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

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Abstract

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

Methods. This was a secondary analysis of an observational cohort study of surgical patients aged ≥45 yr. The exposure of interest was HR > 87, recorded at rest before preoperative cardiopulmonary exercise testing. The predefined outcome measures were the following established predictors of mortality in patients with overt cardiac failure in the general population: ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}co_2$) ratio ≥34, heart rate recovery ≤6 and peak oxygen uptake ($\dot{V}o_2$) ≤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, of whom 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 $\dot{V}o_2$ ≤14 ml kg^{-1} min^{-1}. HR > 87 was independently 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, 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, subclinical cardiac failure.

Clinical trial registration. ISRCTN88456378.

Key words: cardiac failure; heart rate; surgery

More than 1.5 million major surgical procedures are carried out in the UK each year, and one in six patients will experience a complication after surgery.[1] [2] One in 10 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 (HR >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, as treatment with β-blockers or clonidine fails 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 (CPET) can identify cardiopulmonary dysfuntion, autonomic dysfunction, or both, 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 HR is an independent risk factor for the development of heart failure.[4 15 16] Therefore, elevated preoperative HR may indicate underlying subclinical 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 hypothesized that elevated preoperative resting HR (>87 beats min^{-1})[5] was associated with impaired cardiovascular function, autonomic function, or both, consistent with subclinical 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 multicentre observational cohort study of high-risk patients undergoing non-cardiac surgery. The methods have been published previously.[19] The study was approved by Research Ethics Committee (Camden and Islington; MREC:12/LO/0453) and registered (ISRCTN88456378).

Patient population

Patients were eligible for inclusion if they were aged ≥45 yr, were undergoing major surgery predicted to last for >2 h, and were referred for CPET as part of their routine preoperative assessment. Patients provided written informed consent before taking part in the study (before 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 CPET.

Outcome measures

The primary outcomes measures were the following three 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; HR 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, as follows: preoperative pulse pressure, oxygen consumption at the anaerobic threshold, peak oxygen pulse, peak HR, and HR reserve. Full details for the original papers detailing the prognostic value of these variables are provided in Supplementary Table S1.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was carried out at each participating hospital in designated CPET laboratories. Before CPET, participants were instructed to continue their normal medications up to, and including, the day of the test. The 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 (HR), 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 s rest. Participants were instructed to continue cycling as the ramp (in watts) increased, until they were unable to continue because of symptom-limited fatigue. After reaching peak exercise tolerance, continued physiological measurements were recorded during the period of recovery from exercise.

The anaerobic threshold 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 (in millilitres per kilogram per minute) was measured at the anaerobic threshold and at peak exertion. The $\dot{V}_E/\dot{V}_{CO_2}$ was measured at the anaerobic threshold and presented as a ratio. Resting HR was defined as the HR measured before each test after 30 s in the sitting position. Peak HR, which reflects sympathetic activation, was defined as maximal HR achieved during exercise. Heart rate recovery, a measure of parasympathetic activity, was calculated as the difference between peak HR and HR 1 min after the end of peak exercise, thus representing the change in HR during the 1 min after exercise (in beats per minute). Peak oxygen pulse (in millilitres per beat), a surrogate marker for cardiac stroke volume,[20] was calculated as peak oxygen consumption (in millilitres per minute) divided by peak HR (in beats per minute).

Statistical analysis

We used STATA version 14 (StataCorp LP, College Station, TX, USA) to analyse the data. Categorical data were summarized as number (%). Continuous data with a normal distribution were summarized as the mean (SD); continuous data that did not follow a normal distribution were summarized as the median (interquartile range).

