The Clinical Utility of Cardiopulmonary Exercise Testing

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GLOSSARY

AT – Anaerobic threshold, the point at which oxygen delivery to exercising muscle can no longer meet demands and lactic acid begins to accumulate

VO2 – oxygen consumption per minute, expressed in L/min and mL/kg/min

$VO2_{peak}$ – Highest VO2 obtained during an exercise test. If a further increase in workload does not lead to further increase in VO2, i.e. there is a plateau in VO2, this is referred to as **$VO2_{max}$**.

$VO2_{reserve}$ – Difference between resting VO2 and VO2max.

VCO2 – Carbon dioxide production, L/min

VE – Minute ventilation, L/min

VE/VCO2 – Ratio of minute ventilation to CO2 production (how much one is breathing to ventilate off a given amount of CO2), a measure of ventilatory efficiency

INTRODUCTION

Cardiopulmonary exercise testing (CPET) can be conducted in several ways, but most commonly is performed as a progressive incremental exercise test that concludes at exhaustion at maximal exercise capacity. For several reasons, the most important being safety, the test generally is done utilizing a cycle ergometer that has the ability to ramp the work rate over time. During the exam, the patient has extensive safety monitoring – including continuous electrocardiogram (ECG), pulse oximetry, and frequent blood pressure recordings. A physician typically is in attendance for the duration of the test. Additionally, the patient has all inhaled and exhaled gas analyzed – with the ability to determine oxygen consumption (VO2), carbon dioxide elimination (VCO2), tidal volumes, and respiratory flow curves. Before and directly after the test serial spirometry is performed to assess baseline pulmonary function and assess for exercise-induced airway disorders, respectively. See **Figure 1** for typical CPET laboratory set-up and equipment.

Figure 1. Typical CPET laboratory set-up using a cycle ergometer. The monitoring equipment includes continuous ECG, pulse oximetry, sphygmomanometer, flow sensor, and gas analyzer (interface can either be facemask or mouthpiece/noseclip). Also, the equipment has the ability to perform standalone spirometry.

It is well known that static measures of pulmonary and cardiac function (such as pulmonary function testing (PFT) and echocardiography) do not always relate well to dynamic measures during exertion.[1] While other modalities of stress testing are well-suited for a limited evaluation (e.g. a cardiac stress test for ischemia), the extensive cardiopulmonary data obtained by CPET has the potential to determine the overriding factor or system limiting maximal exercise (e.g. cardiac, ventilatory, systemic vascular, mitochondrial, deconditioning or psychological). Further, given that it does not have artificial test stopping points (e.g. HR endpoints), a full evaluation of the cardiopulmonary system can be obtained. Many of performance measures that are obtained during the test are able to be reported as percent predicted using published equations – such as $VO2_{peak}$, work rate, and certain ventilation parameters.

While overwhelmingly the most common indication for CPET is unexplained dyspnea on exertion, this review will examine the evidence supporting other valuable uses for CPET, including in heart failure, evaluation for cardiac transplant, and preoperative evaluation (**Table 1**).

Table 1. Indications for CPET referral. Adapted from ATS/ACCP Statement, 2001[4]

Disease state	Indication
Dyspnea on Exertion	Unexplained dyspnea
Congestive Heart Failure	Guide transplant referral Prognostication Response to medical therapy
Pre-operative, general surgery	Predictive of post-operative complications and mortality Guide post-operative level of care Inform shared decision making
Pre-operative, lung resection	Identify those who will tolerate resection
Lung volume reduction surgery (LVRS)	Identify those most likely to benefit from LVRS Measure functional improvement post-operative
Asthma	Identification of exercise-induced bronchospasm Identification of non-ventilatory exercise limitation
Cystic Fibrosis	Prognostication
COPD	Identification of non-ventilatory exercise limitation Early identification of group 3 pulmonary hypertension
Pulmonary Hypertension	Identify Etiology Prognostication Evaluate response to treatment
Rehabilitation	Determine safety pre-rehabilitation Determine precise rehabilitation prescription Evaluate response to rehabilitation

