Chronotropic incompetence and myocardial injury after non-cardiac surgery: planned secondary analysis of a prospective observational international cohort study

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Summary

Background

Physiological measures of heart failure (HF) are common in surgical patients, despite the absence of a formal diagnosis. Heart rate increases during exercise are frequently blunted in HF (termed chronotropic incompetence (CI)), which primarily reflects beta-adrenoreceptor dysfunction. We examined whether CI was associated with myocardial injury after non-cardiac surgery.

Methods

Pre-defined analysis of an international cohort study where participants aged ≥40 years underwent symptom-limited cardiopulmonary exercise testing before non-cardiac surgery. CI was defined as the ratio of increase in heart rate during exercise to age-predicted maximal increase in heart rate <0.6 (with/without rate-limiting medication). The primary outcome was myocardial injury within 3 days after surgery, defined by high-sensitivity troponin assays (I/T) >99th centile. Explanatory variables were biomarkers for HF ($VE/VCO_2 \geq 34$; $VO_2peak \leq 14ml\ kg\ min^{-1}$; heart rate recovery (HRR) ≤6 beats minute^{-1} one minute post-exercise; preoperative NTpro-BNP >300pg mL^{-1}). Myocardial injury was compared in presence/absence of sympathetic (CI)/parasympathetic (HRR) thresholds indicative of dysfunction. Data are presented as odds ratios [OR] (95% confidence intervals).

Results

CI occurred in 396/1325 (29.9%) participants; 16/1325 (1.2%) had a formal HF diagnosis. 162/1325 (12.2%) patients sustained myocardial injury. Raised NTpro-BNP (indicative of HF) was more common when CI<0.6 (OR 1.57 [1.11-2.23];p<0.01). CI was not associated with myocardial injury (OR: 1.05 [0.74-1.50]; p=0.78), independent of rate-limiting therapy. HRR<12 beats minute^{-1} was associated with myocardial injury in the presence (OR:1.62 [1.05-2.51];p=0.03) or absence (OR:1.60 [1.06-2.39];p=0.02) of CI.

Conclusions

Chronotropic incompetence is common in surgical patients. In contrast to parasympathetic dysfunction, CI is not associated with myocardial injury.

Introduction

Around 30% of patients undergoing non-cardiac surgery sustain clinically asymptomatic myocardial injury, which is strongly associated with mortality during hospital admission.[1-3] Myocardial injury is more likely to occur in patients with preoperative cardiac vagal (parasympathetic) dysfunction, identified by impaired heart rate recovery after exercise.[4] Cardiac vagal autonomic impairment is a common feature in deconditioned surgical patients,[5-7] in whom preoperative cardiopulmonary exercise testing also reveal physiological features of cardiac failure including lower peak oxygen consumption and higher resting heart rate.[8]

While cardiac vagal activity reduces heart rate after exercise, maximal aerobic exercise is facilitated by increases in heart rate principally driven by the sympathetic nervous system.[9-14] The impaired ability to increase heart rate,[4] which is required for increased activity or demand, is broadly defined as chronotropic incompetence (CI).[12] In cardiac failure, high circulating levels of catecholamines result in decreased β-adrenoceptor density and desensitization, which limit β-agonist mediated contractility.[15] Consequently, CI is a robust predictor of mortality in patients with overt, clinically diagnosed cardiac failure.[12]

Here, we hypothesised that chronotropic incompetence identified during preoperative cardiopulmonary exercise testing was associated with myocardial injury within three days after non-cardiac surgery. To identify the relative contributions of sympathetic versus parasympathetic activity associated with myocardial injury, we also compared the relationship between heart rate increase to, and recovery from, exercise and myocardial injury.

Methods

Study design and setting

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-five hospitals in the United Kingdom, Canada, New Zealand and Australia. The study protocol and the main study results were published previously.[2, 16] Research ethics committees reviewed the study and it was conducted in accordance with the principles of the Declaration of Helsinki and the Research Governance Framework.

