Cardiopulmonary Exercise Testing and Surgery

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Abstract

The surgical patient population is increasingly elderly and comorbid and poses challenges to perioperative physicians. Accurate preoperative risk stratification is important to direct perioperative care. Reduced aerobic fitness is associated with increased postoperative morbidity and mortality. Cardiopulmonary exercise testing is an integrated and dynamic test that gives an objective measure of aerobic fitness or functional capacity and identifies the cause of exercise intolerance. Cardiopulmonary exercise testing provides an individualized estimate of patient risk that can be used to predict postoperative morbidity and mortality. This technology can therefore be used to inform collaborative decision-making and patient consent, to triage the patient to an appropriate perioperative care environment, to diagnose unexpected comorbidity, to optimize medical comorbidities preoperatively, and to direct individualized preoperative exercise programs. Functional capacity, evaluated as the anaerobic threshold and peak oxygen uptake ($\dot{V}O_2$peak) predicts postoperative morbidity and mortality in the majority of surgical cohort studies. The ventilatory equivalents for carbon dioxide (an index of gas exchange efficiency), is predictive of surgical outcome in some cohorts. Prospective cohort studies are needed to improve the precision of risk estimates for different patient groups and to clarify the best combination of variables to predict outcome. Early data suggest that preoperative exercise training improves fitness, reduces the debilitating effects of neoadjuvant chemotherapy, and may improve clinical outcomes. Further research is required to identify the most effective type of training and the minimum duration required for a positive effect.

Keywords: cardiopulmonary exercise testing; bicycle ergometry test; preoperative risk assessment

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It is estimated that more than 300 million surgical procedures are performed globally annually, and this number is increasing (1, 2). Surgery is associated with a substantial burden of perioperative morbidity and mortality. This represents a significant public health challenge. Postoperative complications have a long-term impact on mortality up to 10 years after surgery, and consequently avoiding morbidity is increasingly important (3). As life expectancy continues to rise, an increasing proportion of surgical patients are likely to be elderly with multiple comorbidities. This will present challenges to both anesthetists and surgeons. The optimum perioperative management of high-risk patients involves multidisciplinary collaborative decision making (4, 5). Accurate preoperative risk stratification is essential to ensure this process is based on reliable data.

Cardiopulmonary exercise testing (CPET) is an effective preoperative risk stratification tool. CPET variables predict postoperative morbidity and mortality (6). Thus CPET provides an individualized estimate of patient risk that has many uses. Collaborative decision making and patient consent are facilitated. It enables the preoperative triage of patients to appropriate perioperative care (e.g., critical care vs. surgical ward). CPET also facilitates the diagnosis of unexpected comorbidities and the optimization of known medical comorbidities preoperatively. It may be used to direct individualized preoperative exercise programs (7). Finally, it is of value to the anesthesiologist to know where the patient will be managed after surgery. This allows the patient to remain intubated at the end of surgery and to return to an

intensive care unit when previously this had been planned.

CPET for Preoperative Evaluation

CPET is an ideal tool for preoperative evaluation as it provides an objective measure of fitness or functional capacity. It evaluates the integrated function of the cardiac, circulatory, respiratory, and muscle metabolic systems under physiological stress (7–9). In addition, it can identify the cause of exercise intolerance (9, 10).

Preoperative assessment increasingly focuses on the functional impact of comorbidities and the evaluation of functional capacity overall, rather than the evaluation of each comorbidity independently (11). Previously, predominantly static tests of single-organ function were used to predict and evaluate cardiac risk, specifically the risk of cardiac ischemia (12–14). Subsequently it has become evident that cardiac failure is more predictive of postoperative morbidity and mortality than ischemia (15, 16). Furthermore, noncardiac complications are more prevalent than cardiac complications postoperatively (17). Thus the accurate prediction of all domains of postoperative morbidity is important. Guidelines have been updated to highlight the importance of functional capacity (13) and more recently the use of objective testing to evaluate functional capacity (12).

CPET detects and evaluates cardiac and pulmonary dysfunction by identifying the systemic consequences of the increasing oxygen demands of progressive exercise (8, 18). Increased oxygen demand is also one of the major features associated postoperatively with extensive surgery (19). If oxygen demand exceeds supply, there is a transition to increasing anaerobic metabolism resulting in a progressive metabolic acidosis (20, 21). Anaerobic metabolism is ultimately unsustainable and results in organ dysfunction if oxygen supply is not restored (22). This is the case whether the demand is during exercise or perioperatively.

The relationship between myocardial ischemia and ventricular dysfunction is important. Functional myocardial impairment is indicated by characteristic changes in the CPET response profile (23, 24). Myocardial ischemia may sometimes cause ventricular dysfunction, and the two combined significantly increases perioperative risk (25). Conversely, myocardial ischemia detected by 12-lead ECG, is not always accompanied by changes in myocardial function. In this case, the implication is that the ischemia has not caused functional cardiac impairment. The risk burden is less than when functional impairment is present.

CPET is also able to identify impaired functional capacity caused by deconditioning in the absence of medical comorbidities. Surgical patients are often relatively sedentary because of their comorbidities or their lifestyle. Consequently physical deconditioning, as distinct from clinical disease, may contribute to or cause their reduced functional capacity (26). The current preoperative CPET literature suggests that it is the severity of the functional impairment, rather than its etiology, that predicts the postoperative outcome. To date, the perioperative literature does not differentiate between the various causes of functional impairment.

The objectivity of CPET is also an important feature. Patients' self-reported exercise capacity is often inaccurate (27). Furthermore, functional capacity scores including the Duke Activity Status Index have not been validated in the surgical population.

CPET: The Exercise Protocol and the Predictive Variables

CPET is an exercise stress test with concomitant gas exchange analysis. Expired tidal volumes, oxygen and carbon dioxide concentrations, heart rate, and respiratory rate are measured. A number of ventilatory, gas exchange, and cardiovascular variables are derived from these (*see* European Respiratory Society [28] and American Thoracic Society [9] for reviews).

Twelve-lead ECG and oxygen saturations are also continuously monitored.

The Exercise Protocol

The rapid incremental ramp to the limit of tolerance that is used for many other indications is the standard protocol for preoperative CPET (9, 28–30). This is a short protocol, with a low initial work rate and a brief duration of high-intensity exercise. The total test lasts about 10–12 minutes (29). Cycle ergometry is used in preference to treadmill as the exercise mode, as it allows accurate determination of the external work-load and requires less skill (31). Early preoperative CPET studies employed submaximal incremental tests because of safety concerns. These concerns have been allayed such that maximal tests to the limit of tolerance are now routinely used (11).

