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

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Summary

Background

Elevated preoperative heart rate is associated with perioperative myocardial injury and death. In apparently healthy individuals, high resting heart rate is associated with development of cardiac failure. Since patients with overt cardiac failure have poor perioperative outcomes, we hypothesised that subclinical cardiac failure, identified by cardiopulmonary exercise testing, was associated with elevated preoperative heart rate >87 beats.min^{-1} (HR>87).

Methods

Secondary analysis of an observational cohort study of surgical patients aged ≥45 years. The exposure of interest was HR>87, recorded at rest before preoperative cardiopulmonary exercise testing. The pre-defined outcome measures were established predictors of mortality in patients with overt cardiac failure in the general population: $\dot{V}E/\dot{V}CO_2$ ratio ≥34, heart rate recovery ≤6 and peak $\dot{V}O_2$ ≤14 ml.kg^{-1}min^{-1}. We used logistic regression analysis to test for association between HR>87 and markers of cardiac failure. We also examined the relationship between HR>87 and preoperative left ventricular stroke volume in a separate cohort of patients.

Results

HR>87 was present in 399/1250 (32%) patients: 438/1250 (35%) had $\dot{V}E/\dot{V}CO_2$ ratio ≥34, 200/1250 (16%) had heart rate recovery ≤6 and 396/1250 (32%) had peak $\dot{V}O_2$ ≤14ml.kg^{-1}min^{-1}. HR>87 was independently associated with peak $\dot{V}O_2$ ≤14ml.kg^{-1}min^{-1} [odds ratio (OR):1.69 [1.12-3.55]; p=0.01] and heart rate recovery ≤6 (OR:2.02 [1.30-3.14]; p<0.01). However, HR>87 was not associated with $\dot{V}E/\dot{V}CO_2$ ratio ≥34 (OR:1.31 [0.92-1.87]; p=0.14). In a separate cohort HR>87 (33/181;18.5%) was associated with impaired preoperative stroke

volume (OR:3.21 [1.26-8.20]; p=0.01).

Conclusions

Elevated preoperative heart rate is associated with impaired cardiopulmonary performance consistent with clinically-unsuspected, sub-clinical cardiac failure.

Introduction

Over 1.5 million major surgical procedures are carried out in the United Kingdom each year and one in six patients will experience a complication after surgery.[1, 2] One in ten patients will sustain myocardial injury after non-cardiac surgery, which is strongly associated with mortality.[3] However, the presence of coronary artery disease is a poor predictor of morbidity and mortality in these patients.[4] In contrast, elevated preoperative resting heart rate (>87 beats.min^{-1}) is independently associated with myocardial injury and mortality.[5] Although tachycardia may be attributable to acute pathophysiology (e.g. sepsis, systemic inflammation), mechanisms to explain this association remain unclear.[6] Tachycardia may promote myocardial injury through oxygen supply-demand imbalance.[7] However, since treatment with beta-blockers or clonidine fail to reduce the incidence of myocardial injury, other pathophysiological mechanisms are likely to be involved.[8, 9]

Patients with a confirmed diagnosis of cardiac failure syndrome are at very high risk of perioperative mortality.[10, 11] Cardiopulmonary exercise testing can identify cardiopulmonary and/or autonomic dysfunction, and has been used for prognostication in patients with confirmed cardiac failure and for risk assessment before surgery.[12-14] In the general population, elevated resting heart rate is an independent risk factor for the development of heart failure.[4, 15, 16] Therefore, elevated preoperative heart rate may indicate underlying sub-clinical cardiac impairment; thus generating several plausible - and potentially novel - pathophysiological mechanisms that may contribute to perioperative myocardial injury, morbidity and mortality.[5, 7, 17, 18]

We hypothesised that elevated preoperative resting heart rate (>87 beats.min^{-1})[5] was associated with impaired cardiovascular and/or autonomic function consistent with sub-clinical cardiac failure. We tested this hypothesis by evaluating cardiovascular and

autonomic factors derived from preoperative cardiopulmonary exercise testing that are known to be associated with clinical outcome in patients with heart failure.[3]

Methods

Study design

This was a secondary analysis of data obtained prospectively from the Perioperative Morbidity – Heart Rate (POM-HR) study, a multi-centre observational cohort study of high-risk patients undergoing non-cardiac surgery. The methods have been published previously.[19] The study was approved by the NRES Committee London (Camden & Islington; MREC:12/LO/0453) and registered with Controlled Trials (ISRCTN88456378).