DYSPNEA EVALUATION

The most common indication for CPET is unexplained dyspnea or dyspnea out of proportion to disease severity demonstrated on other testing. Unexplained dyspnea or exercise intolerance is considered a Class I indication for CPET referral.[2] Unexplained dyspnea is largely divided into two categories – patients with no obvious cause on routine testing and patients with multiple potential causes. It is most often the case that patients are referred for CPET after they have had a fairly significant evaluation that has been unrevealing – including PFTs, radiographic imaging, echocardiography, and/or cardiac stress testing. Common etiologies of symptoms that may be suggested through CPET include limits on ventilation, exercise-induced bronchoconstriction, cardiac ischemia, heart failure, pulmonary hypertension, and peripheral vascular disease. Additionally, CPET can potentially identify non-cardiopulmonary limitations such as pathologic breathing patterns, obesity, and deconditioning.[3] Assuming a maximal test is performed, the comprehensive nature of a CPET can provide reassurance to a patient and potentially limit further diagnostic testing. Likewise, when a defined etiology of exercise limitation is identified, CPET can guide further therapy and investigations – or help determine which system warrants further therapeutic attention or testing in a patient with several known conditions.[4]

CPET also can be helpful in the evaluation of disability due to exertional symptoms. Often, job-related or exertional complaints are out of proportion to routine testing results used for disability determination (such as PFTs or echocardiography), making it difficult for such patients to receive compensation.[5] Maximal CPET can provide an objective measure of work capacity and possesses the ability to differentiate poor volitional effort from a true physiologic impairment – and may be helpful in select workman's compensation cases.1

CONGESTIVE HEART FAILURE

Outside of the evaluation of dyspnea, CPET has been studied most robustly in the realm of congestive heart failure. There are several roles for comprehensive exercise testing in therapeutic management of heart failure with or without reduced ejection fraction, including prognostication and evaluation for transplant.

CPET has been studied extensively in the evaluation for eligibility for cardiac transplantation. Using CPET to evaluate patients prior to transplant is considered a class IA indication[2], with $VO2_{peak}$ being the variable most often utilized. In one prospective study of patients referred for cardiac transplant, $VO2_{peak}$ of 14cc/kg/minute was used as a cut-off for transplant surgery. Those who were referred for cardiac transplant with $VO2_{peak}$ > 14cc/kg/min who did not receive a transplant had a similar 1- and 2-year survival (94% and 84% respectively) to those who underwent transplant. Those with $VO2_{peak}$ less than that cut-off who did not receive a transplant due to non-cardiac reasons had a significantly lower survival at 1 and 2 years (47% and 32%).[6] While this landmark study was not randomized, and there is a question of conditions that prohibited transplant as contributing to mortality, in practice a cut-off of 14cc/kg/min $VO2_{peak}$ is used to determine the eligibility for cardiac transplant. Further, those who are re-evaluated while awaiting their transplant who are able to increase their $VO2_{peak}$ by at least 2cc/kg/min to at least 12cc/kg/minute are able to be safely removed from the transplant list and show excellent survival (85–100% at 2 years).[7]

It follows that those with higher levels of fitness, as measured by $VO2_{peak}$, are more likely to have better outcomes. This variable has been studied in prognosticating heart failure with both preserved and reduced ejection fraction. Using an outcome of transplant and mechanical support-free survival, patients can be stratified into groups based on their $VO2_{peak,}$ corresponding to Weber class, a functional class analogous to NYHA class. The most fit (defined as >20cc/kg/min) exhibited a 3-year survival of 97%, which was similar to those in the next highest quartile (16–20cc/kg/min). Three-year survival decreased further as $VO2_{peak}$ declined (83% with a $VO2_{peak}$ of 10–16 cc/kg/min and 64% for those <10cc/kg/min 8) (**Table 2**).

