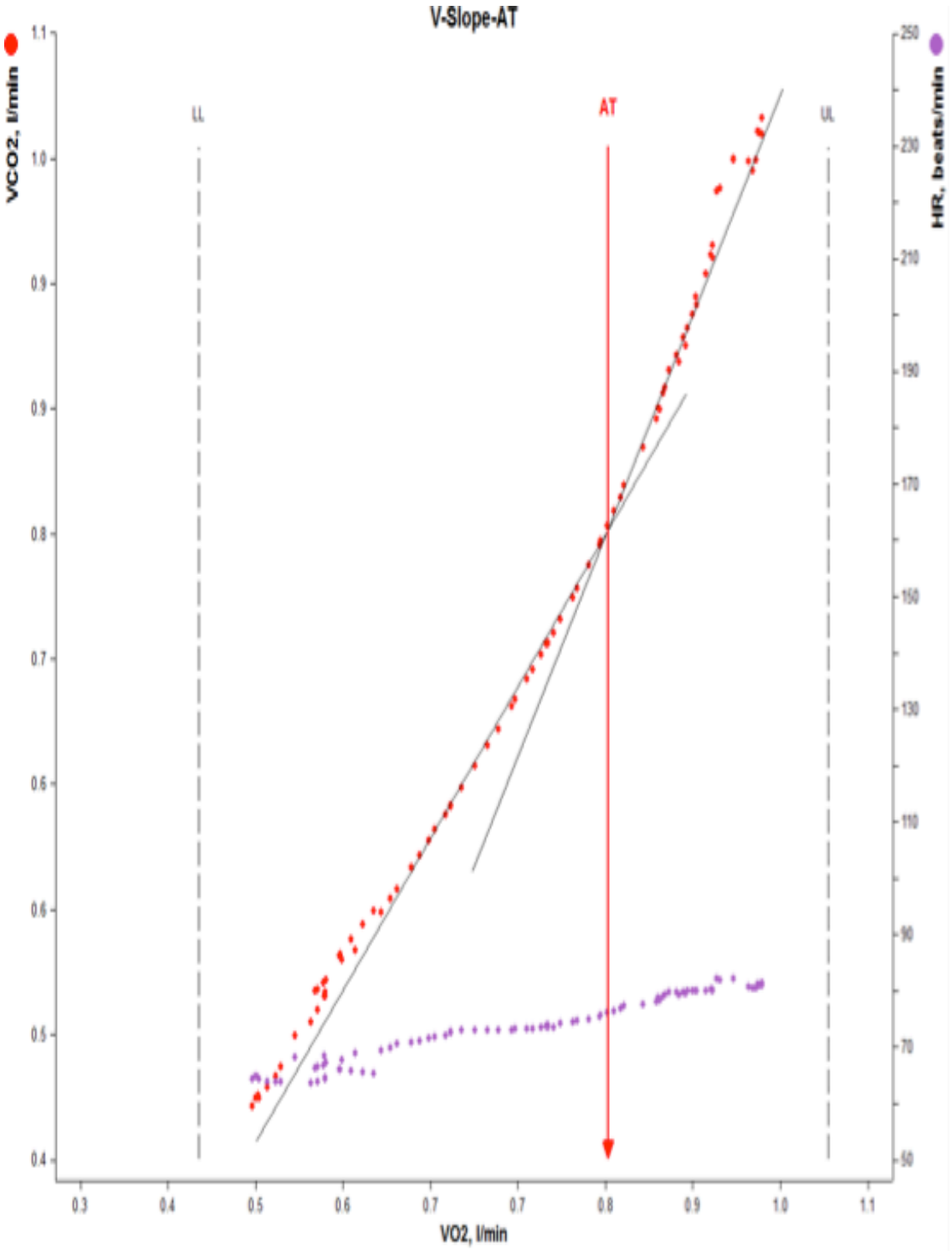


Figure 2.4 – Example plot of VO_2 (x-axis) and VCO_2 (y-axis) with points in red. Black lines show the modified V-slope with Anaerobic threshold (AT) shown as red verticle line. Heart rate (bpm) on secondary y-axis, points in purple.

2. Ventilatory equivalents method. On a plot of ventilatory equivalents for oxygen (V_E/VO_2) and ventilatory equivalents for carbon dioxide (V_E/VCO_2) against time, the anaerobic threshold is the point at which the (V_E/VO_2) rises without a simultaneous increase in (V_E/VCO_2), i.e. a relative increase in the ventilatory equivalents for oxygen (figure 2.5).[304]

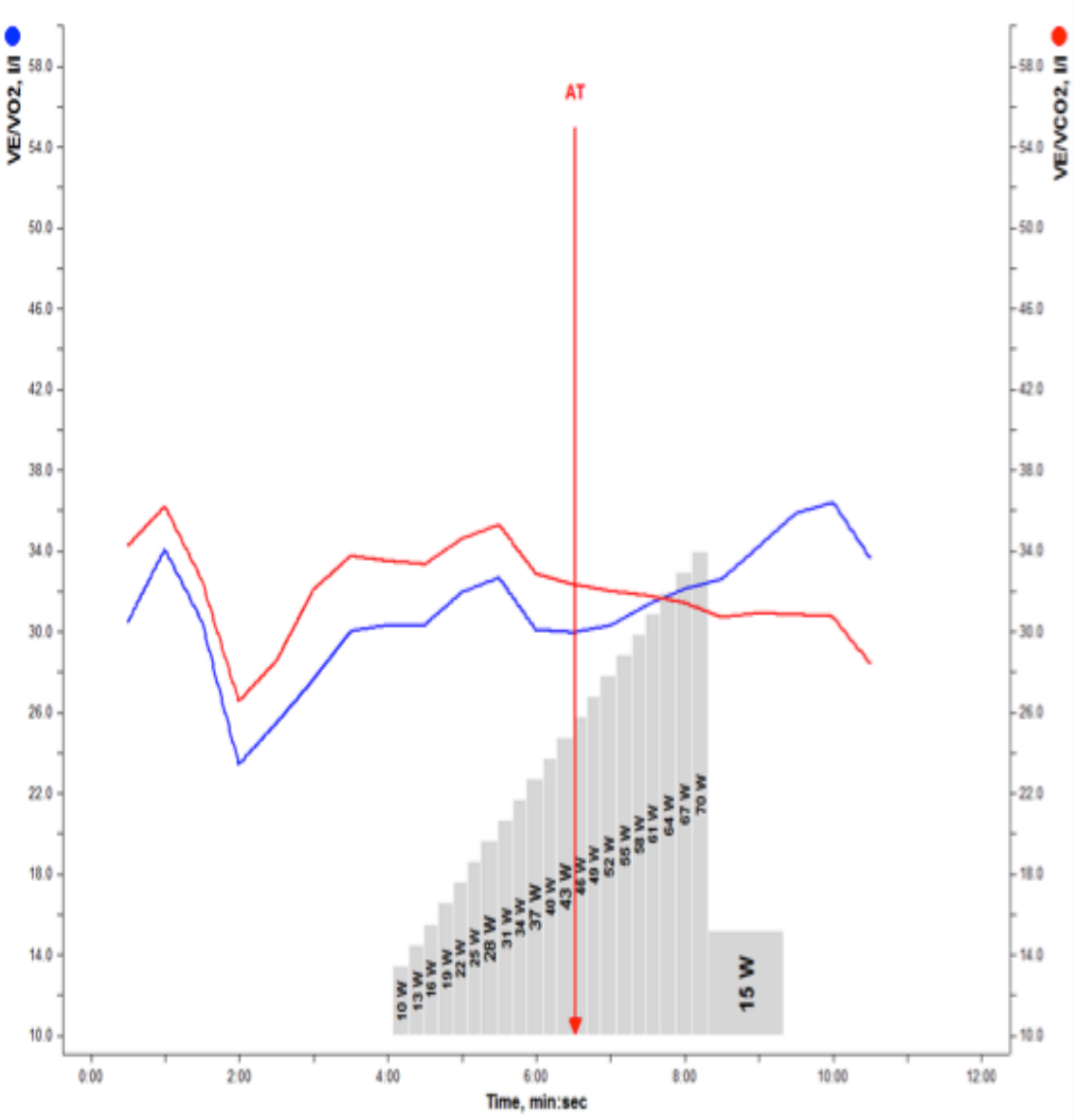


Figure 2.5 – Plot of ventilatory equivalents for oxygen (blue) and carbon dixoide (red), incremental increase in workload in watts (grey) against time. Anaerobic threshold shown as red vertical line.

3. The excess carbon dioxide method. The point at which there is excess production of carbon dioxide, calculated as $(VCO_2)^2/(VO_2)$.[305] (figure 2.6).

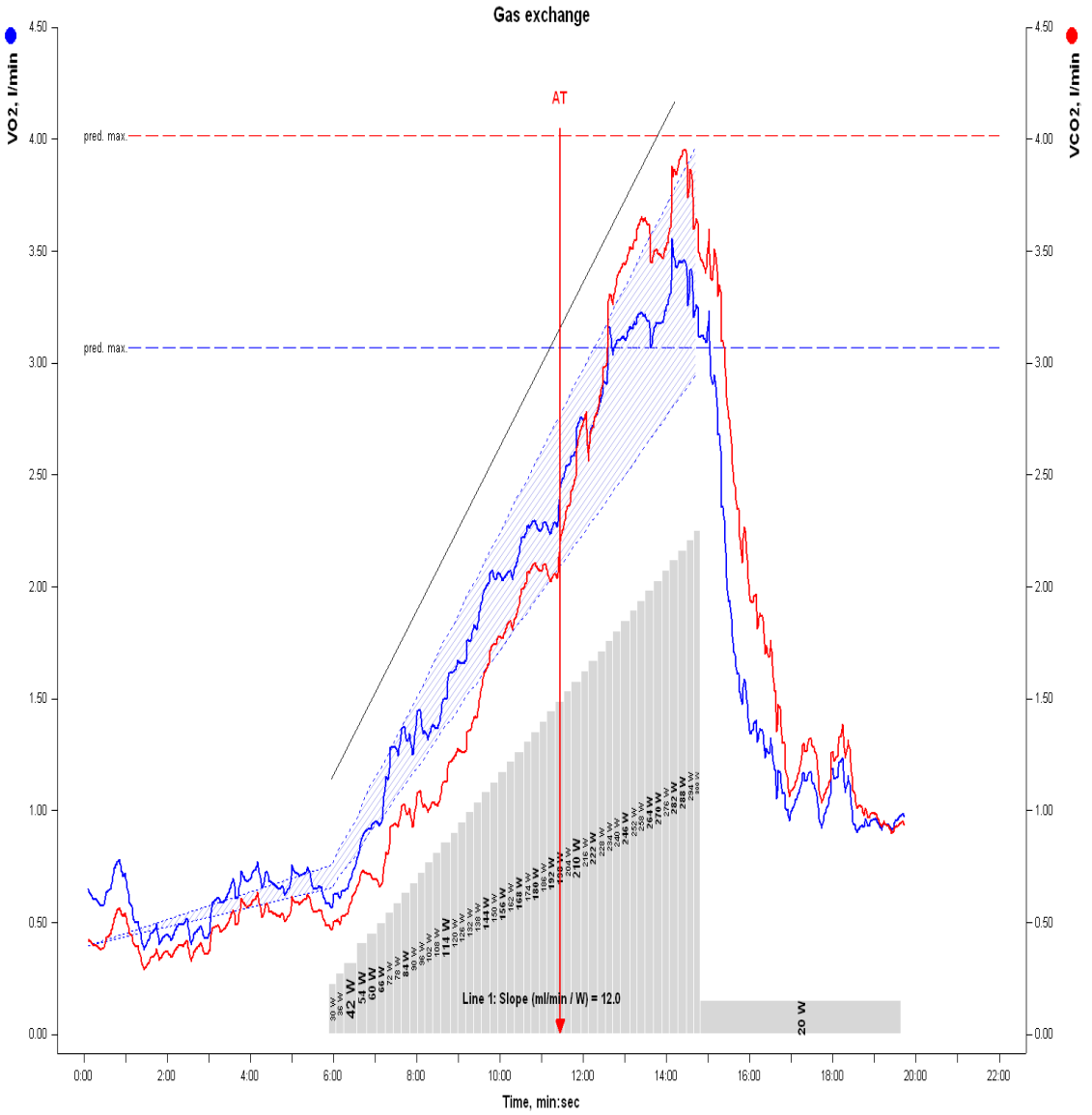


Figure 2.6 – Plot of oxygen consumption (blue) and carbon dixoide production (red) on y-axes, time (minutes) on the x-axis, incremental increase in workload in watts (grey) against time. Anaerobic threshold shown as red vertical line.

2.9.6 Peak and maximal oxygen consumption

Wasserman and colleagues define maximal oxygen consumption as the "highest oxygen consumption achievable as evidenced by failure of oxygen consumption to increase despite increasing work rate."[298] By contrast peak

oxygen consumption is the highest oxygen consumption achieved when “the subject has reached his or her maximum tolerable work rate”.[298] In practice maximal oxygen consumption is rarely measured in the clinical setting since it requires the subject to exercise for a sustained period at their maximal capacity in order to demonstrate static oxygen consumption in the presence of increasing workload, which can be unpleasant or uncomfortable. Peak oxygen consumption is usually expressed as a 10 - 60 second average depending on the protocol being used.[285] In the METS study peak oxygen consumption was calculated as the mean oxygen consumption during the last twenty seconds of the incremental phase of exercise before reaching the limit of exercise tolerance.[303] This was adapted from the approach described by Ferguson and colleagues.[306]

2.9.7 Oxygen pulse

Oxygen pulse is the ratio of oxygen consumption to heart rate at any given time.[285] It is equivalent to the amount of oxygen taken up by the pulmonary circulation during the period of one heart beat and is calculated by dividing oxygen consumption by heart rate at any given time point.[298] The modified Fick equation describes the relationship between oxygen pulse (VO_2/HR) and left ventricular stroke volume (SV), where $C(a\text{-}v)O_2$ is the difference between arterial and mixed-venous oxygen content.[272]

$$VO_2/HR = SV \times C(a\text{-}v)O_2$$

Thus, oxygen pulse provides a non-invasive estimate of left ventricular stroke volume.[285, 298] Oxygen pulse is measured in ml/beat.

2.9.8 Ventilatory equivalent for carbon dioxide (V_E/VCO_2) and slope

At rest and during exercise, minute ventilation (V_E) and carbon dioxide production (VCO_2) are tightly coupled, such that V_E increases in proportion to VCO_2 in a linear fashion at work rates below the anaerobic threshold, regulating arterial carbon dioxide concentration and hence arterial pH.[307-309] The ventilatory equivalent for carbon dioxide is the ratio of V_E to VCO_2 at any given point in time and reflects the relative ventilatory response to carbon dioxide production.[272] The V_E/VCO_2 typically drops to a low point around the anaerobic threshold and subsequently increases in response to elevated minute ventilation as a result of anaerobic respiration, lactic acid production and associated metabolic acidosis.[272] Abnormalities of instantaneous V_E/VCO_2 ratio have been observed in patients with heart failure and patients undergoing preoperative assessment. Time to V_E/VCO_2 nadir is shorter in patients with heart failure compared to healthy controls.[310] In patients undergoing major surgery, V_E/VCO_2 ratio at the anaerobic threshold >34 is associated with postoperative mortality.[58] An alternative measure of V_E and VCO_2 coupling is the V_E/VCO_2 slope, which is the rate of increase of V_E for increasing values of VCO_2.[301] Typically this is calculated using linear regression (i.e. y=mx + c, where m=slope) and reflects ventilatory efficiency throughout exercise.[71] Both V_E/VCO_2 slope and V_E/VCO_2 slope ≥34 are associated with mortality in patients with heart failure.[71] However, there is no consensus regarding whether the instantaneous V_E/VCO_2 ratio at a given point during exercise or the V_E/VCO_2 slope throughout incremental exercise should be used as the principal measure of V_E and VCO_2 coupling. In the METS study the V_E/VCO_2 ratio at the anaerobic threshold was measured.[293]

2.9.9 Heart rate during exercise

Increasing heart rate during exercise is typically related to increasing oxygen consumption in a linear fashion, facilitated by both withdrawal of parasympathetic tone and an increase in sympathetic activity as oxygen requirement increases.[272, 298] Heart rate reserve is the arithmetic difference between age predicted maximal heart rate and achieved maximal heart rate at the end of exercise.[272] In the METS study, heart rate was measured at rest in the sitting position before starting exercise, at peak oxygen consumption, at the end of incremental exercise and at one, three and five minutes into the recovery period after the end of incremental exercise.[295] Reduction in heart rate after the cessation of exercise is mediated initially by increased parasympathetic activity, followed subsequently by reduced sympathetic activity.[89] Heart rate recovery is calculated by subtracting heart rate during the recovery period from the maximum heart rate achieved at the end of exercise.

2.10 Cardiac output monitoring

I used cardiac output monitor data from the OPTIMISE and POM-O trials to test for association between preoperative heart rate and preoperative left ventricular stroke volume. The OPTIMISE trial used the LiDCO^{TM} *rapid* cardiac output monitor and the POM-O trial used the LiDCO^{TM} *Plus* cardiac output monitor (Lidco, London UK). The LiDCO^{TM} *plus* and LiDCO^{TM} *rapid* systems use the 'PulseCO^{TM}' algorithm to calculate stroke volume and heartbeat duration from the arterial pulse pressure waveform.[311] This estimate of cardiac output is calibrated using lithium dilution for the LiDCO^{TM} *plus* system. However, the LiDCO^{TM} *rapid* system is un-calibrated. Heart rate is calculated on a beat-by-beat basis according to the heartbeat duration. The manufacturers report that

the LiDCO™ method of estimating cardiac output is at least as accurate as thermodilution.[312] Whilst there are many studies evaluating both calibrated and non-calibrated cardiac output monitors, none have compared pulse contour analysis of heart rate with more conventional measures e.g. electrocardiogram or pulse-oximetry.

2.11 Collection, preparation and processing of blood samples

Collection of blood samples for troponin testing was performed in both the VISION and METS studies and followed a standardised process, which was similar for both studies. For the VISION study, blood samples were collected between six and twelve hours after the completion of surgery and then again on postoperative days one, two and three.[16] For the METS study, blood samples were collected before surgery at the time of routine preoperative blood sampling and then again on postoperative days one, two and three. For both studies, 5-10mls of blood was sampled into a plain vacuum tube (i.e. clotted sample) and only sampled when patients were in hospital.[313] For the VISION study, blood samples were analysed in the local hospital laboratories, where the troponin assay was Troponin-T (Roche 4th generation Elecsys™ assay – Roche Diagnostics, Basel, Switzerland). For the METS study, participating hospitals in Canada and Australia sent blood samples to their local hospital laboratory for analysis. However, in the United Kingdom, the analysis of laboratory samples was carried out in a single, central laboratory, where the troponin assay was ultra Troponin-I (Siemens Centaur analyser – Siemens Healthcare Diagnostics Inc. Frimley, United Kingdom). Hospitals in Canada and Australia used whichever assay was available in the local hospital laboratory (chapter seven).

2.12 Statistical and data methods

A large part of my work on this thesis was data management, data processing and statistical analysis. Consequently, important learning and development has been in epidemiological, data handling and statistical methods. For this thesis, the purpose of statistical analysis was to identify association between exposures and outcomes, and to determine whether any observed effects were likely to be due to chance, confounding or bias. I took a 'research question' driven approach, rather than a 'data driven' approach, planning each analysis prospectively before looking at the data.[268]

2.12.1 Software packages

I used Microsoft Excel (Microsoft, Redmond, USA) for data manipulation and processing. I used SPSS version 22 (IBM, Armonk, USA) and STATA version 14 (Statacorp, College Station, USA) to analyse the data.

2.12.2 Data management, exploration and cleaning

I received the data sets for the VISION study and OPTIMISE trials in a semi-cleaned format. I received the data sets for the METS and POM-HR studies and the POM-O trial in an un-cleaned format. The preliminary data cleaning for these data sets in Microsoft Excel included:

- Checking the data against the study case report form
- Renaming/recoding variables and creating or amending data dictionaries
- Formatting the type of data field for each variable (e.g. continuous or categorical) and checking this was consistent for all cells for any given variable
- Checking units and decimal places for continuous data

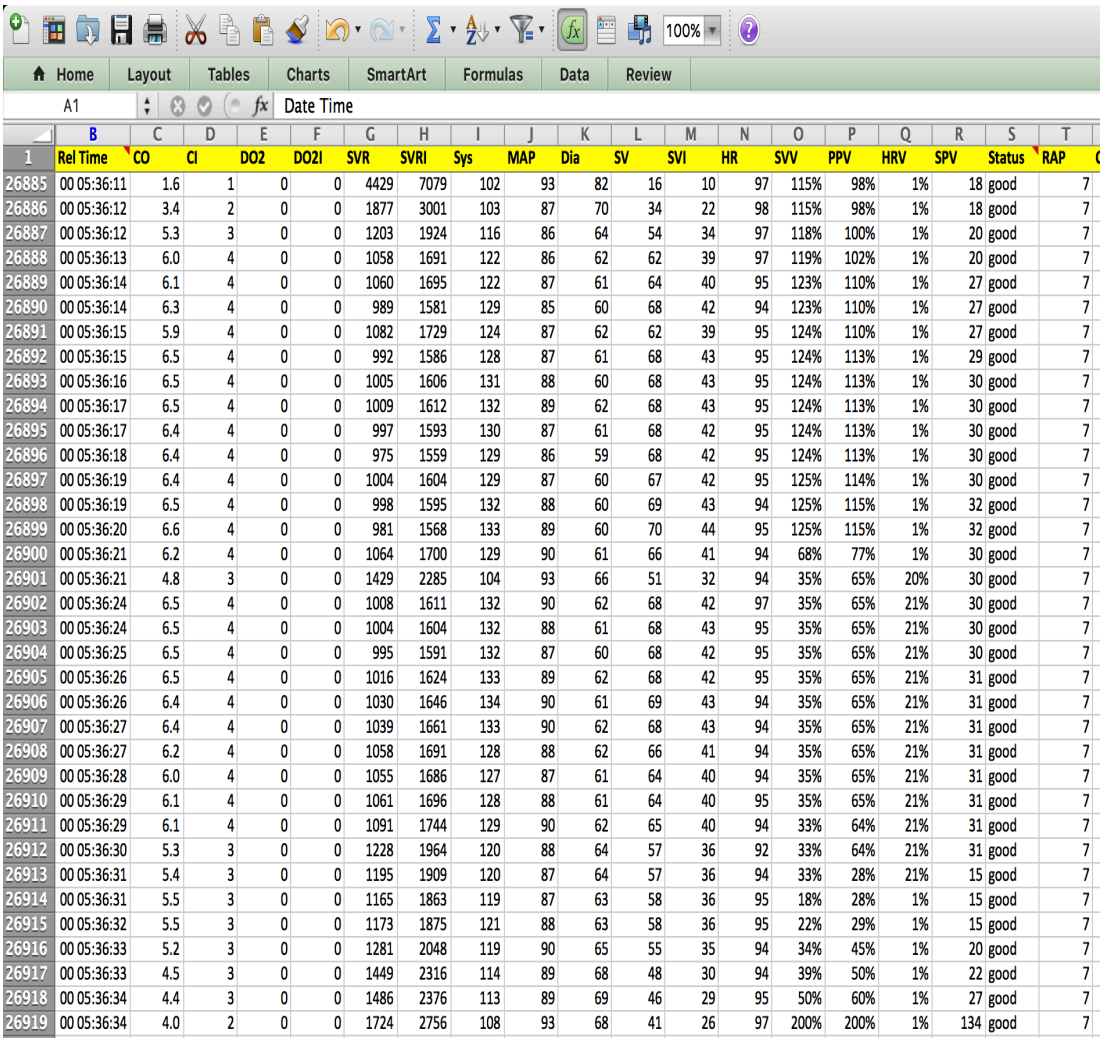
- Coding or recoding categorical data using a number coding system
- Checking for missing data and coding this with a consistent missing data value
- Preparing an analysis data set by removing variables that were not required

The data cleaning in the statistics software package included:

- Importing the Microsoft Excel data into the statistics package
- Assigning variable names
- Assigning data types (continuous, categorical nominal, categorical ordinal)
- Assigning numbers of decimal places
- Setting the missing data values
- Running sense checks on each variable, including: number of cases, number of missing values, mean, standard deviation, median and histograms (for continuous data)
- Checking categorical variable coding and adding category labels
- Generating any new variables required for an analysis

The data from cardiac output monitors from the OPTIMISE and POM-O trials were in a raw data format. These were very large Microsoft Excel documents, with 20 to 50 columns and 20,000 to 80,000 rows. Due to the beat-by-beat nature of data generated from the arterial catheter and the pulse-contour analysis, there were often artefacts in the Microsoft Excel data, for example, a between beat change in heart rate of 300 beats per minute or interruptions due to positioning of the arterial catheter or transducer. It was not possible to rely on a computer program or macro to consistently remove these aberrations, so this required manual checking of each of the 178 files (figure 2.7). This took

approximately five hours per file or ~1000 hours in total. To perform a statistical analysis I required summary data from each cleaned cardiac output monitor file in a single spreadsheet, with rows representing patients and columns representing summary variables. In collaboration with Aaron Lee (Bioinformatics, William Harvey Research Institute), I used a bespoke Python[E] program to extract summary data from each cardiac output monitor file and generate a single summary data sheet for analysis (figure 2.8).



Home | Layout | Tables | Charts | SmartArt | Formulas | Data | Review

A1 | Date Time

	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
1	Rel Time	CO	CI	DO2	DO2I	SVR	SVRI	Sys	MAP	Dia	SV	SVI	HR	SVV	PPV	HRV	SPV	Status	RAP
26885	00 05:36:11	1.6	1	0	0	4429	7079	102	93	82	16	10	97	115%	98%	1%	18	good	7
26886	00 05:36:12	3.4	2	0	0	1877	3001	103	87	70	34	22	98	115%	98%	1%	18	good	7
26887	00 05:36:12	5.3	3	0	0	1203	1924	116	86	64	54	34	97	118%	100%	1%	20	good	7
26888	00 05:36:13	6.0	4	0	0	1058	1691	122	86	62	62	39	97	119%	102%	1%	20	good	7
26889	00 05:36:14	6.1	4	0	0	1060	1695	122	87	61	64	40	95	123%	110%	1%	27	good	7
26890	00 05:36:14	6.3	4	0	0	989	1581	129	85	60	68	42	94	123%	110%	1%	27	good	7
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26893	00 05:36:16	6.5	4	0	0	1005	1606	131	88	60	68	43	95	124%	113%	1%	30	good	7
26894	00 05:36:17	6.5	4	0	0	1009	1612	132	89	62	68	43	95	124%	113%	1%	30	good	7
26895	00 05:36:17	6.4	4	0	0	997	1593	130	87	61	68	42	95	124%	113%	1%	30	good	7
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26897	00 05:36:19	6.4	4	0	0	1004	1604	129	87	60	67	42	95	125%	114%	1%	30	good	7
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26899	00 05:36:20	6.6	4	0	0	981	1568	133	89	60	70	44	95	125%	115%	1%	32	good	7
26900	00 05:36:21	6.2	4	0	0	1064	1700	129	90	61	66	41	94	68%	77%	1%	30	good	7
26901	00 05:36:21	4.8	3	0	0	1429	2285	104	93	66	51	32	94	35%	65%	20%	30	good	7
26902	00 05:36:24	6.5	4	0	0	1008	1611	132	90	62	68	42	97	35%	65%	21%	30	good	7
26903	00 05:36:24	6.5	4	0	0	1004	1604	132	88	61	68	43	95	35%	65%	21%	30	good	7
26904	00 05:36:25	6.5	4	0	0	995	1591	132	87	60	68	42	95	35%	65%	21%	30	good	7
26905	00 05:36:26	6.5	4	0	0	1016	1624	133	89	62	68	42	95	35%	65%	21%	31	good	7
26906	00 05:36:26	6.4	4	0	0	1030	1646	134	90	61	69	43	94	35%	65%	21%	31	good	7
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26908	00 05:36:27	6.2	4	0	0	1058	1691	128	88	62	66	41	94	35%	65%	21%	31	good	7
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26910	00 05:36:29	6.1	4	0	0	1061	1696	128	88	61	64	40	95	35%	65%	21%	31	good	7
26911	00 05:36:29	6.1	4	0	0	1091	1744	129	90	62	65	40	94	33%	64%	21%	31	good	7
26912	00 05:36:30	5.3	3	0	0	1228	1964	120	88	64	57	36	92	33%	64%	21%	31	good	7
26913	00 05:36:31	5.4	3	0	0	1195	1909	120	87	64	57	36	94	33%	28%	21%	15	good	7
26914	00 05:36:31	5.5	3	0	0	1165	1863	119	87	63	58	36	95	18%	28%	1%	15	good	7
26915	00 05:36:32	5.5	3	0	0	1173	1875	121	88	63	58	36	95	22%	29%	1%	15	good	7
26916	00 05:36:33	5.2	3	0	0	1281	2048	119	90	65	55	35	94	34%	45%	1%	20	good	7
26917	00 05:36:33	4.5	3	0	0	1449	2316	114	89	68	48	30	94	39%	50%	1%	22	good	7
26918	00 05:36:34	4.4	3	0	0	1486	2376	113	89	69	46	29	95	50%	60%	1%	27	good	7
26919	00 05:36:34	4.0	2	0	0	1724	2756	108	93	68	41	26	97	200%	200%	1%	134	good	7

Figure 2.7 – An example of a cleaned cardiac output monitor data file showing haemodynamic variables as columns and measurements (beats) as rows.

[E] Python is an open-source programming language. https://www.python.org/about/

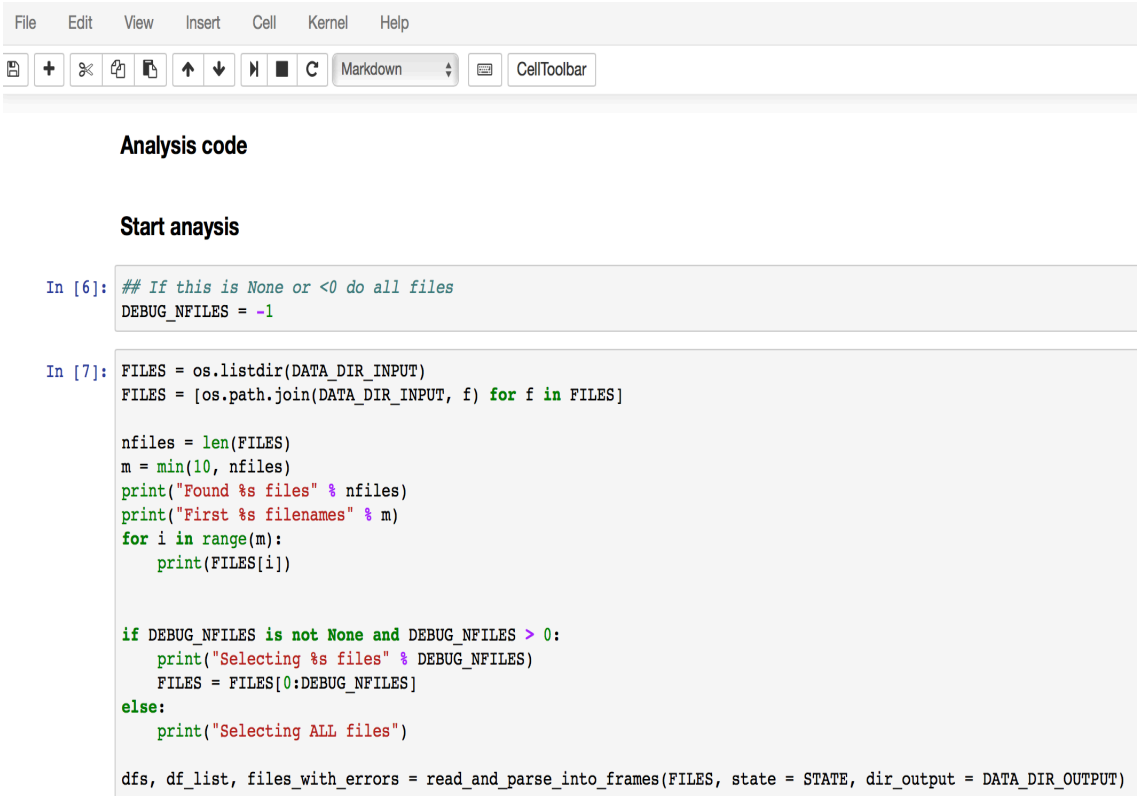

Figure 2.8 – An example of Python code using the Jupyter notebook platform, which was used to generate a single summary data set for statistical analysis.

2.12.3 Descriptive statistics

Normally distributed continuous data were presented as mean with standard deviation and non-normally distributed continuous data were presented as median with inter-quartile range. Categorical data were presented as absolute numbers (n) and a percentage. The acceptable type one error rate, or threshold for statistically significant results of hypothesis testing, was pre-specified as 5% ($p \leq 0.05$). Where effect estimates were presented, crude event rates for the outcome(s) of interest were also presented.

2.12.4 Regression analysis

Regression analysis attempts to describe the relationship between a dependent (outcome) variable and one or more independent (predictor) variables, using a mathematical equation called a model. Univariable analysis models one

independent variable against a single dependent variable. Multivariable analysis models multiple independent variables against a single dependent variable. Linear regression analysis models a continuous dependent variable (y), with a constant (intercept, β_0) and regression coefficients ($\beta_{1,2,3...n}$) for each independent variable ($x_{1,2,3...n}$):[314]

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_2 x_2 \ldots\ldots + \beta_n x_n$$

Logistic regression analysis, along with Poisson and Cox regression, is one of a group of statistical techniques called 'generalised linear models' (GLM).[315] In contrast to linear regression analysis, GLMs model a transformation of the dependent variable. For logistic regression, where the dependent variable is binary, the analysis models the log of the odds of the outcome, i.e. log-linear:

$$\textit{Log odds } (y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_2 x_2 \ldots\ldots + \beta_n x_n$$

Here, the regression coefficient ($\beta_{1,2,3...n}$) represents the change in log odds (logit) of the dependent variable per unit increase in the independent variable ($x_{1,2,3...n}$).[315] The effect estimate for a logistic regression model is expressed as an odds ratio, which is the exponential of the regression coefficient ($\beta_{1,2,3...n}$) for each independent variable.[316] The odds ratio is the likelihood of having the outcome of interest versus not having the outcome of interest.[316] Logistic regression analysis can be used to model categorical variables, grouped continuous variables and continuous variables.[315] A principal assumption for all GLMs is that the relationship between exposure and outcome (or transformed versions of these) follows a straight-line relationship.

In this thesis, I modelled binary outcome measures, e.g. mortality or myocardial injury, using logistic regression analysis. I used multivariable[F] modelling to adjust for the effect of potentially confounding factors. Results were presented as odds ratios with 95% confidence intervals. I used the Wald chi-squared test for hypothesis testing of individual covariates in any given model.[314, 316]

2.12.5 Modelling non-linear independent variables

Linear regression and generalised linear models assume that the dependent variable (or log of the dependent variable) is related to the independent variable(s) in a linear fashion, as shown above.[317] However, this is not always the case. In such a case, linear modelling may under- or over-estimate the strength of association between variables, which may bias the interpretation of the observation.[317]

The commonest, and most widely accepted, approach is to stratify a continuous independent variable and transform it into an ordered categorical variable, for example by sorting the sample according to the variable of interest and dividing into strata (for example quartiles), which would be handled as discrete data rather than continuous data in the model.[318] I used this strategy in all of my analyses.

A second approach is to use non-linear modelling, where the independent variable is not transformed into a categorical variable, but kept in the model as a continuous variable. The two commonest approaches are to use regression splines or polynomial regression. Regression splines are a type of basis

[F] Multivariable analysis models multiple independent variables. Multivariate analysis models multiple dependent variables. See Medical Statistics by Kirkwood & Sterne 2003, page 106.

function, meaning that the relationship between independent and dependent variables are modelled separately over different regions of the independent variable. Thus, several different models might apply over different regions.[319] Polynomial regression fits polynomial functions to the independent variables, which in contrast to regression splines, applies a "global structure on the non-linear function of" the independent variables.[319] This is preferable because a single model describes the relationship between independent and dependent variables over the full range of data. The general form of a polynomial function is:[319]

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2^2 \ldots\ldots + \beta_n x_n^n$$

Royston and *Altman*[320] developed this further to include a defined "family of parametric models",[321] fractional polynomials, where the polynomial functions are limited to a specific set of values: -2, -1, -0.5, 0.5, 1, 2, 3 and log(x).[321] A method for including fractional polynomial terms in a multivariable model was first described by *Sauerbrei* and *Royston,* called multivariable fractional polynomial regression analysis.[322] This combined a "function selection procedure" with standard backwards elimination for the selection of variables.[323] Likelihood ratio statistics (chi-squared) are used for variable selection and for determining the fit of functions in the function selection procedure.[323] This process was later developed into a standard algorithm, which is included in the statistical package STATA and, which can be applied to various types of regression models.[324] The output is the best fitting model, which may or may not include polynomial terms.

In this thesis, I handled continuous exposure variables by ranking the sample according to the variable of interest and then dividing into strata, for example deciles or quintiles, and treating them as categorical data. Where I was concerned that a relationship might not be linear, for example between preoperative heart rate and postoperative myocardial injury, I used multivariable fractional polynomial logistic regression analysis.

2.12.6 Variable selection for inclusion in statistical models

I used an explanatory modelling strategy throughout this thesis. Analyses were pre-specified and based on *a priori* hypotheses of association between exposure and outcome. Analyses were conducted according to prospective analysis plans. Covariates were selected for inclusion in multivariable models based on subject matter knowledge, derived from previous evidence of association with the outcome measures and plausible association with the exposure.[325] This is particularly pertinent where the number of variables is small.[326] In the analyses of the VISION study data, where the sample size was very large, I was able to adjust the analyses for multiple confounding factors. Variables were not selected for inclusion based on univariable association alone.[325] Pre-specified covariates were included in models, even in the absence of statistical significance,[317] since individually some variables may not exert much confounding until they are considered collectively with other factors.[327] I used forced simultaneous entry (all candidate variables included in the model) as opposed to automated stepwise selection, because simulation studies suggest increased risk of over-fitting with the latter approach.[328, 329] In the analyses of the METS and POM-HR data, the comparatively smaller sample size limited the total number of variables I was able to include in multivariable

models, according to the ‘rule of seven’.[16] Therefore I used backwards-stepwise selection to identify variables for inclusion in the final multivariable models, with a pre-specified type one error threshold of 10%.

Chapter three

Preoperative heart rate

Preoperative heart rate and myocardial injury after non-cardiac surgery. A secondary analysis of data from a prospective international cohort study of myocardial injury after non-cardiac surgery.

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3.1 Introduction

At least 1.5 million major surgical procedures are carried out in the United Kingdom every year. Observational data suggest that one in ten patients have elevated concentrations of cardiac troponins in the blood after surgery. Conventional wisdom attributes this to myocardial ischaemia and infarction as a result of atherosclerotic plaque rupture in coronary arteries and subsequent thrombosis.[330] However, fewer than one tenth of patients with troponin elevation (myocardial injury) after surgery experience ischaemic symptoms and <25% have objective evidence of myocardial ischaemia or infarction.[16, 95] Evidence-based treatments for acute coronary syndrome in the non-operative setting, such as aspirin or coronary angioplasty, do not reduce the risk of myocardial injury when given prophylactically before surgery.[100, 101] So while coronary artery thrombosis may cause perioperative myocardial injury in some instances,

it is unlikely to be the predominant pathophysiological process in the majority of cases.

Epidemiological studies in general population cohorts have consistently demonstrated that resting heart rate is associated with cardiovascular morbidity and mortality.[156, 331-333] However, the explanation for this relationship is uncertain. Elevated heart rate is associated with multiple cardiovascular risk factors, so resting tachycardia could be a marker of co-existing cardiovascular disease.[156] However, the association between heart rate and cardiovascular morbidity and mortality appears independent of underlying pathology.[156, 331-334] The prevailing perioperative paradigm is that of oxygen supply-demand imbalance driven myocardial injury, which could be induced by tachycardia. Alternatively, elevated resting heart rate could indicate autonomic nervous system imbalance, either by up-regulation of sympathetic or down-regulation of parasympathetic activity, which has been implicated as a casual factor in several cardiovascular pathologies.[178, 181, 335-337] Consequently, there has been widespread interest in treatments to control heart rate, in both general medical and perioperative patients.[258, 334]

Multiple trials have demonstrated that treatment with beta-blockers, to lower heart rate, can reduce the risk of perioperative myocardial infarction,[166, 258] but at the expense of increased risk of mortality.[166] Consequently, it has been suggested that the optimum dose of beta-blocker may vary from person to person, and that preoperative heart rate may be used to determine the appropriate individualised dosage.[227] However, this remains controversial since the relationship between preoperative heart rate and postoperative cardiac

complications has been subject to only limited investigation.[22, 171-173] Previous studies have not measured cardiac biomarkers to identify myocardial injury, and statistical analyses used arbitrary pre-defined heart rate thresholds.[171-173] Therefore it remains unclear whether or not preoperative heart rate is associated with myocardial injury after non-cardiac surgery, or if there is a heart rate threshold at which the risk of postoperative myocardial injury increases and that could be used to identify patients at risk of postoperative morbidity.

The aim of this analysis was to assess the relationships between preoperative heart rate and cardiovascular outcomes, as has previously been described in the general population. I hypothesised that elevated preoperative heart rate is associated with increased risk of myocardial injury, myocardial infarction (MI) and mortality within 30 days of surgery.

3.2 Methods

This was a secondary analysis of prospectively collected data from the Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) study. The study is described in chapter two and full details of the methods and previous analyses have been published before.[16, 95, 273, 275] Briefly, the study cohort consists of patients aged 45 years or older undergoing non-cardiac surgery under regional or general anaesthesia at one of twelve participating hospitals in eight countries.[16, 95] Patients were excluded if they refused consent or if they had been previously enrolled in the study. Researchers collected a detailed and standardised dataset from patients and their medical notes before and up to 30 days after surgery.

3.2.1 Exposure of interest

The exposure of interest was preoperative heart rate, defined as the last heart rate measurement, as part of routine care, recorded before induction of anaesthesia.

3.2.2 Outcome measures

The primary outcome measure was myocardial injury after non-cardiac surgery (MINS), defined as TnT $\geq$0.03 ng/mL using a Roche 4th generation Elecsys^{TM} assay, adjudicated as due to an ischaemic pathology within 30 days after surgery. This was the definition used in the original report of the VISION study.[95, 113] The adjudication process and blood sampling regime are described in chapter two (methods) and have been published previously.[16, 95, 273, 275]

Secondary outcome measures were myocardial infarction and death within 30 days of surgery. Myocardial infarction was defined according to the third universal definition (troponin elevation in the presence of at least one of: ischaemic symptoms; the development of new or presumed new Q waves, ST segment or T wave changes, or left bundle branch block on the electrocardiogram; the finding of a new or presumed new regional wall motion abnormality on echocardiography).[113, 273] Patients with a troponin elevation <0.04 ng/mL were not investigated for evidence of ischaemia.[273]

3.2.3 Primary statistical analysis

I planned the analysis before taking custody of the data. The data were analysed using SPSS version 22 (IBM, New York, USA). Patients with missing data were handled by list-wise deletion. The sample was ranked according to

integer values of preoperative heart rate and divided the sample into deciles, using cut-points closest to each 10th percentile. Ten groups that contained an approximately equal number of cases were produced and differences in baseline characteristics for each group were compared. Multivariable logistic regression models for heart rate against each outcome measure were constructed, considering each decile as a categorical variable. To avoid isolating any particular heart rate decile as a reference category, I used deviation contrasts to compare each decile to the un-weighted average effect for the whole cohort.[338, 339] Each multivariable model was corrected for covariates that were previously associated with MINS, cardiac events (including MI) or mortality in other perioperative epidemiological research: age (45-64, 65-75, >75 years), current atrial fibrillation, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, previous stroke or transient ischaemic attack, estimated glomerular filtration rate (eGFR <30, 30-44, 45-60, >60 ml/min), chronic obstructive pulmonary disease, neurosurgery, major surgery and urgent/emergency surgery were considered as categorical variables in the multivariable models.[16, 20, 21, 95] The results of multivariable logistic regression analyses were presented as odds ratios (OR) with 95% confidence intervals. Normally distributed data were expressed as mean +/- standard deviation (SD) and non-normally distributed data were expressed as median +/- interquartile range (IQR). Binary data were expressed as percentages.

3.2.4 Secondary analysis

Previous studies have investigated heart rate as a risk factor for cardiac complications using pre-defined heart rate thresholds. To allow comparisons

between my findings and other research, I repeated my analysis using two heart rate thresholds that were previously associated with MI or mortality in the general medical literature (>70 beats per minute [bpm]) and the perioperative literature (>104 bpm).[97, 237] I dichotomised the sample according to each heart rate threshold and constructed multivariable logistic regression models for each outcome measure, corrected for the previous covariates. Heart rate above the threshold was considered as a categorical variable.

3.2.5 Sensitivity analyses

The conventional approach to regression analysis using multi-level categorical variables is to isolate one group as the reference category.[314] To make my analysis comparable to other research, I repeated the multivariable logistic regression analyses using a single heart rate decile as the reference category. To determine the influence of preoperative atrial fibrillation, the commonest perioperative dysrhythmia, I excluded all patients with a previous history of atrial fibrillation and repeated the primary analysis.[340] To determine the influence of emergency surgery, which is an independent risk factor for postoperative morbidity and mortality, I excluded all patients undergoing emergency surgery and repeated the primary analysis.[10, 16] It is plausible that an observed relationship between heart rate and one or more of the outcome measures could be confounded by the use of medications that influence heart rate. The most relevant agents in clinical practice are beta-adrenoceptor antagonists (beta-blockers) and the negatively chronotropic calcium channel blockers, diltiazem and verapamil.[167, 258, 341] To determine the influence of these agents, I conducted a post-hoc analysis by excluding patients that received a beta-blocker and/or a rate limiting calcium channel blocker within 24 hours before

surgery and repeated the primary analysis. In a study of patients undergoing coronary artery bypass grafting, the investigators observed a non-linear relationship between preoperative heart rate and postoperative mortality.[162] To investigate the possibility of a non-linear relationship between heart rate and myocardial injury in more depth, I conducted a post-hoc analysis using multivariable fractional polynomial regression.[342] I have described this technique in chapter two (methods).

