Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice

Natalia C. Berry,[1] Agarwal Manyoo,[2] William M. Oldham,[2] Thomas E. Stephens,[1] Ronald H. Goldstein,[3] Aaron B. Waxman,[1,2] Julie A. Tracy,[1] Peter J. Leary,[4] Jane A. Leopold,[1] Scott Kinlay,[1,5] Alexander R. Opotowsky,[1,6] David M. Systrom,[2] Bradley A. Maron[1,5]

[1]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [3]Department of Pulmonary and Critical Care Medicine, Veterans Affairs Boston Healthcare System, Boston, Massachusetts, USA; [4]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Washington, Seattle, Washington, USA; [5]Department of Cardiology, Veterans Affairs Boston Healthcare System, Boston Massachusetts, USA; [6]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA

Abstract: Invasive cardiopulmonary exercise testing (iCPET) combines full central hemodynamic assessment with continuous measurements of pulmonary gas exchange and ventilation to help in understanding the pathophysiology underpinning unexplained exertional intolerance. There is increasing evidence to support the use of iCPET as a key methodology for diagnosing heart failure with preserved ejection fraction and exercise-induced pulmonary hypertension as occult causes of exercise limitation, but there is little information available outlining the methodology to use this diagnostic test in clinical practice. To bridge this knowledge gap, the operational protocol for iCPET at our institution is discussed in detail. In turn, a standardized iCPET protocol may provide a common framework to describe the evolving understanding of mechanism(s) that limit exercise capacity and to facilitate research efforts to define novel treatments in these patients.

Keywords: pulmonary hypertension, cardiopulmonary exercise testing, protocol.

Pulm Circ 2015;5(4):610-618. DOI: 10.1086/683815.

Basic noninvasive cardiopulmonary exercise testing (CPET) utilizes a multiorgan system assessment to identify pulmonary, cardiovascular, metabolic, and/or neuromuscular causes of impaired exercise intolerance.[1] Established clinical indications for CPET include (1) evaluation of exercise capacity (peak oxygen uptake, $p\dot{V}O_2$) in patients considered for heart transplant, (2) differentiation of cardiac from pulmonary limitations in patients with exertional intolerance, (3) functional-limitation and risk assessment in cardiopulmonary disorders, (4) monitoring clinical response to therapy, and (5) determination of an exercise prescription for cardiopulmonary rehabilitation.[2]

For patients in whom the mechanism of dyspnea or exercise intolerance is not clarified by conventional CPET or by combining CPET with transthoracic echocardiography, which may offer prognostic information through noninvasive assessment of pulmonary arterial–right ventricular coupling,[3] invasive CPET (iCPET) should be considered. Specifically, iCPET is required to diagnose accurately three clinical pathophenotypes associated with exercise limitation: heart failure with preserved left ventricular ejection fraction (HFpEF), exercise-induced pulmonary hypertension (EI-PH), and impaired preload augmentation during exercise (Fig. 1). To accomplish this, iCPET uses contemporaneous invasive pulmonary vascular and systemic hemodynamic monitoring with assessments of gas exchange, heart rhythm, coronary perfusion, and exercise capacity to identify the pathophysiological substrate of exercise limitation. Despite the pivotal role of iCPET in the clinical evaluation of patients with comorbid lung and cardiovascular disease, standardized step-by-step protocols for the application of iCPET in clinical practice are lacking. To bridge this knowledge gap, we review clinically relevant aspects of exercise physiology and draw on experiences from our quaternary iCPET referral center and the published literature to synthesize a detailed protocol for the safe completion of iCPET in the hospital setting. It is anticipated that standardization will allow comparison between studies at different centers and better understand phenotypic differences in treatment response.

NORMAL PULMONARY VASCULAR AND RIGHT VENTRICULAR RESPONSE TO EXERCISE

During exercise, the pulmonary vasculature must accommodate a 5-fold increase in cardiac output.[4] This is accomplished by a marked decrease in pulmonary vascular resistance (PVR) that is far greater in magnitude than is observed in the systemic vasculature (Fig. 2).[5-7]

Address correspondence to Dr. Bradley A. Maron, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 77 Avenue Louis Pasteur, New Research Building, Room 0630-N, Boston, MA 02115, USA. E-mail: bmaron@partners.org.

Submitted March 26, 2015; Accepted August 24, 2015; Electronically published November 5, 2015.

