CHEST

Performance and Interpretation of Invasive Hemodynamic Exercise Testing

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Exertional dyspnea is a common complaint for patients seen in pulmonary, cardiac, and general medicine clinics, and elucidating the cause is often challenging, particularly when physical examination, echocardiography, radiography, and pulmonary function test results are inconclusive. Invasive cardiopulmonary exercise testing has emerged as the gold standard test to define causes of dyspnea and exertional limitation in this population. In this review, we describe the methods for performing and interpreting invasive cardiopulmonary exercise testing, with particular attention to the hemodynamic and blood sampling data as they apply to patients being evaluated for heart failure and pulmonary hypertension. CHEST 2020; 158(5):2119-2129

KEY WORDS: catheterizations; dyspnea; exercise testing; hemodynamics; pulmonary function test

Exertional dyspnea is a common complaint that transcends the gamut of cardiopulmonary diseases.[1] Most of the evaluations used clinically to evaluate for the cause of dyspnea on activity, including physical examination, imaging, spirometry, and laboratory testing, are performed at rest when patients are asymptomatic, and not with activity. A characteristic of both heart failure (HF) and pulmonary vascular diseases is an organ-level inability to cope with the heightened physiologic demands of stress. With the ability to directly assess ventricular filling pressures, pulmonary arterial pressures, cardiac output, pulmonary function, and measures of oxygen transport and use, invasive hemodynamic exercise testing provides a powerful method to directly evaluate for the causes of exertional dyspnea.

Application of invasive exercise testing was widespread until the 1980s, when its use began to wane, for two major reasons: (1) advances in noninvasive modalities such as echocardiography were perceived to permit acquisition of the same information without the need for an invasive procedure, and (2) a paradigm shift occurred in the catheterization laboratory, from having a diagnostic to a therapeutic focus, as advances in percutaneous intervention were emerging. However, over the past decade, a rapid resurgence of invasive cardiopulmonary exercise testing (CPET) has occurred, as it has become apparent that noninvasive tests are frequently unable to provide diagnostic clarity. This article briefly reviews indications for invasive CPET, presents a case highlighting a common diagnosis at invasive CPET, and summarizes how to perform the test and interpret results.

ABBREVIATIONS: AVO_2diff = arterial-venous oxygen content difference; cpc-PH = post-capillary pulmonary hypertension; CPET = cardiopulmonary exercise testing; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure and reduced ejection fraction; LV = left ventricular; PA = pulmonary artery; PAWP = pulmonary arterial wedge positions; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium; RAP = right atrial pressure; RV = right ventricle; VO_2 = oxygen consumption

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Indications for Invasive CPET

Invasive CPET has multiple advantages over noninvasive assessment and is considered the gold standard assessment for dyspnea and exertional limitation.[1-6] Current indications for invasive CPET include the evaluation of patients with dyspnea not clearly defined by noninvasive methods, including HF with preserved ejection fraction (HFpEF), resting or exercise-induced pulmonary hypertension (PH), and other causes of dyspnea, including valvular heart disease, intracardiac shunts, preload failure, and mitochondrial diseases (Table 1).[1-13] In patients with multifactorial dyspnea, such as obstructive lung disease and HFpEF, or patients with components of both lung disease and PH, invasive CPET has the unique ability to define the relative contributions of each pathologic condition to the patient's symptoms. In patients with HF and reduced EF (HFrEF) undergoing evaluation for advanced therapies, invasive CPET can determine the severity of cardiac limitation and also evaluate for peripheral abnormalities beyond the heart.[14] In patients with unexplained dyspnea and ejection fraction of 50% or greater, invasive CPET is most useful in those with intermediate pretest probability of HFpEF based on the H_2FpEF score.[15] In patients with combined HF and pulmonary disease, invasive CPET can provide important clues as to whether the heart or lungs is the severe contributor to symptoms. For example, patients that develop arterial desaturation, or display reduced breathing reserve likely have more severe lung disease, because these are not typical in isolated HF.