Similar to what has been seen in those awaiting heart transplant, patients with systolic heart failure are able to improve their risk of mortality and hospitalization by undergoing exercise training programs. In the large HF-ACTION trial, those undergoing a supervised exercise program were able to increase their $VO2_{peak}$ an average of 4%[9]; with other studies demonstrating that formalized exercise programs can increase $VO2_{peak}$ by 10%–18%.[10,11] In the HF-ACTION trial, $VO2_{peak}$, percent predicted $VO2_{peak}$, and exercise duration had the strongest associations with mortality in both systolic and diastolic heart failure.[9]

Table 2. Survival in Congestive Heart Failure stratified by $VO2_{peak}$. Adapted from Luiz, et al[8]

$VO2_{peak}$	3-year event free survival
>20cc/kg/min (Weber Class A)	97%
16–20cc/kg/min (Weber Class B)	94%
10–16cc/kg/min (Weber Class C)	83%
<10cc/kg/min (Weber Class D)	64%

PREOPERATIVE USE OF CPET IN GENERAL SURGERY

The use of CPET in preoperative risk stratification has been extensively studied. However, unlike in heart failure, the studies in preoperative risk assessment are more heterogenous given the different outcome measures used and the variability inherent in various surgical populations (**Table 3**).

Many studies have demonstrated that low $VO2_{peak}$, early anaerobic threshold, and elevated ratio of maximal ventilation to CO2 production during exercise (VE/VCO2) can predict operative complications and mortality.[12,13,14] Identifying those at higher operative risk via the objective outcomes from CPET can provide valuable information for appropriate patient selection for surgery and when discussing operative risk with patients.

A large systematic review[15] of 37 studies, encompassing 7852 patients, identified which variables were most predictive of poor outcomes relative to a given operation. For hepatic transplant or resection, early anaerobic threshold was most predictive of mortality with a value < 9.9cc/kg/minute predicting 30-day mortality, and < 9.0cc/kg/min predicting 90-day mortality.[16,17,18,19.20,21] In elective abdominal aortic aneurysm (AAA) repair, increased 30- and 90-day mortality was associated with VE/VCO2>42.[22,23,24,25] In elective colorectal surgery, early anaerobic threshold (<11cc/kg/min) and low $VO2_{peak}$ (<10.6cc/kg/min) were both associated with increased 30-day, 90-day and 2-year mortality, as well as increased postoperative length of stay.[26,27,28] In pancreatic surgery, the predictive value of early anaerobic threshold was not as strong, but similar to AAA surgery an increased VE/VCO2 portended an increased mortality.[29,30,31] In studies of other surgical procedures (e.g. upper gastrointestinal, renal transplant, bariatric surgery), the data supporting CPET's prognostic ability for operative risk is not as strong – potentially resulting from lesser inherent operative risk and population differences to the other major surgeries discussed above (i.e. the patients undergoing these procedures may be younger and with less medical comorbidity).[14]

While many small studies have found associations between CPET results and operative complications and mortality, the largest study to date evaluating CPET as a preoperative risk assessment tool, the METS study (Measurement of Exercise Tolerance before Surgery), shows more nuanced results beyond mortality prediction alone. The METS study was a multicenter prospective cohort study evaluating 1,401 patients undergoing non-cardiac surgery. Patients with low $VO2_{peak}$ and earlier anaerobic threshold had increased post-operative complications, including surgical site infections, respiratory failure, ICU length of stay and need for re-operation. Notably, this was in the absence of an increase in postoperative cardiac events.[32]

Table 3. Utility of CPET parameters in predicting post-operative complications and survival. Adapted from Moran, et al[15]

	AT	$VO2_{peak}$	VE/VCO2
Hepatic	**Strong Association**	Equivocal	No association
AAA	Equivocal	Equivocal	Limited Association
Colorectal	**Strong Association**	**Strong Association**	Equivocal
Pancreatic	Limited association	Equivocal	**Strong Association**
Bariatric/Upper GI	No association	No association	No association
Renal Transplant	No association	No association	No association

