Cardiopulmonary Exercise Testing in the Evaluation of Unexplained Dyspnea

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Diagnosis of unexplained exertional dyspnea or fatigue is a significant challenge. When routine cardiac and pulmonary evaluations are unrevealing, cardiopulmonary exercise testing (CPET) with invasive hemodynamic monitoring may reveal the abnormal physiology causing these symptoms. In this review, the authors describe the protocol for invasive CPET at Massachusetts General Hospital, and present cases of exercise-induced pulmonary arterial hypertension and exercise-induced heart failure with preserved ejection fraction, as well as a new entity, preload failure, to demonstrate the utility of invasive CPET in the evaluation of unexplained exertional dyspnea. Indeed, exercise-induced pulmonary hypertension may represent early disease where prompt therapeutic intervention may improve outcome. When compared to noninvasive CPET or exercise stress echocardiography, invasive CPET has significant advantages in identifying the etiology of elevated pulmonary pressures and determining the influence of central hemodynamics on exercise capacity. For this reason, we expect that invasive CPET will assume a more prominent role in the evaluation and management of pulmonary hypertension.

Unexplained exertional dyspnea or fatigue can pose a significant diagnostic challenge to physicians as these symptoms are often relatively mild, poorly characterized, or insidious. Routine cardiac and pulmonary evaluations may be unrevealing. Invasive cardiopulmonary exercise testing (CPET) with pulmonary and radial arterial catheters is uniquely suited to evaluate these symptoms as it provides a general assessment of exercise capacity and defines the specific contributions of any cardiac, pulmonary mechanical, pulmonary vascular, hematologic, muscular, or neurologic limitations. In other words, the test can determine the presence or absence of disease, and if present, the nature of the limitation(s).

Since invasive CPET allows accurate measurement of pulmonary arterial and cardiac filling pressures during exercise, it can be most helpful in characterizing an abnormal response of the circulatory system to exertion. Indeed, exercise-induced pulmonary arterial hypertension (eiPAH) has been shown by CPET to be an early, mild, and symptomatic phase of the PAH spectrum.[1] In this review, we describe the protocol for invasive CPET at Massachusetts General Hospital (MGH) and provide 3 case studies where this testing aided the diagnosis of pulmonary vascular disease.

INVASIVE CPET AT MGH

The MGH Cardiopulmonary Exercise Laboratory performs approximately 150 clinically indicated invasive CPETs per year. The majority of tests are performed for the evaluation of dyspnea or fatigue of unclear etiology, with the balance performed as part of an evaluation for cardiac or pulmonary transplantation. Upon arrival, the patient receives a pulmonary artery catheter through the internal jugular vein in the cardiac catheterization laboratory, where initial, supine, resting pulmonary pressures and cardiac output are measured. Subsequently, a radial artery catheter is placed in the exercise laboratory. If the patient has a pulmonary capillary wedge pressure (PCWP) <5 mm Hg at rest, intravenous normal saline is provided in 0.5 L boluses up to 1.5 L to increase the PCWP above 5 mm Hg. This is standard practice to overcome the effects of volume depletion secondary to the patient's nil per os status prior to the test. The patient then performs a single bout of incremental cycling exercise to exhaustion (Medgraphics CPE 2000, Medical Graphics Corp., St. Paul, MN). The test begins with 2 minutes of rest, followed by 3 minutes of unloaded pedaling. Work is then continuously increased by 6.25 to 25 W/min depending on the patient's subjective exertional tolerance. The test ends when the patient can no longer continue to exercise, usually due to dyspnea, leg fatigue, or both.

