Cardiopulmonary Exercise Testing

Number: 0825

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers cardiopulmonary exercise testing (CPET) medically necessary in any of the following conditions, after performance of standard testing, including echocardiography, and pulmonary function testing with measurement of diffusion capacity and measurement of oxygen desaturation (6-minute walk test):

- Development of exercise prescription to determine intensity of exercise training in cardiac or pulmonary rehabilitation programs in persons with cardiovascular disease or chronic pulmonary disease (see CPB 0021 - Cardiac Rehabilitation (../1_99/0021.html) and CPB 0032 - Pulmonary Rehabilitation (../1_99/0032.html));

- Differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity in persons with known or suspected cardiopulmonary disease when standard testing (e.g.,
cardiopulmonary exercise testing (echocardiography, electrocardiography, and resting pulmonary function tests) is inconclusive or non-diagnostic; or

- Evaluation of exercise capacity and response to therapy in persons with chronic heart failure (CHF) who are being considered for heart transplantation or other advanced therapies; or

- Evaluation of children and adolescents with congenital heart disease, to discriminate between pulmonary and cardiovascular causes of exercise limitation, and to evaluate improvements in exercise tolerance after surgery; or

- Evaluation of certain adults with congenital heart disease: (1) Functional assessment of patients with pulmonary arterial hypertension in congenital heart disease (CHD-PAH); (2) Follow-up of surgically corrected: transposition of the great arteries, d-transposition (dextrotransposition) of the great arteries, atrioventricular septal defect (also known as endocardial cushion defect or AV canal), and Tetralogy of Fallot; (3) Evaluation of Eisenmenger physiology; or

- Evaluation of individuals presenting with heart failure to help determine whether heart failure is the cause of exercise limitations when the contribution of heart failure is uncertain; or

- Evaluation of exercise capacity in persons who are being considered for lung transplantation or lung resection surgery if predicted post-operative forced expiratory volume in 1 second (FEV1) or predicted post-operative diffusing capacity of the lung for carbon monoxide (DLCO) (or both) are less than 30%, or when the performance of the stair-climbing test or the shuttle walk test is not satisfactory; or

- Evaluation of persons with mitochondrial myopathies; or

- Follow-up of individuals who have had a Fontan procedure; or
• Functional evaluation of persons with chronic obstructive pulmonary disease (COPD) when specific questions persist after consideration of basic clinical data, including history, physical examination, chest X-ray, pulmonary function tests (PFTs), and resting electrocardiogram (ECG); or

• Functional and prognostic evaluation of persons with interstitial lung disease when specific questions persist after consideration of basic clinical data, including history, physical examination, chest X-ray, pulmonary function tests (PFTs), and resting electrocardiogram (ECG).

Aetna considers CPET experimental and investigational for any of the following conditions (not an all-inclusive list):

• Evaluation of candidates for allogeneic stem cell transplantation; or

• Evaluation of long QT syndrome (LQTS); or

• First-line diagnostic test of persons presenting with possible cardiac or pulmonary pathology (e.g., asthma, chest pain/early-stage ischemic heart disease, chronic fatigue syndrome, diabetes, fibromyalgia, hyperlipidemia, hypertension, obesity, pectus excavatum, polycystic ovary syndrome, and sickle cell disease; not an all-inclusive list); or

• Functional and prognostic evaluation of persons with cystic fibrosis; or

• Functional and prognostic evaluation of persons with dystrophinopathies (e.g., Becker muscular dystrophy and Duchenne muscular dystrophy) and multiple sclerosis, or

• Prediction of post-operative morbidity/survival in persons undergoing major surgery (e.g., abdominal aortic aneurysm repair, colorectal surgery, hepatic transplant and resection surgery, pancreatic surgery,
renal transplant, and upper gastro-intestinal surgery); or

- Risk stratification of individuals undergoing vascular surgery; or

- Risk stratification of persons with asymptomatic valve diseases (e.g., aortic stenosis); or

- Routine assessment of persons' response to specific therapeutic interventions (e.g., bronchodilators, continuous positive airway pressure, and exercise training; not an all-inclusive list); or

- Routine pre-operative assessment (including evaluation of persons undergoing bariatric surgery); or

- Screening exercise testing.

**Background**

Cardiopulmonary exercise testing (CPET), also known as cardiopulmonary exercise stress testing, is a non-invasive tool that provides a comprehensive evaluation of exercise responses involving the cardiovascular, pulmonary, hematopoietic, neuropsychological, and musculoskeletal systems. Cardiopulmonary exercise testing entails measurements of oxygen uptake (VO2), carbon dioxide output (VCO2), minute ventilation (VE), and other variables in addition to a 12-lead electrocardiography (ECG), blood pressure (BP) monitoring and pulse oximetry. These data are gathered during a maximal symptom-limited incremental exercise test. In certain circumstances, an additional measurement of arterial blood gases may be used to assess pulmonary gas exchange. Measurement of expiratory gases during exercise allows estimation of functional capacity, grades the severity of the impairment, evaluates the response to interventions, tracks disease progression, and assists in differentiating cardiac from pulmonary limitations in exercise tolerance. Cardiopulmonary exercise testing may be carried out on a treadmill or bicycle ergometer. Resting
measurements are made for 3 to 5 minutes; followed by 3 minutes of unloaded cycling as a warm-up period. The workload is then increased at a rate designed to allow reaching maximum work capacity in 8 to 12 minutes. The test continues to symptom limitation (e.g., faintness, pallor, chest pain, severe dyspnea, and inability to continue pedaling or walking) or discontinuation by medical staff as a consequence of significant ECG abnormalities, drop in diastolic or systolic BP greater than 20 mm Hg below the resting value, rise in diastolic BP to greater than 120 mm Hg, rise in systolic BP to greater than 250 mm Hg, severe oxygen desaturation (less than 80 %), or achievement of maximum predicted heart rate (McCarthy and Dweik, 2006). Cardiopulmonary exercise testing is not appropriate for use as a screening test or first line test. Guidelines from the American Thoracic Society state that "In practice, CPET is considered when specific questions persist after consideration of basic clinical data, including history, physical examination, chest X-ray, pulmonary function tests (PFTs), and resting electrocardiogram (ECG)."

Cardiopulmonary exercise testing is performed in candidates for heart transplantation or other advanced therapies. In a prospective study, Myers et al (1998) examined clinical, hemodynamic, and CPET determinants of survival in patients with CHF. A total of 644 patients were included in this study. Age, cause of heart failure, body surface area, cardiac index, ejection fraction, pulmonary capillary wedge pressure, left ventricular dimensions, watts achieved during exercise, heart rate (HR), maximum systolic BP, and VO2 at the ventilatory threshold and at peak exercise were measured at baseline. Uni-variate and multi-variate analyses were carried out for clinical, hemodynamic, and exercise test predictors of death. A Cox hazards model was developed for time of death. During a mean follow-up period of 4 years, 187 patients (29 %) died and 101 underwent transplantation. Actuarial 1-year and 5-year survival rates were 90.5 % and 73.4 %, respectively. Resting systolic BP, watts achieved, peak VO2, VO2 at the ventilatory threshold, and peak HR were greater among
survivors than among non-survivors. Cause of heart failure (coronary artery disease or cardiomyopathy) was a strong determinant of death (relative risk for coronary artery disease, 1.73; p < 0.01). By multi-variate analysis, only peak VO2 was a significant predictor of death. Stratification of peak VO2 above and below 12, 14, and 16 ml/kg per minute demonstrated significant differences in risk for death, but each cut-point predicted risk to a similar degree. The authors concluded that peak VO2 outperforms clinical variables, right-heart catheterization data, exercise time, and other exercise test variables in predicting outcome in severe CHF. Direct measurement of VO2 should be included when clinical or surgical decisions are being made in patients referred for evaluation of CHF or those considered for heart transplantation. Oikawa and colleagues (2003) noted that patients with CHF frequently complain of fatigue and/or dyspnea during daily life. These exertional symptoms can be evaluated by the CPET. Peak VO2, anaerobic threshold, the ratio of the increase in VE to the increase in VCO2, the slope of the increase in VO2 relative to the increase in work rate, and the time constant of VO2 are reported to be useful in evaluating the severity and prognosis of patients with CHF. The information obtained from CPET can be used to select therapeutic option to improve both functional capacity and prognosis, as well as to identify patients with the greatest need for heart transplantation.

