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PREHABILITATION (B RIEDEL AND S JACK, SECTION EDITORS)

Cardiopulmonary Exercise Testing and Other Tests of Functional Capacity

Marissa Ferguson[1] · **Mark Shulman**[1]

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Abstract

Purpose of Review Assessment of functional capacity is a cornerstone of preoperative risk assessment. While subjective clinician assessment of functional capacity is poorly predictive of postoperative outcomes, other objective functional assessment measures may provide more useful information.

Recent Findings Cardiopulmonary exercise testing (CPET) is generally accepted as the gold standard for functional capacity assessment. However, CPET is resource-intensive and not universally available. Simpler objective tests of functional capacity such as the Duke Activity Status Index (DASI) and the 6-min walk test (6MWT) are cheap and efficient. In addition, they predict important postoperative outcomes including death, disability, and myocardial infarction.

Summary Simple preoperative tests such as the DASI may be useful for routine preoperative assessment. CPET may be helpful to investigate further patients with functional status limitation, and to guide prehabilitation and perioperative shared decision-making in high-risk patients.

Keywords Perioperative medicine · Cardiopulmonary exercise testing · Risk assessment · Functional status assessment · Duke Activity Status Index · 6-min walk test

Introduction

Approximately 17% of patients worldwide suffer major postoperative complications [1]. With around 319 million operations performed each year globally, this equates to a significant global burden of disease [2, 3]. A large proportion of postoperative complications occur in the highest risk patients [4]; for example, major postoperative complications occur in 32% of patients with significant co-morbidities [1] and 20% of elderly patients [5]. Major postoperative complications predict long-term survival [6], and early intervention may prevent death after complications ("failure to rescue") [7].

Functional capacity assessment is a cornerstone of preoperative assessment. The key aims of functional status assessment include risk stratification, assessing the response to prehabilitation or preoperative optimization, and guiding shared decision-making and postoperative destination planning, e.g., critical care admission. Of note, most outcomes studied to date are postoperative complications (predominantly cardiovascular complications) or death. However, more recently, there has been increasing recognition that patient-centered outcomes such as postoperative disability-free survival, and quality of life may be equally (or more) important [8, 9].

The American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology/European Society of Anaesthesia (ESC/ESA) guidelines on preoperative cardiovascular assessment both emphasize assessment of functional capacity early in their algorithms [10, 11]. Cardiopulmonary exercise testing (CPET) is generally considered the gold standard for objectively quantifying functional capacity and the ability to meet the metabolic demands of major surgery, but is time-consuming and resource-intensive [12]. Simple objective tests of functional capacity using a structured questionnaire (the Duke Activity Status Index, DASI), and shorter protocolized exercise testing (the 6-min walk test [6MWT] and

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✉ Marissa Ferguson
Marissa.ferguson@austin.org.au

Mark Shulman
Mark.shulman@monash.edu

[1] Austin Hospital, 145 Studley Rd, Heidelberg, VIC, Australia

the incremental shuttle walk test [ISWT]) may also provide valuable preoperative risk information.

Search Strategy

We performed a literature review of PubMed, Medline, and Google Scholar using keywords for the perioperative period and cardiopulmonary exercise testing, Duke Activity Status Index, functional status assessment, and perioperative outcomes (mortality, complications, days at home, and disability-free survival). The search strategy included meta-analyses, systematic reviews, and observational studies.

Subjective Assessment of Functional Capacity

The AHA/ACC and ESC/ESA algorithms for preoperative cardiac risk assessment both recommend proceeding with surgery if the patient has at least moderate functional capacity, defined as ≥ 4 metabolic equivalents (METS) [10, 11]. One MET is the oxygen uptake at rest, generally 3.5 mL/kg/min [13]. Physical activities that require approximately 4 METS include gardening, calisthenics without weights, golfing without a cart, slow swimming, walking 4.5 mph, and mowing the lawn [13].

The AHA/ACC and ESC/ESA guidelines on preoperative cardiovascular assessment include the classic thresholds of climbing a hill or 1–2 flights of stairs as activities requiring > 4 METS [10, 11]. There is evidence that postoperative complications are inversely related to the number of (self-reported) blocks or flights of stairs that a patient can walk or climb, with an inability to walk at least four blocks and climb two flights of stairs associated with an increased risk for major postoperative complications (sensitivity 71%; positive likelihood ratio of 1.3) [14]. However, a large observational study found that subjective clinician assessment has a low sensitivity for identifying patients with poor functional capacity (when correlated with the gold standard of CPET) and was not predictive of postoperative morbidity or mortality among patients undergoing major inpatient non-cardiac surgery [15••].