Throughout the test, breath-by-breath pulmonary gas exchange and minute ventilation are measured by a metabolic cart (Medgraphics CPX/D, Medical Graphics Corp., St. Paul, MN). Mean systemic arterial pressure, end-expiratory right atrial (RAP), and mean pulmonary arterial pressures (mPAP) are measured continuously (CALYSTO Series IV, Witt Biomedical Corp., Melbourne, FL). Heart rate and rhythm are also monitored by continuous 12-lead recording. End-expiratory PCWP is measured at 50% of the a-wave X descent at rest and during each minute of exercise. At peak exercise, the patient is instructed to pause or slow the respiratory rate with the glottis open in an effort to accurately measure central pressures by minimizing the effect of pleural pressure changes. Blood samples are obtained from the pulmonary and radial artery catheters at rest and during each minute of exercise for measurement of PO_2, PCO_2, pH, lactate, hemoglobin concentration ([Hb]), and oxygen saturation. Finally, right and left ventricular ejection fractions (RVEF, LVEF) and left ventricular end diastolic volume (LVEDV) are measured at rest

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Figure 1: Cardiopulmonary exercise testing with invasive hemodynamic monitoring in the MGH Cardiopulmonary Exercise Laboratory. Patients perform a single bout of incremental cycling exercise (A) while gas exchange is monitored by a standard metabolic cart (B). Pulmonary and systemic pressures are continuously monitored (C), as are heart rate and rhythm by 12-lead EKG (D). Systemic arterial and mixed venous blood samples are drawn simultaneously every minute during exercise for blood gas analysis (E), and the PCWP is measured (F). Resting and peak exercise first pass radionuclide ventriculographic scanning is performed to determine RVEF and LVEF and LVEDV (G).

and peak exercise by first-pass radionuclide ventriculography (System 77, Baird Corp., Bedford, MA) (Figure 1).

Maximum effort is indicated by peak heart rate ≥80% of predicted or peak respiratory exchange ratio ≥1.00. Predicted values for VO_2max are based on age, gender, and height.[2] The ventilatory threshold (VT) is determined by the V-slope method.[3] VE/VCO_2 is measured at the VT. Cardiac output (Qt) is calculated from the Fick principle [$Qt = VO_2/(Ca\text{-}vO_2)$], while maximal predicted cardiac output is calculated from the predicted VO_2max and an assumed arterial-venous oxygen content difference equal to the [Hb] per 100 mL blood, using a normal [Hb] equal to 14 g/dL.[4] Pulmonary vascular resistance (PVR) is calculated from (mPAP-PCWP)/Qt.

Each of the 3 cases described below illustrates the utility of invasive exercise testing in the diagnosis of pulmonary vascular disease.

Case 1

Patient 1 is a 27-year-old woman who was referred to the pulmonary clinic at MGH for evaluation of exertional dyspnea in April 2009. Two years before her presentation, the patient was in excellent health. She routinely ran 6 miles daily without difficulty, participated in road races, and was a competitive swimmer in high school and college. In the summer of 2007, she began to experience nausea, muscle aches, dizziness, headache, and breathlessness when she ran. She had no symptoms at rest. Her exertional symptoms worsened until 1 year prior to her presentation, when she was unable to run for more than 5 minutes before developing severe fatigue, breathlessness, and palpitations. Laboratories and a cardiac stress test at that time were normal. She subsequently developed wheezing while running, and chest radiography and pulmonary function testing were normal. Her symptoms were not relieved with a preexercise bronchodilator.

In July 2008, omeprazole was prescribed for possible reflux and laryngospasm causing hyperventilation while running, but did not relieve her symptoms. She was referred for a noninvasive incremental CPET that was normal, with VO_2max 80% of predicted and normal VT (46% of predicted VO_2max) (Figure 2), with a slightly elevated VE/VCO_2 of 38 and low end-tidal PCO_2 ($PetCO_2$). After this CPET, she ran a 15 km race where she developed left leg pain, palpitations, breathlessness, chest pain, nausea, and lightheadedness. She was evaluated on December 15, 2008, for these symptoms, which were attributed to anxiety, and referral to a sports psychiatrist was made.