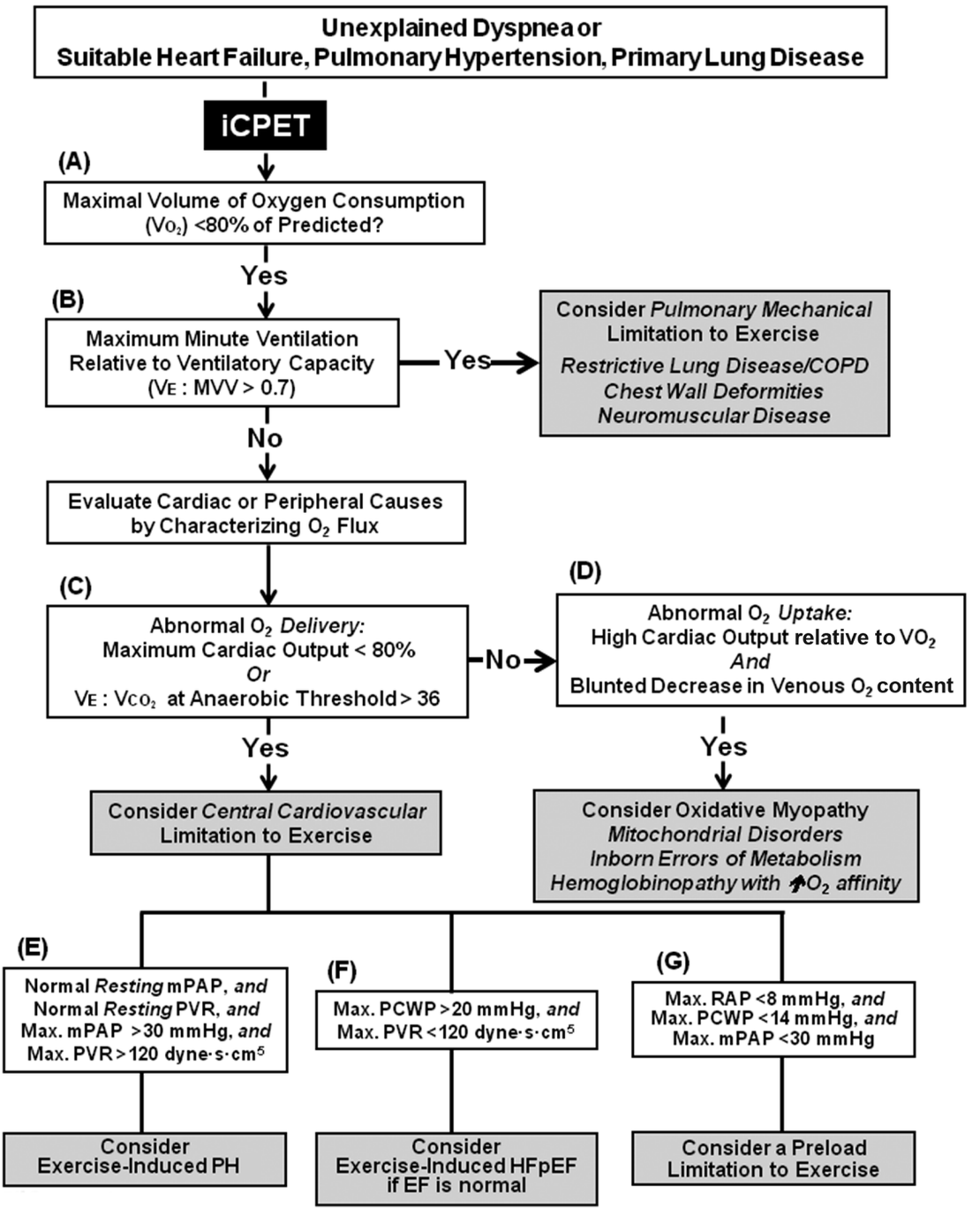


Figure 1. A diagnostic algorithm for interpreting invasive cardiopulmonary exercise testing (iCPET) results. *A*, Assessment of functional capacity is determined by calculating the maximum volume of oxygen consumed per minute (V_{O_2}), which may be performed during conventional cardiopulmonary exercise testing or iCPET. *B*, A disproportional increase in the minute ventilation relative to maximum ventilatory capacity (VE : MVV) indicates a pulmonary mechanical limitation to exercise. *C*, *D*, Alternatively, early achievement of the anaerobic threshold suggests disordered oxygen (O_2) flux that may be a consequence of decreased cardiac output (i.e., abnormal O_2 delivery; *C*) and/or impaired O_2 extraction by skeletal muscle tissue from arterial blood (*D*). This determination and the subsequent analyses, presented in the diagnostic algorithm, require iCPET and cannot be obtained by conventional exercise stress testing alone. *E*–*G*, In patients with a central cardiovascular limit to exercise, specific cardiopulmonary hemodynamics profiles observed during exercise are suggestive of exercise-induced pulmonary hypertension (EI-PH; *E*), exercise-induced heart failure with preserved left ventricular ejection fraction (HFpEF), if the left ventricular ejection fraction (EF) is normal (*F*), or a preload limitation to exercise (*G*). COPD: chronic obstructive pulmonary disease; mPAP: mean pulmonary artery pressure; MVV: maximum voluntary ventilation; PAH: pulmonary arterial hypertension; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; V_{CO_2}: volume of exhaled carbon dioxide. Figure and legend reproduced with some modifications and with permission from Maron et al.[1]

Consequently, this fall in PVR defends normal right ventricular–pulmonary arterial efficiency (i.e., coupling) by mitigating the increase in afterload that would otherwise result from such a large increase in cardiac output.