Participants

Participants were aged 40 years or older, undergoing elective non-cardiac surgery under general anaesthesia and/or regional anaesthesia with a planned overnight stay in hospital, and with at least one of the following perioperative risk factors: intermediate or high-risk surgery, coronary artery disease, heart failure, cerebrovascular disease, diabetes mellitus, preoperative renal insufficiency, peripheral arterial disease, hypertension, a history of tobacco smoking within the previous year or be aged 70 years or more. The exclusion criteria were: planned procedure using only endovascular technique, use of cardiopulmonary exercise testing for risk stratification as part of routine care, insufficient time for cardiopulmonary exercise testing before surgery, presence of an implantable cardioverter-defibrillator, known or suspected pregnancy, previous enrolment in the study, severe hypertension (>180/100 mmHg), active cardiac conditions or other contraindications precluding cardiopulmonary exercise testing.[16, 17] Participants gave written informed consent to take part before surgery.

Study conduct and data collection

Researchers collected data directly from participants and their medical record. A detailed and standardised dataset was collected before surgery, during the hospital stay, and after surgery. One year after surgery, participants were contacted by telephone and underwent a short interview. Each participant underwent cardiopulmonary exercise testing and had blood sampled for NT pro-BNP before surgery, and routine blood sampling for cardiac troponin on the first, second and third day after surgery.

Cardiopulmonary exercise testing (CPET)

Participants underwent preoperative symptom-limited cardiopulmonary exercise testing (CPET) using a standardised incremental ramp protocol using electromagnetically-braked cycle ergometers.[18] The test protocol consisted of spirometry in the seated position, followed by three minutes of rest sitting on the ergometer, followed by three minutes of unloaded pedalling, followed by pedalling with progressively increasing workload. Once the participant reached their peak performance, the exercise test was stopped, the workload reduced to 20W and the participant continued to pedal for five minutes in order to warm-down. Participants were encouraged to pedal at a steady rate of 60 revolutions per minute. Work rates increased by 10W per minute in untrained participants, and by 20-30W per minute in trained participants or those undertaking regular physical activity according to a specific algorithm. Cardiopulmonary function was monitored continuously via electrocardiogram, pulse-oximetry and breath-by-breath measurement of minute ventilation, carbon dioxide production and oxygen consumption. Non-invasive blood pressure was monitored every three minutes. Investigators at each site interpreted each CPET and collected a standardised data set. Peak oxygen consumption was calculated as the mean oxygen consumption during the final twenty seconds of incremental exercise.[19] The anaerobic threshold was identified using the modified V-Slope method, followed by

the ventilatory equivalent and excess carbon dioxide methods.[20] Clinicians at each site were blinded to the results of cardiopulmonary exercise testing, except where there was a safety concern according to pre-defined criteria.[16]

Exposures

The exposure of interest was chronotropic incompetence, defined as chronotropic index <0.6 (CI<0.6) using the method described by Dobre et al.[21] This threshold is prognostically associated with mortality in patients with severe heart failure.[21] Chronotropic index is the ratio of measured increase in heart rate during exercise to the age-predicted maximal increase in heart rate.[12] Heart rate was measured at rest and at peak oxygen consumption during CPET to give the measured increase in heart rate. The most widely accepted method for calculating age-predicted maximal heart rate is 220-age, as described by Astrand.[12, 22] Chronotropic index for the main analysis was calculated using the formula:

Chronotropic index = [peak heart rate – resting heart rate] / [age predicted maximal heart rate – resting heart rate]

However, since various population-dependent thresholds have been derived,[23] it has been suggested to use a CI equation generated in a population most closely matching the population of interest. The equation suggested by Tanaka is recommended for apparently healthy persons, while other equations are recommended for those with known or suspected cardiovascular disease. In this study, we primarily used the Astrand method, and supplemented this with two post-hoc sensitivity analyses. Firstly, calculated CI using the Tanaka method and second using CI (Astrand) as a continuous variable.[24]

