Cardiology

Cardiopulmonary Exercise Testing

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General description of procedure, equipment, technique

What is cardiopulmonary exercise testing?

Cardiopulmonary exercise (CPX) testing is a provocative test that combines standard methods of electrocardiogram (ECG) stress testing with indices of gas exchange. The exercise component entails the same challenges and mechanisms as standard ECG stress testing (i.e., a progressive exercise stimulus [usually on a treadmill or bicycle] in association with continuous ECG, symptom, and serial hemodynamic monitoring).

Just as with standard exercise testing, selection of exercise modality and intensity are critical, with exercise ideally lasting 6 to 12 minutes before symptomatic limitation to provide the optimal diagnostic and prognostic delineations based on ECG, hemodynamics, symptoms, and exercise capacity. Therefore, choice of exercise mode and protocol must be tailored to the capacities and clinical idiosyncrasies of each patient.

Gas exchange indices enhance these standard assessments by substantiating assessments of exercise capacity and by expanding insight regarding physiologic determinants of exercise limitations (pulmonary vs. cardiac vs. peripheral mechanisms).

What are the special benefits of CPX for management of HF patients?

Amid a cardiology armamentarium that offers a vast and growing array of sophisticated imaging modalities, CPX testing provides a distinct and complementary assessment by facilitating a more precise and reliable measurement of a patient's functional capacity and a means to better delineate reasons for exercise limitation. In addition, CPX testing is a well validated tool for evaluating the prognosis of heart failure (HF) patients and measuring responses to HF therapy.

The utility of CPX testing as a prognostic tool has been best studied for heart failure with reduced ejection fraction (HFREF), but a growing body of literature also demonstrates that it provides similar utility for heart failure with preserved ejection fraction (HFPEF).

CPX testing also serves as a diagnostic tool by enabling clinicians to distinguish the etiology of dyspnea or exercise intolerance, sorting between pulmonary, cardiac, and peripheral etiologies through distinctive patterns of gas exchange, cardiac, and hemodynamic responses. Moreover, related diagnostic and prognostic applications of CPX continue to expand in relation to hypertrophic cardiomyopathy, congenital heart disease, and pulmonary hypertension.

Key CPX indices

Mancini et al completed seminal work establishing the value of peak oxygen utilization (VO_2), a standard CPX index as an HFREF prognostic gauge. Over the decades since, multiple investigators have contributed to this literature, validating the utility of peak VO_2, and by demonstrating the utility of additional CPX indices to reinforce prognostic insights.

The minute ventilation to exhaled carbon dioxide ratio (VE/VCO_2 slope) is one of these many complementary indices, but it stands out because it has often been demonstrated to exceed peak VO_2 as a valuable heart failure prognosticator. Peak VO_2, VE/VCO_2 slope, and other CPX indices (exercise oscillatory ventilation [EOV], oxygen uptake efficiency slope [OUES], and end-tidal carbon dioxide [$P_{ET}CO_2$]) are often assessed in aggregate as they have been found to provide synergistic prognostic discrimination.

One key consideration has been the validation of CPX-based prognostic indices that are relatively less dependent on maximal exercise performance. Oxygen consumption at the ventilatory threshold (VAT), VE/VCO_2 slope, and OUES are among the indices that provide an important prognostic perspective at submaximal exercise workloads for patients who may be too limited by disease, deconditioning, or apprehension to achieve a physiologic peak exercise performance.

Why is CPX becoming so widely used?

A key attribute of evolving CPX technology is the progressive ease of gas exchange assessments. Whereas the original measurement of gas exchange entailed cumbersome collection of the air inhaled and exhaled during exercise into bags, new metabolic carts now use a sensor positioned within a tube that is used as a low profile (lightweight, small, comfortable) snorkel or facemask through which the patient breathes room air during exercise. The sensor-based data is both logistically simpler to use, and provides instant, comprehensive perspective in easy-to-read reports.

A robust literature supports enduring CPX test utility to assess HFREF prognosis, including those who are young, old, male or female. CPX has also been validated in those who are frail and functionally limited, as

well as among those who are robust and strong (i.e., discriminating clinically meaningful differences amidst a wide range of intrinsic capacities). Implications of gas exchange are compounded by differences in hemodynamics, arrhythmias, symptoms, ECG changes, or other clinically relevant variables.

Application of CPX testing for dyspnea assessment, congenital heart disease, and pulmonary hypertension are also similar, but the emphasis on pulmonary components of CPX are relatively greater. Baseline pulmonary function testing is often complementary to CPX, as are assessments of breathing reserve (maximum minute ventilation during exercise over the maximum voluntary ventilation at rest) and exercise-related changes in oxygen saturation.

Overall, by linking gas exchange to traditional exercise testing assessment, CPX represents the evolution of a relatively "simple" exercise test into a much more elegant assessment of mechanisms and physiology of performance, a perspective which has the potential to refine prognostic and diagnostic assessments, and to enhance the quality of care.

When preexercise spirometry is performed (forced vital capacity [FVC], slow vital capacity [SVC], and maximal voluntary ventilation [MVV]), additional information concerning underlying lung disease and the contribution of lung dysfunction to exercise limitation can be assessed. Performing serial postexercise forced vital capacity measurements (and comparing to pre-exercise) can help identify respiratory muscle fatigue, vocal cord dysfunction, and exercise-induced bronchospasms.

In patients with heart failure, CPX testing is used to quantify severity of disease risk stratification, determine the effectiveness of treatments, establish transplant candidacy, and determine the contribution of other comorbidities to the patient's functional limitation.

Basic technical precepts

Generally, these procedures are performed on a motor-driven treadmill, or electrically/mechanically braked cycle ergometer. Other modalities (i.e., Nu-Step or arm-only ergometer) can be used, but these are rarely used and not discussed in this chapter.

There are benefits and drawbacks to performing CPX testing on a treadmill or a cycle ergometer. Some exercise labs prefer the treadmill with the rationale that it has the potential to generate a greater maximal exercise workload and because it is more like the typical, weight-bearing activities performed by patients in their daily activities.

However, other labs prefer the cycle ergometer as a relatively more stable exercise stimulus for patients inherently prone to hemodynamic instability, arrhythmia, and/or other unsteadiness. Cycle ergometer also has particular advantages for patients with significant orthopedic/gait/balance issues where treadmill testing may be stopped before reaching cardiovascular or pulmonary limitations.