3.3 Results

16,079 patients were recruited to the VISION study from twelve hospitals in eight countries between 6th August 2007 and 11th January 2011.[95] I excluded cases with missing data describing preoperative heart rate or patient outcomes. 1,197/15,087 patients (7.9%) sustained MINS, 454/16,007 patients (2.8%) sustained MI and 315/16,037 patients (2.0%) died, within 30 days of surgery. Participants that were missing pre-defined covariates were excluded from multivariable analyses (figure 3.1). I have presented the baseline characteristics in table 3.1. The incidences of the outcome measures is greater for heart rates >96 bpm compared to the other heart rate deciles. The highest decile was associated with increased incidences of preoperative atrial fibrillation ($p<0.01$), diabetes ($p<0.01$), peripheral vascular disease ($p<0.01$), previous stroke or transient ischaemic attack ($p<0.01$), chronic obstructive pulmonary disease ($p=0.02$), eGFR <30ml/min ($p<0.01$) and eGFR 30-44ml/min ($p<0.01$).

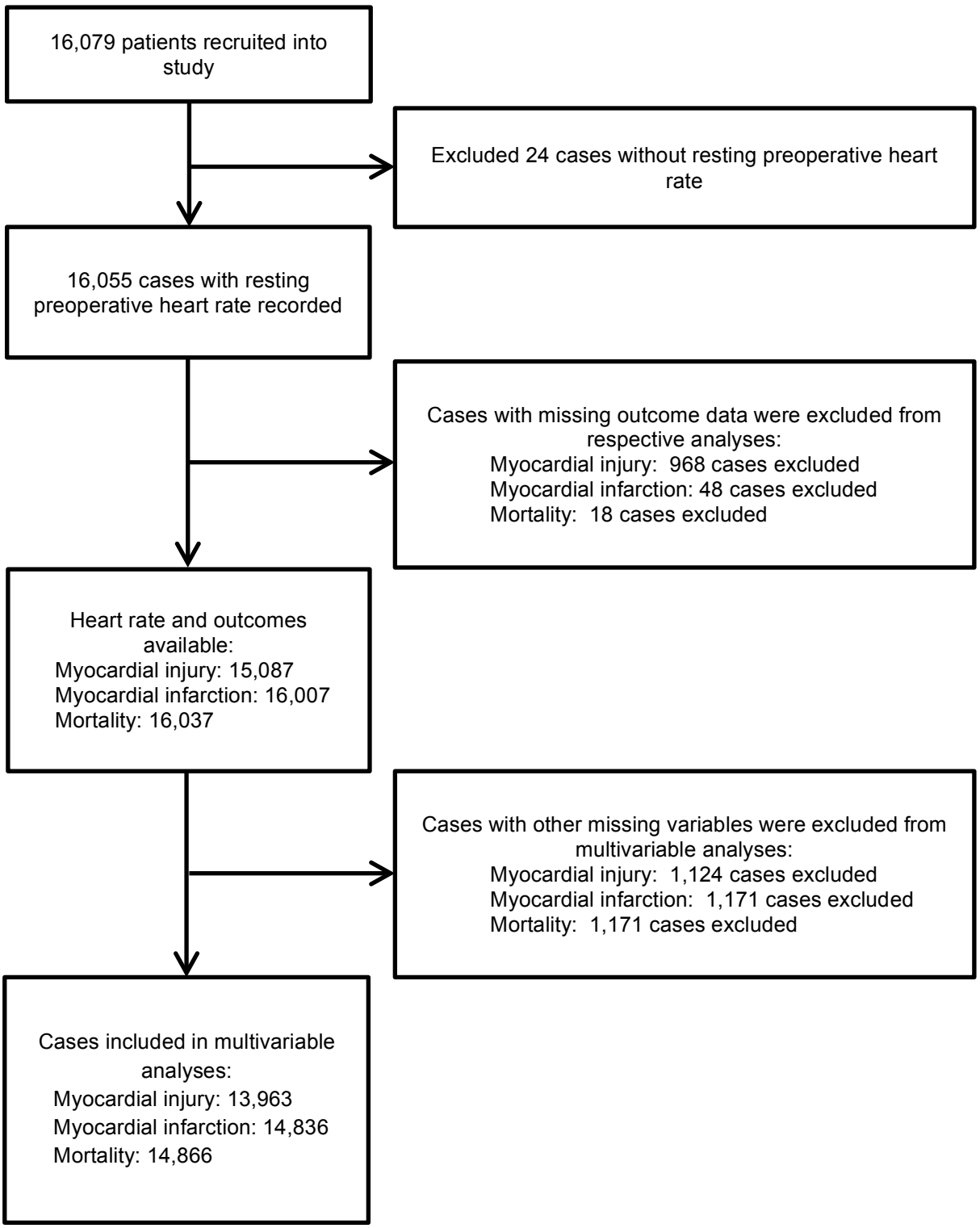

Figure 3.1. STROBE diagram showing the number of cases included and excluded from each analysis.[343]

Table 3.1. Baseline patient characteristics. Descriptive data stratified by preoperative heart rate decile, presented as frequencies with percentages (%) or means with standard deviations (SD). Data rounded to nearest whole number. Heart rate (beats per minute), systolic blood pressure and pulse pressure (mmHg).

Preoperative resting heart rate deciles (bpm)	Whole	<60	60-64	65-68	69-71	72-74	75-79	80-82	83-87	88-96	>96
Number of cases (n)	16055	1515	1676	1579	1464	1318	2019	1649	1352	1989	1494
Mean age (SD)	65 (12)	66 (11)	66 (11)	66 (12)	64 (12)	65 (12)	65 (12)	65 (12)	65 (12)	65 (13)	65 (13)
Sex											
Male (%)	7739 (48)	915 (60)	888 (53)	795 (50)	704 (48)	634 (48)	914 (45)	784 (48)	578 (43)	871 (44)	667 (45)
Female (%)	8316 (52)	600 (40)	788 (47)	784 (50)	760 (52)	684 (52)	1105 (55)	865 (52)	774 (57)	1118 (56)	827 (55)
Mean preoperative heart rate (SD)	77 (15)	54 (5)	62 (2)	67 (1)	70 (1)	73 (1)	77 (1)	81 (1)	85 (1)	91 (3)	107 (11)
Mean preoperative systolic blood pressure (SD)	140 (24)	137 (24)	138 (24)	137 (24)	136 (22)	140 (23)	139 (23)	141 (24)	140 (23)	144 (23)	145 (25)
Mean preoperative pulse pressure (SD)	61 (19)	62 (20)	62 (20)	61 (20)	59 (19)	61 (19)	60 (19)	61 (19)	60 (19)	62 (19)	61 (20)
Comorbid disorder (%)											
Atrial fibrillation	545 (3)	46 (3)	44 (3)	39 (2)	46 (3)	32 (2)	56 (3)	67 (4)	39 (3)	79 (4)	97 (6)
Diabetes	3153 (20)	258 (17)	294 (18)	281 (18)	278 (19)	243 (18)	411 (20)	341 (21)	264 (20)	422 (21)	355 (24)
Hypertension	8171 (51)	808 (53)	887 (53)	791 (50)	693 (47)	636 (48)	1031 (51)	848 (51)	686 (51)	1006 (51)	771 (52)
Coronary artery disease	1947 (12)	284 (19)	256 (15)	227 (14)	182 (12)	133 (10)	215 (11)	172 (10)	145 (11)	175 (9)	153 (10)
Peripheral vascular disease	858 (5)	71 (5)	106 (6)	87 (6)	77 (5)	59 (5)	116 (6)	78 (5)	56 (4)	106 (5)	102 (7)
Previous stroke or transient ischaemic attack	1167 (7)	123 (8)	121 (7)	107 (7)	101 (7)	89 (7)	134 (7)	108 (7)	77 (6)	164 (8)	140 (9)
Chronic obstructive pulmonary disease	1337 (8)	116 (7)	128 (8)	118 (7)	120 (8)	108 (8)	156 (8)	147 (9)	112 (8)	180 (9)	149 (10)
Active cancer	2031 (13)	176 (12)	213 (13)	193 (12)	188 (13)	195 (15)	234 (12)	231 (14)	180 (13)	218 (11)	199 (13)
Preoperative eGFR, ml/min/1.73m^2 (%)											
<30	564 (4)	50 (4)	48 (3)	38 (3)	41 (3)	45 (4)	65 (4)	59 (4)	38 (3)	87 (5)	93 (7)
30-44	831 (5)	81 (6)	81 (5)	76 (5)	71 (5)	55 (4)	111 (6)	72 (5)	64 (5)	114 (6)	104 (7)
45-60	1579 (10)	166 (12)	165 (11)	176 (12)	145 (11)	106 (9)	175 (9)	166 (11)	135 (11)	198 (11)	145 (10)
>60	11938 (74)	1105 (79)	1267 (81)	1157 (80)	1108 (81)	1020 (83)	1505 (8)	1216 (80)	1014 (81)	1467 (79)	1060 (76)
Surgical procedure category (%)											
Elective	13745 (86)	1377 (91)	1530 (91)	1413 (89)	1304 (89)	1149 (87)	1776 (88)	1409 (85)	1118 (83)	1585 (80)	1084 (73)
Urgent	483 (3)	28 (2)	35 (2)	28 (2)	33 (2)	30 (2)	45 (2)	44 (3)	51 (4)	80 (4)	109 (7)
Emergency	1826 (11)	110 (7)	111 (7)	138 (9)	126 (9)	139 (11)	198 (10)	196 (12)	183 (14)	324 (16)	301 (20)
Major surgery (%)	9576 (60)	868 (57)	946 (56)	905 (57)	817 (56)	798 (61)	1202 (60)	980 (59)	846 (63)	1253 (63)	969 (65)
Outcome measures (%)											
Myocardial injury	1197 (8)	103 (7)	105 (7)	100 (7)	100 (7)	70 (6)	131 (7)	117 (8)	119 (9)	169 (9)	177 (13)
Myocardial infarction	454 (3)	35 (2)	34 (2)	39 (3)	43 (3)	25 (2)	53 (3)	45 (3)	39 (3)	55 (3)	84 (6)
Mortality	315 (2)	13 (1)	19 (1)	16 (1)	22 (2)	14 (1)	34 (2)	30 (2)	22 (2)	52 (3)	91 (7)

3.3.1 Primary analysis

The results of multivariable logistic regression analyses for preoperative heart rate deciles as categorical variables against MINS, MI, and mortality within 30 days of surgery are reported in table 3.2 and figure 3.2. Most of the associations observed on univariable analysis remained significant on multivariable analysis. In particular, heart rates in the highest decile (>96 bpm) were associated with MINS (OR 1.48 [1.23 – 1.77]; p <0.01), MI (OR 1.71 [1.34 – 2.18]; p <0.01) and mortality (OR 3.16 [2.45-4.07]; p <0.01). Heart rates in the ninth decile (88-96 bpm) were also associated with mortality (OR 1.46 [1.08 – 1.97]; p=0.01), but not with MINS or MI. Heart rates in the 8^{th} decile (83-87 bpm) and 5^{th} decile (73-74 bpm) were associated with MINS (OR 1.36 [1.11-1.66]; p<0.01 and OR 0.71 [0.55-0.91]; p=0.01, respectively), but not MI or mortality. Heart rates in the lowest decile (<60 bpm) were associated with lower mortality rates than other deciles (OR 0.50 [0.29 – 0.88]; p=0.02), but this group was not associated with MINS or MI (figure 3.2). For comparison, I present the results of univariable logistic regression analysis of heart rate deciles against the outcome measures, showing un-adjusted odds ratios in table 3.3.

3.3.2 Secondary analysis

I repeated the multivariable analysis for two binary heart rate thresholds. Preoperative heart rate >104 bpm was associated with MINS (OR 1.38 [1.21-1.57]; p<0.01), MI (OR 1.35 [1.14-1.61]; p<0.01) and mortality (OR 1.89 [1.60-2.24]; p<0.01), as shown in table 3.4. Heart rate >70 bpm was associated with MINS (OR 1.09 [1.01-1.17]; p=0.02) and mortality (OR 1.52 [1.30-1.77]; p<0.01), but not MI (table 3.5).

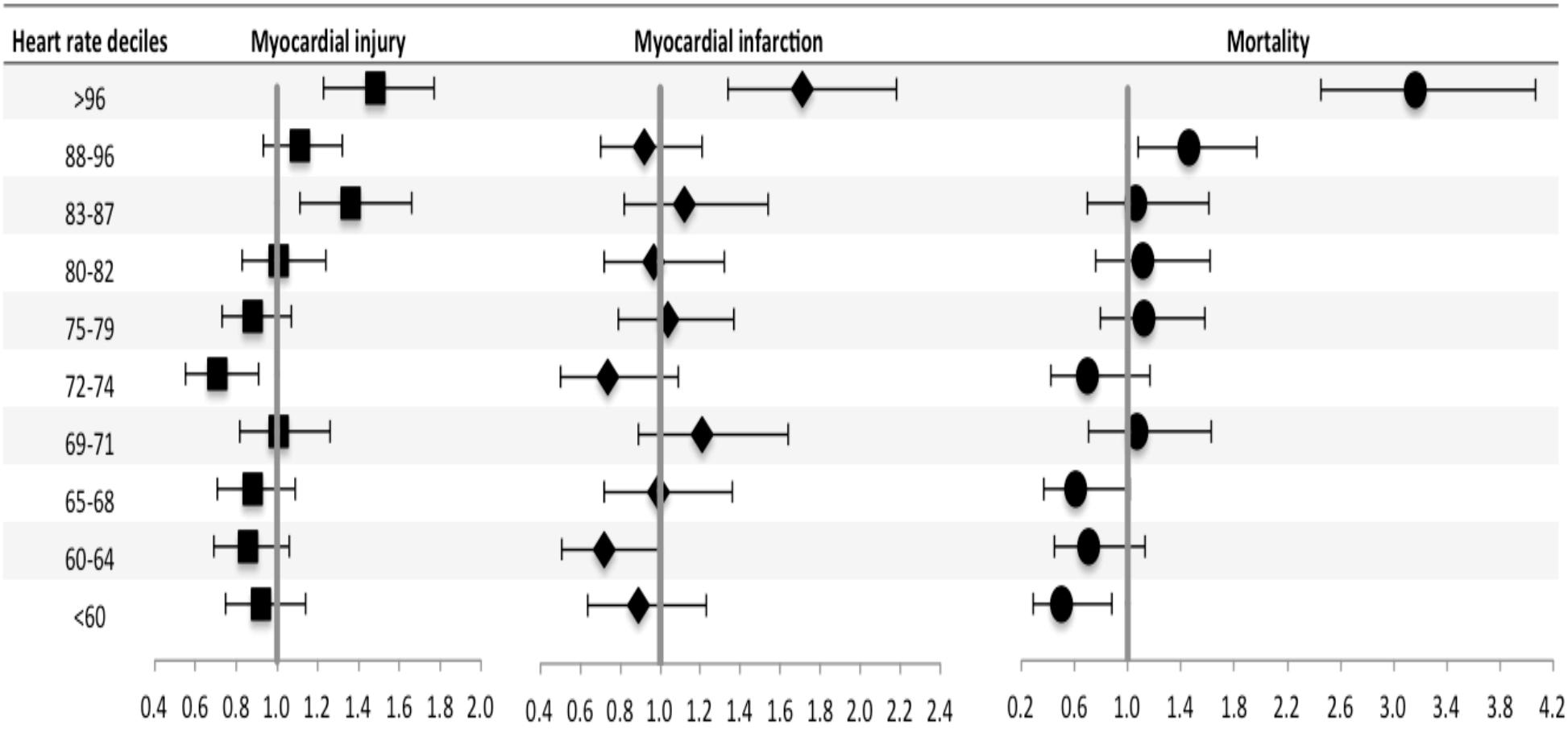

Figure 3.2. Forest plot showing the odds ratios for myocardial injury, myocardial infarction and mortality by each heart rate (HR) decile (beats per minute), with 95% confidence intervals.

Table 3.2. Multivariable logistic regression models for preoperative heart rate deciles. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Each heart rate decile was compared to the un-weighted average heart rate for the whole sample.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.08 (0.90-1.30)	0.43	1.16 (0.87-1.55)	0.30	1.64 (1.17-2.30)	<0.01
>75	2.08 (1.74-2.48)	<0.01	1.90 (1.45-2.49)	<0.01	2.41 (1.73-3.35)	<0.01
Male sex	1.40 (1.22-1.61)	<0.01	1.04 (0.85-1.28)	0.70	1.27 (0.99-1.63)	0.06
History of atrial fibrillation	1.53 (1.18-2.00)	<0.01	1.29 (0.90-1.85)	0.17	0.97 (0.60-1.56)	0.89
History of diabetes	1.39 (1.19-1.61)	<0.01	1.21 (0.97-1.52)	0.10	0.98 (0.73-1.32)	0.91
History of hypertension	1.31 (1.12-1.54)	<0.01	1.41 (1.10-1.80)	0.01	0.98 (0.75-1.29)	0.89
History of heart failure	1.59 (1.26-1.99)	<0.01	1.67 (1.24-2.25)	<0.01	1.38 (0.92-2.10)	0.12
History of coronary artery disease	1.48 (1.25-1.76)	<0.01	2.23 91.77-2.81)	<0.01	0.96 (0.68-1.34)	0.80
History of peripheral vascular disease	2.17 (1.77-2.65)	<0.01	2.11 (1.60-2.78)	<0.01	1.75 (1.21-2.53)	<0.01
History of stroke or transient ischaemic attack	1.46 (1.20-1.78)	<0.01	1.14 (0.85-1.52)	0.37	1.53 (1.10-2.15)	0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.75 (8.69-13.29)	<0.01	3.98 (2.96-5.36)	<0.01	2.95 (2.01-4.31)	<0.01
30-44	2.51 (2.02-3.19)	<0.01	1.69 (1.22-2.34)	<0.01	1.58 (1.07-2.36)	0.02
45-60	1.68 (1.39-2.03)	<0.01	1.40 (1.04-1.87)	0.02	0.94 (0.63-1.40)	0.77
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.18 (0.97-1.45)	0.10	1.17 (0.83-1.49)	0.46	1.93 (1.40-2.65)	<0.01
Neurosurgery	1.14 (0.87-1.51)	0.34	0.58 (0.35-0.98)	0.04	1.82 (1.71-2.82)	0.01
Urgent or emergency surgery	1.82 (1.54-2.15)	<0.01	2.14 (1.70-2.69)	<0.01	3.11 (2.41-4.02)	<0.01
Major surgery	1.66 (1.42-1.93)	<0.01	2.19 (1.71-2.80)	<0.01	1.51 (1.13-2.02)	0.01
Preoperative heart rate (beats per minute)						
<60	0.92 (0.75-1.14)	0.46	0.89 (0.64-1.23)	0.48	0.50 (0.29-0.88)	0.02
60-64	0.86 (0.69-1.06)	0.15	0.72 (0.51-1.01)	0.06	0.71 (0.45-1.13)	0.15
65-68	0.88 (0.71-1.09)	0.26	0.99 (0.72-1.36)	0.96	0.61 (0.37-1.02)	0.06
69-71	1.01 (0.82-1.26)	0.91	1.21 (0.89-1.64)	0.23	1.07 (0.71-1.63)	0.74
72-74	0.71 (0.55-0.91)	0.01	0.74 (0.50-1.09)	0.13	0.70 (0.42-1.17)	0.18
75-79	0.88 (0.73-1.07)	0.21	1.04 (0.79-1.37)	0.79	1.12 (0.79-1.58)	0.53
80-82	1.01 (0.83-1.24)	0.90	0.97 (0.72-1.32)	0.85	1.11 (0.76-1.62)	0.58
83-87	1.36 (1.11-1.66)	<0.01	1.12 (0.82-1.54)	0.47	1.06 (0.70-1.61)	0.78
88-96	1.11 (0.93-1.32)	0.23	0.92 (0.70-1.21)	0.92	1.46 (1.08-1.97)	0.01
>96	1.48 (1.23-1.77)	<0.01	1.71 (1.34-2.18)	<0.01	3.16 (2.45-4.07)	<0.01

Table 3.3. Univariable (unadjusted) logistic regression models for preoperative heart rate deciles. Dependent variables are myocardial injury, myocardial infarction, and mortality within 30 days of surgery. Each heart rate decile was compared to the un-weighted average heart rate for the whole sample.

	Myocardial Injury		Myocardial Infarction		Mortality	
Heart rate deciles	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
<60	0.92 (0.76-1.11)	0.40	0.85 (0.62-1.17)	0.31	0.52 (0.32-0.87)	0.01
60-64	0.85 (0.70-1.02)	0.08	0.74 (0.54-1.02)	0.07	0.69 (0.45-1.06)	0.09
65-68	0.86 (0.71-1.04)	0.11	0.91 (0.67-1.23)	0.54	0.62 (0.39-0.98)	0.04
69-71	0.94 (0.77-1.14)	0.51	1.09 (0.81-1.45)	0.57	0.92 (0.62-1.38)	0.70
72-74	0.71 (0.57-0.89)	<0.01	0.70 (0.48-1.01)	0.05	0.65 (0.40-1.06)	0.09
75-79	0.88 (0.75-1.05)	0.15	0.97 (0.75-1.26)	0.82	1.04 (0.74-1.44)	0.83
80-82	0.98 (0.82-1.17)	0.80	1.01 (0.76-1.34)	0.95	1.12 (0.79-1.59)	0.52
83-87	1.21 (1.01-1.45)	0.04	1.07 (0.79-1.45)	0.66	1.00 (0.67-1.49)	0.99
88-96	1.19 (1.02-1.40)	0.03	1.03 (0.79-1.33)	0.85	1.63 (1.23-2.15)	<0.01
>96	1.80 (1.54-2.10)	<0.01	2.14 (1.72-2.67)	<0.01	3.92 (3.11-4.94)	<0.01

Table 3.4. Preoperative heart rate threshold of 104 beats per minute. Multivariable logistic regression models for myocardial injury, myocardial infarction, and mortality, all within 30-days of non-cardiac surgery. Preoperative heart rate was stratified according to a threshold of 104 beats per minute.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.07 (0.89-1.29)	0.47	1.15 (0.87-1.54)	0.32	1.60 (1.14-2.24)	<0.01
>75	2.05 (1.72-2.45)	<0.01	1.88 (1.44-2.47)	<0.01	2.37 (1.70-3.29)	<0.01
Male sex	1.38 (1.20-1.58)	<0.01	1.02 (0.83-1.26)	0.83	1.21 (0.95-1.55)	0.12
History of atrial fibrillation	1.53 (1.18-2.00)	<0.01	1.30 (0.91-1.86)	0.16	0.97 (0.60-1.57)	0.91
History of diabetes	1.40 (1.20-1.63)	<0.01	1.22 (0.98-1.53)	0.08	1.01 (0.75-1.35)	0.97
History of hypertension	1.32 (1.13-1.55)	<0.01	1.40 (1.09-1.78)	<0.01	0.99 (0.75-1.31)	0.95
History of heart failure	1.60 (1.27-2.00)	<0.01	1.69 (1.26-2.28)	<0.01	1.40 (0.92-2.11)	0.11
History of coronary artery disease	1.45 (1.23-1.72)	<0.01	2.19 (1.74-2.76)	<0.01	0.87 (0.63-1.22)	0.43
History of peripheral vascular disease	2.15 (1.75-2.63)	<0.01	2.11 (1.60-2.78)	<0.01	1.77 (1.23-2.55)	<0.01
History of stroke or transient ischaemic attack	1.45 (1.20-1.77)	<0.01	1.14 (0.85-1.51)	0.39	1.53 (1.10-2.14)	0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.69 (8.66-	<0.01	3.96 (2.94-5.32)	<0.01	2.97 (2.03-4.35)	<0.01
30-45	2.50 (2.01-3.10)	<0.01	1.70 (1.23-2.34)	<0.01	1.57 (1.06-2.34)	0.03
45-60	1.68 (1.39-2.03)	<0.01	1.40 (1.05-1.88)	0.02	0.94 (0.63-1.39)	0.74
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.21 (0.99-1.47)	0.07	1.13 (0.85-1.51)	0.40	2.04 (1.49-2.80)	<0.01
Neurosurgery	1.14 (0.86-1.50)	0.36	0.58 (0.35-0.98)	0.04	1.75 (1.13-2.70)	0.01
Urgent or emergency surgery	1.88 (1.59-2.21)	<0.01	2.22 (1.77-2.79)	<0.01	3.50 (2.72-4.50)	<0.01
Major surgery	1.67 (1.43-1.95)	<0.01	2.19 (1.71-2.80)	<0.01	1.56 (1.17-2.08)	<0.01
Heart rate >104 bpm	1.38 (1.21-1.57)	<0.01	1.35 (1.14-1.61)	<0.01	1.89 (1.60-2.24)	<0.01

Table 3.5. Preoperative heart rate threshold of 70 beats per minute. Multivariable logistic regression models for myocardial injury, myocardial infarction, and mortality, all within 30-days of non-cardiac surgery. Preoperative heart rate was stratified according to a threshold of 70 beats per minute.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.07 (0.89-1.28)	0.49	1.15 (0.86-1.53)	0.35	1.58 (1.13-2.20)	<0.01
>75	2.03 (1.70-2.42)	<0.01	1.85 (1.41-2.42)	<0.01	2.27 (1.63-3.15)	<0.01
Male sex	1.38 (1.20-1.59)	<0.01	1.03 (0.84-1.26)	0.81	1.26 (0.98-1.61)	0.07
History of atrial fibrillation	1.61 (1.24-2.09)	<0.01	1.37 (0.96-1.95)	0.09	1.08 (0.67-1.74)	0.74
History of diabetes	1.39 (1.20-1.62)	<0.01	1.22 (0.98-1.53)	0.08	0.99 (0.74-1.33)	0.96
History of hypertension	1.31 (1.12-1.53)	<0.01	1.38 (1.08-1.77)	0.01	0.97 (0.74-1.28)	0.84
History of heart failure	1.58 (1.26-1.99)	<0.01	1.67 (1.24-2.25)	<0.01	1.37 (0.91-2.07)	0.14
History of coronary artery disease	1.47 (1.24-1.74)	<0.01	2.20 (1.74-2.77)	<0.01	0.94 (0.67-1.31)	0.70
History of peripheral vascular disease	2.15 (1.76-2.63)	<0.01	2.11 (1.60-2.79)	<0.01	1.78 (1.24-2.57)	<0.01
History of stroke or transient ischaemic attack	1.47 (1.21-1.78)	<0.01	1.14 (0.85-1.52)	0.38	1.55 (1.11-2.16)	0.01
Preoperative eGFR (ml/min)						
<30	10.83 (8.77-	<0.01	4.06 (3.02-5.46)	<0.01	3.17 (2.17-4.62)	<0.01
30-45	2.54 (2.05-3.15)	<0.01	1.75 (1.27-2.41)	<0.01	1.72 (1.16-2.54)	<0.01
45-60	1.69 (1.40-2.05)	<0.01	1.41 (1.05-1.89)	0.02	0.97 (0.65-1.44)	0.87
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.20 (0.98-1.46)	0.08	1.13 (0.84-1.51)	0.42	1.95 (1.42-2.67)	<0.01
Neurosurgery	1.14 (0.86-1.50)	0.36	0.58 (0.34-0.98)	0.04	1.79 (1.16-2.76)	<0.01
Urgent or emergency surgery	1.91 (1.62-2.25)	<0.01	2.30 (1.83-2.89)	<0.01	3.53 (2.75-4.54)	<0.01
Major surgery	1.66 (1.43-1.94)	<0.01	2.19 (1.71-2.81)	<0.01	1.55 (1.16-2.07)	<0.01
Heart rate >70 bpm	1.09 (1.01-1.17)	0.02	1.06 (0.95-1.18)	0.29	1.52 (1.30-1.77)	<0.01

3.3.3 Sensitivity analyses

My principal findings remained similar when I repeated the regression analyses using a single decile (60-64 bpm) as the reference category (table 3.6), except that heart rates in the lowest decile were no longer associated with postoperative mortality (OR 0.71 [0.33-1.54]; p=0.39), heart rates 72-74bpm were no longer associated with myocardial injury (OR 0.83 [0.58-1.17]; p=0.28) and heart rates 69-71bpm were associated with myocardial infarction (OR 1.68 [1.03-2.73]; p=0.04). To examine the potential confounding effect of preoperative tachyarrhythmia, I repeated the regression analyses excluding cases with current atrial fibrillation, the most common perioperative arrhythmia.[340] When I excluded cases with current atrial fibrillation or emergency surgery, the results were very similar to the main results (tables 3.7-3.12). The association between the highest decile of heart rate and each of the three outcome measures was not affected by the exclusion of patients who received a beta-blocker and/or a rate limiting calcium channel blocker within 24 hours before surgery (table 3.13). The odds ratios for MINS, MI, and 30 day mortality were 1.52 (1.24-1.85; p<0.01), 1.83 (1.38-24.1; p<0.01), and 2.90 (2.19-3.84; p<0.01), respectively. However, heart rates <60 bpm were no longer negatively associated with mortality (OR 0.61 [0.33-1.12]; p = 0.11).

Table 3.6. Sensitivity analysis using heart rate 60-64bpm as the reference category. Multivariable model. Dependent variables were myocardial injury, myocardial infarction and mortality within 30 days of surgery. Each heart rate decile was compared to the second decile of heart rate (60-64bpm).

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.08 (0.90-1.30)	0.43	1.16 (0.87-1.55)	0.30	1.64 (1.17-2.30)	<0.01
>75	2.08 (1.74-2.48)	<0.01	1.90 (1.45-2.49)	<0.01	2.41 (1.73-3.35)	<0.01
Male sex	1.40 (1.22-1.61)	<0.01	1.04 (0.85-1.28)	0.70	1.27 (0.99-1.63)	0.06
History of atrial fibrillation	1.53 (1.18-2.00)	<0.01	1.29 (0.90-1.85)	0.17	0.97 (0.60-1.56)	0.89
History of diabetes	1.39 (1.19-1.61)	<0.01	1.21 (0.97-1.52)	0.10	0.98 (0.73-1.32)	0.91
History of hypertension	1.31 (1.12-1.54)	<0.01	1.41 (1.10-1.80)	0.01	0.98 (0.75-1.29)	0.89
History of heart failure	1.59 (1.26-1.99)	<0.01	1.67 (1.24-2.25)	<0.01	1.38 (0.92-2.10)	0.12
History of coronary artery disease	1.48 (1.25-1.76)	<0.01	2.23 (1.77-2.81)	<0.01	0.96 (0.68-1.34)	0.80
History of peripheral vascular disease	2.17 (1.77-2.65)	<0.01	2.11 (1.60-2.78)	<0.01	1.75 (1.21-2.53)	<0.01
History of stroke or transient ischaemic attack	1.46 (1.20-1.78)	<0.01	1.14 (0.85-1.52)	0.37	1.53 (1.10-2.15)	0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.75 (8.69-13.29)	<0.01	3.98 (2.96-5.36)	<0.01	2.95 (2.01-4.31)	<0.01
30-45	2.51 (2.02-3.12)	<0.01	1.69 (1.22-2.34)	<0.01	1.58 (1.07-2.36)	0.02
45-60	1.68 (1.39-2.03)	<0.01	1.40 (1.04-1.87)	0.02	0.94 (0.63-1.40)	0.77
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.18 (0.97-1.45)	0.10	1.12 (0.83-1.49)	0.46	1.93 (1.40-2.65)	<0.01
Neurosurgery	1.14 (0.87-1.51)	0.34	0.58 (0.35-0.98)	0.04	1.82 (1.17-2.82)	<0.01
Urgent or emergency surgery	1.82 (1.54-2.15)	<0.01	2.14 (1.70-2.69)	<0.01	3.11 (2.41-4.02)	<0.01
Major surgery	1.66 (1.42-1.93)	<0.01	2.19 (1.71-2.80)	<0.01	1.51 (1.13-2.02)	<0.01
Preoperative heart rate (beats per minute)						
<60	1.08 (0.79-1.48)	0.63	1.23 (0.74-2.05)	0.42	0.71 (0.33-1.54)	0.39
60-64 (reference)	-	-	-	-	-	-
65-68	1.03 (0.75-1.42)	0.84	1.38 (0.84-2.26)	0.20	0.86 (0.41-1.81)	0.69
69-71	1.18 (0.86-1.63)	0.30	1.68 (1.03-2.73)	0.04	1.51 (0.78-2.93)	0.22
72-74	0.83 (0.58-1.17)	0.28	1.03 (0.59-1.80)	0.91	0.99 (0.47-2.08)	0.98
75-79	1.03 (0.77-1.39)	0.83	1.45 (0.91-2.30)	0.12	1.58 (0.85-2.91)	0.15
80-82	1.19 (0.87-1.61)	0.28	1.35 (0.83-2.21)	0.23	1.57 (0.83-2.95)	0.17
83-87	1.59 (1.17-2.16)	<0.01	1.57 (0.95-2.58)	0.08	1.49 (0.77-2.91)	0.24
88-96	1.30 (0.98-1.73)	0.07	1.28 (0.80-2.05)	0.30	2.06 (1.15-3.68)	0.02
>96	1.73 (1.29-2.31)	<0.01	2.38 (1.52-3.71)	<0.01	2.24 (2.55-7.75)	<0.01

Table 3.7. Sensitivity analysis excluding atrial fibrillation cases. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Each heart rate decile was compared to the un-weighted average heart rate for the whole sample.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.08 (0.90-1.31)	0.42	1.20 (0.90-1.61)	0.22	1.71 (1.21-2.40)	<0.01
>75	2.08 (1.74-2.50)	<0.01	1.93 (1.45-2.55)	<0.01	2.44 (1.74-3.43)	<0.01
Male sex	1.38 (1.20-1.60)	<0.01	0.99 (0.80-1.24)	0.95	1.26 (0.98-1.64)	0.08
History of diabetes	1.44 (1.23-1.69)	<0.01	1.26 (0.99-1.59)	0.06	0.99 (0.73-1.35)	0.95
History of hypertension	1.27 (1.08-1.50)	<0.01	1.37 (1.06-1.78)	0.02	0.91 (0.69-1.22)	0.54
History of heart failure	1.70 (1.32-2.19)	<0.01	1.74 (1.25-2.42)	<0.01	1.24 (0.76-2.00)	0.39
History of coronary artery disease	1.61 (1.35-1.92)	<0.01	2.47 (1.93-3.16)	<0.01	1.00 (0.70-1.44)	0.99
History of peripheral vascular disease	2.09 (1.68-2.59)	<0.01	2.02 (1.50-2.73)	<0.01	1.68 (1.13-2.51)	0.01
History of stroke or transient ischaemic attack	1.48 (1.20-1.83)	<0.01	1.01 (0.73-1.40)	0.94	1.55 (1.08-2.23)	0.02
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.40 (8.33-12.98)	<0.01	3.91 (2.84-5.38)	<0.01	2.31 (2.22-4.91)	<0.01
30-45	2.49 (1.98-3.13)	<0.01	1.71 (1.21-2.42)	<0.01	1.53 (0.99-2.37)	0.05
45-60	1.70 (1.39-2.07)	<0.01	1.49 (1.10-2.02)	0.01	1.01 (0.67-1.52)	0.96
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.20 (0.97-1.48)	0.10	1.24 (0.92-1.69)	0.16	2.12 (1.53-2.95)	<0.01
Neurosurgery	1.19 (0.90-1.58)	0.22	0.59 (0.35-1.02)	0.06	1.92 (1.23-2.98)	<0.01
Urgent or emergency surgery	1.94 (1.64-2.30)	<0.01	2.23 (1.75-2.84)	<0.01	3.21 (2.46-4.19)	<0.01
Major surgery	1.62 (1.38-1.91)	<0.01	2.15 (1.65-2.79)	<0.01	1.51 (1.12-2.05)	0.01
Preoperative heart rate (beats per minute)						
<60	0.90 (0.71-1.11)	0.30	0.87 (0.61-1.23)	0.43	0.53 (0.30-0.93)	0.03
60-64	0.82 (0.66-1.03)	0.09	0.69 (0.48-0.99)	0.05	0.71 (0.44-1.15)	0.16
65-68	0.90 (0.72-1.12)	0.33	1.05 (0.76-1.45)	0.77	0.60 (0.35-1.02)	0.06
69-71	1.01 (0.81-1.27)	0.92	1.14 (0.82-1.58)	0.44	1.03 (0.67-1.59)	0.89
72-74	0.73 (0.56-0.94)	0.01	0.79 (0.54-1.17)	0.24	0.73 (0.44-1.23)	0.24
75-79	0.89 (0.73-1.08)	0.24	1.05 (0.79-1.40)	0.72	1.17 (0.82-1.66)	0.40
80-82	0.95 (0.77-1.18)	0.64	0.88 (0.62-1.23)	0.45	1.04 (0.70-1.56)	0.85
83-87	1.39 (1.13-1.71)	<0.01	1.13 (0.81-1.58)	0.46	1.09 (0.71-1.67)	0.70
88-96	1.12 (0.94-1.35)	0.22	0.90 (0.67-1.21)	0.48	1.41 (1.03-1.93)	0.03
>96	1.57 (1.30-1.90)	<0.01	1.87 (1.45-2.42)	<0.01	3.18 (2.44-4.15)	<0.01

Table 3.8. Sensitivity analysis excluding emergency cases. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Each heart rate decile was compared to the un-weighted average heart rate for the whole sample.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.09 (0.89-1.33)	0.39	1.20 (0.87-1.66)	0.26	1.71 (1.16-2.52)	0.01
>75	2.10 (1.73-2.56)	<0.01	2.26 (1.67-3.07)	<0.01	2.58 (1.74-3.83)	<0.01
Male sex	1.42 (1.21-1.65)	<0.01	1.07 (0.85-1.35)	0.58	1.34 (0.99-1.80)	0.06
History of atrial fibrillation	1.88 (1.42-2.48)	<0.01	1.48 (1.00-2.21)	0.05	1.13 (0.65-1.97)	0.66
History of diabetes	1.33 (1.12-1.58)	<0.01	1.15 (0.88-1.49)	0.30	0.85 (0.59-1.23)	0.40
History of hypertension	1.24 (1.04-1.48)	0.02	1.26 (0.95-1.67)	0.10	1.03 (0.74-1.43)	0.87
History of heart failure	1.46 (1.14-1.89)	<0.01	1.44 (1.01-2.04)	0.04	1.13 (0.67-1.91)	0.65
History of coronary artery disease	1.56 (1.30-1.88)	<0.01	2.41 (1.85-3.13)	<0.01	1.11 (0.75-1.64)	0.61
History of peripheral vascular disease	2.03 (1.62-2.55)	<0.01	2.12 (1.55-2.90)	<0.01	1.45 (0.91-2.29)	0.12
History of stroke or transient ischaemic attack	1.50 (1.21-1.87)	<0.01	1.14 (0.82-1.59)	0.42	1.88 (1.28-2.77)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	11.80 (9.32-14.93)	<0.01	4.07 (2.87-5.77)	<0.01	2.22 (1.33-3.71)	<0.01
30-45	2.71 (2.13-3.44)	<0.01	1.73 (1.20-2.51)	<0.01	1.54 (0.95-2.49)	0.08
45-60	1.65 (1.33-2.04)	<0.01	1.38 (1.00-1.93)	0.05	0.78 (0.47-1.27)	0.32
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.24 (1.00-1.54)	0.05	1.09 (0.79-1.52)	0.59	2.19 (1.52-3.14)	<0.01
Neurosurgery	1.13 (0.84-1.52)	0.41	0.57 (0.33-1.00)	0.05	1.98 (1.22-3.21)	0.01
Urgent or emergency surgery	1.94 (1.40-2.68)	<0.01	2.28 (1.49-3.51)	<0.01	3.47 (2.26-5.32)	<0.01
Major surgery	1.68 (1.42-1.99)	<0.01	2.44 (1.84-3.24)	<0.01	1.23 (0.89-1.71)	0.21
Preoperative heart rate (beats per minute)						
<60	0.88 (0.70-1.10)	0.25	0.79 (0.55-1.14)	0.21	0.39 (0.19-0.77)	0.01
60-64	0.83 (0.67-1.04)	0.11	0.70 (0.48-1.02)	0.07	0.77 (0.47-1.28)	0.31
65-68	0.87 (0.69-1.09)	0.22	0.95 (0.67-1.35)	0.78	0.62 (0.34-1.11)	0.11
69-71	1.08 (0.86-1.36)	0.51	1.37 (1.00-1.89(	0.05	1.15 (0.72-1.84)	0.55
72-74	0.73 (0.56-0.95)	0.02	0.81 (0.53-1.22)	0.31	0.60 (0.32-1.15)	0.13
75-79	0.84 (0.68-1.04)	0.10	0.96 (0.70-1.32)	0.81	1.26 (0.85-1.87)	0.26
80-82	1.04 (0.83-1.29)	0.76	1.04 (0.74-1.47)	0.82	1.42 (0.93-2.15)	0.10
83-87	1.33 (1.06-1.66)	0.01	0.99 (0.68-1.46)	0.98	0.83 (0.47-1.45)	0.51
88-96	1.15 (0.95-1.40)	0.16	1.00 (0.73-1.38)	0.98	1.58 (1.10-2.27)	0.01
>96	1.52 (1.24-1.87)	<0.01	1.71 (1.27-2.30)	<0.01	3.38 (2.47-4.62)	<0.01

Table 3.9. Sensitivity analysis excluding atrial fibrillation cases. Multivariable logistic regression models for myocardial injury, myocardial infarction and mortality, all within 30-days of non-cardiac surgery. Preoperative heart rate was stratified according to a threshold of 70 beats per minute.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.07 (0.89-1.30)	0.48	1.18 (0.88-1.59)	0.26	1.65 (1.17-2.32)	<0.01
>75	2.03 (1.69-2.43)	<0.01	1.87 (1.41-2.48)	<0.01	2.29 (1.63-3.22)	<0.01
Male sex	1.37 (1.18-1.58)	<0.01	0.98 (0.79-1.22)	0.87	1.26 (0.98-1.63)	0.08
History of diabetes	1.45 (1.24-1.70)	<0.01	1.28 (1.01-1.62)	0.05	1.01 (0.74-1.36)	0.98
History of hypertension	1.27 (1.08-1.50)	<0.01	1.36 (1.05-1.76)	0.02	0.91 (0.69-1.22)	0.54
History of heart failure	1.70 (1.32-2.19)	<0.01	1.73 (1.25-2.41)	<0.01	1.24 (0.77-2.00)	0.38
History of coronary artery disease	1.59 (1.33-1.90)	<0.01	2.42 (1.90-3.09)	<0.01	0.97 (0.68-1.39)	0.89
History of peripheral vascular disease	2.07 (1.67-2.56)	<0.01	2.02 (1.49-2.72)	<0.01	1.70 (1.14-2.52)	<0.01
History of stroke or transient ischaemic attack	1.48 (1.20-1.83)	<0.01	1.01 (0.73-1.39)	0.96	1.56 (1.09-2.24)	0.02
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.57 (8.48-13.17)	<0.01	4.03 (2.94-5.54)	<0.01	3.63 (2.45-5.37)	<0.01
30-45	2.50 (1.99-3.14)	<0.01	1.76 (1.25-2.49)	<0.01	1.64 (1.06-2.52)	0.03
45-60	1.72 (1.40-2.09)	<0.01	1.50 (1.11-2.04)	<0.01	1.04 (0.69-1.56)	0.86
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.22 (0.98-1.50)	0.07	1.27 (0.94-1.72)	0.12	2.17 (1.57-3.01)	<0.01
Neurosurgery	1.19 (0.90-1.58)	0.22	0.60 (0.35-1.02)	0.06	1.90 (1.23-2.95)	<0.01
Urgent or emergency surgery	2.05 (1.73-2.42)	<0.01	2.41 (1.90-3.06)	<0.01	3.62 (2.79-4.69)	<0.01
Major surgery	1.63 (1.39-1.92)	<0.01	2.17 (1.67-2.82)	<0.01	1.56 (1.15-2.12)	<0.01
Heart rate threshold (beats per minute)						
>70	1.11 (1.03-1.19)	<0.01	1.08 (0.96-1.21)	0.21	1.53 (1.30-1.80)	<0.01

Table 3.10. Sensitivity analysis excluding atrial fibrillation cases. Multivariable logistic regression models for myocardial injury, myocardial infarction and mortality, all within 30-days of non-cardiac surgery. Preoperative heart rate was stratified according to a threshold of 104 beats per minute.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.08 (0.89-1.30)	0.45	1.20 (0.89-1.60)	0.24	1.67 (1.19-2.35)	<0.01
>75	2.06 (1.72-2.47)	<0.01	1.91 (1.45-2.54)	<0.01	2.41 (1.72-3.39)	<0.01
Male sex	1.35 (1.17-1.56)	<0.01	0.98 (0.79-1.21)	0.82	1.21 (0.93-1.56)	0.15
History of diabetes	1.46 (1.24-1.71)	<0.01	1.27 (1.01-1.61)	0.05	1.02 (0.75-1.38)	0.92
History of hypertension	1.28 (1.09-1.51)	<0.01	1.37 (1.05-1.77)	0.02	0.93 (0.70-1.23)	0.60
History of heart failure	1.71 (1.33-2.20)	<0.01	1.75 (1.26-2.44)	<0.01	1.25 (0.77-2.02)	0.36
History of coronary artery disease	1.56 (1.31-1.86)	<0.01	2.40 (1.88-3.06)	<0.01	0.90 (0.63-1.29)	0.56
History of peripheral vascular disease	1.08 (1.68-2.57)	<0.01	2.02 (1.50-2.73)	<0.01	1.70 (1.14-2.52)	<0.01
History of stroke or transient ischaemic attack	1.47 (1.20-1.82)	<0.01	1.01 (0.73-1.40)	0.95	1.56 (1.09-2.23)	0.02
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.39 (8.33-12.95)	<0.01	3.91 (2.84-5.37)	<0.01	3.38 (2.27-5.03)	<0.01
30-45	2.47 (1.96-3.11)	<0.01	1.72 (1.22-2.43)	<0.01	1.50 (0.98-2.32)	0.07
45-60	1.69 (1.39-2.07)	<0.01	1.47 (1.10-2.01)	0.01	1.00 (0.67-1.51)	0.99
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.22 (0.99-1.51)	0.07	1.26 (0.93-1.71)	0.13	2.22 (1.60-3.08)	<0.01
Neurosurgery	1.19 (0.90-1.57)	0.23	0.60 (0.35-1.03)	0.06	1.94 (1.19-2.85)	<0.01
Urgent or emergency surgery	2.02 (1.70-2.39)	<0.01	2.33 (1.83-2.96)	<0.01	3.58 (2.76-4.66)	<0.01
Major surgery	1.64 (1.39-1.93)	<0.01	2.16 (1.66-2.80)	<0.01	1.57 (1.16-2.13)	<0.01
Heart rate threshold (beats per minute)						
>104	1.42 (1.24-1.63)	<0.01	1.39 (1.15-1.68)	<0.01	1.92 (1.61-2.30)	<0.01

