Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study

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Summary
Background Functional capacity is an important component of risk assessment for major surgery. Doctors’ clinical subjective assessment of patients’ functional capacity has uncertain accuracy. We did a study to compare preoperative subjective assessment with alternative markers of fitness (cardiopulmonary exercise testing [CPET], scores on the Duke Activity Status Index [DASI] questionnaire, and serum N-terminal pro-B-type natriuretic peptide [NT pro-BNP] concentrations) for predicting death or complications after major elective non-cardiac surgery.

Methods We did a multicentre, international, prospective cohort study at 25 hospitals: five in Canada, seven in the UK, ten in Australia, and three in New Zealand. We recruited adults aged at least 40 years who were scheduled for major non-cardiac surgery and deemed to have one or more risk factors for cardiac complications (eg, a history of heart failure, stroke, or diabetes) or coronary artery disease. Functional capacity was subjectively assessed in units of metabolic equivalents of tasks by the responsible anaesthesiologists in the preoperative assessment clinic, graded as poor (<4), moderate (4–10), or good (>10). All participants also completed the DASI questionnaire, underwent CPET to measure peak oxygen consumption, and had blood tests for measurement of NT pro-BNP concentrations. After surgery, patients had daily electrocardiograms and blood tests to measure troponin and creatinine concentrations until the third postoperative day or hospital discharge. The primary outcome was death or myocardial infarction within 30 days after surgery, assessed in all participants who underwent both CPET and surgery. Prognostic accuracy was assessed using logistic regression, receiver-operating-characteristic curves, and net risk reclassification.

Findings Between March 1, 2013, and March 25, 2016, we included 1401 patients in the study. 28 (2%) of 1401 patients died or had a myocardial infarction within 30 days of surgery. Subjective assessment had 19·2% sensitivity (95% CI 14·2–25) and 94·7% specificity (93·2–95·9) for identifying the inability to attain four metabolic equivalents during CPET. Only DASI scores were associated with predicting the primary outcome (adjusted odds ratio 0·96, 95% CI 0·93–0·99; p=0·03).

Interpretation Subjectively assessed functional capacity should not be used for preoperative risk evaluation. Clinicians could instead consider a measure such as DASI for cardiac risk assessment.

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Introduction
International clinical practice guidelines emphasise the assessment of preoperative cardiopulmonary fitness, or functional capacity, as an important component of estimating patients’ risks for major morbidity and mortality after surgery.1 For example, the American College of Cardiology and American Heart Association recommend that patients proceed directly to elective intermediate and major non-cardiac surgery if they are capable of more than four metabolic equivalents of tasks of activity without symptoms.1 The usual standard of care for assessing preoperative functional capacity involves doctors assessing patients, then making subjective estimates of their fitness (ie, subjective assessment). Although these estimates are easily implementable into clinical practice, subjective assessment has limitations, including little agreement with validated measures of functional capacity,1 and poor accuracy when used to predict postoperative death or complications.3,4 These limitations point to the need for better alternatives to assess preoperative functional capacity.

Possible alternative options are cardiopulmonary exercise testing (CPET), which has been described as a gold standard non-invasive assessment of exercise tolerance, and the Duke Activity Status Index (DASI),5 which is a standardised questionnaire correlated with gold-standard measures of functional capacity. Additionally, although no blood test can directly measure functional capacity, N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentrations might indirectly fulfil this role.5
Research in context

Evidence before this study

Estimation of cardiopulmonary fitness, or functional capacity, is an important component of risk assessment before major non-cardiac surgery. This estimation typically involves subjective assessment, where doctors interview patients and make a subjective judgment of their fitness. To assess the validity of this commonly used measure of functional capacity, we used the terms (“prediction” OR “preoperative evaluation” OR “risk prediction”) AND (“surgery” AND “complications”) AND (“exercise capacity” OR “activities of daily living” OR “functional capacity”) to search the PubMed database for English-language articles on relevant studies published before Dec 31, 2017. The search was supplemented with hand-searches of reference lists from relevant reviews and practice guidelines. Previous research was limited to single-centre studies with small sample sizes or a high risk of bias. In these studies, subjective assessment showed poor agreement with validated questionnaires, and an inconsistent association with postoperative complications.