Primary outcome

The primary outcome measure was myocardial injury, defined as blood troponin T or I

concentration greater than the limit of the reference range (99th centile) for each assay, within 72 hours after surgery. Troponin assays differed between participating hospitals and are listed in supplementary table 1. The secondary outcome was all-cause mortality at one-year after surgery. Additional pre-defined explanatory outcomes were: preoperative NT pro-BNP >300pmol/L, a threshold used to predict postoperative cardiovascular events in surgical patients[25] and heart failure in community cohorts,[26] and preoperative CPET-derived markers of sub-clinical heart failure (VE/VCO2 ≥34, VO2peak ≤14ml.kg.min^{-1}, and heart rate recovery ≤ 6 beats per minute at one minute after the end of exercise).[27]

Statistical analysis

We used STATA version 14 (STATACorp LP, Texas, USA) to analyse the data. We excluded the small number of participants without a record of the exposure or outcome. We ranked the sample by chronotropic index and dichotomised it according to a threshold of <0.6 (CI<0.6), to define groups with and without chronotropic incompetence. We presented baseline characteristics for the whole cohort and stratified by chronotropic incompetence. Firstly, we used univariable logistic regression analysis to test for association between chronotropic incompetence and myocardial injury. Second, we constructed multivariable logistic regression models, adjusted for covariates that are known to be associated with perioperative myocardial injury and routinely used for preoperative risk assessment: age >70 years, male gender, preoperative renal insufficiency, peripheral vascular disease, existing diagnosis of heart failure, coronary artery disease, hypertension, diabetes mellitus, obstructive lung disease, cerebrovascular disease, high-risk surgery and pre-existing atrial fibrillation.[28-33] We used backwards stepwise selection to identify variables for inclusion in the final model, with a type one error threshold of <0.1. Missing data were handled by list-wise deletion. The results of

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. The threshold for statistical significance was $p \leq 0.05$.

Secondary analyses

We repeated the primary analysis using mortality within one year after surgery, a binary categorical variable, as the outcome measure. We previously described a relationship between preoperative resting heart rate and sub-clinical heart failure.[27] To explore whether chronotropic incompetence is associated with a phenotype of heart failure in this cohort, we repeated the primary analysis using the following outcome measures, which are biomarkers known to be predictive of poor clinical outcome in overt heart failure: NT pro-BNP >300pmol/L, VO_2 peak ≤14 ml/kg/min, VE/VCO_2 at the anaerobic threshold ≥34 and heart rate recovery ≤ 6 beats per minute.[27]

We have previously demonstrated that parasympathetic autonomic dysfunction is associated with myocardial injury.[BJA in press] In order to draw direct comparisons between sympathetic and parasympathetic dysfunction, we examined the prevalence of physiological markers of impaired sympathetic and parasympathetic function using chronotropic incompetence and heart rate recovery respectively. We used a widely accepted definition of parasympathetic dysfunction, heart rate recovery < 12 (HRR<12) beats per minute during the first minute after the end of exercise.[9]

Sensitivity analyses

Resting heart rate and the heart rate response to exercise can be influenced by

medications such as beta-blockers and rate-limiting calcium channel antagonists, which may influence the results of our analysis. We handled this in three ways. First, we repeated the primary analysis including beta-blockers and diltiazem/verapamil as covariates in the multivariable model. Second, we repeated the primary analysis excluding patients receiving beta-blocker and diltiazem/verapamil. Third, we examined whether the use of beta-blockade/calcium channel blocker altered participants' ability to exceed a RER>1.05, since RER<1.05 indicates submaximal effort, or that the test was terminated prematurely.[12]

Our main analysis used the Astrand method. We also performed a post-hoc sensitivity analysis, which repeated the primary analysis using age-predicted maximal heart rate calculated by the Tanaka method, since we suspect that a significant proportion of surgical patients have subclinical cardiac failure.[27] We primarily defined chronotropic incompetence as chronotropic index <0.6, as described in studies of patients with heart failure. However, studies in other populations have defined chronotropic incompetence as chronotropic index <0.8.[34] Therefore we repeated the primary analysis using CI<0.8 as the exposure, as well as examining CI as a continuous variable.