Table 3.11. Sensitivity analysis excluding emergency cases. Multivariable logistic regression models for myocardial injury, myocardial infarction and mortality, all within 30-days of non-cardiac surgery. Preoperative heart rate was stratified according to a threshold of 70 beats per minute.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.08 (0.88-1.32)	0.46	1.19 (0.86-1.64)	0.29	1.66 (1.13-2.44)	0.01
>75	2.04 (1.68-2.48)	<0.01	2.20 (1.62-2.98)	<0.01	2.45 (1.66-3.63)	<0.01
Male sex	1.40 (1.20-1.63)	<0.01	1.05 (0.83-1.32)	0.72	1.31 (0.98-1.77)	0.07
History of atrial fibrillation	1.97 (1.49-2.60)	<0.01	1.56 (1.05-2.33)	0.03	1.26 (0.72-2.18)	0.42
History of diabetes	1.34 (1.13-1.59)	<0.01	1.17 (0.90-1.52)	0.23	0.87 (0.61-1.25)	0.45
History of hypertension	1.24 (1.04-1.48)	0.02	1.24 (0.94-1.64)	0.13	1.03 (0.74-1.43)	0.86
History of heart failure	1.45 (1.13-1.86)	<0.01	1.43 (1.01-2.03)	0.04	1.08 (0.64-1.83)	0.77
History of coronary artery disease	1.54 (1.28-1.85)	<0.01	2.36 (1.82-3.06)	<0.01	1.10 (0.75-1.63)	0.62
History of peripheral vascular disease	2.02 (1.61-2.53)	<0.01	2.12 (1.55-2.90)	<0.01	1.47 (0.93-2.34)	0.10
History of stroke or transient ischaemic attack	1.51 (1.22-1.88)	<0.01	1.16 (0.84-1.62)	0.36	1.91 (1.30-2.80)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	11.86 (9.38-15.01)	<0.01	4.13 (2.92-5.86)	<0.01	2.29 (1.37-3.82)	<0.01
30-45	2.72 (2.14-3.46)	<0.01	1.74 (1.20-2.52)	<0.01	1.60 (0.99-2.59)	0.05
45-60	1.66 (1.34-2.06)	<0.01	1.38 (0.99-1.93)	0.05	0.80 (0.49-1.31)	0.38
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.26 (1.02-1.57)	0.04	1.11 (0.80-1.54)	0.53	2.21 (1.54-3.18)	<0.01
Neurosurgery	1.13 (0.84-1.51)	0.43	0.56 (0.32-0.99)	0.04	1.93 (1.19-3.12)	<0.01
Urgent surgery	2.11 (1.53-2.92)	<0.01	2.58 (1.70-3.93)	<0.01	4.19 (2.76-6.35)	<0.01
Major surgery	1.69 (1.43-2.00)	<0.01	2.46 (1.85-3.26)	<0.01	1.26 (0.91-1.74)	0.17
Heart rate threshold (beats per minute)						
>70	1.09 (1.01-1.18)	0.02	1.06 (0.94-1.20)	0.33	1.57 (1.32-1.88)	<0.01

Table 3.12. Sensitivity analysis excluding emergency cases. Multivariable logistic regression models for myocardial injury, myocardial infarction and mortality, all within 30-days of non-cardiac surgery. Preoperative heart rate was stratified according to a threshold of 104 beats per minute.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.08 (0.89-1.32)	0.45	1.19 (0.87-1.64)	0.28	1.65 (1.12-2.43)	0.01
>75	2.06 (1.70-2.50)	<0.01	2.23 (1.65-3.03)	<0.01	2.47 (1.67-3.66)	<0.01
Male sex	1.39 (1.19-1.62)	<0.01	1.04 (0.82-1.31)	0.75	1.24 (0.92-1.67)	0.15
History of atrial fibrillation	1.86 (1.40-2.47)	<0.01	1.48 (0.99-2.20)	0.06	1.16 (0.67-2.03)	0.60
History of diabetes	1.35 (1.14-1.60)	<0.01	1.18 (0.91-1.53)	0.21	0.90 (0.62-1.29)	0.55
History of hypertension	1.25 (1.05-1.49)	0.01	1.24 (0.94-1.64)	0.13	1.03 (0.74-1.43)	0.86
History of heart failure	1.48 (1.15-1.90)	<0.01	1.47 (1.04-2.08)	0.03	1.13 (0.67-1.90)	0.66
History of coronary artery disease	1.53 (1.27-1.84)	<0.01	2.36 (1.82-3.06)	<0.01	1.02 (0.69-1.50)	0.94
History of peripheral vascular disease	2.01 (1.61-2.52)	<0.01	2.12 (1.55-2.89)	<0.01	1.46 (0.92-2.32)	0.10
History of stroke or transient ischaemic attack	1.50 (1.21-1.86)	<0.01	1.15 (0.83-1.59)	0.41	1.84 (1/25-2.71)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	11.78 (9.31-14.90)	<0.01	4.07 (2.87-5.77)	<0.01	2.23 (1.33-3.74)	<0.01
30-45	2.69 (2.12-3.42)	<0.01	1.70 (1.17-2.47)	<0.01	1.51 (0.93-2.45)	0.10
45-60	1.65 (1.33-2.04)	<0.01	1.38 (0.99-1.91)	0.06	0.77 (0.47-1.26)	0.30
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.27 (1.02-1.57)	0.03	1.11 (0.80-1.54)	0.53	2.32 (1.62-3.33)	<0.01
Neurosurgery	1.13 (0.84-1.51)	0.42	0.57 (0.33-1.00)	0.05	1.83 (1.13-2.96)	0.01
Urgent surgery	2.01 (1.45-2.78)	<0.01	2.33 (1.52-3.58)	<0.01	3.95 (2.58-6.04)	<0.01
Major surgery	1.70 (1.44-2.02)	<0.01	2.46 (1.85-3.26)	<0.01	1.29 (0.93-1.78)	0.13
Heart rate threshold (beats per minute)						
≤104	0.68 (0.59-0.79)	<0.01	0.69 (0.56-0.85)	<0.01	0.53 (0.43-0.66)	<0.01
>104	1.46 (1.26-1.70)	<0.01	1.44 (1.17-1.78)	<0.01	1.88 (1.52-2.33)	<0.01

Table 3.13. Sensitivity analysis excluding beta-blockers and rate limiting calcium channel blockers. Multivariable logistic regression models for myocardial injury, myocardial infarction and mortality, all within 30-days of non-cardiac surgery.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.01 (0.88-1.36)	0.41	1.08 (0.76-1.53)	0.67	1.70 (1.18-2.44)	<0.01
>75	2.28 (1.86-2.81)	<0.01	1.88 (1.35-2.60)	<0.01	2.34 (1.63-3.35)	<0.01
Male sex	1.27 (1.07-1.49)	<0.01	0.80 (0.62-1.03)	<0.01	1.20 (0.91-1.57)	0.20
History of AF	1.75 (1.22-2.51)	<0.01	1.29 (0.78-2.13)	0.33	0.82 (0.42-1.58)	0.55
History of diabetes	1.31 (1.08-1.58)	<0.01	1.29 (0.97-1.72)	0.08	0.99 (0.71-1.38)	0.94
History of hypertension	1.19 (0.99-1.42)	0.06	1.20 (0.90-1.59)	0.21	0.99 (0.74-1.33)	0.94
History of heart failure	1.76 (1.30-2.38)	<0.01	2.09 (1.42-3.08)	<0.01	1.23 (0.72-2.09)	0.45
History of coronary artery disease	1.56 (1.24-1.97)	<0.01	2.37 (1.74-3.23)	<0.01	1.02 (0.67-1.54)	0.94
History of peripheral vascular disease	1.85 (1.42-2.40)	<0.01	2.01(1.40-2.90)	<0.01	1.86 (1.22-2.82)	<0.01
History of stroke or transient ischaemic attack	1.52 (1.19-1.94)	<0.01	1.15 (0.79-1.68)	0.47	1.67 (1.14-2.44)	0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	12.83 (9.90-16.61)	<0.01	3.95 (2.70-5.80)	<0.01	3.34 (2.16-5.15)	<0.01
30-45	2.90 (2.24-3.77)	<0.01	1.94 (1.30-2.90)	<0.01	1.85 (1.19-2.89)	<0.01
45-60	1.72 (1.36-2.16)	<0.01	1.56 (1.09-2.24)	0.01	1.04 (0.67-1.60)	0.87
>60 (reference)	-	-	-	-	-	-
History of chronic obstructive pulmonary disease	1.36 (1.07-1.71)	0.01	1.53 (1.09-2.15)	0.01	2.24 (1.59-3.16)	<0.01
Neurosurgery	1.23 (0.89-1.69)	0.21	0.65 (0.34-1.21)	0.17	1.99 (1.25-3.17)	<0.01
Urgent or emergency surgery	1.81 (1.49-2.18)	<0.01	2.35 (1.80-3.08)	<0.01	3.32 (2.51-4.38)	<0.01
Major surgery	1.74 (1.45-2.09)	<0.01	2.27 (1.68-3.09)	<0.01	1.63 (1.18-2.25)	<0.01
Preoperative heart rate (beats per minute)						
<60	0.92 (0.70-1.21)	0.56	0.81 (0.50-1.32)	0.40	0.61 (0.33-1.12)	0.11
60-64	0.92 (0.71-1.19)	0.51	0.68 (0.42-1.10)	0.11	0.61 (0.34-1.10)	0.10
65-68	0.98 (0.76-1.26)	0.85	1.21 (0.81-1.80)	0.35	0.73 (0.42-1.28)	0.27
69-71	1.00 (0.78-1.26)	0.99	1.08 (0.72-1.60)	0.72	1.07 (0.67-1.70)	0.78
72-74	0.65 (0.48-0.87)	<0.01	0.60 (0.35-1.02)	0.06	0.73 (0.42-1.28)	0.27
75-79	0.87 (0.70-1.09)	0.23	1.08 (0.78-1.50)	0.64	1.09 (0.75-1.60)	0.65
80-82	0.97 (0.76-1.23)	0.78	0.92 (0.63-1.36)	0.68	1.03 (0.67-1.57)	0.91
83-87	1.37 (1.09-1.72)	<0.01	1.26 (0.88-1.82)	0.21	0.97 (0.61-1.54)	0.89
88-96	1.08 (0.88-1.31)	0.48	1.01 (0.74-1.40)	0.94	1.52 (1.10-2.09)	0.01
>96	1.52 (1.24-1.85)	<0.01	1.83 (1.38-2.41)	<0.01	2.90 (2.19-3.84)	<0.01

3.3.4 Fractional polynomial analysis

The results of the multivariable fractional polynomial regression analysis confirms the linear association between heart rate and the risk of myocardial injury. A function plot of partial predictor + residual against increasing heart rate for the best fitting model is shown in figure 3.3, illustrating that as heart rate increases, the risk of myocardial injury increases in a linear fashion.

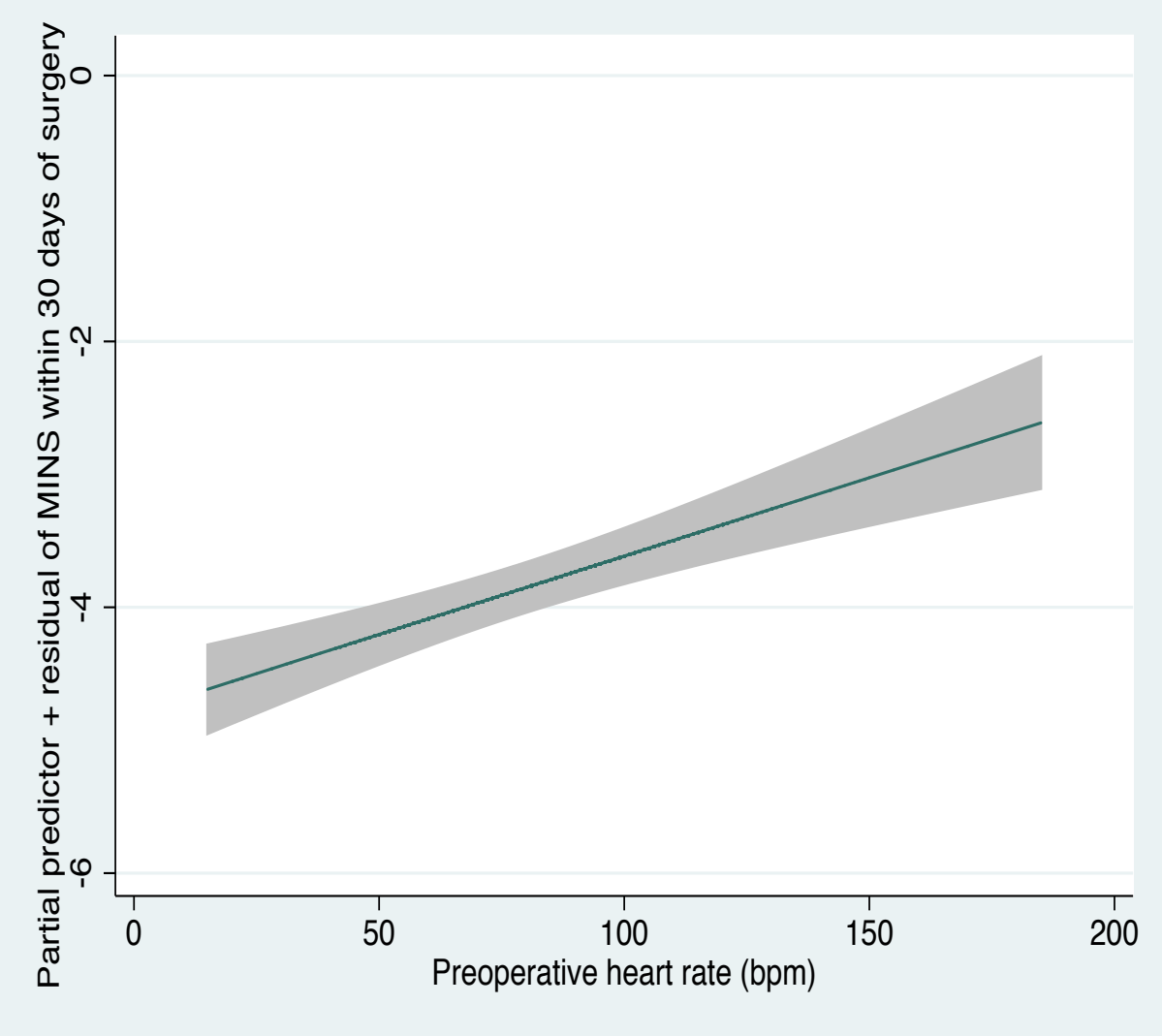

Figure 3.3. Function plot of the multivariable fractional polynomial logistic regression model. The x-axis shows preoperative heart rate and the y-axis is the partial predictor + residual. The grey region indicates the 95% confidence interval. The partial predictor is the heart rate component of the regression equation plus the intercept. The residual is the residual variation between the regression line and the observed data. The function plot shows how a given term in a regression model varies across the data range. Here, heart rate varies in a linear fashion, indicating a linear relationship with myocardial injury.

3.4 Discussion

The principal finding of this analysis is that elevated preoperative heart rate is associated with increased odds of MINS, MI, and death within 30 days of surgery. When I examined the entire range of heart rates, the highest decile (>96 bpm) was consistently associated with greater odds of each of these outcomes, while heart rate >87bpm was also associated with mortality. Heart rates in the first decile (<60 bpm) were associated with lower odds of mortality, but not MINS or MI. I found similar, but weaker, associations with pre-defined heart rate thresholds of >70 bpm and >104 bpm, which were identified from the existing general medical and perioperative literature. The absence of association between heart rates below the tenth decile and outcomes implies that the signal seen with the binary thresholds is predominantly due to higher event rates in patients with heart rates >96 bpm.

My results contrast with those of population-based studies in which incremental increases in resting heart rate are associated with higher long-term rates of cardiovascular events across the whole heart rate spectrum.[156, 331-333] While I observed a linear relationship between preoperative heart rate and myocardial injury, analysis of heart rate deciles suggests that this is due to associations at the extremes of the heart rate (i.e. very high or very low) and not across the entire data range. If a biologically plausible relationship exists between heart rate and clinical outcomes, it may have different profiles in patients undergoing surgery compared to the general population. This might be due to different underlying physiological mechanisms of harm, or due to the effect of perioperative factors superimposed on to a common pathophysiology. Consequently, my data suggests that previous perioperative studies using

arbitrary pre-defined heart rate thresholds may not accurately represent the relationship between heart rate and clinical outcomes, whilst the findings of population-based studies may not be generalisable to the perioperative period. My results raise the question of whether heart rate reduction is a potential therapeutic target to reduce the risk of perioperative cardiovascular events. However, a previous large randomised controlled trial found mortality and stroke risk was increased by beta-blocker therapy.[166] In my study, 2,727 (17.0%) patients received a beta-blocker or negatively chronotropic calcium channel blocker within 24 hours before surgery. After excluding these cases from the analysis, the independent association between heart rates >96 bpm and the outcomes remained. However, the potentially protective association between heart rates <60 bpm and mortality was no longer statistically significant, suggesting that the observed association may be confounded by rate-controlling medication (i.e. due to beta-blocker or calcium channel antagonists). Alternatively, this might suggest that rate-limiting medication was merely a marker of underlying heart disease. In either case, these data should be interpreted with caution since they are observational in nature and participants were not randomly assigned to heart rate control. Given this uncertainty, it is unclear whether therapeutic control of perioperative heart rate would influence clinical outcome.

The observed associations between elevated preoperative heart rate and postoperative outcomes are consistent with several plausible biological mechanisms by which tachycardia could promote cardiac complications.[97, 160] The majority of perioperative myocardial infarctions are thought to arise not from the rupture of atheromatous coronary plaque, as in the general population,

but as the result of protracted myocardial ischaemia.[96] The imbalance between myocardial oxygen supply and demand, and subsequent myocardial ischaemia, is proposed to be caused by multiple factors, including anaemia, hypotension and hypoxia.[96] In this model, anaemia and hypoxia could contribute to oxygen supply-demand imbalance by reducing the supply of oxygen to respiring tissue, for example due to impaired oxygen carrying capacity in anaemia or hypoxaemia as a result of respiratory insufficiency, which is not uncommon in the perioperative period. Hypotension can reduce coronary perfusion pressure, which could impair oxygen delivery to the myocardium.[75] However, the most prominent candidate mechanism of oxygen supply-demand imbalance is tachycardia, which could promote supply-demand imbalance by increasing oxygen consumption (demand) relative to a fixed supply, or at very high heart rates, reduced supply due to poor ventricular filling and impaired coronary perfusion.[75, 96, 97] This is supported by evidence from a study in anaesthetised dogs with fixed coronary stenoses where tachycardia-induced myocardial ischaemia for four hours caused sub-endocardial necrosis.[160]

Alternatively, elevated heart rate may simply be a marker of another, as yet unidentified, pathological process that causes myocardial injury. Tachycardia has multiple potential causes in the perioperative period, including: postoperative pain,[344] hypotension,[345, 346] autonomic nervous system dysfunction[85], systemic inflammation[277, 334, 347, 348] and reduction in heart rate limiting medications, some which could also cause myocardial injury.[96, 239] An association between heart rate *before* surgery and perioperative myocardial injury suggests that elevated heart rate may represent a distinct preoperative physiological state, pathology or chronic condition. For example, both heart

failure and autonomic nervous system dysfunction can cause tachycardia, either through sympathetic stimulation or parasympathetic inhibition in the case of autonomic dysfunction, or in response to impaired left ventricular stroke volume or impaired cardiac output in the case of heart failure.[85, 158] Both are associated with morbidity after surgery.[178, 349, 350] In this analysis, I was able to adjust for pre-existing symptomatic heart failure. However, there may be residual confounding by patients with undiagnosed or sub-clinical heart failure, and the prevalence of autonomic dysfunction in this cohort is unknown. In addition, whether or not sub-clincal heart failure or autonomic dysfunction are associated with perioperative myocardial injury has not been tested. Further research is needed to determine the underlying mechanism of perioperative myocardial injury and whether the association between heart rate and myocardial injury is causative in nature.

This analysis has several limitations. The influences of pre-medication and anxiety on heart rate are well established.[351-353] In an attempt to standardise the heart rate measurement, preoperative heart rate was recorded before and as close to the induction of anaesthesia as possible. The potential confounding influence of atrial fibrillation, the commonest population-based tachyarrhythmia, was assessed both through the adjustment of the multivariable models and a sensitivity analysis.[354, 355 340] Atrial fibrillation was present in only 6% of patients in the top decile and the removal of these cases had little impact on my findings. Nor did exclusion of patients taking beta-blockers or rate limiting calcium channel blockers, or patients undergoing emergency surgery. The strengths of my analyses derive from the multi-centre study design and large patient sample. The sample reflects a wide spectrum of non-cardiac surgery

taking place in hospitals in a number of countries, making the results relevant to the majority of surgical patients. The routine measurement of TnT allowed me to identify sub-clinical myocardial injury in addition to subjective clinical outcomes. I planned the statistical analysis before taking custody of the data and used multivariable models to correct for confounding factors. However, like all observational studies, my results may be susceptible to un-measured confounding. For example, the highest heart rate decile may include cases where the myocardial injury occurred before surgery, something we were unable to account for in our analysis.[114, 356, 357] Nor was the presence of a pacemaker recorded, although it is likely that these patients comprised only a small percentage of the study population.

3.5 Conclusion

Elevated preoperative heart rate was associated with MINS, MI and mortality within 30 days after surgery. This was primarily due to significantly higher event rates in patients amongst the highest decile of heart rate. However, it is unclear whether this represents a causative association or unmeasured confounding. Further research is needed to understand the relationship between heart rate and postoperative myocardial injury, and to clarify whether or not heart rate reduction in selected patient could reduce perioperative myocardial ischaemic events.

Chapter four

Preoperative pulse pressure

Preoperative pulse pressure and myocardial injury after non-cardiac surgery. A secondary analysis of data from a prospective international cohort study of myocardial injury after non-cardiac surgery.

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4.1 Introduction

The risk of perioperative cardiovascular complications associated with elevated arterial blood pressure before surgery is unclear.[189, 195, 201] Internationally, the prevalence of poorly controlled blood pressure in patients with hypertension is high, while a significant proportion of the general population have undiagnosed hypertension.[358] In England, ~7.8 million people are hypertensive (14% of the population), while a further ~5.6 million people are thought to have undiagnosed hypertension (10% of the population).[359] Thus, it is not uncommon for patients to present with high blood pressure on the day of surgery, and procedures are frequently cancelled at short notice as a result. [188, 190, 360] This scenario, familiar to both anaesthetists and surgeons, reflects widespread uncertainty about whether or not isolated elevated blood pressure readings increase the risk of perioperative cardiovascular complications.[190] Recent clinical guidelines suggest that surgery can be undertaken safely if the preoperative blood

pressure is below 160/110 mmHg.[188, 191] However, this guidance, which varies internationally,[192] is derived from a very limited evidence base constructed from small studies that use subjective clinical outcome measures, rather than objective biochemical markers of harm (e.g. troponin) and mortality.[201, 202]

In the general population, elevated pulse pressure - the difference between systolic and diastolic blood pressure – is associated with the subsequent development of myocardial infarction and congestive cardiac failure, independently of high systolic and diastolic blood pressures, and controlled hypertension (including 'white coat' hypertension).[147, 148, 212, 213] Pulse pressure reflects a composite of left ventricular stroke volume, cardiac contractility and arterial wall compliance, key factors that influence perioperative cardiovascular performance.[279, 281] Pulse pressure before surgery may therefore refine risk assessment for perioperative cardiovascular complications in patients undergoing non-cardiac surgery. However, preoperative pulse pressure has not been widely investigated.

I hypothesised that elevated pulse pressure was associated with an increased risk of myocardial injury within 30 days of non-cardiac surgery, independently of preoperative systolic arterial pressure.

4.2 Methods

I undertook a secondary analysis of the Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) study data set. VISION was a prospective international observational cohort study, which I have described in detail in chapter two (methods) and has been previously published.[16, 95, 273, 275]

Participants were aged 45 years or older and underwent non-cardiac surgery using general or regional anaesthesia, and with an expected overnight hospital stay. Researchers collected a detailed and standardised dataset from patients and their medical records, before and during the 30 days after surgery. A past history of hypertension was defined by a previous physician diagnosis. Clinical staff measured arterial blood pressure in millimetres of mercury (mmHg) as part of routine patient care according to local practice. Specific details of the equipment used to measure blood pressure are not available, although in most cases this will have been using the oscillometric, non-invasive technique.

4.2.1 Exposures of interest

Preoperative arterial blood pressure was defined as the systolic and diastolic arterial pressure measurements before and closest to the induction of anaesthesia. Preoperative arterial pulse pressure was defined as the arithmetic difference between preoperative systolic and diastolic arterial pressures.

4.2.2 Outcome measure

The primary outcome measure was myocardial injury after non-cardiac surgery (MINS), defined as any serum Troponin T (TnT) measurement ≥0.03ng/mL using a Roche 4th generation assay judged due to an ischaemic aetiology, within 30 days of surgery. This definition is used by the ESA-ESICM taskforce for perioperative clinical outcomes and was previously defined in the VISION study cohort.[16, 95, 113] I describe the TnT assay, blood sampling and adjudication of raised serum TnT concentrations, which have been published previously, in the methods chapter (chapter 2).[16, 95, 273, 275]

4.2.3 Statistical analysis

I planned the statistical analysis before taking custody of the data. I used SPSS version 22 (IBM, New York, USA) and STATA version 14 (StataCorp LP, Texas, USA) to analyse the data. The sample was ordered according to integer values of preoperative pulse pressure and divided into five approximately equal groups (quintiles) using cut-points closest to each 20th percentile. Participants with missing data were excluded by list-wise deletion. Baseline characteristics of the cohort were stratified by pulse pressure quintiles. Binary data were expressed as percentages, normally distributed continuous data as mean with standard deviation (SD) and non-normally distributed continuous data as median with interquartile range (IQR).

I used multivariable logistic regression analysis to test for association between pulse pressure and MINS. Pulse pressure quintiles were considered as an ordered categorical variable. To avoid isolating any single pulse pressure quintile as the reference group, deviation contrasts were used to compare each pulse pressure category to the un-weighted average effect across the whole sample.[338, 339] The models were corrected for potential confounding variables that were associated with myocardial injury or cardiac complications in previous perioperative studies: coronary artery disease, atrial fibrillation, heart failure, peripheral vascular disease, diabetes, age (45-64, 65-75, >75 years), previous stroke or transient ischaemic attack, chronic obstructive pulmonary disease, estimated glomerular filtration rate (eGFR), neurosurgery, urgent/emergency surgery and major surgery.[16, 20, 21, 95] eGFR was considered a categorical variable and divided into four groups (<30, 30-44, 45-60, >60 ml/min), to be consistent with previous research in the field.[16] The selection of covariates was

based on prior evidence of association with the dependent variable or similar clinical outcomes, rather than using univariable analysis or p-value based approaches.[361, 362] Covariates were treated as categorical variables. Odds ratios were converted to risk ratios using Grant's equation.[363]

4.2.4 Post-hoc analyses

To determine whether or not the relationship between elevated pulse pressure and myocardial injury was independent of systolic blood pressure I undertook a post-hoc analysis. The primary analysis was repeated including systolic blood pressure as a covariate in the multivariable model. Firstly, the sample was ranked by systolic blood pressure and divided into five approximately equal quintiles of preoperative systolic blood pressure, which were included in the statistical model using a deviation contrast. Secondly, the primary analysis was repeated including preoperative systolic blood pressure as a continuous variable in the multivariable model. Thirdly, the sample was stratified according to arterial pulse pressure >62mmHg (derived from the results of the primary analysis) and elevated systolic blood pressure of >160mmHg according to recent consensus guidelines.[188] To aid the comparison between systolic blood pressure and pulse pressure, I conducted a post-hoc analysis to identify a systolic blood pressure threshold associated with pulse pressure >62 mmHg. The sample was divided into ten approximately equal groups according to preoperative systolic blood pressure and the planned multivariable logistic regression analysis was repeated using systolic blood pressure deciles as the independent variable and pulse pressure >62 mmHg as the dependent variable.

4.2.5 Sensitivity analyses

Since hypertension is associated with cardiac complications and long-term mortality in the general population, I repeated the primary analysis using myocardial infarction (MI) and all-cause mortality within 30-days of surgery as additional outcome measures.[141] MI was defined by clinical criteria according to the third universal definition, comprising troponin elevation in the presence of clinical symptoms or dynamic electrocardiographic/echocardiographic changes suggestive of myocardial ischaemia.[113] Surgical procedures performed as an emergency carry a higher risk of morbidity and mortality.[10, 16] To account for potential confounding by urgency of surgery, I repeated the analysis excluding cases of emergency surgery. In the primary analysis, isolating an arbitrary group of multi-level categorical variables as the reference category in the logistic regression models was avoided, in order to reduce bias. However, to make my analysis comparable to other research using reference specific groups, the primary analysis was repeated using an indicator contrast with pulse pressure ≤45 mmHg as the reference group.[314] Patients with heart failure are at high risk of perioperative cardiovascular complications and heart failure can influence blood pressure and, by extension, pulse pressure. To determine whether or not the observed association was confounded by heart failure, the analysis was repeated including only patients with a pre-existing diagnosis of heart failure.[349, 350] To investigate the possibility of a non-linear relationship between pulse pressure and myocardial injury, I conducted a post-hoc analysis using multivariable fractional polynomial regression (chapter two - methods).[342, 364]

4.3 Results

16,079 patients were recruited into the study between 6th August 2007 and 11th January 2011. After excluding participants that were missing data for preoperative pulse pressure or myocardial injury, 15,057 remained (figure 4.1 and table 4.1). The mean age of participants was 65 (+/-11.8) years, 7,289 (48.4%) were male and the majority (85.9%) underwent elective surgery. The frequency of co-morbidities progressively increased across pulse pressure quintiles one to five (<45 mmHg, 46-53 mmHg, 54-62 mmHg, 63-75 mmHg and >75 mmHg; table 4.1). Advanced age, diabetes mellitus, pre-existing hypertension, previous stroke or TIA, peripheral vascular disease, and eGFR <30 ml/min/1.73m^2 were significantly more common in pulse pressure quintiles 4 and 5 compared to other quintiles of pulse pressure (table 4.2).

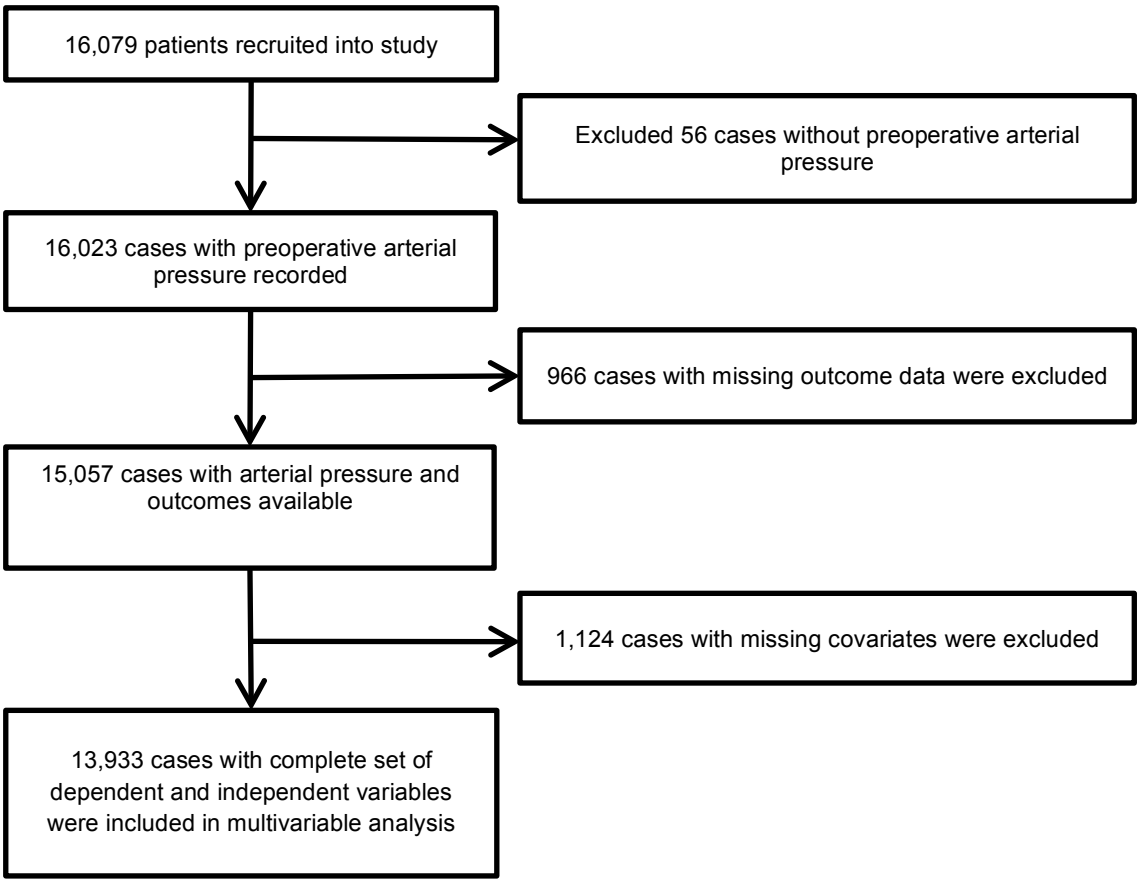

Figure 4.1 STROBE diagram showing the number of patients included and excluded from the primary analysis.[343]

Table 4.1. Baseline patient characteristics. Data stratified by preoperative pulse pressure quintiles, presented as frequencies with percentages (%) or means with standard deviations (SD). Data rounded to nearest whole number. Preoperative pulse pressure in mmHg. Estimated glomerular filtration rate (eGFR).

Preoperative pulse pressure (mmHg)	Whole cohort	≤45	46-53	54-62	63-75	>75
Number of cases (n)	15057	3448	2657	2949	2980	3023
Mean age (SD)	65 (11.8)	60 (10.7)	62 (11.0)	65 (11.4)	68 (11.3)	72 (10.9)
Sex						
Male (%)	7289 (48.4)	1799 (52.2)	1363 (51.3)	1426 (48.4)	1421 (47.7)	1280 (42.3)
Mean preoperative pulse pressure (SD)	60.5 (19.0)	38.3 (5.8)	49.7 (2.1)	58.2 (2.5)	68.7 (3.6)	89.5 (12.4)
Comorbid disorder (%)						
Atrial fibrillation	499 (3.3)	107 (3.1)	73 (2.7)	102 (3.5)	103 (3.5)	114 (3.8)
Diabetes	2934 (19.5)	447 (13.0)	418 (15.7)	595 (20.2)	634 (21.3)	840 (27.8)
Hypertension	7670 (50.9)	1252 (36.3)	1160 (43.7)	1494 (50.7)	1713 (57.5)	2051 (67.8)
Congestive cardiac failure	697 (4.6)	119 (3.5)	110 (4.1)	119 (4.0)	163 (5.5)	186 (6.2)
Coronary artery disease	1820 (12.1)	332 (9.6)	270 (10.2)	339 (11.5)	383 (12.9)	496 (16.4)
Peripheral vascular disease	799 (5.3)	119 (3.5)	111 (4.2)	130 (4.4)	169 (5.7)	270 (8.9)
Previous stroke or transient ischaemic attack	1067 (7.1)	129 (3.7)	122 (4.6)	198 (6.7)	257 (8.6)	361 (11.9)
Chronic obstructive pulmonary disease	1268 (8.4)	254 (7.4)	196 (7.4)	234 (7.9)	297 (10.0)	287 (9.5)
Active cancer	1917 (12.7)	451 (13.1)	364 (13.7)	379 (12.9)	385 (12.9)	338 (11.2)
Preoperative eGFR, ml/min/1.73m^{-2} (%)						
<30	514 (3.7)	88 (2.9)	61 (2.5)	73 (2.7)	116 (4.1)	176 (6.1)
30-44	751 (5.4)	114 (3.7)	91 (3.7)	126 (4.6)	156 (5.6)	264 (9.1)
45-60	1490 (10.7)	230 (7.5)	207 (8.5)	266 (9.8)	341 (12.2)	446 (15.4)
>60	11185 (80.2)	2648 (86.0)	2085 (85.3)	2261 (82.9)	2184 (78.1)	2007 (69.4)
Surgical procedure category (%)						
Elective	12935 (85.9)	2981 (86.5)	2313 (87.1)	2544 (86.3)	2556 (85.8)	2541 (84.1)
Urgent	430 (2.9)	86 (2.5)	80 (3.0)	96 (3.3)	77 (2.6)	91 (3.0)
Emergency	1692 (11.2)	381 (11.0)	264 (9.9)	309 (10.5)	347 (11.6)	391 (12.9)
Major surgery (%)	9096 (60.4)	1959 (56.8)	1540 (58.0)	1727 (58.6)	1910 (64.1)	1960 (64.8)
Outcome measures (%)						
Myocardial injury	1191 (7.9)	198 (5.7)	141 (5.3)	201 (6.8)	279 (9.4)	372 (12.3)

Table 4.2. Multivariable logistic regression models for preoperative pulse pressure >62 mmHg. Dependent variable is pulse pressure >62 mmHg. Results given as odds ratios with 95% confidence intervals.

	Pulse pressure > 62 mmHg	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	2.26 (2.07-2.45)	<0.01
>75	3.59 (3.26-3.96)	<0.01
Male sex	0.82 (0.76-0.88)	<0.01
History of atrial fibrillation	0.62 (0.51-0.75)	<0.01
History of diabetes	1.31 (1.20-1.43)	<0.01
History of hypertension	1.44 (1.34-1.56)	<0.01
History of heart failure	0.89 (0.76-1.05)	0.18
History of coronary artery disease	0.90 (0.81-1.01)	0.07
History of peripheral vascular disease	1.26 (1.08-1.47)	<0.01
History of stroke or transient ischaemic attack	1.45 (1.26-1.65)	<0.01
Preoperative eGFR (ml/min/1.73m^2)		
<30	1.39 (1.16-1.67)	<0.01
30-44	1.05 (0.90-1.23)	0.50
45-60	1.08 (0.97-1.22)	0.17
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.01 (0.89-1.14)	0.94
Neurosurgery	1.23 (1.06-1.42)	0.01
Urgent or emergency surgery	1.08 (0.98-1.20)	0.13
Major surgery	1.06 (0.98-1.14)	0.14

4.3.1 Primary analysis

Participants who were missing predefined covariates were excluded from the multivariable logistic regression analyses (figure 4.1). Myocardial injury was more frequent among participants in the two highest pulse pressure quintiles (>62 mmHg) compared to other quintiles. Preoperative pulse pressure >62 mmHg was associated with myocardial injury amongst patients in quintile 4 (63-75 mmHg, RR 1.14 [1.01-1.28]; p=0.03), and quintile 5 (>75 mmHg, RR 1.15 [1.03-1.29]; p=0.02) independent of confounding factors (table 4.3 and figure 4.2). Pulse pressure of 46-53 mmHg was associated with reduced incidence of myocardial injury (RR 0.83 [0.72-0.96]; p=0.02).

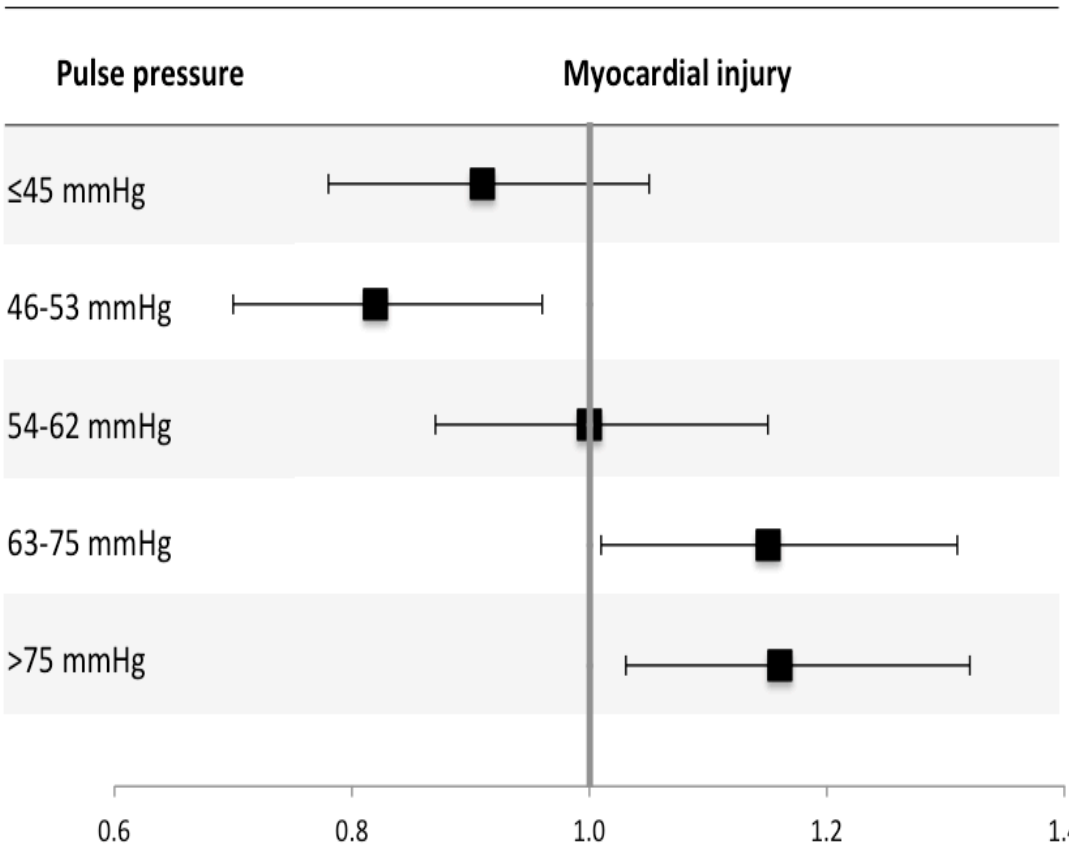

Figure 4.2. Forest plot showing the relative odds of myocardial injury for each quintile of preoperative pulse pressure. The x-axis shows odds ratios for myocardial injury within 30 days of surgery. The full statistical model is presented in table 4.3.

Table 4.3. Multivariable logistic regression models for preoperative pulse pressure. Dependent variable is myocardial injury within 30 days of surgery. Preoperative pulse pressure was divided into quintiles and treated as a categorical variable. Results given as odds ratios with 95% confidence intervals. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	1.02 (0.84-1.22)	0.87
>75	1.88 (1.57-2.25)	<0.01
Male sex	1.39 (1.21-1.59)	<0.01
History of atrial fibrillation	1.67 (1.28-2.17)	<0.01
History of diabetes	1.38 (1.18-1.60)	<0.01
History of hypertension	1.28 (1.09-1.50)	<0.01
History of heart failure	1.59 (1.27-2.00)	<0.01
History of coronary artery disease	1.45 (1.22-1.71)	<0.01
History of peripheral vascular disease	2.13 (1.74-2.61)	<0.01
History of stroke or transient ischaemic attack	1.43 (1.18-1.74)	<0.01
Preoperative eGFR (ml/min/1.73m^2)		
<30	10.78 (8.73-13.32)	<0.01
30-44	2.55 (2.06-3.17)	<0.01
45-60	1.67 (1.38-2.03)	<0.01
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.21 (0.99-1.48)	0.06
Neurosurgery	1.10 (0.84-1.45)	0.48
Urgent or emergency surgery	1.97 (1.67-2.32)	<0.01
Major Surgery	1.68 (1.44-1.96)	<0.01
Pulse pressure quintiles (mmHg)		
≤45	0.91 (0.78-1.05)	0.20
46-53	0.82 (0.70-0.96)	0.02
54-62	1.00 (0.87-1.15)	0.96
63-75	1.15 (1.01-1.31)	0.03
>75	1.16 (1.03-1.32)	0.02

4.3.2 Post-hoc analyses

When I repeated the primary multivariable analysis adjusted for preoperative systolic blood pressure divided into quintiles and considered as an ordered categorical variable, pulse pressure 63-75 mmHg and >75 mmHg remained associated with myocardial injury (RRs 1.20 [1.05-1.37]; p<0.01 and 1.25 [1.06-1.48]; p<0.01 respectively). However, preoperative systolic blood pressure was not associated with myocardial injury (table 4.4 and figure 4.3). When the primary multivariable analysis was repeated adjusting for preoperative systolic blood pressure as a continuous variable, elevated pulse pressure remained associated with myocardial injury, but systolic blood pressure was not associated with myocardial injury (table 5.5). When I stratified the cohort by pulse pressure >62 mmHg and systolic blood pressure >160 mmHg, pulse pressure >62 mmHg was independently associated with myocardial injury, irrespective of systolic blood pressure (table 4.6). Multivariable logistic regression analysis showed that systolic blood pressures >139 mmHg were independently associated with pulse pressure >62 mmHg (table 4.7).

Table 4.4. Multivariable logistic regression model to predict myocardial injury after non-cardiac surgery. Dependent variable is myocardial injury within 30 days of surgery. Preoperative pulse pressure was divided into quintiles and treated as a categorical variable. Preoperative systolic blood pressure was divided into quintiles and included as a covariate. Results given as odds ratios with 95% confidence intervals. Estimated glomerular filtration rate (eGFR).

Covariates	odds ratio	p-value
Age (years)		
45-64 (reference)	-	-
65-75	1.01 (0.84-1.22)	0.93
>75	1.86 (1.55-2.23)	<0.01
Male sex	1.40 (1.22-1.60)	<0.01
History of atrial fibrillation	1.67 (1.29-2.17)	<0.01
History of diabetes	1.37 (1.18-1.60)	<0.01
History of hypertension	1.29 (1.10-1.51)	<0.01
History of heart failure	1.58 (1.25-1.98)	<0.01
History of coronary artery disease	1.44 (1.21-1.70)	<0.01
History of peripheral vascular disease	2.13 (1.74-2.60)	<0.01
History of stroke or transient ischaemic attack	1.44 (1.18-1.75)	<0.01
Preoperative eGFR (ml/min/1.73m^2)		
<30	10.70 (8.66-13.22)	<0.01
30-44	2.56 (2.06-3.17)	<0.01
45-60	1.67 (1.38-2.03)	<0.01
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.20 (0.98-1.47)	0.08
Neurosurgery	1.11 (0.84-1.46)	0.47
Urgent or emergency surgery	1.97 (1.67-2.32)	<0.01
Major surgery	1.68 (1.44-1.97)	<0.01
Systolic blood pressure quintiles (mmHg)		
<120	1.07 (0.91-1.24)	0.43
120-131	1.19 (0.97-1.44)	0.09
132-143	0.95 (0.83-1.10)	0.52
144-159	0.93 (0.80-1.07)	0.29
≥160	0.90 (0.75-1.07)	0.24
Pulse pressure quintiles (mmHg)		
≤45	0.81 (0.67-0.98)	0.03
46-53	0.78 (0.66-0.93)	<0.01
54-62	1.01 (0.87-1.17)	0.91
63-75	1.22 (1.06-1.41)	<0.01
>75	1.28 (1.07-1.54)	<0.01

Figure 4.3. Forest plot showing the relative odds of myocardial injury for each quintile of preoperative pulse pressure, adjusted for quintiles of preoperative systolic pressure. The x-axis shows odds ratios for myocardial injury within 30 days of surgery. The full statistical model is presented in table 4.4.