Added value of this study

Our multicentre prospective cohort study (Measurement of Exercise Tolerance before Surgery) assessed patients before they underwent major elective non-cardiac surgery and compared the prognostic accuracy of subjective assessment against three alternative measures: the Duke Activity Status Index (DASI) questionnaire, cardiopulmonary exercise testing (CPET) to measure peak oxygen consumption, and serum N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentrations. In a sample of 1401 adult participants at 25 hospitals, lower DASI scores predicted 30-day death or myocardial infarction, and 30-day death or myocardial injury; higher NT pro-BNP concentrations predicted 30-day death or myocardial injury, and 1-year death; and lower peak oxygen consumption predicted complications. Subjective assessment did not predict any outcomes.

Implications of all the available evidence

Subjective assessment of functional capacity should not be used for preoperative risk assessment. This commonly used practice does not accurately identify patients with poor fitness or those at increased risk for postoperative morbidity and mortality. As alternatives, clinicians could consider more objective measures, such as DASI questionnaires and NT pro-BNP testing to assess perioperative cardiac risk, and perhaps CPET to predict complications after major elective non-cardiac surgery.

Methods

Study design and participants

We did a multicentre, international, prospective cohort study (Measurement of Exercise Tolerance before Surgery [METS]) at 25 hospitals: five in Canada, seven in the UK, ten in Australia, and three in New Zealand. The study’s objectives, design, and methods have been previously reported. Details of the methods are in the appendix.

Participants were aged 40 years or older, scheduled for elective non-cardiac surgery under general or regional anaesthesia (or both) with a minimum of one overnight hospital stay, and deemed to have at least one risk factor for cardiac complications or at least one risk factor for having coronary artery disease (appendix). All participants provided written informed consent, and each centre obtained research ethics board approval before commencing recruitment.

Procedures

During the period from recruitment to 1 day before surgery, participants underwent symptom-limited incremental CPET on a computer-controlled, electromagnetically braked cycle ergometer using a standardised protocol (appendix). This assessment usually occurred during a separate hospital visit after the date of recruitment. On the basis of a prespecified assessment of the plotted CPET data, trained investigators at each centre determined patients’ peak oxygen consumption and anaerobic threshold.

Participants also underwent three other preoperative assessments of functional capacity. First, responsible anaesthesiologists in the preoperative assessment clinic (on the date of recruitment) or operating theatre (on the day of surgery) were asked to make a subjective judgment of participants’ functional capacity after assessing their usual preoperative history. Subjectively assessed functional capacity was classified as poor (<4 metabolic equivalents), moderate (4–10 metabolic equivalents), or good (>10 metabolic equivalents). The poor category included cases where anaesthesiologists were uncertain about patients’ functional capacity, typically due to pre-existing conditions such as arthritis or peripheral arterial disease. Second, participants completed the DASI questionnaire on the date of recruitment (appendix). Third, blood samples were drawn at any point between recruitment and surgery to measure serum NT pro-BNP concentrations. These samples were stored at −70°C to −80°C at each study site, then analysed at the Aberdeen Royal Infirmary (Aberdeen, UK) using the Siemens Vista immunoassay analyser (Siemens Healthcare Diagnostics, Frimley, UK). Participants, health-care providers, and outcome adjudicators were masked to CPET and NT pro-BNP results, and health-care providers and outcome adjudicators were masked to DASI scores; specifically,
the study’s central laboratory, exercise testing facilities, and exercise testing laboratories did not report these specific measurements to masked individuals. The exceptions were cases of myocardial ischaemia or substantial new arrhythmias during CPET, in which case these specific findings, but not peak oxygen consumption or anaerobic threshold results, were revealed to healthcare providers.