The American Thoracic Society (ATS)/American College of Chest Physicians (ACCP)'s statement on CPET (2003) noted that this approach has been used for over a decade as a standard assessment tool of CHF, especially to determine candidacy for heart transplantation. The ATS/ACCP (2003) also listed evaluation of undiagnosed exercise intolerance, prescription of pulmonary rehabilitation, as well as evaluation of lung, heart, and heart-lung transplantation as indications for CPET. Furthermore, Ingle (2008) stated that CPET is a well-established tool for stratifying cardiovascular risk in patients with CHF. Important prognostic variables include a reduced
peak VO2, which has a central use in the selection criteria of heart transplantation, as well as the abnormal relation between VE and VCO2, often referred to as the elevated VE/VCO2 slope.

Cardiopulmonary exercise testing has also been used for pre-operative evaluation for lung cancer resection surgery or lung volume reduction surgery. Beckles et al (2003) stated that the pre-operative physiologic assessment of patients being considered for surgical resection of lung cancer must consider the immediate peri-operative risks from co-morbid cardiopulmonary disease, the long-term risks of pulmonary disability, and the threat to survival due to inadequately treated lung cancer. As with any planned major surgery, especially in a population predisposed to atherosclerotic cardiovascular disease by cigarette smoking, a cardiovascular evaluation is an important component in assessing peri-operative risks. Measurements of the forced expiratory volume in 1 second (FEV1) and the diffusing capacity of the lung for carbon monoxide (DLCO) should be viewed as complementary physiologic tests for assessing risk related to pulmonary function. If there is evidence of interstitial lung disease on radiographical studies or undue dyspnea on exertion, even though the FEV1 may be adequate, a DLCO should be obtained. In patients with abnormalities in FEV1 or DLCO identified pre-operatively, it is essential to estimate the likely post-resection pulmonary reserve. The amount of lung function lost in lung cancer resection can be estimated by using either a perfusion scan or the number of segments removed. A predicted post-operative FEV1 or DLCO less than 40 % indicates an increased risk for peri-operative complications, including death, from lung cancer resection. Exercise testing should be performed in these patients to further define the peri-operative risks prior to surgery. Formal CPET is a sophisticated tool that includes recording the exercise ECG, HR response to exercise, VE, and VO2 per minute, and allows calculation of maximal oxygen consumption (VO2max). Risk for peri-operative complications
can generally be stratified by VO2max. Patients with pre-operative VO2max greater than 20 ml/kg/min are not at increased risk of complications or death; VO2max less than 15 ml/kg/min indicates an increased risk of peri-operative complications; and patients with VO2max less than 10 ml/kg/min have a very high risk for post-operative complications. Alternative types of exercise testing include stair climbing, the shuttle walk, and the 6-min walk test (6MWT). Desaturation during an exercise test has been associated with an increased risk for peri-operative complications.

Lung volume reduction surgery (LVRS) for patients with severe emphysema is a controversial procedure. Some reports document substantial improvements in lung function, exercise capability, and quality of life in highly selected patients with emphysema following LVRS. Case series of patients referred for LVRS indicate that perhaps 3 to 6% of these patients may have co-existing lung cancer. Anecdotal experience from these case series suggested that patients with extremely poor lung function can tolerate combined LVRS and resection of the lung cancer with an acceptable mortality rate and good post-operative outcomes. Combining LVRS and lung cancer resection should probably be limited to those patients with heterogeneous emphysema, particularly emphysema limited to the lobe containing the tumor (Beckles et al, 2003). DeCamp and colleagues (2008) stated that potential candidates for LVRS should undergo extensive evaluation and preparation to minimize peri-operative risks and optimize surgical outcomes. Initial screening includes spirometry, diffusion capacity, lung volumes by body plethysmography, and high-resolution computerized tomography scanning.

Patients who have been successfully screened must complete a pre-operative pulmonary rehabilitation program of 6 to 10 weeks duration. During the pulmonary rehabilitation program, medical therapy should be maximized. Post-rehabilitation studies include CPET, arterial blood gas analysis, oxygen titration, 6MWT, and cardiac testing. The evaluation process
aims at defining the severity and distribution of emphysema and attempts to eliminate those who do not meet criteria outlined by the National Emphysema Treatment Trial. Optimal candidates have upper-lobe-predominant emphysema and acceptable operative risks.

The ACCP’s practice guidelines on physiologic evaluation of the patient with lung cancer being considered for resectional surgery (Colice et al, 2007) stated that CPET for measuring VO2max should be performed to further define the peri-operative risk of surgery; a VO2max of less than 15 ml/kg/min indicates an increased risk of peri-operative complications. Alternative types of exercise testing (e.g., stair climbing, the shuttle walk, and the 6MWT) should be considered if CPET is unavailable.

Cardiopulmonary exercise testing is being used increasingly in a wide spectrum of clinical applications including pectus excavatum, polycystic ovary syndrome, and sickle cell disease (Malek and Coburn, 2008, Giallauria et al, 2008, and Das et al, 2008). However, there is insufficient evidence that CPET should be used as a screening tool or as a first-line test. The ATS/ACCP statement on CPET (2003) noted that this approach is generally not considered a first-line test, and is usually used when the diagnosis is still uncertain after standard work up with resting pulmonary function tests or ECG. Furthermore, the American Heart Association (AHA) Council on Clinical Cardiology’s statement on exercise testing in asymptomatic adults (Lauer et al, 2005) noted that a wealth of data indicate that exercise testing can be used to evaluate and refine prognosis, especially when emphasis is placed on non-ECG measures (e.g., exercise capacity, chronotropic response, HR recovery, and ventricular ectopy). Nevertheless, randomized trial data on the clinical value of screening exercise testing are absent. It is unclear if a strategy of routine screening exercise testing in selected subjects reduces the
risk for premature mortality or major cardiac morbidity. The writing group from the AHA believed that a large-scale randomized study of such a strategy should be carried out.

Forshaw and associates (2008) stated that CPET may identify patients at high risk of post-operative cardiopulmonary morbidity and mortality. These investigators evaluated the utility of CPET before esophagectomy. A total of 78 consecutive patients (64 men) with a median age of 65 years (range of 40 to 81 years) underwent CPET before esophagectomy (50 % transhiatal; 50 % transthoracic). Measured variables included anaerobic threshold (AT) and VO2peak. Outcome measures were post-operative morbidity and mortality, length of hospital stay, and unplanned intensive therapy unit admission. Cardiopulmonary complications occurred in 33 (42 %) patients and non-cardiopulmonary complications in 19 (24 %). One in-hospital death (1.3 %) occurred, and 13 patients (17 %) required an unplanned intensive therapy unit admission. The level of VO2peak was significantly lower in patients with post-operative cardiopulmonary morbidity (p = 0.04). The area under a receiver operating characteristic curve was 0.63 (95 % confidence interval [CI], 0.50 to 0.76) for the VO2peak and 0.62 (95 % CI, 0.49 to 0.75) for AT. An AT cutoff of 11 ml/kg/min was a poor predictor of post-operative cardiopulmonary morbidity. The authors concluded that although the VO2peak was significantly lower in those patients who developed cardiopulmonary complications, CPET is of limited value in predicting post-operative cardiopulmonary morbidity in patients undergoing esophagectomy.