Commercially available metabolic carts are available and widely used to measure the ventilatory and gas exchange parameters. Despite the sophistication of modern metabolic carts, it still takes a well-trained individual to maintain and operate these carts.

This is particularly important in recognizing when the cart is not working properly during a test. We endorse the use of a trained exercise physiologist with credentialing from the American College of Sports Medicine

(Clinical Exercise Specialist or Registered Clinical Exercise Physiologist). Both of these credentials require 500-600 hours of practical experience working with a variety of patients that includes exercise testing, prescription, and counseling.

Many metabolic carts can incorporate ECG and ergometer (treadmill or bike) controls, allowing stress systems to be incorporated into a single device with an external exercise stimulus.

Discussion of the specific types of gas analyzers and flow/volume transducers, and the positives and negatives of each are beyond the scope of this chapter.

Indications and patient selection

Assessing the functional capacity and prognosis of patients with HFREF remains the most common indication for CPX testing. However, given the large number of HFREF patients, many assert that application of CPX should be restricted to a subset of HFREF patients.

In general, CPX provides a reliable means to assess HF patients whose self-reported functional capacity does not correspond to their clinical presentation or to other indices of disease severity. Poor performance on a walk-type test may also serve as a useful means to gauge who will benefit from a more accurate prognostic assessment using CPX testing.

For example, Guazzi et al provided a useful account of using CPX in relation to a 6-minute walking test (i.e., showing that a low 6-minute walk distance provides a useful perspective to identify those most functionally impaired [and at greatest prognostic risk] who could then be further evaluated by CPX). Heart failure patients with severe disease and who are being considered for advanced therapies (e.g., transplant or LVAD) are also appropriate candidates for CPX.

The expanding field of HFPEF management has also highlighted high morbidity and mortality associated with the disease. CPX holds the potential to delineate those patients at greatest risk. However, unlike HFREF, there is no definitive therapy that can be predicated on functional measures, thus even as HFPEF can be functionally debilitating, integration of CPX is often omitted from routine management.

In contrast, the application of CPX in regard to dyspnea assessment is a burgeoning field. The growing population of adults with multiple comorbidities and frailty, with related issues of old age, obesity, and polypharmacy often confounding diagnosis and management leaves many physicians struggling to distinguish etiology of dyspnea and/or exercise decline. CPX provides a valuable tool to sort through pertinent differentials, often clarifying management priorities.

Application to congenital heart disease and pulmonary hypertension is similar, as each is based on the overall assessment of functional capacity, with capacity to delineate pulmonary versus cardiac limitations, and serving as a guide among therapeutic choices.

In several centers, invasive CPX testing with pulmonary artery catheters and arterial lines in place provides a sophisticated means to diagnose exercise-induced intracardiac and pulmonary abnormalities, such as

functional mitral regurgitation and exercise-induced pulmonary hypertension, both of which can be associated with significant morbidity and mortality despite near normal resting indices.

Contraindications

Well-established contraindications to exercise testing have been established by the American Heart Association, American Thoracic Society, and the American College of Sports Medicine. A summary of exercise contraindications is listed in Table 1. These criteria should be evaluated prior to ordering the test, as well as the day of the exercise test.

Table 1.n
Contraindications to Exercise Testing

Arrhythmias, as well as signs and symptoms of decompensation, can occur between the time the test was ordered and the time it is done. Laboratory staff should be trained to recognize these dynamics and respond appropriately.

Patients must be able to exercise on a motorized treadmill or stationary cycle ergometer (unless other exceptional testing options such as an arm ergometer or Nustep are also available).

A contraindication that does not specifically appear on the above-mentioned list is related to the weight limits of the exercise equipment itself. This should be considered prior to ordering the test. Most treadmills have a weight-limit between 159 and 204 kg (350 and 450 lb).

Performing treadmill testing on patients whose weights exceed these limits will likely result in damage to the treadmill and will affect the speed of the belt. Most upright cycle ergometers have a weight limit between 113 and 159 kg (250 and 350 lb). Performing bicycle testing on patients whose weights exceed these limits may lead to collapse of the seat post and likely injury to the patient.

For patients who require oxygen therapy, it is technically difficult to provide supplemental oxygen during CPX. Although specialized equipment is available to do this, it is not usually found outside of research settings.

Details of how the procedure is performed

Equipment needed to perform CPX testing include: Metabolic cart, stress ECG system, blood pressure monitor and cuff, pulse oximeter and probe, pneumotach, mouthpiece, and nose clip (or facemask).

Prior to the patient's arrival, the metabolic cart calibration should be performed according to the manufacturer's recommendations. Record the current temperature (°C), relative humidity (%), and barometric pressure (mm Hg) of the lab. Gas calibration should be performed with precision-grade reference and calibration gases (gas cylinders provided by the manufacturer are precision mixes). Room air should never be used as the reference.

The quality of the results is significantly dependent on the patient's understanding of what is expected of them during the procedure. So, a discussion of the exercise test should precede the exercise test. This can be done in conjunction with obtaining the patient's informed consent, as this discussion should include what will be measured, how these will be measured, when the exercise will end, and the risks involved with the test.

Since the patient will be on a mouthpiece (or wearing a mask) throughout the exercise, talking may (and often will) cause air leaks. So, clear hand signals and gestures should be discussed. This should be repeated just prior to doing the exercise…a brief "quiz" can help re-enforce the important gestures (i.e., signal that the patient needs to stop).

Once informed consent is obtained, the patient's relevant medical history, medications, and current symptoms (if any) should be reviewed.

The patient's height and weight should be measured prior to the exercise test with shoes removed.

In addition to the mouthpiece and nose clip (or facemask), a 12-lead ECG in the standard stress configuration, appropriately sized blood pressure cuff, and pulse oximetry probe need to be placed on the patient.

Finger pulse oximetry may be hampered by poor peripheral circulation. Alternative use of ear or forehead probes may provide more reliable O_2 saturation assessments.

Pre-exercise spirometry provides information that is helpful in discerning how much influence comorbid conditions (COPD, obesity, interstitial lung disease [ILD]) are contributing to the patient's symptoms and functional limitations.

Perform three repeatable FVC maneuvers (which meets ATS criteria for reliability and repeatability). Perform at least one SVC maneuver. Perform at least two MVV (do not exceed four attempts due to fatigue and dizziness) procedures attempting to motivate the patient to obtain the largest ventilation possible.