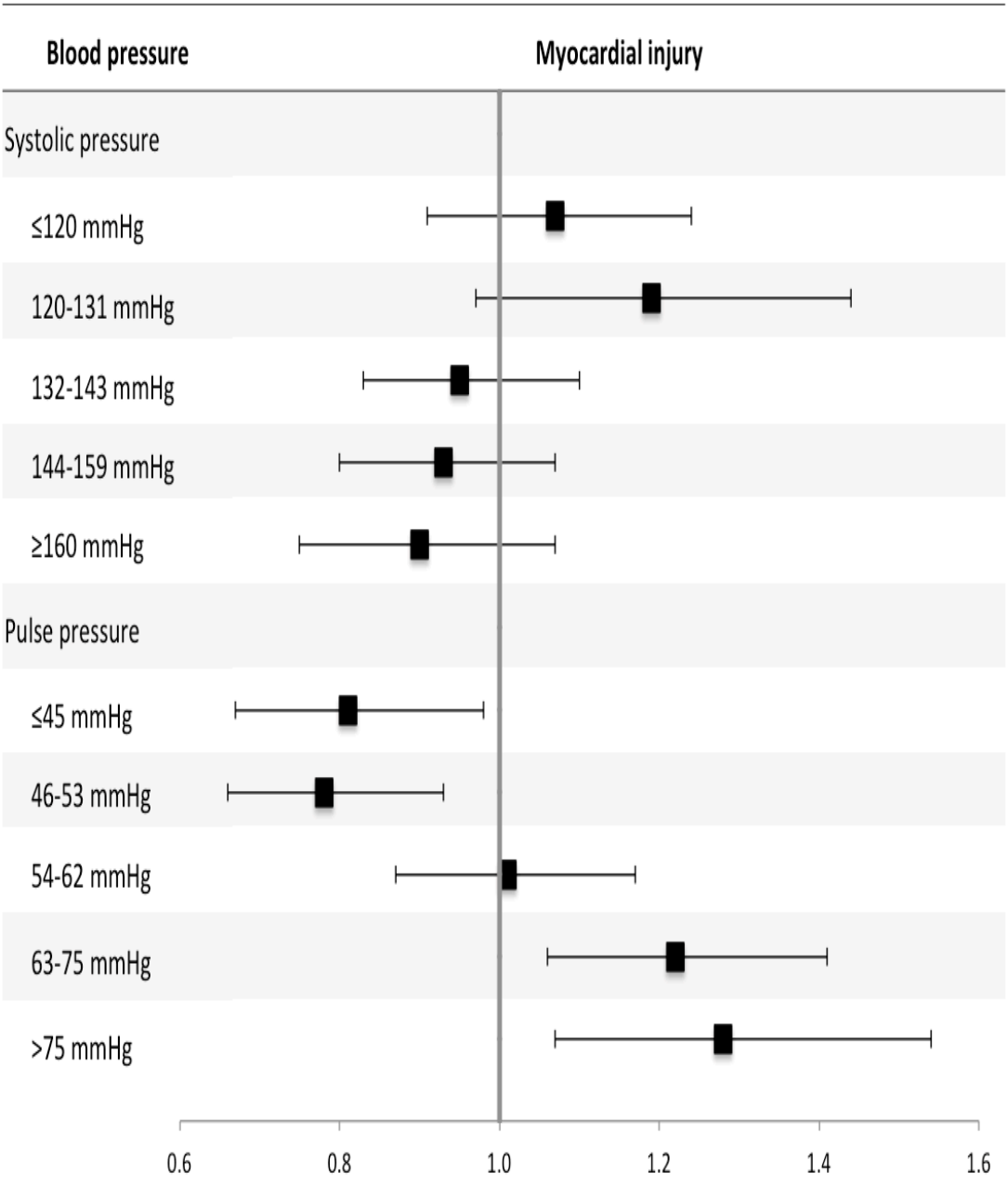

Table 4.5. Sensitivity analysis including systolic blood pressure as a continuous variable. Dependent variable is myocardial injury within 30 days of surgery. Results presented as odds ratios with 95% confidence intervals.

	Myocardial injury	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	1.01 (0.84-1.22)	0.92
>75	1.87 (1.56-2.24)	<0.01
Male sex	1.39 (1.21-1.60)	<0.01
History of atrial fibrillation	1.67 (1.28-2.17)	<0.01
History of diabetes	1.37 (1.18-1.60)	<0.01
History of hypertension	1.39 (1.10-1.51)	<0.01
History of heart failure	1.59 (1.26-1.99)	<0.01
History of coronary artery disease	1.44 (1.22-1.70)	<0.01
History of peripheral vascular disease	2.13 (1.74-2.61)	<0.01
History of stroke or transient ischaemic attack	1.44 (1.18-1.75)	<0.01
Preoperative eGFR (ml/min/1.73m^2)		
<30	10.74 (8.69-13.27)	<0.01
30-44	2.55 (2.06-3.17)	<0.01
45-60	1.67 (1.38-2.02)	<0.01
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.20 (0.98-1.47)	0.07
Neurosurgery	1.11 (0.84-1.46)	0.46
Urgent or emergency surgery	1.97 (1.68-2.32)	<0.01
Major surgery	1.68 (1.44-1.96)	<0.01
Systolic blood pressure (mmHg)	0.99 (0.99-1.00)	0.19
Pulse pressure quintiles (mmHg)		
≤45	0.85 (0.70-1.01)	0.07
46-53	0.79 (0.67-0.94)	<0.01
54-62	0.99 (0.86-1.15)	0.94
63-75	1.18 (1.03-1.35)	0.02
>75	1.27 (1.06-1.52)	<0.01

Table 4.6. Multivariable logistic regression models for preoperative pulse pressure and hypertension status. The dependent variable is myocardial injury within 30 days of surgery. The sample was divided into four groups according to preoperative pulse pressure (PP) and preoperative systolic blood pressure (SBP): (1) systolic blood pressure ≤160mmHg and preoperative pulse pressure ≤62mmHg, (2) systolic blood pressure >160mmHg and preoperative pulse pressure ≤62mmHg, (3) systolic blood pressure ≤160mmHg and preoperative pulse pressure >62mmHg and (4) systolic blood pressure >160mmHg and preoperative pulse pressure >62mmHg. The reference category was systolic blood pressure ≤160mmHg and preoperative pulse pressure ≤62mmHg. Results given as odds ratios with 95% confidence intervals. eGFR = estimated glomerular filtration rate.

	Myocardial Injury	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	1.02 (0.85-1.23)	0.82
>75	1.90 (1.59-2.27)	<0.01
Male sex	1.38 (1.20-1.59)	<0.01
History of atrial fibrillation	1.67 (1.29-2.17)	<0.01
History of diabetes	1.38 (1.19-1.61)	<0.01
History of hypertension	1.29 (1.10-1.51)	<0.01
History of heart failure	1.58 (1.26-1.99)	<0.01
History of coronary artery disease	1.45 (1.22-1.71)	<0.01
History of peripheral vascular disease	2.14 (1.75-2.62)	<0.01
History of stroke or transient ischaemic attack	1.44 (1.19-1.76)	<0.01
Preoperative eGFR (ml/min/1.73m^2)		
<30	10.75 (8.70-13.28)	<0.01
30-44	2.55 (2.06-3.16)	<0.01
45-60	1.67 (1.39-2.03)	<0.01
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.21 (0.99-1.48)	0.06
Neurosurgery	1.11 (0.85-1.47)	0.45
Urgent or emergency surgery	1.98 (1.68-2.32)	<0.01
Major surgery	1.68 (1.44-1.96)	<0.01
Pulse pressure and hypertension status		
SBP ≤160mmHg, PP≤62mmHg (reference)	-	-
SBP >160mmHg, PP≤62mmHg	0.66 (0.29-1.48)	0.31
SBP ≤160mmHg, PP>62mmHg	1.27 (1.08-1.49)	<0.01
SBP >160mmHg, PP>62mmHg	1.23 (1.03-1.46)	0.02

Table 4.7. Multivariable logistic regression model to predict pulse pressure >62 mmHg. Dependent variable is pulse pressure >62 mmHg. Number of cases with pulse pressure >62mmHg and the total for each covariate. Results are reported as odds ratios with 95% confidence intervals.

	Pulse pressure > 62 mmHg		
Covariates	**Number of cases/total**	**odds ratio**	**p-value**
Age (years)			
45-64 (reference)	1950/7467	-	-
65-75	1955/4133	2.11 (1.87-2.38)	<0.01
>75	2098/1359	3.43 (2.99-3.94)	<0.01
Male sex	2701/7289	0.64 (0.58-0.71)	<0.01
History of atrial fibrillation	217/499	0.72 (0.55-0.95)	0.02
History of diabetes	1474/2934	1.28 (1.13-1.45)	<0.01
History of hypertension	3764/7670	0.96 (0.86-1.07)	0.42
History of heart failure	349/697	1.21 (0.95-1.53)	0.13
History of coronary artery disease	879/1820	1.21 (1.03-1.42)	0.18
History of peripheral vascular disease	439/799	1.24 (0.99-1.51)	0.06
History of stroke or transient ischaemic attack	618/1067	1.12 (0.92-1.36)	0.26
Preoperative eGFR (ml/min/1.73m^2)			
<30	292/514	1.74 (1.31-2.31)	<0.01
30-44	420/751	0.97 (0.78-1.22)	0.79
45-60	787/1490	1.10 (0.94-1.30)	0.24
>60 (reference)	4191/11185	-	-
History of chronic obstructive pulmonary disease	584/1268	1.52 (1.27-1.81)	<0.01
Neurosurgery	395/975	1.00 (0.81-1.24)	1.00
Urgent or emergency surgery	906/2122	0.93 (0.80-1.08)	0.33
Major surgery	3870/9096	1.19 (1.07-1.32)	<0.01
Systolic blood pressure groups (mmHg)			
≤110	101/1693	0.14 (0.12-0.18)	<0.01
111-119	9/1548	0.01 (0.01-0.06)	<0.01
120-125	31/1266	0.05 (0.04-0.07)	<0.01
126-131	220/1584	0.33 (0.28-0.39)	<0.01
132-138	378/1522	0.67 (0.58-0.78)	<0.01
139-143	555/1486	1.26 (1.10-1.45)	0.01
144-150	988/1692	3.08 (2.69-3.53)	<0.01
151-159	966/1314	6.22 (5.33-7.26)	<0.01
160-171	1306/1477	16.83 (14.05-20.17)	<0.01

4.3.3 Sensitivity analyses

When I excluded cases where surgery was performed as an emergency (table 4.8), pulse pressure >75 mmHg remained associated with myocardial injury (RR 1.20 [1.06-1.36]; p<0.01). However, the association between pulse pressure 63-75 mmHg and myocardial injury was not significant (RR 1.14 [1.00-1.29]; p=0.058). When I repeated the analysis using an indicator contrast (i.e. comparison with a reference group rather than cohort average) with pulse pressure ≤45 mmHg as the reference group the results were similar (table 4.9). When I repeated the analysis for only participants with a pre-existing diagnosis of heart failure, I observed no association between pulse pressure and myocardial injury (table 4.10). When I repeated the main analysis for the additional outcome measures myocardial infarction and mortality, I excluded participants with missing independent and dependent variables: 452/15,975 (2.8%) participants sustained myocardial infarction and 313/16,005 (2.0%) died. Pulse pressure of >75 mmHg was associated with myocardial infarction (RR 1.26 [1.07-1.50]; p<0.01), but pulse pressure was not associated with mortality (table 4.11).

Table 4.8. Sensitivity analysis excluding emergency cases. Multivariable logistic regression models for preoperative pulse pressure. Dependent variable is myocardial injury within 30 days of surgery. Preoperative pulse pressure was divided into quintiles and treated as a categorical variable. Results given as odds ratios with 95% confidence intervals.

	Myocardial Injury	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	1.02 (0.28-1.24)	0.88
>75	1.86 (1.53-2.27)	<0.01
Male sex	1.40 (1.21-1.64)	<0.01
History of atrial fibrillation	2.07 (1.56-2.74)	<0.01
History of diabetes	1.31 (1.11-1.56)	<0.01
History of hypertension	1.20 (1.01-1.44)	0.04
History of heart failure	1.46 (1.14-1.88)	<0.01
History of coronary artery disease	1.52 (1.26-1.82)	<0.01
History of peripheral vascular disease	2.00 (1.60-2.51)	<0.01
History of stroke or transient ischaemic attack	1.47 (1.88-1.83)	<0.01
Preoperative eGFR (ml/min/1.73m^2)		
<30	11.69 (9.24-14.80)	<0.01
30-44	2.72 (2.15-3.47)	<0.01
45-60	1.64 (1.32-2.03)	<0.01
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.28 (1.03-1.59)	0.03
Neurosurgery	1.08 (0.81-1.45)	0.60
Urgent or emergency surgery	2.21 (1.60-3.04)	<0.01
Major surgery	1.70 (1.44-2.02)	<0.01
Pulse pressure quintiles (mmHg)		
≤45	0.86 (0.73-1.01)	0.07
46-53	0.81 (0.68-0.97)	0.02
54-62	1.03 (0.88-1.20)	0.71
63-75	1.15 (1.00-1.32)	0.06
>75	1.22 (1.07-1.40)	<0.01

Table 4.9. Sensitivity analysis using indicator contrast with pulse pressure less than 45 mmHg as the reference category. Multivariable logistic regression models for preoperative pulse pressure. Dependent variable is myocardial injury within 30 days of surgery. Results presented as odds ratios with 95% confidence intervals.

	Myocardial injury	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	1.02 (0.84-1.22)	0.87
>75	1.88 (1.57-2.25)	<0.01
Male sex	1.39 (1.21-1.59)	<0.01
History of atrial fibrillation	1.67 (1.28-2.17)	<0.01
History of diabetes	1.38 (1.18-1.60)	<0.01
History of hypertension	1.28 (1.09-1.50)	<0.01
History of heart failure	1.59 (1.27-2.00)	<0.01
History of coronary artery disease	1.45 (1.22-1.71)	<0.01
History of peripheral vascular disease	2.13 (1.74-2.61)	<0.01
History of stroke or transient ischaemic attack	1.43 (1.18-1.74)	<0.01
Preoperative eGFR ($ml/min/1.73m^2$)		
<30	10.78 (8.73-13.32)	<0.01
30-44	2.55 (2.06-3.17)	<0.01
45-60	1.67 (1.38-2.03)	<0.01
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.21 (0.99-1.48)	0.06
Neurosurgery	1.10 (0.84-1.45)	0.48
Urgent or emergency surgery	1.97 (1.67-2.32)	<0.01
Major surgery	1.68 (1.44-1.96)	<0.01
Pulse pressure quintiles (mmHg)		
≤45	-	-
46-53	0.90 (0.70-1.16)	0.43
54-62	1.11 (0.88-1.39)	0.39
63-75	1.27 (1.02-1.58)	0.03
>75	1.28 (1.04-1.59)	0.02

Table 4.10. Sensitivity analysis including only participants with a pre-existing diagnosis of heart failure. Multivariable logistic regression models for preoperative pulse pressure. Dependent variable is myocardial injury within 30 days of surgery. Results presented as odds ratios with 95% confidence intervals.

	Myocardial injury	
Covariates	**odds ratio**	**p-value**
Age (years)		
45-64 (reference)	-	-
65-75	0.35 (0.18-0.68)	<0.01
>75	1.03 (0.59-1.79)	0.92
Male sex	1.74 (1.14-2.67)	0.01
History of atrial fibrillation	1.10 (0.68-1.80)	0.69
History of diabetes	1.04 (0.66-1.62)	0.87
History of hypertension	1.01 (0.57-1.81)	0.96
History of coronary artery disease	1.21 (0.80-1.85)	0.37
History of peripheral vascular disease	3.50 (2.05-6.00)	<0.01
History of stroke or transient ischaemic attack	1.71 (1.03-2.82)	0.04
Preoperative eGFR (ml/min/1.73m^2)		
<30	7.53 (4.39-12.92)	<0.01
30-44	2.19 (1.24-3.85)	<0.01
45-60	1.09 (0.58-2.06)	0.79
>60 (reference)	-	-
History of chronic obstructive pulmonary disease	1.00 (0.61-1.62)	0.99
Neurosurgery	0.74 (0.28-1.95)	0.55
Urgent or emergency surgery	2.22 (1.33-3.69)	<0.01
Major surgery	1.39 (0.88-2.19)	0.16
Pulse pressure quintiles (mmHg)		
≤45	0.97 (0.62-1.51)	0.88
46-53	0.97 (0.61-1.55)	0.91
54-62	0.94 (0.60-1.45)	0.76
63-75	1.08 (0.74-1.59)	0.69
>75	1.05 (0.73-1.52)	0.79

Table 4.11. Sensitivity analysis including all cases for dependent variables myocardial infarction and mortality within 30 days of surgery. Multivariable logistic regression models for preoperative pulse pressure. Preoperative pulse pressure was divided into quintiles and treated as a categorical variable. Results given as odds ratios with 95% confidence intervals.

	Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)				
45-64 (reference)	-	-	-	-
65-75	1.08 (0.81-1.44)	0.59	1.65 (1.17-2.32)	<0.01
>75	1.69 (1.28-2.22)	<0.01	2.45 (1.74-3.45)	<0.01
Male sex	1.04 (0.84-1.28)	0.73	1.17 (0.92-1.50)	0.21
History of atrial fibrillation	1.42 (0.99-2.04)	0.05	1.12 (0.70-1.81)	0.63
History of diabetes	1.20 (0.96-1.50)	0.12	1.04 (0.78-1.39)	0.79
History of hypertension	1.34 (1.05-1.72)	0.02	0.99 (0.75-1.30)	0.92
History of heart failure	1.68 (1.25-2.27)	<0.01	1.33 (0.88-2.01)	0.18
History of coronary artery disease	2.18 (1.73-2.75)	<0.01	0.85 (0.61-1.18)	0.33
History of peripheral vascular disease	2.08 (1.58-2.75)	<0.01	1.80 (1.25-2.59)	<0.01
History of stroke or transient ischaemic attack	1.11 (0.83-1.48)	0.48	1.59 (1.14-2.22)	<0.01
Preoperative eGFR (ml/min/1.73m^2)				
<30	4.00 (2.98-5.38)	<0.01	3.25 (2.23-4.75)	<0.01
30-44	1.74 (1.26-2.41)	<0.01	1.71 (1.15-2.53)	<0.01
45-60	1.39 (1.04-1.87)	0.03	0.94 (0.63-1.40)	0.77
>60 (reference)	-	-	-	-
History of chronic obstructive pulmonary disease	1.15 (0.86-1.53)	0.36	2.02 (1.47-2.77)	<0.01
Neurosurgery	0.56 (0.34-0.95)	0.03	1.67 (1.08-2.57)	0.02
Urgent or emergency surgery	2.35 (1.88-2.94)	<0.01	3.93 (3.06-5.03)	<0.01
Major Surgery	2.22 (1.74-2.85)	<0.01	1.61 (1.20-2.14)	<0.01
Pulse pressure quintiles (mmHg)				
≤45	0.86 (0.68-1.09)	0.21	1.26 (0.99-1.60)	0.06
46-53	0.88 (0.69-1.12)	0.30	1.18 (0.91-1.52)	0.22
54-62	0.95 (0.77-1.18)	0.66	0.82 (0.63-1.07)	0.14
63-75	1.09 (0.90-1.32)	0.39	0.98 (0.78-1.24)	0.89
>75	1.27 (1.07-1.52)	<0.01	0.84 (0.67-1.06)	0.14

4.3.3 Fractional polynomial analysis

Multivariable fractional polynomial regression analysis confirmed that the relationship between increasing pulse pressure and the probability of myocardial injury was linear in nature (figure 4.4).

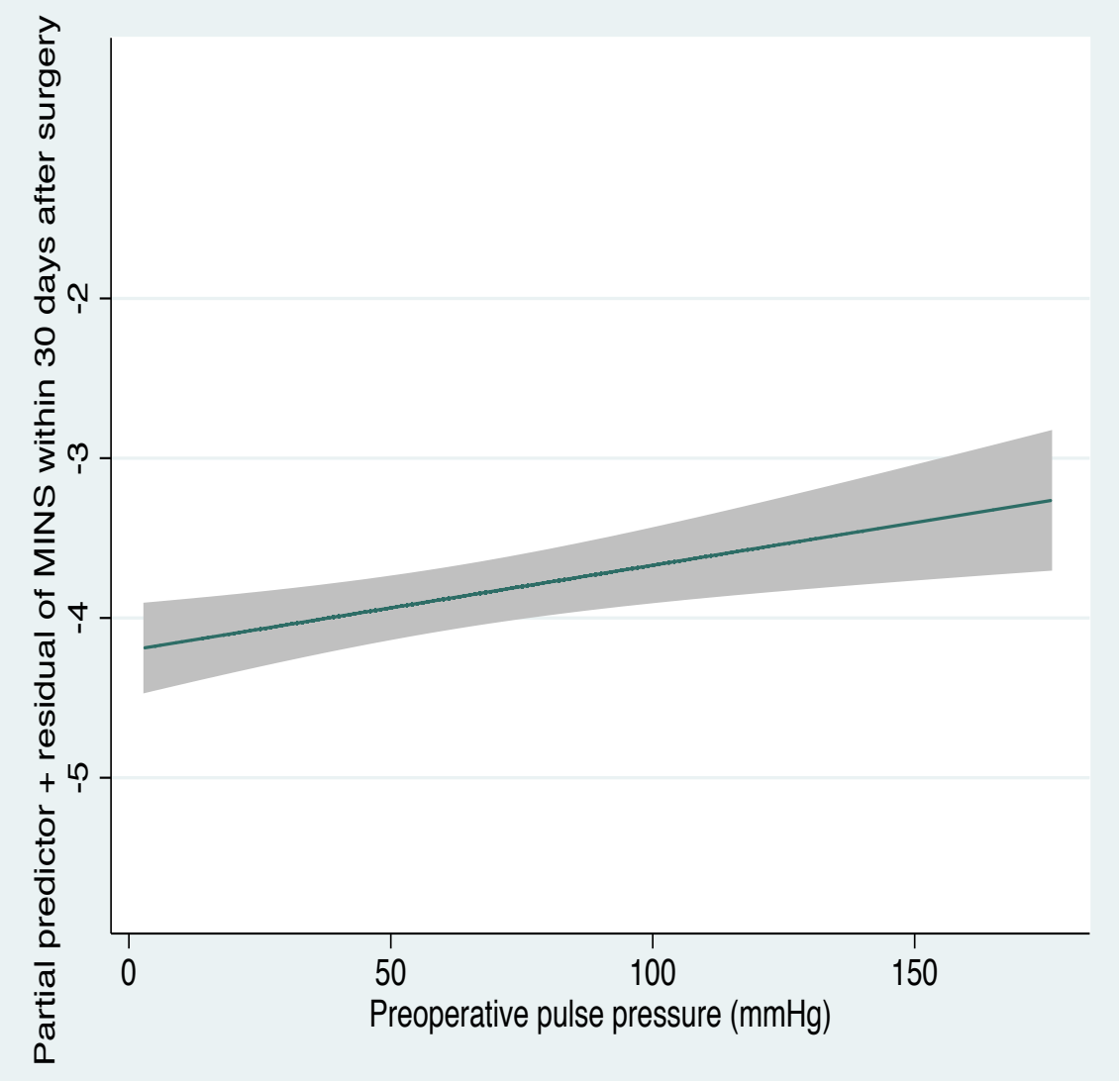

Figure 4.4. Function plot of the one-term multivariable fractional polynomial logistic regression model. The x-axis shows preoperative pulse pressure in mmHg and the y-axis is the partial predictor + residual. The grey region indicates the 95% confidence interval. The partial predictor is the pulse pressure component of the regression equation plus the intercept. The residual is the residual variation between the regression line and the observed data. The function plot shows how a given term in a regression model varies across the data range. The data suggest a linear relationship between pulse pressure and myocardial injury.

5.4 Discussion

The principal finding of this analysis of ~14,000 patients is that elevated preoperative pulse pressure (>62 mmHg) occurred in two out of every five patients and is associated with myocardial injury, defined as TnT ≥0.03ng/mL judged due to an ischaemic aetiology within 30 days after non-cardiac surgery. This association persists after adjusting for preoperative systolic blood pressure. Patients with elevated preoperative systolic blood pressure (>160 mmHg) were only at increased risk of myocardial injury if the preoperative pulse pressure was >62 mmHg.

A preoperative diagnosis of arterial hypertension has been reported to have a small but significant influence on cardiovascular morbidity following non-cardiac surgery,[200, 365, 366] However, previous studies were heterogeneous and did not use a robust, independently prognostic biomarker for myocardial injury (troponin) as the primary endpoint or undertake prospective data collection in a large selection of patients. Consequently, the impact of high blood pressure immediately before surgery has remained unclear.[367-369] My data suggest that, in the preoperative setting, pulse pressure is a better predictor of the development of myocardial injury, compared to systolic blood pressure. Whilst the degree of association between elevated pulse pressure and myocardial injury was modest, due to the high volume of surgical treatment (~8 million in the UK per year), this could still have a clinically significant impact on patient outcomes.[19] At the population level, small increases in risk from multiple independent factors are widely considered to be central to the development of non-communicable disease. This thesis centres around identifying simple

exposures that could be used to predict, or modified to prevent or treat, perioperative disease.

This analysis identifies a relationship between preoperative pulse pressure and perioperative myocardial injury, an association that is independent of age and systolic blood pressure. Several large, international non-operative registry studies have reported that elevated pulse pressure confers increased risk of multiple adverse cardiovascular events independent of systolic blood pressure.[147, 148, 212, 213] Pulse pressure widens with age as a result of increasing systolic and falling diastolic blood pressures. In the Framingham study, increasing age was associated with a shift from diastolic to systolic blood pressure, and then to pulse pressure, as the predominant predictor of cardiovascular disease.[143] The prospective cardiovascular Münster (PROCAM) study reported that normotensive older men with higher pulse pressure were at increased risk of cardiac events, similar to the increased risk of myocardial injury in elderly men I found in this analysis.[147]

The underlying pathophysiological mechanisms that link pulse pressure to myocardial injury may be explained by four different, but potentially interlinked, mechanisms. Firstly, elevated systolic blood pressure can cause left ventricular hypertrophy and increase end-systolic myocardial stress, which are independently associated with cardiovascular mortality.[216, 217] Secondly, lower diastolic blood pressure relative to left ventricular end-diastolic pressure reduces coronary perfusion pressure and oxygen supply to the myocardium,[218] which may promote myocardial ischaemia.[147, 217] Thirdly, elevated pulse pressure is associated with smaller aortic lumen areas, and larger end-diastolic

left ventricular volumes suggesting that patients with high pulse pressures may have aorto-ventricular decoupling, characterised by a larger cardiac output than can be accommodated by the gauge of the aorta.[214, 370] It is plausible that aorto-ventricular decoupling could be exacerbated by fluid shifts or inotropic agents commonly seen in the perioperative period, which may lead to ventricular overload and impaired cardiac output, despite preserved systolic function. This could explain the increased risk of morbidity in patients with elevated pulse pressure, since impaired cardiac output in the perioperative period is associated with increased organ dysfunction and poorer clinical outcomes.[279, 281] Fourthly, arterial blood pressure is regulated by baroreceptors, which detect arterial wall stretch on a beat-by-beat basis.[75] Elevated pulse pressure is associated with increased aortic wall stiffness,[214] and impaired baroreflex sensitivity (a biomarker of parasympathetic dysfunction) in elderly men and women,[215] healthy middle-aged volunteers,[371] and patients with diabetes mellitus.[372] Impaired baroreflex sensitivity is a principal cause of labile hypertension[373] and is associated with cardiovascular morbidity after major surgery.[178] Therefore the observed association between elevated pulse pressure and myocardial injury could be explained by parasympathetic dysfunction.

My analysis has several strengths. This is one of the largest prospective cohort studies to investigate the influence of blood pressure immediately prior to surgery on clinical outcomes after non-cardiac surgery.[374] The sample included patients undergoing a variety of non-cardiac surgical procedures at multiple international centres, so my results are relevant to the majority of patients having non-cardiac surgery. The large sample size allowed adjustment for a large number of confounding variables, including systolic blood pressure.

However, there may be residual, un-measured confounding. The primary outcome measure, myocardial injury, is an objective biochemical endpoint that lacks the subjectivity associated with clinical outcome measures used in previous studies.[198, 202]

My analysis also has several weaknesses. Preoperative arterial blood pressure was measured by local clinical staff at each participating hospital before the induction of anaesthesia. The oscillometric technique was used in the majority of cases, but the specific measurement apparatus, timing and location of measurement varied between centres and the exact details are not known. Since this was intended to be a pragmatic analysis, I do not believe this adversely affected the results or interpretation. However, non-invasive blood pressure measurement is less reliable that intra-arterial measurement.[375] It is possible that pre-medication could influence preoperative arterial blood pressure, although the practice of premedication is uncommon in participating centres (particularly since recent evidence shows that preoperative sedation fails to improve outcomes).[376] Omission of usual anti-hypertensive therapy before surgery, for example angiotensin converting enzyme inhibitors, may have contributed to high blood pressure readings in patients with established hypertension. However, I did not have access to these data and so was unable to perform sensitivity analyses to address this question. The association between elevated pulse pressure and myocardial injury appeared independent of urgency of surgery, which is a potential confounding variable, due to expected lower preoperative blood pressures as a result of sepsis or blood loss. The data used in this analysis was derived from the first VISION study cohort and so preoperative troponin measurements were not available.[16, 115] Therefore

the incidence of preoperative myocardial injury is unknown, although I would only expect this to occur in a small proportion of cases.[377] The analysis was repeated using myocardial infarction and mortality as outcome measures, to aid comparisons within the perioperative literature. However, myocardial infarction is a clinically derived outcome and is subject to bias. I attempted to limit this by using standard definitions and excluding this from the main analysis.

The association between pulse pressure and myocardial injury was lost when the analysis was restricted only to participants with a confirmed diagnosis of heart failure. This is counterintuitive since lower pulse pressure is independently associated with mortality in patients with reduced ejection fraction heart failure, so I had expected to observe a negative association between increasing pulse pressure and risk of myocardial injury.[72] The results are more consistent with the more variable relationship between pulse pressure and clinical outcomes in patients with preserved ejection fraction heart failure.[72, 378] Therefore, the data may reflect un-measured heterogeneity within the cohort of patients with diagnosed heart failure in this data set. However, in the absence of routine preoperative echocardiography in the VISION cohort, it is not possible to comment on whether there were differences in the relationship between pulse pressure and myocardial injury in patients with preserved or reduced ejection fraction heart failure. I am also unable to determine whether undiagnosed aortic regurgitation was a potential confounding factor, although this is unlikely given that the population prevalence of aortic regurgitation is less than 2%.[379] The relationships between pulse pressure, preserved/reduced ejection fraction heart failure and postoperative outcomes, including long-term survival, requires further exploration.

4.5 Conclusion

The results of this analysis help to address a daily clinical dilemma for anaesthetists and surgeons, by establishing that preoperative pulse pressure can refine the interpretation of elevated blood pressure on the day of surgery. These data suggest that patients with elevated pulse pressure are at higher risk of myocardial injury and, where limited time is available to reduce blood pressure (e.g. cancer surgery), may benefit from closer perioperative monitoring. In particular, surveillance for myocardial injury may be warranted in this higher-risk group.[95] Conversely, the results should reassure clinicians that in this cohort, patients with high preoperative systolic blood pressure but normal pulse pressure were not at increased risk of myocardial injury. These data suggest that a reappraisal of guidelines for managing elevated blood pressure on the day of surgery may be warranted, particularly since abnormal pulse pressure could be a modifiable risk factor. Further research is needed to determine the underlying pathophysiological mechanism responsible for the association between elevated pulse pressure and myocardial injury.

Chapter five

Intraoperative heart rate and blood pressure

A secondary analysis of data from a prospective international multi-centre cohort study of myocardial injury after non-cardiac surgery

This chapter is in press with Anesthesia and Analgesia (2017).

5.1 Introduction

The aetiology of perioperative myocardial injury is unclear. In a large and generalisable cohort of patients undergoing non-cardiac surgery I have previously identified that both elevated preoperative heart rate (chapter 3) and elevated preoperative pulse pressure (chapter 4) are associated with increased risk of perioperative myocardial injury. These data suggest that abnormal preoperative heart rate and arterial pressure may contribute to the causal pathway for perioperative myocardial injury.[96, 97] Yet it is unclear whether this is also true for heart rate and blood pressure *during* surgery.

In opposition the traditional plaque rupture and thrombosis model of myocardial infarction, the prevailing paradigm of perioperative myocardial injury is myocardial oxygen supply-demand imbalance during surgery (a period of increased physiological stress), leading to ischaemia, cellular necrosis and troponin release into the circulation.[96] However, other plausible mechanisms of troponin release have been proposed, including: inflammation leading to

increased cell membrane permeability; increased cardiac myocyte turnover; and extracellular transport of troponin via membrane vesicles.[98, 380] Changes in intraoperative heart rate and blood pressure, either separately or in combination, have been implicated as potential triggers for oxygen supply-demand imbalance and perioperative cardiovascular complications.[96, 169, 203, 381-383] However, previous research has largely focused on intraoperative hypotension, with little consideration of intraoperative heart rate or hypertension.[203, 381, 384] The majority of previous studies were retrospective in design and/or used subjective clinically-defined outcome measures and not objective biochemical outcome measures.[171, 173, 203, 385, 386] Attempts to control elevated heart rate with beta-blockers have consistently demonstrated a reduction in the risk of myocardial infarction, but at the expense of increased risk of mortality and stroke, likely due to hypotension.[166, 261] However, despite this, the clinical impact of interaction between intraoperative heart rate and blood pressure remains largely unexplored.[173] Similarly, the influence of the duration of abnormal heart rate or blood pressure on the development of myocardial injury is uncertain and under-investigated.[173, 384, 387, 388]

In this chapter I tested whether high or low intraoperative heart rate or systolic blood pressure, in isolation or combination, were associated with myocardial injury or mortality within 30 days of non-cardiac surgery in the VISION study cohort. In addition, I tested whether the duration of high or low heart rate/systolic blood pressure was associated with myocardial injury within 30 days of non-cardiac surgery.

5.2 Methods

This was a secondary analysis of a prospective international observational cohort study, the Vascular Events in Non-cardiac Surgery Cohort Evaluation (VISION) study.[16] I have described the study in detail in chapter 2 (methods) and the study methods have been published previously.[16, 95, 273, 275] I planned the analysis prospectively before I was given access to the data. Participants were aged ≥45 years, undergoing non-cardiac surgery using general or regional anaesthesia, and with a planned postoperative hospital stay of at least one night. Clinical staff measured heart rate and blood pressure before and during surgery as part of routine medical care according to local practice. Blood pressure was measured using the oscillometric non-invasive technique.

5.2.1 Exposures of interest

The exposures of interest were elevated or reduced heart rate or blood pressure during surgery, pre-defined by consensus of the VISION study investigators before the study started. Elevated heart rate was defined as any single measurement >100 beats per minute during surgery. Reduced heart rate was defined as any single measurement <55 beats per minute during surgery. Elevated systolic blood pressure was defined as any single measurement >160 mmHg during surgery. Reduced systolic blood pressure was defined as any single measurement <100 mmHg during surgery. Heart rate and blood pressure data were collected by researchers who reviewed the anaesthetics charts and patient records. The duration of heart rate and systolic blood pressure above or below these thresholds was also recorded.

5.2.2 Outcome measures

The primary outcome measure was myocardial injury after non-cardiac surgery (MINS), according to the VISION study definition: serum Troponin T (TnT) ≥0.03ng/mL (4th generation assay) within 30 days after surgery, adjudicated as due to an ischemic pathology, which excludes non-ischaemic causes of transient troponin elevation.[95, 113] I have described the blood sampling regime, the TnT assay and the adjudication process in chapter 2 (methods) and this has also been published previously.[16, 95, 273, 275]

The secondary outcome measure was all-cause mortality within 30 days after surgery. The tertiary outcome was myocardial infarction within 30 days of surgery, defined according to the third universal definition (serum troponin elevation in the presence of at least one of: ischemic symptoms; the development of new or presumed new Q waves, ST segment or T wave changes, or left bundle branch block on the electrocardiogram; or the finding of a new or presumed new regional wall motion abnormality on echocardiography).[94]

5.2.3 Statistical analysis

I analysed the data using SPSS (IBM, New York, USA). Cases that were missing a record of highest or lowest intraoperative heart rate or systolic blood pressure, or outcome data, were excluded from respective analyses by list-wise deletion. I sorted and dichotomised the sample according to predefined thresholds for highest intraoperative heart rate (>100 bpm), lowest intraoperative heart rate (<55 bpm), highest intraoperative systolic blood pressure (>160 mmHg) and lowest intraoperative systolic blood pressure (<100

mmHg). I considered these as categorical variables. I presented demographic data stratified according to these groups. Continuous data that followed a normal distribution were presented as mean (standard deviation), continuous data that did not follow a normal distribution were presented as median (interquartile range), and binary categorical data as frequencies with percentages.

I used multivariable logistic regression analysis to test for associations between independent variables (exposures) and myocardial injury. The reference groups were: heart rate ≤100 bpm for highest heart rate, heart rate ≥55 bpm for lowest heart rate, systolic blood pressure ≤160 mmHg for highest systolic pressure and systolic blood pressure ≥100 mmHg for lowest systolic pressure. Each multivariable model was adjusted for potentially confounding factors known to be associated with myocardial injury, cardiovascular complications or mortality in other perioperative research: age (45-64, 65-75, >75 years), current atrial fibrillation, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, previous stroke or transient ischaemic attack, estimated glomerular filtration rate (eGFR <30, 30-44, 45-60, >60 ml/min), chronic obstructive pulmonary disease, neurosurgery, major surgery and urgent/emergency surgery were considered as categorical variables in the multivariable models.[16, 20, 21, 389] These analyses were repeated for the secondary and tertiary outcomes. The results of logistic regression analyses were presented as odds ratios (OR) with 95% confidence intervals.

There is some evidence that association between low blood pressure during surgery and clinical outcomes may vary according to the duration of the

hypotensive episode in a non-linear fashion.[384, 390] Therefore, I wanted to test whether the duration of high or low systolic blood pressure or heart rate was associated with myocardial injury. I stratified duration of intraoperative heart rate >100 bpm / <55 bpm or systolic blood pressure >160 mmHg / <100 mmHg into quartiles and repeated the primary multivariable logistic regression analysis for quartiles of duration as the exposure of interest and myocardial injury as the outcome. The reference categories were patients with 'normal' heart rate or systolic blood pressure, for example in the analysis of duration of heart rate > 100 bpm, the reference group was patients with heart rate ≤ 100 bpm. To examine the relative influence of heart rate and systolic blood pressure on myocardial injury, I categorised the cohort according to combinations highest/lowest heart rate and highest/lowest systolic blood pressure. I repeated primary statistical analysis using these categorical variables.

5.2.4 Power calculation

For the primary (myocardial injury) analysis the available sample size was 15,019. Given a type I error rate of 5% and a background incidence of MINS of 7.9%, I have >99% power to detect a 1.8% absolute difference in the incidence of myocardial injury for participants with intraoperative heart rate >100 bpm. The minimum sample size required to detect an absolute difference of 1.8% in the incidence of myocardial injury, assuming a type I error rate of 5% and power of 99% is 4,967 participants. For the secondary and tertiary outcomes, assuming a type I error rate of 5% and a total sample of 15,019, I have 99% power to detect an absolute difference of 2.1% (2.0% vs 4.1%) in the incidence of mortality for participants with intraoperative heart rate >100bpm and 99% power to detect an absolute difference of 0.9% (2.8% vs 3.7%) in the incidence

of myocardial infarction. The minimum sample sizes required to detect these differences would be 1,639 participants for mortality and 8,082 participants for myocardial infarction.

5.2.5 Sensitivity analyses

Emergency surgery is associated with increased risk of adverse postoperative outcomes; patients undergoing emergency surgery may be more likely to be tachycardic or hypotensive. Therefore, to determine the influence of emergency surgery, I excluded all emergency cases and repeated the primary analyses. Similarly, patients with atrial fibrillation are at higher risk of postoperative cardiovascular complications and may have higher heart rates. Therefore, to determine the influence of atrial fibrillation, I repeated the primary heart rate analyses after excluding all cases with a previous history of atrial fibrillation. Heart rate limiting medications have previously been shown to reduced the risk of myocardial infarction after surgery.[166] Therefore, I excluded patients that received a beta-blocker and/or a calcium channel blocker within 24 hours before surgery and repeated the primary analysis of heart rate. In the primary analysis I categorised heart rate and systolic blood pressure as either high or low and compared this to a pre-defined normal range. However, this did not take account of patients who had both a high *and* low heart rate or systolic blood pressure during surgery. Therefore, I undertook a post hoc sensitivity analysis where I categorised heart rate as: 55-100 bpm / minimum heart rate < 55 bpm / maximum heart rate > 100 bpm / minimum heart rate < 55bpm and maximum heart rate > 100 bpm; and systolic blood pressure as: 100 – 160 mmHg / minimum systolic pressure < 100 mmHg / maximum systolic pressure > 160 mmHg / minimum systolic pressure < 100 mmHg and maximum systolic

pressure > 160 mmHg. I repeated the primary analysis to test for association between these four-level heart rate and systolic blood pressure variables and MINS.

To confirm whether the relationships between duration of highest/lowest heart rate or systolic blood pressure and myocardial injury was linear or non-linear, I undertook additional analyses using fractional polynomial regression using STATA version 14 (StataCorp, USA). This technique is described in detail in chapter 2 (statistical methods).[342]

5.3 Results

16,079 patients were recruited to the VISION study from twelve hospitals in eight countries.[16] 1,197/15,109 patients (7.9%) sustained MINS, 454/16,031 patients (2.8%) sustained MI and 315/16,061 patients (2.0%) died, within 30 days of surgery. Baseline characteristics are presented in table 5.1. Cases included in multivariable analyses are shown in figure 5.1.

5.3.1 Intraoperative heart rate

Highest intraoperative heart rate >100 bpm was associated with increased odds of MINS (OR 1.27 [1.07 – 1.50]; p <0.01), myocardial infarction (OR 1.34 [1.05 – 1.70]; p=0.02) and mortality (OR 2.65 [2.06 – 3.41]; p <0.01). Lowest intraoperative heart rate <55 bpm was associated with reduced odds of MINS (OR 0.70 [0.59 – 0.82]; p <0.01), myocardial infarction (OR 0.75 [0.58 - 0.97]; p=0.03) and mortality (OR 0.58 [0.41 – 0.81]; p <0.01) (tables 5.2-5.4 and figure 3.2). Duration of intraoperative heart rate >100 bpm for longer than 30 minutes was associated with MINS (OR 2.22 [1.71 – 2.88]; p <0.01) compared to participants with intraoperative heart rate ≤100 bpm (figure 5.3 and table 5.5). Heart rate <55 bpm for any duration was associated with reduced odds of MINS and there was a trend towards reduced likelihood of MINS as duration of heart rate < 55bpm increased (figure 5.3 and table 5.6).

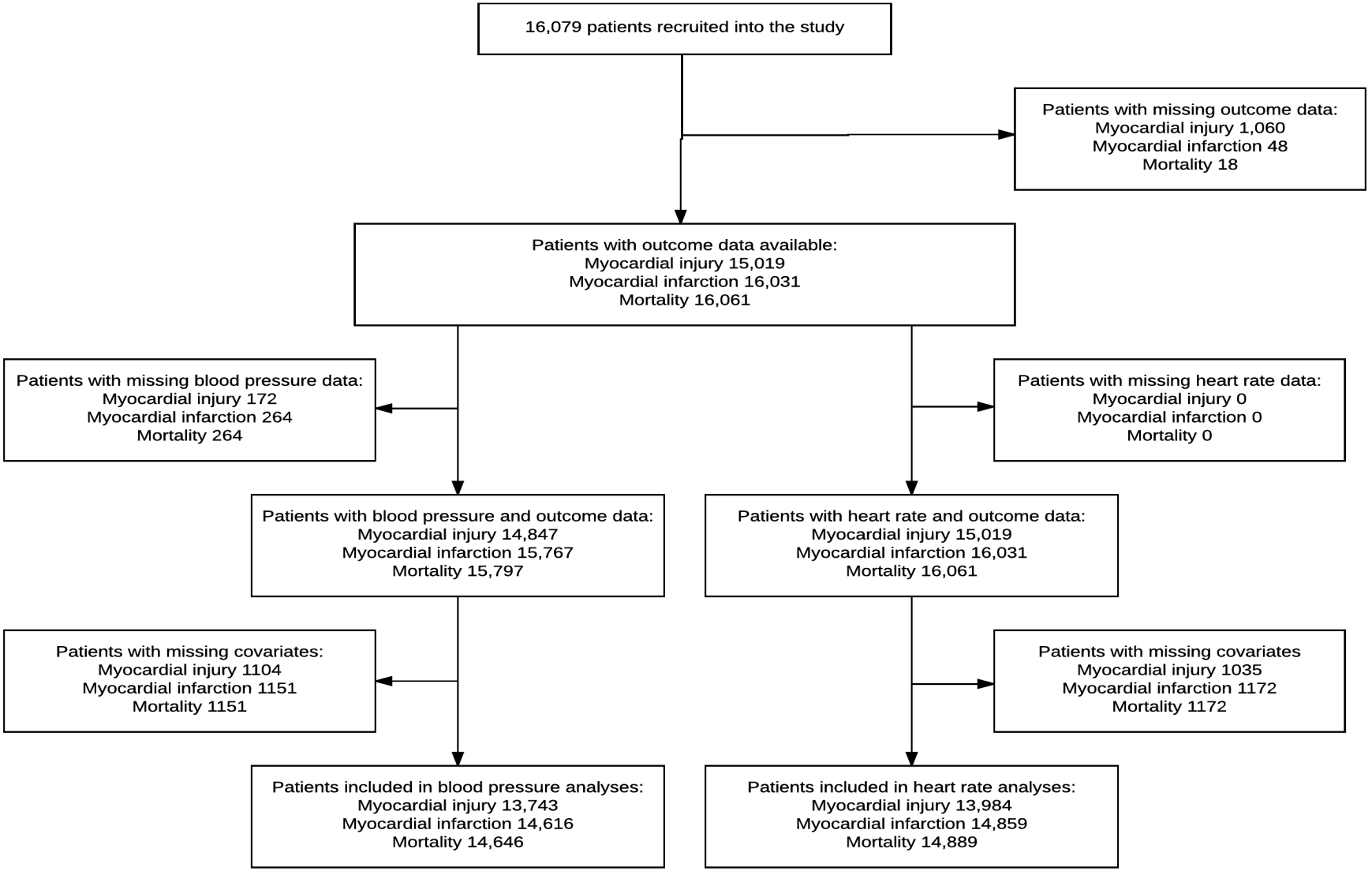

Figure 5.1. Patient flow diagram showing the number of cases included in each analysis.