Two variables are used to describe exercise capacity (functional capacity) in perioperative CPET: the anaerobic threshold (AT) and peak oxygen uptake ($\dot{V}O_2$peak).

The Anaerobic Threshold

The AT is a widely used measure of submaximal or sustainable exercise capacity. It is defined as the oxygen uptake during incremental exercise above which arterial lactate begins to rise in a sustained manner above resting levels (32). This reflects an increasing contribution of glycolysis (anaerobic metabolism) to overall metabolism (33). The rise in lactate results from its synthesis via glycolysis exceeding its clearance rate, causing an associated metabolic acidosis (34). The cause of this imbalance remains controversial (35). It occurs at lower exercise intensity in the presence of oxygen supply limitation (35–39). The anaerobic threshold is one of several terms used to describe this threshold behavior. Other terms include lactate threshold, lactic acidosis threshold, ventilatory threshold, and gas exchange threshold (7). Anaerobic threshold is the preferred term in the perioperative literature.

The anaerobic threshold is conventionally estimated noninvasively, using the rapid incremental exercise test, with well-established criteria (7, 9, 18, 40). The key trigger is the generation of an "excess" carbon dioxide load at the anaerobic threshold consequent to buffering of the metabolic acidosis by intramuscular bicarbonate. This results in characteristic changes readily detected by graphical analysis (*see* Figure 1).

Anaerobic threshold criterion 1 (Figure 1, panel 1): "Excess" $\dot{V}CO_2$ above the anaerobic threshold identified by the V-slope methods. The increased ratio of glycolysis to oxidative phosphorylation above the anaerobic threshold causes

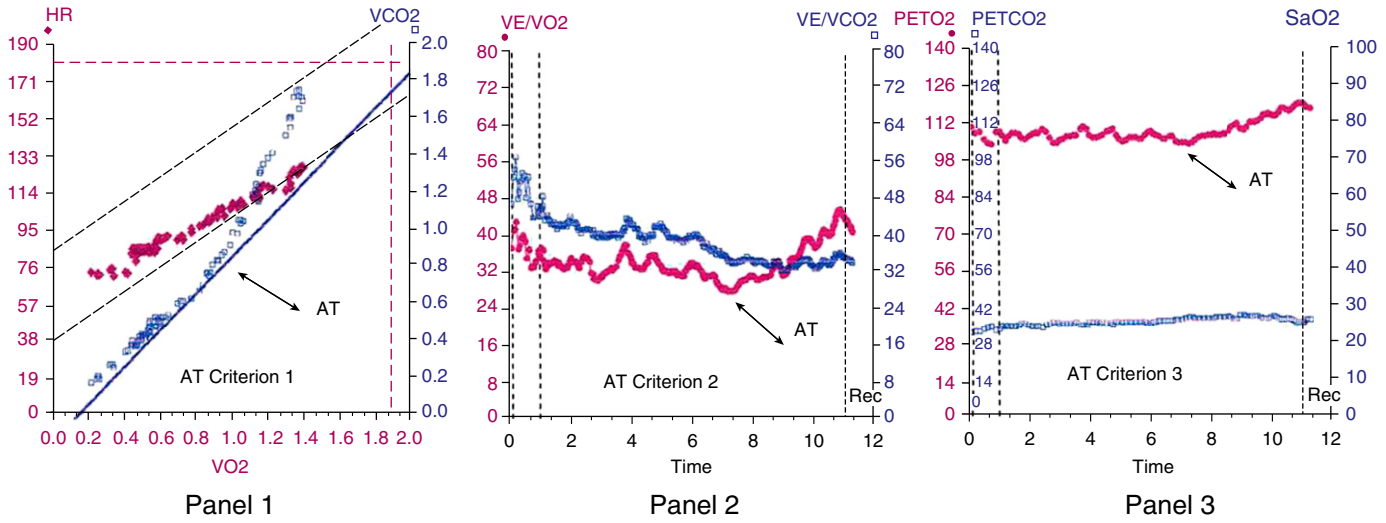

Figure 1. The anaerobic threshold (AT) derived and confirmed from differing data. *Panel 1:* Criterion 1, showing the AT determined by the inflection point in the $\dot{V}O_2/\dot{V}CO_2$ slope (the modified V slope) (*blue points*). The *sloped parallel dashed lines* show the range of normal heart rate response. *Panel 2:* Criterion 2/3, showing the AT confirmed at the nadir of the $\dot{V}E/\dot{V}O_2$ slope. Absence of rise in $\dot{V}E/\dot{V}CO_2$ at this point excludes hyperventilation relative to carbon dioxide. *Panel 3:* Criterion 2/3, showing the AT confirmed at the point where the partial pressure of end-tidal oxygen slope rises. Absence of fall in the partial pressure of end-tidal carbon dioxide excludes hyperventilation relative to carbon dioxide. In *panels 2* and *3*, the *vertical dashed lines* show the onset and completion of exercise. HR = heart rate; P_{ETCO_2} = end-tidal carbon dioxide tension; P_{ETO_2} = end-tidal oxygen tension; Rec = recovery; Sa_{O_2} = arterial oxygen saturation; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; $\dot{V}E/\dot{V}O_2$ = ventilatory equivalent for oxygen; $\dot{V}O_2$ = oxygen uptake.

pulmonary carbon dioxide output ($\dot{V}CO_2$) to increase at a greater rate than pulmonary oxygen uptake ($\dot{V}O_2$). This is identified as an inflection point in the carbon dioxide output–oxygen uptake relationship. The inflection point is identified as the breakpoint in the $\dot{V}CO_2$–$\dot{V}O_2$ response from a line with a gradient of one (modified V slope) or as the intersection of two linear regressions of the two linear portions of the $\dot{V}CO_2$–$\dot{V}O_2$ response (V slope) (40).

Anaerobic threshold criterion 2 (Figure 1, panels 2 and 3): Hyperventilation relative to oxygen: the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and end-tidal oxygen response. At the anaerobic threshold, the excess $\dot{V}CO_2$ generated from anaerobic glycolysis results in a proportional increase in expired minute volume ($\dot{V}E$). There is no equivalent increase in oxygen uptake at this point. As a consequence, there is hyperventilation relative to oxygen uptake. This is visualized by two criteria:

- Figure 1, panel 2: The $\dot{V}E/\dot{V}O_2$ time relationship, having been flat or decreasing, begins to increase and does not return to baseline.
- Figure 1, panel 3: The end-tidal oxygen tension (P_{ETO_2})–$\dot{V}O_2$ relationship, having been declining or flat, begins to increase and does not return to baseline.