Compared to the baseline level, mean pulmonary artery pressure (mPAP) may increase by approximately 2-fold during exercise, to a peak mPAP of 30 mmHg and a peak pulmonary artery systolic pressure (PASP) of 50 mmHg.[8] The normal upper limit of mPAP appears to depend on the magnitude of increase in cardiac output and may differ by sex. In one study of 113 healthy volunteers evaluated by echocardiography at rest and at maximal supine exercise, a stepwise increase in maximal mPAP was observed relative to peak cardiac output (pCO): mPAP at exercise < 34 mmHg at a CO < 10 L/min, mPAP < 45 mmHg at a CO < 20 L/min, and mPAP < 52 mmHg at a CO < 30 L/min.[9]

In normal individuals, pulmonary capillary wedge pressure (PCWP) is expected to increase somewhat with exercise, which occurs as a consequence of intrinsic limitations to left ventricular lusitropy and physical constraints of the pericardium and from an accelerated heart rate and decreased diastolic time. In highly trained athletes, however, the anticipated changes to cardiopulmonary hemodynamics at rest and during exercise differ, compared to those in the general population. D'Andrea and colleagues[10] performed transthoracic echocardiography in 615 elite strength and endurance athletes to investigate the distribution of PASP in the athletically remodeled heart. In this study, resting PASP was elevated modestly, compared to that in nonathletes, but did not exceed 40 mmHg. Elevated PASP in athletes likely reflects increases in cardiac stroke volume, cardiac cavity size, and left ventricular mass that occur as a consequences of physical conditioning.[10] This observation is supported by findings from others; for example, in one study of 15 highly trained endurance athletes, the PASP measured echocardiographically was 54 mmHg at peak exercise. Importantly, in this study, the tricuspid regurgitant velocity–to–right ventricular outflow tract velocity time integral ratio ($TRV/RVOT_{VTI}$) was <0.2, which is consistent with a normal PVR despite increased cardiac output during exercise.[11]

While a decrease in PVR to <1.5 Wood units provoked by exercise is generally regarded as normal,[12] the effect of age and sex on the anticipated PVR and mPAP response to exercise has also been studied. In one meta-analysis[4] of normal individuals undergoing invasive hemodynamic assessment (n = 1,187), sex did not significantly influence mPAP at rest or with exercise. In one smaller study, premenopausal status in women was associated with lower PVR during exercise, suggesting that differences in pulmonary circulatory distensibility may relate to the interaction of sex and age.[9] Along these lines, an important association between age alone and mPAP during exercise was also observed. Compared to that in healthy subjects 24–50 years old (n = 33), resting mPAP was increased minimally in healthy subjects >70 years old (n = 9; 13.0 ± 2.7 vs. 15.4 ± 2.5 mmHg). However, this difference was exaggerated during exercise; compared to that in the older cohort, mPAP was significantly lower in the younger cohort.[4]

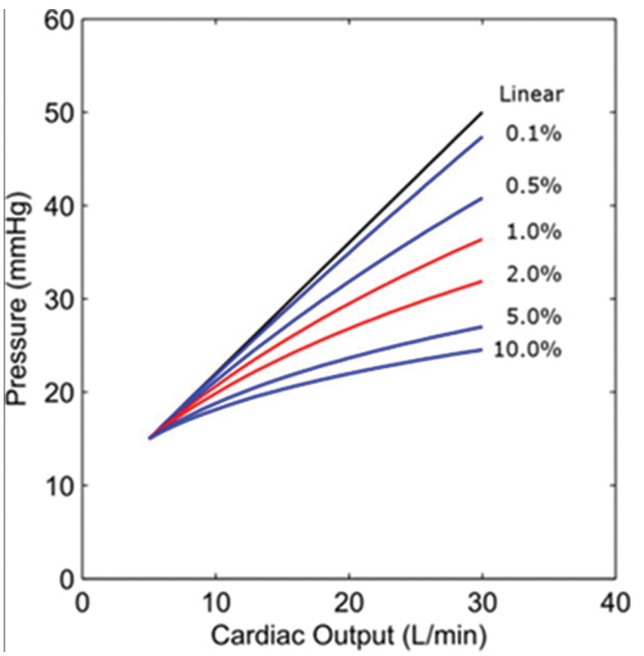


Figure 2. Modeling of the relationship between cardiac output and mean pulmonary artery pressure (mPAP). Under physiological conditions, the pulmonary vascular distensibility coefficient approximates 1%–2%, which results in a curvilinear relationship between cardiac output and mPAP. Adapted with permission from Lewis et al.[5] and Naeije et al.[6]

HFpEF

Patients with HFpEF tend to have normal biventricular systolic function but may demonstrate significant limitations to exercise in the absence of substantial pulmonary, metabolic, or neuromuscular disease. The hallmark of HFpEF exercise pathophysiology is an increased PCWP of >20 mmHg at peak physical activity that is due to decreased left ventricular compliance.[12,13] The mPAP also rises, but this occurs as a consequence of, and in parallel with, elevations in PCWP. Generally, patients with exercise limitation due to HFpEF have a normal PVR at rest that does not exceed 1.5 Wood units at peak activity. Nevertheless, chronic HFpEF is associated with adverse pulmonary vascular remodeling, abnormal pulmonary vascular reactivity, and impaired compliance, which may be demonstrated by an increased PVR measured at rest or elicited by exercise.[14]

PULMONARY ARTERIAL HYPERTENSION (PAH) AND EI-PH

PAH is a rare cause of dyspnea and fatigue with exertion. The pathobiology of PAH is characterized, in part, by endothelial dysfunction mediated by the interplay of genetic and molecular factors that promotes a specific histopathophenotype characterized by intimal hypertrophy, plexogenic lesions, and subtotal luminal obstruction of distal pulmonary arterioles.[15] Clinically, PAH is defined according to the following hemodynamic criteria assessed by right heart catheterization (RHC) at rest: mPAP ≥ 25 mmHg, PVR > 3 Wood units, and PCWP ≤ 15 mmHg. Early diagnosis

of PAH is critical in the contemporary era, in which 5 drug classes are available to improve patient quality of life and, possibly, survival.