Alternative exercise methods include echocardiography and noninvasive CPET. Exercise echocardiography provides valuable information, including assessments of ventricular structure and function and valve disease, but is less accurate at assessing filling pressures.[3,16] Echocardiography can provide estimates of pulmonary artery pressure during exercise, but high-quality data may be obtainable in only 50% of patients, and the severity of PH during exercise is often underestimated.[17] One advantage of echocardiography is the ability to perform simultaneous lung ultrasound, which enables evaluation of increases in pulmonary congestion during stress.[18,19]

Noninvasive CPET is useful to evaluate for cardiac, pulmonary parenchymal, or vascular pathologic conditions, and other causes for dyspnea such as deconditioning.[20-22] CPET represents the gold standard method to assess aerobic capacity (peak oxygen consumption [VO_2]) as well as novel indexes reflecting ventilatory efficiency, while providing an objective assessment of patient effort. However, CPET provides no direct measurement of cardiac filling pressures, pulmonary artery (PA) pressures, or cardiac output, and these components are frequently necessary to make or refute the diagnosis. In patients with unexplained dyspnea, noninvasive CPET without invasive assessment displays inadequate ability to discriminate HFpEF from noncardiac causes of dyspnea.[23]

Resting invasive hemodynamic assessment is useful if abnormalities are apparent at steady state, but it has limited sensitivity because many patients display impairments only during exercise.[2] Alternative stressors to exercise, such as saline loading, provide some value but are inferior to exercise testing.[24] Thus, bringing the sophisticated expired gas analysis techniques of CPET together with invasive exercise evaluation provides the most robust and direct method to evaluate the causes for exercise intolerance. To illustrate its utility, we present a case of a typical patient presenting with dyspnea, in which the correct diagnosis was only achieved after invasive CPET.

Case

A 72-year-old woman presented for evaluation of dyspnea on exertion. She had a history of hypertension, diabetes, sleep apnea, and obesity. Over the past 2 years, her dyspnea progressed to the point that she could no longer walk more than one block on level ground without stopping because of dyspnea. Low-dose loop diuretics were initiated empirically, with no improvement in symptoms.

Examination revealed a mildly obese woman in no acute distress. BP was 142/78 mm Hg, with a heart rate of 72 beats per minute, respiratory rate 12 breaths per minute, and peripheral saturation 98% on room air. BMI was 33.2. On examination, jugular venous pressure and cardiac auscultation were normal, lung fields were clear, and there was only trace edema. Laboratory evaluation showed normal hemoglobin, renal function, and N-terminal pro B-type natriuretic peptide levels. ECG showed normal sinus rhythm without significant abnormalities. Chest radiographs revealed clear lung fields, normal cardiac silhouette, and mild aortic calcification. Echocardiogram demonstrated normal biventricular size and function, no chamber hypertrophy, normal biatrial volumes, and no significant valve disease. There was grade I left ventricular (LV) diastolic dysfunction, but LV filling pressures were estimated to be normal by Doppler echocardiography.

TABLE 1] Indications for Invasive CPET by Specific Diagnoses

Diagnosis	Diagnostic Criteria	Comments[a]	References
Heart failure with preserved ejection fraction (HFpEF)	• PAWP ≥15 mm Hg at rest *or* • PAWP ≥25 mm Hg with exercise *or* • ΔPAWP/ΔCO slope >2 mm Hg/L/min	• May have reduced CO reserve[b] • May have reduced AVO_2diff[c]	• Borlaug, 2010[2] • Obokata et al, 2017[3] • Pieske et al, 2019[12] • Eisman et al, 2018[10] • McCallister et al, 1968[34] • Parker and Thadani, 1979[35] • Esfandiari et al, 2019[36]
Resting or Exercise-Induced Pulmonary Hypertension (PH)	• Mean PAP ≥20 mm Hg at rest *or* • Mean PAP >30 mm Hg and TPR >3 WU with exertion *or* • ΔPAP/ΔCO slope >3 mm Hg/L/min	• Define as predominant precapillary, postcapillary, or combined • Precapillary PH defined by PVR ≥3 WU • PVR cutoffs with exercise less well-defined	• Simonneau et al, 2019[13] • Lewis et al, 2013[7] • Ho et al, 2020[41] • Herve et al, 2015[11]
Pulmonary or Ventilatory Limitation	• Resting or exercise-induced hypoxemia • Reduced breathing reserve[d] <15% predicted	• Perform testing on room air • Arterial line essential to measure blood gas, do not rely on finger oximetry	• Maron et al, 2013[4]
Heart Failure with reduced Ejection Fraction (HFrEF)	• Same pressure criteria as for HFpEF (above) • May have reduced CO reserve[b] • May have reduced AVO_2diff[c]	• Can be helpful in evaluation of HFrEF for transplant to verify true CO reserve limitation	• Chomsky et al, 1996[14]
Low Gradient Severe Aortic Stenosis	• LV-Ao gradient >40 mm Hg with aortic tracing showing slurred and diminished upstroke during exercise • PAWP and LVEDP ≥25 mm Hg with exercise	• Likely HFpEF with nonsignificant AS if exercise PAWP elevated but LV-Ao gradient <40 mm Hg	…
Mitral or Tricuspid Regurgitation	• Large V waves in RAP or PAWP • Elevated RAP or PAWP that worsens with exercise	• Need simultaneous echocardiogram or exercise ventriculogram to assess regurgitation severity	…
Mitral Stenosis	• Increased PAWP-LV gradient with exercise • Exercise-induced development or worsening of post-capillary PH	• Need concurrent echocardiogram for mitral inflow gradient given PAWP overestimates true gradient	…