After surgery, participants underwent daily electrocardiograms and blood sampling to measure troponin and creatinine concentrations, until the third postoperative day or hospital discharge (whichever came first). Research personnel followed participants each day throughout their hospital stay to ascertain the presence of specific complications (appendix). The severity of complications was categorised as mild, moderate, severe, or fatal using a modified Clavien-Dindo classification scheme.9,10 After hospital discharge, participants were contacted at 30 days and 1 year after surgery to ascertain vital status. Details of the follow-up process are in the appendix.

**Outcomes**

The primary outcome was death or myocardial infarction within 30 days after surgery. The secondary outcome was death within 1 year after surgery. Myocardial infarction was diagnosed by an adjudication committee that used the third universal definition of myocardial infarction11 while remaining masked to CPET, DASI, and NT pro-BNP results. Other outcomes of interest were death or myocardial injury within 30 days after surgery, and moderate or severe (including fatal) complications during the index admission to hospital. Myocardial injury was defined as postoperative troponin concentrations exceeding both the 99th percentile of the normal reference population, and the threshold at which the assay coefficient of variation was 10%. Moderate or severe complications were included as an endpoint because these events have been associated with poor preoperative functional capacity, especially when measured objectively by CPET.12,13

**Statistical analysis**

The sample size calculation was based on comparing the area under the curve (AUC) of the receiver-operating-characteristic (ROC) curves for peak oxygen consumption versus subjective assessment with respect to predicting myocardial infarction or death within 30 days of surgery. During the design of the study, we initially calculated that a sample size of 1180 was required on the basis of underlying assumptions of an outcome event rate of 8%, correlation of 0·5 between peak oxygen consumption and subjective assessment, an AUC of 0·65 for subjective assessment, an AUC of 0·75 for peak oxygen consumption, and 90% power to detect this difference in AUC values (two-sided α of 0·05). To account for 10% of participants not undertaking CPET or surgery, we aimed to recruit 1312 participants. After recruiting about half the original planned sample size, this calculation was reassessed based on two factors identified in the accumulating study data. First, we noted that about 20% of participants did not either undertake CPET or undergo their planned surgeries. Second, the event rate for the primary outcome was instead projected to be approximately 5%. The overall sample size was therefore increased to 1723 participants to account for up to 20% of recruited individuals not being eligible for the primary analysis, and a primary outcome event rate of 5%, while retaining the power of 80%. We remained masked to all data on the principal exposures (ie, CPET results, DASI scores, and NT pro-BNP concentrations) during the sample size re-estimation.

All participants who undertook both CPET and surgery were included in the primary analysis; CPET performance was characterised by peak oxygen consumption. For each outcome of interest, we built separate nested logistic regression models that sequentially included baseline clinical characteristics followed by the exposure of interest.

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**Figure 1:** Participant screening, recruitment, and follow-up

CPET=cardiopulmonary exercise testing.
(ie, subjective assessment, peak oxygen consumption, anaerobic threshold, DASI scores, or NT pro-BNP). We modelled NT pro-BNP concentrations using a logarithmic transformation to reduce the potential effect of extreme values within its highly skewed distribution. The statistical significance of prognostic information from additional predictors was based on the increase in log statistic and area under the ROC curve.\(^{17}\)

In the model predicting death or myocardial injury by 30 days, the baseline variables were age, sex, and RCRI score. The baseline variables in the model predicting moderate-or-severe complications were age, sex, and high-risk surgery, which was defined as intraperitoneal, intrathoracic, or suprainguinal vascular procedures.\(^{14,15}\) These covariates were selected a priori based on previous evidence, their inclusion in guideline-recommended assessment algorithms,\(^{1,16}\) and the need to prevent model overfitting. Additionally, the covariates mirror clinically sensible factors typically considered during preoperative assessment. We calculated the area under the ROC curve of models with successively more predictors, and models with only the individual exposure of interest (eg, peak oxygen consumption). Prognostic information from these models was compared using the continuous net reclassification improvement (NRI) statistic and area under the ROC curve.\(^{9}\)

To address whether preoperative functional capacity might have better prognostic value in more invasive surgical procedures, a post-hoc subset analysis was done in some patients undergoing body cavity surgery, which was defined as intrathoracic, intraperitoneal,
retroperitoneal or pelvic (ie, urological or gynaecological) procedures.