Anaerobic threshold criterion 3 (Figure 1, panels 2 and 3): There is no hyperventilation relative to carbon dioxide. Ventilation during exercise is closely linked to carbon dioxide output. Ventilation increases sufficiently with the excess carbon dioxide above the anaerobic threshold to maintain arterial and end-tidal partial pressure for carbon dioxide (Figure 1, panel 3) and the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) (Figure 1, panel 2) at preanaerobic threshold levels. Consequently, the hyperventilation relative to oxygen identified in criterion 2 above, should not be accompanied by hyperventilation relative to carbon dioxide.

Thus, at the anaerobic threshold inflection point identified by criteria 1 and 2 above:

- The $\dot{V}E/\dot{V}CO_2$ should remain constant or continue to decrease at the point where $\dot{V}E/\dot{V}O_2$ starts to rise (at the AT).
- There is no reciprocal decrease in partial pressure of end-tidal carbon dioxide as the partial pressure of end-tidal oxygen rises at the anaerobic threshold.

The anaerobic threshold is an objective variable that is either detectable or not. If present, it cannot be volitionally altered by the patient. However, there is some interrater variability in identifying the anaerobic threshold from the CPET results and it cannot be determined in all patients (41). Importantly, in more than 30 case cohort studies it predicts postoperative outcomes in a wide range of surgical specialties with more precision than other CPET variables (6).

Peak Oxygen Uptake

$\dot{V}O_2$peak is defined as the highest oxygen uptake attained during a rapid incremental exercise test. $\dot{V}O_2$peak can be influenced by volitional effort and consequently may not reflect the physiological maximum for the patient. Despite this, it has considerable clinical usefulness for predicting outcome in a variety of clinical cohorts (7, 9). $\dot{V}O_2$peak should not be confused with the maximum oxygen uptake ($\dot{V}O_2$max), which is the highest oxygen uptake achievable by the subject. $\dot{V}O_2$max is defined as the metabolic rate at which oxygen uptake plateaus despite further increases in work rate (42). $\dot{V}O_2$max is consequently a physiological maximum end point. However, not all subjects will achieve a plateau in $\dot{V}O_2$ during CPET, which limits its clinical usefulness (7, 43).

In the perioperative context, $\dot{V}O_2$peak has been shown to predict postoperative complications and mortality in the majority

of cohorts in major abdominal surgery and thoracic surgery (6, 44–46).

Ventilatory Equivalent for Carbon Dioxide

The ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) is a measure of the efficiency of gas exchange. It reflects ventilation–perfusion matching and physiological dead space. In some, but not all general surgical cohorts, $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold predicts all domains of postoperative morbidity and mortality (Table 1) (47, 48). Likewise, in thoracic surgery the $\dot{V}E/\dot{V}CO_2$ slope predicts postoperative morbidity and mortality after lung resection (49). In some cohorts $\dot{V}E/\dot{V}CO_2$ predicts postoperative pulmonary complications in particular. It may be that the reduced gas exchange efficiency indicated by the high $\dot{V}E/\dot{V}CO_2$ results in less tolerance of postoperative atelectasis or hypoventilation and thereby increased susceptibility to pulmonary complications.

Risk Stratification and Perioperative Triage

Perioperative CPET is used to quantify perioperative risks, thereby guiding the decision to operate and the process of consent. The data are also used to triage high-risk patients to enhanced care environments (25).

The first publication related to the use of CPET for the evaluation of general surgical patients was in 1993 (30). Subsequently, more than 35 cohort studies have confirmed the association between CPET variables and surgical outcome in general surgical patients. These have been synthesized in a systematic review and are summarized in Table 1 (6).

In the majority of studies both anaerobic threshold and $\dot{V}O_2$peak were associated with outcome. Abnormal $\dot{V}E/\dot{V}CO_2$ reflecting increased dead space was also associated with both mortality and morbidity in some case series (47, 48, 50), but not in others (51, 52).

In the seminal study by Older, Smith, and colleagues, a threshold value for the anaerobic threshold of 11 ml/kg/min was selected to identify high-risk patients based on criteria used for the diagnosis of heart failure (30). In a follow-on prospective study, patients were triaged to ward-based or intensive care on the basis of their anaerobic threshold, with a reduction in cardiac mortality (25). Subsequently, area under the receiver operating curve analysis has been used to identify risk thresholds in a variety of surgical cohorts. The majority of more recent studies have reported a lower anaerobic threshold of 9–10 ml/kg/min to identify a high-risk group (Table 1). This probably reflects a combination of different patient populations, changes in surgical technique, and improvements in perioperative care. Laparoscopic surgery will result in a reduced surgical stress response (53). Certainly some types of surgery present a greater physiological challenge than others (esophagectomy vs. laparoscopic colectomy). Different processes of care may also affect risk thresholds—some patients are routinely admitted to a critical care environment postoperatively (e.g., esophagectomy, liver resection). Others are routinely cared for on general wards (e.g., colorectal surgery). Perioperative care in a critical care environment may compensate for a reduced physiological reserve (54). Further studies are required to explore this variability and to improve the precision of perioperative risk prediction. In particular, large multicenter cohorts are required.

Risk thresholds have been expressed as metabolic rates indexed to body weight for both anaerobic threshold and $\dot{V}O_2$peak. There are problems associated with this approach at the extremes of weight, with the possibility of overestimating risk in obese patients or underestimating risk in cachectic patients. Two case series in bariatric patients before bariatric surgery have suggested that anaerobic threshold and $\dot{V}O_2$peak indexed to body weight do have predictive usefulness in morbidly obese patients (55). Furthermore, the thresholds for identifying a group at high risk of postoperative complications were similar to other case cohorts (11 ml/min/kg for anaerobic threshold and 16 ml/min/kg for $\dot{V}O_2$peak). In patients with a low body mass index (BMI), body weight should be considered when interpreting the risk implications of the CPET data. Further case series are needed in low- and high-BMI subject to identify the most appropriate index for oxygen uptake and to identify appropriate risk thresholds.