Brown and colleagues (2008) stated that 6MWT and CPET are used to evaluate impairment in emphysema. However, the extent of impairment in these tests as well as the correlation of these tests with each other and lung function in advanced emphysema is not well characterized. During screening for the National Emphysema Treatment Trial, maximum ergometer CPET and 6MWT were performed in 1218
individuals with severe COPD with an average FEV1 of 26.9 +/- 7.1 % predicted. Predicted values for 6MWT and CPET were calculated from reference equations. Correlation coefficients and multi-variable regression models were used to determine the association between lung function, quality of life (QOL) scores, and exercise measures. The two forms of exercise testing were correlated with each other (r = 0.57, p < 0.0001). However, the impairment of performance on CPET was greater than on the 6MWT (27.6 +/- 16.8 versus 67.9 +/- 18.9 % predicted). Both exercise tests had similar correlation with measures of QOL, but maximum exercise capacity was better correlated with lung function measures than 6-min walk distance. After adjustment, 6-min walk distance had a slightly greater association with total St George’s Respiratory Questionnaire score than maximal exercise (effect size 0.37 +/- 0.04 versus 0.25 +/- 0.03 % predicted/unit). Despite advanced emphysema, patients are able to maintain 6-min walk distance to a greater degree than maximum exercise capacity. Moreover, the 6MWT may be a better test of functional capacity given its greater association with QOL measures whereas CPET is a better test of physiologic impairment.

Pulmonary arterial hypertension (PAH) is a debilitating chronic disorder of the pulmonary vasculature. It is characterized by a persistent elevation in pulmonary arterial pressure with normal left-sided pressures, differentiating it from left-sided heart disease. Symptoms progress from shortness of breath and decreasing exercise tolerance to right heart failure, with peripheral edema and marked functional limitation. Exercise-induced syncope, worsening symptoms at rest, and intractable right heart failure indicate critical disease. Pulmonary arterial hypertension may be idiopathic with no identifiable cause or associated with collagen vascular diseases, drugs, HIV, liver disease, and/or congenital heart disease. Familial or genetically mediated PAH accounts for a small percentage of
cases. The 6MWT is the current standard to assess exercise capacity in patients with PAH (Traiger, 2007; Gomberg-Maitland et al, 2007).

Cardiopulmonary exercise testing has also been used in the management of patients with PAH, especially in assessing exercise tolerance. Guazzi and Opasich (2005) noted that the importance of studying the pathophysiological bases and clinical correlates of exercise limitation in patients with PAH is well-established. Two modes of exercise testing, the 6MWT and CPET, are currently proposed for diagnostic, therapeutic, as well as prognostic finalities. The 6MWT is inexpensive, feasible and is thought to better reproduce daily life activities and to reliably detect therapeutic benefits. On the other hand, CPET requires the patients' maximal effort and does not provide a reliable quality of life measure. However, it is highly reproducible and provides insights into the pathophysiological mechanisms that lead to exercise intolerance.

The ACCP's clinical practice guidelines on prognosis of PAH (McLaughlin et al, 2004) stated that in patients with idiopathic PAH, low VO2max and low peak exercise systolic BP and diastolic BP as determined by CPET may be used to predict a worse prognosis. Furthermore, the European Respiratory Society (ERS)'s Task Force (Palange et al, 2007) recommended the use of CPET for functional and prognostic evaluation of patients with primary pulmonary hypertension.

In a case report on the utility of CPET to detect and track early-stage ischemic heart disease, Chaudhry and colleagues (2010) concluded that "this study illustrates the potential value of CPET in the primary prevention setting to detect and track early-stage ischemic heart disease ......Research in this area should continue to more firmly establish the clinical role of CPET in the evaluation of ischemic heart disease (macrovascular or microvascular) for the purpose of improving preventive cardiac care and thus reducing long-term health are costs".
The American College of Cardiology (ACC)/AHA Task Force on Practice Guidelines guidelines for exercise testing (Gibbons et al, 1997) stated that ventilatory gas exchange analysis during exercise testing is a useful adjunctive tool in assessment of patients with cardiovascular and pulmonary disease. Measures of gas exchange primarily include VO2, VCO2, VE, and ventilatory/anaerobic threshold. VO2 at maximal exercise is considered the best index of aerobic capacity and cardiorespiratory function. Estimation of maximal aerobic capacity using published formulas without direct measurement is limited by physiological and methodological inaccuracies. Data derived from exercise testing with ventilatory gas analysis have proved to be reliable and important in evaluation of patients with heart failure. Such data are only partly influenced by resting left ventricular dysfunction. Maximal exercise capacity does not necessarily reflect the daily activities of patients with heart failure. Use of this technique in stratification of ambulatory heart failure patients has improved ability to identify those with the poorest prognosis, who should be considered for heart transplantation. The ACC/AHA published a partial update to these guidelines (Gibbons et al, 2002), however, there was no change in regard to CPET.

The European Respiratory Society (ERS)'s Task Force (Palange et al, 2007) also provided the following recommendations (ranging from "A", the highest, to "D", the lowest) regarding the clinical use of CPET:

<table>
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<tr>
<th>Indication</th>
<th>Recommendation grade</th>
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<tbody>
<tr>
<td>Detection of exercise-induced bronchoconstriction</td>
<td>A</td>
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<tr>
<td>Detection of exercise-induced arterial oxygen desaturation</td>
<td>B</td>
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<tr>
<td>Activity</td>
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<td>Functional evaluation of subjects with unexplained exertional dyspnea and/or exercise intolerance and normal resting lung and heart function</td>
<td>D</td>
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<tr>
<td>To recognize specific disease exercise response patterns that may help in the differential diagnosis of ventilatory versus circulatory causes of exercise limitation</td>
<td>C</td>
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<tr>
<td>Functional and prognostic evaluation of patients with COPD</td>
<td>B, C</td>
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<td>Functional and prognostic evaluation of patients with ILD</td>
<td>B, B</td>
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<td>Functional and prognostic evaluation of patients with CF</td>
<td>C, C</td>
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<td>Functional and prognostic evaluation of patients with PPH</td>
<td>B, B</td>
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<tr>
<td>Functional and prognostic evaluation of patients with CHF</td>
<td>B, B</td>
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<tr>
<td>Evaluation of interventions (Maximal incremental test)</td>
<td>C</td>
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<tr>
<td>Evaluation of interventions (High-intensity constant work-rate “endurance” tests)</td>
<td>B</td>
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<tr>
<td>Prescription of exercise training</td>
<td>B</td>
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The authors stated that with the use of this rigorous grading system, "A" is relatively rare and "B" is usually considered the best achievable. The low power recommendation grades are reflective not so much of well-powered statistical judgments as they are of weakness in the density of the relevant evidence base. Such areas should be regarded as important priorities for future investigation.

The American Heart Association (AHA)'s scientific statement on CPET in adults (Balady et al, 2010) stated that CPET has been studied and found to be useful in the following clinical applications (not an all-inclusive list):

- Development of the exercise prescription in patients with cardiovascular disease or stroke
- Evaluation of disability in patients with cardiac or pulmonary disease
- Evaluation of patients with heart failure
- Evaluation of patients with mitochondrial myopathies
- Evaluation of patients with unexplained dyspnea.