Exertional symptoms associated with an increase or attenuated decrease in PVR during exercise have been described in patients with resting cardiopulmonary hemodynamics that do not meet criteria for PAH and for whom an alternative cause of functional limitation is not known.[16] Although there are no universally accepted criteria for the diagnosis of EI-PH,[17] peak mPAP > 30 mmHg, PVR > 1.5 Wood units, and PCWP < 20 mmHg at peak exercise are linked to clinically evident symptomology, substantially decreased peak $\dot{V}O_2$, cardiac output, and right ventricular ejection fraction as well as diminished quality of life.[12] In the absence of sufficiently powered outcome data characterizing the effect of abnormal cardiopulmonary hemodynamic measurements during exercise on hard clinical end points, it is important to consider that the spectrum of risk associated with mPAP, PVR, and/or PCWP levels near but below these cut-off values is not known. In addition, the ramifications of nonstandardized methods for recording and interpreting mPAP and PCWP reported across clinical studies on defining abnormally increased left heart pressure during exercise remain an area of active investigation.[18,19] Furthermore, the mechanism(s) underpinning EI-PH pathogenesis are incompletely characterized, although impaired flow-mediated endothelial synthesis of the potent vasodilator (and antimitogenic) molecule nitric oxide has been suggested.[20]

IMPAIRED PRELOAD AUGMENTATION DURING EXERCISE (PRELOAD FAILURE)

In contrast to HFpEF and EI-PH, which are characterized by pulmonary hypertension, we have identified ~8% of patients referred for iCPET in our practice who demonstrate a central cardiac limitation to exercise (i.e., low pCO) associated with low biventricular filling pressures (right atrial pressure [RAP] and PCWP), blunted stroke volume augmentation with exercise, and smaller right and left ventricular end-diastolic volumes at peak exercise.[21] These data suggest that inadequate preload augmentation may also limit aerobic capacity in a subset of patients with exertional symptoms. This fundamental concept has been theoretically and experimentally described extensively. From our clinical experience, we believe that this diagnosis should be considered in patients with peak RAP < 7 mmHg, peak PCWP < 13 mmHg, ΔRAP < 3 mmHg, or ΔPCWP < 7 mmHg, particularly in the absence of other etiologies of reduced pCO. The etiology of inadequate volume return to the heart remains unclear; however, several patients with postural orthostatic tachycardia syndrome have demonstrated this exercise phenotype, suggesting that neurohumoral control of the vascular system may be impaired.[22] This observation serves as a starting point for the consideration of additional diagnostic testing (i.e., screening for adrenal insufficiency, tilt-table testing, nerve conduction studies) and therapeutic intervention (i.e., hydration, increased sodium intake, fludrocortisone, pyridostigmine, midodrine, graded exercise training), although there are no longitudinal studies to support any specific recommendation.[1]

DETERMINING ELIGIBILITY AND INDICATION FOR iCPET

The specific clinical scenarios optimally suited for iCPET have been reviewed elsewhere in detail.[1,2] Generally, patients with exertional dyspnea and fatigue with unknown etiology or where symptoms are incompletely explained by other diagnostic testing may be considered for exercise hemodynamic testing. Invasive CPET may also be appropriate in patients with competing cardiopulmonary causes of exertional dyspnea if conventional therapeutic approaches are unsuccessful or if the dominant pathophysiology is unclear (e.g., severe obstructive lung disease and mitral regurgitation before the consideration of valve replacement). Determining iCPET candidacy hinges further on the availability of traditional baseline assessments for all cardiopulmonary patients, including an extensive medical history, a thorough physical examination, recent laboratory studies (e.g., complete blood count, thyroid-stimulating hormone), pulmonary-function testing with diffusing capacity, a chest radiograph, and a resting transthoracic echocardiogram in accordance with expert consensus guidelines for right heart assessment.[23,24] Other testing may be indicated in specific situations; the most common examples are computed tomography of the chest with or without intravenous contrast to evaluate for parenchymal or structural lung disease.

CONTRAINDICATIONS TO iCPET

Patients who are anticoagulated excessively or have severe thrombocytopenia are at increased risk. Patients with a contraindication to central venous access are not candidates for iCPET. Additional common relative contraindications to exercise testing apply to iCPET, including severe/symptomatic aortic stenosis, decompensated congestive heart failure, unstable coronary syndromes, inability to exercise, severe pulmonary hypertension, unstable arrhythmias, or syncope.[25]

CPET PROTOCOL

The following is a stepwise approach to the application of iCPET in clinical practice.