An advantage of CPET as a risk stratification tool is that it predicts postoperative complications in a variety of clinical domains, rather than predicting a single type of complication. The Postoperative Morbidity Survey has been used to characterize complications in several case cohorts in a variety of surgical specialties (*see* Table 1 for details) (51, 56). This survey evaluates morbidity in seven domains, including the following: cardiac, pulmonary, gastrointestinal, renal, infection, hematological, and neurological. Functional capacity has been shown to predict morbidity in the majority of domains, not just cardiac or pulmonary complications (51). Furthermore, anaerobic threshold can predict traditionally surgical complications, such as the incidence of pancreatic leak in patients postpancreatoduodenectomy (57). In this case series an anaerobic threshold below 10.1 ml/min/kg identified a group at high risk for a pancreatic leak postoperatively, with greater precision than bilirubin levels, BMI, and pancreatic duct size.

Risk Assessment of Patients with Lung Cancer

CPET also has usefulness in the preoperative evaluation of patients with lung cancer and is included in several international guidelines (32, 45, 46, 58). There is ongoing debate about the best method of selecting patients to test, for example, on the basis of lung function test results (<80% of predicted FEV_1 or diffusing capacity of the lung for carbon monoxide) (45) or on the basis of cardiac risk or the risk of postoperative dyspnea (58). $\dot{V}O_2$peak is the variable that has been used most widely to define a high-risk surgical group. Patients with a $\dot{V}O_2$peak greater than 20 ml/kg/min are at low risk of complications and mortality (59, 60). In contrast, those with a $\dot{V}O_2$peak below 10 ml/kg/min are at high risk of postoperative morbidity and mortality (an 8- and 13-fold increased risk, respectively, in comparison with the low-risk group in one case series) (44, 45). It has been suggested that if surgery is proposed in such patients, they should be considered for pulmonary rehabilitation preoperatively and managed in a high-care setting perioperatively (61). Patients with a $\dot{V}O_2$peak of 10–15 ml/min/kg represent an intermediate-risk group (62, 63).

More recently, the ventilatory efficiency curve or the gradient of the ratio of ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$) has been proposed as a better

Table 1. Published articles showing cardiopulmonary exercise testing performed before specified surgery*

Author, Year, Journal (Ref.)	Patients	n	AT Association and Risk Threshold (*ml/kg/min*)	$\dot{V}O_2$ Peak Association and Risk Threshold (*ml/kg/min*)	$\dot{V}E/\dot{V}CO_2$	Outcome
			Major Intraabdominal Surgery			
Older, 1993, *Chest* (30)	Major intraabdominal	187	Y < 11	Submaximal tests not measured	Y	CVS mortality
Older, 1999, *Chest* (25)	Major intraabdominal	548	Y < 11	Submaximal tests not measured	Y	Mortality
Wilson, 2010, *Br J Anaesth* (47)	Major intraabdominal	847	Y < 10.9	Submaximal tests not measured	>34	Mortality
Snowden, 2010, *Ann Surg* (51)	Major intraabdominal	116	Y < 10.1	Y	N	Morbidity, D7 POMS
Hightower, 2010, *Br J Anaesth* (73)	Major intraabdominal	32	Y	N	N	Morbidity, self-defined
James, 2014, *Br J Anaesth* (100)	Major intraabdominal	83	Y			Major adverse cardiac events, morbidity
Colson, 2012, *Br J Anaesth* (74)	Major thoracoabdominal surgery	1,725	N	N		Mortality, 5 yr
			Colorectal Surgery			
Lai, 2013, *Br J Anaesth* (75)	Colorectal surgery	269	Y < 11, no CPET or no AT			Mortality, 2 yr; LOS
West, 2014, *Br J Anaesth* (76)	Colon resections	136	Y < 10.1	Y < 16.7	Y	Morbidity, D5 POMS, Clavien–Dindo
West, 2014, *Br J Surg* (77)	Rectal resections	105	Y < 10.6	Y < 18.6	—	Morbidity, D5 POMS, Clavien–Dindo
			Abdominal Aortic Aneurysm Surgery			
Nugent, 1998, *Ir J Med Sci* (78)	AAA	30	N	N < 20 increased morbidity	—	Mortality
Hartley, 2012, *Br J Surg* (79)	AAA	415	Y < 10.2	Y < 15	Y	Mortality
Prentis, 2012, *J Vasc Surg* (80)	AAA (84 open 101 EVAR)	185	Y < 10	Y	—	Morbidity, self-defined; ICU LOS, LOS
Goodyear, 2013, *Perioper Med* (*Lond*) (81)	AAA	188	Y < 11	—	—	Mortality, LOS, cost
Carlisle, 2007, *Br J Surg* (50)	AAA	130	Y	Y	Y > 42	Mortality, midterm
Grant, 2015, *Br J Anaesth* (82)	AAA	506	Y < 10.2	Y < 15	Y	Mortality, 3 yr: 86.4% cf. 59.9% for high-risk
			Hepatobiliary Surgery			
Snowden, 2013, *Ann Surg* (83)	Major hepatobiliary	389	Y	Y	Y	Mortality, LOS
Junejo, 2012, *Br J Surg* (48)	Hepatic resection	108	Y < 9.9	Y	Y > 35	Mortality, morbidity, POMS, Clavien–Dindo
Kaibori, 2013, *BMC Gastroenterol* (84)	Hepatectomy	61	Y < 11.5			Mortality, morbidity, Clavien–Dindo
Dunne, 2014, *J Surg Oncol* (85)	Liver surgery	197	N	N	N	Morbidity, Clavien–Dindo
Ausania, 2012, *Br J Surg* (57)	Whipples	124	Y < 10.1	Y	Y	Morbidity, POMS, pancreatic leak
Ausania, 2012, *Ann R Coll Surg Engl* (101)	Pancreatic (palliative double bypass)	50	N			Morbidity, 50%; POMS
Chandrabalan, 2013, *HPB* (*Oxford*) (86)	Pancreatic surgery	100	Y < 10			Postoperative pancreatic leak, LOS, Clavien–Dindo
Junejo, 2014, *Ann Surg Oncol* (87)	Pancreaticoduodenectomy	64	N	N	Y > 41	Mortality, self-defined
Prentis, 2012, *Liver Transpl* (88)	Liver transplant	60	Y < 9			Mortality, 90 d
Epstein, 2004, *Liver Transpl* (89)	Liver transplant	59	Y	Y		Mortality
Bernal, 2014, *Liver Transpl* (90)	Liver transplant	223	Y	Y		Mortality

(Continued)

Table 1. (*Continued*)