The AHA's scientific statement on CPET in adults (Balady et al, 2010) also listed the following emerging and less well-studied clinical applications of CPET (not an all-inclusive list):

- Evaluation of patients with congenital heart disease
- Evaluation of patients with cardiac arrhythmias and pacemakers
- Evaluation of patients with ischemic heart disease
- Evaluation of patients with pulmonary hypertension
- Pre-operative evaluation of patients undergoing pulmonary resection or bariatric surgery.

The AHA scientific statement (Balady et al, 2010) also stated that more studies are needed to rigorously evaluate if CPET provides additional discriminatory diagnostic and prognostic value over and above that provided by standard exercise tests.
and other clinical variables. In addition, more studies are needed to assess the increasing number of variables that can be derived from CPET, as well as their utility in many conditions that affect the cardiovascular and pulmonary systems.

Young and colleagues (2012) performed a systematic review of CPET in the pre-operative evaluation of patients with abdominal aortic aneurysm or peripheral vascular disease requiring surgery. Review methods and reporting were according to the PRISMA guidelines. Studies were eligible if they reported CPET-derived physiological parameters in patients undergoing abdominal aortic aneurysm repair or lower extremity arterial bypass. Data were extracted regarding patient populations and correlation between CPET and surgical outcomes including mortality, morbidity, critical care bed usage and length of hospital stay. These researchers identified a total of 1,301 articles. Although 53 abstracts referred to the index vascular procedures, only 7 articles met inclusion criteria. There were no data from randomized controlled trials. Data from prospective studies did not comprehensively correlate CPET and surgical outcomes in patients with abdominal aortic aneurysms. There were no studies reporting CPET in patients undergoing lower extremity arterial bypass. Major limitations included small sample sizes, lack of blinding, and an absence of reporting standards. The authors concluded that the paucity of robust data precludes routine adoption of CPET in risk-stratifying patients undergoing major vascular surgery. They stated that the use of CPET should be restricted to clinical trials and experimental registries, reporting to consensus-defined standards.

Marzolini et al (2012) noted that despite the importance of exercise training in mitigating cardiovascular risk, the development of exercise programs for people post-stroke has been limited by lack of feasibility data concerning CPET to inform the exercise prescription. These researches examined the feasibility of CPETs for developing an exercise prescription
in people greater than or equal to 3 months post-stroke. Cardiopulmonary exercise testing results from 98 consecutively enrolled patients post-stroke with motor impairments and 98 age- and sex-matched patients with coronary artery disease were examined at baseline and after 6 months of exercise training. The proportion of patients with stroke and coronary artery disease attaining an intensity sufficient for prescribing exercise at baseline was 68.4 % versus 82.7 %, respectively (p = 0.02) and 84.7 % versus 83.8 % (p = 0.9) at 6 months. Women were less likely than men post-stroke to achieve a sufficient intensity at baseline (40 % versus 80.9 %, p < 0.001) but not at 6 months (78.3 % versus 87.1, p = 0.3). A clinically relevant abnormality occurred in 11.2 % of stroke and 12.2 % of patients with coronary artery disease on baseline CPETs (p = 0.8) and 10.6 % of stroke and 5.9 % of patients with coronary artery disease on the 6-month CPET (p = 0.4). No serious cardiovascular events occurred during 349 CPETs. The authors concluded that most patients after stroke achieved a level of exertion during the CPET sufficient to inform an exercise prescription. At least 1 of 10 patients post-stroke developed a clinically relevant abnormality on baseline and post-program CPETs with no serious cardiovascular events. Moreover, they state that these data supported the feasibility and safety of CPETs for prescribing exercise post-stroke; and strategies to improve use of baseline CPETs for women post-stroke require further investigation. The clinical value of CPET for prescribing exercise to people after stroke needs to be ascertained in well-designed studies.

The third edition of the American College of Chest Physicians’ evidence-based clinical practice guidelines on "Physiologic evaluation of the patient with lung cancer being considered for resectional surgery" (Brunelli et al, 2013) states that "The preoperative physiologic assessment should begin with a cardiovascular evaluation and spirometry to measure the FEV1 and the diffusing capacity for carbon monoxide (DLCO). Predicted post-operative (PPO) lung functions should be calculated. If the % PPO FEV1 and % PPO DLCO values are
both > 60 %, the patient is considered at low risk of anatomic lung resection, and no further tests are indicated. If either the % PPO FEV1 or % PPO DLCO are within 60 % and 30 % predicted, a low technology exercise test should be performed as a screening test. If performance on the low technology exercise test is satisfactory (stair climbing altitude > 22 m or shuttle walk distance > 400 m), patients are regarded as at low risk of anatomic resection. A cardiopulmonary exercise test is indicated when the PPO FEV1 or PPO DLCO (or both) are < 30 % or when the performance of the stair-climbing test or the shuttle walk test is not satisfactory. A peak oxygen consumption (V˙O2 peak) < 10 ml/kg/min or 35 % predicted indicates a high risk of mortality and long-term disability for major anatomic resection. Conversely, a V˙O2 peak > 20 mL/kg/min or 75 % predicted indicates a low risk”. The authors concluded that a careful pre-operative physiologic assessment is useful for identifying those patients at increased risk with standard lung cancer resection and for enabling an informed decision by the patient about the appropriate therapeutic approach to treating his or her lung cancer. This pre-operative risk assessment must be placed in the context that surgery for early-stage lung cancer is the most effective currently available treatment of this disease.

A European Respiratory Society Task Force (2007) stated that clear evidence now exists for the utility of CPET in children and adolescents with congenital heart diseases. The guidelines cite evidence that CPET may help to discriminate between pulmonary, cardiovascular and deconditioning causes of exercise limitation in congenital heart diseases. The authors state that CPET has been used to evaluate improvements in exercise tolerance after heart surgery. The guidelines note that the use of exercise testing to assess the long-term prognosis of children with CHD have not been reported.
American Heart Association/ American College of Cardiology Foundation’s scientific statement on "The evaluation of syncope" (Strickberger et al, 2006) did not mention cardiopulmonary exercise testing for evaluating patients with syncope.

Evaluation of Dystrophinopathies (e.g., Becker Muscular Dystrophy and Duchenne Muscular Dystrophy)

In a pilot study, Bartels et al (2015) determined exercise response during CPET in children and adolescents with dystrophinopathies. Exercise response on CPET was compared with a standard care test protocol. A total of 9 boys (aged 10.8 ± 4.7 years) with Becker muscular dystrophy (n = 6) and Duchenne muscular dystrophy (n = 3) were included. The feasibility of the CPET was similar to a standard care test protocol, and no serious adverse events occurred. In 67% of the subjects with normal or only mildly impaired functional capacity, the CPET could be used to detect moderate-to-severe cardiopulmonary exercise limitations. The authors concluded that CPET appeared to be a promising outcome measure for cardiopulmonary exercise limitations in youth with mild functional limitations. They stated that further research with larger samples is needed to confirm current findings and investigate the additional value of the CPET to longitudinal follow-up of cardiomyopathy and the development of safe exercise programs for youth with dystrophinopathies.