On December 18, 2008, she developed acutely worse symptoms now with presyncope and was seen by her primary care physician whose evaluation was notable for a D-dimer elevated at 2236, and so she was referred to the emergency department of another hospital for evaluation. Pulmonary CT angiography demonstrated multiple bilateral pulmonary emboli, 2 wedge infarctions, and multiple bilateral deep vein thromboses. An echocardiogram showed RV strain. She did not receive thrombolysis given her hemodynamic stability and the risk of bleeding into the infarcted lung. She was anticoagulated with low molecular weight heparin as a bridge to warfarin. At the time of her presentation, she was taking oral contraceptive pills, which were discontinued at discharge, and she denied recent travel, smoking, cancer, and any family or personal history of clotting. A hypercoagulability evaluation was notable for the Factor V Leiden mutation.

Despite therapeutic anticoagulation, the patient presented to the pulmonary clinic at this hospital 4 months later with persistent exertional dyspnea, nausea, palpitations, and lightheadedness, which occurred 5 minutes after running at a slow pace. Her symptoms quickly resolved with rest. She had no other significant past medical, family, or social history. Her physical exam was notable for a BMI of 23, pulse of 52 bpm, blood pressure of 110/70 mm Hg, and respiratory rate of 16 breaths per minute. The jugular venous pressure was 5 cm H_2O with sustained hepatojugular reflux. The lung exam was normal. The heart exam was notable for a loud P2 without murmur or gallop rhythm. An EKG showed sinus bradycardia with an incomplete right bundle

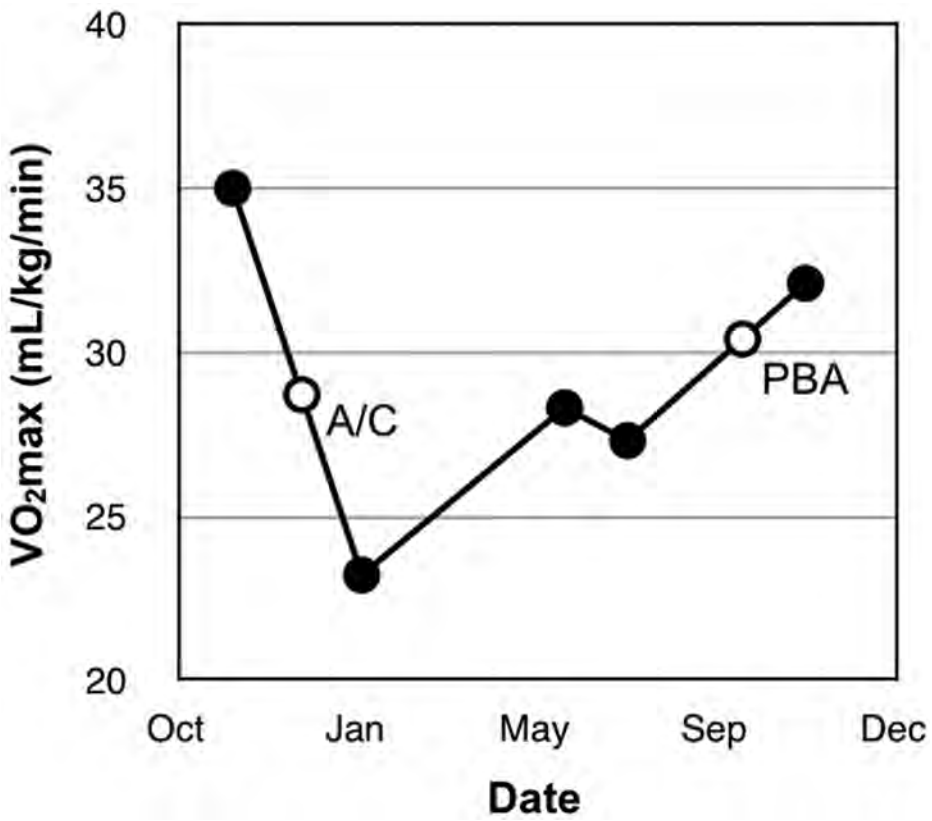

Figure 2: Patient 1 changes in VO_2max over time. On the initial noninvasive CPET, the patient had a VO_2max of 35 mL/kg/min (80% of predicted), which decreased markedly because of multiple, large pulmonary emboli diagnosed in December, at which time the patient was started on anticoagulation (A/C). Her exercise capacity recovered partially after this insult, but plateaued prior to the pulmonary balloon angioplasty (PBA), after which she had significant recovery, presumably as a consequence of decreased pulmonary arterial hypertension.