(Continued)

TABLE 1 *(Continued)*

Diagnosis	Diagnostic Criteria	Comments[a]	References
Preload Failure	• Reduced cardiac output reserve[b] *and* • Peak RAP<8 mm Hg, PAWP <14 mm Hg, with mean PAP <30 mm Hg	• Consider POTS or autonomic or adrenal insufficiency • Rule out hypovolemia	• Oldham et al, 2016[8]
Mitochondrial Disease	• Reduced peak VO_2 with higher than expected PA saturation • Low AVO_2diff but elevated lactate • High cardiac output reserve (>150% predicted)	• Should have normal filling pressures and PAP with exercise • May also be noted in some patients with profound deconditioning	• Taivassalo et al, 2003[9]

Ao = Aorta; AVO_2diff = arterial-venous oxygen content difference; CO = cardiac output; LV = left ventricle; PA = pulmonary artery; PAP = pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; POTS = postural orthostatic tachycardia syndrome; RAP = right atrial pressure; TPR = total pulmonary resistance as mean PAP divided by CO; VO_2 = oxygen consumption; WU = Woods units.

[a]All of the disorders shown may cause reduced peak VO_2.

[b]ΔCO with exercise should be $>\Delta VO_2 \times 4.8$.

[c]AVO_{2diff} should increase to approximate the plasma hemoglobin.

[d]Breathing reserve = (maximum voluntary ventilation [MVV] – exercise minute ventilation [V_E])/MVV.

PA systolic pressure was estimated at 40 mm Hg, with a normally sized and collapsible inferior vena cava. Given the discordance between severe exertional symptoms and relatively mild abnormalities on resting evaluation, and the intermediate probability of HFpEF based the H_2FpEF score of 4, she was referred for invasive CPET. The protocol for the procedure is outlined in Figure 1.

In the catheterization laboratory, with the patient under mild sedation while lying supine, access was obtained in the right internal jugular vein using a micropuncture catheter (Cook) followed by placement of a 9 Fr sheath (Arrow). Access was also obtained in the right radial artery using a 4 Fr micropuncture catheter. Solid-state pressure transducers were leveled at mid-chest. A 7 Fr balloon-tipped catheter (Balloon wedge, Arrow) was advanced to the right atrium (RA). A wire micromanometer (Aeris PressureWire, Abbott Laboratories) was then advanced through a Tuohy-Borst sidearm adapter to the tip of the balloon-tipped catheter and balanced to the mean fluid-filled RA pressure. RA pressure was measured continuously through the sidearm of the 9 Fr jugular sheath, after documenting equalization between the sidearm pressure and the catheter pressure. Transthoracic echocardiography was performed simultaneously with catheterization to evaluate for valve disease and lung congestion.

Pressures in the RA, PA, right ventricle (RV), and pulmonary arterial wedge positions (PAWP) were measured at end-expiration, using the mean of three or more beats. PAWP position was confirmed via appearance on fluoroscopy, characteristic waveforms, and saturation of 94% or greater, with mean pressure taken at mid-A wave. Cardiac output was determined by the Fick method from directly measured VO_2 (MedGraphics) together with blood sampling to measure oxygen contents and PO_2 obtained from the radial artery and PA to calculate arterial-venous oxygen content difference (AVO_2diff).

Hemodynamics at rest indicated normal biventricular filling pressures, with right atrial pressure (RAP) 6 mm Hg and PAWP 10 mm Hg, mild PH (PA 35/15 mm Hg; mean of 22 mm Hg), and low-normal cardiac output of 3.8 L/min (index, 2.2 L/min/m^2, Table 2 and Fig 2). Pulmonary vascular resistance (PVR) was elevated at 3.2 WU. Echocardiography showed no mitral regurgitation, and lung ultrasound revealed 1 B-line artifact at rest.