Move the patient to the treadmill/cycle ergometer for exercise test. If performing a bike test, with the patient sitting on the bike, adjust the seat so that the patient's leg has a soft bend in it during the down stroke. Obtain resting ECG, BP, and pulse oximetry while the patient is seated resting prior to placing the mouthpiece or facemask.

Have the patient place the mouthpiece in his/her mouth, replace nose clips and secure all cables. Choose appropriate protocol and perform 1 to 2 minutes of rest while seated. Then, stand patient up and record the ECG, BP, and pulse oximetry while standing (this is not performed for the bike test).

Start the exercise and continue the test until exhaustion, until the patient requests to stop, or symptoms/ECG changes/blood pressure changes indicate it is unsafe to continue the test. The person conducting the test should have a goal of getting the patient to reach a respiratory exchange ratio (RER) ≥1.10 as a threshold of high exertion. However, the exercise protocol should not be stopped simply for reaching this goal.

Moreover, it is important to emphasize that many patients cannot reach this ideal RER due to deconditioning or other functional limitations (e.g., intrinsic pulmonary disease, peripheral arterial disease [PAD],

orthopedic pathology). In some instances, patients with HF may be near the plateau of the Frank-Starling curve, which may cause excessive dyspnea such that the test terminates while RER is still below 1.1.

During the exercise, record HR, BP, rating of perceived exertion (RPE), and symptoms at least every other minute, and at peak exercise. Record at least 30 seconds of metabolic data during recovery, and monitor ECG and BP until HR falls below 100 bpm, BP returns to near-resting levels, and symptoms have resolved. Record the reason the patient stopped, the peak RPE, and the severity of any symptoms that occurred during or after exercise.

Since exercise-induced bronchospasm (EIB) is also a common etiology of exercise limitation and/or dyspnea, post-exercise spirometry is also recommended immediately after exercise and at 5- to 10-minute intervals over 20 minutes.

Interpretation of results

Correctly interpreting the results of CPX testing in HF patients can be a difficult task, as these results depend on numerous factors including the quality of the test, the patient's level of effort, and the fact that many HF patients have comorbidities such as COPD, anemia, and orthopedic issues that can influence the test results significantly.

In general, when interpreting a CPX test, we look to classify the results of the testing into three categories: (1) a primary HF or other CV limitation; (2) a primary pulmonary limitation; or (3) a primary noncardiopulmonary limitation (obesity, PAD, orthopedic or deconditioning, or a peripheral myopathy).

We have provided a stepwise approach and some guiding principles we use when evaluating the results of a CPX test:

Step 1: Evaluate the reason for stopping test. Most HF patients give their reason for stopping a test as dyspnea or leg fatigue. If the test is stopped due to oxygen desaturation during exercise then this is almost always a primary pulmonary limitation as even patients with advanced HF won't desaturate unless they are in acute HF or have significant underlying lung disease.

Patients who stop for orthopedic issues or peripheral arterial disease are usually obvious. Technicians should be instructed not to stop patients simply because they have reached their maximum predicted heart rate or RER ≥1.10 as this can often lead to submaximal tests.

Step 2: Look at the spirometry and peak VE/MVV ratio. We recommend that spirometry (FVC, SVC and MVV) be performed before and after exercise.

Patients with a resting forced expiratory volume in 1 second (FEV_1) <1.0L or FEV_1/FVC <70% are often pulmonary limited and will have a VE/MVV ratio at peak >80%. To check for EIB, the FEV_1 and FVC should be repeated immediately after exercise and then again at 5- to 10-minute intervals over 20 minutes.

Patients with EIB will have a drop in their $FEV_1$by at least 15% from baseline, while the FVC stays relatively stable. If both the FEV_1 and FVC drop proportionately, preserving the FEV_1/FVC ratio, we attribute this to respiratory muscle fatigue and not bronchospasm.

The MVV provides a general sense of maximum ventilatory capacity, and it is used for comparison to the maximum VE obtained during exercise. Whereas the FEV_1 and FVC are usually relatively easy to measure and are reproducible, the MVV can be technically more challenging to measure accurately as patients often feel dizzy during the maneuver.

As a quick check for accuracy, we typically compare the MVV to the FEV_1 and look for whether the MVV is to be about 40x the FEV_1. If the measured MVV is FEV_1 x 30, it may reflect intrinsic respiratory muscle weakness, suboptimal technique, and/or poor patient effort.

The VE/MVV ratio is calculated using the maximum VE achieved during exercise divided by the MVV measured during resting spirometry. Dyspnea typically ensues at VE/MVV ratios >60%, with cessation of exercise occurring nearly uniformly at ratios <80%..

Thus, in subjects who attain a VE/MVV >80% during testing, we typically classify them as primarily lung or ventilatory-limited. The breathing reserve (BR) calculated as {(1 – VE/MVV) x 100%} is often reported and a BR of 20% or less suggests a ventilatory limitation to exercise. Additionally, the SVC provides a quantification of the inspiratory capacity and it is expected that the tidal volume at peak exercise should be 60-80% of the inspiratory capacity. When this ratio exceeds 80%, it strongly correlates with the sensation of not being able to get a deep enough breath.

Step 3: Look at the RER. The respiratory exchange ratio is a calculated value obtained by dividing the expired CO_2 by the inspired O_2. As exercise progresses and lactic acid is produced, the amount of CO_2 produced exceeds the O_2 consumed and the RER increases.

In general the RER should be between 0.70 and 0.80 prior to exercise. However, it is not unusual to see patients with high levels of pre-test anxiety have a stable RER around 1.0 only to have this drop down in the initial moments of the exercise stimulus.

A peak RER of 1.10 or greater is considered a standard of high effort and suggests that the peak VO_2 obtained in the test provides an accurate estimate of the patient's true maximal functional capacity. However, it is not uncommon for patients to give a subjective maximum effort but fail to reach a peak RER of 1.10, such as when patients are deconditioned and/or limited by pulmonary disease, PAD, or other medical conditions.

Previous data has shown that in experienced labs about 50% of subjects will attain a peak RER >1.10 and 70% will attain >1.05. In patients who fail to reach an RER >1.05, we look for other indicators of a maximum effort or advanced disease patterns such as an early flattening of the VO_2 and/or the O_2-pulse curve, a VE/MVV ratio >80%, or a markedly elevated VE/VCO_2 slope.