Patient population

Patients were eligible for inclusion if they were aged 45 years or more, were 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). The exclusion criteria were refusal of consent or contraindications to CPET. These criteria are very similar to the eligibility criteria for the VISION study.[3]

Data collection

In POM-HR before surgery, patient age, gender, operative time, established measures of preoperative risk (including diabetes mellitus, cardiac and cerebrovascular disease) and haemoglobin were recorded. All participants underwent preoperative cardiopulmonary exercise testing (CPET).

Outcome measures

The primary outcomes measures were three cardiopulmonary exercise test (CPET) derived variables that are established and independent predictors of mortality in patients with cardiac

failure: ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) ≥34, heart rate recovery ≤6 and peak oxygen consumption ($\dot{V}O_2$) ≤14 ml.kg^{-1}min^{-1}.[12] 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, peak heart rate and heart rate reserve. Full details for the original papers detailing the prognostic value of these variables is provided in supplementary table 1.

Cardiopulmonary exercise testing (CPET)

CPET was carried out at each participating hospital in designated CPET laboratories. Prior to CPET, participants were instructed to continue their normal medications up to, and including, the day of the test. CPET was conducted using a standard incremental ramp protocol to maximal exercise tolerance using an electromagnetically braked cycle ergometer. Equipment was calibrated before each test, including calibration of the gas-analyser using standard reference gases. During CPET continuous 12-lead electrocardiography (heart rate), intermittent sphygmomanometry (arterial blood pressure) and breath-by-breath measurement of gas exchange were performed. Before each test, arterial blood pressure and heart rate were measured in the sitting position after at least 30 seconds rest. Participants were instructed to continue cycling as the ramp (watts) increased, until they were unable to continue due to symptom-limited fatigue. After reaching peak exercise tolerance, continued physiological measurements were recorded during the period of recovery from exercise.

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 ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$). Oxygen consumption (ml.kg^{-1}min^{-1}) was measured at the anaerobic threshold and at peak exertion.

The ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) 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, which reflects sympathetic activation, was defined as maximal heart rate achieved during exercise. Heart rate recovery, a measure of parasympathetic activity, 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 beats.minute^{-1}. Peak oxygen pulse (ml.beat^{-1}), a surrogate marker for cardiac stroke volume,[20] was calculated as peak oxygen consumption (ml.min^{-1}) divided by peak heart rate (beats.min^{-1}).

Statistical analysis

We 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.

We dichotomised the sample according to heart rate >87 beats.min^{-1} and summarised descriptive physiological variables for each group.[5] We used a t-test to identify differences in continuous data between groups and chi-squared test to identify differences in categorical data between groups. We used logistic regression analysis to test for association between elevated preoperative heart rate > 87 beats.minute^{-1} and each outcome measure, first using univariable analysis. In addition, we 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 beats.min^{-1}. We 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.[3, 21] We chose to include RCRI as this is routinely used as a risk score to predict MINS and as a comparator with new risk stratification modalities (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.

Preoperative left ventricular stroke volume and autonomic analyses

We undertook a post-hoc analysis of data from the OPTIMISE and POM-O trials (ISRCTN: 76894700 and 04386758, respectively), the principle findings and methods of which have been published elsewhere.[18, 22] We tested the hypothesis that preoperative resting heart rate >87 beats.min^{-1} was associated with a cardiac failure phenotype by assessing preoperative left ventricular stroke volume and autonomic measures in patients undergoing major abdominal surgery. We restricted our analysis 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. We dichotomised the cohort according to a mean preoperative heart rate threshold of >87 beats.min^{-1} and compared mean beat-by-beat preoperative left ventricular stroke volume between groups using a t-test. We used logistic regression analysis to test for association between mean preoperative heart rate >87 beats.min^{-1} 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.[23]

We also assessed the relative contributions of sympathetic/parasympathetic modulation of preoperative heart rate >87 in the POM-O cohort by analysing time and frequency-domain measures in accordance with ACC/AHA Task Force guidelines as reported previously.[24, 25] Parasympathetic cardiac activity was assessed using two time-domain

measures: Root Mean Square of the Successive Differences (RMSSD) and pNN50, which reports the proportion of consecutive NN intervals that differ by more than 50ms. In addition, the high frequency component of heart rate power spectral analysis was quantified. The low frequency/High Frequency ratio was calculated to assess sympathetic-parasympathetic balance, a relative higher value for which indicates dominant sympathetic modulation of heart rate.