branch block. An echocardiogram was notable for mild tricuspid insufficiency, right atrial dilation, dilated inferior vena cava with limited respirophasic variation, an estimated RV systolic pressure (RVSP) of 35 mm Hg, with a mildly, diffusely hypokinetic RV. Repeat CT pulmonary angiography showed multiple bilateral webs related to organized, chronic pulmonary emboli. Given concern for chronic thromboembolic pulmonary hypertension, the patient was referred for invasive CPET.

Notably, the patient had normal pulmonary pressures when measured in the catheterization laboratory (Table 1); however, the invasive CPET was diagnostic of eiPAH (Tables 1 and 2) based on decreased VO_2max, early VT, elevated VE/VCO_2 at the VT, high dead space fraction (VD/VT), increased A-a gradient, decreased RVEF, decreased $PetCO_2$, and increased mPAP and PVR with exercise. The etiology was presumably chronic thromboembolic pulmonary hypertension given chronic deep vein thrombosis (DVT) and pulmonary emboli. Results of the CT angiography were consistent with distal disease, which was not thought to be amenable to surgical pulmonary arterial endarterectomy; however, the patient did undergo percutaneous balloon angioplasty of the distal pulmonary arteries in September 2009, and started tadalafil 40 mg daily. At her most recent follow-up in May 2010, the patient had returned to running 4 miles daily without exertional symptoms.

Case 2

Patient 2 is a 55-year-old woman who was referred to the pulmonary clinic at MGH for evaluation of exertional dyspnea in November 2009. In 1994, she underwent a renal transplant due to complications of lupus. Since the winter of 1995, she has noted progressively worsening shortness of breath with exertion. At the time of her presentation, she was having difficulties climbing stairs or vacuuming. Her symptoms were associated with wheezes and chest discomfort with no cough. An extensive evaluation had already been completed by the time she arrived to this hospital. Exercise treadmill tests were negative for coronary ischemia. In 2006, coronary angiography was normal and resting right heart catheterization showed

Table 1: Hemodynamic measurements upon pulmonary arterial catheterization, at rest, and at peak exercise

		Qt	HR	SV	SBP	DBP	RAP	mPAP	PCWP	PVR
Case 1	Cath		65		113	77	6	23	10	
eiPAH	Rest	5.3	73	73	150	69	2	25	7	272
	Peak	14.6	189	77	163	98	3	62	19	236
Case 2	Cath	5.9*	70	84	135	77	1	14	8	81
eiHFpEF	Rest	4.8	75	63	128	67	-3	9	4	84
	Peak	9.1	111	82	160	86	3	32	26	53
Case 3	Cath	6.0*	62	96	122	76	2	9	6	40
PLF	Rest	7.2	117	61	105	50	-1	11	3	89
	Peak	14.4	170	85	118	60	1	12	8	22

*Qt in the catheterization laboratory is measured by thermodilution.

Table 2: Gas exchange and first pass radionuclide scanning variables

	Case 1	Case 2	Case 3
Diagnosis	**eiPAH**	**eiHFpEF**	**PLF**
VO_2max, % predicted	72	58	46
VT, % VO_2max predicted	27	32	22
VE/VCO_2 (VT)	41	41	44
VD/VT (rest), %	21	26	
VD/VT (peak), %	30	13	
$PetCO_2$ (rest)	27	27	27
$PetCO_2$ (peak)	24	22	24
RVEF (rest), %	41	54	57
RVEF (peak), %	30	49	62
LVEF (rest), %	65	69	71
LVEF (peak), %	66	59	68
LVEDV (rest), mL	116	102	105
LVEDV (peak), mL	122	151	99

normal pressures (RAP 7, mPAP 12, PCWP 8 mm Hg). In 2009, a dobutamine stress echocardiogram showed a normal ejection fraction, mild aortic stenosis (mean gradient 15 mm Hg), mild mitral and mild-moderate tricuspid regurgitation, an RVSP of 41 mm Hg, and no evidence of ischemia. A chest CT showed a few scattered areas of scarring. Exercise oximetry was normal and pulmonary function testing revealed a mildly reduced DLCO.