Table 5.1. Baseline patient characteristics. Descriptive data stratified by binary thresholds for highest and lowest intraoperative heart rate (HR) and systolic blood pressure (SBP), presented as frequencies with percentages (%) or means with standard deviations (SD). Age rounded to nearest whole number. Heart rate in beats per minute (bpm) and systolic blood pressure in mmHg. Highest intraoperative heart rate >100 bpm (HR >100); lowest intraoperative heart rate <55 bpm (HR <55); Highest systolic blood pressure >160 mmHg (SBP >160); lowest systolic blood pressure <100 mmHg (SBP <100); estimated glomerular filtration rate (eGFR). Missing cases shown in figure 5.1.

Intraoperative HR or SBP groups	Whole	HR >100	HR <55	SBP >160	SBP <100
Number of cases (n)	16079	2936	4256	4754	9891
Mean age (SD)	65 (11.9)	64 (12.3)	65 (11.3)	68 (11.6)	64 (11.6)
Sex					
Male (%)	7763 (48.3)	1448 (49.3)	2118	2197 (46.2)	4702 (47.5)
Female (%)	8316 (51.7)	1488 (50.7)	2138	2557 (53.8)	5189 (52.5)
Comorbid disorder (%)					
Atrial fibrillation	545 (3.4)	142 (4.8)	106 (2.5)	171 (3.6)	281 (2.8)
Diabetes	3153 (19.6)	626 (21.3)	744 (17.5)	1163 (24.5)	1785 (18.0)
Hypertension	8171 (50.8)	1304 (44.4)	2226	2844 (59.8)	4754 (48.1)
Heart failure	761 (4.7)	121 (4.1)	184 (4.3)	256 (5.4)	405 (4.1)
Coronary artery disease	1947 (12.1)	247 (8.4)	608 (14.3)	674 (14.2)	1054 (10.7)
Peripheral vascular disease	858 (5.3)	127 (4.3)	238 (5.6)	316 (6.6)	421 (4.3)
Previous stroke or transient ischaemic attack	1167 (7.3)	279 (9.5)	317 (7.5)	533 (11.2)	643 (6.5)
Chronic obstructive pulmonary disease (COPD)	1337 (8.3)	205 (7.0)	269 (6.3)	396 (8.3)	797 (8.1)
Preoperative eGFR, ml/min/1.73m^2 (%)					
<30	564 (3.5)	131 (4.7)	104 (2.6)	195 (4.3)	311 (3.4)
30-45	831 (5.2)	171 (6.1)	224 (5.7)	336 (7.4)	459 (5.0)
45-60	1579 (9.8)	241 (8.6)	457 (11.5)	592 (13.0)	904 (9.9)
>60	11938 (74.2)	2254 (80.6)	3179	3416 (75.3)	7483 (81.7)
Surgical procedure category (%)					
Elective	13765 (85.6)	2312 (78.7)	3881	4020 (84.6)	8512 (86.1)
Urgent	485 (3.0)	162 (5.5)	83 (2.0)	170 (3.6)	317 (3.2)
Emergency	1828 (11.4)	462 (15.7)	292 (6.9)	564 (11.9)	1062 (10.7)
Major surgery (%)	9600 (59.7)	1774 (60.4)	2477	2956 (62.2)	6075 (61.4)
Outcome measures (%)					
Myocardial injury	1197 (7.4)	257 (9.7)	233 (5.8)	436 (10.0)	711 (7.7)
Myocardial infarction	454 (2.8)	109 (3.7)	88 (2.1)	185 (2.8)	276 (2.8)
Mortality	315 (2.0)	119 (4.1)	49 (1.2)	91 (1.9)	222 (2.2)

Table 5.2. Summary multivariable logistic regression models for highest and lowest intraoperative heart rate and systolic blood pressure.
Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days after surgery. Highest intraoperative heart rate was dichotomised according to a threshold of >100 beats per minute (bpm) with heart rate ≤100 bpm as the reference category. Lowest intraoperative heart rate was dichotomised according to the threshold of <55 bpm with heart rate ≥55 bpm as the reference category. Highest intraoperative systolic blood pressure was dichotomised according to a threshold of >160 mmHg with systolic blood pressure ≤160 mmHg as the reference category. Lowest intraoperative systolic blood pressure was dichotomised according to the threshold of <100 mmHg with systolic blood pressure ≥100 mmHg as the reference category. Results of adjusted analyses are presented with unadjusted analyses for comparison. Full multi-variable models are presented in tables 5.3, 5.4, 5.7 and 5.8.

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Highest intraoperative heart rate >100 bpm						
Unadjusted	1.31 (1.14-1.52)	<0.01	1.42 (1.15-1.78)	<0.01	2.79 (2.21-3.51)	<0.01
Adjusted	1.27 (1.07-1.50)	<0.01	1.34 (1.05-1.70)	0.02	2.65 (2.06-3.41)	<0.01
Lowest intraoperative heart rate <55 bpm						
Unadjusted	0.66 (0.57-0.76)	<0.01	0.66 (0.52-0.84)	<0.01	0.51 (0.37-0.69)	<0.01
Adjusted	0.70 (0.59-0.82)	<0.01	0.75 (0.58-0.97)	0.03	0.58 (0.41-0.81)	<0.01
Highest intraoperative systolic blood pressure >160 mmHg						
Unadjusted	1.48 (1.30-1.67)	<0.01	1.67 (1.38-2.03)	<0.01	0.96 (0.75-1.23)	0.75
Adjusted	1.16 (1.01-1.34)	0.04	1.34 (1.09-1.64)	0.01	0.76 (0.58-0.99)	0.04
Lowest intraoperative systolic blood pressure <100mmHg						
Unadjusted	0.94 (0.83-1.06)	0.28	0.97 (0.80-1.17)	0.72	1.49 (1.16-1.91)	<0.01
Adjusted	1.21 (1.05-1.39)	0.01	1.21 (0.98-1.49)	0.07	1.81 (1.39-2.37)	<0.01

Table 5.3. Multivariable logistic regression models for maximum intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of >100 beat per minute (bpm). Heart rate ≤100 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.09 (0.91-1.31)	0.39	1.17 (0.88-1.55)	0.29	1.61 (1.15-2.25)	<0.01
>75	2.06 (1.72-2.45)	<0.01	1.87 (1.43-2.45)	<0.01	2.35 (1.69-3.27)	<0.01
Male sex	1.37 (1.20-1.57)	<0.01	1.02 (0.83-1.26)	0.83	1.18 (0.92-1.51)	0.19
History of atrial fibrillation	1.58 (1.22-2.06)	<0.01	1.33 (0.93-1.90)	0.12	1.00 (0.62-1.62)	0.99
History of diabetes	1.40 (1.20-1.63)	<0.01	1.22 (0.98-1.53)	0.08	1.02 (0.77-1.37)	0.88
History of hypertension	1.31 (1.12-1.54)	<0.01	1.39 (1.08-1.77)	0.01	0.99 (0.75-1.30)	0.92
History of heart failure	1.60 (1.27-2.00)	<0.01	1.70 (1.27-2.30)	<0.01	1.45 (0.97-2.19)	0.07
History of coronary artery disease	1.45 (1.23-1.72)	<0.01	2.21 (1.76-2.78)	<0.01	0.96 (0.69-1.34)	0.81
History of peripheral vascular disease	2.17 (1.77-2.65)	<0.01	2.13 (1.62-2.81)	<0.01	1.84 (1.27-2.65)	<0.01
History of stroke or transient ischaemic attack	1.43 (1.18-1.74)	<0.01	1.11 (0.83-1.48)	0.47	1.40 (1.00-1.96)	0.05
History of chronic obstructive pulmonary disease	1.22 (1.00-1.50)	0.05	1.15 (0.86-1.53)	0.35	2.09 (1.52-2.86)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.76 (8.72-13.29)	<0.01	4.01 (2.98-5.38)	<0.01	3.03 (2.07-4.42)	<0.01
30-44	2.50 (2.02-3.10)	<0.01	1.72 (1.25-2.37)	<0.01	1.65 (1.11-2.44)	0.01
45-60	1.68 (1.39-2.04)	<0.01	1.42 (1.06-1.90)	0.02	0.99 (0.67-1.47)	0.97
>60 (reference)	-	-	-	-	-	-
Neurosurgery	1.12 (0.85-1.48)	0.42	0.57 (0.34-0.97)	0.04	1.70 (1.10-2.63)	0.02
Urgent or emergency surgery	1.93 (1.64-2.27)	<0.01	2.29 (1.83-2.87)	<0.01	3.46 (2.69-4.44)	<0.01
Major surgery	1.66 (1.42-1.94)	<0.01	2.21 (1.72-2.83)	<0.01	1.57 (1.18-2.10)	<0.01
Maximum intraoperative heart rate (bpm)						
>100	1.27 (1.07-1.50)	<0.01	1.34 (1.05-1.70)	0.02	2.65 (2.06-3.41)	<0.01

Table 5.4. Multivariable logistic regression models for minimum intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of <55 beats per minute (bpm). Heart rate ≥55 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.09 (0.91-1.31)	0.35	1.17 (0.88-1.55)	0.29	1.54 (1.10-2.15)	0.01
>75	2.05 (1.72-2.44)	<0.01	1.86 (1.42-2.43)	<0.01	2.22 (1.60-3.09)	<0.01
Male sex	1.39 (1.21-1.59)	<0.01	1.03 (0.84-1.27)	0.75	1.22 (0.96-1.56)	0.11
History of atrial fibrillation	1.59 (1.23-2.07)	<0.01	1.35 (0.95-1.93)	0.10	1.11 (0.69-1.78)	0.66
History of diabetes	1.39 (1.20-1.62)	<0.01	1.22 (0.98-1.53)	0.08	1.03 (0.77-1.38)	0.83
History of hypertension	1.31 (1.12-1.53)	<0.01	1.38 (1.08-1.76)	0.01	0.96 (0.73-1.26)	0.75
History of heart failure	1.58 (1.25-1.98)	<0.01	1.68 (1.24-2.26)	<0.01	1.37 (0.91-2.06)	0.13
History of coronary artery disease	1.46 (1.23-1.73)	<0.01	2.20 (1.75-2.77)	<0.01	0.90 (0.65-1.26)	0.55
History of peripheral vascular disease	2.17 (1.77-2.65)	<0.01	2.11 (1.60-2.79)	<0.01	1.79 (1.24-2.57)	<0.01
History of stroke or transient ischaemic attack	1.46 (1.20-1.77)	<0.01	1.13 (0.85-1.51)	0.41	1.52 (1.09-2.12)	0.01
History of chronic obstructive pulmonary disease	1.19 (0.97-1.45)	0.10	1.12 (0.84-1.50)	0.44	1.98 (1.45-2.70)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.71 (8.67-13.23)	<0.01	4.01 (2.98-5.39)	<0.01	3.15 (2.16-4.59)	<0.01
30-44	2.54 (2.05-3.15)	<0.01	1.74 (1.26-2.40)	<0.01	1.71 (1.16-2.53)	<0.01
45-60	1.69 (1.40-2.05)	<0.01	1.43 (1.07-1.91)	0.02	0.98 (0.66-1.45)	0.91
>60 (reference)	-	-	-	-	-	-
Neurosurgery	1.17 (0.88-1.54)	0.28	0.59 (0.35-0.99)	0.05	1.72 (1.11-2.66)	0.02
Urgent or emergency surgery	1.89 (1.61-2.22)	<0.01	2.30 (1.83-2.88)	<0.01	3.71 (2.89-4.75)	<0.01
Major surgery	1.66 (1.42-1.93)	<0.01	2.20 (1.71-2.81)	<0.01	1.60 (1.20-2.14)	<0.01
Minimum intraoperative heart rate (bpm)						
<55	0.70 (0.59-0.82)	<0.01	0.75 (0.58-0.97)	0.03	0.58 (0.41-0.81)	<0.01

Table 5.5 Full adjusted logistic regression model for duration of intraoperative heart rate >100 beats per minute. Multivariable logistic regression analysis. Dependent variable is myocardial injury within 30 days of surgery. Duration of heart rate >100 beats per minute (bpm) was stratified into quartiles. The reference group was participants with heart rate ≤ 100 beats per minute. Estimated glomerular filtration rate (eGFR).

Covariates	odds ratio	p-value
Age (years)		
45-64 (reference)	-	-
65-75	1.10 (0.91-1.32)	0.33
>75	2.09 (1.75-2.49)	<0.01
Male sex	1.37 (1.19-1.57)	<0.01
Comorbid disease		
Atrial fibrillation	1.54 (1.19-2.01)	<0.01
Diabetes	1.39 (1.19-1.62)	<0.01
Hypertension	1.32 (1.12-1.54)	<0.01
Heart failure	1.59 (1.27-2.00)	<0.01
Coronary artery disease	1.45 (1.23-1.72)	<0.01
Peripheral vascular disease	2.16 (1.76-2.54)	<0.01
Previous stroke or transient ischaemic attack	1.43 (1.18-1.74)	<0.01
Chronic obstructive pulmonary disease	1.22 (1.00-1.49)	0.05
eGFR (ml/min/1.73m^2)		
<30	10.47 (8.47-12.94)	<0.01
30-45	2.45 (1.97-3.03)	<0.01
45-60	1.68 (1.38-2.03)	<0.01
>60 (reference)	-	-
Neurosurgery	1.13 (0.86-1.49)	0.38
Urgent or emergency surgery	1.89 (1.60-2.23)	<0.01
Major surgery	1.63 (1.40-1.91)	<0.01
Duration of heart rate >100 bpm		
<5 minutes	0.92 (0.67-1.25)	0.58
5 - 10 mintues	0.93 (0.62-1.38)	0.71
11 - 30 minutes	1.07 (0.79-1.46)	0.66
>30 minutes	2.22 (1.71-2.88)	<0.01

Table 5.6. Full adjusted logistic regression model for duration of intraoperative heart rate <55 beats per minute. Multivariable logistic regression analysis. Dependent variable is myocardial injury within 30 days of surgery. Duration of heart rate <55 beats per minute (bpm) was stratified into quartiles. The reference group was participants with heart rate ≥ 55 beats per minute. Estimated glomerular filtration rate (eGFR).

Covariates	odds ratio	p-value
Age		
45-64	ref	ref
65-75	1.09 (0.91-1.31)	0.35
>75	2.05 (1.72-2.44)	<0.01
Male sex	1.39 (1.21-1.59)	<0.01
Comorbid disease		
Existing atrial fibrillation	1.59 (1.23-2.07)	<0.01
Diabetes	1.39 (1.20-1.62)	<0.01
Hypertension	1.31 (1.12-1.54)	<0.01
Heart failure	1.57 (1.25-1.98)	<0.01
Coronary artery disease	1.46 (1.24-1.73)	<0.01
Peripheral vascular disease	2.17 (1.77-2.66)	<0.01
Previous stroke or transient ischaemic attack	1.46 (1.20-1.77)	<0.01
Chronic obstructive pulmonary disease	1.18 (0.97-1.45)	0.10
eGFR (ml/min/1.73m^2)		
<30	10.70 (8.66-13.22)	<0.01
30-45	2.54 (2.05-3.15)	<0.01
45-60	1.70 (1.40-2.05)	<0.01
>60	ref	ref
Neurosurgery	1.17 (0.89-2.05)	0.26
Urgent or emergency surgery	1.89 (1.61-2.23)	<0.01
Major surgery	1.66 (1.42-1.94)	<0.01
Duration of heart rate <55 bpm		
<14 minutes	0.72 (0.53-0.98)	0.04
14 - 30 minutes	0.75 (0.57-1.00)	0.05
31 - 65 minutes	0.69 (0.51-0.95)	0.02
> 65 minutes	0.64 (0.47-0.86)	<0.01

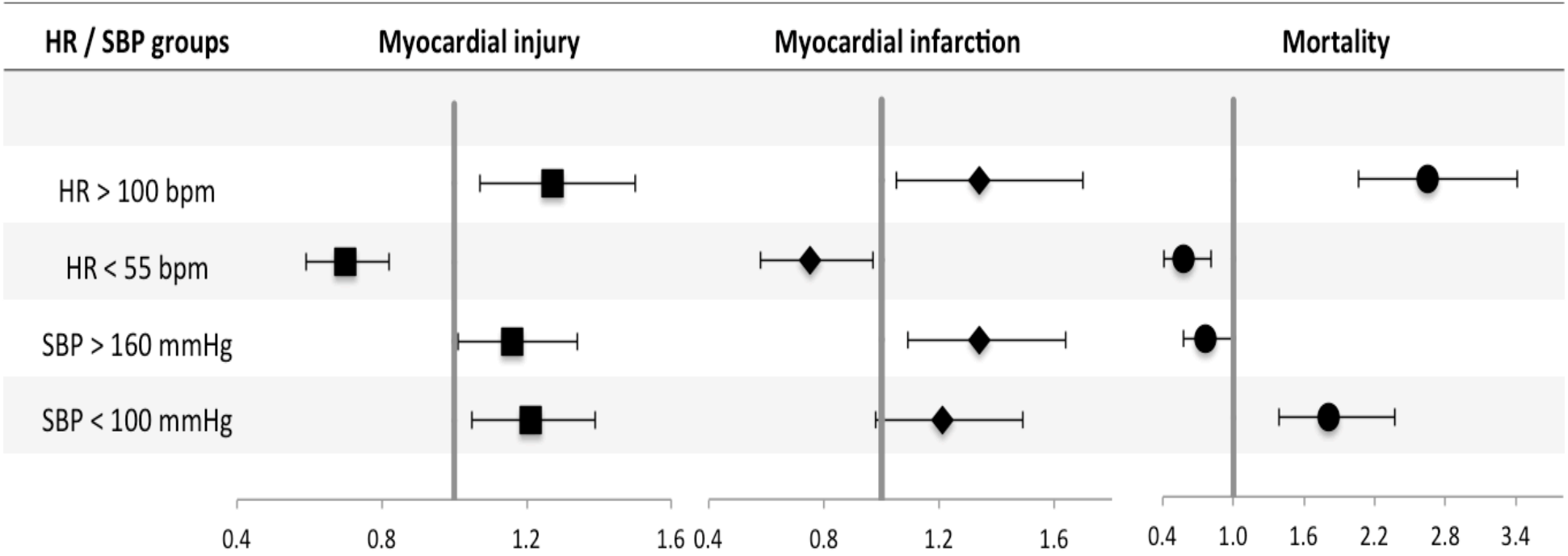

Figure 5.2. Forest plot summarizing multivariable logistic regression models for highest and lowest intraoperative heart rate (HR) and systolic blood pressure (SBP). Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days after surgery. Highest intraoperative heart rate was dichotomised according to a threshold of >100 beats per minute (bpm) with heart rate ≤100 bpm as the reference category. Lowest intraoperative heart rate was dichotomised according to the threshold of <55 bpm with heart rate ≥55 bpm as the reference category. Highest intraoperative systolic blood pressure was dichotomised according to a threshold of >160 mmHg with systolic blood pressure ≤160 mmHg as the reference category. Lowest intraoperative systolic blood pressure was dichotomised according to the threshold of <100 mmHg with systolic blood pressure ≥100 mmHg as the reference category. The x-axis shows odds ratios and the error bars show 95% confidence intervals. Full multi-variable models are presented in tables 5.3, 5.4, 5.7 and 5.8.

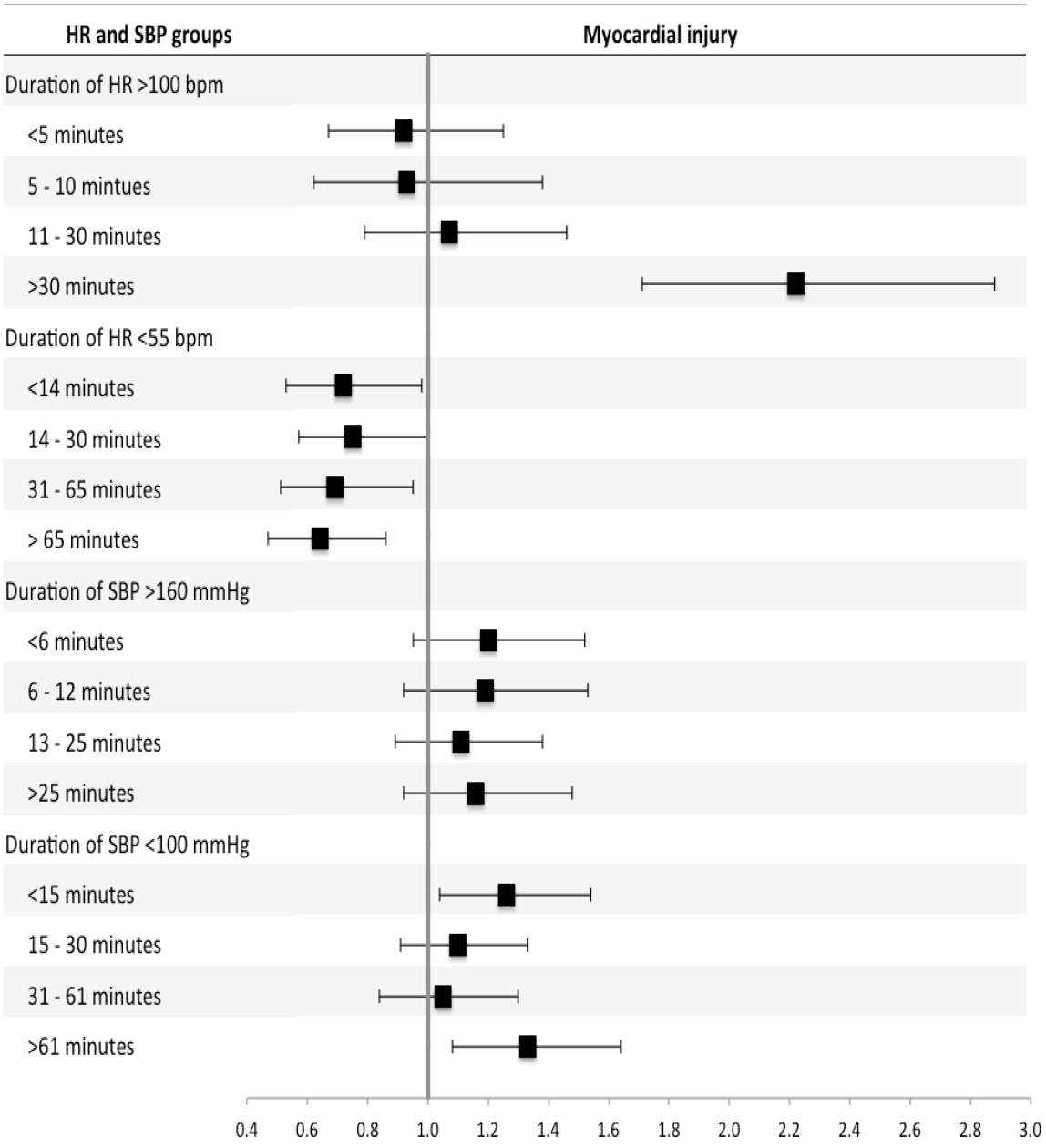

Figure 5.3. Forest plot summarizing multivariable logistic regression models for the duration of high/low intraoperative heart rate (HR) and systolic blood pressure (SBP). The dependent variable was myocardial injury within 30 days after surgery. There were four separate regression models for duration of: intraoperative heart rate >100 beats per minute (bpm), intraoperative heart rate <55 bpm intraoperative systolic blood pressure >160 mmHg and intraoperative systolic blood pressure <100 mmHg. For each model, duration was stratified into four approximately equal quartiles. The reference categories were patients with 'normal' heart rate or systolic blood pressure, for example in the analysis of duration of heart rate > 100 bpm, the reference group was patients with heart rate ≤ 100 bpm. The x-axis shows odds ratios and the error bars show 95% confidence intervals. The full multivariable regression models are presented in tables 5.5, 5.6, 5.9 and 5.10.

5.3.2 Intraoperative systolic blood pressure

Highest intraoperative systolic blood pressure >160mmHg was associated with increased odds of MINS (OR 1.16 [1.01 – 1.34]; p=0.04) and myocardial infarction (OR 1.34 [1.09 – 1.64]; p=0.01) and reduced odds of mortality (OR 0.76 [0.58 – 0.99]; p=0.04). Lowest intraoperative systolic blood pressure <100mmHg was associated with increased odds of MINS (OR 1.21 [1.05 – 1.39]; p=0.01) and mortality (OR 1.81 [1.39 – 2.37]; p <0.01), but was not associated with myocardial infarction (OR 1.21 [0.98-1.49]; p=0.07) (table 5.2, 5.7 and 5.8, and figure 5.2). Duration of systolic blood pressure >160 mmHg was not associated with MINS (figure 5.3 and table 5.9). In comparison, duration of systolic blood pressure <100 mmHg for <15 minutes or >61 minutes was associated with MINS (OR 1.26 [1.04-1.54]; p=0.02 and OR 1.33 [1.08-1.64]; p<0.01 respectively) (figure 5.3 and table 5.10).

Table 5.7. Full adjusted logistic regression model for highest intraoperative systolic blood pressure. Multivariable logistic regression analysis. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative systolic blood pressure was dichotomised according to a threshold of >160 mmHg. Systolic blood pressure ≤160 mmHg was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.07 (0.89-1.29)	0.46	1.14 (0.85-1.52)	0.39	1.59 (1.14-2.22)	<0.01
>75	2.06 (1.72-2.47)	<0.01	1.82 (1.39-2.39)	<0.01	2.29 (1.64-3.19)	<0.01
Male sex	1.35 (1.18-1.56)	<0.01	1.01 (0.82-1.24)	0.96	1.16 (0.91-1.49)	0.23
History of atrial fibrillation	1.68 (1.29-2.19)	<0.01	1.44 (1.01-2.06)	0.05	1.10 (0.68-1.78)	0.71
History of diabetes	1.38 (1.18-1.61)	<0.01	1.23 (0.98-1.54)	0.08	1.03 (0.77-1.39)	0.83
History of hypertension	1.30 (1.11-1.53)	<0.01	1.36 (1.06-1.74)	0.02	0.97 (0.73-1.27)	0.81
History of heart failure	1.55 (1.23-1.96)	<0.01	1.65 (1.22-2.24)	<0.01	1.33 (0.88-2.02)	0.18
History of coronary artery disease	1.44 (1.22-1.71)	<0.01	2.12 (1.68-2.68)	<0.01	0.88 (0.63-1.23)	0.46
History of peripheral vascular disease	2.25 (1.83-2.76)	<0.01	2.22 (1.68-2.92)	<0.01	1.86 (1.29-2.68)	<0.01
History of stroke or transient ischaemic attack	1.46 (1.20-1.78)	<0.01	1.14 (0.86-1.52)	0.37	1.60 (1.14-2.24)	<0.01
History of chronic obstructive pulmonary disease	1.22 (0.99-1.49)	0.06	1.19 (0.89-1.59)	0.25	1.93 (1.41-2.66)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.76 (8.69-13.32)	<0.01	4.01 (2.97-5.41)	<0.01	3.25 (2.23-4.75)	<0.01
30-44	2.51 (2.02-3.12)	<0.01	1.75 (1.27-2.42)	<0.01	1.70 (1.14-2.53)	<0.01
45-60	1.63 (1.34-1.97)	<0.01	1.39 (1.03-1.86)	0.03	0.92 (0.62-1.38)	0.70
>60 (reference)	-	-	-	-	-	-
Neurosurgery	1.13 (0.86-1.50)	0.38	0.59 (0.35-0.99)	0.05	1.67 (1.08-2.59)	0.02
Urgent or emergency surgery	1.99 (1.69-2.34)	<0.01	2.35 (1.88-2.95)	<0.01	3.95 (3.08-5.07)	<0.01
Major surgery	1.67 (1.43-1.95)	<0.01	2.16 (1.69-2.77)	<0.01	1.66 (1.24-2.22)	<0.01
Maximum intraoperative systolic blood pressure (mmHg)						
>160	1.16 (1.01-1.34)	0.04	1.34 (1.09-1.64)	0.01	0.76 (0.58-0.99)	0.04

Table 5.8. Full adjusted logistic regression model for lowest intraoperative systolic blood pressure. Multivariable logistic regression analysis. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative systolic blood pressure was dichotomised according to a threshold of <100 mmHg. Systolic blood pressure ≥100 mmHg was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury		Myocardial Infarction		Mortality	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Age (years)						
45-64 (reference)	-	-	-	-	-	-
65-75	1.09 (0.91-1.32)	0.36	1.16 (0.87-1.55)	0.32	1.62 (1.16-2.26)	0.01
>75	2.13 (1.78-2.55)	<0.01	1.91 (1.45-2.50)	<0.01	2.39 (1.71-3.33)	<0.01
Male sex	1.35 (1.17-1.55)	<0.01	1.00 (0.81-1.23)	0.99	1.19 (0.93-1.52)	0.17
History of atrial fibrillation	1.68 (1.29-2.19)	<0.01	1.41 (0.98-2.02)	0.06	1.19 (0.74-1.91)	0.48
History of diabetes	1.40 (1.20-1.63)	<0.01	1.23 (0.98-1.55)	0.07	1.04 (0.78-1.40)	0.78
History of hypertension	1.32 (1.12-1.55)	<0.01	1.40 (1.09-1.80)	0.01	0.97 (0.73-1.27)	0.97
History of heart failure	1.56 (1.24-1.97)	<0.01	1.65 (1.22-2.23)	<0.01	1.38 (0.91-2.09)	0.13
History of coronary artery disease	1.45 (1.22-1.72)	<0.01	2.13 (1.69-2.69)	<0.01	0.91 (0.66-1.27)	0.59
History of peripheral vascular disease	2.29 (1.87-2.81)	<0.01	2.25 (1.70-2.97)	<0.01	1.91 (1.32-2.75)	<0.01
History of stroke or transient ischaemic attack	1.48 (1.21-1.80)	<0.01	1.17 (0.88-1.56)	0.29	1.57 (1.12-2.20)	0.01
History of chronic obstructive pulmonary disease	1.20 (0.98-1.47)	0.08	1.15 (0.86-1.54)	0.35	1.92 (1.40-2.64)	<0.01
Preoperative eGFR (ml/min/1.73m^2)						
<30	10.82 (8.74-13.40)	<0.01	4.00 (2.96-5.39)	<0.01	3.26 (2.23-4.76)	<0.01
30-44	2.52 (2.03-3.13)	<0.01	1.76 (1.28-2.43)	<0.01	1.73 (1.17-2.57)	0.01
45-60	1.63 (1.34-1.98)	<0.01	1.39 (1.04-1.87)	0.03	0.91 (0.61-1.37)	0.66
>60 (reference)	-	-	-	-	-	-
Neurosurgery	1.13 (0.86-1.50)	0.38	0.60 (0.36-1.00)	0.05	1.58 (1.02-2.44)	0.04
Urgent or emergency surgery	1.99 (1.69-2.34)	<0.01	2.35 (1.88-2.95)	<0.01	3.89 (3.04-4.99)	<0.01
Major surgery	1.66 (1.42-1.94)	<0.01	2.15 (1.67-2.75)	<0.01	1.61 (1.20-2.16)	<0.01
Minimum intraoperative systolic blood pressure (mmHg)						
<100	1.21 (1.05-1.39)	0.01	1.21 (0.98-1.49)	0.07	1.81 (1.39-2.37)	<0.01

Table 5.9. Full adjusted logistic regression model for duration of intraoperative systolic blood pressure >160 mmHg. Multivariable logistic regression analysis. Dependent variable is myocardial injury within 30 days of surgery. Duration of systolic blood pressure (SBP) >160 mmHg was stratified into quartiles. The reference group was participants with SBP ≤160 mmHg. Estimated glomerular filtration rate (eGFR).

Covariates	odds ratio	p-value
Age		
45-64	ref	ref
65-75	1.07 (0.89-1.29)	0.47
>75	2.00 (1.68-2.39)	<0.01
Male sex	1.38 (1.21-1.59)	<0.01
Comorbid disease		
Existing atrial fibrillation	1.64 (1.26-2.13)	<0.01
Diabetes	1.40 (1.20-1.63)	<0.01
Hypertension	1.29 (1.10-1.51)	<0.01
Heart failure	1.59 (1.26-1.99)	<0.01
Coronary artery disease	1.43 (1.21-1.69)	<0.01
Peripheral vascular disease	2.15 (1.76-2.63)	<0.01
Previous stroke or transient ischaemic attack	1.44 (1.18-1.75)	<0.01
Chronic obstructive pulmonary disease	1.23 (1.01-1.50)	0.04
eGFR (ml/min/1.73m^2)		
<30	10.87 (8.80-13.42)	<0.01
30-45	2.51 (2.02-3.11)	<0.01
45-60	1.67 (1.38-2.02)	<0.01
>60	ref	ref
Neurosurgery	1.11 (0.84-1.46)	0.48
Urgent or emergency surgery	1.98 (1.69-2.33)	<0.01
Major surgery	1.67 (1.43-1.94)	<0.01
Duration of systolic blood pressure >160 mmHg		
<6 minutes	1.20 (0.95-1.52)	0.13
6 - 12 minutes	1.19 (0.92-1.53)	0.18
13 - 25 minutes	1.11 (0.89-1.38)	0.38
>25 minutes	1.16 (0.92-1.48)	0.21

Table 5.10. Full adjusted logistic regression model for duration of intraoperative systolic blood pressure <100 mmHg. Multivariable logistic regression analysis. Dependent variable is myocardial injury within 30 days of surgery. Duration of systolic blood pressure (SBP) <100 mmHg was stratified into quartiles. The reference group was participants with SBP ≥100 mmHg. Estimated glomerular filtration rate (eGFR).

Covariates	odds ratio	p-value
Age		
45-64	ref	ref
65-75	1.10 (0.91-1.32)	0.34
>75	2.09 (1.75-2.50)	<0.01
Male sex	1.38 (1.20-1.58)	<0.01
Comorbid disease		
Existing atrial fibrillation	1.63 (1.25-2.12)	<0.01
Diabetes	1.41 (1.21-1.64)	<0.01
Hypertension	1.31 (1.12-1.53)	<0.01
Heart failure	1.58 (1.26-1.99)	<0.01
Coronary artery disease	1.44 (1.22-1.71)	<0.01
Peripheral vascular disease	2.18 (1.78-2.67)	<0.01
Previous stroke or transient ischaemic attack	1.47 (1.21-1.78)	<0.01
Chronic obstructive pulmonary disease	1.21 (0.99-1.u48)	0.06
eGFR (ml/min/1.73m^2)		
<30	10.92 (8.84-13.49)	<0.01
30-45	2.52 (2.03-3.12)	<0.01
45-60	1.67 (1.38-2.03)	<0.01
>60	ref	ref
Neurosurgery	1.10 (0.83-1.45)	0.50
Urgent or emergency surgery	1.99 (1.70-2.35)	<0.01
Major surgery	1.64 (1.41-1.91)	<0.01
Duration of systolic blood pressure <100 mmHg		
<15 minutes	1.26 (1.04-1.54)	0.02
15 - 30 minutes	1.10 (0.91-1.33)	0.33
31 - 61 minutes	1.05 (0.84-1.30)	0.69
>61 minutes	1.33 (1.08-1.64)	<0.01

5.3.3 Intraoperative heart rate and systolic blood pressure

The association between heart rate (HR) and myocardial injury was modified by systolic blood pressure (SBP); shown in figure 5.4 and tables 5.11-5.14. The incidence of MINS in patients with hypotension (SBP <100 mmHg) and tachycardia (HR >100bpm) was 176/1906 (9.2%) and had higher odds of MINS (OR 1.42 [1.15-1.76]; p<0.01), compared to patients with hypotension in the absence of tachycardia (499/6632 [7.5%]; OR 1.20 [1.03-1.40]; p=0.02) or patients with tachycardia in the absence of hypotension (76/736 [10.3%]; OR 1.26 [0.94-1.69]; p=0.13), where the reference group was patients without hypotension or tachycardia. Patients with hypertension (SBP >160 mmHg) without bradycardia (HR <55 bpm) were at increased risk of MINS (326/2802 [11.6%]; OR 1.22 (1.04-1.43); p=0.02). However, bradycardia was associated with less risk of MINS, regardless of highest systolic blood pressure (figure 5.4). A similar effect was seen for hypotension with/without bradycardia (figure 5.4).

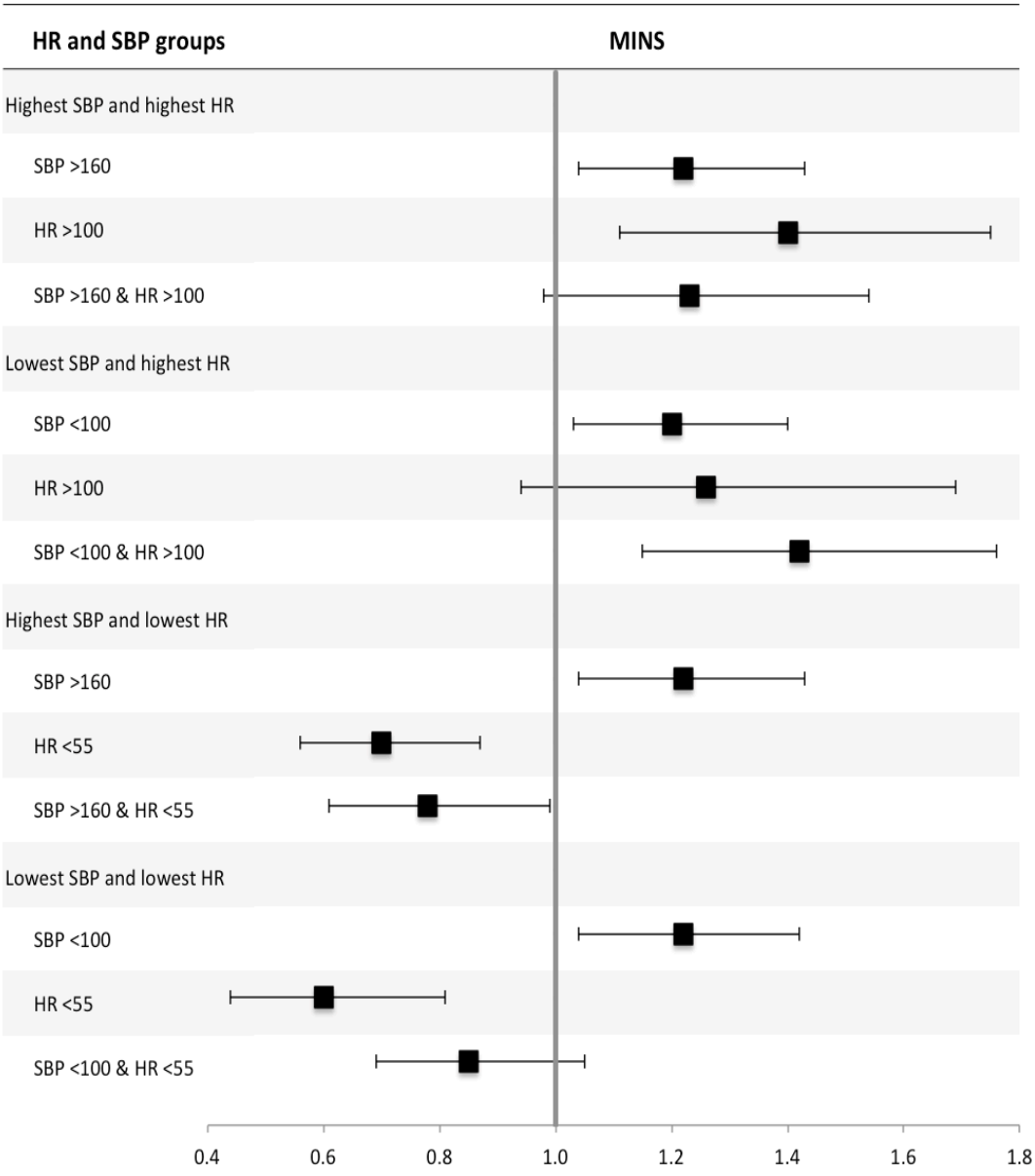

Figure 5.4. Forest plot summarising multivariable logistic regression models for combinations of highest/lowest intraoperative systolic blood pressure (SBP) and heart ate (HR). The dependent variable was myocardial injury within 30 days after surgery. The sample was categorised according to highest intraoperative systolic blood pressure (SBP) >160 mmHg, lowest intraoperative SBP <100 mmHg, highest intraoperative heart rate (HR) >100 beats per minute (bpm) and lowest intraoperative HR <55 bpm. For highest SBP and HR the reference group was SBP ≤160 & HR ≤100, for lowest SBP and highest HR the reference group was SBP ≥100 & HR ≤100, for highest SBP and lowest HR the reference group was SBP ≤160 & HR ≥55 and for lowest SBP and lowest HR the reference group was SBP ≥100 & HR ≥55. The x-axis shows odds ratios and the error bars show 95% confidence intervals. The results presented are summaries of adjusted analyses (as per the primary analysis). Full multivariable models are presented in tables 5.11-5.14.

Table 5.11. Multivariable logistic regression model for combinations of high intraoperative systolic blood pressure and high heart rate. The dependent variable is myocardial injury within 30 days after surgery. The sample was categorised according to highest intraoperative systolic blood pressure (SBP) >160 mmHg, and highest intraoperative heart rate (HR) >100 beats per minute (bpm). The reference group was SBP ≤160mmHg and heart rate ≤100 bpm. The analysis was corrected for potentially confounding factors; estimated glomerular filtration rate (eGFR). Results presented as odds ratios with 95% confidence intervals (95% CI) with lower and upper bounds shown.

	Myocardial Injury			
		95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**
Age (years)				
45-64 (reference)	-	-	-	-
65-75	1.09	0.90	1.31	0.39
>75	2.09	1.75	2.50	0.00
Male sex	1.35	1.18	1.55	0.00
Comorbid disease				
Existing atrial fibrillation	1.65	1.27	2.15	0.00
Diabetes	1.37	1.17	1.60	0.00
Hypertension	1.31	1.12	1.54	0.00
Heart failure	1.57	1.24	1.97	0.00
Coronary artery disease	1.46	1.23	1.73	0.00
Peripheral vascular disease	2.27	1.85	2.78	0.00
Previous stroke or transient ischaemic attack	1.45	1.19	1.76	0.00
Chronic obstructive pulmonary disease	1.22	1.00	1.50	0.05
eGFR (ml/min/1.73m^2)				
<30	10.59	8.55	13.1	0.00
30-45	2.49	2.01	3.10	0.00
45-60	1.63	1.34	1.98	0.00
>60 (reference)	-	-	-	-
Neurosurgery	1.14	0.86	1.51	0.36
Urgent or emergency surgery	1.94	1.65	2.29	0.00
Major surgery	1.66	1.42	1.95	0.00
Maximum SBP and maximum HR				
SBP ≤160 & HR ≤100 (reference)	-	-	-	-
SBP >160 & HR ≤100	1.22	1.04	1.43	0.02
SBP ≤160 & HR >100	1.40	1.11	1.75	0.00
SBP >160 & HR >100	1.23	0.98	1.54	0.07

Table 5.12. Multivariable logistic regression model for combinations of low intraoperative systolic blood pressure and high heart rate. The dependent variable is myocardial injury within 30 days after surgery. The sample was categorised according to lowest intraoperative systolic blood pressure (SBP) <100 mmHg, and highest intraoperative heart rate (HR) >100 beats per minute (bpm). The reference group was SBP ≥100mmHg and heart rate ≤100 bpm. The analysis was corrected for potentially confounding factors; estimated glomerular filtration rate (eGFR). Results presented as odds ratios with 95% confidence intervals (95% CI) with lower and upper bounds shown.

	Myocardial Injury			
		95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**
Age (years)				
45-64 (reference)	-	-	-	-
65-75	1.10	0.92	1.33	0.30
>75	2.16	1.80	2.58	0.00
Male sex	1.35	1.17	1.55	0.00
Comorbid disease				
Existing atrial fibrillation	1.63	1.25	2.13	0.00
Diabetes	1.38	1.19	1.61	0.00
Hypertension	1.33	1.13	1.56	0.00
Heart failure	1.57	1.24	1.97	0.00
Coronary artery disease	1.47	1.24	1.74	0.00
Peripheral vascular disease	2.30	1.88	2.83	0.00
Previous stroke or transient ischaemic attack	1.47	1.21	1.79	0.00
Chronic obstructive pulmonary disease	1.21	0.98	1.48	0.07
eGFR (ml/min/1.73m^2)				
<30	10.70	8.64	13.25	0.00
30-45	2.52	2.02	3.13	0.00
45-60	1.64	1.35	1.99	0.00
>60 (reference)	-	-	-	-
Neurosurgery	1.14	0.86	1.51	0.37
Urgent or emergency surgery	1.95	1.65	2.29	0.00
Major surgery	1.65	1.41	1.93	0.00
Maximum SBP and maximum HR				
SBP ≥100 & HR ≤100 (reference)	-	-	-	-
SBP <100 & HR ≤100	1.20	1.03	1.40	0.02
SBP ≥100 & HR >100	1.26	0.94	1.69	0.13
SBP <100 & HR >100	1.42	1.15	1.76	0.00

Table 5.13. Multivariable logistic regression model for combinations of high intraoperative systolic blood pressure and low heart rate. The dependent variable is myocardial injury within 30 days after surgery. The sample was categorised according to highest intraoperative systolic blood pressure (SBP) >160 mmHg, and lowest intraoperative heart rate (HR) <55 bpm. The reference group was SBP ≤160mmHg and heart rate ≥55 bpm. The analysis was corrected for potentially confounding factors; estimated glomerular filtration rate (eGFR). Results presented as odds ratios with 95% confidence intervals (95% CI) with lower and upper bounds shown.