Cardiopulmonary Exercise Testing

CPET objectively evaluates the integrated function of the cardiorespiratory system and cellular respiration at the tissue level [16]. It involves baseline resting gas exchange(oxygen uptake, carbon dioxide production) analysis, followed by exercise stress testing (generally using a bicycle ergometer) continuous ECG monitoring, and breath-by-breath gas exchange analysis to peak exercise. Vital sign measurement and gas exchange analysis are also measured during the recovery phase after exercise [13]. While there are several commonalities between the stress of exercise and the perioperative stress response, such as increased heart rate and myocardial work, other critical pathophysiologic changes that may predispose to postoperative complications cannot be replicated (e.g., prothrombotic alterations in hemostasis, endothelial dysfunction, anemia, hypotension) [17–19].

Preoperative CPET for risk prediction increased in clinical use during the 1990s after several small observational studies suggested that CPET may be useful in predicting perioperative morbidity and mortality [20, 21]. Key CPET variables include the peak oxygen uptake (peak VO2) and the oxygen uptake at the anerobic threshold (AT) [22, 23].

Peak Oxygen Uptake and the Anerobic Threshold

The ability to achieve ≥ 4 METS functional capacity emerged as a key functional status threshold in major guidelines for preoperative cardiovascular risk assessment [10, 11]. This threshold was supported by a number of small observational studies suggesting that a peak VO2 < 15 mL/kg/min (roughly < 4 METS) is associated with postoperative mortality and complications after intra-abdominal, aortic, and thoracic surgery [24–28, 29••]. In general, a peak VO2 greater than 20 mL/kg/min is associated with a low risk for perioperative morbidity and mortality after non-cardiac surgery [25]. However, the association between peak VO2 and perioperative outcomes is not consistent and was only present in 45% of studies identified in a recent systematic review [29••]. Of note, the peak VO2 is effort-dependent, and factors other than exercise capacity such as patient motivation and joint pain may affect performance [23].

The anerobic threshold is the oxygen uptake at which lactate production begins to increase and reflects a shift from aerobic to anerobic (glycolytic) metabolism [22]. The AT is effort-independent, although there is greater inter-observer measurement error compared to the peak VO2 [23]. Numerous small observational studies have found an association between an AT < 9–11 mL/kg/min and postoperative complications and mortality after non-cardiac surgery [20, 27, 28, 30–36]. Studies using an AT threshold of 9–11 mL/kg/min have demonstrated high negative predictive values (94–100%) for postoperative mortality, although this likely reflects the low incidence of this outcome [29••]. Similar to peak VO2, the association between AT and perioperative outcomes is not consistent and was only present in 51% of studies identified in a recent systematic review [29••].

A limitation of the CPET evidence to date has been poor study methodology [37]. All studies on preoperative CPET identified during the literature search for the 2017 Canadian Cardiovascular Society Guidelines were of "very low" quality [38]. Systematic reviews have identified frequent study limitations including small sample size, single-center design, heterogeneous patient populations, variable CPET methodology and outcome measurement, and high risk for bias due to infrequent blinding [29••, 34].

The largest and most rigorously conducted study investigating CPET for perioperative risk prediction is the measurement of exercise tolerance for surgery (METS) study. This blinded prospective multicenter cohort study compared preoperative subjective assessment, objective functional assessment (CPET, DASI), and biomarkers (NT-proBNP) for predicting death or complications after major elective non-cardiac surgery among patients with risk factors for cardiac complications [15••]. The primary outcome was the accuracy of CPET in predicting 30-day mortality and non-fatal MI; secondary outcomes included 12-month mortality and postoperative complications. The peak VO2 and AT were not predictive of either the primary or secondary endpoints and were also not predictive of disability-free survival in a sub-study [39•]. However, on post-hoc analysis, the peak VO2 was predictive of moderate or severe postoperative complications including surgical site infection, respiratory failure, pneumonia, critical care readmission, and reoperation.

Other CPET-Derived Variables

CPET provides a large array of other variables in addition to the peak VO2 and the AT. Markers of cardiac and pulmonary pathology on CPET may suggest organ-specific pathology and prompt further investigation. Indicators of exercise-induced myocardial ischemia on CPET include ECG changes, the duration of oxygen pulse flattening (oxygen uptake divided by heart rate), and the presence of an inflection point in the graph comparing oxygen uptake vs. work rate [40].