Sample size estimation

As a planned secondary analysis of a prospectively collected data, the sample size was determined based on the comparisons being made in the principal analysis which has been published previously.[35] We estimated that CI may be present in up to ~30% participants. Overall, 12.6% of participants in METS sustained perioperative myocardial injury. If participants with CI had a higher incidence of ~16%, at least 1305 particpants' data would be required to detect a clinically significant difference (α=0.05; 1-β=80%).

Results

1741 patients were recruited into the METS study between 1st March 2013 and 25th March 2016. After predefined exclusions of patients, we analysed data obtained from 1325 participants (Figure 1). CI<0.6 was present in 396/1325 (29.9%) study participants, of whom 816/1325 (61.7%) were male (Table 1).

Markers of severe cardiac failure

CI<0.6 was associated with elevated preoperative NT pro-BNP >300pg.mL^{-1} (OR 1.57 [1.11-2.23]; p<0.01), adjusted for potentially confounding factors. CI<0.6 was also associated with three independent measures of moderate-severe heart failure (table 3). CI<0.6 was more commonly found in patients with VE/VCO_2 ≥34 (OR 1.40 [1.09-1.81]; p<0.01), VO_2 peak ≤ 14 (OR 7.57 [5.50-10.43]; p<0.01) and heart rate recovery ≤6 beats per minute during the first minute after the end of exercise (OR 2.63 [1.97-3.52]; p<0.01).

Primary clinical outcome: myocardial injury

162/1325 (12.2%) patients sustained myocardial injury within three days after surgery, which occurred in 50/396 (12.6%) patients with CI <0.6 and 112/928 (12.1%) patients with CI≥0.6. There was no difference in the odds of myocardial injury amongst patients with CI<0.6 compared to those with CI>0.6 (unadjusted OR: 1.05 [0.74-1.50]; p=0.78). In the multivariable analysis, CI<0.6 was not associated with myocardial injury (p>0.60).

Secondary outcome: sympathetic versus parasympathetic measures and myocardial injury

We examined the prevalence of physiological markers of impaired sympathetic and parasympathetic function using chronotropic incompetence and heart rate recovery

respectively. We found that 169 (12.8%) had low CI alone, 294 (22.2%) had HRR<12 alone, and 227 (17.2%) had both HRR<12 and CI<0.6. When we repeated the primary analysis using HRR<12 and CI<0.6 as the exposures, we found that only HRR<12 was associated with myocardial injury (sup. table 1).

Secondary outcome: postoperative mortality

33/1325 (2.5%) patients died within 1 year of surgery. On univariable analysis, postoperative mortality was more frequent amongst patients with CI<0.6 (16/396 [4.0%]) compared to patients without CI<0.6 (17/928 [1.8%]; unadjusted odds ratio [OR] 2.26 [1.13-4.51]; p=0.02. However, on multivariable analysis, CI<0.6 and mortality were not associated (OR 1.98 [0.97-4.02]; p=0.06; table 2 and figure 2).

Sensitivity analyses

When we repeated the primary and secondary analysis including preoperative use of beta-blockers, diltiazem or verapamil as covariates, the results were very similar (sup. table 2). Similar proportions of patients receiving these drugs achieved RER >1.05. When we repeated the primary analysis excluding patients receiving beta-blockers, diltiazem or verapamil CI<0.6 was not associated with myocardial injury (OR 7.20 [0.60 – 87.02]; p=0.12) in univariable analysis. The multivariable model did not converge due to collinearity between variables. We could not complete regression analysis for mortality because an insufficient number of patients died. When we repeated the primary analysis using age-predicted maximum heart rate calculated using the method described by Tanaka et al, CI<0.6 was not associated with myocardial injury (OR 1.10 [0.78-1.53]; p=0.59) or mortality (OR 1.50 [0.75-2.99]; p=0.25) on univariable analysis. In multivariable analysis, CI<0.6 was removed from the stepwise models at the p>0.56 level for both outcomes. When we repeated the analysis using CI<0.8 as the exposure, CI<0.8