	Myocardial Injury			
		95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**
Age (years)				
45-64 (reference)	-	-	-	-
65-75	1.09	0.90	1.31	0.38
>75	2.08	1.74	2.49	0.00
Male sex	1.37	1.19	1.57	0.00
Comorbid disease				
Existing atrial fibrillation	1.65	1.27	2.15	0.00
Diabetes	1.36	1.17	1.59	0.00
Hypertension	1.31	1.12	1.54	0.00
Heart failure	1.55	1.23	1.95	0.00
Coronary artery disease	1.47	1.24	1.75	0.00
Peripheral vascular disease	2.27	1.85	2.79	0.00
Previous stroke or transient ischaemic attack	1.46	1.20	1.77	0.00
Chronic obstructive pulmonary disease	1.18	0.96	1.45	0.11
eGFR (ml/min/1.73m^2)				
<30	10.61	8.57	13.14	0.00
30-45	2.52	2.03	3.13	0.00
45-60	1.64	1.35	1.99	0.00
>60 (reference)	-	-	-	-
Neurosurgery	1.18	0.89	1.57	0.24
Urgent or emergency surgery	1.88	1.59	2.22	0.00
Major surgery	1.66	1.42	1.94	0.00
Maximum SBP and maximum HR				
SBP ≤160 & HR ≥55 (reference)	-	-	-	-
SBP >160 & HR ≥55	1.22	1.04	1.43	0.02
SBP ≤160 & HR <55	0.70	0.56	0.87	0.00
SBP >160 & HR <55	0.78	0.61	0.99	0.05

Table 5.14. Multivariable logistic regression model for combinations of low intraoperative systolic blood pressure and low heart rate. The dependent variable is myocardial injury within 30 days after surgery. The sample was categorised according to highest intraoperative systolic blood pressure (SBP) <100 mmHg, and lowest intraoperative heart rate (HR) <55 bpm. The reference group was SBP ≥100mmHg and heart rate ≥55 bpm. The analysis was corrected for potentially confounding factors; estimated glomerular filtration rate (eGFR). Results presented as odds ratios with 95% confidence intervals (95% CI) with lower and upper bounds shown.

	Myocardial Injury			
		95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**
Age (years)				
45-64 (reference)	-	-	-	-
65-75	1.11	0.92	1.34	0.26
>75	2.17	1.82	2.60	0.00
Male sex	1.36	1.18	1.56	0.00
Comorbid disease				
Existing atrial fibrillation	1.64	1.26	2.13	0.00
Diabetes	1.38	1.18	1.61	0.00
Hypertension	1.33	1.13	1.56	0.00
Heart failure	1.55	1.23	1.95	0.00
Coronary artery disease	1.49	1.25	1.77	0.00
Peripheral vascular disease	2.32	1.89	2.85	0.00
Previous stroke or transient ischaemic attack	1.49	1.23	1.82	0.00
Chronic obstructive pulmonary disease	1.16	0.95	1.42	0.15
eGFR (ml/min/1.73m^2)				
<30	10.65	8.60	13.20	0.00
30-45	2.55	2.05	3.17	0.00
45-60	1.65	1.36	2.00	0.00
>60 (reference)	-	-	-	-
Neurosurgery	1.19	0.90	1.58	0.22
Urgent or emergency surgery	1.88	1.59	2.22	0.00
Major surgery	1.64	1.40	1.92	0.00
Maximum SBP and maximum HR				
SBP ≥100 & HR ≥55 (reference)	-	-	-	-
SBP <100 & HR ≥55	1.22	1.04	1.42	0.02
SBP ≥100 & HR <55	0.60	0.44	0.81	0.00
SBP <100 & HR <55	0.85	0.69	1.05	0.13

5.3.4 Sensitivity analyses

When I repeated the primary analyses excluding 1828 participants undergoing emergency surgery, the results were similar (tables 5.15-5.18). When the primary heart rate analysis was repeated excluding 2727 participants that received either a beta-blocker or rate-limiting calcium channel blocker within 24 hours before surgery, the results were very similar (tables 5.19 and 5.20). However, the association between the lowest intraoperative heart rate <55 bpm and reduced mortality was no longer statistically significant (OR 0.71 [0.49 – 1.03]; p=0.07). When the primary heart rate analysis was repeated excluding 545 participants with pre-existing atrial fibrillation, the results were very similar (tables 5.21 and 5.22). However, the association between highest intraoperative heart rate >100 bpm and MI was only a trend (OR 1.29 [0.99 – 1.67]; p=0.06). A post-hoc analysis that categorised heart rate and SBP into two four-level categorical variables (table 5.23) generated similar results to the primary analysis (tables 5.24 and 5.25), except that the association between maximum SBP >160 mmHg and MINS was no longer statistically significant (OR 1.22 [0.97-1.52]; p=0.08). The combination of minimum SBP <100 mmHg and maximum SBP >160 mmHg was associated with MINS (OR 1.42 [1.16-1.75]; p<0.01). However, the combination of minimum heart rate <55 bpm and maximum heart rate >100 bpm was not associated with MINS (OR 0.70 [0.44-1.13]; p=0.15). To account for possible increased type I error associated with multiple comparisons in the analysis of duration of high or low HR/SBP, I undertook Bonferroni corrections. The results remained similar: longest durations of SBP <100 mmHg (>61 minutes), HR >100 bpm (>30 mins) and HR <55 bpm (>55 mins) remained associated with MINS. However, associations between intermediate durations and MINS were not statistically significant.

Table 5.15. Sensitivity analysis excluding participants undergoing emergency surgery. Multivariable logistic regression models for highest intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of >100 beat per minute (bpm). Heart rate ≤100 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.10	0.90	1.34	0.35	1.22	0.88	1.68	0.23	1.69	1.15	2.49	0.01
>75	2.08	1.72	2.53	<0.01	2.24	1.65	3.04	<0.01	2.52	1.70	3.73	<0.01
Male sex	1.38	1.19	1.61	<0.01	1.05	0.83	1.32	0.70	1.24	0.92	1.67	0.16
Comorbid disease												
History of atrial fibrillation	1.93	1.46	2.55	<0.01	1.51	1.02	2.25	0.04	1.16	0.67	2.03	0.60
History of diabetes	1.34	1.13	1.59	<0.01	1.17	0.90	1.51	0.24	0.90	0.63	1.28	0.55
History of hypertension	1.24	1.04	1.48	0.02	1.24	0.94	1.64	0.13	1.03	0.74	1.44	0.85
History of heart failure	1.47	1.14	1.89	<0.01	1.47	1.04	2.08	0.03	1.14	0.68	1.91	0.63
History of coronary artery disease	1.53	1.28	1.84	<0.01	2.38	1.84	3.09	<0.01	1.14	0.77	1.67	0.51
History of peripheral vascular disease	2.04	1.63	2.55	<0.01	2.14	1.56	2.92	<0.01	1.49	0.94	2.38	0.09
History of stroke or transient ischaemic attack	1.47	1.19	1.83	<0.01	1.13	0.81	1.57	0.48	1.68	1.14	2.49	0.01
History of chronic obstructive pulmonary disease	1.28	1.03	1.59	0.03	1.12	0.81	1.56	0.48	2.33	1.63	3.35	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	11.84	9.37	14.98	<0.01	4.11	2.90	5.82	<0.01	2.26	1.35	3.80	<0.01
30-44	2.68	2.11	3.41	<0.01	1.72	1.19	2.49	<0.01	1.56	0.96	2.52	0.07
45-60	1.65	1.34	2.05	<0.01	1.41	1.01	1.95	0.04	0.83	0.51	1.35	0.46
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.11	0.82	1.48	0.51	0.56	0.32	0.97	0.04	1.77	1.09	2.87	0.02
Urgent surgery	2.12	1.54	2.92	<0.01	2.58	1.70	3.90	<0.01	3.87	2.54	5.90	<0.01
Major surgery	1.70	1.44	2.01	<0.01	2.48	1.87	3.29	<0.01	1.30	0.94	1.80	0.12
Maximum intraoperative heart rate (bpm)												
>100	1.38	1.14	1.66	<0.01	1.46	1.10	1.93	0.01	2.82	2.08	3.82	<0.01

Table 5.16. Sensitivity analysis excluding participants undergoing emergency surgery. Multivariable logistic regression models for lowest intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of <55 beat per minute (bpm). Heart rate ≥55 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.10	0.90	1.34	0.35	1.21	0.88	1.67	0.23	1.61	1.10	2.37	0.02
>75	2.06	1.70	2.51	<0.01	2.22	1.64	3.01	<0.01	2.38	1.61	3.51	<0.01
Male sex	1.40	1.20	1.62	<0.01	1.06	0.84	1.33	0.65	1.27	0.95	1.71	0.11
Comorbid disease												
History of atrial fibrillation	1.95	1.48	2.58	<0.01	1.55	1.04	2.30	0.03	1.30	0.75	2.24	0.35
History of diabetes	1.35	1.14	1.59	<0.01	1.17	0.91	1.52	0.23	0.92	0.64	1.31	0.64
History of hypertension	1.24	1.04	1.47	0.02	1.23	0.93	1.63	0.15	1.01	0.73	1.40	0.96
History of heart failure	1.44	1.12	1.85	0.01	1.44	1.02	2.04	0.04	1.08	0.64	1.80	0.78
History of coronary artery disease	1.53	1.28	1.84	<0.01	2.35	1.81	3.04	<0.01	1.06	0.72	1.55	0.77
History of peripheral vascular disease	2.04	1.63	2.55	<0.01	2.12	1.55	2.90	<0.01	1.48	0.94	2.34	0.09
History of stroke or transient ischaemic attack	1.51	1.22	1.87	<0.01	1.16	0.83	1.61	0.38	1.87	1.27	2.75	<0.01
History of chronic obstructive pulmonary	1.24	0.99	1.54	0.06	1.10	0.80	1.53	0.56	2.25	1.57	3.22	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	11.73	9.27	14.84	<0.01	4.06	2.87	5.76	<0.01	2.26	1.35	3.78	<0.01
30-44	2.74	2.16	3.48	<0.01	1.74	1.20	2.52	<0.01	1.63	1.01	2.63	0.05
45-60	1.67	1.35	2.06	<0.01	1.41	1.01	1.95	0.04	0.82	0.51	1.33	0.42
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.15	0.85	1.54	0.37	0.57	0.33	1.00	0.05	1.78	1.10	2.88	0.02
Urgent surgery	2.15	1.56	2.95	<0.01	2.72	1.81	4.09	<0.01	4.56	3.03	6.87	<0.01
Major surgery	1.70	1.44	2.01	<0.01	2.47	1.86	3.28	<0.01	1.32	0.95	1.82	0.10
Minimum intraoperative heart rate (bpm)												
<55	0.70	0.59	0.83	<0.01	0.76	0.58	1.00	<0.05	0.57	0.39	0.83	<0.01

Table 5.17. Sensitivity analysis excluding participants undergoing emergency surgery. Multivariable logistic regression models for highest intraoperative systolic blood pressure. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative systolic blood pressure (SBP) was dichotomised according to a threshold of >160 mmHg. SBP ≤160 mmHg was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.09	0.89	1.33	1.18	1.18	0.86	1.64	0.31	1.67	1.13	2.45	0.01
>75	2.09	1.71	2.54	2.18	2.18	1.60	2.97	<0.01	2.45	1.65	3.62	<0.01
Male sex	1.37	1.18	1.60	1.03	1.03	0.81	1.30	0.81	1.21	0.90	1.63	0.20
Comorbid disease												
History of atrial fibrillation	2.06	1.55	2.73	<0.01	1.64	1.10	2.44	0.02	1.28	0.73	2.24	0.39
History of diabetes	1.32	1.11	1.57	<0.01	1.17	0.90	1.52	0.24	0.90	0.62	1.29	0.56
History of hypertension	1.23	1.03	1.47	0.02	1.21	0.91	1.61	0.18	1.01	0.72	1.41	0.96
History of heart failure	1.41	1.09	1.82	0.01	1.40	0.98	1.99	0.06	1.03	0.60	1.76	0.92
History of coronary artery disease	1.50	1.25	1.81	<0.01	2.27	1.74	2.94	<0.01	1.03	0.70	1.52	0.88
History of peripheral vascular disease	2.08	1.66	2.61	<0.01	2.20	1.61	3.01	<0.01	1.55	0.97	2.46	0.07
History of stroke or transient ischaemic attack	1.51	1.22	1.88	<0.01	1.16	0.84	1.61	0.38	1.99	1.35	2.93	<0.01
History of chronic obstructive pulmonary disease	1.28	1.03	1.59	0.03	1.17	0.84	1.62	0.35	2.20	1.53	3.18	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	11.86	9.35	15.05	<0.01	4.15	2.91	5.90	<0.01	2.39	1.43	4.01	<0.01
30-44	2.68	2.11	3.41	<0.01	1.75	1.21	2.54	<0.01	1.58	0.97	2.58	0.06
45-60	1.58	1.27	1.96	<0.01	1.35	0.96	1.88	0.08	0.74	0.45	1.23	0.25
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.12	0.83	1.51	0.46	0.58	0.33	1.02	0.06	1.74	1.07	2.81	0.03
Urgent surgery	2.16	1.57	2.99	<0.01	2.55	1.67	3.88	<0.01	4.83	3.19	7.31	<0.01
Major surgery	1.70	1.43	2.01	<0.01	2.40	1.81	3.19	<0.01	1.37	0.99	1.90	0.06
Maximum intraoperative systolic blood pressure (mmHg)												
>160	1.22	1.05	1.43	0.01	1.40	1.11	1.77	0.01	0.78	0.57	1.08	0.13

Table 5.18. Sensitivity analysis excluding participants undergoing emergency surgery. Multivariable logistic regression models for lowest intraoperative systolic blood pressure. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative systolic blood pressure (SBP) was dichotomised according to a threshold of <100 mmHg. SBP ≥100 mmHg was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.11	0.91	1.36	0.30	1.21	0.88	1.68	0.24	1.71	1.16	2.51	0.01
>75	2.19	1.80	2.67	<0.01	2.33	1.71	3.17	<0.01	2.59	1.74	3.84	<0.01
Male sex	1.37	1.17	1.59	<0.01	1.03	0.81	1.30	0.83	1.24	0.92	1.67	0.15
Comorbid disease												
History of atrial fibrillation	2.03	1.54	2.70	<0.01	1.59	1.07	2.37	0.02	1.37	0.79	2.37	0.27
History of diabetes	1.34	1.13	1.59	<0.01	1.18	0.90	1.53	0.23	0.91	0.64	1.31	0.63
History of hypertension	1.25	1.04	1.49	0.02	1.25	0.94	1.66	0.12	1.00	0.72	1.39	0.98
History of heart failure	1.43	1.10	1.84	0.01	1.41	0.99	2.01	0.06	1.09	0.65	1.85	0.75
History of coronary artery disease	1.52	1.26	1.82	<0.01	2.30	1.77	2.98	<0.01	1.08	0.73	1.58	0.71
History of peripheral vascular disease	2.14	1.71	2.69	<0.01	2.28	1.66	3.12	<0.01	1.57	0.99	2.49	0.06
History of stroke or transient ischaemic attack	1.55	1.25	1.93	<0.01	1.21	0.87	1.67	0.26	1.93	1.31	2.85	<0.01
History of chronic obstructive pulmonary disease	1.27	1.02	1.58	0.03	1.13	0.82	1.57	0.46	2.21	1.54	3.18	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	12.02	9.47	15.25	<0.01	4.15	2.92	5.91	<0.01	2.47	1.47	4.14	<0.01
30-44	2.69	2.11	3.42	<0.01	1.76	1.21	2.55	<0.01	1.61	1.00	2.60	0.05
45-60	1.60	1.29	1.98	<0.01	1.36	0.98	1.90	0.07	0.74	0.45	1.23	0.24
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.12	0.83	1.51	0.46	0.59	0.34	1.03	0.07	1.70	1.05	2.75	0.03
Urgent surgery	2.16	1.56	2.98	<0.01	2.52	1.65	3.85	<0.01	4.58	3.02	6.94	<0.01
Major surgery	1.68	1.42	2.00	<0.01	2.38	1.79	3.17	<0.01	1.32	0.95	1.84	0.10
Minimum intraoperative systolic blood pressure (mmHg)												
<100	1.32	1.13	1.55	<0.01	1.43	1.12	1.82	<0.01	1.81	1.31	2.49	<0.01

Table 5.19. Sensitivity analysis excluding participants receiving beta-blockers or rate-limiting calcium channel blockers within 24 hours before surgery. Multivariable logistic regression models for highest intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of >100 beat per minute (bpm). Heart rate ≤100 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.12	0.90	1.39	0.32	1.09	0.77	1.54	0.64	1.68	1.17	2.41	0.01
>75	2.27	1.85	2.79	<0.01	1.85	1.34	2.57	<0.01	2.28	1.59	3.27	<0.01
Male sex	1.24	1.05	1.45	0.01	0.78	0.60	1.00	0.05	1.10	0.84	1.44	0.51
Comorbid disease												
History of atrial fibrillation	1.79	1.25	2.55	<0.01	1.28	0.77	2.12	0.34	0.81	0.42	1.57	0.54
History of diabetes	1.31	1.09	1.58	0.01	1.30	0.98	1.72	0.07	1.01	0.73	1.40	0.96
History of hypertension	1.20	1.01	1.44	0.04	1.20	0.91	1.59	0.21	1.02	0.76	1.37	0.91
History of heart failure	1.75	1.30	2.36	<0.01	2.14	1.46	3.14	<0.01	1.32	0.79	2.22	0.30
History of coronary artery disease	1.56	1.24	1.96	<0.01	2.40	1.77	3.27	<0.01	1.05	0.70	1.58	0.83
History of peripheral vascular disease	1.86	1.44	2.42	<0.01	2.08	1.45	2.98	<0.01	1.99	1.31	3.01	<0.01
History of stroke or transient ischaemic attack	1.49	1.17	1.90	<0.01	1.13	0.77	1.64	0.54	1.58	1.08	2.32	0.02
History of chronic obstructive pulmonary disease	1.40	1.11	1.76	0.01	1.56	1.12	2.19	0.01	2.42	1.72	3.40	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	12.75	9.86	16.48	<0.01	4.00	2.73	5.85	<0.01	3.47	2.25	5.35	<0.01
30-44	2.89	2.23	3.75	<0.01	1.97	1.32	2.94	<0.01	1.94	1.25	3.01	<0.01
45-60	1.72	1.36	2.16	<0.01	1.60	1.13	2.29	0.01	1.11	0.72	1.70	0.64
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.20	0.87	1.65	0.27	0.63	0.34	1.18	0.15	1.90	1.20	3.02	0.01
Urgent or emergency surgery	1.91	1.58	2.30	<0.01	2.53	1.95	3.30	<0.01	3.69	2.81	4.85	<0.01
Major surgery	1.74	1.45	2.09	<0.01	2.33	1.72	3.16	<0.01	1.71	1.24	2.36	<0.01
Maximum intraoperative heart rate (bpm)												
>100	1.28	1.06	1.55	0.01	1.46	1.11	1.93	0.01	2.23	1.69	2.94	<0.01

Table 5.20. Sensitivity analysis excluding participants receiving beta-blockers or rate-limiting calcium channel blockers within 24 hours before surgery. Multivariable logistic regression models for lowest intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of <55 beat per minute (bpm). Heart rate ≥55 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.12	0.90	1.39	0.32	1.09	0.77	1.54	0.63	1.62	1.13	2.32	0.01
>75	2.26	1.84	2.77	<0.01	1.83	1.32	2.54	<0.01	2.16	1.51	3.09	<0.01
Male sex	1.25	1.07	1.47	0.01	0.79	0.61	1.02	0.07	1.12	0.85	1.46	0.42
Comorbid disease												
History of atrial fibrillation	1.83	1.28	2.62	<0.01	1.35	0.82	2.23	0.24	0.90	0.47	1.74	0.76
History of diabetes	1.30	1.08	1.56	0.01	1.28	0.97	1.70	0.09	1.01	0.73	1.41	0.95
History of hypertension	1.19	1.00	1.42	0.05	1.18	0.89	1.56	0.24	1.00	0.75	1.35	0.98
History of heart failure	1.75	1.30	2.36	<0.01	2.10	1.43	3.09	<0.01	1.23	0.73	2.07	0.43
History of coronary artery disease	1.56	1.24	1.97	<0.01	2.38	1.75	3.23	<0.01	1.00	0.66	1.50	0.99
History of peripheral vascular disease	1.86	1.43	2.41	<0.01	2.05	1.43	2.94	<0.01	1.94	1.29	2.93	<0.01
History of stroke or transient ischaemic attack	1.53	1.20	1.95	<0.01	1.15	0.79	1.68	0.46	1.71	1.17	2.50	0.01
History of chronic obstructive pulmonary disease	1.36	1.08	1.71	0.01	1.51	1.08	2.12	0.02	2.34	1.68	3.28	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	12.67	9.80	16.39	<0.01	4.03	2.75	5.88	<0.01	3.72	2.42	5.71	<0.01
30-44	2.92	2.26	3.79	<0.01	2.01	1.35	3.00	<0.01	2.05	1.33	3.18	<0.01
45-60	1.72	1.37	2.17	<0.01	1.60	1.12	2.28	0.01	1.09	0.71	1.68	0.68
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.26	0.91	1.73	0.16	0.66	0.36	1.24	0.20	1.89	1.19	3.00	0.01
Urgent or emergency surgery	1.88	1.56	2.27	<0.01	2.52	1.94	3.28	<0.01	3.96	3.02	5.20	<0.01
Major surgery	1.73	1.45	2.08	<0.01	2.32	1.71	3.14	<0.01	1.75	1.27	2.42	<0.01
Minimum intraoperative heart rate (bpm)												
<55	0.67	0.54	0.82	<0.01	0.58	0.41	0.83	<0.01	0.71	0.49	1.03	0.07

Table 5.21. Sensitivity analysis excluding participants with pre-existing atrial fibrillation. Multivariable logistic regression models for maximum intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of >100 beat per minute (bpm). Heart rate ≤100 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.09	0.91	1.32	0.35	1.20	0.90	1.61	0.22	1.67	1.19	2.36	<0.01
>75	2.06	1.72	2.47	<0.01	1.89	1.43	2.50	<0.01	2.37	1.69	3.33	<0.01
Male sex	1.35	1.17	1.56	<0.01	0.98	0.79	1.21	0.84	1.17	0.91	1.52	0.22
Comorbid disease												
History of diabetes	1.46	1.25	1.71	<0.01	1.28	1.01	1.62	0.04	1.04	0.77	1.41	0.81
History of hypertension	1.28	1.08	1.50	<0.01	1.36	1.05	1.75	0.02	0.92	0.69	1.23	0.57
History of heart failure	1.72	1.34	2.21	<0.01	1.77	1.28	2.46	<0.01	1.33	0.83	2.13	0.24
History of coronary artery disease	1.57	1.31	1.87	<0.01	2.42	1.90	3.09	<0.01	1.01	0.71	1.44	0.96
History of peripheral vascular disease	2.09	1.69	2.60	<0.01	2.03	1.51	2.74	<0.01	1.74	1.17	2.59	0.01
History of stroke or transient ischaemic attack	1.45	1.18	1.79	<0.01	0.99	0.72	1.37	0.96	1.43	1.00	2.06	0.05
History of chronic obstructive pulmonary disease	1.25	1.01	1.54	0.04	1.29	0.96	1.75	0.10	2.34	1.69	3.23	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	10.45	8.38	13.02	<0.01	3.96	2.88	5.45	<0.01	3.40	2.29	5.05	<0.01
30-44	2.46	1.95	3.09	<0.01	1.74	1.23	2.45	<0.01	1.56	1.01	2.40	0.04
45-60	1.70	1.39	2.07	<0.01	1.51	1.12	2.05	0.01	1.06	0.71	1.59	0.77
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.17	0.89	1.55	0.27	0.59	0.34	1.01	0.06	1.80	1.16	2.80	0.01
Urgent or emergency surgery	2.07	1.75	2.45	<0.01	2.43	1.92	3.08	<0.01	3.57	2.75	4.63	<0.01
Major surgery	1.63	1.39	1.91	<0.01	2.18	1.68	2.84	<0.01	1.59	1.17	2.15	<0.01
Maximum intraoperative heart rate (bpm)												
>100	1.31	1.10	1.56	<0.01	1.29	0.99	1.67	0.06	2.57	1.97	3.35	<0.01

Table 5.22. Sensitivity analysis excluding participants with pre-existing atrial fibrillation. Multivariable logistic regression models for minimum intraoperative heart rate. Dependent variables are myocardial injury, myocardial infarction and mortality within 30 days of surgery. Intraoperative heart rate was dichotomised according to a threshold of <55 beat per minute (bpm). Heart rate ≥55 bpm was the reference category. Estimated glomerular filtration rate (eGFR).

	Myocardial Injury				Myocardial Infarction				Mortality			
		95% CI				95% CI				95% CI		
Covariates	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**	**odds ratio**	**Lower**	**Upper**	**p-value**
Age												
45-64 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
65-75	1.10	0.91	1.32	0.34	1.21	0.90	1.62	0.21	1.60	1.14	2.25	0.01
>75	2.05	1.71	2.46	<0.01	1.88	1.42	2.49	<0.01	2.24	1.60	3.14	<0.01
Male sex	1.36	1.18	1.57	<0.01	0.99	0.80	1.23	0.92	1.22	0.95	1.58	0.13
Comorbid disease												
History of diabetes	1.45	1.24	1.70	<0.01	1.27	1.01	1.61	0.05	1.06	0.78	1.43	0.73
History of hypertension	1.27	1.08	1.50	<0.01	1.35	1.04	1.74	0.02	0.90	0.68	1.19	0.45
History of heart failure	1.69	1.32	2.18	<0.01	1.75	1.26	2.42	<0.01	1.26	0.79	2.01	0.33
History of coronary artery disease	1.58	1.32	1.88	<0.01	2.42	1.89	3.08	<0.01	0.94	0.66	1.33	0.72
History of peripheral vascular disease	2.08	1.68	2.58	<0.01	2.01	1.49	2.72	<0.01	1.69	1.14	2.50	0.01
History of stroke or transient ischaemic attack	1.47	1.19	1.82	<0.01	1.00	0.72	1.38	0.98	1.52	1.06	2.18	0.02
History of chronic obstructive pulmonary disease	1.21	0.98	1.49	0.08	1.26	0.93	1.71	0.13	2.22	1.60	3.06	<0.01
Preoperative eGFR (ml/min/1.73m^2)												
<30	10.42	8.36	12.99	<0.01	3.98	2.90	5.47	<0.01	3.61	2.44	5.34	<0.01
30-44	2.49	1.98	3.13	<0.01	1.75	1.24	2.47	<0.01	1.62	1.05	2.49	0.03
45-60	1.72	1.41	2.09	<0.01	1.52	1.12	2.06	0.01	1.06	0.71	1.58	0.79
>60 (reference)	-	-	-	-	-	-	-	-	-	-	-	-
Neurosurgery	1.22	0.92	1.62	0.16	0.61	0.35	1.04	0.07	1.80	1.16	2.80	0.01
Urgent or emergency surgery	2.03	1.72	2.40	<0.01	2.42	1.91	3.06	<0.01	3.82	2.95	4.95	<0.01
Major surgery	1.63	1.39	1.91	<0.01	2.17	1.67	2.82	<0.01	1.63	1.20	2.20	<0.01
Minimum intraoperative heart rate (bpm)												
<55	0.68	0.58	0.81	<0.01	0.75	0.58	0.98	0.04	0.63	0.45	0.88	0.01

Table 5.23. Post-hoc analysis for four-level heart rate and systolic pressure variables. Baseline data stratified by heart rate (HR) in beats per minute and systolic blood pressure (SBP) in mmHg. Estimated glomerular filtration rate (eGFR). Myocardial injury after non-cardiac surgery (MINS).

	Intraoperative heart rate (HR)				Intraoperative systolic blood pressure (SBP)			
	HR 55-100	**HR <55**	**HR >100**	**HR >100 & <55**	**SBP 100-160**	**SBP <100**	**SBP >160**	**SBP >160 & <100**
Number of cases (n)	8022	3202	2051	465	3491	6081	1711	2457
Mean age (SD)	66.0 (11.8)	66.2 (11.2)	64.2 (12.4)	63.6 (11.4)	66.3 (11.7)	63.4 (11.4)	70.1 (11.7)	67.3 (11.3)
Sex								
Male (%)	3838 (47.8)	1603 (50.1)	1024 (49.9)	244 (52.5)	1835 (52.6)	2938 (48.3)	769 (44.9)	1167 (47.5)
Female (%)	4184 (52.2)	1599 (49.9)	1027 (50.1)	221 (47.5)	1656 (47.4)	3143 (51.7)	942 (55.1)	1290 (52.5)
Comorbid disorder (%)								
Atrial fibrillation	267 (3.3)	87 (2.7)	109 (5.3)	12 (2.6)	155 (4.4)	173 (2.8)	66 (3.9)	81 (3.3)
Diabetes	1627 (20.3)	584 (18.2)	477 (23.3)	74 (15.9)	716 (20.5)	1019 (16.8)	452 (26.4)	575 (23.4)
Hypertension	4221 (52.6)	1772 (55.3)	960 (46.8)	185 (39.8)	1795 (51.4)	2817 (46.3)	1119 (65.4)	1407 (57.3)
Heart failure	408 (5.1)	155 (4.8)	91 (4.4)	11 (2.4)	195 (5.6)	244 (4.0)	107 (6.3)	119 (4.8)
Coronary artery disease	990 (12.3)	500 (15.6)	185 (9.0)	34 (7.3)	482 (13.8)	625 (10.3)	287 (16.8)	315 (12.8)
Peripheral vascular disease	439 (5.5)	199 (6.2)	98 (4.8)	10 (2.2)	218 (6.2)	246 (4.0)	152 (8.9)	130 (5.3)
Previous stroke or transient ischemic attack	522 (6.5)	238 (7.4)	213 (10.4)	34 (7.3)	234 (6.7)	304 (5.0)	211 (12.3)	258 (10.5)
Chronic obstructive pulmonary disease	809 (10.1)	223 (7.0)	164 (8.0)	15 (3.2)	331 (9.5)	524 (8.6)	149 (8.7)	207 (8.4)
Preoperative eGFR, ml/min/1.73m^2 (%)								
<30	304 (3.8)	87 (2.7)	105 (5.1)	8 (1.7)	130 (3.7)	199 (3.3)	95 (5.6)	80 (3.3)
30-45	407 (5.1)	187 (5.8)	129 (6.3)	17 (3.7)	167 (4.8)	277 (4.6)	159 (9.3)	137 (5.6)
45-60	852 (10.6)	390 (12.2)	183 (8.9)	35 (7.5)	372 (10.7)	533 (8.8)	239 (14.0)	316 (12.9)
>60	6459 (80.5)	2538 (79.3)	1634 (79.7)	405 (87.1)	2822 (80.8)	5072 (83.4)	1218 (71.2)	1924 (78.3)
Surgical procedure category (%)								
Elective	6906 (86.1)	2964 (92.6)	1591 (77.6)	419 (90.1)	3022 (86.6)	5297 (87.1)	1449 (84.7)	2112 (86.0)
Urgent	217 (2.7)	56 (1.7)	122 (5.9)	10 (2.2)	85 (2.4)	175 (2.9)	49 (2.9)	96 (3.9)
Emergency	899 (11.2)	182 (5.7)	338 (16.5)	36 (7.7)	384 (11.0)	609 (10.0)	213 (12.4)	249 (10.1)
Major surgery (%)	4950 (61.7)	1951 (60.9)	1289 (62.8)	258 (55.5)	1963 (56.2)	3825 (62.9)	1070 (62.5)	1590 (64.7)
MINS (%)	674 (8.4)	197 (6.2)	226 (11.0)	20 (4.3)	252 (7.2)	440 (7.2)	190 (11.1)	235 (9.6)

Table 5.24. Post-hoc analysis for heart rate as a four-level categorical variable. Multivariable logistic regression model. Dependent variable is myocardial injury after non-cardiac surgery (MINS). Estimated glomerular filtration rate (eGFR).

	Myocardial injury	
Covariates	**odds ratio**	**p-value**
Age		
45-64 (reference)	-	-
65-75	1.11 (0.92-1.33)	0.30
>75	2.14 (1.79-2.56)	<0.01
Male sex	1.35 (1.18-1.55)	<0.01
Comorbid disease		
Existing atrial fibrillation	1.60 (1.23-2.08)	<0.01
Diabetes	1.37 (1.17-1.59)	<0.01
Hypertension	1.33 (1.13-1.56)	<0.01
Heart failure	1.56 (1.23-1.96)	<0.01
Coronary artery disease	1.49 (1.25-1.76)	<0.01
Peripheral vascular disease	2.29 (1.86-2.81)	<0.01
Previous stroke or transient ischaemic attack	1.46 (1.20-1.78)	<0.01
Chronic obstructive pulmonary disease	1.18 (0.96-1.44)	0.11
eGFR (ml/min/1.73m^2)		
<30	10.47 (8.45-13.00)	<0.01
30-45	2.52 (2.02-3.13)	<0.01
45-60	1.65 (1.36-2.00)	<0.01
>60 (reference)	-	-
Neurosurgery	1.19 (0.90-1.58)	0.22
Urgent or emergency surgery	1.85 (1.56-2.18)	<0.01
Major surgery	1.66 (1.42-1.94)	<0.01
Intraoperative heart rate (bpm)		
Maximum and minimum 55-100 (reference)	-	-
Minimum <55	0.73 (0.61-0.88)	<0.01
Maximum >100	1.27 (1.06-1.52)	0.01
Minimum <55 & maximum >100	0.70 (0.44-1.13)	0.15

Table 5.25. Post-hoc analysis for systolic blood pressure as a four-level categorical variable. Multivariable logistic regression model. Dependent variable is myocardial injury after non-cardiac surgery (MINS). Estimated glomerular filtration rate (eGFR).

	Myocardial injury	
Covariates	**odds ratio**	**p-value**
Age		
45-64 (reference)	-	-
65-75	1.09 (0.90-1.31)	0.38
>75	2.11 (1.77-2.53)	<0.01
Male sex	1.36 (1.18-1.56)	<0.01
Comorbid disease		
Existing atrial fibrillation	1.69 (1.30-2.20)	<0.01
Diabetes	1.38 (1.18-1.61)	<0.01
Hypertension	1.31 (1.11-1.53)	<0.01
Heart failure	1.56 (1.24-1.97)	<0.01
Coronary artery disease	1.45 (1.23-1.72)	<0.01
Peripheral vascular disease	2.28 (1.86-2.80)	<0.01
Previous stroke or transient ischaemic attack	1.47 (1.21-1.79)	<0.01
Chronic obstructive pulmonary disease	1.21 (0.99-1.48)	0.07
eGFR (ml/min/1.73m^2)		
<30	10.80 (8.73-13.38)	<0.01
30-45	2.51 (2.02-3.12)	<0.01
45-60	1.62 (1.34-1.97)	<0.01
>60 (reference)	-	-
Neurosurgery	1.12 (0.85-1.48)	0.42
Urgent or emergency surgery	1.99 (1.69-2.34)	<0.01
Major surgery	1.65 (1.41-1.93)	<0.01
Intraoperative systolic blood pressure (mmHg)		
Maximum and minimum 100 - 160 (reference)	-	-
Minimum <100	1.24 (1.04-1.49)	0.02
Maximum >160	1.22 (0.97-1.52)	0.08
Minimum <100 & maximum >160	1.42 (1.16-1.75)	<0.01

5.3.5 Fractional polynomial analysis

Multivariable fractional polynomial analysis demonstrates that the duration of intraoperative heart rate >100 bpm was associated with myocardial injury in a non-linear fashion. The function plot (figure 5.5A) shows the duration of elevated heart rate component of the model (duration x regression coefficient) and the intercept, sometimes called the 'partial predictor', plus the residual (the residual variation between the observed data and the regression line), plotted against increasing heart rate.[323, 324] The function plot is used to illustrate how a particular term in a given model varies over the data range. In this case, the function plot (figure 5.5A) shows that the duration of elevated heart rate term in the model varies in a curvilinear fashion, indicating that the relationship between duration of elevated heart rate and myocardial injury is non-linear. This analysis also showed that the durations of low heart rate, and high/low systolic blood pressure were related to myocardial injury in a linear fashion (figure 5.5B-D).

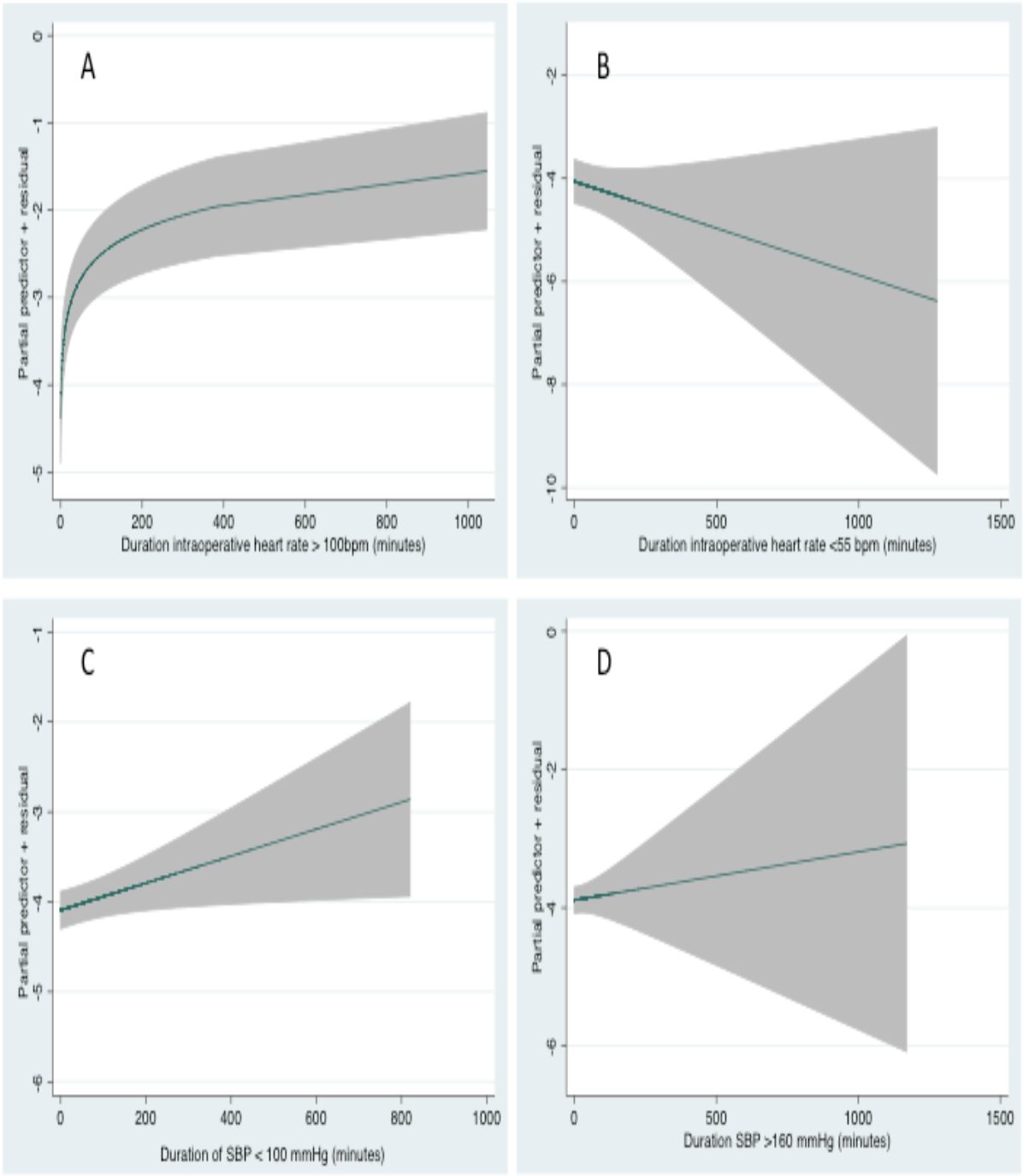

Figure 5.5. Function plots of fractional polynomial regression models for (A) Duration of intraoperative heart rate > 100 beats per minute (bpm), (B) Duration of intraoperative heart rate < 55 bpm, (C) Duration of intraoperative systolic blood pressure < 100 mmHg and (D) Duration of intraoperative systolic blood pressure > 160 mmHg. The x-axes show time in minutes and the y-axes, the partial predictor + residual. The partial predictor is the duration component of the regression equation plus the intercept. The residual is the residual variation between the regression line and the observed data. The function plot shows how a given term in a regression model varies across the data range. Here, duration of intraoperative HR > 100 bpm (panel A) varies in a curvilinear fashion, while the remaining plots show linear relationships.

5.4 Discussion

The principal finding of this analysis is that intraoperative tachycardia, hypotension and hypertension are independently associated with myocardial injury and mortality. Here, I demonstrate the effect of combinations of intraoperative heart rate and systolic blood pressure suggesting that the association between hypotension and myocardial injury is increased in the presence of tachycardia and reduced in the presence of bradycardia. Prolonged durations of tachycardia and hypotension were associated with increased risk of myocardial injury. Furthermore, intraoperative bradycardia was associated with reduced risk of myocardial injury and mortality.

My results are consistent with studies demonstrating association between intraoperative hypotension and postoperative adverse events following non-cardiac surgery.[166, 171, 173, 203, 381, 391] However, unlike my study, these were small and mostly retrospective studies that did not use objective biomarkers as outcome measure. This is the first study to identify relationships between high intraoperative heart rate/systolic blood pressure and increased risk of perioperative myocardial injury, and low intraoperative heart rate and reduced risk of myocardial injury. While the observational nature of my data does allow me to infer causal relationships, it is reasonable to hypothesise that avoidance of either very high heart rate, or very high/low systolic blood pressures during surgery may be clinically beneficial. Data from clinical trials suggest that treatment with beta-blockers (which lower heart rate) can reduce the risk of myocardial infarction after non-cardiac surgery, but at the expense of larger increases in the risk of mortality and stroke.[166, 258] However, it is difficult to disentangle the effect of heart rate from the effect of beta-blockers and the

degree of interaction between these variables. In this study, 2,727 (16.9%) patients received a beta-blocker or negatively chronotropic calcium channel blocker within 24 hours before surgery. I repeated the primary analysis after removing these cases and found that the associations between maximum intraoperative heart rate and the outcomes were unchanged. However, the negative association between minimum intraoperative heart rate < 55bpm and mortality was no longer statistically significant. In other words, the 'protective' association between low heart rate and reduced risk of mortality was lost in patients not receiving a beta-blocker or calcium channel antagonist. However, it is not possible to infer a causative relationship due to the observational nature of the data. This contrasts with the results of previous clinical trials where heart rate lowering medication was associated with increased mortality.[166] Further research is needed to investigate potential mechanisms underlying this observation, in addition to trials of new heart rate control methods that avoid hypotension.

These data suggest that very high or very low intraoperative heart rate and blood pressure may be key factors that, alone or in combination, contribute to the development of myocardial injury. The most widely accepted model suggests that most perioperative myocardial injury is caused by extended periods of myocardial ischaemia as a result of oxygen supply-demand imbalance in cardiac muscle.[96] In this context, intraoperative hypotension or tachycardia may reduce myocardial perfusion pressure leading to reduced myocardial oxygen supply. Similarly, elevated systolic pressure, which increases end-systolic stress, may cause myocardial oxygen demand to exceed the available supply, resulting in relative hypoperfusion of the cardiac muscle

and myocardial injury.[147] My results are consistent with a myocardial oxygen supply-demand imbalance hypothesis, given the increasing risk of myocardial injury as the duration of tachycardia or hypotension increased. This is supported by the results of animal studies, where tachycardia induces sub-endocardial myocardial necrosis at a rate correlated with the duration of ischaemia.[160] It is also possible that my observations are due to confounding by other factors. The analyses were adjusted for multiple perioperative variables that are known to be associated with cardiovascular morbidity and mortality after surgery. However, it was not possible to account for confounding by other unmeasured factors. Therefore, I cannot exclude the possibility that tachycardia/hypertension/hypotension are merely markers of other conditions or treatment interventions that may promote myocardial injury.[277, 347, 348, 392, 393] In addition, this analysis was limited to intraoperative heart rate and blood pressure, although, other analyses suggest that abnormalities of preoperative heart rate and blood pressure are also associated with myocardial injury after surgery (chapters three and four). Further research is needed into the potential for preoperative identification of patients at risk of myocardial injury.[17, 279]

A strength of this analysis is the large sample size derived from multiple centres in multiple countries, giving robust external validity and making the results generalisable to the vast majority of patients undergoing non-cardiac surgery. The primary outcome was an objective biomarker, rather than a potentially subjective, clinically defined outcome, which may have reduced information bias. Furthermore, since more than nine out of ten patients with postoperative troponin elevation are asymptomatic and only one quarter have electrocardiographic or echocardiographic evidence of ischaemia, previous

studies using clinically defined outcomes are likely to have underestimated the incidence of postoperative myocardial injury, which my analysis should have avoided.[95] Conversely, my analysis used data from a Roche 4th generation troponin assay, which will underestimate the incidence of myocardial injury compared to newer highly sensitive assays. Thus, I would like to repeat this study using highly sensitive troponin assays. The detailed nature of the VISION database allowed the analysis to be adjusted for confounding factors using multivariable regression modelling, including pre-existing atrial fibrillation.

This analysis also has some limitations. I cannot exclude the influence of unmeasured confounding. For example, the use of intraoperative cardiac medication, the presence of cardiac pacemakers and the incidence of preoperative troponin elevation are all unknown, although the frequency of these is likely to be low.[114, 356] The association between elevated heart rate may have been confounded by the presence of preoperative atrial fibrillation. I corrected for this by including pre-existing atrial fibrillation in the multivariable models and through a sensitivity analysis. Additional sensitivity analyses that excluded cases of emergency surgery, and patients receiving preoperative beta-blockers or rate limiting calcium channel antagonists were also performed. Continuous measurements of intraoperative heart rate and blood pressure were not recorded as part of this study; therefore the analysis was limited to summary data for intraoperative heart rate and blood pressure based on pre-defined consensus thresholds. Since measurements of heart rate or blood pressure were not time-stamped, analyses of combinations of abnormal heart rate and blood pressure did not necessarily constitute simultaneous or contemporaneous

episodes. Future computational research using continuously recorded heart rate or blood pressure data could be considered.

5.5 Conclusion

Intraoperative tachycardia and extremes of systolic blood pressure are associated with increased risk of myocardial injury after non-cardiac surgery. In addition, the duration of intraoperative hypotension and tachycardia are also associated with perioperative myocardial injury. Further targeted interventional studies using intraoperative heart rate and/or blood pressure thresholds that I have identified may help identify strategies to reduce perioperative cardiac complications.