Results

1,572 surgical patients underwent CPET at one of five participating United Kingdom hospitals. We excluded cases that were missing complete CPET data or pre-defined covariates, leaving 1,250 patients for the final analysis (Supplementary Figure 1). Patient characteristics are presented in table 1. Resting preoperative heart rate >87 beats min^{-1} 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 beats.min^{-1} compared to those with HR≤87 beats.min^{-1} (table 1). 52/1250 (4.2%) patients had an established diagnosis of heart failure and 162/1250 (13.0%) had a diagnosis of ischaemic heart disease. Patients with resting HR>87 beats.min^{-1} had elevated heart rates recorded immediately before surgery, the time point at which the VISION study recorded preoperative variables.[3]

Primary analysis

Of 1250 patients 438 (35%) had $\dot{V}E/\dot{V}CO_2$ ratio ≥34, 200 (16%) had heart rate recovery ≤6 and 396 (32%) had peak $\dot{V}O_2$ ≤14 ml.$kg^{-1}min^{-}1$. The results of the logistic regression analyses for heart rate > 87 beats.$minute^{-1}$ against the primary outcome measures are shown in table 2. After correcting for potential confounding factors heart rate >87 beats.$minute^{-1}$ was associated with peak $\dot{V}O_2$ ≤14 ml.$kg^{-1}min^{-1}$ (odds ratio (OR) 1.69 [1.12-3.55]; p=0.01) and heart rate recovery ≤6 (OR 2.02 [1.30-3.14]; p<0.01). However, heart rate >87 beats.$minute^{-1}$ was not associated with $\dot{V}E/\dot{V}CO_2$ ratio ≥34 (OR 1.31 [0.92-1.87]; p=0.14).

Secondary analysis

Patients with resting heart rate >87 beats.$minute^{-1}$ had lower peak oxygen consumption, oxygen consumption at the anaerobic threshold and ($\dot{V}_E/\dot{V}CO_2$) ratios (table 3). Peak oxygen

pulse, a robust measure of left ventricular stroke volume, was lower in patients with resting heart rate >87 beats.minute^{-1} beats.min^{-1}.[20] Resting heart rate >87 beats.min^{-1} was not associated with oxygen consumption at the anaerobic threshold <11.1ml.kg.min^{-1} (OR 1.24 [0.98-1.59]; p=0.08) using univariable logistic regression analysis. However, resting heart rate >87 beats.min^{-1} was associated with peak oxygen pulse <12ml.beat^{-1} (OR 2.80 [2.19-3.58]; p<0.01)) using univariable logistic regression analysis. Patients with heart rate ≤87 beats.min^{-1} had near normal predicted oxygen pulse, when expressed as a percentage of population-specific normal values (94.9% (95%CI: 93.0-96.9). By contrast, percentage predicted peak oxygen pulse was 15.2% (95%CI: 12.3-18.1) lower in patients with resting heart rate >87 beats.min^{-1} (p<0.01). Patients with resting heart rate >87 beats.min^{-1} 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 resting heart rate >87 beats.min^{-1}.

Sensitivity analysis

In patients with heart failure the prognostic threshold for peak oxygen consumption is lower (≤12ml.kg.min^{-1}) in patients receiving beta-blockers. We performed a sensitivity analysis by repeating the primary univariable logistic regression using the lower threshold in patients taking beta-blockers (247/1250). However, we did not identify association between impaired oxygen consumption and HR>87 (OR 1.37 [0.63-2.96]; p=0.43).