Author, Year, Journal (Ref.)	Patients	n	AT Association and Risk Threshold (*ml/kg/min*)	$\dot{V}O_2$ Peak Association and Risk Threshold (*ml/kg/min*)	$\dot{V}E/\dot{V}CO_2$	Outcome
Neviere, 2014, *Am J Transplant* (91)	Liver transplant	263	N	Y		Morbidity
			Upper Gastrointestinal Surgery			
Nagamatsu, 1994, *Nippon Kyobu Geka Gakkai Zasshi* (92)	Esophagectomy	52	Y	Y	—	Cardiopulmonary morbidity, self-defined
Nagamatsu, 2001, *J Thorac Cardiovasc Surg* (93)	Esophagectomy	91	Y	Y < 800	—	Cardiopulmonary morbidity, self-defined
Moyes, 2013, *Ann R Coll Surg* (94)	Upper GI	108	Y < 9, 42% complication vs. 29%	Y		Cardiopulmonary morbidity, common terminology criteria/self-defined
McCullough, 2006, *Chest* (52)	Bariatric	109	Y	Y < 15.6	N	Morbidity, self-defined; mortality composite
Hennis, 2012, *Br J Anaesth* (55)	Bariatric	106	Y < 11	Y	Y	Morbidity, POMS D5
			Urological Surgery			
Prentis, 2013, *BJU Int* (95)	Radical cystectomy	82	Y < 12	Y	—	Morbidity, LOS, Clavien–Dindo
Ting, 2013, *J Am Soc Nephrol* (96)	Kidney transplant	70	Y < 40% predicted			Mortality
Tolchard, 2015, *BJU Int* (97)	Radical cystectomy	105	Y < 11		Y > 33	Clavien–Dindo, high-risk 5.5× more likely complications; increased LOS; heart failure significant cause of death
Ulubay, 2010, *Ann Transplant* (98)	Renal and cardiac transplant	16	Y		Y	Heart transplant had lower AT and raised $\dot{V}E/\dot{V}CO_2$
			Thoracic Surgery			
Brunelli, 2012, *Ann Thorac Surg* (49)	Pulmonary resection	225	N	Y	Y	$\dot{V}E/\dot{V}CO_2$ slope better predictor of pulmonary complications
Brutsche, 2000, *Eur Respir J* (60)	Non–small cell lung cancer resection	125	N	Y	Y	Maximal oxygen uptake was predictor of postoperative complications
Benzo, 2007, *Respir Med* (44)	Meta-analysis of lung resection cancer patients	955	N	Y	N	$\dot{V}O_2$max (?peak) predictor of postoperative complications
Bolliger, 1995, *Am J Respir Crit Care Med* (62)	Lung resection (not all carcinoma)	80	N	Y	N	$\dot{V}O_2$max (?peak) predictor of postoperative complications
Win, 2005, *Chest* (63)	Non–small cell lung cancer resection	101	N	Y	N	Percentage of predicted $\dot{V}O_2$peak better indicator of surgical outcome

Definition of abbreviations: AAA = abdominal aortic aneurysm; AT = anaerobic threshold; Clavien–Dindo = standardized postoperative morbidity index covering all domains of morbidity (99); CPET = cardiopulmonary exercise testing; CVS = cardiovascular; D5, D7 = Day 5, Day 7; EVAR = endovascular aneurysm repair; GI = gastrointestinal; ICU = intensive care unit; LOS = length of stay; N = no; POMS = Postoperative Morbidity Survey (a survey of postoperative complications covering eight domains [56]); $\dot{V}CO_2$ = pulmonary carbon dioxide output; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = pulmonary oxygen uptake; Y = yes.

*A list of published articles with cardiopulmonary exercise testing performed before specified surgery is shown. Each article is referenced. It shows what variables were used in the determination of surgical risk. Column 4, anaerobic threshold; column 5, $\dot{V}O_2$peak; column 6, $\dot{V}E/\dot{V}CO_2$.

predictor of postoperative complications and death (49, 64, 65). A $\dot{V}E/\dot{V}CO_2$ gradient of more than 35 identifies a high-risk group. Further studies are required to clarify whether the risks of a low $\dot{V}O_2$peak and increased $\dot{V}E/\dot{V}CO_2$ are additive and how they should be incorporated into risk evaluation algorithms.

The advent of thoracoscopic surgery has introduced further uncertainty. Perioperative morbidity and mortality is lower in thoracoscopic surgery when

compared with open thoracotomy (66). To date, the relationship between exercise capacity and ventilatory efficiency and clinical outcomes in this cohort has not been extensively reported (67). The risk thresholds are consequently less certain for thoracoscopic surgery and multicenter prospective cohorts are required to clarify these.

Perioperative CPET for Collaborative Decision Making

The decision to proceed to surgery in an increasingly comorbid and elderly surgical population is complex. Multidisciplinary input from surgeons, physicians, intensivists, oncologists, geriatricians, and anesthetists is required to contribute to a truly collaborative decision. Such decisions should be made in partnership with the patient in a shared decision-making process (5). The data derived from CPET can contribute to this process by providing an individualized evaluation of comorbidities and perioperative risk.

Surgery for cancer, in particular, is now commonly part of a complex set of interventions (e.g., neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, immunotherapy). The interactions between these interventions are likely to alter the risk–benefit equation for each treatment element for each patient. Two studies have confirmed the adverse impact of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy on objectively measured physical fitness and subsequently on surgical outcome (68, 69). In patients with poor fitness at diagnosis, the benefits of neoadjuvant chemotherapy may be outweighed by the additional perioperative risks incurred from the associated reduction in physical fitness that this therapy can produce. Multidisciplinary teams will increasingly be needed to help assess the risks and benefits of the various treatment options for individual patients.

Perioperative CPET for Prehabilitation

CPET identifies a cohort of patients with reduced exercise capacity preoperatively who are at risk of a poor surgical outcome. Prehabilitation programs aim to improve fitness and thereby improve outcome in these high-risk patients. The advent of neoadjuvant therapies has opened up a time window to train patients before major cancer operations where previously the pressure of reducing the time between diagnosis and surgery precluded such an intervention. Preliminary data confirm the feasibility of this approach in intraabdominal surgical patients (4, 70).

High-intensity interval training programs individualized by objectively measured CPET variables have been successfully used to improve fitness (71). Supervised exercise training in elective aortic aneurysm patients has been demonstrated to improve outcome in a randomized clinical trial (72). There are currently more than 30 ongoing clinical trials involved with exercise in surgical patients registered with the clinical trials database (ClinicalTrials.gov, accessed July 1, 2017). Further studies are needed to improve understanding of the optimal type, intensity, and duration of preoperative exercise interventions.