Chapter six

Cardiopulmonary and autonomic impairment

Elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment in high-risk surgical patients

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6.1 Introduction

I have previously found that elevated intraoperative heart rate and elevated preoperative heart rate were associated with myocardial injury and mortality after non-cardiac surgery, in chapters five and three respectively.[273, 274] These findings are consistent with an oxygen supply-demand imbalance model of perioperative myocardial injury, where transient mismatch between oxygen delivery and oxygen consumption in the myocardium causes cellular injury, detectable as troponin release.[96] While it is plausible that tachycardia could promote myocardial injury via this mechanism, there is insufficient evidence to support a causal link. Meanwhile, evidence that elevated resting heart rate *before* surgery is associated with myocardial injury raises the question of whether tachycardia may be a marker of an underlying pathological process or disease state that could cause or contribute to myocardial injury.[273, 387]

In the general population, elevated resting heart rate is an independent risk factor for the subsequent development of heart failure.[158, 159, 394] In the perioperative setting, patients with a confirmed diagnosis of heart failure syndrome are twice as likely to die within 30 days after non-cardiac surgery, compared to patients without heart failure.[349, 350] Cardiopulmonary exercise testing (CPET) can identify cardiopulmonary and/or autonomic impairment and has been used for prognostication in patients with confirmed heart failure.[70, 71, 179] CPET is also used for surgical risk assessment in one third of UK hospitals, where, on preoperative testing, similar patterns of CPET variables can be observed as in patients with confirmed heart failure.[1, 57, 58] Therefore, elevated heart rate before surgery may indicate underlying sub-clinical heart failure, which may be detectable with CPET. This could generate several plausible pathophysiological mechanisms that may contribute to perioperative myocardial injury and mortality.[96, 273, 281, 395]

I hypothesised that elevated preoperative resting heart rate (>87 bpm) [273] was associated with impaired cardiopulmonary and/or autonomic function consistent with sub-clinical cardiac failure. I tested this hypothesis by evaluating cardiopulmonary and autonomic factors derived from preoperative cardiopulmonary exercise testing that are known to be associated with clinical outcome in patients with heart failure.[16]

6.2 Methods

This was a secondary analysis of prospectively collected data from the Perioperative Morbidity – Heart Rate (POM-HR) study, a multi-centre observational cohort study of high-risk patients undergoing non-cardiac surgery. I have described the methods in chapter two and data from the study has been published previously.[396, 397] Patients were aged 45 years or more, scheduled for major surgery predicted to last for more than two hours, and were referred for cardiopulmonary exercise testing (CPET) as part of their routine preoperative assessment. These criteria are very similar to the eligibility criteria for the VISION study.[16] Researchers collected a standardised data set before, during and after surgery from patients and their medical records.

6.2.1 Cardiopulmonary exercise testing (CPET)

All participants underwent preoperative symptom-limited CPET, which was carried out at each participating hospital in designated CPET laboratories. I have described the procedures for cardiopulmonary exercise testing in detail in chapter two (methods).[397] The anaerobic threshold (AT) was determined by two independent assessors according to published guidelines using the modified V-slope method and confirmed by ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2). Oxygen consumption (ml/kg/min) was measured at the anaerobic threshold and at peak exertion. The ventilatory equivalent for carbon dioxide (V_E/VCO_2) was measured at the anaerobic threshold and presented as a ratio. Resting heart rate was defined as heart rate measured before each test after 30 seconds in the sitting position. Peak heart rate was defined as maximal heart rate achieved during exercise. Heart rate recovery, was calculated as the difference between peak heart rate and heart rate one

minute after the end of peak exercise, thus representing the change in heart rate during the one minute after exercise in bpm. Peak oxygen pulse (ml/beat), a surrogate marker for cardiac stroke volume,[398] was calculated as peak oxygen consumption (ml/min) divided by peak heart rate (bpm).

6.2.2 Exposure of interest

The exposure of interest was preoperative resting heart rate >87 bpm. I have previously identified this threshold as associated with postoperative myocardial injury and mortality in chapter three.[273]

6.2.3 Outcome measures

The primary outcome measures were three CPET-derived variables that are established and independent predictors of mortality in patients with confirmed heart failure: ventilatory equivalent for carbon dioxide (V_E/VCO_2) ≥34, heart rate recovery ≤6 bpm and peak oxygen consumption (VO_2) ≤14 ml/kg/min.[70] Secondary outcome measures were other CPET-derived cardiopulmonary and autonomic variables known to be associated with postoperative clinical outcomes or cardiovascular morbidity in the general population: preoperative pulse pressure, oxygen consumption at the anaerobic threshold, peak oxygen pulse and peak heart rate. Full details for the original papers detailing the prognostic value of these variables are described in the introduction (section 1.1.5).

6.2.4 Statistical analyses

I planned the analysis before accessing the data. I used STATA version 14 (StataCorp LP, Texas, USA) to analyse the data. Categorical data were summarised as number with percentage. Continuous data with a normal distribution were summarised as mean with standard deviation; continuous data that do not follow a normal distribution were summarised as median with interquartile range. Missing data were handled by list-wise deletion. I dichotomised the sample according to heart rate >87 bpm and summarised descriptive physiological variables for each group.[273] I used a t-test to identify differences in continuous variables between groups and a chi-squared test to identify differences in categorical data between groups. I used logistic regression analysis to test for association between elevated preoperative heart rate >87 bpm and each outcome measure, first using univariable analysis. Then, I tested whether pre-existing cardiovascular medication (beta-blockers, calcium channel antagonists, diuretics, nitrates, anti-platelet agents, statins or angiotensin converting enzyme inhibitors/receptor blockers) were associated with heart rate >87 bpm. I subsequently used multivariable analysis to correct for potential confounding by age (>75 years), gender and cardiovascular co-morbidity as determined by Revised Cardiac Risk Index (RCRI) >2.[16, 20] I chose to include RCRI as this is routinely used as a risk score to predict perioperative cardiovascular complications and as a comparator with new risk stratification tools (e.g. preoperative coronary computed tomographic angiography).[3] The results of logistic regression analyses were presented as odds ratios with 95% confidence intervals; $p \leq 0.05$ was considered statistically significant.

6.2.5 Preoperative left ventricular stroke volume

I wanted to test the hypothesis that preoperative resting heart rate >87 bpm was associated with a heart failure phenotype in a separate data set and using a different method. Therefore, I undertook a post-hoc analysis of data from the OPTIMISE and POM-O trials. These trials have been described in chapter two and the principal findings and methods published previously.[279, 281, 397] I assessed whether preoperative resting heart rate >87 bpm was associated with impaired left ventricular stroke volume in patients undergoing major abdominal surgery. The analysis was restricted to haemodynamic data collected from cardiac output monitors before and during surgery, which provided detailed beat-by-beat measurements of heart rate, cardiac output and stroke volume. The cohort was dichotomised according to a mean preoperative heart rate threshold of >87 bpm and compared mean beat-by-beat preoperative left ventricular stroke volume between groups using a t-test. Logistic regression analysis tested for association between mean preoperative heart rate >87 bpm and impaired preoperative stroke volume <57ml, defined according to previous research in patients with heart failure, corrected for age >75 years, gender and history of ischaemic heart disease.[399]

6.3 Results

1,572 surgical patients underwent CPET at one of five participating United Kingdom hospitals. Cases that were missing complete CPET data or pre-defined covariates were excluded, leaving 1,250 patients for the final analysis (figure 6.1). Patient characteristics are presented in table 6.2. Resting preoperative heart rate >87 bpm was recorded in 399/1250 (31.9%) patients. Age, body mass index, cardiovascular risk factors (as defined by Revised Cardiac Risk Index) and resting systolic blood pressure were similar for patients with heart rate >87 bpm compared to those with heart rate ≤87 bpm (table 6.2). 52/1250 (4.2%) patients had an established diagnosis of heart failure and 162/1250 (13.0%) had a diagnosis of ischaemic heart disease

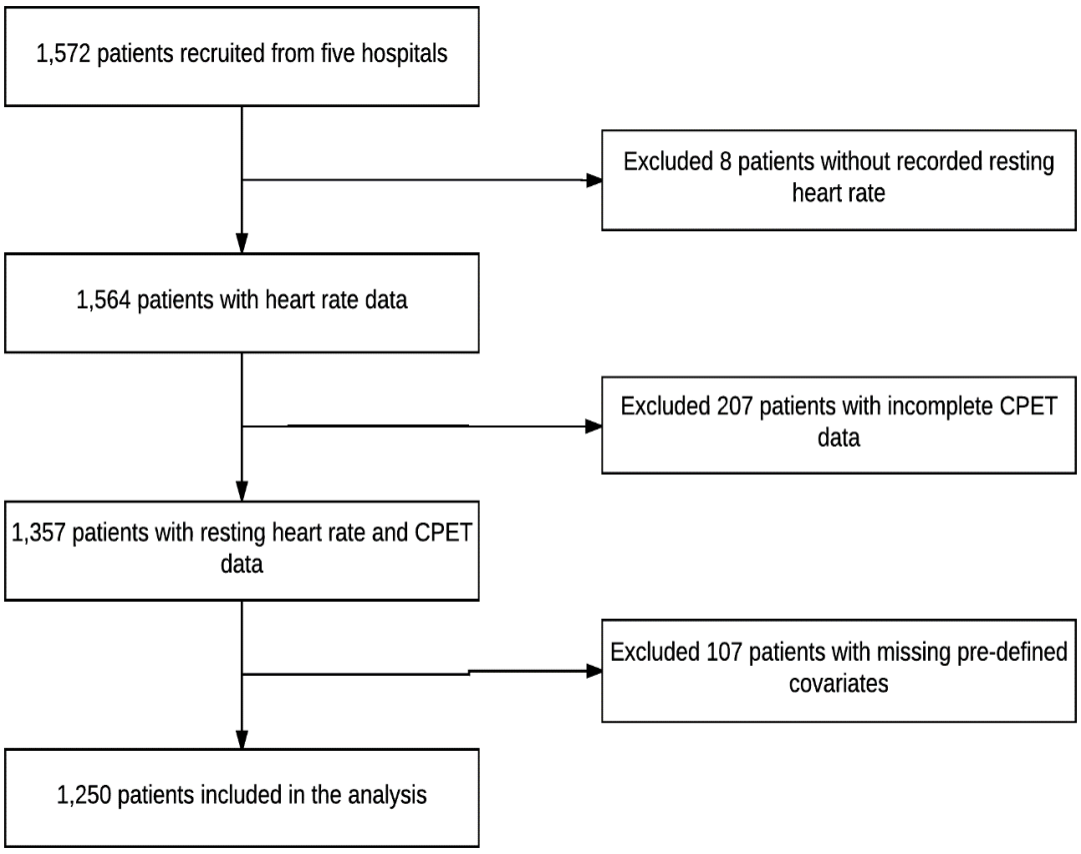

Figure 6.1. STROBE diagram showing patients included in the primary analysis

Table 6.1. Baseline patient characteristics. Descriptive data stratified by resting heart rate >87 bpm, presented as frequencies with percentages (%) or mean (standard deviation; SD). Heart rate (HR) data in >87 bpm, blood pressure data in millimetres of mercury (mmHg). Other units as indicated. Hypothesis testing using t-test for continuous data and chi-squared test for categorical data. Angiotensin converting enzyme inhibitor (ACEi), Angiotensin receptor blocker (ARB).

Characteristic	HR >87	HR ≤87	p-value
Number of patients	399	851	-
Age (SD)	66.8 (10.0)	68.5 (9.6)	<0.01
Female gender (%)	139 (34.8)	231 (27.1)	<0.01
Body Mass Index (SD)	27.7 (5.6)	27.4 (4.9)	0.33
Diabetes mellitus (%)	69 (17.3)	111 (13.0)	0.05
Revised Cardiac Risk Index			<0.01
1	170 (42.6)	296 (34.8)	-
2	204 (51.1)	433 (50.8)	-
3	21 (5.2)	101 (12.3)	-
4	4 (1.0)	19 (4.8)	-
Type of surgery (%)			<0.01
Colorectal	133 (34.5)	283 (34.3)	-
Upper gastrointestinal	70 (18.1)	115 (14.0)	-
Vascular	33 (8.5)	126 (15.3)	-
Urology	74 (19.2)	186 (22.6)	-
Hepatobilliary	25 (6.5)	53 (6.4)	-
Maxillofacial	26 (6.7)	38 (4.6)	-
Gynaecological	9 (2.3)	1 (0.1)	-
Other	16 (4.1)	22 (2.7)	-
Preoperative medication (%)			
Beta-blocker	38 (9.5)	208 (24.7)	<0.01
Calcium channel antagonist	65 (30.4)	107 (22.2)	0.02
Diuretic	31 (14.5)	63 (13.1)	0.62
Nitrate	13 (3.3)	50 (5.9)	0.05
Anti-platelet	52 (24.3)	166 (34.5)	0.07
Statin	77 (19.3)	199 (23.5)	0.09
ACEi/ARB	119 (30.0)	246 (29.1)	0.75

6.3.1 Primary analysis

Of 1250 patients 438 (35%) had V_E/VCO_2 ratio ≥34, 200 (16%) had heart rate recovery ≤6 bpm, and 396 (32%) had peak VO_2 ≤14 $ml.kg^{-1}min^{-}1$. The results of the logistic regression analyses for heart rate >87 bpm against the primary outcome measures are shown in table 6.2. After correcting for potential confounding factors, heart rate >87 bpm was associated with peak VO_2≤14 ml/kg/min (odds ratio (OR) 1.69 [1.12-3.55]; p=0.01) and heart rate recovery ≤6 bpm (OR 2.02 [1.30-3.14]; p<0.01). However, heart rate >87 bpm was not associated with V_E/VCO_2 ratio ≥34 (OR 1.31 [0.92-1.87]; p=0.14).

Table 6.2. Logistic regression analysis. Univariable (unadjusted) analysis and multivariable analysis including variables significantly associated with the outcome measure in univariable analysis and age >75 years, male gender and Revised Cardiac Risk Index (RCRI) >2. The dependent variable was heart rate >87 bpm. Results presented as odds ratios with 95% confidence intervals, with p-value.

	Univariable analysis		**Multivariable analysis**	
Characteristic	Odds ratio	p-value	Odds ratio	p-value
Age >75 years	0.78 (0.59-1.04)	0.09	0.87 (0.59-1.28)	0.48
Male gender	0.70 (0.54-0.90)	<0.01	0.79 (0.54-1.16)	0.23
Revised Cardiac Risk Index >2	0.41 (0.26-0.64)	<0.01	0.56 (0.30-1.03)	0.06
Peak oxygen consumption ≤14	1.39 (1.08-1.78)	0.01	1.69 (1.12-3.55)	0.01
V_E/VCO_2 at anaerobic threshold ≥34	1.59 (1.24-2.03)	<0.01	1.31 (0.92-1.87)	0.14
Heart rate recovery ≤6 bpm	1.96 (1.44-2.67)	<0.01	2.02 (1.30-3.14)	<0.01
Preoperative medications				
Beta-blocker	0.32 (0.22-0.47)	<0.01	0.37 (0.22-0.61)	<0.01
Calcium channel antagonist	1.52 (1.06-2.19)	0.02	1.71 (1.15-2.55)	<0.01
Diuretic	1.12 (0.71-1.79)	0.62	-	-
Nitrate	0.54 (0.29-1.00)	0.05	0.37 (0.12-1.17)	0.09
Anti-platelet	0.61 (0.42-0.88)	<0.01	0.75 (0.49-1.15)	0.19
Statin	0.78 (0.58-1.04)	0.10	-	-
ACEi/ARB	1.04 (0.80-1.36)	0.75	-	-

6.3.2 Secondary analysis

Patients with heart rate >87 bpm had lower peak oxygen consumption, oxygen consumption at the anaerobic threshold and (V_E/VCO_2) ratios (table 6.3). Peak oxygen pulse, a measure of left ventricular stroke volume, was lower in patients with heart rate >87 bpm.[398] Heart rate >87 bpm was not associated with oxygen consumption at the anaerobic threshold <11.1 ml/kg/min (OR 1.24 [0.98-1.59]; p=0.08) using univariable analysis. However, heart rate >87 bpm was associated with peak oxygen pulse <12 ml/beat (OR 2.80 [2.19-3.58]; p<0.01). Patients with heart rate ≤87 bpm had near normal predicted oxygen pulse, when expressed as a percentage of population-specific normal values (94.9% [93.0-96.9]). By contrast, percentage predicted peak oxygen pulse was (15.2% [12.3-18.1]) lower in patients with heart rate >87 bpm (p<0.01). Patients with heart rate >87 bpm exhibited higher peak heart rates during CPET. Heart rate recovery, the longer duration of which reflects impaired parasympathetic reactivation following cessation of peak exercise, was prolonged in patients with heart rate >87 bpm.

6.3.3 Sensitivity analysis

In patients with heart failure and receiving beta-blockers, the prognostic threshold for peak oxygen consumption (≤12ml/kg/min) is lower than in patients not receiving beta-blockers. I performed a sensitivity analysis by repeating the primary univariable logistic regression using the lower threshold in patients taking beta-blockers (247/1250). However, association between impaired oxygen consumption and HR>87 was not identified (OR 1.37 [0.63-2.96]; p=0.43).

Table 6.3. Physiological and cardiopulmonary exercise test variables. Data stratified by resting heart rate >87 bpm, presented as frequencies with percentages (%) or means with standard deviations (SD). Hypothesis testing with t-test for continuous data and chi-squared test for categorical data. Heart rate (HR) data in >87 bpm, blood pressure data in millimetres of mercury (mmHg), rounded to the nearest whole number. Other units are shown. Oxygen consumption (VO_2), carbon dioxide production (VCO_2).

Characteristic	Whole cohort	HR >87	HR≤87	p-value
Preoperative haemodynamic variables				
Resting heart rate (bpm)	81 (16)	99 (10)	73 (10)	<0.01
Systolic blood pressure (mmHg)	146 (23)	147 (23)	145 (23)	0.23
Diastolic blood pressure (mmHg)	82 (13)	84 (12)	81 (13)	<0.01
Pulse pressure (mmHg)	63 (20)	62 (20)	65 (19)	0.09
Mean arterial pressure (mmHg)	102 (14)	104 (14)	101 (15)	<0.01
Preoperative CPET variables				
VO_2 at the anaerobic threshold (ml/kg/min)	11.3 (3.0)	11.2 (2.7)	11.4 (3.1)	0.21
Peak oxygen consumption (ml/kg/min)	17.3 (5.0)	16.8 (4.8)	17.6 (5.1)	<0.01
V_E/VCO_2 at anaerobic threshold	31.6 (5.9)	32.7 (5.7)	31.1 (5.9)	<0.01
Peak oxygen pulse (ml/beat)	13.1 (3.4)	11.6 (2.9)	13.8 (3.5)	<0.01
Peak heart rate (bpm)	134 (23.0)	145 (19)	128 (23)	<0.01
Heart rate increase (bpm)	53 (21)	46.1 (20.3)	55.8 (21.1)	<0.01
Heart rate recovery (bpm)	16 (14)	13 (15)	18 (13)	<0.01

6.3.4 Preoperative left ventricular stroke volume

I further examined cardiac function in a separate cohort of patients. 181 patients with mean age 68 years (SD 9) that underwent major surgery in the OPTIMISE and POM-O trials had complete beat-by-beat cardiac output monitor data available for analysis (figure 6.3). From both trials, patients with preoperative heart rate >87 bpm had lower mean preoperative stroke volume (mean difference 23.5 [8.0-38.9] ml; p=0.03). Preoperative heart rate >87 bpm was associated with impaired preoperative stroke volume <57ml (OR 3.21 [1.26-8.20]; p=0.01), taking into account patients with an established preoperative diagnosis of heart failure (table 6.4).

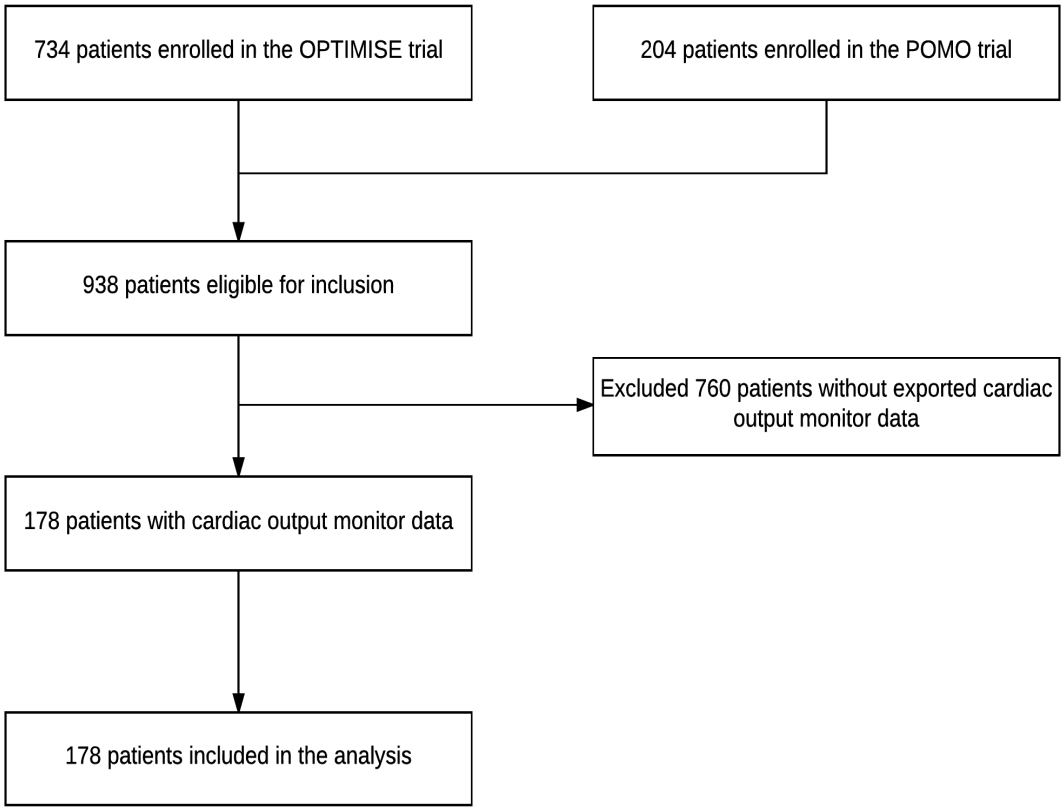

Figure 6.2. STROBE diagram showing patients from the POM-O and OPTIMISE trials that were included in the post-hoc analysis of left ventricular function.

Table 6.4. Logistic regression analysis of patients in the POM-O and OPTIMISE trials. Univariable (unadjusted) and multivariable (adjusted) analyses for heart rate >87 bpm against impaired stroke volume (<57ml) and sub-clinical impaired stroke volume (impaired stroke volume in the absence of an existing diagnosis of heart failure). Multivariable analyses are adjusted for age >75 years, male gender and history of ischaemic heart disease. Results presented as odds ratios with 95% confidence intervals, with p-value.

Characteristic	odds ratio	p-value
Univariable analysis for impaired stroke volume		
Heart rate >87 bpm	2.45 (1.10-5.47)	0.03
Univariable analysis for sub-clinical impaired stroke volume		
Heart rate >87 bpm	2.55 (1.09-5.99)	0.03
Multivariable analysis for impaired stroke volume		
Heart rate >87 bpm	3.09 (1.21-7.86)	0.02
Age >75 years	1.64 (0.69-3.88)	0.26
Male gender	0.63 (0.29-1.37)	0.24
History of ischaemic heart disease	0.44 (0.15-1.30)	0.14
Multivariable analysis for sub-clinical impaired stroke volume		
Heart rate >87 bpm	3.21 (1.26-8.20)	0.01
Age >75 years	1.43 (0.60-3.44)	0.42
Male gender	0.58 (0.27-1.28)	0.18
History of ischaemic heart disease	0.46 (0.16-1.34)	0.16

6.4 Discussion

The principal finding of this analysis is that resting preoperative heart rate >87 bpm is associated with cardiopulmonary and parasympathetic autonomic impairment, compatible with physiologically significant heart failure. This pathophysiological phenotype was observed in up to one third of patients. However, only 4% of the cohort had a clinical diagnosis of heart failure syndrome, suggesting that the majority of these patients have sub-clinical or undiagnosed disease causing physiological limitation that is revealed by a standardised, incremental ramp exercise test. These findings are supported by an analysis of haemodynamic data from two other studies, where preoperative heart rate >87 bpm was associated with impaired left ventricular function. These data suggest that elevated preoperative heart rate, as observed in chapter three, is unlikely to be caused by an acute pathophysiological process, for example sepsis, anxiety or inflammation.[387] Instead, my results offer a plausible explanation of how elevated preoperative heart rate might be related to increased risk of perioperative myocardial injury and mortality: through a phenotype of cardiopulmonary and autonomic impairment, indicative of sub-clinical heart failure. This is consistent with previous reports confirming that patients with an established diagnosis of preoperative heart failure have substantially higher morbidity and mortality after non-cardiac surgery.[349]

The temporality of the relationship between tachycardia and heart failure is unclear. However, evidence from the general population suggests that high heart rate might cause heart failure. In apparently healthy men and women, the risk of subsequently developing heart failure increases with increasing resting heart rate.[158, 159] In the EPIC-Norfolk study, a 10 bpm increase in resting heart

rate was independently associated with an 11% increase in risk of developing heart failure.[158] While the Rotterdam Study, which sampled 4768 apparently healthy volunteers over a 15-year period, demonstrated that in men each 10 bpm increase in heart rate was associated with increased risk of developing heart failure, within six months after study enrolment.[159] Similarly, a study of patients with supraventricular tachycardia suggests that sustained elevated heart rate can induce heart failure in the absence of structural heart disease.[400] Elevated heart rate also increases the risk of heart failure in the presence of established hypertension, coronary artery disease and valvular heart disease.[401] Thus, elevated resting heart rate appears to be an independent risk factor for the development of heart failure in healthy older men in the general population. This gender bias mirrors the results of the VISION study, where male gender was an independent risk factor for MINS and mortality.

The majority of the evidence in favour of association between heart rate and heart failure in the general population is derived from studies of heart failure syndrome, which requires a clinical diagnosis. My results suggest that sub-clinical or undiagnosed physiological heart failure may be eight times more common than symptomatic heart failure syndrome. So it is possible that studies of apparently healthy volunteers, with results suggesting a causal link between tachycardia and heart failure, may have enrolled participants with pre-existing sub-clinical heart failure. This is consistent with the so called 'Will Rogers phenomenon', where the prevalence of a disease increases with introduction of a more sensitive diagnostic test, but the severity of the disease reduces due to earlier detection, thus giving the illusion of improved survival rates.[402] However, in this case it is not possible to determine whether or not tachycardia in

participants that later developed clinical heart failure syndrome was caused by pre-existing sub-clinical heart failure. Or, in other words, the temporality of exposure and outcome cannot be determined.

Several pathophysiological mechanisms could link resting heart rate, heart failure and perioperative myocardial injury. The predominant causal model of perioperative myocardial injury centres on myocardial oxygen supply-demand imbalance,[96] and it seems intuitive that this could be induced by tachycardia through negative effects on coronary blood flow.[96] However, my study identifies plausible alternative pathological explanations for the development of perioperative myocardial injury or mortality. At peak exercise, oxygen pulse is a surrogate measure of left ventricular stroke volume.[398] Notably, the oxygen pulse measurements in patients with HR >87 bpm were similar to patients with mild-to-moderate heart failure,[22] and data from cardiac output monitors suggest impaired left ventricular stroke volume in these patients. This is compatible with the hypothesis that heart rate is increased as result of low stroke volume, in order to maintain cardiac output - a relationship that is consistently seen in patients with heart failure.[159] This hypothesis is further supported by the observed relationship between elevated heart rate and reduced oxygen consumption, which is independent of age, gender and heart disease in medical patients.[403] Low stroke volume, and hence oxygen delivery, may be exacerbated by anaesthesia, leading to intraoperative hypotension and associated end-organ hypoperfusion - including myocardial injury.[404] Parasympathetic autonomic impairment can also be linked with cardiac ischaemia after non-cardiac surgery. Reduction in heart rate after peak exercise

- heart rate recovery - is due to parasympathetic reactivation during the first few minutes of recovery.[405]

Reduced cardiac vagal activity can promote cardiac injury through several mechanisms.[96, 406] First, inhibition of dorsal vagal motor neuronal stimulation in rats and mice reduces cardiac contractility, impairs exercise performance and up-regulates G-protein receptor kinase 2 (GRK2) and arrestin, which are also up-regulated in patients with heart failure.[407] Similarly, baroreflex impairment, indicative of parasympathetic dysfunction, is associated with reduced cardiac contractility and GRK2 up-regulation in critical illness.[186] Second, vagal inhibition promotes ischaemia/reperfusion injury and ventricular dysrhythmias, compared to low-level vagus nerve stimulation, leading to increased myocardial infarction size in dogs and rabbits.[408, 409] Increased vagal tone, induced by high-intensity interval training, reduces ventricular dysrhythmias in patients with heart failure.[410] Third, vagal stimulation can inhibit the production of reactive oxygen species in mice and nicotinic acetylcholine receptor stimulation can inhibit TNF-alpha, a pro-inflammatory cytokine, in cardiac myocytes.[411, 412]

Using observations from the VISION study to plan physiological assessment using two independent approaches is a major strength of this analysis. The large number of patients and multi-centre nature of the POM-HR cohort give the results good external validity. Although increasing chronological age is associated with declining cardiopulmonary and autonomic function, multivariable logistic analysis found that the association between elevated heart rate and impaired cardiorespiratory performance was independent of age.[413, 414] There were also significant weaknesses, including the observational design,

which cannot, by definition, establish causality. I considered potential confounding factors by adjusting for various established clinical risk factors and cardiovascular drug therapy, for example beta-blockers, which are known to influence heart rate. Heart rate is mathematically coupled with some CPET variables, in particular, oxygen pulse at peak exercise is derived by dividing peak oxygen consumption by contemporaneous HR – so if HR is high then oxygen pulse will, by definition, be decreased. However, it is notable that I have shown an association between raised HR *prior* to CPET and decreased oxygen pulse at peak. Moreover, an association between pre-CPET HR>87 and unfavourable CPET measures was also apparent for VO_2 and V_E/VCO_2 at AT, variables which are not mathematically coupled to heart rate. There were no data regarding intraoperative vasopressor use, which could underestimate the extent and/or effect of clinically relevant hypotension on clinical outcomes. My results may be confounded by factors that were not measured; for example, I am unaware of the incidence of obstructive sleep apnoea in this sample, which is known to be associated with autonomic impairment.[415, 416]

6.5 Conclusion

In summary, elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment indicative of subclinical heart failure. Perioperative myocardial injury might at least partially be explained by subclinical cardiac failure. Further research targeting abnormal cardiovascular and autonomic phenotypes may improve clinical outcomes, including development of individualised approaches to care of high-risk surgical patients.

Chapter seven

Heart rate recovery

Parasympathetic autonomic dysfunction and myocardial injury after non-cardiac surgery: results of the METS study

7.1 Introduction

The pathophysiological mechanism underlying perioperative myocardial injury is uncertain. Myocardial injury is more frequent among patients with common cardiovascular risk factors, as defined by the Revised Cardiac Risk Index (RCRI).[20, 95, 273] However, in this group of patients, several treatments for myocardial infarction that are routinely used in the non-operative setting do not prevent myocardial injury in the perioperative period.[100, 101, 166] Similarly, the degree of atherosclerosis, measured using computed tomography coronary angiogram, correlates poorly with the risk of perioperative myocardial injury.[394] This suggests that while the pathophysiological mechanism responsible for perioperative myocardial injury is likely to be associated with the RCRI and its constituent risk factors, it is unlikely to be coronary atherosclerosis *per se*.

I have previously identified that elevated heart rate before and during surgery is associated with perioperative myocardial injury, and that resting tachycardia before surgery is associated with parasympathetic autonomic dysfunction.[273, 274, 397] Parasympathetic autonomic dysfunction is a plausible candidate pathophysiological mechanism for myocardial injury, and is associated with each cardiovascular risk factor in the RCRI, including: diabetes mellitus,[179]

ischaemic heart disease,[180] cardiac failure,[181] renal impairment[182] and stroke.[183, 184] It has been implicated in the development of cardiovascular disease in the general population,[417] principally due to the loss of cardio-protective vagal activity, which is known to increase production of nitric oxide[418] and anti-inflammatory cytokines,[419] inhibit the renin-angiotensin axis[420] and inhibit cardiac dysrhythmia formation.[185] In the perioperative setting, two out of five high-risk patients are thought to have low baroreflex sensitivity or reduced heart recovery after preoperative exercise, suggesting a degree of parasympathetic impairment.[178, 186] My data from chapter six suggests that one third of high-risk surgical patients are at risk of cardiopulmonary and autonomic dysfunction. This may be clinically significant, since there is some evidence that parasympathetic dysfunction is associated with clinically defined complications after surgery.[178] However, whether or not parasympathetic dysfunction is associated with biochemical myocardial injury after surgery remains untested.

Data from previous chapters indicates that elevated preoperative heart rate and parasympathetic dysfunction may form part of a phenotype of sub-clinical heart failure that is prevalent in patients undergoing non-cardiac surgery, and which may promote myocardial injury. However, whether or not parasympathetic dysfunction is associated with perioperative myocardial injury has not been tested. I hypothesised that parasympathetic autonomic dysfunction, as defined by prolonged heart rate recovery after preoperative cardiopulmonary exercise testing, was associated with increased risk of myocardial injury after non-cardiac surgery. I further hypothesised that previously identified CPET-derived markers of sub-clinical heart failure were associated with impaired heart rate recovery in this cohort.

7.2 Methods

This was a pre-defined secondary analysis of the Measurement of Exercise Tolerance before Surgery (METS) study, an international prospective observational cohort study of preoperative assessment before non-cardiac surgery at twenty-three hospitals in Canada, the United Kingdom, Australia and New Zealand. I have described the study methods in chapter two and the study protocol was published previously.[1] Participants were aged 40 years or older, undergoing elective non-cardiac surgery under general anaesthesia and/or regional anaesthesia. Researchers at each site collected a detailed and standardised dataset directly from participants and their medical records, before surgery, and at 30 days and one year after surgery.

7.2.1 Cardiopulmonary exercise testing

Each participant underwent preoperative symptom-limited cardiopulmonary exercise testing (CPET) using a standardised incremental ramp protocol on electromagnetically-braked cycle ergometers. The CPET protocol is described in detail in chapter two. Investigators at each site interpreted each CPET using a standardised case report form. CPET variables of interest included: peak oxygen consumption, anaerobic threshold, ventilatory equivalent for carbon dioxide, and heart rate recovery during the first minute after the end of exercise. Clinicians outside of the research team were blinded to the results of cardiopulmonary exercise testing, except where there was a safety concern according to pre-defined criteria.[1]

7.2.2 Blood sampling

Blood was sampled before surgery and on the first, second and third days after surgery, as long as the participant remained in hospital. In Canada, Australia and New Zealand, serum cardiac troponin (either I or T isoforms) was measured in preoperative and postoperative samples at local hospital laboratories, according to local policy. In the UK, serum cardiac troponin was measured in preoperative and postoperative samples at a single central laboratory. A summary of the troponin assays used at each centre is summarised in table 7.1. N-terminal pro-B-type natriuretic peptide (NT pro-BNP) was measured in all preoperative samples at a single central laboratory.

7.2.3 Exposures of interest

The exposure of interest was impaired heart rate recovery, defined as reduction in heart rate of less than or equal to twelve beats per minute during the first minute after the end of preoperative cardiopulmonary exercise testing. This threshold was previously identified as an independent predictor of mortality in both general and surgical cohorts.[90, 186]

7.2.4 Outcome measures

The primary outcome was myocardial injury, defined as postoperative troponin measurement greater than the limit of the reference range for any given assay (table 7.1), within 72 hours after surgery. Additional pre-defined explanatory outcomes were: preoperative NT pro-BNP >300pmol/L, a threshold used to identify heart failure in community cohorts[421] and Revised Cardiac Risk Index (RCRI).[422]

Table 7.1. A summary of troponin assays used at each centre. The cut-off value is the limit of the normal range, above which the participant would be considered to have myocardial injury.

Assay	Cut-off value	Number of centres
Troponin-I Abbott Architect Immunoassay	>70 ng/L	1
Troponin-I Abbott assay	>20 ng/L	1
Troponin-I Abbott high-sensitivity assay	>25 ng/L	2
Troponin-I Abbott high-sensitivity assay	Males >25 ng/L, Females >15 ng/L	3
Troponin-I Beckman-Coulter assay	>30 ng/L	3
Troponin-I Centaur CP high-sensitivity assay	>40 ng/L	8
Troponin-T Roche high-sensitivity (STAT) assay	>14 ng/L	4
Troponin-T Roche high-sensitivity assay	>29 ng/L	1

7.2.5 Statistical analysis

The analysis was planned before taking custody of the data. I used STATA version 14 (STATACorp LP, Texas, USA). The small number of participants without a record of heart rate recovery or missing covariates were excluded. The sample was ranked by heart rate recovery at one minute after the end of incremental exercise and dichotomised according to a threshold of ≤12 beats per minute. This threshold is prognostically associated with subsequent cardiovascular morbidity in the general population.[90] Baseline characteristics for the whole cohort were presented and stratified by heart rate recovery. Normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data were expressed as median ± interquartile range (IQR). Binary data were expressed as percentages.

I used univariable logistic regression analysis to test for association between impaired heart rate recovery and myocardial injury. Next, using a previously published method for stratifying patients at risk of perioperative myocardial injury, the cohort were divided into three groups according to Revised Cardiac Risk Index (low-risk [RCRI 0 points], intermediate-risk [RCRI 1-2 points] or high-risk [RCRI 3-6 points]), which represents multiple cardiovascular risk factors known to be associated with perioperative myocardial injury.[16, 20, 21, 95, 273, 275, 422] A multivariable logistic regression model for the association between impaired heart rate recovery and myocardial injury was constructed and adjusted for Revised Cardiac Risk Index, where the low-risk group was considered the reference category. Finally, the multivariable logistic regression model was adjusted for component cardiovascular risk factors of the RCRI, including: coronary artery disease, congestive cardiac failure, diabetes mellitus requiring

insulin therapy and preoperative renal impairment (creatinine >177 μmol/L).[20, 422] The results of logistic regression analyses were presented as odds ratios (OR) with 95% confidence intervals. The threshold for statistical significance was p≤ 0.05.

7.2.6 Secondary analysis

I presented both mean heart rate recovery and the proportion of participants with impaired heart rate recovery for each RCRI group and used univariable logistic regression to test for association between RCRI-defined risk groups and impaired heart rate recovery, where the lowest-risk group was considered the reference category. Mean heart rate recovery and the proportion of participants with impaired heart rate recovery stratified by NT pro-BNP were presented, using groups identified in the VISION study (unpublished). A relationship between impaired preoperative heart rate recovery and sub-clinical heart failure was previously described in chapter six.[397] To explore whether impaired preoperative heart rate recovery is associated with a phenotype of heart failure in this cohort, the primary analysis was repeated for the following outcome measures, which are biomarkers known to be predictive of poor clinical outcome in overt heart failure: NT pro-BNP >300 pg/mL, VO_2 peak ≤14 ml/kg/min and V_E/VCO_2 at the anaerobic threshold ≥34.[397]

7.2.7 Sensitivity analysis

To take account of potential confounding by heart rate limiting medications, the primary analysis was repeated including heart rate limiting cardiovascular medications (beta-blockers and calcium channel antagonists) as covariates.

7.3 Results

1741 patients were recruited into the METS study between February 2013 and March 2016. After excluding participants that did not undergo preoperative cardiopulmonary exercise testing, did not proceed to surgery or had missing data, data obtained from 1325 participants were analysed (figure 7.1).

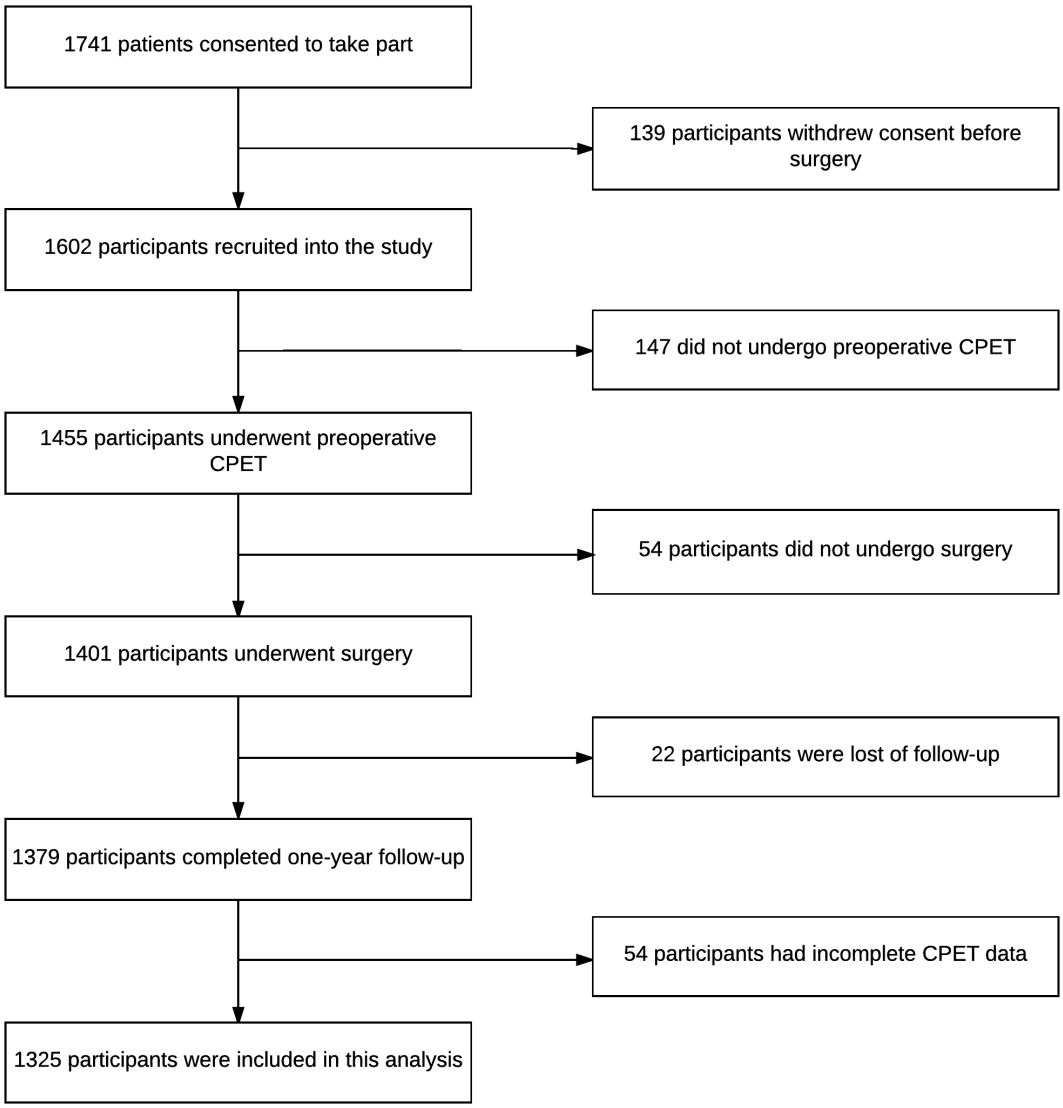

Figure 7.1. Patient flow diagram showing the number of cases included in the analysis.

Table 7.2. Baseline patient characteristics. Descriptive data stratified by preoperative heart rate recovery (HRR) ≤12 beats per minute in the first minute after the end of cardiopulmonary exercise testing. Data are presented as frequencies with percentages (%) or means with standard deviations (SD). Continuous data are reported to one decimal place and categorical data are rounded to the nearest whole number. ASA = American Society of Anesthesiologists.

	Whole cohort	HRR ≤12	HRR >12
Number of cases	1325	547	778
Age	64.2 (10.3)	66.7 (10.0)	62.5 (10.2)
Male sex (%)	815 (61.5)	314 (57.4)	501 (64.4)
Pre-existing conditions (%)			
Atrial fibrillation	49 (3.7)	22 (4.0)	27 (3.5)
Diabetes	247 (18.6)	125 (22.9)	122 (15.7)
Hypertension	725 (54.7)	336 (61.4)	389 (50.0)
Heart failure	17 (1.3)	11 (2.0)	6 (0.8)
Ischaemic heart disease	152 (11.5)	83 (15.2)	69 (8.9)
Peripheral vascular disease	37 (2.8)	17 (3.1)	20 (2.6)
Cerebrovascular disease	54 (4.1)	28 (5.1)	26 (3.3)
Chronic obstructive pulmonary disease	155 (11.7)	81 (14.8)	74 (9.5)
Preoperative creatinine >177 μmol/L	100 (7.6)	43 (7.9)	57 (7.3)
Surgical procedure type (%)			
Vascular	25 (1.9)	14 (2.6)	11 (1.4)
Intra-peritoneal or retroperitoneal	434 (32.8)	178 (32.5)	256 (32.9)
Urological or gynaecological	397 (30.0)	160 (29.3)	237 (30.5)
Intra-thoracic	30 (2.3)	11 (2.0)	19 (2.4)
Orthopaedic	312 (23.6)	131 (24.0)	181 (23.3)
Head and neck	82 (6.2)	34 (6.2)	48 (6.2)
Other	45 (3.4)	19 (3.5)	26 (3.4)
High-risk surgery (%)	749 (56.5)	310 (56.7)	439 (56.4)
ASA grade (%)			
I	99 (7.5)	33 (6.0)	66 (8.5)
II	779 (58.9)	302 (55.3)	477 (61.4)
III	427 (32.3)	203 (37.2)	224 (28.8)
IV	18 (1.4)	8 (1.5)	10 (1.3)
Preoperative medication (%)			
Beta-blockers	215 (16.2)	120 (21.9)	95 (12.2)
Diltiazem or Verapamil	26 (2.0)	14 (2.6)	12 (1.5)
Insulin therapy	54 (4.1)	26 (4.8)	28 (3.6)
Revised cardiac risk index			
0	419 (31.6)	167 (30.5)	252 (32.4)
1 - 2	870 (65.7)	354 (64.7)	516 (66.3)
≥ 3	36 (2.7)	26 (4.8)	10 (1.3)

7.3.1 Primary analysis

Heart rate recovery ≤12 bpm was recorded in 547/1325 patients (41.3%). Across the whole cohort 168/1325 (12.7%) patients sustained myocardial injury (table 7.2), compared to 85/547 (15.5%) patients with HRR ≤12 bpm and 83/778 (10.7%) patients with HRR >12 bpm (odds ratio (OR) 1.54 [1.11-1.23]; p<0.01; table 7.3).