Evaluation of Multiple Sclerosis

van den Akker and colleagues (2015) examined the feasibility and safety of CPET in patients with multiple sclerosis (MS). PubMed, EMBASE, CINAHL, SPORTDiscus, PsycINFO, ERIC, and the Psychology and Behavioral Sciences Collection were searched up to October 2014. References from retrieved articles were examined to identify additional relevant studies. Inclusion of original studies was on the basis of performance of maximal CPET, description of the protocol, and participants
with definite MS aged greater than or equal to 18 years. No language restrictions were applied. The quality of CPET reporting in included studies was scored according to a structured checklist considering 10 feasibility (e.g., test abnormalities) and 12 safety quality criteria (e.g., adverse events). Structured data extraction was performed for these feasibility and safety features of CPET. A total of 46 studies were included, comprising 1,483 patients with MS, with a mean age ± SD of 42.0 ± 5.8 years and a median Expanded Disability Status Scale (EDSS) score of 2.8 (first quartile = 2.1; third quartile = 3.9; range of average EDSS scores, 0.75 to 5.8). Quality of reporting on CPET varied from 3 to 13 out of a possible 22 quality points. The percentage of test abnormalities (feasibility) was 10.0%, primarily because of an inability to maintain pedaling at a specific resistance. The percentage of adverse events (safety) was 2.1%; all adverse events were temporary. The authors concluded that CPET is feasible provided that the CPET modality is tailored to the physical abilities of the patient. Furthermore, CPET is safe when recommended precautions and safety measures are implemented. Moreover, they stated that future optimization of CPET will require protocolized testing and the implementation of standard reporting procedures.

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feasibility and safety features of CPET. A total of 46 studies were included, comprising 1,483 patients with MS, with a mean age ± SD of 42.0 ± 5.8 years and a median EDSS score of 2.8 (first quartile = 2.1; third quartile = 3.9; range of average EDSS scores, 0.75 to 5.8). Quality of reporting on CPET varied from 3 to 13 out of a possible 22 quality points. The percentage of test abnormalities (feasibility) was 10.0 %, primarily because of an inability to maintain pedaling at a specific resistance. The percentage of adverse events (safety) was 2.1 %. All adverse events were temporary. The authors concluded that based on the available data, CPET is feasible provided that the CPET modality is tailored to the physical abilities of the patient. Furthermore, CPET is safe when recommended precautions and safety measures are implemented. However, they stated that future optimization of CPET will require protocolized testing and the implementation of standard reporting procedures.

Prediction of Post-Operative Morbidity / Survival in Persons Undergoing Major Surgery

Kasivisvanathan et al (2015) examined if CPET may predict which patients are at risk for adverse outcomes after undergoing hepatic resection surgery. High-risk patients undergoing elective, 1-stage, open hepatic resection were pre-operatively assessed using CPET. Morbidity, as defined by the post-operative morbidity survey (POMS), was assessed on post-operative day 3. A total of 104 patients underwent pre-operative CPET and were included in the analysis. Of these, 73 patients (70.2 %) experienced post-operative morbidity. Oxygen consumption at anaerobic threshold (V˙O2 at AT, ml/kg/min) was the only CPET predictor of post-operative morbidity on multi-variable analysis, with an area under the curve (AUC) of 0.66 [95 % CI: 0.55 to 0.76]. In patients requiring a major hepatic resection (3 or more segments), a V˙O2 at AT of less than 10.2 ml/kg/min gave an AUC of 0.79 (95 % CI: 0.68 to 0.86) with 83.9 % sensitivity and 52.0 % specificity, 80.6 % positive predictive value (PPV) and 62.5 %
negative predictive value (NPV). The authors concluded that the application of a cut-off value for $V' \text{O}_2$ at AT of less than 10.2 ml/kg/min in patients undergoing major hepatic resection may be useful for predicting which patients will experience morbidity. These findings need to be validated by well-designed studies.

Levett and Grocott (2015) evaluated the current and future role of CPET in the context of enhanced recovery after surgery (ERAS) programs. There is substantial literature confirming the relationship between physical fitness and peri-operative outcome in general. The few small studies in patients undergoing surgery within an ERAS program described less fit individuals having a greater incidence of morbidity and mortality. There is evidence of increasing adoption of peri-operative CPET, particularly in the United Kingdom. Although CPET-derived variables have been used to guide clinical decisions about choice of surgical procedure and level of peri-operative care as well as to screen for uncommon co-morbidities, the ability of CPET-derived variables to guide therapy and thereby improve outcome remains uncertain. Recent studies have reported a reduction in CPET-defined physical fitness following neoadjuvant therapies (chemo- and radio-therapy) prior to surgery. Preliminary data suggested that this effect may be associated with an adverse effect on clinical outcomes in less fit patients. Early reports suggested that CPET-derived variables can be used to guide the prescription of exercise training interventions and thereby improve physical fitness in patients prior to surgery (i.e., pre-habilitation). The impact of such interventions on clinical outcomes remains uncertain. The authors concluded that peri-operative CPET is finding an increasing spectrum of roles, including risk evaluation, collaborative decision-making, personalized care, monitoring interventions, and guiding prescription of pre-habilitation. They stated that these indications are potentially of importance to patients having
surgery within an ERAS program, but there are currently few publications specific to CPET in the context of ERAS programs.

Grant et al (2015) examined if CPET can identify patients at risk of reduced survival after abdominal aortic aneurysm (AAA) repair. Prospectively collected data from consecutive patients who underwent CPET before elective open or endovascular AAA repair (EVAR) at 2 tertiary vascular centers between January 2007 and October 2012 were analyzed. A symptom-limited maximal CPET was performed on each patient. Multivariable Cox proportional hazards regression modelling was used to identify risk factors associated with reduced survival. The study included 506 patients with a mean age of 73.4 (range of 44 to 90) years; 82.6 % were men and 64.6 % underwent EVAR. The in-hospital mortality was 2.6 %. The median follow-up was 26 months. The 3-year survival for patients with 0 or 1 sub-threshold CPET value was 86.4 % compared with 59.9 % for patients with 3 sub-threshold CPET values. Risk factors independently associated with survival were female sex [hazard ratio = 0.44, 95 % CI: 0.22 to 0.85, p = 0.015], diabetes (hazard ratio = 1.95, 95 % CI: 1.04 to 3.69, p = 0.039), pre-operative statins (hazard ratio = 0.58, 95 % CI: 0.38 to 0.90, p = 0.016), hemoglobin g/dL (hazard ratio = 0.84, 95 % CI: 0.74 to 0.95, p = 0.006), peak VO2 (less than 15 ml/kg/min) (hazard ratio = 1.63, 95 % CI: 1.01 to 2.63, p = 0.046), and at anaerobic threshold greater than 42 (hazard ratio = 1.68, 95 % CI: 1.00 to 2.80, p = 0.049). The authors concluded that CPET variables are independent predictors of reduced survival after elective AAA repair and can identify a cohort of patients with reduced survival at 3 years post-procedure. Moreover, they stated that CPET is a potentially useful adjunct for clinical decision-making in patients with AAA.

In a systematic review, Moran and colleagues (2016) evaluated the ability of CPET to predict post-operative outcome. The following databases were searched: PubMed, Embase, PEDro, the Cochrane Library, Cinahl, and AMED. A
total of 37 full-text articles were included. Data extraction included the following: author, patient characteristics, setting, surgery type, post-operative outcome measure, and CPET outcomes. Surgeries reviewed were hepatic transplant and resection (n = 7), abdominal aortic aneurysm (AAA) repair (n = 5), colorectal (n = 6), pancreatic (n = 4), renal transplant (n = 2), upper gastro-intestinal (GI) (n = 4), bariatric (n = 2), and general intra-abdominal surgery (n = 12). Cardiopulmonary exercise testing-derived cut-points, peak oxygen consumption and anaerobic threshold (AT) predicted the following post-operative outcomes: 90 day to 3 year survival (AT 9 to 11 ml/kg/min) and intensive care unit (ICU) admission (AT less than 9.9 to 11 ml/kg/min) after hepatic transplant and resection, 90-day survival after AAA repair (15 ml/kg/min), length of stay (LOS) and morbidity after pancreatic surgery (AT less than 10 to 10.1 ml/kg/min), and mortality and morbidity after intra-abdominal surgery (AT 10.9 and less than 10.1 ml/kg/min, respectively). The authors concluded that CPET is a useful pre-operative risk-stratification tool that can predict post-operative outcome. Moreover, they stated that further research is needed to justify the ability of CPET to predict post-operative outcome in renal transplant, colorectal, upper GI, and bariatric surgery.