Conclusions

Reduced aerobic fitness is associated with worse perioperative outcomes in all domains of morbidity and mortality. CPET provides a method of objectively evaluating fitness and thereby individually risk-stratifying patients. This information can be used to guide collaborative decision making, the choice of surgical procedure, and the perioperative care environment. There is a need for multicenter prospective cohort studies to improve the precision of risk estimates for various patient groups and to clarify the best combination of variables to predict outcome. Early data suggest that preoperative exercise training improves fitness and may improve clinical outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; 372:139–144.

2 Rose J, Weiser TG, Hider P, Wilson L, Gruen RL, Bickler SW. Estimated need for surgery worldwide based on prevalence of diseases: a modelling strategy for the WHO Global Health Estimate. *Lancet Glob Health* 2015;3:S13–S20.

3 Moonesinghe SR, Harris S, Mythen MG, Rowan KM, Haddad FS, Emberton M, Grocott MP. Survival after postoperative morbidity: a longitudinal observational cohort study. *Br J Anaesth* 2014;113: 977–984.

4 Levett DZ, Edwards M, Grocott M, Mythen M. Preparing the patient for surgery to improve outcomes. *Best Pract Res Clin Anaesthesiol* 2016;30:145–157.

5 Glance LG, Osler TM, Neuman MD. Redesigning surgical decision making for high-risk patients. *N Engl J Med* 2014;370:1379–1381.

6 Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *Br J Anaesth* 2016;116:177–191.

7 Wasserman K, Hansen C, Stringer W, Sietsema K, Sun C, Whipp B. Principles of exercise testing and interpretation. Philadelphia: Lippincott Williams & Wilkins; 2011.

8 Wasserman K. Diagnosing cardiovascular and lung pathophysiology from exercise gas exchange. *Chest* 1997; 112:1091–1101.

9 American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.

10 Wasserman K. Anerobic threshold. In: Mooren F, editor. Encyclopedia of exercise medicine in health and disease. Berlin: Springer-Verlag; 2011.

11 Levett DZ, Grocott MP. Cardiopulmonary exercise testing for risk prediction in major abdominal surgery. *Anesthesiol Clin* 2015; 33:1–16.

12 Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, *et al*. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014;64:e77–e137.

13 Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kerstein JR,

et al.; ACC/AHA Task Force Members. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2007;116:1971–1996.
14 Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MG, Poss R, Ho KKL, *et al*. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043–1049.
15 Hernandez AF, Whellan DJ, Stroud S, Sun JL, O'Connor CM, Jollis JG. Outcomes in heart failure patients after major noncardiac surgery. *J Am Coll Cardiol* 2004;44:1446–1453.
16 van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38 047 patients. *Circulation* 2011;124:289–296.
17 Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ; Participants in the VA National Surgical Quality Improvement Program, *et al*. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005;242:326–341; discussion 341–323.
18 Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease: use of the V-slope method for anaerobic threshold determination. *Chest* 1988;94:931–938.
19 Older P, Smith R. Experience with the preoperative invasive measurement of haemodynamic, respiratory and renal function in 100 elderly patients scheduled for major abdominal surgery. *Anaesth Intensive Care* 1988;16:389–395.
20 Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, Whipp BJ. Anaerobic (lactic acidosis) threshold. In: Exercise testing and interpretation, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 561.
21 Beaver WL, Wasserman K, Whipp BJ. Bicarbonate buffering of lactic acid generated during exercise. *J Appl Physiol* 1986;60:472–478.
22 Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. *Intensive Care Med* 1994;20:203–209.
23 Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna G, D'Eusanio G. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003;24:1304–1313.
24 Belardinelli R, Lacalaprice F, Tiano L, Mucai A, Perna GP. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. *Int J Cardiol* 2014;174:337–342.
25 Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest* 1999;116:355–362.
26 Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. *Circulation* 1997;96:517–525.
27 Struthers R, Erasmus P, Holmes K, Warman P, Collingwood A, Sneyd JR. Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle walk, and cardiopulmonary exercise testing in general surgical patients. *Br J Anaesth* 2008;101: 774–780.
28 ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. *Eur Respir J* 1997;10:2662–2689.
29 Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. *J Appl Physiol* 1981;50:217–221.
30 Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993;104:701–704.
31 Porszasz J, Casaburi R, Somfay A, Woodhouse LJ, Whipp BJ. A treadmill ramp protocol using simultaneous changes in speed and grade. *Med Sci Sports Exerc* 2003;35:1596–1603.
32 Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *Am J Cardiol* 1964; 14:844–852.
33 Wasserman K. The anaerobic threshold measurement in exercise testing. *Clin Chest Med* 1984;5:77–88.
34 Brooks GA. The lactate shuttle during exercise and recovery. *Med Sci Sports Exerc* 1986;18:360–368.
35 Whipp BJ, Ward SA. The physiological basis of the "anaerobic threshold" and implications for clinical cardiopulmonary exercise testing. *Anaesthesia* 2011;66:1048–1049, author reply 1049–1050.
36 Connett R, Sahlin K. Control of glycolysis and glycogen metabolism. New York: Oxford University Press; 1996.
37 Myers J, Ashley E. Dangerous curves: a perspective on exercise, lactate, and the anaerobic threshold. *Chest* 1997;111:787–795.
38 Lindinger M, Whipp BJ. The anaerobic threshold: fact or misinterpretation? In: Taylor N, Groeller H, editors. Physiological bases of human performance during work and exercise. London: Churchill Livingstone; 2008.
39 Clanton TL, Hogan MC, Gladden LB. Regulation of cellular gas exchange, oxygen sensing, and metabolic control. *Compr Physiol* 2013;3:1135–1190.
40 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60: 2020–2027.
41 Kothmann E, Danjoux G, Owen SJ, Parry A, Turley AJ, Batterham AM. Reliability of the anaerobic threshold in cardiopulmonary exercise testing of patients with abdominal aortic aneurysms. *Anaesthesia* 2009;64:9–13.
42 Hill AV. Muscular activity and carbohydrate metabolism. *Science* 1924;60:505–514.
43 Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:1451, author reply 1451.
44 Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: a meta-analysis. *Respir Med* 2007;101:1790–1797.
45 Brunelli A, Belardinelli R, Refai M, Salati M, Socci L, Pompili C, Sabbatini A. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest* 2009;135:1260–1267.
46 Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5 Suppl): e166S–e190S.
47 Wilson RJ, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010;105:297–303.
48 Junejo MA, Mason JM, Sheen AJ, Moore J, Foster P, Atkinson D, Parker MJ, Siriwardena AK. Cardiopulmonary exercise testing for preoperative risk assessment before hepatic resection. *Br J Surg* 2012;99:1097–1104.
49 Brunelli A, Belardinelli R, Pompili C, Xiumé F, Refai M, Salati M, Sabbatini A. Minute ventilation–to-carbon dioxide output ($\dot{V}_E/\dot{V}_{CO_2}$) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg* 2012;93: 1802–1806.
50 Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007;94:966–969.
51 Snowden CP, Prentis JM, Anderson HL, Roberts DR, Randles D, Renton M, Manas DM. Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Ann Surg* 2010;251: 535–541.
52 McCullough PA, Gallagher MJ, Dejong AT, Sandberg KR, Trivax JE, Alexander D, Kasturi G, Jafri SM, Krause KR, Chengelis DL, *et al*. Cardiorespiratory fitness and short-term complications after bariatric surgery. *Chest* 2006;130:517–525.