1. Patient counseling

Discuss sequential phases of the iCPET study and obtain consent.

a. RHC and radial artery access placement:
   i. In patients for whom the diagnosis of unexplained dyspnea is unresolved despite alternative testing, including noninvasive CPET, RHC during iCPET is required to evaluate for specific forms of cardiopulmonary disease. RHC is safe, and, although complication rates vary by center, the risk of death in one large clinical study of patients (n = 7,218) with severe pulmonary hypertension was 0.055% (n = 4); serious adverse events occurred in 1.1% of patients (n = 76), predominately as a result of bleeding at the site of vascular access.[26] Additional complications include accidental arterial catheterization and transient arrhythmia during passage of the catheter through the right cardiac chambers. To minimize the risk of complication, cardiac catheterization is performed

uniformly with the assistance of ultrasound and fluoroscopic guidance at our center.

ii. Radial artery canalization is generally well tolerated; complications are uncommon and include, but are not exclusive to, temporary or permanent vessel occlusion, pseudoaneurysm formation, infection, and, rarely, air embolism. Local pain at the site of cannulation, however, is common and may persist for days.

b. If the exercise testing is not performed in the catheterization laboratory, the patient is transported, with appropriate healthcare provider supervision, from the cardiac catheterization laboratory to the iCPET suite with continued cardiac rhythm and pulmonary artery (PA) monitoring, the latter to avoid inadvertent and sustained wedging of the catheter or retraction into the right ventricular cavity.

c. Each vascular access site (i.e., radial, internal jugular) is monitored at each stage.

d. The patient is familiarized with study devices (e.g., cycle ergometer, pneumotachograph, metabolic cart, waveform screen for pulmonary arterial catheter and radial line, electrocardiography [ECG] leads).

e. Review stages of CPET:

i. Preparatory phase/setup.

ii. Warm-up phase.

iii. Exercise phase.

iv. Recovery phase.

2. Components of iCPET (Video 1)

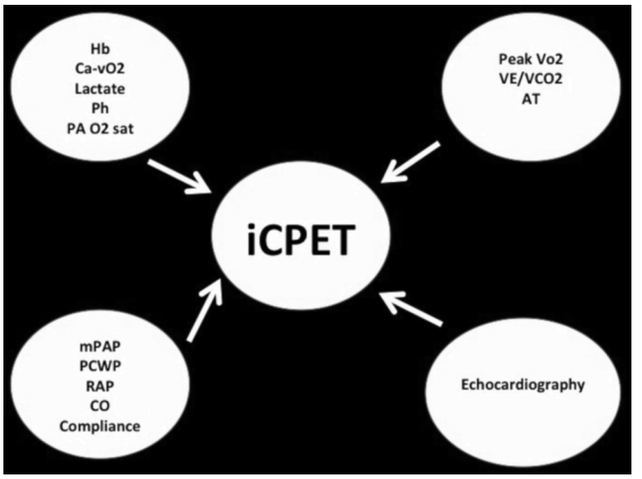
a. Cycle ergometer. In our laboratory, an upright cycle ergometer is used for exercise stress, where the resistance (i.e., work) is continually and linearly increased until symptomatic exhaustion. A semisupine cycle ergometer or treadmill may also be used. In rare cases where these modalities are not possible, arm ergometry may be used, but this precludes radial arterial access, and measurement is limited to PA monitoring.

b. The metabolic cart contains gas analyzers and a pneumotachograph for breath-by-breath measurements of expired O_2 and CO_2 and ventilation with calculation of $\dot{V}O_2$ and $\dot{V}CO_2$. The metabolic cart can also be used to perform spirometry to measure or calculate maximum voluntary ventilation (MVV = 35 × FEV1), where FEV1 is forced expiratory volume in 1 second.

c. Continuous 12-lead ECG to monitor heart rate, rhythm, and signs of ischemia.

d. Peripheral noninvasive oxyhemoglobin saturation level (SpO_2) monitoring.

e. Hemodynamic monitoring and vascular access. Continuous measurements of systemic blood pressure are taken through the radial artery catheter; central venous, right atrial, right ventricular, and pulmonary arterial pressures are measured at rest and during exercise via the PA catheter. The PCWP is determined by balloon inflation every minute during exercise.



Video 1. Still image from a video of maximum voluntary ventilation acquired at rest before invasive cardiopulmonary exercise testing (iCPET). The patient is instructed to inspire and expire maximally for 15 seconds, and the total volume (i.e., bulk flow of air) is recorded by spirometry (video 1, available online). AT: anaerobic threshold; Ca-vO_2: O_2 content of arterial–mixed venous blood; CO: cardiac output; Hb: hemoglobin; mPAP: mean pulmonary artery pressure; O_2 sat: oxygen saturation; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; VCO_2: volume of exhaled carbon dioxide; VE: minute ventilation; VO_2: oxygen uptake.

f. Vascular access. Blood samples from radial and pulmonary arterial catheters are also drawn every minute to measure blood gases and pH. Cardiac output is calculated every minute via the direct Fick method using co-oximeter-measured SaO_2 and SvO_2 (arterial oxyhemoglobin saturation level and central venous oxygen saturation, respectively) and measured $\dot{V}O_2$. Plasma lactate is also measured, generally via the radial artery.