was not associated with myocardial injury (OR 0.87 [0.62-1.21]; p=0.41) or mortality (OR 1.15 [0.56-2.36]; p=0.70) on univariable analysis. In multivariable analysis, CI<0.8 was removed from the stepwise model at the p>0.19 level (myocardial injury) and the p>0.97 level (mortality). When we repeated the analysis using CI as a continuous variable, CI was not associated with myocardial injury (OR 1.20 (0.68-2.09); p 0.53) or mortality (OR 0.78 (0.38-1.62); p0.51).

Discussion

The principal finding of this analysis was that preoperative chronotropic incompetence – an impaired ability to increase heart rate in response to exercise - was not associated with myocardial injury within three days after surgery. By comparing sympathetic versus parasympathetic activity during exercise, heart rate recovery, rather than increase, was associated with myocardial injury. We also confirmed the deconditioned phenotype of subclinical cardiac failure in preoperative patients, since chronotropic incompetence was associated with elevated preoperative NT pro-BNP, a preoperative risk factor for postoperative cardiovascular morbidity and a biomarker for heart failure in the general population. Moreover, a strong association between chronotropic incompetence and CPET-derived markers for heart failure.[27, 36] These data confirm our previous findings in a large prospective cohort that almost one third of patients undergoing non-cardiac surgery exhibit a clinical phenotype of sub-clinical cardiac failure that is frequently accompanied by significant autonomic impairment.[27, 32]

We defined chronotropic incompetence using an established threshold of chronotropic index, which is prognostically associated with increased mortality in longitudinal cohorts of patients with heart failure.[21] Our results do not support a link between beta-adrenoceptor dysfunction, as identified using chronotropic incompetence, and myocardial injury. The inability to increase heart rate in patients with CI suggests that a direct link between heart rate-demand mismatch is unlikely to underpin myocardial injury. However, it is plausible that CI could promote myocardial injury through indirect links. The failure to increase cardiac output under certain perioperative circumstances, which requires heart rate elevation, may promote hypotensive episodes linked to myocardial injury as indicated by the POISE trial of metoprolol.[37] Similarly, failure to meet metabolic demands during surgery may drive organ injury, which in turn could increases the risk of myocardial injury. The precise mechanism leading to a decrease in

β_1-adrenergic receptor expression and desensitisation in cardiac failure is unclear, but may involve oxidative stress[38] driven by chronic systemic inflammation.[39] Our finding that chronotropic incompetence is associated with reduced survival after non-cardiac surgery is consistent with similar observations in patients with heart failure,[12, 21, 22, 40-42] supporting the hypothesis that there is a cohort of surgical patients with severe, yet sub-clinical, heart failure.[27]

A notable strength of our study is that the results have high external validity due to the prospective, international, multi-centre nature of the study cohort, which makes our findings readily generalisable to the majority of intermediate and high-risk surgical patients. The primary outcome, myocardial injury, is an objective, biomarker defined endpoint and not subject to observer bias. Clinicians at each participating hospital were blinded to the results of the preoperative cardiopulmonary exercise tests. Therefore, measurement of chronotropic incompetence did not influence perioperative care.

Our analysis also has several limitations. Due to the observational study design, we are unable to draw conclusions regarding potential causal association between chronotropic incompetence and either myocardial injury or mortality. As with any observational study, it is possible that our results may be influenced by unmeasured confounding. The primary outcome was myocardial injury and the sample size for the study, which was based on cardiovascular outcomes, was appropriate for this outcome. However, the study was not powered to detect differences in mortality and therefore we advise that inferences regarding mortality should be with caution.