53 Buunen M, Gholghesaei M, Veldkamp R, Meijer DW, Bonjer HJ, Bouvy ND. Stress response to laparoscopic surgery: a review. *Surg Endosc* 2004;18:1022–1028.

54 Swart M, Carlisle JB. Case-controlled study of critical care or surgical ward care after elective open colorectal surgery. *Br J Surg* 2012;99: 295–299.

55 Hennis PJ, Meale PM, Hurst RA, O'Doherty AF, Otto J, Kuper M, Harper N, Sufi PA, Heath D, Montgomery HE, *et al*. Cardiopulmonary exercise testing predicts postoperative outcome in patients undergoing gastric bypass surgery. *Br J Anaesth* 2012;109:566–571.

56 Grocott MP, Browne JP, Van der Meulen J, Matejowsky C, Mutch M, Hamilton MA, Levett DZ, Emberton M, Haddad FS, Mythen MG. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol* 2007;60: 919–928.

57 Ausania F, Snowden CP, Prentis JM, Holmes LR, Jaques BC, White SA, French JJ, Manas DM, Charnley RM. Effects of low cardiopulmonary reserve on pancreatic leak following pancreaticoduodenectomy. *Br J Surg* 2012;99:1290–1294.

58 Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, Kerr K, Macfie A, McGuigan J, Padley S, *et al*.; British Thoracic Society; Society for Cardiothoracic Surgery in Great Britain and Ireland. Guidelines on the radical management of patients with lung cancer. *Thorax* 2010;65:iii1–iii27.

59 Kozower BD, Sheng S, O'Brien SM, Liptay MJ, Lau CL, Jones DR, Shahian DM, Wright CD. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. *Ann Thorac Surg* 2010;90:875–881; discussion 881–873.

60 Brutsche MH, Spiliopoulos A, Bolliger CT, Licker M, Frey JG, Tschopp JM. Exercise capacity and extent of resection as predictors of surgical risk in lung cancer. *Eur Respir J* 2000;15:828–832.

61 Brunelli A. Risk assessment for pulmonary resection. *Semin Thorac Cardiovasc Surg* 2010;22:2–13.

62 Bolliger CT, Jordan P, Solèr M, Stulz P, Grädel E, Skarvan K, Elsasser S, Gonon M, Wyser C, Tamm M, *et al*. Exercise capacity as a predictor of postoperative complications in lung resection candidates. *Am J Respir Crit Care Med* 1995;151:1472–1480.

63 Win T, Jackson A, Sharples L, Groves AM, Wells FC, Ritchie AJ, Laroche CM. Cardiopulmonary exercise tests and lung cancer surgical outcome. *Chest* 2005;127:1159–1165.

64 Torchio R, Guglielmo M, Giardino R, Ardissone F, Ciacco C, Gulotta C, Veljkovic A, Bugiani M. Exercise ventilatory inefficiency and mortality in patients with chronic obstructive pulmonary disease undergoing surgery for non–small-cell lung cancer. *Eur J Cardiothorac Surg* 2010; 38:14–19.

65 Shafiek H, Valera JL, Togores B, Torrecilla JA, Sauleda J, Cosio BG. Risk of postoperative complications in chronic obstructive lung diseases patients considered fit for lung cancer surgery: beyond oxygen consumption. *Eur J Cardiothorac Surg* 2016;50:772–779.

66 Falcoz PE, Puyraveau M, Thomas PA, Decaluwe H, Hürtgen M, Petersen RH, Hansen H, Brunelli A; ESTS Database Committee and ESTS Minimally Invasive Interest Group. Video-assisted thoracoscopic surgery versus open lobectomy for primary non–small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg* 2016;49:602–609.

67 Begum SS, Papagiannopoulos K, Falcoz PE, Decaluwe H, Salati M, Brunelli A. Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO_2 max: a case-matched analysis from the ESTS database. *Eur J Cardiothorac Surg* 2016;49:1054–1058, discussion 1058.

68 West MA, Loughney L, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients. *Eur J Surg Oncol* 2014;40:1421–1428.

69 Jack S, West MA, Raw D, Marwood S, Ambler G, Cope TM, Shrotri M, Sturgess RP, Calverley PM, Ottensmeier CH, *et al*. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. *Eur J Surg Oncol* 2014;40:1313–1320.

70 Moran J, Guinan E, McCormick P, Larkin J, Mockler D, Hussey J, Moriarty J, Wilson F. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: a systematic review and meta-analysis. *Surgery* 2016;160: 1189–1201.

71 West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth* 2015;114:244–251.

72 Barakat HM, Shahin Y, Khan JA, McCollum PT, Chetter IC. Preoperative supervised exercise improves outcomes after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Ann Surg* 2016;264:47–53.

73 Hightower CE, Riedel BJ, Feig BW, Morris GS, Ensor JE Jr, Woodruff VD, Daley-Norman MD, Sun XG. A pilot study evaluating predictors of postoperative outcomes after major abdominal surgery: physiological capacity compared with the ASA physical status classification system. *Br J Anaesth* 2010;104:465–471.

74 Colson M, Baglin J, Bolsin S, Grocott MP. Cardiopulmonary exercise testing predicts 5 yr survival after major surgery. *Br J Anaesth* 2012; 109:735–741.

75 Lai CW, Minto G, Challand CP, Hosie KB, Sneyd JR, Creanor S, Struthers RA. Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. *Br J Anaesth* 2013;111:607–611.