Preoperative left ventricular stroke volume and perioperative autonomic function

We further examined cardiac and autonomic 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

(supplementary figure 2). From both trials, patients with preoperative heart rate >87 beats.min^{-1} had lower mean preoperative stroke volume (mean difference 23.5 [8.0-38.9] ml; p=0.03). Preoperative heart rate >87 beats.min^{-1} was associated with impaired preoperative stroke volume <59ml (OR 3.21 [1.26-8.20]; p=0.01), taking into account patients with an established preoperative diagnosis of heart failure (supplementary table 2). We also performed a detailed analysis of autonomic data captured in the POM-O cohort, to delineate the components of preoperative tachycardia. Heart rate was higher throughout the intraoperative period in patients with preoperative heart rate >87 beats.min^{-1} (Figure 1). Preoperative heart rate >87 beats.min^{-1} was chiefly associated with measures indicative of lower parasympathetic activity (Figure 1b-d). This was accompanied by similar sympathetic activity (LF) between groups (not shown), but higher LF/HF ratio (Figure 1e), reflecting dominant sympathetic autonomic modulation of heart rate in patients with heart rate >87 beats.min^{-1} due to loss of cardiac vagal tone. Spontaneous baroreflex sensitivity (Figure 1f) was also lower in patients with preoperative heart rate >87 beats.min^{-1}. Higher lactate was observed at the end of surgery in patients with preoperative heart rate >87 beats.min^{-1} (OR of lactate>2mmol.L^{-1}: 3.05 [1.21-7.65]; Figure 1g).

Discussion

The principal finding of this generalizable, multi-centre cohort study is that resting preoperative heart rate >87 beats.minute^{-1} is associated with marked cardiorespiratory and autonomic impairment, compatible with the pathophysiological hallmarks of significant - yet sub-clinical - cardiac failure. These findings are reinforced by interrogation of perioperative haemodynamic data from the OPTIMISE and POM-O trials. In this cohort, elevated preoperative heart rate >87 beats.minute^{-1} is common and cannot be accounted for by acute pathophysiology causing relative tachycardia (e.g. sepsis, systemic inflammation).[6] Taken together, this 'reverse-translational' approach provides a physiological framework affording further insight into why elevated resting heart rate is independently associated with perioperative myocardial injury and excess mortality.[3] Our results show that elevated resting heart rate is associated with several features of impaired cardiorespiratory and autonomic function indicative of sub-clinical cardiac failure. This is consistent with previous reports confirming that patients with an established diagnosis of cardiac failure preoperatively have substantially higher morbidity and mortality after non-cardiac surgery.[10]

Resting heart rate is progressively associated with increasing risk of incident heart failure in otherwise apparently healthy men and women.[15, 16] Experimental data show that sustained elevated heart rate induces cardiac failure in the absence of structural or atherosclerotic heart disease.[26] However, elevated heart rate does also appear to increase the risk of heart failure in individuals with established hypertension, coronary heart disease and valvular heart disease.[27] The EPIC-Norfolk study showed that a 10 beats.minute^{-1} increase in resting heart rate was independently associated with an 11% increase in risk of developing cardiac failure.[15] The 15 year Rotterdam Study of 4768 apparently healthy individuals, with a similar age to our cohort, showed that incremental increases of 10 beats.min^{-1} in men was associated with the development heart failure within 6 months of study enrolment.[16] Thus,

elevated resting heart rate is an independent risk factor for the development of heart failure in healthy older men in the general population, mirroring the gender imbalance evident in VISION, where male gender was an independent risk factor for MINS/mortality. The Rotterdam cohort study also established that the reproducibility of the association between heart rate and development of heart failure was not influenced by the measurement method of heart rate, as we also found in our study where heart rate was similar before CPET and immediately preoperatively.[16]

Several mechanisms may mechanistically link resting heart rate, incident heart failure and perioperative myocardial injury. A causal link between elevated heart rate, myocardial oxygen demand, coronary blood flow and myocardial injury has long been postulated, chiefly through myocardial oxygen supply/demand imbalance. However, our study also identifies alternative pathological explanations for the development of MINS/perioperative mortality. At peak exercise, oxygen pulse is a robust surrogate measure of left ventricular stroke volume.[20] Notably, the oxygen pulse measurements in patients with HR >87 beats.minute^{-1} were similar to patients with mild-to-moderate heart failure.[22] This is compatible with the hypothesis that heart rate is increased as result of lower stroke volume, in order to maintain cardiac output- a relationship that is also observed consistently in patients with heart failure. 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.[28] Low stroke volume, and hence oxygen delivery, may be exacerbated by anaesthesia, leading to intraoperative hypotension and associated end-organ hypoperfusion - including myocardial and renal injury.[29]

Autonomic impairment is also mechanistically linked with preoperative cardiac ischaemia and postoperative morbidity following non-cardiac surgery. Sympathetic and parasympathetic components may independently contribute to MINS. Reduction in heart rate

after peak exercise -heart rate recovery - is due to parasympathetic reactivation during the first few minutes of recovery.[30] Reduced cardiac vagal activity promotes cardiac injury through the loss of cardioprotective mechanisms, including rate control and metabolic reprogramming.[7, 31] Patients with relatively increased sympathetic activity, as manifest by higher resting heart rate, are more likely to receive sympatholytic medication. In the context of our findings, the use of clonidine and/or beta-blockade in these patients may precipitate hypotension given that higher heart rate is associated with impaired stroke volume/cardiac contractility.