We dichotomized the sample according to HR >87 beats min^{-1} and summarized descriptive physiological variables for each group.[5] We used Student's unpaired t-test to identify differences in continuous data between groups and the χ^2 test to identify differences in categorical data between groups. We used logistic regression analysis to test for association between elevated preoperative HR >87 beats min^{-1} and each outcome measure, first using univariable analysis. In addition, we tested whether pre-existing cardiovascular medication (β-blockers, calcium channel antagonists, diuretics, nitrates, anti-platelet agents, statins, or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) were associated with HR >87 beats min^{-1}. We subsequently used multivariable analysis to correct for potential confounding by age (>75 yr), gender, and cardiovascular co-morbidity as determined by Revised Cardiac Risk Index (>2.[3] [21] We chose to include Revised Cardiac Risk Index because this is routinely used as a risk score to predict myocardial injury after non-cardiac surgery (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 (CIs). A value of $P \leq 0.05$ 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 principal findings and methods of which have been published elsewhere.[18] [22] We tested the hypothesis that preoperative resting HR >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 HR, cardiac output, and stroke volume. We dichotomized the cohort according to a mean preoperative HR threshold of >87 beats min^{-1} and compared mean beat-by-beat preoperative left ventricular stroke volume between groups using Student's unpaired 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 <57 ml, defined according to previous research in patients with heart failure, corrected for age >75 yr, gender, and history of ischaemic heart disease.[23]

We also assessed the relative contributions of sympathetic/ parasympathetic modulation of preoperative HR >87 beats min^{-1} 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 >50 ms. In addition, the high-frequency component of HR power spectral analysis was quantified. The low-frequency/high-frequency ratio was calculated to assess sympathetic–parasympathetic balance, for which a relative higher value indicates dominant sympathetic modulation of heart rate.

Results

One thousand five hundred and seventy-two surgical patients underwent CPET at one of five participating UK hospitals. We excluded patients who were missing complete CPET data or predefined covariates, leaving 1250 patients for the final analysis (Supplementary Fig. S1). Patient characteristics are presented in Table 1. Resting preoperative HR >87 beats min^{-1} was recorded in 399/1250 (31.9%) patients. Age, BMI, cardiovascular risk factors (as defined by Revised Cardiac Risk Index), and resting systolic blood pressure were similar for patients with HR >87 beats min^{-1} compared with those with HR $\leq$ 87 beats min^{-1} (Table 1). Fifty-two of 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]

Table 1 Baseline patient characteristics. Descriptive data stratified by resting heart rate (HR) >87 beats min^{-1}, presented as the frequency (%) or mean (SD). Heart rate data in beats min^{-1}; blood pressure data in millimetres of mercury. Other units are as indicated. Hypothesis testing was done using Student's unpaired t-test for continuous data and the χ^2 test for categorical data. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Characteristic	HR > 87	HR $\leq$ 87	P-value
Number of patients	399	851	–
Age [yr; mean (SD)]	66.8 (10.0)	68.5 (9.6)	<0.01
Female gender [n (%)]	139 (34.8)	231 (27.1)	<0.01
BMI [kg m^{-2}; mean (SD)]	27.7 (5.6)	27.4 (4.9)	0.33
Diabetes mellitus [n (%)]	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 [n (%)]			<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)	–
Hepatobiliary	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 [n (%)]			
β-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
ACE-I or ARB	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 yr, male gender, and Revised Cardiac Risk Index >2. The dependent variable was heart rate >87 beats min^{-1}. Results are presented as odds ratios (95% confidence intervals), with P-value. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; $\dot{V}_E/\dot{V}co_2$, ventilatory equivalent for carbon dioxide

Characteristic	Univariable analysis		Multivariable analysis	
	Odds ratio	P-value	Odds ratio	P-value
Age >75 yr	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^{-1} min^{-1}	1.39 (1.08–1.78)	0.01	1.69 (1.12–3.55)	0.01
$\dot{V}_E/\dot{V}CO_2$ at anaerobic threshold ≥34	1.59 (1.24–2.03)	<0.01	1.31 (0.92–1.87)	0.14
Heart rate recovery ≤6 beats min^{-1}	1.96 (1.44–2.67)	<0.01	2.02 (1.30–3.14)	<0.01
Preoperative medications				
β-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 are stratified by resting heart rate >87 beats min^{-1}, presented as the frequency (%) or mean (SD). Hypothesis testing was with Student's unpaired *t*-test for continuous data and the χ^2 test for categorical data. Heart rate data in beats min^{-1}; blood pressure data in millimetres of mercury, rounded to the nearest whole number. Other units are shown. CPET, cardiopulmonary exercise test; HR, heart rate; $\dot{V}_E/\dot{V}co_2$, ventilatory equivalent for carbon dioxide