Her other medical history was notable for hypertension, hyperlipidemia, and gastroesophageal reflux disease. She quit smoking in 1989 after 14 pack-years. She was taking cyclosporine, mycophenolate mofetil, prednisone, atenolol, digoxin, lisinopril, furosemide, aspirin, atorvastatin, albuterol, famotidine, estradiol, medroxyprogesterone, and allopurinol. Her family history was unremarkable. Physical exam revealed a BMI of 26, pulse of 73 bpm, blood pressure of 141/83 mm Hg, and respiratory rate of 16 breaths per minute. She appeared well. The lungs were clear to auscultation. The cardiovascular exam was notable for a systolic murmur. She had no peripheral edema. Given the extensive prior evaluation, she was referred for noninvasive CPET, where her VO_2max was 48% of predicted after 4.5 minutes of exercise with an early VT and increased VE/VCO_2 at the VT, consistent with a cardiovascular limit to exercise. A pulmonary vascular limit was suggested by the decreased DLCO and decreased $PetCO_2$ with normal biventricular ejection fractions at rest and exercise. Digoxin was discontinued as the patient attained only 53% of her predicted maximal heart rate, suggesting a component of chronotropic incompetence. Given these results, the patient was referred for invasive CPET for diagnosis or exclusion of eiPAH or heart failure with a preserved ejection fraction (HFpEF).

As in Case 1, the resting pulmonary arterial pressures were normal (Table 1); however, with exercise, the mPAP increased due to an increase in PCWP from 4 to 26 mm Hg, with a fall in PVR. This is consistent with eiHFpEF. Additionally, stroke volumes (SV) determined by FPRVS and the Fick principle were nearly identical, arguing against hemodynamically significant valvular disease during exercise. The patient is currently considering enrollment in a trial of PDE5 inhibition in the treatment of HFpEF.

Case Three

Patient 3 is an 18-year-old woman who was referred to the cardiology clinic at MGH for evaluation of syncope and exertional chest pain and dyspnea in July 2008. Since 2006, the patient has had 4 syncopal episodes during a variety of activities (running, brushing teeth, showering), which were preceded by lightheadedness, nausea, and diaphoresis. Additionally, she has had decreasing tolerance for exercise on an elliptical machine, developing chest pain, dyspnea, nausea, and dizziness progressively earlier during her workouts. These symptoms forced an end to exercise and limited her ability to walk long distances. Previous event monitoring was negative and Holter monitoring revealed 1 episode of asymptomatic supraventricular tachycardia. Pulmonary function testing was normal as was chest MRI. An echocardiogram was normal, with an estimated RVSP of 27 mm Hg.

Her medical history was notable for a deficiency of Factor XI with a mild bleeding tendency. She was taking oral contraceptive pills. Otherwise, her social and family histories were unremarkable. The physical exam showed a BMI of 19, pulse of 76 bpm, blood pressure of 102/62 mm Hg with no change upon standing, and respiratory rate of 14 breaths per minute. Cardiovascular and pulmonary examinations were normal. The patient was referred for cardiac MRI, which confirmed a structurally normal heart with normal ventricular size, morphology, and function. She was referred for noninvasive CPET, where she had a VO_2max 56% predicted with early VT and increased VE/VCO_2 at the VT, consistent with a central cardiovascular limit to exercise. Throughout exercise, a progressive decline in $PetCO_2$ was noted, which could be consistent with pulmonary arterial hypertension or hyperventilation. An invasive CPET was recommended to identify the etiology of the cardiovascular limit.