Warnakulasuriya and co-workers (2017) examined if CPET has additive value to other scoring systems in predicting post-operative outcomes following bariatric surgery. Data were collected retrospectively on 398 patients who underwent CPET between October 2008 and April 2013; CPET data, medical history, complication rates and LOS were obtained from patient records. Data was analyzed to examine the relationship between CPET and other scoring systems with post-operative outcome. A total of 250 patients underwent Roux-en-Y gastric bypass or sleeve gastrectomy. Median LOS was 4 days (inter-quartile range [IQR] 4 to 6 days) and 41 patients (16.4%) developed a complication. Adjusted data showed a risk difference for complications of 17% (95% CI: 9 to 25%) between high- and low-risk patients stratified by
OSMRS alongside a 27% (95% CI: 12 to 45%) longer LOS. Variation in anaerobic threshold (AT) or peak oxygen uptake (VO2) showed no significant relationship with complications or LOS. Among high OSMRS risk patients, there was no significant difference in complications or LOS when CPET data were added to this analysis. The authors concluded that CPET did not add any incremental value in predicting post-operative outcomes in the bariatric population compared to the obesity surgery mortality risk score (OSMRS), which is strongly predictive of LOS and complication following bariatric surgery.

Stubbs and colleagues (2020) noted that CPET is used within the United Kingdom for pre-operative risk stratification. Despite this, CPET's performance in predicting adverse events (AEs) has not been systematically evaluated within the framework of classifier performance. After prospective registration on PROSPERO (CRD42018095508), these researchers systematically identified studies where CPET was used to aid in the prognostication of mortality, cardiorespiratory complications, and unplanned ICU admission in individuals undergoing non-cardiopulmonary surgery. For all included studies, these investigators extracted or calculated measures of predictive performance while identifying and critiquing predictive models encompassing CPET derived variables. These researchers identified 36 studies for qualitative review, from 27 of which measures of classifier performance could be calculated. They found studies to be highly heterogeneous in methodology and quality with high potential for bias and confounding; and found 7 studies that presented risk prediction models for outcomes of interest. Of these, only 4 studies outlined a clear process of model development; assessment of discrimination and calibration were carried out in only 2; and only 1 study undertook internal validation. No scores were externally validated.

Systematically identified and calculated measures of test performance for CPET demonstrated mixed performance. Data were most complete for anaerobic threshold (AT) based
predictions: calculated sensitivities ranged from 20 to 100 % when used for predicting risk of mortality with high NPVs (96 to 100 %). In contrast, PPV was poor (2.9 to 42.1 %); PPV appeared to be generally higher for cardiorespiratory complications, with similar sensitivities. Similar patterns were observed for the association of peak VO2 (sensitivity 85.7 to 100 %, PPV 2.7 to 5.9 %) and VE/VCO2 (sensitivity 27.8 % to 100 %, PPV 3.4 to 7.1 %) with mortality. The authors concluded that this systematic review highlighted potential limitations of CPET by generating common and novel measures of test performance. Specifically, given the frequency of complications in studies these investigators highlighted the low values of PPV, although far from perfect for gating access to surgery or critical care they may help inform a process of shared decision-making before surgery. The performance of CPET in day-to-day practice may be improved if a sufficiently high risk population could be identified for it to be employed in. The high NPV offered by CPET may be testament to accuracy of its underlying physiological rationale. However, based on these findings, and those from a recent high-quality prospective study (Wijeysundera et al, 2018) the precision of CPET for reliably identifying individuals who would suffer post-operative cardiorespiratory complications appeared poor.

Risk Stratification of Persons with Asymptomatic Valve Diseases

Levy and colleagues 920140 stated that risk stratification in asymptomatic patients with severe aortic stenosis (AS) is based on exercise test results. However, differentiating between pathological and physiological breathlessness during exercise is sometimes challenging. Cardiopulmonary exercise testing may improve quantification of cardiopulmonary exercise capacity in patients with valve diseases. In a pilot study, these researchers evaluated the ability of CPET to detect abnormal responses to exercise and a clinical end-point (occurrence of European Society of Cardiology guidelines
surgical class I triggers). A total of 43 consecutive patients
(mean age of 69 ± 13 years; 31 men) with no reported
symptoms and severe AS (aortic valve surface area less than
1 cm² or indexed aortic valve surface area less than or equal
to 0.6 cm²/m²) prospectively underwent symptom-limited
CPET. Twelve (28%) patients had an abnormal exercise test
(AET) with symptoms (abnormal dyspnea n = 11; angina n =
1). Both VE/VCO₂ slope greater than 34 (hazard ratio = 5.76,
95% CI: 1.086 to 30.587; p = 0.04) and peak VO₂ less than or
equal to 14 ml/kg/min (hazard ratio 6.01, 95% CI: 1.153 to
31.275; p = 0.03) were independently associated with an AET.
Furthermore, VE/VCO₂ slope greater than 34 (hazard ratio
3.681, 95% CI: 1.318 to 10.286; p = 0.013) and peak VO₂
less than or equal to 14 ml/kg/min (hazard ratio 3.058, 95%
CI: 1.074 to 8.713; p = 0.036) were independent predictors of
reaching the clinical end-point. The authors concluded that
CPET is a useful tool for characterizing breathlessness during
an exercise test in apparently asymptomatic patients with AS.
Peak VO₂ less than or equal to 14 ml/kg/min and VE/VCO₂
slope greater than 34 were associated with an AET and the
occurrence of European Society of Cardiology guideline
surgical class I triggers. The findings of this pilot study need to
be validated by well-designed studies.

In a review on "Exercise testing in asymptomatic severe aortic
stenosis", Magne et al (2014) stated that exercise stress test is
now recommended by current guidelines in asymptomatic
patients and may provide incremental prognostic value.
Indeed, the development of symptoms during exercise or an
abnormal BP response are associated with poor outcome and
should be considered as an indication for surgery, as
suggested by the most recently updated European Society of
Cardiology 2012 guidelines. Exercise stress echocardiography
may also improve the risk stratification and identify
asymptomatic patients at higher risk of a cardiac event. When
the test is combined with imaging, echocardiography during
exercise should be recommended rather than post-exercise
echocardiography. During exercise, an increase greater than
18 to 20 mm Hg in mean pressure gradient, absence of improvement in left ventricular ejection fraction (i.e., absence of contractile reserve), and/or a systolic pulmonary arterial pressure greater than 60 mm Hg (i.e., exercise pulmonary hypertension) are suggestive signs of advanced stages of the disease and impaired prognosis. Hence, exercise stress test may identify resting asymptomatic patients who develop exercise abnormalities and in whom surgery is recommended according to current guidelines. Exercise stress echocardiography may further unmask a subset of asymptomatic patients (i.e., without exercise stress test abnormalities) who are at high risk of reduced cardiac event free survival. In these patients, early surgery could be beneficial, whereas regular follow-up seems more appropriate in patients without echocardiographic abnormalities during exercise. This review does not mention the use of CPET.