Cardiac filling pressures increased with passive leg raise, before exercise, predominantly in the left heart (RAP,

Steps for Invasive CPET

1. Obtain access into the right internal jugular vein (9 Fr sheath) and right radial artery (eg, 4 Fr monitoring line).
2. Start measurement of oxygen consumption (VO_2) for calculation of Fick Cardiac Output through mouthpiece or tight-fitting mask. This expired gas analysis continues throughout the remainder of the case.
3. Prepare and flush 7 Fr BW with a MM advanced through a sidearm.
4. Insert BW into the right atrium. Level the MM to the fluid-filled catheter and obtain RAP.
5. Transduce and record pressures from the radial arterial line, the right IJ sheath (RAP) and the BW at each stage.
6. Pass BW into the right ventricle. Verify no drift in the MM, and then record pressures.
7. Pass BW into the PA. Verify no drift in the MM and record pressures. Obtain blood gas samples from the PA, SVC (to rule out left to right shunt) and radial arterial line simultaneously. Annotate the time of blood sampling to correspond with the expired gas analysis for Fick output.
8. With flush on, advance BW in the PAWP position. Confirm PAWP position with waveform analysis, fluoroscopic appearance, and saturation > 94%. Transduce pressure, verifying no drift in the MM, and record pressures.
9. Place feet into cycle ergometer pedals. After 30 secs with feet up, take records while in PAWP position.
10. Begin exercise protocol (20 Watts). The duration of this stage is 3 mins for tests without simultaneous imaging and 5 mins if imaging is being performed to allow adequate time for image acquisition. After 2 – 4 mins, pressure data and blood samples obtained as in the baseline phase.
11. Advance to next stage, in older adults with dyspnea, we generally use 20 W stage increments (3 min each) until peak.
12. Measurements of PAWP, PA, RAP, and arterial pressure tracings and arterial/PA blood samples 30 secs prior to stage end for each incremental stage. Obtain Borg scores for perceived dyspnea and exertion at each stage.
13. When perceived patient effort reaches maximal tolerated effort (ie, Borg perceived effort score > 16, Borg dyspnea score > 6), repeat steps 11 and 12. Confirmatory evidence of maximal effort includes respiratory exchange ratio > 1.05.
14. Once all measurements obtained, stop exercise. Recovery pressure records taken at 1 min post exercise.
15. Remove patient's feet from the bike pedals and remove BW catheter from the sheath after all information obtained. Remove access sites per usual protocol.

Figure 1 – *Steps for invasive CPET. BW = balloon wedge; CPET = cardiopulmonary exercise testing; Fr = French; MM = micromanometer; PA = pulmonary artery; PAWP = pulmonary arterial wedge pressure; RAP = right atrial pressure; VO_2 = oxygen consumption.*

9 mm Hg; PAWP, 20 mm Hg; Fig 2). Supine exercise was then initiated on a cycle ergometer, starting at a 20-Watt workload (60 rpm). Hemodynamic and gas exchange measurements were obtained continuously. After 3 minutes exercise at a 20-Watt workload, pressures were recorded and blood samples obtained. Borg perceived effort and dyspnea scores were recorded. After completing the 20-Watt stage, workload was increased to 40 Watts. After 1.5 minutes at 40 Watts, the patient became highly symptomatic and reached volitional fatigue, unable to continue further and reporting Borg perceived effort score of 18 of 20 and respiratory exchange ratio of 1.22, defining peak exercise conditions. Hemodynamic measurements were repeated and blood samples collected to measure mixed venous and arterial blood gases, together with arterial lactate.

Measurements at peak exercise revealed RAP 15 mm Hg, PAWP 31 mm Hg, and PA 70/41 mm Hg, mean of 54 mm Hg (Table 2). There was a striking increase in the amplitude of the PAWP V wave to 50 mm Hg (asterisk, Fig 2). Cardiac output reserve was mildly reduced but within the normal range at 89% predicted (Table 2). Echocardiography showed no evidence of significant mitral regurgitation, but there was an increase in the number of sonographic B-lines, consistent with development of acute pulmonary congestion during exercise.