Given the relatively low filling pressures initially noted upon placement of the pulmonary artery catheter (Table 1), the patient received 1.5 L of intravenous normal saline before the start of the test. Despite this, her ventricular filling pressures remained low throughout exercise, consistent with the low LVEDV determined by FPRVS (Table 2) and low Qtmax (77% predicted). The patient was anemic, with a [Hb] of 11.5 g/dL, which also limited VO_2max. Interestingly, the Ca-vO_2 was 8.4 mL/100 mL blood, suggesting an additional impairment of systemic oxygen extraction, as this should approximately equal the [Hb]. Given low resting filling pressures that failed to augment with exercise despite volume repletion, this patient was diagnosed with preload failure.

The patient was referred for tilt table testing that was diagnostic of postural orthostatic tachycardia syndrome (POTS). After 10 minutes, her pulse increased to 142 bpm and blood pressure decreased to 77/42 mm Hg. Given this result, the patient was prescribed midodrine, increased salt intake, and compression stockings. With these interventions, her symptoms resolved and she was able to exercise without limitation. She underwent extensive endocrine and neurologic evaluations for adrenal and autonomic insufficiency that were normal.

DISCUSSION

Each of the 3 cases above describes a patient with long-standing, unexplained exertional dyspnea who had undergone an extensive evaluation prior to her presentation to MGH. These cases illustrate how elusive these diagnoses may be, primarily due to the absence of symptoms at rest. Unfortunately, this may lead to a premature diagnosis of a psychiatric limitation to exercise, as in Case 1, where anxiety was diagnosed and a referral to a sports psychiatrist was made. The first benefit of CPET is in determining the presence or absence of disease based on VO_2max, which was 80% of predicted (borderline low) with the initial noninvasive CPET in Case 1. The additional benefit of invasive testing is determining the nature of the limitation as illustrated in all 3 cases, where noninvasive testing was abnormal and suggestive of a cardiac or pulmonary vascular limitation, but a more specific etiology could not be clearly identified. Indeed, all 3 cases had noninvasive studies that showed a low VO_2max, early VT, and elevated VE/VCO_2. The addition of hemodynamic monitoring allowed the differentiation between pulmonary arterial and venous hypertension and the identification of low cardiac filling pressures. This is of critical importance as the further evaluation and treatment for these conditions (eiPAH, eiHFpEF, and PLF) are quite different.

Exercise-induced PAH has been defined as mPAP $\geq$30 mm Hg, PVR $\geq$80 dyne·s·cm^{-5}, and PCWP $<$20 mm Hg during exercise with normal resting pulmonary pressures[1] (compared to resting PAH with mPAP $\geq$25 mm Hg[5]). Physiologic parameters from invasive CPET, such as VO_2max, Qtmax, mPAP, and PVR, from patients with eiPAH were intermediate between normal subjects and those with resting PAH, which may suggest this is an early form of PAH where early diagnosis and treatment could improve outcomes. However, there are limited data regarding the natural history of eiPAH[6] and the decision to treat remains controversial.[7] Our practice is to initiate treatment, and anecdotal reports suggest clinical improvement in symptoms.

Similarly, eiHFpEF, defined by an elevation of PCWP $\geq$25 mm Hg with normal resting pressures and normal ejection fraction, may also represent an early form of disease.[8] Again, the natural history of eiHFpEF is unknown, but these patients may likely benefit from the initiation of targeted medical therapy to alleviate exertional symptoms and prevent further cardiac and vascular remodeling.