Recently published data from our laboratory (Chase et al 2013) suggests that in univariate and multivariate analysis, the VE/VCO_2 >35 remains strongly prognostic irrespective of RER. Furthermore, when a subjective maximum effort is observed (i.e., significant symptoms reported by patient and/or observation by experienced lab staff), a peak VO_2 <14 ml/kg/min appears to remain prognostic irrespective of RER. Notably many studies have demonstrated enduring prognostic values of VO_2 even when RER is lower than 1.1. Despite this, it is important that laboratory staff provide encouragement and reassurance to the patient to achieve a RER >1.10. In our lab we generally disregard the peak VO_2 when RER is <1.00. Notably, our own

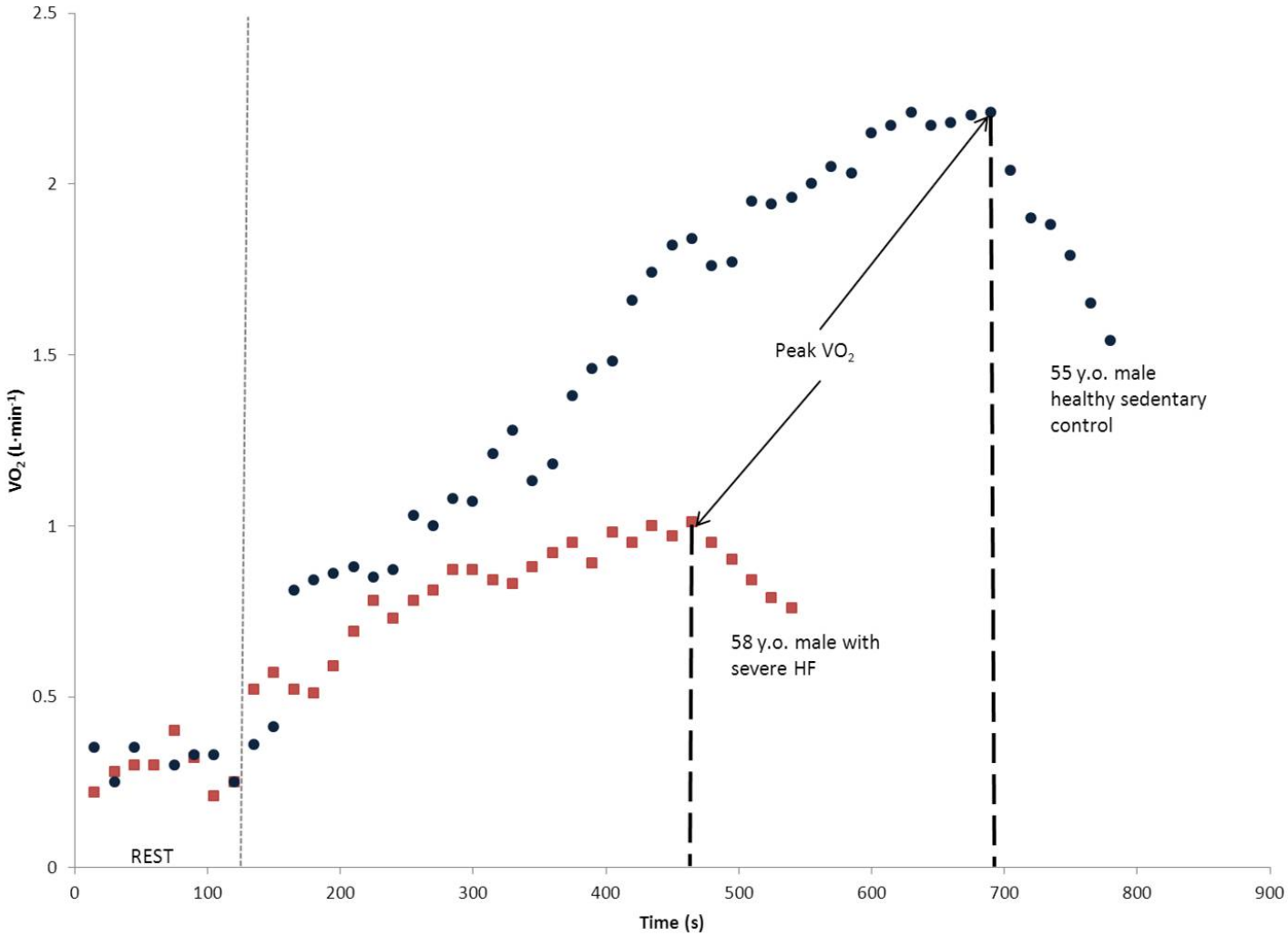
analyses demonstrated that even peak VO_2 values associated with very low RERs (<1.0) remained prognostic, albeit, much less reliably than VO_2 values associated with higher RER values.

Data from our laboratory suggests that in patients with a VE/VCO_2 slope ≥45, the peak VO_2 remains predictive despite a peak RER <1.05. RER values greater >1.5 are typically suggestive of equipment malfunction but can also be seen in patients with mitochondrial disorders.

Step 4: Read the peak VO_2 (Figure 1). In terms of measuring the degree of a patient's HF, prognosis, and transplant candidacy, peak VO_2 is usually assessed as a normalized value, (i.e., milliliters of O_2 consumed per kilogram of body weight per minute (ml/kg/min) and has long been the gold standard of CPX testing. Prior to the widespread use of beta-blockers, the cutoff for heart transplant was a peak VO_2 ≤14 ml/kg/min.

Figure 1.

Assessment of Peak Oxygen Utilization. Patient with severe HF versus matched sedentary control. Both participants performed the Modified Naughton Protocol on the treadmill.



In the beta-blocker era, this figure has dropped to ≤12 ml/kg/min. In general we view the 12 to 14 ml/kg/min as a gray zone. If a patient has a severe subjective functional limitation and there are other indicators of severe HF (i.e., markedly elevated VE/VCO_2 slope or low O_2 pulse as detailed below) we will take this into account and refer to transplant at the higher cut-off.

In looking at a test to determine the actual peak VO_2, we recommend using 15- or 20-second intervals on the time down data. We review the data to make sure that the increase in VO_2 is relatively consistent throughout the test and there are not big jumps or drop-offs that might indicate an air leak or other problems. Traditionally, the peak VO_2 is selected as the highest value obtained during the last minute of exercise.