LUNG RESECTION

Pulmonary function testing performs well in identifying those at low risk for postoperative complications from anatomic lung resection (e.g. lobectomy). However, for those with marginal lung function, the use of CPET in the preoperative evaluation is suggested to help determine appropriate patients for surgery.[33,34] Multiple studies have demonstrated that postoperative mortality was best predicted by $VO2_{peak.}$[35] For example, in one cohort, those with $VO2_{peak}$ > 20cc/kg/min had no post-resection deaths, and those with $VO2_{peak}$ < 10cc/kg/min had highest rates of death (29%) and complications (43%).[36] In another small cohort, those with $VO2_{peak}$ > 15cc/kg/min but FEV1 < 33% had no fatalities after resection, supporting the use of CPET in those with otherwise prohibitively low FEV1.[37]

LUNG VOLUME REDUCTION SURGERY

Lung volume reduction surgery (LVRS) has been shown to be effective in upper lobe predominant emphysema patients. In carefully selected patients, LVRS may improve mortality, quality of life, and exercise capacity.[38] In the National Emphysema Treatment Trial, over 1,000 patients were randomized to LVRS or maximum medical therapy. CPET was used to identify those who may benefit most from resection, and found that impaired peak work rate was the best predictor of who would have the most clinical benefit[39] (cut-off <25 W in women and <40 W in men). In follow-up studies after surgery, those who undergo LVRS have been shown to have improvements in $VO2_{peak}$, work-load achieved, and VE/VCO2.[40]

PULMONARY DISEASE

Asthma

An obvious utility of CPET is the identification of exercise-induced bronchoconstriction. While a specific protocol can be used (rapid increase to 90% of peak predicted HR for 6 minutes while breathing dry air[41]), usually patients are being evaluated as part of a general dyspnea work-up. As such, evaluating for declines in serial post-exercise spirometries at multiple intervals can be helpful in this determination. CPET can also determine other etiologies of exercise intolerance that are common in asthma and not related to bronchospasm. Asthmatic patients can develop steroid myopathies, deconditioning and primary hyperventilation, all of which can influence exercise tolerance.[42] Identification of non-bronchospastic causes of dyspnea may serve to limit further steroids and step-ups in therapy.[43] Similar to other cardio-pulmonary conditions, CPET can be used to assess objective responses to therapy, such as an increase in $VO2_{peak}$ and reduction in dynamic hyperinflation with exercise.[44]

Cystic fibrosis (CF)

Cardiopulmonary exercise testing can provide valuable prognostic information in CF. One longitudinal study of CF patients over an 8-year period found that $VO2_{peak}$ correlated well with overall survival., When stratified into tertiles based on pulmonary function, the 8-year survival was 83%, 51%, and 28% from highest to lowest functional group, respectively.[45]

Chronic Obstructive Pulmonary Disease (COPD)

Patients with COPD often possess multiple other comorbid conditions that can affect exercise tolerance (e.g. coronary disease, heart failure, pulmonary hypertension, anemia, depression) and it can be difficult to ascertain which etiology one should focus additional therapy.[46] CPET may be able to discriminate the factor most responsible for exercise intolerance and enable the clinician to better direct therapy and guidance to their patient.[47] For example, in COPD patients with similar FEV1, CPET was shown to have the ability to detect COPD-CHF overlap, suggested by an elevated VE/VCO2 slope and nadir, as well as a decreased end-tidal CO2.[48]

CPET may also provide a non-invasive early measure of World Health Organization group 3 pulmonary hypertension (PH), a type of pulmonary hypertension due to primary lung pathology. In a retrospective analysis of COPD patients with available right heart catheterization and CPET data, a more significantly elevated VE/VCO2 slope and VE/VCO2 nadir suggested co-morbid PH in those with COPD compared to those with COPD alone, and exertional hypoxemia was more common in those with PH.[49] In another study of outpatient COPD patients without a diagnosis of CHF, exertional hypoxemia and elevated VE/VCO2 were significantly associated with a later finding of PH.[50]

However, in practice, there can be a large overlap in CPET findings between those with COPD alone and COPD associated with comorbidities, and as such it is recommended that CPET utilization should be determined on a case-by-case basis for COPD patients with dyspnea.[51]