It is possible that our results could have been influenced by the definition of chronotropic incompetence. We defined this as chronotropic index <0.6, which is a poor prognostic indicator in patients with heart failure.[27] However, some studies in other populations have used a different threshold of CI<0.8.[34] When we repeated the analysis using CI<0.8, the results were very similar. Chronotropic index was calculated as the

proportion of age-predicted maximum heart rate reached during preoperative exercise. As with any pragmatic study of exercise, there is an underlying assumption that the heart rate recorded at peak exertion is an accurate measure of maximal heart rate. Due to the clinical nature of the study, we were unable to confirm this with repeated measurements, so there is a possibility that some measurements of maximum heart rate might not represent true maximal values. However, more than 80% of the cohort achieved an end-exercise respiratory exchange ratio of >1.05, which is generally accepted to represent peak effort.[12]

There are several methods for calculating age-predicted maximum heart rate, which could potentially influence the results. We chose the method described by Astrand, which is the most widely accepted, as the primary method.[24] However, we recalculated age-predicted maximum heart rate using the Tanaka method and the results were very similar.[23] When we repeated the analysis using chronotropic index as a continuous variable, we did not identify a relationship with myocardial injury. However, this method assumes a linear relationship between chronotropic index and the risk myocardial injury, which may not be true.

Resting heart rate or change in heart rate may be influenced by rate-limiting medications. However, when we repeated the analysis after removing the 224 patients receiving beta-blocker or rate-limiting calcium channel antagonists, our results were similar. We also repeated multivariable analysis including treatment with beta-blockers or rate-limiting calcium channel anatagonists as separate terms in the model and our results were very similar. Cardiopulmonary exercise tests were conducted and interpreted by investigators at 24 participating hospitals, so there is potential for observer bias and/or measurement error between centres. However, this was mitigated through the prospective use of a standardised cardiopulmonary exercise test protocol and case report form.[16] It is possible that a potential relationship between chronotropic incompetence and myocardial

injury may have been confounded by intraoperative hypotension. However, when we repeated the primary analysis adding intraoperative vasopressor use (a surrogate marker of hypotension) as a covariate, the results were unchanged.

Conclusion

Chronotropic incompetence was associated with both impaired cardiopulmonary/autonomic function and elevated NT pro-BNP (indicating sub-clinical heart failure). However, in contrast to parasympathetic measures, CI was not linked to myocardial injury. These data suggest that a mechanistic role for sympathetic dysregulation in myocardial injury is unlikely, and adds further support to the hypothesis that cardiac vagal dysfunction is the predominant autonomic influence in determining myocardial injury and perioperative outcome.[5, 27, 32, 33, 43, 44]

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Authors' contributors

TEFA and GLA conceived the hypothesis. TEFA, RP, BHC, DW and GLA designed the analysis plan. TEFA performed the data analysis with input from GLA. The manuscript was drafted by TEFA and GLA with input from RP, and revised following critical review by all authors.

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Table 1. Baseline patient characteristics.