Strengths of this study include the observation that resting heart rate was comparable both before CPET and on the day of surgery. The 'reverse translational' approach, using observations from the VISION study to plan detailed physiological assessment using two independent approaches in a substantial number of patients, suggests these data are generalizable. 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.[32, 33] Significant weaknesses include the observational design, which cannot, by definition, establish causality. However, we considered potential confounding factors by adjusting for various established clinical risk factors and cardiovascular drug therapy, for example beta-blockers, which are know to affect heart rate. Heart rate is mathematically coupled with some CPET variables: in particular, oxygen pulse at peak 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 we have shown an association rather between raised HR *prior* to CPET decreased oxygen pulse at peak. Moreover, an association between pre CPET HR>87 and unfavourable CPET measures was also apparent for $\dot{V}O_2$ and $\dot{V}_E/\dot{V}O_2$ at AT, variables which are not mathematically

coupled to heart rate. A lack of data on intraoperative vasopressor use, other than norepinephrine, is likely to underestimate the extent and/or effect of clinically relevant hypotension on clinical outcomes and intraoperative haemodynamic measures. Our results may be confounded by factors that were not measured, for example we are unaware of the incidence of obstructive sleep apnoea in this sample, which is known to be associated with autonomic impairment.[34, 35]

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

Conflict of interest statement

RP holds research grants, and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Medtronic, and Edwards Lifesciences, and is a member of the Associate editorial board of the British Journal of Anaesthesia; there are no other relationships or activities that could appear to have influenced the submitted work. GLA is a member of the Associate editorial board of Intensive Care Medicine Experimental. TEFA is the trainee representative to the Perioperative Exercise Testing and Training Society. All other authors declare no conflict of interests.

Author Contributions

Conceived and designed the study: GLA. Performed the experiments: POM-HR investigators. Designed the analysis and analysed the data: TEFA/GLA. Wrote the first draft of the manuscript: TEFA/GLA. Contributed to the writing of the manuscript: TEFA/RMP/GM/AL/GLA. ATICMJE criteria for authorship read and met: TEFA/RMP/GM/AL/GLA/ POM-HR investigators. Agree with manuscript results and conclusions: TEFA/RMP/GLA/ POM-HR investigators.

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Figure legends

Figure 1. Elevated heart rate and autonomic measures from post-hoc analysis of the POM-O cohort. The analysis included data from 187 patients recruited from the POM-O trial. A. Resting mean (95%CI) heart rate (HR) before surgery, stratified by heart rate >87 beats.min^{-1}. B. Mean (95%CI) Root Mean Square of the Successive Differences (RMSSD), a time-domain measure of parasympathetic modulation of heart rate. C. Mean (95%CI) pNN50, an additional time-domain measure of parasympathetic modulation of heart rate that reports the fraction of consecutive NN intervals that differ by more than 50ms. D. Median (IQR) preoperative values for high frequency (parasympathetic) component of heart rate power spectral analysis. E. Median (IQR) preoperative values for LF/HF ratio, a higher value for which indicates dominant sympathetic modulation of heart rate. F. Spontaneous baroreflex sensitivity (mean (95%CI)) G. Venous lactate measurements (mean (95%CI)) at the end of intraoperative period. Asterisk denotes p<0.01.