76 West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S, Grocott MP. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. *Br J Anaesth* 2014;112: 665–671.

77 West MA, Parry MG, Lythgoe D, Barben CP, Kemp GJ, Grocott MP, Jack S. Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. *Br J Surg* 2014;101: 1166–1172.

78 Nugent AM, Riley M, Megarry J, O'Reilly MJ, MacMahon J, Lowry R. Cardiopulmonary exercise testing in the pre-operative assessment of patients for repair of abdominal aortic aneurysm. *Ir J Med Sci* 1998;167:238–241.

79 Hartley RA, Pichel AC, Grant SW, Hickey GL, Lancaster PS, Wisely NA, McCollum CN, Atkinson D. Preoperative cardiopulmonary exercise testing and risk of early mortality following abdominal aortic aneurysm repair. *Br J Surg* 2012;99:1539–1546.

80 Prentis JM, Trenell MI, Jones DJ, Lees T, Clarke M, Snowden CP. Submaximal exercise testing predicts perioperative hospitalization after aortic aneurysm repair. *J Vasc Surg* 2012;56:1564–1570.

81 Goodyear SJ, Yow H, Saedon M, Shakespeare J, Hill CE, Watson D, Marshall C, Mahmood A, Higman D, Imray CH. Risk stratification by pre-operative cardiopulmonary exercise testing improves outcomes following elective abdominal aortic aneurysm surgery: a cohort study. *Perioper Med* (*Lond*) 2013;2:10.

82 Grant SW, Hickey GL, Wisely NA, Carlson ED, Hartley RA, Pichel AC, Atkinson D, McCollum CN. Cardiopulmonary exercise testing and survival after elective abdominal aortic aneurysm repair. *Br J Anaesth* 2015;114:430–436.

83 Snowden CP, Prentis J, Jacques B, Anderson H, Manas D, Jones D, Trenell M. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Ann Surg* 2013;257:999–1004.

84 Kaibori M, Ishizaki M, Matsui K, Nakatake R, Sakaguchi T, Habu D, Yoshiuchi S, Kimura Y, Kon AH. Assessment of preoperative exercise capacity in hepatocellular carcinoma patients with chronic liver injury undergoing hepatectomy. *BMC Gastroenterol* 2013;13:119.

85 Dunne DF, Jones RP, Lythgoe DT, Pilkington FJ, Palmer DH, Malik HZ, Poston GJ, Lacasia C, Jack S, Fenwick SW. Cardiopulmonary exercise testing before liver surgery. *J Surg Oncol* 2014;110: 439–444.

86 Chandrabalan VV, McMillan DC, Carter R, Kinsella J, McKay CJ, Carter CR, Dickson EJ. Pre-operative cardiopulmonary exercise testing predicts adverse post-operative events and

non-progression to adjuvant therapy after major pancreatic surgery. *HPB* (*Oxford*) 2013;15:899–907.
87 Junejo MA, Mason JM, Sheen AJ, Bryan A, Moore J, Foster P, Atkinson D, Parker MJ, Siriwardena AK. Cardiopulmonary exercise testing for preoperative risk assessment before pancreaticoduodenectomy for cancer. *Ann Surg Oncol* 2014;21:1929–1936.
88 Prentis JM, Manas DM, Trenell MI, Hudson M, Jones DJ, Snowden CP. Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation. *Liver Transpl* 2012;18:152–159.
89 Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transpl* 2004;10:418–424.
90 Bernal W, Martin-Mateos R, Lipcsey M, Tallis C, Woodsford K, McPhail MJ, Willars C, Auzinger G, Sizer E, Heneghan M, *et al*. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. *Liver Transpl* 2014;20:54–62.
91 Neviere R, Edme JL, Montaigne D, Boleslawski E, Pruvot FR, Dharancy S. Prognostic implications of preoperative aerobic capacity and exercise oscillatory ventilation after liver transplantation. *Am J Transplant* 2014;14:88–95.
92 Nagamatsu Y, Yamana H, Fujita H, Hiraki H, Matsuo T, Mitsuoka M, Hayashi A, Kakegawa T. The simultaneous evaluation of preoperative cardiopulmonary functions of esophageal cancer patients in the analysis of expired gas with exercise testing [article in Japanese]. *Nippon Kyobu Geka Gakkai Zasshi* 1994;42: 2037–2040.
93 Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. *J Thorac Cardiovasc Surg* 2001;121:1064–1068.
94 Moyes LH, McCaffer CJ, Carter RC, Fullarton GM, Mackay CK, Forshaw MJ. Cardiopulmonary exercise testing as a predictor of complications in oesophagogastric cancer surgery. *Ann R Coll Surg Engl* 2013;95:125–130.
95 Prentis JM, Trenell MI, Vasdev N, French R, Dines G, Thorpe A, Snowden CP. Impaired cardiopulmonary reserve in an elderly population is related to postoperative morbidity and length of hospital stay after radical cystectomy. *BJU Int* 2013;112: E13–E19.
96 Ting SM, Iqbal H, Kanji H, Hamborg T, Aldridge N, Krishnan N, Imray CH, Banerjee P, Bland R, Higgins R, *et al*. Functional cardiovascular reserve predicts survival pre-kidney and post-kidney transplantation. *J Am Soc Nephrol* 2014;25:187–195.
97 Tolchard S, Angell J, Pyke M, Lewis S, Dodds N, Darweish A, White P, Gillatt D. Cardiopulmonary reserve as determined by cardiopulmonary exercise testing correlates with length of stay and predicts complications after radical cystectomy. *BJU Int* 2015;115: 554–561.
98 Ulubay G, Ulasli S, Kupeli E, Yilmaz E, Sezgin A, Haberal M. Value of exercise testing to estimate post-operative complications and mortality in solid organ recipients: a preliminary study. *Ann Transplant* 2010;15:11–20.
99 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, *et al*. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187–196.
100 James S, Jhanji S, Smith A, O'Brien G, Fitzgibbon M, Pearse RM. Comparison of the prognostic accuracy of scoring systems, cardiopulmonary exercise testing, and plasma biomarkers: a single-centre observational pilot study. *Br J Anaesth* 2014;112:491–497.
101 Ausania F, Vallance AE, Manas DM, Prentis JM, Snowden CP, White SA, Charnley RM, French JJ, Jaques BC. Double bypass for inoperable pancreatic malignancy at laparotomy: postoperative complications and long-term outcome. *Ann R Coll Surg Engl* 2012; 94:563–568.