Table 7.3. Impaired heart rate recovery and myocardial injury. The independent variable was impaired heart rate recovery (≤12 beats per minute within the first minute after the end of incremental exercise). The dependent variable was myocardial injury within 72 hours after the end of surgery. Results of three separate analyses are presented. First, univariable (unadjusted) logistic regression analysis. Second, multivariable logistic regression adjusting for Revised Cardiac Risk Index (RCRI) as an ordered categorical variable. Third, multivariable logistic regression analyses adjusting for component cardiovascular risk factors of the RCRI, which are included as separate terms in the model. Results are presented as odds ratios with 95% confidence intervals and associated p-values.

	Myocardial Injury	
Covariates	**odds ratio**	**p-value**
Univariable analysis		
Heart rate recovery ≤12 beats per minute	1.54 (1.11-2.13)	<0.01
Multivariable analysis 1		
RCRI	-	-
0 (reference)	-	-
1-2	0.72 (0.51-1.01)	0.06
≥3	1.69 (0.75-3.80)	0.20
Heart rate recovery ≤12 beats per minute	1.50 (1.08-2.08)	0.02
Multivariable analysis 2		
Coronary artery disease	2.22 (1.44-3.44)	<0.01
Congestive cardiac failure	0.55 (0.12-2.54)	0.45
Previous stroke or transient ischaemic attack	1.48 (0.73-3.00)	0.28
Diabetes mellitus requiring insulin	1.20 (0.56-2.56)	0.64
Preoperative creatinine >177 μmol/L	0.66 (0.33-1.31)	0.24
Heart rate recovery ≤12 beats per minute	1.45 (1.05-2.02)	0.03

7.3.2 Secondary analyses

The proportion of participants with heart rate recovery ≤12 bpm increased with higher Revised Cardiac Risk Index score (Figure 7.2A). Similarly, mean heart rate recovery progressively declined in patients with increasing frequency of RCRI-defined risk factors (Figure 7.2B). Participants with three or more RCRI-defined cardiovascular risk factors were more likely to have impaired heart rate recovery compared to those with none (RCRI ≥3: 26/36 [72.2%] versus RCRI=0: 167/419 [39.9%]; OR 3.92 [1.84-8.34]; p<0.01). The proportion of participants with heart rate recovery ≤12 bpm increased with increasing concentrations of preoperative NT pro-BNP (Figure 7.3A). Mean heart rate recovery declined in patients with increasing concentrations of preoperative NT pro-BNP (Figure 7.3B). Elevated preoperative NT pro-BNP (>300 pg/mL) was measured in 207/1325 patients (15.6%), of whom only 11/207 (5.3%) had a pre-existing clinical diagnosis of heart failure.

Cardiopulmonary performance stratified by heart rate recovery is shown in table 7.4. Heart rate recovery ≤12 bpm was associated with preoperative NT pro-BNP >300pg/mL (OR 1.85 [1.36-2.51]; p<0.01), V_E/VCO_2 ≥ 34 (OR 2.20 [1.74-2.77]; p<0.01) and VO_2 peak ≤ 14 (OR 3.11 [2.34-4.13]; p<0.01) adjusted for RCRI (table 7.5). Mean heart rate recovery was lower in participants with resting heart rate >87 bpm (11.7 [9.7] versus 16.1 [12.7]; p<0.01). Participants with impaired heart rate recovery were more than twice as likely to have preoperative heart rate >87 bpm (OR 2.36 [1.82-3.06]; p<0.01).

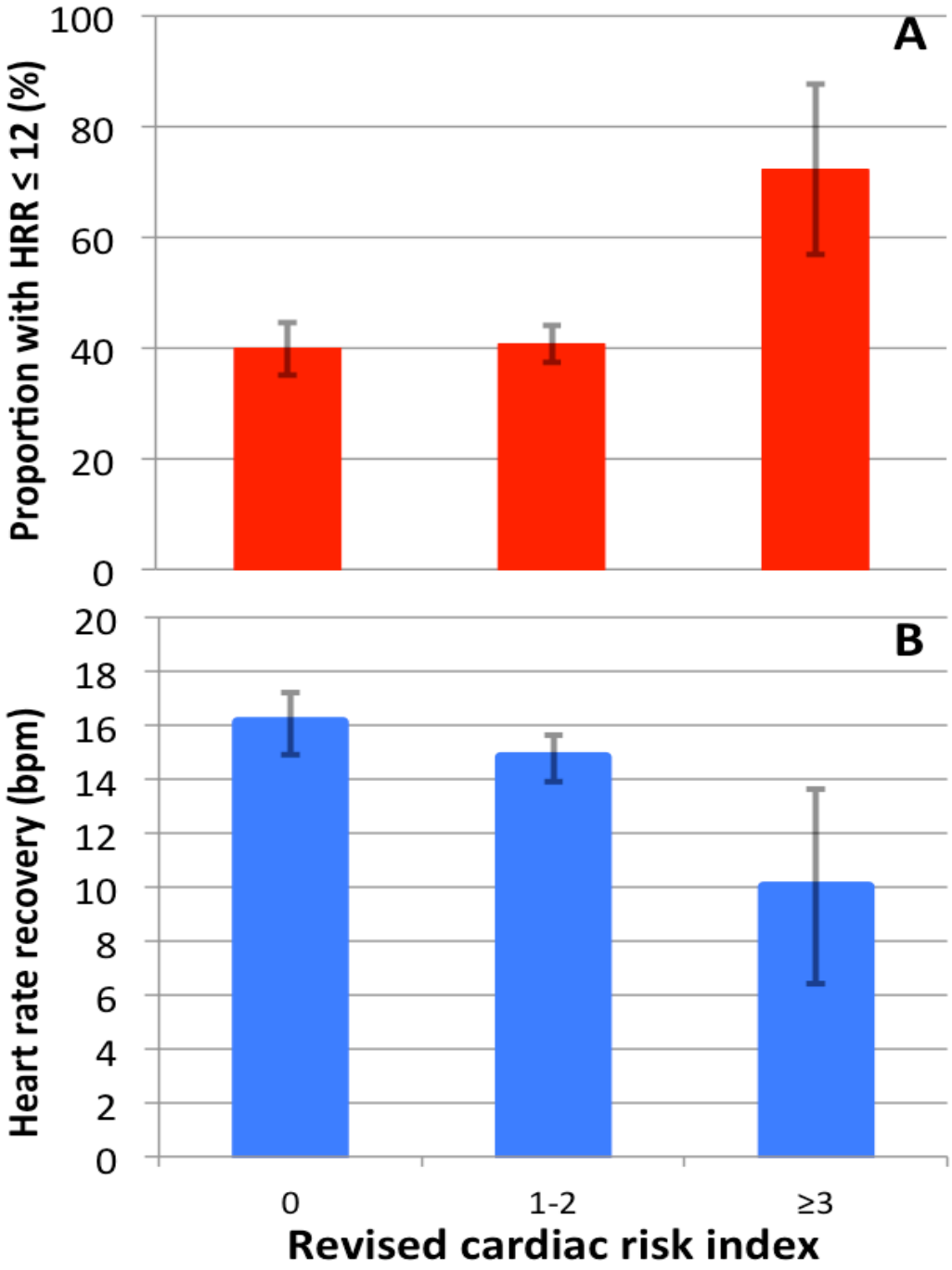

Figure 7.2. Bar charts showing (A) the proportion (%) of participants with heart rate recovery (HRR) less than or equal to 12 beats per minute, and (B) mean heart rate recovery (beats per minute), stratified by the Revised Cardiac Risk Index. Error bars indicate the 95% confidence interval. 167/419 patients with RCRI = 0 had heart rate recovery ≤ 12 beats per minute, 354/870 patients with RCRI = 1-2 had heart rate recovery ≤ 12 beats per minute and 26/36 patients with RCRI ≥ 3 had heart rate recovery ≤ 12 beats per minute. The proportion of patients with heart rate recovery ≤ 12 beats per minute was significantly greater for RCRI ≥ 3 compared to the other two groups ($p<0.01$).

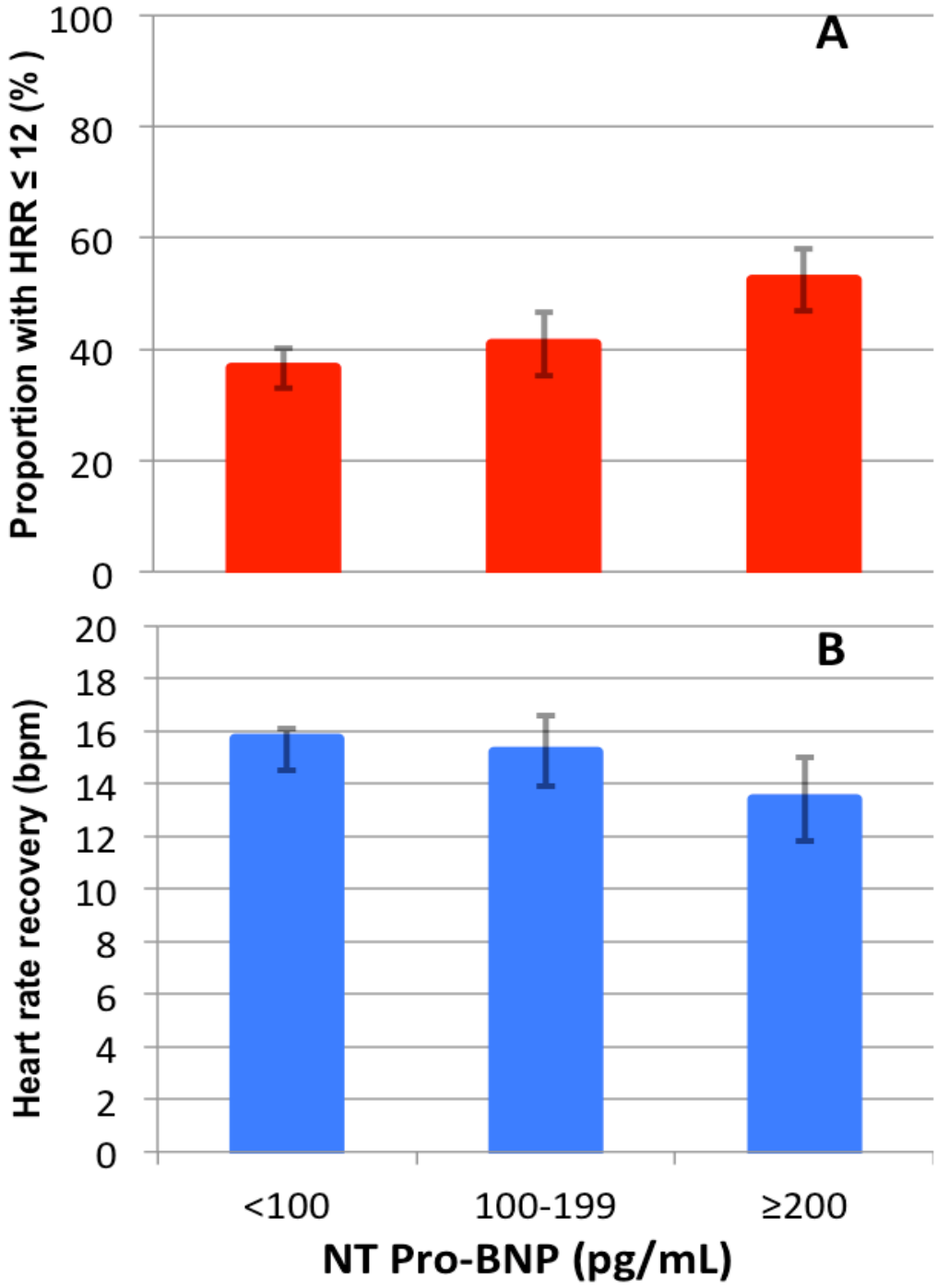

Figure 7.3. Bar charts showing (A) the proportion (%) of participants with heart rate recovery (HRR) less than or equal to 12 beats per minute, and (B) mean heart rate recovery (beats per minute), stratified by NT Pro-BNP concentration. 263/719 (36.6%) patients with NT Pro-BNP ≤100 pg.mL^{-1} had heart rate recovery ≤ 12 beats per minute, 119/291 (40.9%) patients with NT Pro-BNP 100-199 pg.mL^{-1} had heart rate recovery ≤ 12 beats per minute and 165/315 (52.4%) patients with NT Pro-BNP ≤100 pg.mL^{-1} had heart rate recovery ≤ 12 beats per minute.

Table 7.4. Cardiopulmonary exercise test variables stratified by impaired heart rate recovery. Impaired heart rate recovery was defined as ≤12 beats per minute within the first minute after the end of incremental exercise. Continuous variables were presented as means with standard deviations and categorical variables were presented as frequency (n) with percentage (%). Hypothesis testing for difference in means used a two-tailed unpaired t-test. VO_2 = oxygen consumption, VCO_2 = carbon dioxide production, V_E = minute ventilation, RER = respiratory exchange ratio.

	Whole cohort	HRR ≤12	HRR >12	p-value
Resting heart rate >87 beats/min, n (%)	310 (23.4)	178 (32.5)	132 (17.0)	<0.01
Oxygen pulse at rest (ml/beat)	4.7 (2.4)	4.4 (2.0)	5.0 (2.6)	<0.01
VO_2 peak (ml/kg/min)	19.3 (6.4)	17.1 (5.6)	20.8 (6.5)	<0.01
Heart rate at VO_2 peak (bpm)	134 (24)	127 (25)	139 (21)	<0.01
Oxygen pulse at VO_2 peak (ml/beat)	12.3 (4.4)	11.6 (4.3)	12.8 (4.3)	<0.01
VO_2 at anaerobic threshold (ml/kg/min)	12.7 (4.1)	11.6 (3.4)	13.4 (4.4)	<0.01
V_E/VCO_2 at the anaerobic threshold	31.8 (5.6)	33.3 (6.2)	30.8 (5.0)	<0.01
V_E/VO_2 at the anaerobic threshold	29.0 (6.0)	30.3 (6.7)	28.1 (5.3)	<0.01
RER at end of exercise	1.14 (0.14)	1.12 (0.14)	1.16 (0.13)	<0.01

Table 7.5. Impaired heart rate recovery and markers of heart failure. The independent variable was impaired heart rate recovery (≤12 beats per minute within the first minute after the end of incremental exercise). The dependent variables were NT pro-BNP >300 pg/mL, ventilatory equivalent for carbon dioxide (V_E/VCO_2) at the anaerobic threshold ≥ 34 and peak oxygen consumption (VO_2) ≤ 14ml/kg/minute. Results of univariable (unadjusted) and multivariable (adjusted) logistic regression analyses are presented as odds ratios with 95% confidence intervals and associated p-values. Multivariable analyses were adjusted for Revised Cardiac Risk Index (RCRI).

	NT pro-BNP >300 pg.mL^{-1}		V_E/VCO_2 ≥34		VO_2 peak ≤14 ml/kg/min	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Univariable analysis						
Heart rate recovery ≤12 beats per minute	1.98 (1.47-2.68)	<0.01	2.16 (1.71-2.71)	<0.01	3.17 (2.39-4.20)	<0.01
Multivariable analysis						
RCRI	-	-	-	-	-	-
0 (reference)	-	-	-	-	-	-
1-2	1.23 (0.87-1.72)	0.24	0.86 (0.67-1.10)	0.23	0.97 (0.72-1.32)	0.86
≥3	6.41 (3.11-13.22)	<0.01	0.55 (0.26-1.16)	0.11	1.72 (0.82-3.62)	0.15
Heart rate recovery ≤12 beats per minute	1.85 (1.36-2.51)	<0.01	2.20 (1.74-2.77)	<0.01	3.11 (2.34-4.13)	<0.01

7.3.3 Sensitivity analyses

When I corrected the primary analysis for heart rate-limiting medication, the results were similar to the primary analysis (table 7.6).

Table 7.6. Impaired heart rate recovery and myocardial injury. Sensitivity analysis adjusting for heart rate limiting cardiovascular medications. The independent variable was impaired heart rate recovery (≤12 beats per minute within the first minute after the end of incremental exercise). The dependent variable was myocardial injury within 72 hours after the end of surgery. Results of univariable (unadjusted) and multivariable (adjusted) logistic regression analyses are presented as odds ratios with 95% confidence intervals and associated p-values. Multivariable analyses were included age >70 years and Revised Cardiac Risk Index (RCRI) as covariates.

	Myocardial Injury	
Covariates	**odds ratio**	**p-value**
Univariable analysis		
Heart rate recovery ≤12 beats per minute	1.54 (1.11-2.13)	<0.01
Multivariable analysis		
RCRI	-	-
0 (reference)	-	-
1-2	0.70 (0.50-0.99)	0.05
≥3	1.40 (0.61-3.20)	0.42
Preoperative beta-blockers	1.60 (1.07-2.39)	0.02
Preoperative diltiazem or verapamil	1.66 (0.61-4.50)	0.32
Heart rate recovery ≤12 beats per minute	1.43 (1.02-1.99)	0.03

7.4 Discussion

The principal finding of this analysis was that impaired heart rate recovery after exercise, a marker of parasympathetic autonomic dysfunction, was associated with myocardial injury within the first 72 hours after non-cardiac surgery. I identified parasympathetic dysfunction using a heart rate recovery threshold that is associated with cardiovascular morbidity and mortality in the general population. These results are consistent with evidence from another surgical cohort that impaired heart rate recovery after preoperative exercise is associated with poorer postoperative clinical outcomes.[178, 186] In addition, participants with three or more cardiovascular risk factors, as defined by the Revised Cardiac Risk Index, had significantly lower heart rate recovery compared to participants with two or fewer cardiovascular risk factors. This supports my hypothesis that preoperative cardiovascular risk factors are pathophysiologically linked to myocardial injury through a common underlying mechanism involving parasympathetic autonomic dysfunction. It may also explain why many of these risk factors have been repeatedly associated with perioperative myocardial injury, even though the cumulative risk is not dependent on the specific variables incorporated into the RCRI.[16, 95, 273, 275, 397]

In keeping with my findings from chapter six, parasympathetic dysfunction was associated with elevated resting heart rate, as well as CPET and plasma biomarker evidence of sub-clinical heart failure.[397] This suggests that resting tachycardia, parasympathetic dysfunction and sub-clinical heart failure may all be part of the same preoperative phenotype. However, I am unable to establish the temporality of exposures and since my data are observational in nature, it is not possible to define a causal chain.

It is possible that tachycardia is the predominant pathophysiological mechanism, causing heart failure and myocardial injury. Evidence from cohort studies in the general population indicate that elevated heart rate is associated with later development of heart failure,[158, 159] while sustained tachycardia in healthy volunteers and patients with hypertension and ischaemic heart disease induces cardiac impairment.[400, 401] However, since heart rate is regulated by the autonomic nervous system, it seems counterintuitive that tachycardia could induce autonomic nervous system dysfunction.[85, 423, 424]

Alternatively, primary heart failure may cause tachycardia, autonomic dysfunction and myocardial injury. Poor left ventricular function can drive elevation in heart rate to maintain cardiac output, so it is reasonable to conclude that tachycardia is marker of heart failure, sub-clinical or otherwise.[60, 75] In addition, autonomic dysfunction is common in patients with established heart failure and patients with CPET evidence of physiological cardiac impairment.[70, 71] In this chapter I have shown that autonomic dysfunction is associated with objective biomarker evidence of heart failure.[421] Changes in cardiac vagal tone are evident from the very early stages of left ventricular impairment, both in terms of ganglionic activity and distribution and concentration of muscarinic receptors.[185] However, while there is growing experimental evidence that autonomic nervous system dysfunction plays an important role in the early development of heart failure[425] it remains unclear whether autonomic dysfunction arises in response to heart failure or causes heart failure. Alternatively, the preoperative phenotype I have observed may be multi-factorial and not driven by a single pathological process.

Parasympathetic dysfunction is a plausible pathophysiological mechanism for perioperative myocardial injury, and may offer an explanation of the association between elevated preoperative heart rate and myocardial injury (chapter three). Parasympathetic dysfunction drives resting tachycardia and is common in patients with heart failure.[185] It is prevalent in people with cardiovascular disease,[337, 426, 427] in patients with known risk factors for perioperative myocardial injury,[179-184] and is associated with subsequent mortality in these groups.[93] Baroreflex impairment, a marker of parasympathetic dysfunction, occurs in over 40% of high-risk surgical patients and is associated with postoperative cardiovascular complications.[178] Parasympathetic activity, via the cardiac vagus nerve, protects the heart through several mechanisms[182, 349, 427, 428] previously discussed in chapter six, including: increased cardiac contractility and down-regulation of GRK2[186, 407] and arrestin;[407] inhibition of dysrhythmias and ischaemic/reperfusion injury;[408-410] and inhibition of reactive oxygen species and pro-inflammatory cytokine production. [411, 412] Loss of this protection may predispose patients with cardiopulmonary and autonomic impairment, as I have observed, to myocardial injury.[213, 363, 427, 428]

Parasympathetic dysfunction could cause myocardial injury through at least three potential mechanisms. Firstly, vagal activity - regulated by the dorsal motor nucleus - is a key determinant of aerobic exercise capacity.[407] Inability to increase cardiac output during surgery, mediated by the vagus nerve, could explain the association between parasympathetic dysfunction and increased risk of myocardial injury after surgery.[407] In experimental models, impaired parasympathetic function is associated with nicotinamide adenine dinucleotide phosphate oxidase subunit-2-mediated up-regulation of G-protein-coupled

receptor kinase 2 expression in cardiomyocytes, which impairs cardiac contractility.[186] This may explain, in part, the observed phenotype of sub-clinical heart failure in these patients. Secondly, parasympathetic activity may have anti-inflammatory effects, limiting myocardial injury in several experimental models.[429, 430] Since efferent[431] and afferent[432] vagal nerve activity can reduce inflammation, via acetylcholine[433] and vasoactive intestinal peptide[434] release. This is consistent with data from surgical patients with reduced heart rate recovery who exhibit elevated neutrophil-lymphocyte ratios, a marker of chronic inflammation that is associated with perioperative cardiovascular morbidity and mortality.[435] Similarly, preoperative baroreflex dysfunction is associated with increased risk of infectious complications after major surgery.[178] Finally, cardiac vagal activity can attenuate the propagation of cardiac arrhythmias, including atrial fibrillation, which are associated with plasma troponin elevation.[436, 437]

This analysis has several strengths. Firstly, the prospective, international, multi-centre design makes the results generalisable to the majority of intermediate to high-risk patients undergoing non-cardiac surgery. Secondly, the primary outcome, myocardial injury, is an objective biochemical indicator of myocardial injury. The METS study was designed as a pragmatic observational study of preoperative assessment and took a pragmatic approach to outcome assessment. Thus outside of the UK, where all biomarker measurements were carried out at a central laboratory, troponin measurements were carried out at each participating hospital. This resulted in a variety of troponin assays being used. So while this is reflective of worldwide clinical practice and is likely to boost generalisability of the results, the consistency of outcome assessment between centres is less robust than for the VISION study, where identical

troponin assays were used. Other limitations of this analysis include the observational design, precluding any conclusions regarding causality. Cardiopulmonary exercise tests in the METS study were conducted at multiple hospitals using a variety of apparatus and interpreted by investigators at each hospital, which introduces the potential for measurement error and/or observer bias. However, this was mitigated by the prospective use of a standardised exercise testing protocol and interpretation guidelines as well as a standard case report form for collecting exercise test data.[1] The addition of intraoperative hemodynamic data would add further insight into the relationship between parasympathetic autonomic dysfunction, impaired aerobic capacity and hypotension, which is associated with perioperative myocardial injury. Although previous studies have established that impaired heart rate recovery is strongly associated with other measures of parasympathetic autonomic dysfunction, the lack of other autonomic measures in this study limits generalisability beyond CPET-derived parameters.

7.5 Conclusion

Parasympathetic autonomic dysfunction, characterised by impaired heart rate recovery after preoperative exercise testing, is associated with myocardial injury after non-cardiac surgery; and globally impaired cardiopulmonary performance and elevated plasma NT pro-BNP, indicative of sub-clinical heart failure, which was present in 15% of patients. These data suggest that parasympathetic autonomic dysfunction is a plausible mechanism that contributes to perioperative myocardial injury.

Chapter eight

Conclusions and future work

In this thesis I set out to identify modifiable cardiovascular risk factors for perioperative myocardial injury using epidemiological methods. Observations from the general population and from patients with heart failure were tested in five perioperative cohorts. While it was possible to identify haemodynamic risk factors for perioperative myocardial injury, the preoperative phenotype of patients at risk of myocardial injury remains complex. My results suggest that elevated preoperative heart rate, impaired autonomic function and subclinical heart failure are part of the same preoperative phenotype, which may be present in one in six patients undergoing in-patient non-cardiac surgery. However, the underlying pathophysiology remains unclear. Further research is needed to describe the pathological processes responsible for myocardial injury, which may include parasympathetic autonomic dysfunction and/or sub-clinical heart failure, and to help target novel therapeutic strategies for those patients who are most at risk.

8.1 Summary of results

Myocardial injury occurs in 10-40% of patients undergoing non-cardiac surgery, depending on the definition; it is predominantly asymptomatic and without diagnostic ischaemic features; and is strongly associated with death.[16, 103, 115] Data from the general population suggest that patients with elevated heart rate or blood pressure are at greater risk of major cardiac events and death.[152, 153, 156, 157, 332, 333] Using data from the international, multi-centre VISION cohort, I

found that patients with high heart rate before surgery had increased risk of myocardial injury and patients with low heart rate before surgery had reduced risk of myocardial injury. These findings were replicated using data collected during surgery, where patients with high heart rate, or high or low systolic blood pressure during surgery were at greater risk of myocardial injury, compared to those without heart rate or blood pressure abnormality. Conversely, patients with a low heart rate during surgery were at lower risk of myocardial injury. These results were independent of potentially confounding factors such as urgency of surgery, older age or ischaemic heart disease, and support the hypothesis that tachycardia promotes myocardial injury through imbalance between myocardial oxygen supply and demand. However, since interventional trials of heart rate limiting medication, like beta-blockers, have failed to reduce the risk of myocardial injury, it may be more likely that elevated heart rate is a marker of another pathophysiological mechanism that causes myocardial injury.

There is uncertainty among anaesthetists and surgeons regarding the management of hypertension before surgery, which may result in cancelled procedures.[92, 189, 190] In the general population elevated arterial pulse pressure is associated with cardiovascular complications.[147, 213, 370] In chapter four, VISION study data were used to identify that elevated preoperative pulse pressure was associated with increased risk of perioperative myocardial injury, independent of previous history of hypertension and preoperative systolic blood pressure. Therefore, patients with elevated pulse pressure may warrant closer monitoring during the perioperative period.

In the general population, elevated resting heart rate is associated with subsequent development of heart failure,[158, 159] which is risk factor for perioperative morbidity and mortality.[349, 350] Cardiopulmonary exercise testing can identify cardiopulmonary and/or autonomic impairment, and is used for prognostication in patients with heart failure syndrome,[70, 71, 438] as well as risk assessment before surgery.[1] In chapter six, cardiopulmonary exercise testing was used to identify cardiopulmonary and autonomic impairment in patients undergoing high-risk non-cardiac surgery, identifying that elevated preoperative heart rate was associated with impaired cardiopulmonary and autonomic function, suggestive of heart failure. However, only a small proportion of these patients had a clinical diagnosis of heart failure syndrome. In a separate cohort of high-risk patients undergoing abdominal surgery, elevated preoperative heart rate was associated with impaired left ventricular stroke volume. Taken together, these findings suggest that preoperative tachycardia is a marker of subclinical or undiagnosed heart failure.

Approximately one in three high-risk surgical patients have impaired autonomic function.[178] In the general population this is associated with elevated resting heart rate.[92] In chapter seven, preoperative cardiopulmonary exercise testing was used to identify patients with impaired parasympathetic autonomic function in a prospective international multi-centre observational cohort, where parasympathetic dysfunction was associated with postoperative myocardial injury, elevated resting heart rate and CPET and plasma biomarker evidence of heart failure. This suggests that elevated resting heart rate, parasympathetic dysfunction and subclinical heart failure are all part of the same preoperative clinical phenotype.

In summary, I have identified that elevated heart rate before and during surgery, elevated preoperative pulse pressure, both very high and very low systolic blood pressure during surgery, and impaired heart rate recovery after preoperative exercise are associated with increased risk of perioperative myocardial injury. Furthermore, elevated preoperative heart rate is associated with parasympathetic dysfunction and objective evidence of sub-clinical physiological heart failure, which mirrors evidence from studies of the general population. This suggests that in surgical patients, elevated preoperative heart rate, impaired parasympathetic function and subclinical heart failure are likely to be part of the same preoperative phenotype, which may be present in approximately 15% of patients undergoing non-cardiac surgery. Furthermore, it is not possible to determine whether or not the observed associations reflect causal relationships. Therefore, further research is needed to characterise the underlying pathophysiological mechanism of perioperative myocardial injury and to develop novel, and potentially personalised, therapeutic approaches to treating these patients.

8.2 Strengths and weaknesses

The research described in this thesis has several strengths. Firstly, the explanatory (research question driven) analysis strategy, where analyses were planned before taking custody of the data, reduces both analytical and reporting biases. In the small number of cases where exploratory analyses were undertaken (for example, in some of the analyses of the POM-HR data), these were clearly labelled as post-hoc. Secondly, in contrast to the majority of previous studies in this field, the primary outcome of interest was myocardial injury, defined according to the objective measurement of cardiac troponin,

rather than a clinically defined outcome measure. This reduced the influence of observer bias due to the subjective assessment and interpretation of clinical data. Thirdly, I was fortunate to have access to data from the VISION study, one of the largest prospective observational cohort studies in the field of anaesthesia and perioperative medicine.[16, 115] This was the landmark study that identified and defined myocardial injury after non-cardiac surgery (MINS). Therefore, when undertaking research into potential risk factors for MINS, it was helpful to use the original derivation cohort that was used to initially describe this phenomenon. The standardised and detailed nature of the VISION dataset, combined with the very large sample size, allowed statistical adjustments for potentially confounding factors to be made. This is important because there are several factors that could potentially explain the observed relationships between the variables of interest and MINS, which have been accounted for. Due to the international multi-centre study design, the results are generalisible to a wide spectrum of patients undergoing non-cardiac surgery worldwide. Fourthly, the secondary hypotheses relating to sub-clinical heart failure, which further the analysis and support my interpretation of the results, were tested in multiple datasets, utilising several different diagnostic modalities, including: exercise testing, objective measurement of left ventricular stroke volume and objective measurement of cardiac biomarkers (NT pro-BNP).

My approach also has several weaknesses. Firstly, the data included here are observational in nature. Therefore, it is not possible to draw conclusions regarding causative mechanisms. Further research is required to confirm my thesis. Secondly, the results are generated from secondary analyses of data collected for other purposes. Common limitations of this approach are that

important covariates may be absent or that complete data may not be available for a sub-population of interest.[268] However, due to the standardised and detailed nature of case report forms for the studies in question, the risk of this is low. In the VISION study, some information regarding intraoperative medications and cardiac function were unavailable. However, it is unlikely that this adversely affected the interpretation of the results. Furthermore, this methodological approach is a principal strength of the analysis, in that it was possible to answer the research questions through efficient use of data that would otherwise be wasted. Thirdly, the analyses were adjusted for multiple potential confounding factors. However, in common with any clinical research, there is a risk of further confounding by unmeasured factors. Fourthly, in the VISION study, measurements of heart rate and blood pressure were made by clinical staff according to local policy at participating hospitals, so were not standardised. However, this could be viewed as a strength, since these pragmatic data reflect 'real world' clinical practice, which increases the external validity of the results. Finally, in the METS and POM-HR studies, while cardiopulmonary exercise tests were carried out according to standardised protocols, the interpretation of the tests was carried out by clinicians at each individual hospital and were not standardised. Therefore the results may be influenced by inter-observer variation in the interpretation of key exercise test variables. However, similar to measurement of heart rate in the VISION study, these data reflect local practice at each hospital and increase the external validity of the results.

8.3 Directions for future research

I have identified that elevated preoperative heart rate and pulse pressure, high or low intraoperative systolic blood pressure, elevated intraoperative heart rate, and impaired heart rate recovery after preoperative exercise are all associated with increased risk of perioperative myocardial injury. In addition, there is a, hitherto unrecognised, group of surgical patients with a phenotype of subclinical heart failure. However, before proposing therapeutic strategies for prevention and treatment of myocardial injury and subclinical heart failure, further research is required in order to better understand the population of patients at risk and to investigate the underlying pathophysiology.

The pathophysiological mechanism(s) responsible for perioperative myocardial injury are unclear. In the majority of cases it is unlikely to be atherosclerotic plaque rupture and subsequent thrombosis, typically seen with acute coronary syndrome. Objective measures of atherosclerosis correlate poorly with perioperative myocardial injury,[394] and standard treatments for acute coronary syndrome, for example angioplasty or aspirin, do not prevent perioperative cardiac events when given prophylactically.[100, 101] Instead, opinion leaders support a putative mechanism of oxygen supply-demand imbalance due to the combination of a fixed flow limitation in the coronary arteries and increased demand in respiring cardiac muscle.[96] My results support this hypothesis, since tachycardia, hypertension and hypotension could all plausibly contribute to increased oxygen demand in the myocardium. However, treatment with the negatively chronotropic agents beta-blockers or clonidine fails to reduce the incidence of myocardial injury, leaving two explanations. Firstly, pathophysiological mechanisms other than tachycardia-induced oxygen supply-

demand imbalance are involved in the development of perioperative myocardial injury. This is supported by data from chapters six and seven, which identify that autonomic dysfunction, defined according to impaired heart rate recovery, is associated with myocardial injury and that elevated preoperative heart rate is associated with a preoperative phenotype of sub-clinical heart failure. However, further research is required to understand if, and how, impairment of autonomic and cardiopulmonary function contributes to myocardial injury and subsequently how this may be exploited as a therapy. The second possible explanation is that in the previous trials of negative chronotropes (principally beta-blockers), the treatment may not have been targeted with sufficient precision to elicit safe treatment effect due to an incomplete understanding of the population of patients at risk. This hypothesis seems intuitive since, compared to other pathologies, very little is known about perioperative myocardial injury. Therefore, it is conceivable that were negative chronotropes to be targeted at a narrower subgroup of the surgical population than in previous trials, according to a particular 'at-risk' phenotype (e.g. elevated heart rate, sub-clinical heart failure, parasympathetic dysfunction), a treatment effect may be identified that outweighs previously observed side effects. Therefore, further research is required to determine whether abnormal heart rate and blood pressure, as described in this thesis, represent causal risk factors for myocardial injury, and whether these biomarkers could be used to identify patients at risk of perioperative morbidity and/or as a target for novel treatments.

The primary outcome of interest was myocardial injury, defined according to increased concentrations of cardiac troponins in postoperative blood samples. This outcome measure was chosen because it is very common, occurring in

approximately one in ten patients undergoing non-cardiac surgery. It is predominantly asymptomatic, therefore affecting patients without their knowledge or that of their clinicians, and is strongly associated with subsequent postoperative mortality.[16, 95, 115] For these reasons, there is growing interest in routine postoperative screening for myocardial injury.[387, 439] However, the mechanism of mortality following myocardial injury is unknown and it is unclear whether myocardial injury is a causal risk factor for mortality or a marker of some, as yet unknown, pathological process. In addition, the long-term consequences of myocardial injury in patients that survive the immediate postoperative period are unknown. In the absence of these data, it is hard to justify a screening programme and to recommend potential therapies for clinical trials and ultimately for clinical practice. Therefore, translational research is needed to identify the underlying pathology linking myocardial injury and mortality, and to develop potential treatments. In addition to this, further epidemiological research is needed to determine the long-term impact of perioperative myocardial injury, for example on long-term survival, quality of life and cardiac function.

Finally, using multiple methods, I have identified a sub-group of surgical patients with features of subclinical heart failure. However, other than prevalence, little is known about this group of surgical patients. Therefore, I propose a prospective observational cohort study to resolve this. A detailed preoperative clinical and physiological phenotype would be described using biochemical biomarkers of cardiac function, dynamic tests of cardiac function using cardiopulmonary exercise testing, and static tests of cardiac function using echocardiography. Participants would receive postoperative follow-up to

measure clinical outcomes after surgery. Such a study would help to determine whether subclinical heart failure is associated with postoperative complications as well as mortality, and whether all patients with subclinical heart failure are at risk, or whether association is restricted to specific sub-groups, such as patients with reduced ejection fraction.

In summary, I have identified that abnormalities of heart rate and blood pressure, before and during surgery, are associated with increased risk of perioperative myocardial injury. Further to this, elevated preoperative heart rate is associated with subclinical heart failure and parasympathetic autonomic dysfunction, characterised by impaired heart rate recovery after preoperative exercise. The preoperative phenotype of patients at risk of myocardial injury is complex, and elevated preoperative heart rate, impaired parasympathetic function and subclinical heart failure seem to be part of the same preoperative phenotype, present in ~15% of patients undergoing non-cardiac surgery. Further research is needed to determine how and why myocardial injury occurs and to develop novel, and potentially personalised, therapeutic approaches.

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Appendix 1: Researcher development training

	Domain				
	A	**B**	**C**	**D**	**Total**
Conference Attendance (Half day)	2.5	1	0	0	3.5
Conference Attendance (One day)	19	10	0	0	29
Conference Attendance (Three days)	27	18	0	0	45
Conference Attendance (Two days)	16	8	0	0	24
Conference attendance sub-total	**18**	**12**	**0**	**0**	**30**
CAPD Course	3	5.5	3.5	4	16
Core research knowledge or methods course	100	0	0	0	100
Other Teaching/demonstrating training	0	1.5	0	1.5	3
Course/event attendance sub-total	**103**	**7**	**3.5**	**5.5**	**119**
Fast-track ethical approval	1	0	3	1	5
Ethical approval sub-total	**1**	**0**	**3**	**1**	**5**
External funding application >£10,000	15	15	25	15	70
Funding application sub-total	**15**	**15**	**25**	**15**	**70**
Conference Presentation (Oral)	9	9	0	12	30
Conference Presentation (Poster)	3	3	0	4	10
Giving presentations sub-total	**12**	**12**	**0**	**16**	**40**
Representing Research Group at meeting or committee	0	0	11.5	10.5	22
Meeting/club/reading group attendance sub-total	**0**	**0**	**11.5**	**10.5**	**22**
Organising Conference (with external speaker(s))	4	0	4	4	12
Organising events/seminars sub-total	**4**	**0**	**4**	**4**	**12**
Conference Attendance - internal to QM	3	2	0	2	7
Conference Presentation (oral/poster)	3	3	0	4	10
Course/event Attendance	90	5	5	13	113
Doctoral College Debate 2014	0	1	1	0	2
Ethical Approval for Study - Clinical	0	0	10	0	10
External course/workshop/event attendance	0	0	5	2	7
Organising an event/seminar/conference	9	6	9	16	40
Participation in Post-graduate Society events	0	1	0	0	1
Presenting - internal to QM	2	2	0	4	8
Other sub-total	**107**	**20**	**30**	**41**	**198**
Mentoring/supervising of Project Student	2	1	0	2	5
Teaching/demonstrating/marking/preparation	0	12	0	12	24
Teaching sub-total	**2**	**13**	**0**	**14**	**29**
Publication - review paper	1	0	0	3	4
Refereed Publication (e.g. Journal Paper) acceptance	4	0	0	16	20
Written publications sub-total	**5**	**0**	**0**	**19**	**24**
Total	**267**	**79**	**77**	**126**	**549**

Vitae Researcher Development Framework, where one point represents at least one hour of training. Knowledge and intellectual abilities (A), Personal effectiveness (B), Research governance and organisation (C) and Engagement, Influence and Impact (D).

Appendix 2: Conference presentations

T. Abbott, G. Ackland, A. Archbold, A. Wragg, R.Rodseth, R. Pearse. Association between intraoperative heart rate and postoperative myocardial injury. Evidence Based Perioperative Medicine congress, 4-6th July 2017

T. Abbott, R. Pearse, A. Archbold, A. Wragg, R.Rodseth, G. Ackland. Preoperative pulse pressure and postoperative myocardial injury. Evidence Based Perioperative Medicine congress, 4-6th July 2017

T. Abbott, R. Pearse, G. Minto, A. Lee, G. Ackland. Elevated preoperative heart rate is associated with cardiopulmonary and autonomic dysfunction in high-risk surgical patients. Evidence Based Perioperative Medicine congress, 4-6th July 2017

T. Abbott. 'Preoperative blood pressure and myocardial injury'. *Clinical Pharmacology group, Barts Health*. 17th June 2016

T. Abbott. 'Preoperative heart rate and myocardial injury'. *London Academy of Anaesthesia meeting*. 23rd May 2016

T. Abbott, G. Ackland, A. Archbold, A. Wragg, R.Rodseth, R. Pearse. Association between intraoperative heart rate and postoperative myocardial injury. ESICM congress, Berlin, 6 October 2015

T. Abbott, G. Ackland, A. Archbold, A. Wragg, R.Rodseth, R. Pearse. Association between preoperative heart rate and postoperative myocardial injury. Evidence Based Perioperative Medicine congress, 1 July 2015

T. Abbott, G. Ackland, A. Archbold, A. Wragg, R.Rodseth, R. Pearse. Association between preoperative heart rate and postoperative myocardial injury. GAT Annual Scientific Meeting, Manchester, 18 June 2015

T. Abbott, G. Ackland, A. Archbold, A. Wragg, P. Devereaux, R. Pearse. Association between preoperative heart rate and postoperative myocardial injury. Anaesthetic Research Society, London, 21 April 2015

T. Abbott. 'Can preoperative physiology predict postoperative outcome?' *Perioperative medicine research day, William Harvey Research Institute.* 25th November 2014

T. Abbott. 'An introduction to the Measurement of Exercise Tolerance before Surgery study.' Anaesthesia research forum, *The Royal London Hospital.* 7th July 2014

Appendix 3: Additional CPET methods

Contraindications to cardiopulmonary exercise testing

The ATS/ACCP recommended contraindications to CPET are listed below.[272]

Absolute contraindications:

- Acute myocardial infarction within 3-5 days
- Unstable angina
- Uncontrolled arrhythmia causing symptoms or haemodynamic compromise
- Syncope
- Active endocarditis
- Acute myocarditis or pericarditis
- Uncontrolled heart failure
- Acute pulmonary embolus or pulmonary infarction
- Thrombus of lower extremities
- Suspected dissecting aneurysm
- Uncontrolled asthma
- Pulmonary oedema
- Room air desaturation ≤85%
- Respiratory failure
- Acute non-cardipulmonary disorder that may affect exercise performance or be aggravated by exercise (e.g. infection, renal failure, thyrotoxicosis)
- Mental impairment leading to inability to cooperate

Relative contraindications:

- Left main coronary stenosis or equivalent
- Moderate stenotic valvular heart disease
- Severe untreated arterial hypertension at rest (>200mmHg systolic, or >120mmHg diastolic)
- Tachyarrythmias or bradyarrythmias
- High-degree AV block
- Hypertrophic cardiomyopathy
- Significant pulmonary hypertension
- Advanced or complicated pregnancy
- Electrolyte abnormalities
- Orthopaedic impairment that compromises exercise performance

Stopping a CPET

Since the purpose of a CPET is to determine the participant's cardiopulmonary fitness through exercise to the limit of their tolerance, the most common reason for stopping a test was at the request of the participant due to symptom-limited fatigue. The ATS/ACCP recommend the following safety criteria for stopping a CPET:[272]

- Chest pain suggestive of myocardial ischaemia
- Ischaemic ECG changes
- Complex ectopy
- Second or third degree heart block
- Fall in systolic blood pressure >20 mmHg from highest value during CPET
- Hypertension >250 mmHg systolic or >120 mmHg diastolic

- Severe oxygen desaturation ≤80% when accompanied by symptoms and signs of hypoxemia
- Sudden pallor
- Loss of coordination
- Mental confusion
- Dizziness of faintness
- Signs of respiratory failure

The METS study standard operating procedure for CPET stipulated the following additional stopping criteria:[295]

- Pedal rate >50RPM cannot be maintained
- Participant is fatigued and requests to stop the test

Adverse events during CPET

The METS study protocol required the following clinical occurrences during CPET to be reported as adverse events in line with the adverse event reporting standard operating procedure, which I helped to write:[440]

- Angina or chest pain suggestive of angina
- Arrhythmia: sustained ventricular tachycardia or multifocal premature ventricular contractions, supraventricular tachycardia, new onset second or third degree heart block, new onset atrial fibrillation or flutter, or new onset bradycardia
- Ischaemic electrocardiographic changes: ST segment elevation >1mm in leads without diagnostic Q waves (other than V1 or aVR) or excessive ST depression >2mm horizontal or down-sloping ST-segment depression

- Hypertensive response (systolic blood pressure >250 mmHg and/or a diastolic pressure >120 mmHg)
- Fall in systolic blood pressure >20 mmHg from the highest value during CPET
- Signs of respiratory failure or severe oxygen desaturation (<80% when accompanied by signs or symptoms of severe hypoxia)
- Syncope, pre-syncope, sudden pallor, loss of coordination or mental confusion

Appendix 4: Published journal articles

T. E. F. Abbott, G. L. Ackland, R. A. Archbold, A. Wragg, E. Kam, T Ahmad, A. W. Khan, E. Niebrzegowska, R. N. Rodseth, P. J. Devereaux and R. M. Pearse. Preoperative heart rate and myocardial injury after non-cardiac surgery: results of the VISION study. British Journal of Anaesthesia 2016; 117 (2): 172-181.

T. E. F. Abbott, R. M. Pearse, R. A. Archbold, A. Wragg, E. Kam, T Ahmad, A. W. Khan, E. Niebrzegowska, R. N. Rodseth, P. J. Devereaux and G. L. Ackland. Association between preoperative pulse pressure and perioperative myocardial injury: an international observational cohort study of patients undergoing non- cardiac surgery. British Journal of Anaesthesia 2017; 119 (1): 78-86.

T. E. F. Abbott, G. Minto, A. Lee, R. M. Pearse, G. L. Ackland. Elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment in high-risk surgical patients. British Journal of Anaesthesia 2017; 119 (1): 87-94.

T. E. F. Abbott, R. M. Pearse, R.A. Archbold, T. Ahmad, A. Wragg, R. N. Rodseth, P. J. Devereaux and G. L. Ackland. A prospective international multi-centre cohort study of intraoperative heart rate and systolic blood pressure, and myocardial injury after non-cardiac surgery: results of the VISION study. Anesthesia & Analgesia 2017 (accepted manuscript).