Although resting measurements suggested mild pre-capillary PH, exercise findings indicated significant left heart disease in setting of combined pre-capillary and post-capillary PH (cpc-PH). Thus, the correct diagnosis of HFpEF with cpc-PH was reached.

Interpretation

Proper interpretation of results from invasive CPET requires careful and integrated evaluation of pressure waveforms, blood gas and lactate data, expired gas analyses, and assessment of cardiac output and AVO_2diff reserve (Table 2). Not all centers use the same exercise protocols, and methods for interpretation also may vary. Although it is feasible to perform CPET on supplemental oxygen in research settings, we require that patients exercise on room air if expired gas analysis will be performed. Additional measures such as ventilatory efficiency and breathing reserve are also

TABLE 2] Invasive CPET Results for the Case

Results	Rest	Peak Exercise
Heart rate, bpm	75	144
Systolic BP, mm Hg	174	238
Mean BP, mm Hg	117	172
Right atrial pressure, mm Hg	6	15
Mean PAWP, mm Hg	10	31
PAWP V wave, mm Hg	10	50
PA systolic pressure, mm Hg	35	70
PA mean pressure, mm Hg	22	54
Cardiac output, L/min	3.9	6.6
Cardiac output reserve, %	…	89
Mean PA/CO slope, mm Hg/L/min	…	11.9
PAWP/CO slope, mm Hg/L/min	…	7.2
SVR, dyne/sec*cm^5	2,306	1,900
PVR, WU	3.2	3.5
Hemoglobin, g/dL	15.1	16.1
Arterial saturation, %	96	97
Arterial PO_2, mm Hg	76	85
PA saturation, %	74	50
PA PO_2, mm Hg	35	27
VO_2, mL/min	174	680
VO_2, mL/kg/min	2.2	8.6
AVO_2diff, mL/dL	4.5	10.2
Respiratory exchange ratio	…	1.22
Lactate, mmol/L	…	5.5

Predicted cardiac output reserve is equal to 6*ΔVO_2. Cardiac output reserve is then calculated as observed minus rest CO divided by predicted cardiac output reserve. See Table 1 legend for expansion of abbreviations.

obtained from expired gas analysis but are beyond the scope of this review and discussed in detail elsewhere.[20-22]

All pressures are measured at end-expiration, which is when intrapleural pressure is closest to zero, lungs are at functional reserve capacity, and minimal airflow is impacting intracardiac pressures. During exercise, some have advocated for use of pressures averaged over the entire respiratory system rather than end-expiration.[6] We agree that this approach is preferred when evaluating patients with obstructive lung disease in whom intrinsic positive end-expiratory pressure develops, or in patients that "press" during respiration, or other conditions that render the lung-chest wall unit stiffer, as in some forms of pulmonary disease or prior chest wall irradiation. For such patients in whom changes in intrathoracic pressure are dramatic and considered to contribute to elevated intravascular pressures, we will report both end-expiratory and respiratory means in tandem. Although some clinicians prefer to report PAWP using only the mean of the respiratory cycle for all patients, end-expiratory values can be readily obtained and accurately reflect the transmural hydrostatic pressure in the pulmonary veins and capillaries. Indeed, end-expiratory PAWP was found to display a stronger relationship with the development of lung congestion as compared with PAWP averaged over the respiratory cycle.[19]

Mean PAWP and RA pressures are classically measured at mid-A wave, but as illustrated by this case, one must note the presence of large V waves, which markedly increase pulmonary capillary pressure and upstream PA pressure load. We do not use the traditional Swan-Ganz catheter for invasive CPET. Because the direct Fick method is used to measure CO, no thermodilution ejections are required. More importantly, the multiple small lumens markedly reduce the frequency response of the thermodilution catheter, promoting ringing artifact that compromises signal quality. Our practice for exercise studies is to advance a micromanometer wire through the single-lumen balloon-tipped catheter. This provides a much higher frequency response and higher quality data, as indicated by the striking differences in the fluid-filled and micromanometer tracings in Figure 2.