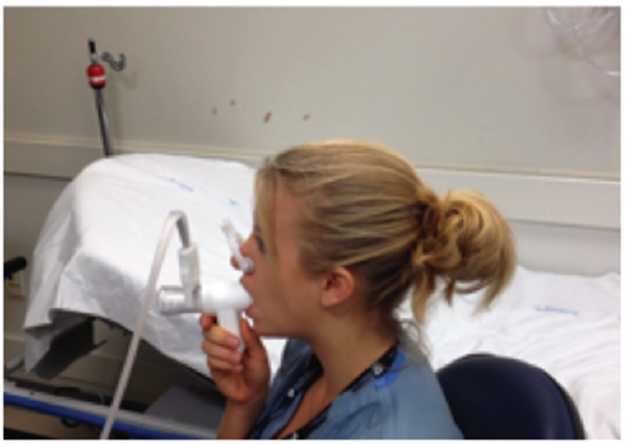
3. Pulmonary function testing, RHC, and radial artery catheterization

a. Before catheterization, spirometry is performed to record forced vital capacity (FVC), FEV1, FEV1/FVC, and MVV (either measured or estimated by FEV1 × 35; video 2). In patients for whom neuromuscular disease is a consideration, the MVV should be measured before and after exercise.

b. Exercise flow volume loops and inspiratory capacity measurements may be obtained during exercise in specific patients, such as those where there is suspicion of a vascular ring or who have pulmonary disease of unclear severity.[27]

c. Standard sterile technique applies to RHC and radial artery cannulation, performed in a cardiac catheterization laboratory by an experienced operator.

d. Blood pressure and oxyhemoglobin saturation levels are recorded in each of the following vascular compartments



Video 2. Still image from a video of invasive cardiopulmonary testing elements in clinical practice (video 2, available online).

with the patient supine: superior vena cava, right atrium, right ventricle, and main PA. Cardiac output is measured with the Fick method according to the following formula: Qt = $\dot{V}_{O_2}$/C(a-v)$_{O_2}$, where Qt is cardiac output, $\dot{V}_{O_2}$ is the volume of oxygen consumption, and C(a-v)$_{O_2}$ is the O_2 content of arterial–mixed venous blood.[1]

e. In the absence of a contraindication to further testing on resting RHC (e.g., severe pulmonary hypertension, decompensated heart failure), the catheter port is disconnected from the pressure-monitoring system and reconnected to a portable pressure transducer and monitor.
f. Calibration. The PA and PCWP are recorded under fluoroscopy to ensure proper location of the catheter tip. The patient is then moved to the upright position, and the pressure calibrator is opened to ambient air ("zeroed"), calibrated, and leveled to the fourth intercostal space at the midaxillary line, approximately 5 cm below the angle of Louis or 3 finger breadths below the axilla, which is in the plane of the right atrium in most patients.[28]
g. The monitored patient is then transferred, under the supervision of appropriate healthcare provider escort, to the iCPET suite.

4. iCPET suite

a. In addition to the components required for iCPET (see above), our iCPET suite contains the WITT biomedical hemodynamic monitoring system for pressure measurements and an advanced cardiopulmonary life-support emergency cart.
b. Staff required. At our facility, 4 appropriately trained medical personnel are involved in performing the invasive cardiopulmonary exercise test (iCPET):

   i. An exercise physiologist supervises the metabolic cart and timer, coordinates the timing of blood draws and PCWP measurements, provides encouragement and direction ("coaching") to the patient, anticipates the end of the test from symptoms and metabolic data, and is positioned to obtain arterial blood gas, pH, and lactate samples appropriately (see item c in "6. Performing the iCPET").
   ii. A second exercise physiologist manages the waveform recorder and records the systemic and PA pressures and PCWP at the appropriate time intervals (see item c in "6. Performing the iCPET").
   iii. A physician assistant, nurse practitioner, or physician performs the PA catheter balloon inflation to obtain wedge pressure tracing at the appropriate time intervals (see item c in "6. Performing the iCPET"), as well as obtaining mixed venous blood gases and pH from the distal PA catheter port at the appropriate time intervals.
   iv. A physician is present and supervises the test.

5. Determining the exercise protocol

a. Pedal resistance increases during the exercise test at a linear rate after a freewheel period. The rate of increase is determined according to each patient's prior exercise test performance or self-reported baseline fitness level, to aim for an 8–12-minute symptom-limited test as follows:
   i. 10 W/min for sedentary patients.
   ii. 15 W/min if patients are able to perform light exercise: functional capacity is limited to walking slowly, cooking, washing dishes, or other low aerobic activities of daily living.
   iii. 20 W/min if patients are able to perform moderate exercise: functional capacity is limited to walking at brisk pace (4 mph); heavy house cleaning, such as vacuuming or mopping; and other similar forms of housework, including the use of a powered lawn mower.
   iv. 25 W/min or more for patients who routinely perform strenuous exercise: functional capacity limits allow patient to jog (~6 mph), bicycle (~15 mph), or participate in organized sports such as tennis or basketball.
b. Patients pedal at a continuous rate of approximately 60 cycles/min as resistance increases throughout the exercise bout. The exercise physiologist plays an important role in monitoring the cycling rate. The goal exercise time duration is exercise at least 5 minutes.