Le (2017) noted that patients with moderate-to-severe AS (aortic valve area [AVA] of less than 1.3 cm2) who were judged as asymptomatic or equivocal symptomatic from AS were included in the study. Patients with left ventricular ejection fraction (LVEF) of less than 50 % were not included; 29 % of the referred patients were judged asymptomatic and 71 % equivocal symptomatic from their valve disease. The mean age was 72 years and 90 % of the patients had an AVA-index (AVAI) of less than 0.6 cm2/m2. By clinical evaluation in the out-patient clinic, 48 % were judged as having functional limitation corresponding to New York Heart Association (NYHA) greater than or equal to II. The study participants had CPET at inclusion, and, if relevant, pre- and 9 months post-aortic valve replacement (AVR). CPET was feasible in 130 of 131 study participants recruited across 19 months. The coefficient of variability by test-retest was 5.4 % and 4.6 % for peak oxygen consumption (pVO2) and peak oxygen pulse (pO2pulse = pVO2/peak HR), respectively. The stroke volume (SV) generally increased with exercise, also in those with peak flow velocity across the aortic valve (Vmax) greater than 5 m/s, greater than 4 m/s, and less than 4 m/s but with high valvulo-
arterial impedance (Zva greater than 5.5 mm Hg/(ml·m²)). This was found both when assessed by inert gas re-breathing and by the pO2pulse/hemoglobin index. Both resting and exercise SV were lower for the latter group, with Vmax of less than 4 m/s but high valvulo-arterial impedance. A pVO2 of less than 83 % of the predicted, which corresponded to the lower 95 % percentile found in the healthy sedentary population, was predicted independently by lower SV during exercise, lower HR during exercise, lower FEV1, and by higher ventilation/carbon dioxide exhaustion rate (VE/VCO2), but not by the severity of the AS as determined by echocardiography.

According to the CPET results, the patients were prospectively grouped into 3 groups: (i) normal pVO2 (greater than 83 % of predicted) and pO2pulse (greater than 95 % of predicted); (ii) subnormal pVO2 or pO2pulse that according to CPET could be explained by causes other than hemodynamic compromise; (iii) subnormal pVO2 and pO2pulse. Groups (i) and (ii) followed an initial conservative strategy, whereas group (iii) was referred for angiogram and Heart Team evaluation for AVR. Patients were followed for an average of 24 months and, in groups (i) and (ii), 1 patient (0.9 %) suffered cardiac death and 7 were hospitalized with HF (6.7 %). The patient who died and another patient with HF had both previously, during the study, declined AVR. For groups (i) and (ii), the rate of the combined end-point progression to cardiac death, hospitalization with HF, or AVR was 37.5 %, which appeared lower than what was reported in the literature by conventional assessment and strategy for younger asymptomatic patients with comparable echocardiographic severity of AS. The end-point progression to cardiac death, hospitalization with HF, or AVR with improvement in pVO2 or in the Physical Component Score of the SF-36 health-related QOL score was reached in 25.6 % in groups (i) + (ii) and in 62.5 % in group (iii) (p = 0.003). A decreased pO2pulse, which expressed SV at peak exercise, predicted this endpoint. In 73 operated patients without left ventricular dysfunction and no coronary stenosis, including 37 patients
from the above-mentioned study, a CPET 9 months post-AVR showed that the pVO2, on average, was less than that predicted (mean of 89% of the predicted) and 35% of the patients had a subnormal pVO2 (less than 83% of that predicted). A pre-operative mean gradient of less than 40 mm Hg across the aortic valve, the presence of atrial fibrillation (AF), and a permanent pacemaker post-AVR all predicted a post-AVR pVO2 of less than 83% of that predicted. For the 37 patients with a pre-AVR CPXET a post-operative decrease of greater than 10% in the absolute pVO2 was noted in 30% and an increase greater than 10% in 24% of patients. A decrease of greater than 10% in pVO2 was predicted by pre-operative mean gradient of less than 40 mm Hg and an increase in pVO2 was predicted by pre-operative AVAI of less than 0.4 cm²/m² and pre-operative pO2pulse of less than the median in the study population (less than 98% of that predicted). The authors concluded that in this group of patients, where clinical assessment was difficult and conventional exercise testing was regarded as less useful, CPET showed high feasibility and reproducibility; thus, it has potential as a useful tool for serial monitoring. In general, the SV increased during exercise, including in patients with severe AS or decreased resting SV. CPET provided information on hemodynamics and the physiologic components that determine decreased pVO2. They noted that CPET appeared useful to identify (i) patients with a low risk of cardiac death and low risk of progression to symptoms from the AS, and (ii) patients with hemodynamic compromise who improve in functional capacity after AVR. Patients with a pre-operative mean gradient of less than 40 mm Hg across the aortic valve, with the presence of AF or who have a permanent pacemaker, post-operatively appeared to benefit less from AVR, whereas the benefit appeared larger in those with more severe AS and a decreased pO2pulse. These findings may be of importance for decisions and information of patients before AVR.
The author stated that this study was the first in its field and therefore the cut-offs for CPET measures were not clearly established earlier, and that some of the predictors were defined post-hoc. Thus, the present study may be seen as a pilot study. Also, the follow-up was only from 1 to 3 years. To evaluate the prognostic value of CPET, a longer follow-up may be optimal. These investigators stated that CPET therefore has potential as a useful tool for serial monitoring.

Evaluation of Candidates for Allogeneic Stem Cell Transplantation

In a proof-of-concept study, Kim and colleagues (2017) examined the feasibility and safety of CPET in patients with leukemia following chemotherapy. Patients with histologically confirmed hematologic malignancies were selected in this study. These researchers evaluated CPET, between receiving chemotherapy and undergoing stem cell transplantation after 2 weeks. They recorded exercise testing and physiologic parameters during CPET between January 2013 to May 2015. All patients were subjected to symptoms limited to exercise testing, according to the Modified Bruce Protocol. These investigators noted that if respiratory exchange ratio of over 1.10 was attained, participants would be considered to have successfully completed CPET. They divided all subjects into 2 groups: (i) normal group -- normal range of resting HR; and (ii) higher group, HR of over 100 beats/min). A total of 30 patients were enrolled. All participants had no adverse effects during the exercise test. Mean peak double product was 26,998.60 mmHg·beats/min (range of 15,481 to 41,004), and mean peak oxygen consumption (VO2 peak) was 22.52 ± 4.56 ml/kg/min. Significant differences were observed in the normal group with VO2 peak (mean of 24.21 ml/kg/min; p = 0.027) and number of prior intensive chemotherapy, compared to the higher group (mean of 1.95; p = 0.006). The authors concluded that these findings indicated that CPET in leukemia patients before stem cell transplantation was very safe, and was an efficient method to screen for patients with poor
cardiac functions. They stated that as CPET presented parameters that revealed cardiopulmonary functions, including VO2 peak, double product and exercise capacity, CPET would help to predict the physical performance or general condition of the leukemia patients. Moreover, they stated that larger prospective trials in homogenous populations are needed to further clarify the use of CPET in this setting. In particular, they noted that larger adequately powered prospective studies are needed to systematically evaluate the clinical utility and importance of CPET in allogeneic stem cell transplantation.