When evaluating peak VO_2, we compare the measured value to the predicted value derived from the Wasserman equations based on the patient's age and gender. The reason for this is that a pVO_2 of 14.5 ml/kg/min may be relatively normal for an 80 year-old woman while a peak VO_2 of 25 ml/kg/min may represent a significant limitation for a 23-year-old former athlete. In general, we usually use the following classification:

- Normal: measured peak VO_2 80% or greater of predicted
- Mild limitation: measured peak VO_2 60% to 79% predicted
- Moderate limitation: measured peak VO_2 40% to 69% predicted
- Severe limitation: measured peak VO_2 <40% predicted

When looking at the peak VO_2, it is important to take the patient's body habitus into account. Since the peak VO_2 is measured per kilogram of body weight, morbidly obese patients can have a falsely low peak VO_2.Lavie et al 2013 found when peak VO2 falls below 14 ml/kg/min in obese patients, a closer consideration should be made regarding their body habitus.

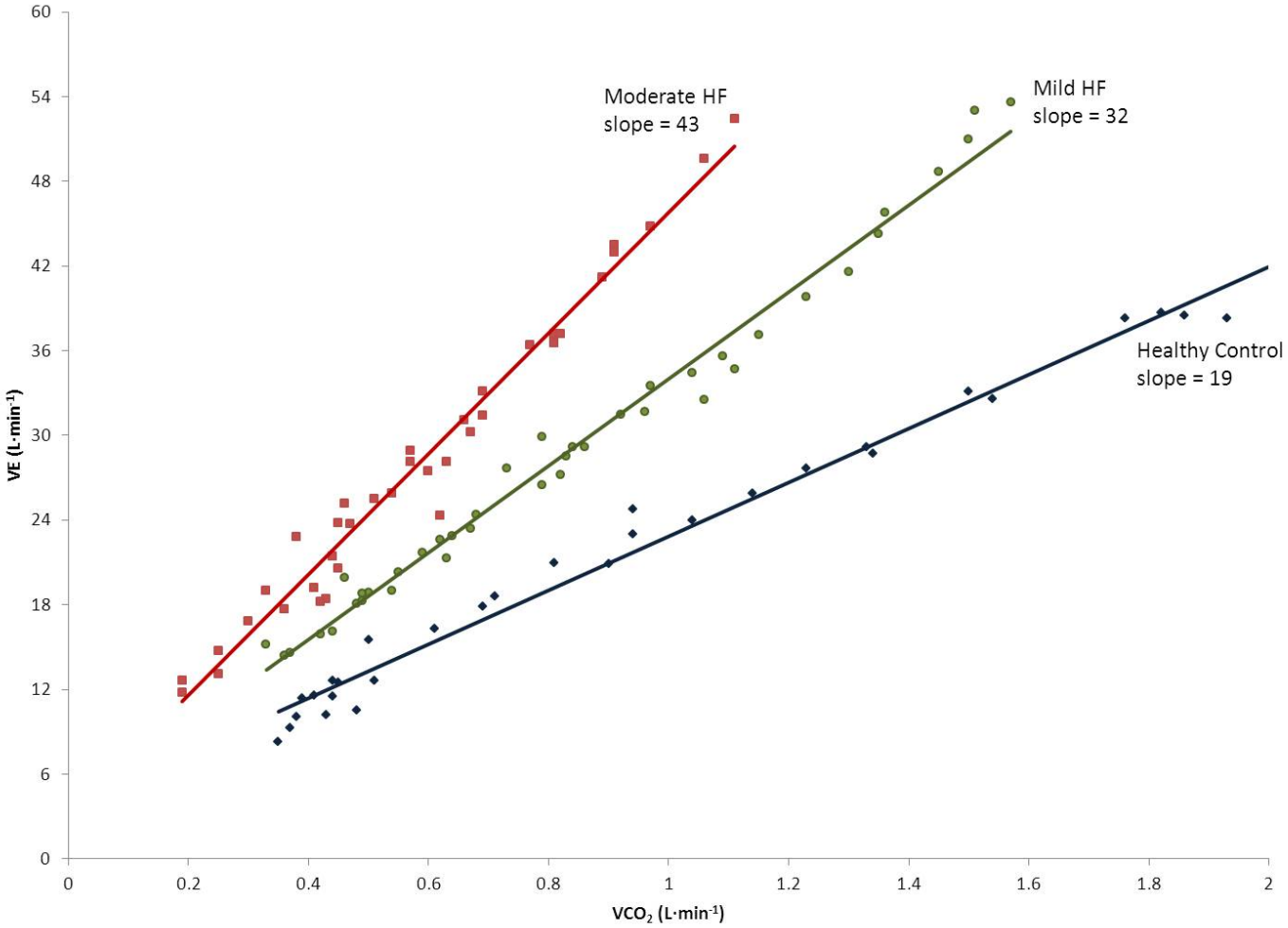
For patients with BMI ≥30 some labs correct VO_2 for lean body weight by taking the absolute measured peak VO_2 (in ml/min) and divide it by the patient's predicted lean body weight. Several studies have demonstrated a positive correlation between BMI and lean body mass. Furthermore, studies that have controlled for BMI have demonstrated reductions in lean body mass with worsening HF. So, understanding this relationship can provide a better insight into patients' prognoses. While studies have shown the prognostic value of the peak VO_2 can be improved by using weight-adjusted figures, this practice has not been widely accepted.

Yet even while this relatively novel strategy may not have widespread acceptance for formal HF decision making, it helps clarify the impact of obesity on a patient's functional limitations.

Step 5: Measure the VE/VCO_2 slope (Figure 2) and assess for EOV. The VE/VCO_2 slope is a measure of ventilatory efficiency and in several recent studies has outperformed peak VO_2 and other CPX variables in predicting adverse events (hospitalizations and death) in HF patients. It is one of the primary variables we use in interpreting a CPX test.

Figure 2.

Assessment of VE/VCO2 slope in healthy control (athlete) compared to patients with mild and moderate HF.