Analyses were done with R (version 3.4.0), statistical significance was defined by a two-tailed p value of less than 0·05, and no adjustments were made for multiple comparisons. Because missing data were uncommon, a complete case analysis was done. Additionally, these missing data pertained to baseline information that was likely missing completely at random.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between March 1, 2013, and March 25, 2016, 1741 patients (23% of eligible patients who consented to participate) were recruited at 25 hospitals, with 1401 (81%) undergoing CPET and surgery (figure 1). Of these 1401 participants in the primary cohort, 1399 (99·9%) completed a 30-day follow-up and 1378 (98%) completed a 1-year follow-up. Participants’ median age was 65 years (IQR 57–72), 39% were female, and 91% were classified as American Society of Anesthesiologists Physical Status (ASA-PS) 2 or 3 (table 1). Most participants underwent major abdominal, pelvic, or orthopaedic procedures. Data were missing for less than 4% of participants.

The CPET exercise protocol was terminated early in 11% of participants, with the most common reasons being inability to pedal, fatigue, or a safety-based indication (table 2). Mean peak oxygen consumption was 19·2 mL/kg per min (SD 6·5) and mean anaerobic threshold was 12·6 mL/kg per min (4·1). 110 (8%) of patients had an anaerobic threshold below the suggested high risk threshold of 11 mL/kg per min.18 Because missing data were uncommon, a complete case analysis was done. Additionally, these missing data pertained to baseline information that was likely missing completely at random.

| Interval to CPET to surgery (days) | 9 (5–21) |
| Reasons for early termination of CPET | 157 (11%) |
| Safety-based indication | 23 (2%) |
| Fatigue | 31 (2%) |
| Shortness of breath | 11 (<1%) |
| Unable to pedal | 76 (5%) |
| Unable to tolerate mouthpiece or mask | 12 (<1%) |
| Technical problems with equipment | 4 (<1%) |

Data are median (IQR) or n (%). CPET=cardiopulmonary exercise testing. AT=anaerobic threshold. ECG=electrocardiogram.

Table 2: Characteristics of CPET assessments

After surgery, 194 (14%) participants had in-hospital moderate or severe complications.

By 30 days after surgery, five (<1%) participants had died, 24 (2%) had a myocardial infarction, 28 (2%) had the primary outcome of death or myocardial infarction, and 176 (13%) had died or had a myocardial injury. By 1 year after surgery, 38 participants (3%) had died. Of the moderate or severe complications, the more frequent events were respiratory failure, pneumonia, surgical site infection, re-operation, and unexpected critical care unit admission (appendix).

Subjectively assessed preoperative functional capacity had no significant adjusted association with the four main study outcomes (appendix). A significant adjusted association and significant risk reclassification with peak oxygen consumption was observed only with respect to moderate or severe complications (table 3). Anaerobic threshold showed no significant association or risk reclassification with the main outcomes. DASI scores showed significant adjusted associations with the primary outcome of death or myocardial infarction by
Discussion

Preoperative subjective assessment neither accurately identified patients with poor cardiopulmonary fitness nor predicted postoperative morbidity and mortality. The DASI questionnaire improved prediction of 30-day myocardial infarction or death, and 30-day myocardial injury or death; and NT pro-BNP concentrations improved prediction of 30-day myocardial injury or death, and 1-year death. Formal assessment of cardiopulmonary fitness, based on peak oxygen consumption during CPET, improved prediction of moderate or severe postoperative complications.

In our study, subjective assessment of preoperative functional capacity consistently performed poorly. Although it had construct validity, in that peak oxygen consumption was generally lower in patients judged to be less fit, subjective assessment correctly identified only 16% of patients who achieved a peak less than 14 mL/kg per min, which is consistent with less than 4 metabolic equivalents. Further, subjective assessment did not predict postoperative myocardial infarction, myocardial injury, or myocardial complications, confirming findings from a single-centre retrospective cohort study that relied on an administrative database for outcome ascertainment. Based on these findings, subjective assessment should not be used to assess patients’ risks of major postoperative cardiac complications.