6. Performing the iCPET (video 1)

a. Preparation phase:
   i. Demographic and other patient characteristics are recorded systematically on a patient report form (appendix, available online).
   ii. Patient is positioned on ergometer with seat height adjusted to comfort, with total or near-total leg extension at nadir of pedal trajectory.
   iii. The 12-lead ECG system is activated with standard lead positioning.

iv. With the patient on the cycle ergometer, the radial and PA catheter waveform recorders are connected and zeroed and leveled according to the methods and landmarks described in item c in "3. Pulmonary function testing, RHC, and radial artery catheterization" above.
v. Pulse oximeter is connected to the WITT monitoring system or other recording system for continuous Sa_{O_2} monitoring. The validity of noninvasive Sa_{O_2} assessment is supported by comparing reported heart rate to the ECG heart rate and subsequently validated in comparison to radial artery Sa_{O_2} measurements.
vi. The mouthpiece for the pneumotachograph and metabolic cart should be fitted and nose clip placed, followed by baseline ventilation and pulmonary gas exchange measurements recorded over a 2-minute period.
vii. Baseline arterial blood gas (ABG), Sv_{O_2}, and plasma lactate are measured.
viii. Baseline systemic and pulmonary arterial pressures, central venous pressure (RAP), and PCWP are measured.

b. Warm-up, or "freewheel," phase:
i. Patients will warm up without resistance, or "freewheel," for 3 minutes; during this time, all pressure transducers are leveled again to account for subtle changes in posture that may occur with movement of exercise.
ii. Continuous ventilation and pulmonary gas exchange measurements are recorded.
iii. Repeat ABG, venous blood gas (VBG), pH, and plasma lactate are measured after 90 seconds of freewheeling.
iv. Repeat systemic and pulmonary arterial pressures, central venous pressure, and PCWP are recorded after 90 seconds of freewheeling.

c. Exercise phase:
i. Metabolic cart–driven resistance is added to the pedal stroke at the predetermined rate.
ii. Blood samples for ABG, VBG, pH, and plasma lactate measurements are drawn at 1-minute intervals.
iii. PCWP is measured at 1-minute intervals. During each PA catheter balloon inflation, the patient is asked to passively exhale (i.e., expiration through an open glottis) and "skip" 1 or 2 breaths while maintaining an open glottis; this ensures minimal contribution of expiratory pleural pressure to and avoids overestimation of the PCWP reading.[29] This approach can be untenable, and if the patient is unable to do the slow breath maneuver during exercise, an electronic mean is taken through the respiratory cycle.
iv. Central venous (RAP), systemic arterial, and PA pressures are recorded continuously through passive exhalation.
v. Peak exercise is defined as the point in time at which the patient is unable to maintain 60 revolutions/min cycle rate.
vi. ABG, VBG, pH, Sv_{O_2}, and plasma lactate are measured at peak exercise.
vii. The mPAP and PCWP are measured at peak exercise.
viii. Coaching is permissible; the goal is achieve at least 5 minutes, though preferably 8–12 minutes, of exercise before the completion of the test.

d. Recovery phase:
i. The cycle ergometer resistance returns to 0 W/min.
ii. The patient cycles for approximately 1 additional minute.
iii. After 1 minute and 2 minutes of recovery, 1 mL of blood is sampled for ABG, VBG, pH, Sv_{O_2}, and plasma lactate, and PAP and PCWP are measured (appendix).
iv. Patient is transferred, with the appropriate healthcare provider escort, to an area for recovery, and the blood pressure and heart rhythm are monitored frequently. The PAP and blood lactate levels are monitored at 30- and 60-minute time points if the catheters are tolerated by the patient. The PA catheter is then removed while the patient is instructed to hum. The catheter insertion site is compressed with direct pressure for at least 5 minutes, and occlusive dressing is applied and maintained at the puncture site for 24 hours. The radial artery catheter is then removed, firm but not occlusive pressure is applied to the insertion site for a minimum of 10 minutes, and a pressure bandage applied is applied and maintained for 24 hours. The patient is instructed against lifting for 48 hours and asked to contact the exercise staff in the event of bleeding, hematoma, redness, rash, finger pain, and/or cyanosis at either the PA or radial artery insertion sites.

7. Indications for study cancellation or termination

a. ECG signifying myocardial injury current or potentially lethal arrhythmias.
b. Systemic hypotension (e.g., systolic blood pressure < 90 mmHg).
c. Extreme hypertension (e.g., systolic blood pressure > 220 mmHg).
d. Syncope, presyncope, or lightheadedness.
e. Sa_{O_2} < 88%.
f. Severely elevated PCWP (>40 mmHg) during exercise.

CONCLUSIONS

Invasive CPET is an important consideration in the clinical evaluation of patients with unexplained exertional intolerance despite conventional diagnostic testing. By leveraging the simultaneous assessment of full cardiopulmonary hemodynamics and gas exchange performance during exercise, iCPET is well positioned to diagnose EI-PH, HFpEF, and failure to augment right ventricular pressure as occult causes of exertional dyspnea. Our experience suggests that a

multidisciplinary approach to the application of iCPET that involves pulmonologists, cardiologists, physician assistants, and exercise physiologists is necessary for the completion of a safe and accurate study in clinical practice. With an increased number of patients diagnosed with unexplained dyspnea,[2,30] it is hoped that the implementation of a standardized iCPET protocol will enhance the dialogue by which clinicians discuss the pathophysiology of exertional dyspnea and expand efforts to identify novel treatments for patients afflicted with this condition.