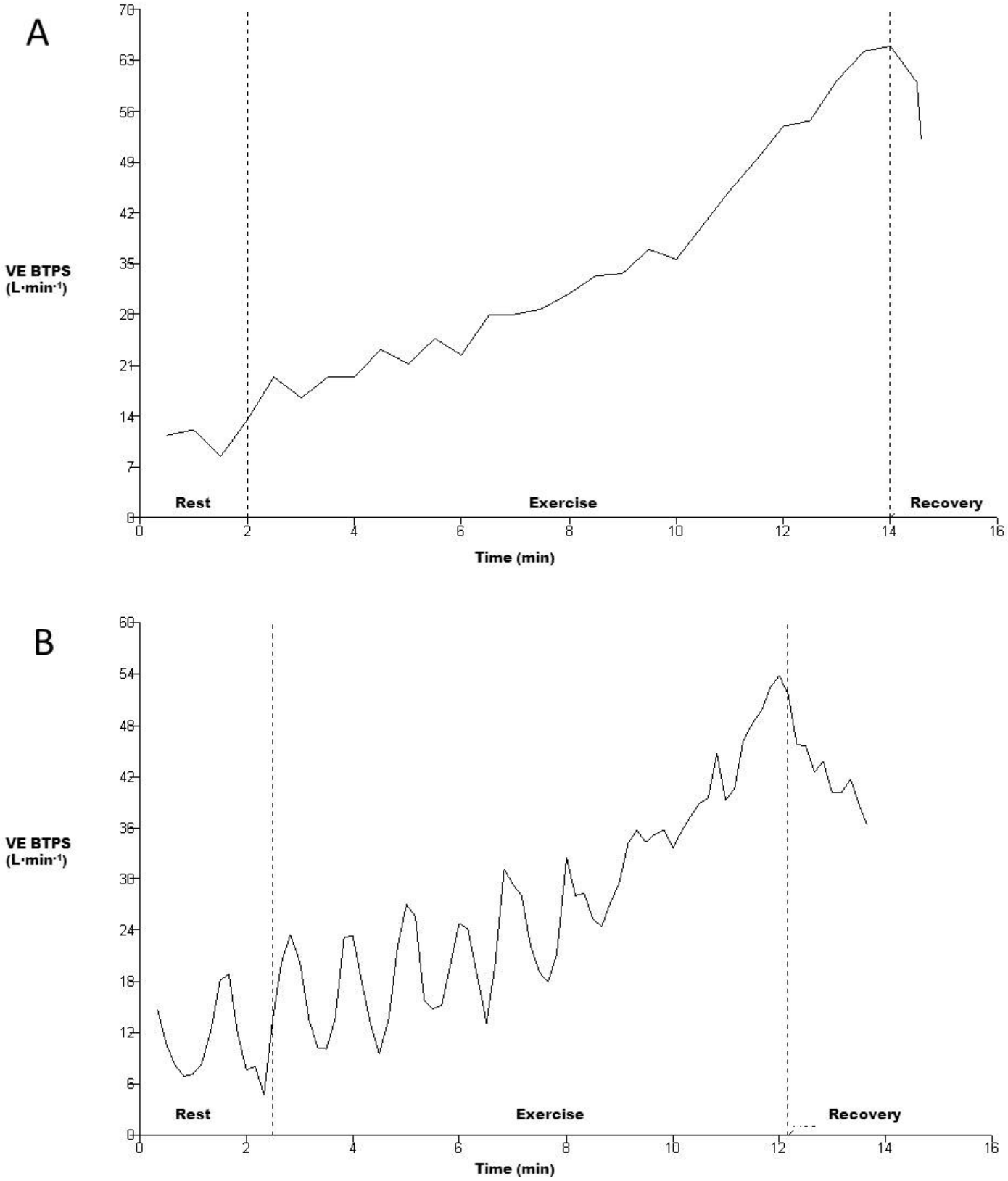
VE/VCO_2 slope values >34 have been shown to portend a worse prognosis in patients with HF; the risk increases with rising VE/VCO_2 values with the highest risk group having slopes ≥45. Severe COPD, pulmonary hypertension, and other parenchymal lung diseases can have a profound effect on the VE/VCO_2 slope, and this parameter should be used carefully in patients with evidence of severe lung disease on their resting spirometry.

At end exercise, hyperventilation can cause a marked increase in the measured ventilation and thus a steeping of the VE/VCO_2 curve. Thus many suggest that the VE/VCO_2 slope should be measured from rest up until the anaerobic threshold. However, studies of patients with HF have shown that measuring the VE/VCO_2 across the entire time of the exercise stimulus increases predictive ability of the parameter, and thus it is typical to determine VE/VCO_2 as a slope derived from the entire exercise provocation.

Assess for EOV (Figure 3). Exercise oscillatory ventilation (also sometimes referred to as exercise oscillatory breathing) is the exercise equivalent of Cheyne-Stokes respirations, in which there are significant oscillations in ventilation that persist through greater than 60% of the exercise test. Studies have shown that EOV correlates with a low cardiac output during exercise and portends an extremely poor short-term prognosis in heart failure patients.

Figure 3.

Assessment of Exercise Oscillatory Ventilation. A) Normal, linear, ventilatory response. B) Exercise oscillatory ventilation.