Notably, more objective assessment of cardiopulmonary fitness with CPET did not improve most aspects of preoperative risk assessment. Consistent with previous evidence, peak oxygen consumption measured during CPET was predictive of postoperative complications; however, most of these events were pulmonary complications, surgical site infections, unexpected critical care unit admissions, and re-operations. By contrast, peak oxygen consumption and anaerobic threshold were not associated with postoperative myocardial infarction or myocardial injury, somewhat contradicting the emphasis of practice guidelines on functional capacity for preoperative cardiac risk evaluation. These findings occurred within the context of our study addressing several important limitations in the current evidence base, in that it masked CPET results (unlike most previous studies), and implemented standardised outcome surveillance in a large, generalisable, multicentre sample. There are several possible explanations for our results. First, the previous evidence supporting a link between fitness and perioperative cardiac risk had limitations; eg, many of the studies were done more than 30 years ago, and have limited generalisability to contemporary patients and surgeries. Other studies had few outcome events or associations of only weak magnitudes. Second, low peak oxygen consumption or anaerobic threshold might not be the ideal CPET-based indicator of the underlying causal

30 days after surgery and with death or myocardial injury by 30 days after surgery. Additionally, DASI scores showed significant risk reclassification with death or myocardial injury by 30 days. NT pro-BNP concentrations showed significant adjusted associations and significant risk reclassification with death by 1 year after surgery and death or myocardial injury by 30 days after surgery. When the main study analyses were repeated in the post-hoc subset, the results remained qualitatively unchanged (appendix).
mechanisms for perioperative myocardial infarction. Other metrics, such as an exaggerated exercise-mediated heart rate response, might be better indicators of perioperative cardiac risk.

The DASI questionnaire had construct validity as a measure of functional capacity in surgical patients, consistent with previous research, and also improved prediction of postoperative myocardial infarction and myocardial injury. Our findings confirmed non-operative data indicating enhanced risk prediction using this questionnaire, supported guideline suggestions for using objective scales to assess functional capacity, and indicate opportunities for straightforward improvements in clinical practice. Specifically, the simple DASI questionnaire can be easily implemented into most perioperative practice settings, although further studies are needed to define optimal risk-specific thresholds in DASI scores, and develop reliable non-English versions of the questionnaire. An important area of residual uncertainty is why DASI scores were associated with postoperative cardiac events, yet peak oxygen consumption was not. Given the only moderate correlation between DASI scores and peak oxygen consumption, a possible explanation is that DASI also measures somewhat different constructs, such as musculoskeletal strength, frailty, and self-imposed physical limitations.

Confirming results from a previous individual patient data meta-analysis, increased preoperative NT pro-BNP concentrations were associated with increased risks of postoperative 30-day death or myocardial injury in the METS study cohort; additionally, increased concentrations also predicted increased 1-year mortality. These findings support recommendations in recent practice guidelines to incorporate natriuretic-peptide testing into preoperative risk assessment strategies. We noted only slight-to-fair correlation between NT pro-BNP concentrations and measures of exercise capacity (ie, peak oxygen consumption and DASI). This low correlation suggests that NT pro-BNP measures are a construct distinct from exercise capacity, and raises the possibility of enhancing preoperative assessment by combining measures of functional capacity and NT pro-BNP in future risk prediction models.

Our study had several limitations. First, despite increasing the original projected sample size, the primary and secondary outcomes occurred fewer times than anticipated. To some extent, the risks of death within 30 days of surgery (ie, 0–4%) and 30-day death or myocardial infarction in the METS study cohort; additionally, increased concentrations also predicted increased 1-year mortality. These findings support recommendations in recent practice guidelines to incorporate natriuretic-peptide testing into preoperative risk assessment strategies. We noted only slight-to-fair correlation between NT pro-BNP concentrations and measures of exercise capacity (ie, peak oxygen consumption and DASI). This low correlation suggests that NT pro-BNP measures are a construct distinct from exercise capacity, and raises the possibility of enhancing preoperative assessment by combining measures of functional capacity and NT pro-BNP in future risk prediction models.
of the exposures of interest with two more frequent outcomes: myocardial injury and moderate or severe postoperative complications. Myocardial injury and postoperative complications are clinically and prognostically important outcomes.32–34 Our general findings with respect to prediction of 30-day myocardial infarction or death were qualitatively unchanged in the complementary analysis pertaining to 30-day myocardial injury or death.