The prognostic significance of an abnormal stress ECG depends on the workload at which ischemic signs or symptoms develop, with greater significance given to onset at low workload [41]. Oxygen pulse flattening and an abnormal oxygen uptake vs. work rate may reflect ischemia-induced left ventricular dysfunction and the inability to increase stroke volume to meet elevated tissue oxygen delivery demands during exercise [42]. These parameters may identify exercise-induced ischemia even in the absence of ECG changes [40].

Abnormal heart rate responses to exercise may also predict adverse outcomes. Both an impaired and an exaggerated heart rate response to exercise may be suggestive of underlying cardiac pathology [23]. A delayed heart rate recovery after exercise is a surrogate for vagal dysfunction and may predict postoperative complications [43]. For example, a post-exercise heart rate reduction ≤ 12 beats/min from peak exercise was associated with postoperative myocardial injury among 1741 patients enrolled in a planned METS sub-study [44•].

The ventilatory equivalent for carbon dioxide at anaerobic threshold (VE/VCO2) represents the gas exchange capacity of the lungs, and is a surrogate for ventilation-perfusion matching and physiologic dead space [22]. A VE/VCO2 > 34–42 is associated with postoperative mortality and complications [24, 30, 35, 45]. However, this association has not been uniformly demonstrated; only 36% of CPET studies identified in a recent systematic review found an association between VE/VCO2 and postoperative outcomes [29••].

The Duke Activity Status Index

The DASI is a structured 12-item survey assessing the ability to complete various physical tasks [46]. The DASI score ranges from 0 to 58.2 and can be used to calculate a predicted peak oxygen consumption (predicted peak $VO2 = 0.43 \times DASI + 9.6$) [46]. There is modest correlation between the DASI score and peak VO2, and DASI has a moderate ability to predict a peak VO2 > 15 mL/kg/min (AUC 0.77) [47]. A simplified modified version of the DASI (m-DASI) questionnaire using four or five questions may have similar ability to identify patients with at least moderate functional capacity [48]. A score of three using the four-question m-DASI questionnaire is associated with a 59% probability of achieving an AT > 11 mL/kg/min and a 71% probability of achieving an VO2 peak > 16 mL/kg/min [49].

In the METS study, DASI was the only independent predictor of 30-day death or non-fatal myocardial infarction [15••]. Furthermore, on a sub-study, DASI was the only independent predictor of 12-month disability-free survival [39•]. A threshold DASI score of < 34 (corresponding to a peak VO2 of 17–18 mL/kg/min) may be used to identify patients at elevated risk for myocardial injury/infarction, moderate to severe postoperative complications, or new postoperative disability [50•].

Walking Tests

The 6-min walk test (6MWT) is a sub-maximal exercise test that involves a patient walking on the flat back and forth between two distance markers. Early observational data suggested that it had good ability to discriminate between moderate (> 11 mL/kg/min) and low (< 11 mL/kg/min) AT in patients awaiting major non-cardiac surgery, with lower and upper distance cut-points of < 427 and > 563 m [51]. A sub-study of 574 patients enrolled in the METS study found poor correlation between the 6MWT and 30-day quality of recovery or 12-month new postoperative disability [39•]. However, comparing the lowest tertile (< 435 m) versus the highest tertile (> 510 m) predicted new disability and 12-month disability-free survival on post-hoc analysis, and a 6MWT < 350 m had 90% sensitivity and 73% specificity for predicting 12-month disability [39•]. For these outcome measures, the 6MWT was equivalent or superior to CPET.

The incremental shuttle walk test (ISWT) involves walking on the flat between two points at increasing speed [52]. In contrast to the 6MWT, the increasing pace during the ISWT simulates peak functional capacity testing using a ramp protocol. The ISWT has moderate to good correlation with the peak VO2 measured using CPET [47, 52], and threshold of > 360 m has a high positive predictive value for a peak VO2 > 15 mL/kg/min and an AT > 11 mL/kg/min on CPET based on the results of one small observational study [47] (Table 1). However, the utility of the ISWT has not been evaluated in large prospective studies in the perioperative period.

Functional Status Assessment in Practice

The DASI is a cheap and simple objective test of functional capacity, and is more accurate at predicting postoperative outcomes that subjective clinician assessment. Preoperative CPET may be useful in select patients, particularly those identified as high-risk using the DASI questionnaire. CPET is more useful for predicting major postoperative complications compared to cardiac risk prediction. There is a margin of error in all CPET parameters, and a single cut-off to discriminate between high versus low risk may be overly simplistic [54]. No single CPET variable has uniformly been found to predict postoperative outcomes [29••], and the utility of different CPET variables may differ depending upon the type of surgery and underlying patient comorbidities [37].