Descriptive data stratified by preoperative chronotropic incompetence (defined as chronotropic index [CI] <0.6). 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	CI<0.6	CI≥0.6
Number of cases (n)	1324	396	928
Mean age (SD)	64.2 (10.4)	64.8 (10.5)	64.0 (10.3)
Age ≥70 years (%)	447 (33.8)	149 (37.6)	298 (32.1)
Male sex (%)	817 (61.7)	236 (59.6)	581 (62.6)
Comorbid disorder (%)			
Atrial fibrillation	50 (3.8)	23 (5.8)	27 (2.9)
Diabetes mellitus	243 (18.4)	90 (22.7)	153 (16.5)
Hypertension	725 (54.8)	238 (60.1)	487 (52.5)
Diagnosis of congestive cardiac failure	16 (1.2)	10 (2.5)	6 (0.7)
Coronary artery disease	153 (11.6)	72 (18.2)	81 (8.7)
Peripheral vascular disease	39 (3.0)	18 (4.6)	21 (2.3)
Previous stroke or transient ischaemic attack	52 (3.9)	25 (6.3)	27 (2.9)
Chronic obstructive pulmonary disease (COPD)	163 (12.3)	74 (18.7)	89 (9.6)
Preoperative eGFR <60ml/min/1.73m2	108 (8.2)	45 (11.4)	63 (6.8)
Surgical procedure type(%)			
Vascular	23 (1.7)	12 (3.0)	11 (1.2)
Intra-peritoneal or retroperitoneal	29 (2.2)	5 (1.3)	24 (2.6)
Urological or gynaecological	437 (33.0)	131 (33.1)	306 (33.0)
Intra-thoracic	306 (23.3)	107 (27.0)	199 (21.4)
Orthopeadic	398 (30.1)	106 (26.8)	292 (31.5)
Head and neck	87 (6.6)	23 (5.8)	64 (6.9)
Other	39 (3.0)	11 (2.8)	28 (3.0)
High-risk surgery (%)	756 (57.1)	221 (55.8)	535 (57.7)
ASA grade (%)			
I	99 (7.5)	24 (6.1)	75 (8.1)
II	772 (58.4)	207 (52.3)	565 (61.0)
III	433 (32.8)	159 (40.2)	274 (29.6)
IV	18 (1.4)	6 (1.5)	12 (1.3)
Preoperative medication (%)			
Beta-blockers	213 (16.1)	137 (34.6)	76 (8.2)
Diltiazem or Verapamil	25 (1.9)	11 (2.8)	14 (1.5)
Haemodynamic variables			
Resting heart rate (beats per minute)	77 (14.3)	75 (15.2)	78 (3.7)
Resting systolic blood pressure (mmHg)	129 (18.1)	127 (9.0)	130 (17.6)
Resting pulse pressure (mmHg)	51 (16.5)	51 (17.9)	52 (15.8)

Table 2. Chronotropic Incompetence and one-year mortality.
The independent variable was chronotropic incompetence (defined as chronotropic index [CI] <0.6). The dependent variable was mortality within the one-year follow-up period. Results of two separate analyses are presented. First, univariable (unadjusted) logistic regression analysis. Second, multivariable logistic regression adjusting for three variables found to be associated with the dependent variable. The following variables were excluded from the final multivariable model: diabetes mellitus, peripheral vascular disease, atrial fibrillation, high-risk surgery, previous stroke or transient ischaemic attack, clinical diagnosis of heart failure, and preoperative renal insufficiency. Results are presented as odds ratios with 95% confidence intervals and associated p-values. Transient Ischaemic Attack (TIA); Chronic Obstructive Pulmonary Disease (COPD).

	Mortality	
Covariates	**odds ratio**	**p-value**
Univariable analysis		
Chronotropic Incompetence	2.26 (1.13-4.51)	0.02
Multivariable analysis		
Male sex	2.22 (0.98-5.03)	0.06
History of stroke or TIA	3.00 (0.99-9.03)	0.05
History of COPD	2.61 (1.17-5.86)	0.02
CI <0.6	1.98 (0.97-4.02)	0.06

Table 3. Chronotropic incompetence and markers of heart failure.
The independent variable was chronotropic incompetence (defined as chronotropic index [CI] <0.6). The dependent variables were NT pro-BNP >300 pg.mL^{-1}, ventilatory equivalent for carbon dioxide (VE/VCO_2) at the anaerobic threshold ≥ 34, peak oxygen consumption (VO_2) ≤ 14ml/kg/minute and heart rate recovery (HRR) ≤6 beats per minute within the first minute after the end of exercise. Results of univariable (unadjusted) and multivariable (adjusted) logistic regression analyses are presented as odds ratios with 95% confidence intervals and associated p-values. Variables were selected for inclusion in the multivariable model using stepwise selection. Chronic Obstructive Pulmonary Disease (COPD); Transient Ischaemic Attack (TIA).