The authors stated that this study had several drawbacks: (i) the potential for selection bias because of the transparent purpose of the investigation, and the exclusion of patients with prohibitive co-morbid disease. Nevertheless, this proof-of-concept study of patients with leukemia demonstrated the safety of testing of this nature, and provided data regarding the exercise capacity and functional status of these patients, (ii) these researchers did not evaluate the association of initial CPET and disease-free, recurrence-free or overall survival rate. They only had information on death from any cause; the specific cause of death was not known, and (iii) the small number of patients (n = 30) precluded multi-variate analyses.

Management of Patients Post-Fontan Procedure

An UpToDate review of management of patients post-Fontan procedure (Johnson JM, Connolly HM, 2018) stated that cardiopulmonary exercise testing is performed regularly to identify changes in exercise capacity, arrhythmias, or desaturation with exercise that may prompt further evaluation.

Udholm and colleagues (2018) noted that exercise impairment is common in Fontan patients. These investigators reviewed available literature to determine the prognostic value of exercise capacity in older adolescent and adult Fontan
patients with respect to late outcome. Additionally, they reviewed the determinants of exercise capacity in Fontan patients and changes in exercise capacity over time. PubMed, CINAHL, Embase, the Cochrane Library and Scopus were searched systematically for studies reporting exercise capacity and late outcome such as mortality, cardiac transplantation and hospitalization. Studies were eligible for inclusion if more than 30 patients were included and mean age was greater than or equal to 16 years. A total of 4,722 studies were identified by the systematic search; 7 studies fulfilled the inclusion and exclusion criteria. The total number of patients was 1,664 adult Fontan patients. There were 149 deaths and 35 heart transplantations. All eligible studies were retrospective cohort studies. The correlation between exercise capacity and late outcome was identified, and HRs were reported. The authors concluded that this systematic review provided an overview of exercise capacity prognostic value in older adolescent and adult Fontan patients. Decline in VO2, heart rate variables and exercise oscillatory ventilation (EOV) were the best predictors of death and transplantation, although no clear consensus was reached. Several variables were strong and independent predictors of hospitalization and morbidity. Even though multiple unanswered questions regarding the prognostic value of CPET exist, the authors would recommend an individualized evaluation with focus on decline in peak VO2, the presence of EOV and impaired chronotropic parameters. Moreover, they stated that there is a need for further studies to explore a combination of these dynamic physiological variables and biomarkers such as pro-brain natriuretic peptide to enhance the risk assessment in Fontan patients.

The authors stated that this study had several drawbacks. The number of studies conducted about this subject was few. Most of the studies included in this systematic review were retrospective, single-center registries. Although these studies provided valuable outcomes information, selection or follow-up bias could not be excluded. Exercise protocols differed in
exercise modality between studies, however were comparable. Some Fontan patients were not able to perform CPET adequately and was excluded, thus, omitting the poorest patients. Importantly, across different studies, there was large variation in the criteria of maximal exercise effort of peak gas (respiratory exchange ratio) and their definitions of late outcome. Particularly secondary morbidity outcome differed, where number of deaths was included in some of them. The number of deaths was small in some studies, making multi-variable analysis impossible. Lastly, CPET may not be sensitive to non-cardiac secondary morbidities such as Fontan-associated liver disease.

**Surgical Risk Stratification in Adults with Congenital Heart Disease**

Guidelines on the management of adults with congenital heart disease from the American College of Cardiology and the American Heart Association (Warnes, et al., 2008) identified the following indications for CPET in adults with congenital heart disease: (i) functional assessment of patients with pulmonary arterial hypertension in congenital heart disease (CHD-PAH); (ii) followup of congenitally corrected transposition of the great arteries; (iii) followup of surgically corrected atrioventricular septal defect; (iv) followup of surgically repaired tetralogy of Fallot; (v) evaluation of dextrotransposition of the great arteries; 6) evaluation of Eisenmenger physiology.

Birkey and colleagues (2018) stated that adult congenital heart disease (ACHD) patients often require repeat cardio-thoracic surgery, which may result in significant morbidity and mortality. Currently, there are few pre-operative risk assessment tools available. In the general adult population, pre-operative CPET has a predictive value for post-operative morbidity and mortality following major non-cardiac surgery. The utility of CPET for risk assessment in ACHD patients requiring cardio-thoracic surgery has not been evaluated. Retrospective chart
review was conducted on 75 ACHD patients who underwent CPET less than 12 months prior to major cardio-thoracic surgery at Children's Hospital of Wisconsin. Minimally invasive procedures, cardiomyopathy, acquired heart disease, single ventricle physiology, and heart transplant patients were excluded. Demographic information, CPET results, and peri-operative surgical data were collected. The study population was 56% male with a median age of 25 years (range of 17 to 58). Prolonged post-operative LOS correlated with increased ventilatory efficiency slope ($p = 0.007$). Prolonged intubation time correlated with decreased peak HR ($p = 0.008$), decreased exercise time ($p = 0.002$), decreased heart rate response ($p = 0.008$) and decreased relative peak oxygen consumption ($p = 0.034$). Post-operative complications were documented in 59% of patients. The authors concluded that while trends were noted between post-operative complications and some measurements of exercise capacity, none met statistical significance. They stated that future studies may further define the relationship between exercise capacity and post-operative morbidity in ACHD patients.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>94621</td>
<td>Pulmonary stress testing; complex (including measurements of CO2 production, O2 uptake, and electrocardiographic recordings)</td>
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Other CPT codes related to the CPB:
<table>
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<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>33615</td>
<td>Repair of complex cardiac anomalies (eg, tricuspid atresia) by closure of atrial septal defect and anastomosis of atria or vena cava to pulmonary artery (simple Fontan procedure)</td>
</tr>
<tr>
<td>33617</td>
<td>Repair of complex cardiac anomalies (eg, single ventricle) by modified Fontan procedure</td>
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</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- C34.00 - C34.92 Malignant neoplasm of bronchus and lung
- I42.0 - I43 Cardiomyopathy
- I50.1 - I50.9 Heart Failure
- J40 - J44.9 Chronic bronchitis, emphysema and other chronic obstructive pulmonary disease
- J47.0 - J47.9 Bronchiectasis
- J67.0 - J67.9 Hypersensitivity pneumonitis due to organic dust
- J84.111 - J84.117 Idiopathic interstitial pneumonia
- Q20.0 - Q28.9 Congenital malformations of the circulatory system
- Q67.6 Pectus excavatum
- R06.02 Shortness of breath
- Z76.82 Awaiting organ transplant status [lung]
- Z85.118 Personal history of other malignant neoplasm of bronchus and lung

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):
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<td>E08.00 -</td>
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<td>Z13.6</td>
<td>Encounter for screening for cardiovascular disorders</td>
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<td>Z13.810 - Z13.89</td>
<td>Encounter for screening for other specified diseases and disorders [digestive, musculoskeletal, respiratory, nervous systems]</td>
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<tr>
<td>Z68.41 - Z68.45</td>
<td>Body mass index [BMI] 40 or greater, adult</td>
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<tr>
<td>Z79.01 - Z79.899</td>
<td>Long term (current) drug therapy</td>
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</table>

The above policy is based on the following references:


26. Lauer M, Froelicher ES, Williams M, Kligfield P; American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Exercise testing in asymptomatic adults: A statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac


40. Strickberger SA, Benson DW, Biaggioni I, et al; American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke; Quality of Care and Outcomes Research Interdisciplinary Working Group; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF scientific statement on the evaluation of syncope: From the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation In Collaboration With the Heart Rhythm Society. J Am Coll Cardiol. 2006;47(2):473-484.


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Amendment to
Aetna Clinical Policy Bulletin Number: 0825
Cardiopulmonary Exercise Testing

There are no amendments for Medicaid.