ACKNOWLEDGMENTS

Informed consent to participate in this project was obtained for persons appearing in all figures.

Source of Support: This work was supported by the National Institutes of Health (grants 1K08HL111207–01A1 to BAM and U01HL125215–01 to JAL); Pulmonary Hypertension Association, Gilead Research Scholars Fund, Klarman Foundation at Brigham and Women's Hospital, and Cardiovascular Medical Research and Education Fund (CMREF) awards to BAM; and a VA Merit Award to RHG from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development: Clinical Science Research and Development Service.

Conflicts of Interest: BAM receives funding from Gilead Sciences to study pulmonary hypertension. ARO receives funding from Actelion to study pulmonary hypertension and congenital heart disease. ARO is supported by the Dunlevie Family Fund. The other authors have no conflicts to declare.

REFERENCES

1. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. Circulation 2013;127(10):1157–1164.
2. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, et al. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 2012;126(18):2261–2274.
3. Guazzi M, Naeije R, Arena R, Corrá U, Ghio S, Forfia P, Rossi A, Cahalin LP, Bandera F, Temporelli P. Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. Chest 2015;148(1):226–234.
4. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34(4):888–894.
5. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary disease. Circulation 2013;128(13):1470–1479.
6. Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiéry JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. Am J Respir Crit Care Med 2013;187(6):576–583.
7. Manetos C, Dimopoulos S, Tzanis G, Vakrou S, Tasoulis A, Kapelios C, Agapitou V, Ntalianis A, Terrovitis J, Nanas S. Skeletal muscle microcirculatory abnormalities are associated with exercise intolerance, ventilator inefficiency, and impaired autonomic control in heart failure. J Heart Lung Transplant 2011;30(12):1403–1408.
8. Waxman AB. Exercise physiology and pulmonary arterial hypertension. Prog Cardiovasc Dis 2012;55(2):172–179.
9. Argiento P, Vanderpool RR, Mulè M, Russo MG, D'Alto M, Bossone E, Chesler NC, Naeije R. Exercise stress echocardiography of the pulmonary circulation: limits of normal and sex differences. Chest 2012;142(5):1158–1165.
10. D'Andrea A, Naeije R, D'Alto M, Argiento P, Golia E, Cocchia R, Riegler L, et al. Range in pulmonary artery systolic pressure among highly trained athletes. Chest 2011;139(4):788–794.
11. Bidart CM, Abbas AE, Parish JM, Chaliki HP, Moreno CA, Lester SJ. The noninvasive evaluation of exercise-induced changes in PA pressure and pulmonary vascular resistance. J Am Soc Echocardiogr 2007;20(3):270–275.
12. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. Circulation 2008;118(21):2183–2189.
13. Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. Central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. Circ Heart Fail 2015;8(2):278–285.
14. 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 2010;3(5):588–595.
15. Rich S, Rabinovitch M. Diagnosis and treatment of secondary (non–category 1) pulmonary hypertension. Circulation 2008;118(21):2190–2199.
16. Fowler RM, Maoirana AJ, Jenkins SC, Gain KR, O'Driscoll G, Gabbay E. Implications of exercise-induced pulmonary arterial hypertension. Med Sci Sports Exerc 2011;43(16):983–989.
17. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(25 suppl.):D42–D50.
18. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings: how to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med 2014;190(3):252–257.
19. Boerrigter BG, Waxman AB, Westerhof N, Vonk-Noordegraaf A, Systrom DM. Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects. Eur Respir J 2014;43(4):1316–1325.
20. Kane DW, Tesauro T, Koizumi T, Gupta R, Newman JH. Exercise-induced pulmonary vasoconstriction during combined blockade of nitric oxide synthase and beta adrenergic receptors. J Clin Invest 1994;93(2):677–683.
21. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results of clinical invasive cardiopulmonary exercise testing. Pulm Circ (forthcoming).
22. Masuki S, Eisenach JH, Schrage WG, Johnson CP, Dietz NM, Wilkins BW, Sandroni P, Low PA, Joyner MJ. Reduced stroke volume during exercise in postural tachycardia syndrome. J Appl Physiol 2007;103(4):1128–1135.
23. Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB. Right heart failure: toward a common language. J Heart Lung Transplant 2014;33(2):123–126.
24. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23(7):685–713; quiz 786–788.
25. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher G, Forman D, et al. Clinician's guide to cardiopulmonary exercise testing in adults:

a scientific statement from the American Heart Association. Circulation 2010;122(2):191–225.
26. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jaïs X, Marinelli A, Barst RJ, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48(12):2546–2552.
27. Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm Med 2013;2013:956081. doi:10.1155/2013/956081.
28. Scheer BV, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. Crit Care 2002;6(3):199–204.
29. Ryan JJ, Rich JD, Thiruvoipati T, Swamy R, Kim GH, Rich S. Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension. Am Heart J 2012;163(4):589–594.
30. Udelson JE. Heart failure with preserved ejection fraction. Circulation 2011;124(21):e540–e543.