Characteristic	HR > 87 bpm	HR ≤ 87 bpm	P-value
Preoperative haemodynamic variables			
Resting heart rate (beats min^{-1})	99 (10)	73 (10)	<0.01
Systolic blood pressure (mm Hg)	147 (23)	145 (23)	0.23
Diastolic blood pressure (mm Hg)	84 (12)	81 (13)	<0.01
Pulse pressure (mm Hg)	62 (20)	65 (19)	0.09
Mean arterial pressure (mm Hg)	104 (14)	101 (15)	<0.01
Preoperative CPET variables			
Oxygen consumption at anaerobic threshold (ml kg^{-1} min^{-1})	11.2 (2.7)	11.4 (3.1)	0.21
Peak oxygen consumption (ml kg^{-1} min^{-1})	16.8 (4.8)	17.6 (5.1)	<0.01
$\dot{V}_E/\dot{V}CO_2$ at anaerobic threshold	32.7 (5.7)	31.1 (5.9)	<0.01
Peak oxygen pulse (ml beat^{-1})	11.6 (2.9)	13.8 (3.5)	<0.01
Peak HR (beats min^{-1})	145 (19)	128 (23)	<0.01
HR increase (beats min^{-1})	46.1 (20.3)	55.8 (21.1)	<0.01
HR recovery (beats min^{-1})	13 (15)	18 (13)	<0.01

Primary analysis

Of 1250 patients, 438 (35%) had $\dot{V}_E/\dot{V}co_2$ ratio ≥34, 200 (16%) had HR 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 HR >87 beats min^{-1} against the primary outcome measures are shown in Table 2. After correcting for potential confounding factors, HR >87 beats min^{-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 HR recovery ≤6 (OR 2.02 [1.30–3.14]; P<0.01). However, HR >87 beats min^{-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 HR >87 beats min^{-1} had lower peak $\dot{V}o_2$, 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 HR >87 beats min^{-1}.[20] Resting HR >87 beats min^{-1} was not associated with $\dot{V}o_2$ at the anaerobic threshold <11.1 ml kg^{-1} min^{-1} (OR 1.24 [0.98–1.59]; P=0.08) using univariable logistic regression analysis. However, resting HR >87 beats min^{-1} was associated with peak oxygen pulse <12 ml beat^{-1} (OR 2.80 [2.19–3.58]; P<0.01) using univariable logistic regression analysis. Patients
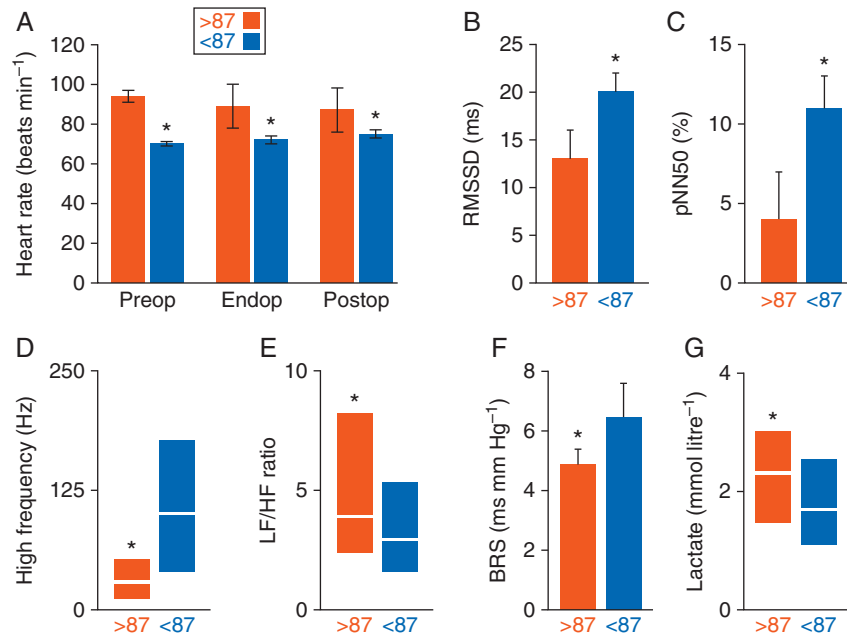
Fig 1 Elevated heart rate and autonomic measures from *post hoc* analysis of the POM-O cohort. The analysis included data from 187 patients recruited from the POM-O trial. (A) Resting mean [95% confidence interval (CI)] heart rate (HR) before surgery, stratified by HR > 87 beats min^{-1}. (B) Mean (95% CI) root mean square of the successive differences (RMSSD), a time-domain measure of parasympathetic modulation of HR. (C) Mean (95% CI) pNN50, an additional time-domain measure of parasympathetic modulation of HR that reports the fraction of consecutive NN intervals that differ by > 50 ms. (D) Median (interquartile range) preoperative values for high-frequency (parasympathetic) component of HR power spectral analysis. (E) Median (interquartile range) preoperative values for low-frequency/high-frequency (LF/HF) ratio, for which a higher value indicates dominant sympathetic modulation of HR. (F) Spontaneous baroreflex sensitivity [mean (95% CI)]. (G) Venous lactate measurements [mean (95% CI)] at the end of the intraoperative period. *P<0.01.