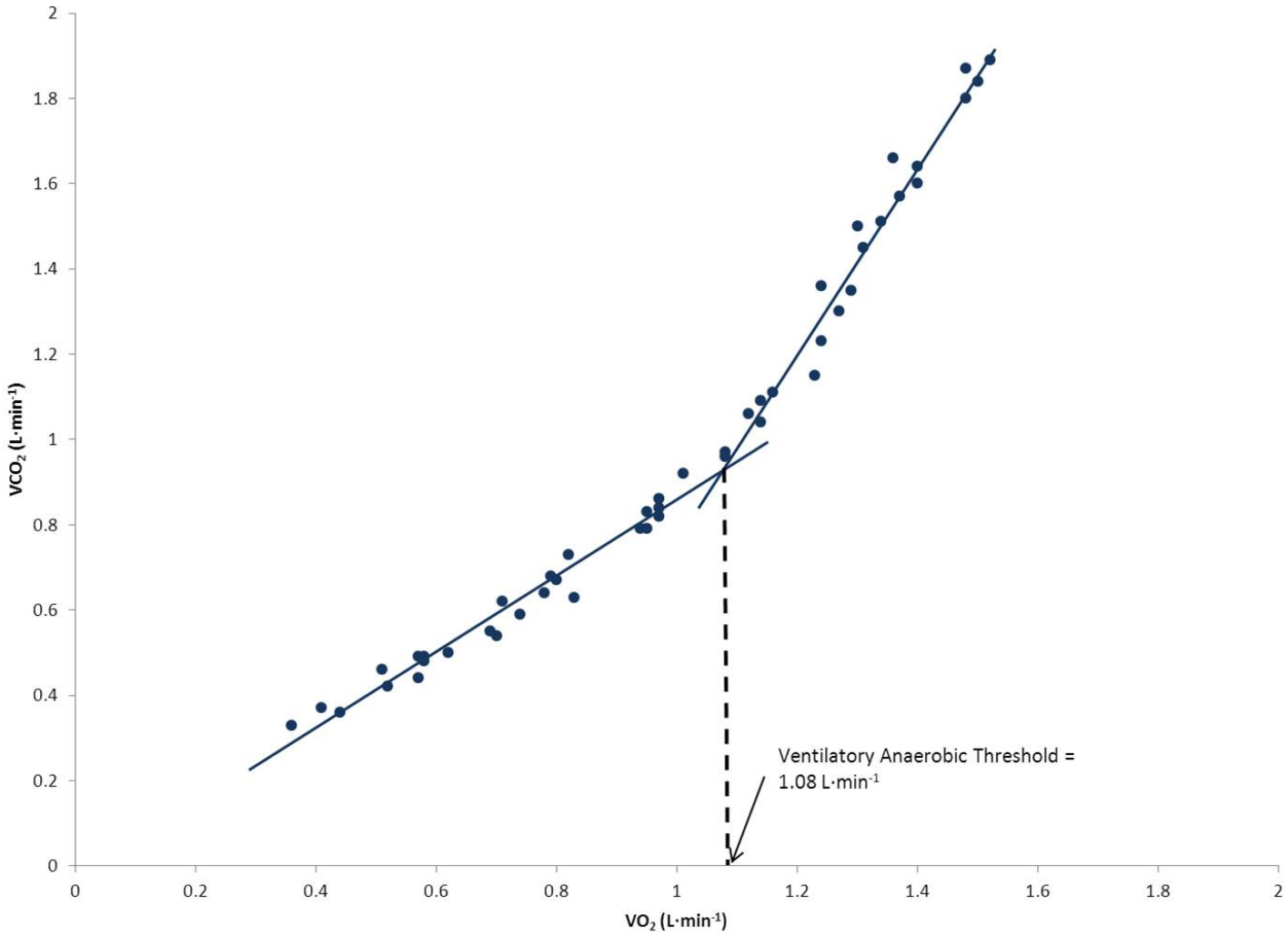


Step 6: Assess the anaerobic threshold (Figure 4). The anaerobic threshold (AT) is the point where the production of CO_2 exceeds the consumption of O_2 due to the production of lactic acid and its breakdown into CO_2 and H_2O. The AT can be measured in several ways but is most commonly measured graphically using the V-slope method and finding the inflection point where the slope of the VCO_2 versus VO_2 curve begins to steepen (this is commonly referred to as the ventilatory anaerobic threshold [VAT]). To further

confirm this point, the absolute VE/VCO_2 should be at its nadir, VE/VO_2 should have reached its lowest point and be increasing, and RER should be increasing.

Figure 4.

Assessment of VO2 at the ventilatory anaerobic threshold.



As the VAT can be determined in the absence of a true maximal effort, many experts have promoted this "effort-independent" variable as a primary measure in CPX testing. However, given the relatively high variability inherent in the VAT and the occasional complexity in measuring it, we recommend that peak VO_2 and VE/VCO_2 slope be used as the primary prognostic indicators from a CPX study, and that VAT be used only as a secondary prognostic indicator.

Normal patients will hit their VAT at a VO_2 equivalent to 50% to 60% of their predicted peak VO_2 while patients with significant HF have a VAT <40% of their predicted peak VO_2. The VAT is highly trainable, and well-conditioned subjects can have a VAT that exceeds 80% peak VO_2.

Step 7:Look at the O_2-pulse. The O_2-pulse, which is measured as the VO_2 (ml/min)/heart rate, provides a surrogate for stroke volume and can be extremely helpful in confirming an HF limitation.

Normal subjects will have a fairly linear rise in their O_2-pulse early in exercise, which then plateaus as they approach their predicted maximum O_2-pulse. In HF patients, the O_2-pulse tends to rise linearly during early exercise but then plateaus quickly and often well below the predicted peak O_2-pulse.

The graph of the measured O_2-pulse versus predicted is provided by most commercial CPX reporting packages. We consider a peak O_2-pulse of 80% or less indicative of a circulatory limitation; with lower numbers suggesting worse HF. One caveat in the use of O_2-pulse is that in patients with chronotropic incompetence the O_2-pulse can be falsely elevated and we suggest caution in using the O_2-pulse in patients whose peak exercise HR is <80% of their age-predicted maximum.

Step 8: Check the partial pressure of end-tidal CO_2, ($P_{ET}CO_2$). This measured variable is reported by most metabolic carts and represents the partial pressure of CO_2 at end expiration. The $P_{ET}CO_2$ decreases with hyperventilation or other processes associated with ventilatory inefficiency.

Studies have shown that patients with HF have lower $P_{ET}CO_2$ values at rest and during exercise than normal subjects. Lower values of $P_{ET}CO_2$ (<36) are strongly predictive of worse HF outcomes (often more so than the low peak VO_2). Given that the $P_{ET}CO_2$ can drop rapidly with end-exercise hyperventilation, this value is typically measured at the VAT.

Overall, in management of advanced HF, salient prognostic indices include low peak VO_2, the percentage of predicted VO_2, elevated VE/VCO_2 slope, EOV, low VAT, reduced O_2-pulse, low $P_{ET}CO_2$, chronotropic incompetence, arrhythmias, and the possibility of ischemia, all in the context of an RER that shows high effort.

Abnormal cardiac variables in the context of a low RER (<1.00) are not interpretable since they may be low only because of poor effort. In the presence of a poor effort, an evaluation of the oxygen uptake efficiency slope (OUES; slope of the VO_2 over the logVE from the beginning to end of exercise) can provide an estimation of the patient's potential functional capacity. This is widely used in pediatric CPX testing, but has been shown to be reliable in adults with correlations exceeding 0.90.

In using CPX as a diagnostic tool to delineate etiology of dyspnea or exercise intolerance, the perspectives provided by PFTs, O_2 saturation, VE/MVV, and other indices provide additional insights.

The AHA scientific statement by Balady et al (2010) provides further details and examples regarding CPX as a diagnostic tool. Important nuances include the fact that pulmonary pathologies may limit exercise capacity to such an extent that key cardiac indices are not obtainable.