While eiPAH and eiHFpEF comprise the majority of diagnoses of unexplained dyspnea in our exercise laboratory, we have identified a cohort of patients, mostly young women, who have a cardiovascular limit to exercise characterized by lower cardiac output due to low cardiac filling pressures, as described in Case 3. For these patients, the limitation appears primarily due to failure to augment preload during exercise, noted by low RAP and PCWP. As per our protocol, all patients are resuscitated with up to 1.5 L of intravenous normal saline, so it is unlikely that volume depletion accounts for this phenomenon. Several of these patients have had positive tilt table testing, and experience some improvement in symptoms with β-receptor antagonists, mineralocorticoids, or midodrine. Interestingly, many of these patients also have evidence of defects in peripheral oxygen extraction, which may suggest a common underlying etiology of PLF at the microcirculatory level. We propose that PLF should be added to the differential diagnosis of unexplained exertional dyspnea or fatigue and is an entity best assessed by invasive hemodynamic monitoring during CPET.

In addition to noninvasive CPET, exercise stress Doppler transthoracic echocardiography (ESE) is another potential alternative to invasive CPET. Certainly echocardiography is a useful screening tool for resting pulmonary hypertension,[5,9] but its interpretation during exercise is complicated by other hemodynamic changes. Specifically, RAP during exercise normally rises beyond the assumed 5 mm Hg.[10,11] While RAP can be estimated at rest by inferior vena cava diameter,[12] this has not been validated during exercise when venous compliance is known to decrease.[13] Additionally, the ESE cannot distinguish pulmonary arterial from venous hypertension. While PCWP, PVR, and Qt have been estimated at rest using Doppler echocardiography in patients with severe pulmonary hypertension,[14] these estimates have also not been validated during exercise. Each of these variables is important to determine. For example, well-trained athletes can develop high RVSP and mPAP, but the decrease in PVR remains entirely normal.[10] While ESE is a promising modality for the evaluation of exercise-induced pulmonary vascular disease, much work remains to validate this approach against direct measures of central hemodynamics.

CONCLUSION

The use of CPET with invasive hemodynamic monitoring is a powerful tool in the diagnosis of unexplained exertional dyspnea or fatigue. This approach may assume a more important role as the clinical significance of exercise-induced pulmonary vascular disease is better understood. If these entities represent an early stage of disease, where treatment will improve outcomes, invasive CPET will be essential in the management of these patients for diagnosis and monitoring response to therapy. Despite the significant resources involved in administering these tests, they are, for now, the best way of obtaining data on central hemodynamics during exercise.

References

1. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. *Circulation*. 2008; 118(21):2183-2189.

2. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir*

Dis. 1984;129(2 Pt 2):S49-S55.
3. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60(6):2020-2027.
4. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
5. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1 suppl): S55-S66.
6. Raeside DA, Chalmers G, Clelland J, Madhok R, Peacock AJ. Pulmonary artery pressure variation in patients with connective tissue disease: 24 hour ambulatory pulmonary artery pressure monitoring. *Thorax*. 1998;53(10):857-862.
7. Alkotob ML, Soltani P, Sheatt MA, et al. Reduced exercise capacity and stress-induced pulmonary hypertension in patients with scleroderma. *Chest*. 2006;130(1):176-181.
8. 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 Jun 11. [Epub ahead of print]
9. Bech-Hanssen O, Selimovic N, Rundqvist B, Wallentin J. Doppler echocardiography can provide a comprehensive assessment of right ventricular afterload. *J Am Soc Echocardiogr*. 2009;22(12):1360-1367.
10. Reeves JT, Moon RE, Grover RF, Groves BM. Increased wedge pressure facilitates decreased lung vascular resistance during upright exercise. *Chest*. 1988;93(3 suppl):97S-99S.
11. Stickland MK, Welsh RC, Petersen SR, et al. Does fitness level modulate the cardiovascular hemodynamic response to exercise? *J Appl Physiol*. 2006;100(6):1895-901.
12. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol*. 1990;66(4):493-496.
13. Sheriff DD, Augustyniak RA, O'Leary DS. Muscle chemoreflex-induced increases in right atrial pressure. *Am J Physiol*. 1998;275(3 Pt 2):H767-H775.
14. Selimovic N, Rundqvist B, Bergh CH, et al. Assessment of pulmonary vascular resistance by Doppler echocardiography in patients with pulmonary arterial hypertension. *J Heart Lung Transplant*. 2007;26(9):927-934.