Second, despite significant efforts by research personnel and study investigators, the consent rate among otherwise eligible patients in our study was only 27%. Nonetheless, this consent rate is somewhat unsurprising when viewed from the perspective of the study setting (ie, anxious patients awaiting major surgery within a short timeframe) and procedures (ie, strenuous exercise testing solely for research purposes). The consent rate is also consistent with several large contemporary prospective studies in surgical patients that had arguably more straightforward study procedures. For example, consent rates were 30% in the POISE-2 trial of aspirin and clonidine in non-cardiac surgery,35 and 36% in the ATACAS trial in cardiac surgery.18

Third, our primary analyses relied on peak oxygen consumption and anaerobic thresholds determined by trained investigators at each individual centre. It is possible that central adjudication of CPET results might have led to different determinations of these measures. Nonetheless, given that our study was designed to be pragmatic and generalisable, our main analyses better represent the prognostic accuracy of peak oxygen consumption or anaerobic thresholds in real world clinical practice. Fourth, the preoperative predictive models in this study had generally low-to-moderate discrimination, with AUC values of 0·74 or lower. This observation could be partly explained by the lower-than-expected outcome event rate, which limited the number of covariates included in regression models. Nonetheless, the discrimination of these models is similar to those from other studies, such as a prospective cohort study where the combination of RCRI score and preoperative coronary CT angiography had an AUC of 0·66 for predicting 30-day death or myocardial infarction.19 Fifth, each hospital used its own preferred troponin assay to detect myocardial infarction or myocardial injury. This pragmatic approach is consistent with many multicentre perioperative studies.51,52 Furthermore, variation in troponin assays does not affect the prognostic importance of myocardial infarction or myocardial injury,51,52 and should not have biased the association between the study exposures and outcomes.

Combined with previous data, the results of our study suggest that DASI scores and natriuretic peptides, such as NT pro-BNP, should supplant subjective assessment for the estimation of perioperative cardiac risk for major non-cardiac surgery. More research is required to define optimum thresholds for these measures and determine how they should be used in combination with other prognostically important information, including alternative preoperative biomarkers (eg, high-sensitivity troponin).53 These other biomarkers might also help to partly address the limitations of NT pro-BNP as a prognostic biomarker in the presence of obesity,6 chronic renal kidney,9 or heart failure with preserved ejection fraction.62

Our findings also indicate that CPET, specifically peak oxygen consumption, can be used to identify patients at increased risk for postoperative complications. Research is needed to define optimal thresholds in peak oxygen consumption, determine the role of central expert adjudication in improving its prognostic accuracy, assess novel CPET-derived metrics of cardiopulmonary fitness (eg, heart rate recovery), and assess possible inter-relationships of CPET-derived metrics with prognostically important comorbidities. For example, lower haemoglobin concentrations are associated with both increased perioperative risk and reduced peak oxygen consumption.63,64

In conclusion, preoperative subjective assessment of functional capacity should not be used in clinical practice because it does not accurately identify patients with poor fitness or those at increased risk for morbidity and mortality after major elective non-cardiac surgery. Clinicians could instead consider more objective measures, such as DASI questionnaires and NT pro-BNP testing for assessing perioperative cardiac risk, and perhaps CPET to predict complications after major elective non-cardiac surgery.

Contributors
DNW, RMP, MAS, TEFA, BLC, JTG, KET, MPWG, PSM, and BHC contributed to the conception and design of the study. DNW, RMP, MAS, TEFA, ET, AA, BLC, JTG, KET, MPWG, CF, PSM, and BHC revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

Declaration of interests
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