For instance, severe lung disease (with associated features such as abnormal PFTs, O_2 desaturation, and low breathing reserve) may limit exercise capacity to the extent that VAT is never achieved. Therefore, accurate interpretation takes both sophistication regarding the interplay of pulmonary, cardiac, and skeletal muscle dynamics, and practice in sorting between how each impacts performance.

An elevated VE/VCO_2 slope suggests increased pulmonary dead space (i.e., areas where gas exchange occurs less efficiently). In HF patients, this can be related to factors such as elevated filling pressures, pulmonary hypertension, decreased cardiac output, abnormal chemo- and ergo-receptor sensitivity, and decreased alveolar membrane conductance.

Alternative and/or additional procedures to consider

Although we consider routine, non-invasive CPX testing the gold standard for assessing the functional capacity and etiology of exercise intolerance in patients with HF or unexplained dyspnea, we occasionally recommend CPX testing with invasive monitoring (pulmonary artery catheter +/- arterial line) for patients with suspected functional mitral regurgitation or exercise-induced pulmonary hypertension.

In the former case we look for a marked increase in the V waves of the wedge pressure tracing during exercise and in the latter we expect the mean PA pressure to start near normal and increase (usually rapidly) to well over 30 mm Hg during exercise with little or no change in the wedge pressure.

Complications and their management

The ATS/ACCP Guidelines suggest that the risk of death during clinical exercise testing is in the order of 2 to 5 per 100,000.

Data from the HF-ACTION study indicated that nonfatal major cardiovascular events (exacerbation of heart failure or angina requiring hospitalization, myocardial infarctions, strokes, transient ischemic attacks, ventricular fibrillation, and sustained ventricular tachycardia) occurred in <0.5 per 1,000 tests. No deaths occurred in any of more than 4000 tests performed for the study.

In our lab, about 8% of CPX tests involving patients with HF have been stopped by the person conducting the test for issues with safety for the patient (unpublished data):

- 41% of these stopped tests were done because of gait and balance issues threatening injury to the patient from falling.
- 26% were stopped due to desaturation detected on pulse oximetry.
- 11% were stopped for hypotensive responses; where another 11% were stopped for hypertensive response.
- 7% had non-sustained ventricular tachycardia (None required ICD discharge).
- 4% had ischemic changes on the ECG, along with significant chest pain warranting stopping the exercise.
- We have had no ventricular fibrillation or sustained ventricular tachycardia.
- To date, we have had no deaths, myocardial infarctions, strokes, transient ischemic attacks, or worsening of HF requiring hospitalizations that were related to the exercise test.

The risk of CPX testing in patients with HF appears to be on par with known or suspected coronary artery disease. As such, the CPX laboratory needs to be equipped exactly the same as any other stress testing laboratories (defibrillator, crash cart, supplemental oxygen, etc.).

In our laboratory, the most common issues are related to gait and balance. We try to minimize thisby performing cycle ergometry testing if it is clear that the patient will have significant difficulty walking on the treadmill.

Furthermore, when using exercise treadmill protocols, exercise laboratory staff routinely spot patients after the exercise stimulus (especially during transfers back to the stretcher for recovery monitoring) to minimize any chances of falls amidst post-exercise fatigue, dizziness, hemodynamic fluctuations, and/or arrhythmias.

What's the evidence?

Arena, R, Myers, J, Guazzi, M. "The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review". *Heart Fail Rev.* vol. 13. 2008. pp. 245-69.

(This review examines the body of evidence, which has used aerobic capacity and ventilatory efficiency as prognostic and diagnostic markers, as well as endpoints in interventional trials.)

Balady, GJ, Arena, R, Sietsema, K. "Clinician's guide to cardiopulmonary exercise testing in adults. A scientific statement from the American Heart Association". *Circulation.* vol. 122. 2010. pp. 191-225.

(Overview of CPX testing that provides comprehensive up-to-date clinical guidelines, physiologic rationale, and references for cardiopulmonary exercise testing. This statement expands upon the utility of CPX as a prognostic versus diagnostic tool, providing added details and examples.)

Borlaug, BA, Nishimura, RA, Sorajja, P, Lam, CS, Redfield, MM. "Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction". *Circ Heart Fail.* vol. 3. 2010. pp. 588-95.

(Study of the utility of invasive CPX to assess dynamic intracardiac pressures with unique bearing on diagnosis/management of HFPEF pulmonary hypertension, congenital heart disease, valvular disease, and other clinical applications.)

Cahalin, LP, Chase, P, Arena, R. "A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure". *Heart Fail Rev.* vol. 18. 2013. pp. 79-94.

(A recent, large meta-analysis providing prognostic information for several CPX-derived variables)

Chase, PJ, Davis, PG, Bensimhon, DR. "The obesity paradox in chronic heart failure: What does it mean". *Curr Heart Fail Rep.* vol. 11. 2014. pp. 111-117.

(Literature review of the "obesity paradox" in patients with HF which particularly focuses on skeletal muscle mass and body fat as they relate to BMI and HF severity. This paper also provides some recommendations for exercise prescription.)

Chase, P, Kenjale, A, Cahalin, LP. "The effect of respiratory exchange ratio on the prognostic value of peak oxygen consumption and ventilatory efficiency in patients with systolic heart failure". *JACC Heart Fail.* vol. 1. 2013. pp. 427-432.

(This is a robust analysis demonstrating the stability of the VE/VCO2 slope over a broad range of RER values and surprisingly the stability of the peak VO2, particularly when RER exceeds 1.00.)

Gibbons, RJ, Balady, GJ, Bricker, JT. "ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to Update the 1997 Exercise Testing Guidelines)". *J Am Coll Cardiol.* vol. 40. 2002. pp. 1531-40.

(This guideline is referenced above, which was used to demonstrate that the risk of exercise testing in patients with known or suspected CAD are similar to CPX testing in patients with HF.)

Guazzi, M, Myers, J, Arena, R. "Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure". *J Am Coll Cardiol.* vol. 46. 2005. pp. 1883-90.

(Assessment of the prognostic value of CPX indices in HFPEF.)

Guazzi, M, Dickstein, K, Vicenzi, M, Arena, R. "Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights". *Circ Heart Fail.* vol. 2. 2009. pp. 549-55.

(Comparison of the prognostic value of the 6-minute walk test and CPX in HF patients.)

Keteyian, SJ, Isaac, D, Thadani, U. "Safety of symptom-limited cardiopulmonary exercise testing in patients with chronic heart failure due to severe left ventricular systolic dysfunction". *Am Heart J.* vol. 158.