with HR ≤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)]. In contrast, percentage predicted peak oxygen pulse was 15.2% (95% CI: 12.3–18.1) lower in patients with resting HR >87 beats min^{-1} (P<0.01). Patients with resting HR >87 beats min^{-1} exhibited higher peak heart rates during CPET. Heart rate recovery, the longer duration of which reflects impaired parasympathetic reactivation after cessation of peak exercise, was prolonged in patients with resting HR >87 beats min^{-1}.

Sensitivity analysis

In patients with heart failure, the prognostic threshold for peak $\dot{V}o_2$ is lower (≤12 ml kg^{-1} min^{-1}) in patients receiving β-blockers. We performed a sensitivity analysis by repeating the primary univariable logistic regression using the lower threshold in patients taking β-blockers (247/1250). However, we did not identify association between impaired $\dot{V}o_2$ and HR >87 beats min^{-1} (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. One hundred and eighty-one patients with mean age 68 (sd 9) yr who underwent major

surgery in the OPTIMISE and POM-O trials had complete beat-by-beat cardiac output monitor data available for analysis (Supplementary Fig. S2). From both trials, patients with pre-operative HR >87 beats min^{-1} had lower mean preoperative stroke volume (mean difference 23.5 [8.0–38.9] ml; P=0.03). Preoperative HR >87 beats min^{-1} was associated with impaired preoperative stroke volume <59 ml (OR 3.21 [1.26–8.20]; P=0.01), taking into account patients with an established preoperative diagnosis of heart failure (Supplementary Table S2). 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 HR >87 beats min^{-1} (Fig. 1). Preoperative HR >87 beats min^{-1} was chiefly associated with measures indicative of lower parasympathetic activity (Fig. 1b–d). This was accompanied by similar sympathetic activity (low frequency) between groups (not shown), but higher low-frequency/high-frequency ratio (Fig. 1e), reflecting dominant sympathetic autonomic modulation of HR in patients with HR >87 beats min^{-1} attributable to loss of cardiac vagal tone. Spontaneous baroreflex sensitivity (Fig. 1f) was also lower in patients with preoperative HR >87 beats min^{-1}. Higher lactate was observed at the end of surgery in patients with preoperative HR >87 beats min^{-1} (OR of lactate >2 mmol litre^{-1}: 3.05 [1.21–7.65]; Fig. 1g).