Invasive CPET may be performed with the patient in either the supine or upright positions. Although our laboratory performs studies each way, our preferred approach is to use supine exercise, in which venous return is maximized, increasing the sensitivity to detect diastolic reserve impairments. Normal ranges are also more familiar in the supine position, which is how cardiac catheterization has been performed since first introduced in the 1940s. It is important to recognize that RA, PA, and PAWP pressures are higher in the supine position as compared with upright. However, prior studies have shown that the changes with exercise are similar in both positions, as are changes in the relationships between PA and PAWP.[25,26] Of note, PVR falls more with upright exercise, particularly at low levels of exercise. With upright exercise, there may be greater ringing artifact and catheter whip, as well as greater variability in PAWP when measured in different West zones, which is less relevant to supine exercise.[27]

To interpret the data from an invasive CPET, one must recognize the normal response to exercise (Table 3). With the onset of exercise, there is an increase in venous

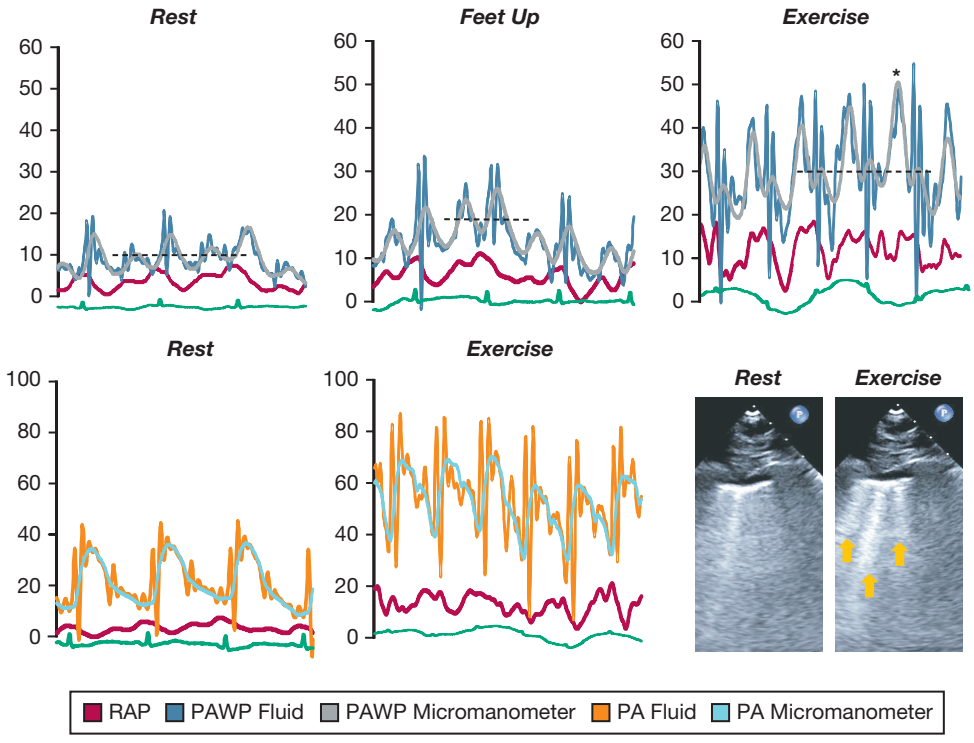

Figure 2 – *Findings at Invasive CPET. The top panels display RAP and PAWP at rest, with feet up, and with peak exercise. The asterisk in the top right panel highlights the large V wave in the PAWP with exercise. Dashed line shows mean PAWP measured at mid A wave. The bottom left and bottom middle panels show the RAP and PA tracings at rest and peak exercise. Note differences in tracing quality of fluid-filled catheters and micromanometer wires. The bottom right panel shows lung ultrasound at rest and with exercise, with the development of B lines (arrows) consistent with acute pulmonary edema in this setting. B lines are vertical, laser-like narrow-based lines originating from pleural surface extending to the bottom of the field. Unlike Z lines, B lines move with the lung during respiration. See Figure 1 legend for expansion of abbrevations.*

return to the heart mediated by the combined actions of the skeletal muscle and respiratory pumps, together with sympathetic-mediated venoconstriction that shifts blood from the capacitance veins to the central circulation. The heart must cope with this increase in venous return by enhancing diastolic relaxation and suction, such that filling pressures do not rise despite abbreviation of the diastolic period due to tachycardia. When venous return (input) exceeds output, there is central congestion. This develops in the lungs in isolated left heart failure, and in the right heart in patients with PH in the absence of left heart failure or other causes of right heart failure.

The "duties" of the LV are fundamentally twofold: (1) to keep the lungs dry by filling to an adequate preload volume without pathologic increase in left atrial pressure, and (2) to pump blood to the body at a rate commensurate with its metabolic needs, reflected by total body VO_2. This latter component is one area in which invasive CPET provides an advantage against other modalities: the ability to measure both oxygen delivery and consumption in tandem. In health, CO increases with respect to VO_2 by a ratio of 6:1.[14,28] By measuring the change in VO_2 (in mL/min) during exercise, one can determine what the expected change in CO would be, if the heart is adequately performing its duty as a pump.