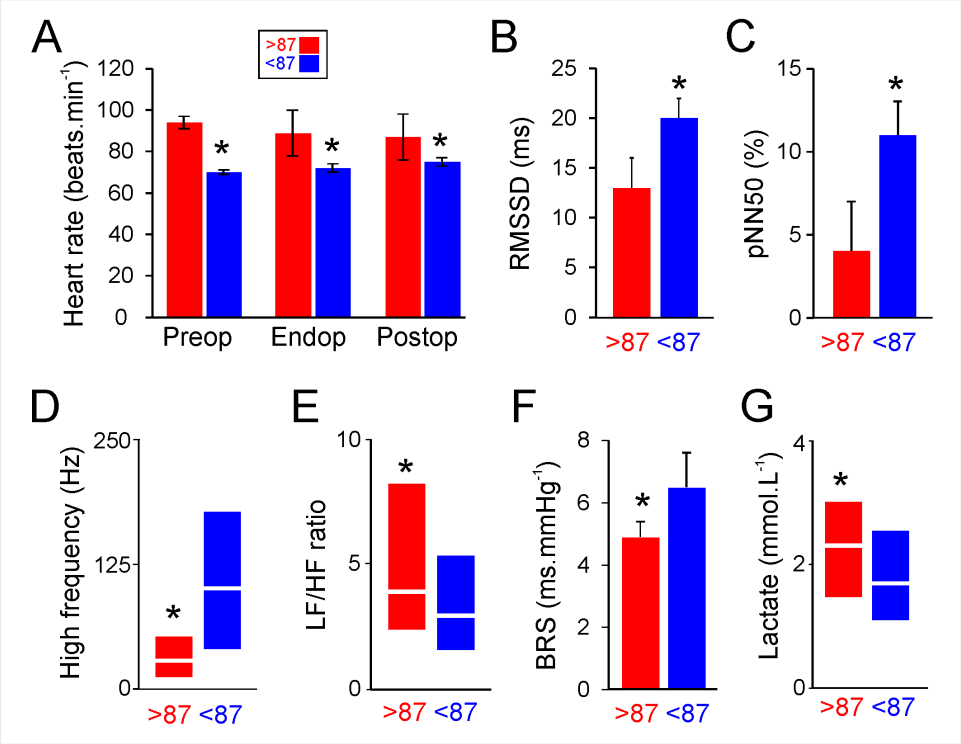

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Table 1. Baseline patient characteristics. Descriptive data stratified by resting heart rate >87 beats.minute^{-1}, presented as frequencies with percentages (%) or mean (standard deviation; SD). Heart rate (HR) data in >87 beats.minute^{-1}, blood 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.

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 anatagonist	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
ACE inhibitor/ Angiotensin receptor	119 (30.0)	246 (29.1)	0.75

Table 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 beats.minute^{-1}. Results presented as odds ratios with 95% confidence intervals, with p-value. Angiotensin Converting Enzyme Inhibitor (ACE-I), Angiotensin Receptor Blocker (ARB).

	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 ml.kg.minute^{-1}	1.39 (1.08-1.78)	0.01	1.69 (1.12-3.55)	0.01
VE/VCO2 at anaerobic threshold ≥34	1.59 (1.24-2.03)	<0.01	1.31 (0.92-1.87)	0.14
Heart rate recovery ≤6 beats.minute^{-1}	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	-	-
ACE-I/ARB	1.04 (0.80-1.36)	0.75	-	-

Table 3. Physiological and cardiopulmonary exercise test variables. Data stratified by resting heart rate >87 beats.minute^{-1}, 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 beats.minute^{-1}, blood pressure data in millimetres of mercury (mmHg), rounded to the nearest whole number. Other units are shown.

Characteristic	**HR >87**	**HR≤87**	**p-value**
Preoperative haemodynamic variables			
Resting heart rate (beats.min^{-1})	99 (10)	73 (10)	<0.01
Systolic blood pressure (mmHg)	147 (23)	145 (23)	0.23
Diastolic blood pressure (mmHg)	84 (12)	81 (13)	<0.01
Pulse pressure (mmHg)	62 (20)	65 (19)	0.09
Mean arterial pressure (mmHg)	104 (14)	101 (15)	<0.01
Preoperative CPET variables			
Oxygen consumption at the anaerobic threshold	11.2 (2.7)	11.4	0.21
Peak oxygen consumption (ml.kg.min^{-1})	16.8 (4.8)	17.6	<0.01
VE/VCO2 at anaerobic threshold	32.7 (5.7)	31.1	<0.01
Peak oxygen pulse (ml.beat^{-1})	11.6 (2.9)	13.8	<0.01
Peak heart rate (beats.min^{-1})	145 (19)	128 (23)	<0.01
Heart rate increase (beats.min^{-1})	46.1	55.8	<0.01
Heart rate recovery (beats.min^{-1})	13 (15)	18 (13)	<0.01