Further research is required to determine whether the integration of CPET into preoperative assessment and management protocols improves postoperative outcomes. Several small observational studies have suggested that preoperative exercise training ("prehabilitation") can improve CPET markers of functional capacity [55, 56], although it is unclear whether this translates into improved postoperative outcomes [57, 58]. Prehabilitation may be particularly important for patients undergoing cancer surgery to attenuate the reduction in functional capacity associated with neoadjuvant chemoradiotherapy [57]. Several multicenter randomized controlled trials are currently in progress investigating whether CPET-guided prehabilitation can reduce major postoperative complications [59–62]. Recently published consensus guidelines will aid in improving the quality of these future perioperative CPET studies [63].

Aside from accuracy, other pragmatic factors such as cost, complexity, availability, time, and expertise requirement are important determinants of the utility of a functional status assessment tool. While CPET is available in 53% of UK trusts [64], availability in other areas of the world is likely to be lower, particular in low and middle-income countries. Furthermore, CPET is problematic in the era of the coronavirus pandemic due to safety concerns for viral transmission and resource limitations due to pressures placed on health systems in caring for infected patients [65].

Preoperative biomarkers such as brain natriuretic peptide (BNP) and troponin are simple, quick, and relatively cheap options for preoperative risk assessment that may complement functional status assessment. The preoperative BNP and N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP)

Table 1 Cut-points that help triage patients at increased risk for postoperative complications

Test	AT < 11 mL/kg/min	AT > 11 mL/kg/min	pVO2 < 15 mL/kg/min	pVO2 > 15 mL/kg/min	Outcome
DASI				> 34 [15••, 50•]	< 34: increased risk for 30-day death or postoperative myocardial infarction and moderate-to-severe complications [50•]
m-DASI		66% probability with 4/4 questions [49]		84% probability with 4/4 questions [49]	
6MWT	< 427 m [51]	> 563 m [51]			< 350 m: 20% chance of significant increase in 12-month disability [39•]
ISWT		> 360 m [47]		> 360 m [47]	
Natriuretic peptides					NT-pro BNP > 92 ng/L or BNP > 300 ng/L: increased postoperative death or MI at 30 days and ≥ 180 days [53]

level both independently predict mortality and cardiac complications after major non-cardiac surgery [53, 66–69] and cardiac surgery [70, 71]. In the METS study, preoperative NT-proBNP was predictive of 12-month mortality and death or myocardial injury within 30 days postoperatively [15••]. Similar to BNP, preoperative troponin levels are associated with postoperative cardiac complications [72–75]. Preoperative natriuretic peptide measurement improves the net risk reclassification in 32% of patients for postoperative mortality or non-fatal MI in addition to baseline clinical variables alone (age, revised cardiac risk index [RCRI], type of surgery, urgency of surgery; net reclassification improvement 32%) [53]. Another advantage of natriuretic peptides over troponins is that risk thresholds have been identified; BNP levels ≥ 92 ng/L or NT-proBNP levels ≥ 300 ng/L are strong independent predictors of postoperative death or MI at 30 days and ≥ 180 days [53]. As a result, the Canadian Cardiac Society guidelines recommend preoperative natriuretic peptide measurement for patients with a > 5% predicted risk of 30-day postoperative cardiovascular death or non-fatal myocardial infarction (age ≥ 65, age 45–64 and significant cardiovascular disease, or RCRI score ≥ 1) [38]. Early postoperative BNP and troponin levels may be even more predictive of postoperative morbidity and mortality than preoperative levels [53, 76]. However, routine clinical use of perioperative biomarker measurement is currently limited by the lack of established postoperative management algorithms demonstrating improved outcomes based on these variables [75].

Conclusions

Functional status assessment is a key component of preoperative risk assessment, although there is not one single parameter or cut-point that reliably discriminates patients at "high-risk" of postoperative complications and/or death. The Duke Activity Status Index is a cheap, simple and objective starting point for functional status assessment, and a DASI score of > 34 has been proposed to replace subjective assessment of reduced functional capacity [77]. Among patients identified as high-risk using the DASI questionnaire, further functional capacity testing such as 6MWT, ISWT and escalation to CPET, with consideration for biomarkers (troponin, BNP) may be useful to guide risk stratification, referral for prehabilitation (CPET), and postoperative destination planning (e.g., ICU).

Declarations

Conflict of interest The authors do not have any potential conflicts of interest to disclose.

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