Discussion

The principal finding of this generalizable, multicentre cohort study is that resting preoperative HR >87 beats min^{-1} is associated with marked cardiorespiratory and autonomic impairment, compatible with the pathophysiological hallmarks of significant, yet subclinical, cardiac failure. These findings are reinforced by interrogation of perioperative haemodynamic data from the OPTIMISE and POM-O trials. In this cohort, elevated preoperative HR >87 beats min^{-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 HR is independently associated with perioperative myocardial injury and excess mortality.[3] Our results show that elevated resting HR is associated with several features of impaired cardiorespiratory and autonomic function indicative of subclinical cardiac failure. This is consistent with previous reports confirming that patients with an established diagnosis of cardiac failure before surgery have substantially higher morbidity and mortality after non-cardiac surgery.[10]

Resting HR 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 HR induces cardiac failure in the absence of structural or atherosclerotic heart disease.[26] However, elevated HR 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 min^{-1} increase in resting HR was independently associated with an 11% increase in risk of developing cardiac failure.[15] The 15 yr 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 were associated with the development heart failure within 6 months of study enrolment.[16] Thus, elevated resting HR 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 HR and development of heart failure was not influenced by the method of measurement of HR, as we also found in our study, where HR was similar before CPET and immediately before surgery.[16]

Several mechanisms may mechanistically link resting HR, incident heart failure, and perioperative myocardial injury. A causal link between elevated HR, 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 or 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 min^{-1} were similar to those of patients with mild-to-moderate heart failure.[22] This is compatible with the hypothesis that HR 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 HR and reduced $\dot{V}o_2$, 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 after non-cardiac surgery. Sympathetic and parasympathetic components may independently contribute to MINS. Reduction in HR after peak exercise (HR recovery) is attributable 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 HR, are more likely to receive sympatholytic medication. In the context of our findings, the use of clonidine, β-blocker, or both in these patients may precipitate hypotension given that higher HR is associated with impaired stroke volume or cardiac contractility.

Strengths of this study include the observation that resting HR 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 that 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 HR 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 β-blockers, which are known to affect HR. Heart rate is mathematically coupled with some CPET variables; in particular, oxygen pulse at peak is derived by dividing peak $\dot{V}o_2$ 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 between raised HR before CPET decreased oxygen pulse at peak. Moreover, an association between pre-CPET HR >87 beats min^{-1} and unfavourable CPET measures was also apparent for $\dot{V}o_2$ and $\dot{V}E/\dot{V}o_2$ at the anaerobic threshold, variables that are not mathematically coupled to HR. A lack of data on intraoperative vasopressor use, other than norepinephrine, is likely to underestimate the extent, effect, or both 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 HR is associated with cardiopulmonary and autonomic impairment indicative of subclinical heart failure. Perioperative myocardial injury might be, at least in part, explained by subclinical cardiac failure. Further research targeting abnormal cardiovascular and autonomic phenotypes may improve clinical outcomes, including development of individualized approaches to care of high-risk surgical patients.

Authors' contributions

Conceived and designed the study: G.L.A.
Performed the experiments: POM-HR investigators

Designed the analysis, analysed the data, and wrote the first draft of the manuscript: T.E.F.A., GLA.

Contributed to the writing of the manuscript: T.E.F.A., R.M.P., G.M., A.L., G.L.A.

ATICMJE criteria for authorship read and met: T.E.F.A., R.M.P., G.M., A.L., G.L.A., POM-HR investigators

Agree with manuscript results and conclusions: T.E.F.A., R.M.P., G.L.A., POM-HR investigators

Supplementary material

Declaration of interest

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