Pulmonary Hypertension

While hemodynamic studies generally define the etiology of PH, certain patterns on CPET may prove helpful when uncertainty exists. Pulmonary hypertension due to left heart disease (group 2 PH) is common but it can occasionally be difficult to discriminate from pulmonary arterial hypertension (PAH; group 1 PH). On CPET, it has been demonstrated that patients with PAH have higher VE/VCO2 slope and lower end-tidal CO2 than those with PH due to left ventricular (LV) dysfunction.[52] Additionally, patients with PAH are more likely to develop exertional hypoxemia during CPET than those with LV failure and those with LV failure may also exhibit a unique pattern of oscillatory ventilation during exercise that will not be present in PAH patients.[53]

Prognosis in patients with PAH and chronic thromboembolic PH (CTEPH) is associated with CPET parameters. In a study of 86 patients with group 1 PH, peak BP below 120mmHg at maximal exercise and $VO2_{peak}$ < 10.4cc/kg/min were associated with 1-year mortality. Survival was highest in those with neither parameter (97%), worse in those with both (23%), and intermediate if only one of the two applied (79%).[54] In a study of patients with PAH or CTEPH, low $VO2_{peak}$ (< 11.2cc/kg/min) predicted significantly lower 1-, 3- and 4-year survival.[55] In another study conducted with PAH and CTEPH patients, a significantly elevated VE/VCO2 slope (>60) and VE/VCO2 nadir >55 were associated with a high risk of death at 2 years.[56]

Few therapeutic trials have used CPET variables as outcome measures, instead preferring to use the submaximal 6MWT for its ease of use. However, several small studies have shown that various PAH treatments improve $VO2_{peak}$.[57,58] Importantly, improvements following treatment in multiple CPET parameters have been shown to correlate with improvements in RV function and survival – including increases in $VO2_{peak}$, peak heart rate, and oxygen pulse (a surrogate for stroke volume).[59]

Rehabilitation

Exercise training is an integral part of pulmonary and cardiac rehabilitation programs. When available, CPET can play a role in ensuring safety prior to beginning an exercise program and can determine an appropriate training intensity leading to a more personalized exercise prescription.[60] Optimal improvement in cardiopulmonary function during a rehabilitation program occurs when consistently targeting a VO2 of 40–80% predicted VO2.[61] In healthy adults, $VO2_{reserve}$ correlates well with heart rate reserve (i.e. amount of VO2 or HR remaining from maximal, respectively) and an objective determination of $VO2_{reserve}$ would not be necessary to guide a rehabilitation prescription.[62] However, in those with congestive heart failure, objective determination of $VO2_{peak}$ and $VO2_{reserve}$ need to be determined, as it has been shown that heart rate reserve and $VO2_{reserve}$ do not correlate well in this population. Objective determination of $VO2_{reserve}$ and the HR at which this occurs enables those undergoing cardiac rehabilitation to exercise at an intensity that will more reliably lead to improvement in cardiovascular fitness and achievement of rehabilitation goals.

In attempt to improve outcomes following an intervention, there is also an emerging role for "pre-habilitation" prior to major surgery. We have discussed elsewhere in this review the association between CPET performance and surgical outcomes. If a patient is able to objectively improve their cardiopulmonary fitness as evidenced by higher $VO2_{peak}$, improved anaerobic threshold, or improved ventilatory efficiency, they may be able to improve their candidacy for surgery and reduce the likelihood of postoperative complications and mortality.[63]

CONCLUSIONS

The comprehensive physiologic information provided by cardiopulmonary exercise testing enables a clinician to gain unique insights into the factors limiting a given patient's maximal exercise and fitness. It is invaluable and most commonly utilized in the assessment of dyspnea, but also holds prognostic information in the longitudinal assessment of cardiac and pulmonary pathologies, as well as guidance regarding appropriateness for a given surgery and risks of postoperative complications. Despite the wide breadth of physiologic information gleaned from this testing, it remains under-utilized and should be considered more often in the care of our patients.

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Disclosure

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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