	NT pro-BNP >300 pmol/L		VE/VCO2 ≥ 34		VO2 peak ≤14 ml/kg/min		HRR ≤6bpm	
Covariates	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**	**odds ratio**	**p-value**
Univariable analysis								
CI <0.6	2.11 (1.56-2.86)	<0.01	1.57 (1.23-2.00)	<0.01	6.44 (4.82-8.59)	<0.01	2.81 (2.11-3.74)	<0.01
Multivariable analysis								
Age ≥70 years	2.82 (2.01-3.95)	<0.01	2.58 (2.02-3.29)	<0.01	1.33 (0.95-1.84)	0.09	1.53 (1.13-2.05)	<0.01
Male sex	-	-	0.55 (0.44-0.71)	<0.01	0.17 (0.12-0.23)	<0.01	0.63 (0.47-0.84)	<0.01
History of atrial fibrillation	11.43 (5.71-22.88)	<0.01	-	-	-	-	-	-
History of heart failure	7.42 (2.01-27.40)	<0.01	-	-	-	-	-	-
History of coronary artery disease	2.56 (1.67-3.93)	<0.01	-	-	-	-	-	-
History of peripheral vascular disease	-	-	-	-	2.62 (1.20-5.73)	0.02	-	-
History of hypertension	1.46 (1.02-2.10)	0.04	-	-	-	-	-	-
History of stroke or TIA	-	-	-	-	-	-	-	-

History of COPD	-	-	1.36 (0.96-1.93)	0.08	-	-	-	-
History of diabetes	-	-	1.31 (0.97-1.77)	0.08	-	-	1.46 (1.02-2.07)	0.04
Preoperative eGFR <60ml/min/1.73m2	3.68 (2.29-5.91)	<0.01	1.67 (1.10-2.53)	0.02	1.90 (1.14-3.15)	0.01	1.67 (1.05-2.66)	0.03
High-risk surgery	-	-	-	-	1.44 (1.05-1.98)	0.03	-	-
CI <0.6	1.57 (1.11-2.23)	0.01	1.40 (1.09-1.81)	<0.01	7.57 (5.50-10.43)	<0.01	2.63 (1.97-3.52)	<0.01

Figure legends

Figure 1. Patient flow diagram showing the number of cases included in the analysis.

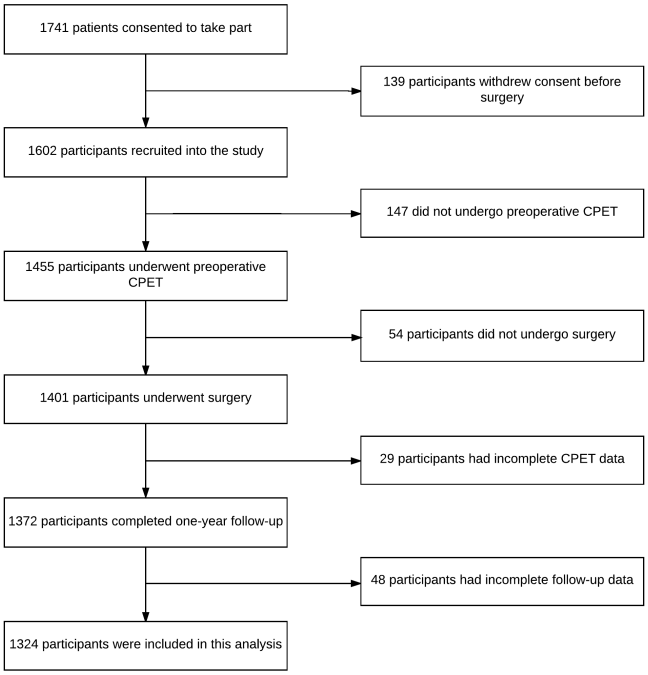

Figure 2. Kaplan-Meier survival plot for chronotropic incompetence (chronotropic index <0.6) versus no chronotropic incompetence (chronotropic index ≥ 0.6).