In the case example, VO_2 increased from 174 to 680 mL/min at peak exercise, a change of 506 mL/min. Thus, the predicted CO increase is 6 × 506 mL/min, or 3.04 L/min. One can calculate the CO reserve, also termed the "exercise factor," by taking the quotient of observed CO reserve (exercise minus rest) divided by the predicted CO increase. Values less than 0.8 or 80% indicate a CO reserve impairment (Table 3) and are frequently observed in both HFrEF and HFpEF.[14,28-30] In this case, the CO reserve was mildly diminished (89%), but not to the level that is considered to reflect a severe CO limitation.

Although CO reserve was relatively preserved, unequivocal evidence was seen of left-sided HF through failure to accomplish duty (1) above. Mean PAWP increased strikingly, from 10 mm Hg at rest to 31 mm Hg at peak exercise. Based on resting

TABLE 3] Normative Data for Rest and Exercise Hemodynamics

Measurement	Normal Resting Values	Normal Exercise Values	Comments
RAP, mm Hg	0-6	<15	Normal range with exercise not well defined
Mean PA, mm Hg	≤20	<30 with TPR<3 WU[a]	Often >30 above age 50 years in normal adults, but not with high TPR
PA/CO slope, mm Hg/L/min	…	<3	Less established for supine exercise
PAWP, mm Hg	<15	<25	Some references indicate normal resting values of ≤12 or ≤15; ≥20 during exercise may be abnormal in patients <50 years of age
PAWP/CO slope, mm Hg/L/min	…	<2	Less established for supine exercise
PVR (WU)	<2-3	<2-3	True normal <2 WU but clinical risk increases >3 WU; PVR should drop with exercise normally
CI/CO, L/min*m^2 or L/min	2.2-4.0, L/min*m^2	>4.8*ΔVO_2, mL/min)	Expected increase in CO is 6 mL/min for each 1-mL/min increase in VO_2[b]

[a]TPR = total pulmonary resistance, defined by mean PA pressure divided by CO.
[b]Predicted cardiac output reserve is equal to 6*ΔVO_2. Cardiac output reserve is then calculated as observed minus rest CO divided by predicted cardiac output reserve. This ratio has been referred to as the exercise factor and should be 0.8 or 80%.

hemodynamics alone, the patient would have been diagnosed with precapillary PH rather than HFpEF, emphasizing the value of provocative assessment with exercise in this cohort to refine the assessment of pulmonary vascular and cardiac reserve.[31] Elevation in PAWP with exercise in patients with HFpEF, as in this case example, is associated with increases in lung congestion,[19,32] alterations in ventilation and ventilatory control,[32] impairments in peak VO_2,[23] increases in morbidity and mortality,[10,33] and of course, symptoms of dyspnea.[32]

Abnormal PAWP is defined by values of 15 mm Hg or higher at rest or 25 mm Hg or higher with exertion (Table 3).[34-36] Notably, this latter partition value coincides with the left atrial pressure at which pulmonary edema develops.[37] With normal aging, there is a greater increase in PAWP during supine exercise because of loss of diastolic reserve,[38,39] but this age difference does not appear to extend to upright exercise.[40] Because the magnitude of increase in PAWP (and PA pressure) varies with flow, there may be advantages to scaling the former to the latter. Recent studies have shown that both a PAWP/CO slope greater than 2 mm Hg/L/min and a mean PA/CO slope greater than 3 mm Hg/L/min are associated with poor outcomes and are therefore considered to reflect left heart failure and pulmonary vascular dysfunction, respectfully (Table 3).[10,41]

Similar to PAWP, RA pressures also increase with exercise in patients with HF and pulmonary hypertension.[17] RA pressure is a surrogate for pericardial pressure, so when RA and PAWP both become elevated in tandem to very high levels, this suggests that the heart has filled to the point at which the pericardium restrains further filling, and there is enhanced ventricular interaction.[42] This is a distinct hemodynamic signature in patients with HF and a key reason for measuring RA pressure continuously throughout the test. In addition, because changes in intrathoracic pressure are directly transmitted to the adjacent pericardium, this too will affect RA pressure. Patients with HFpEF and elevated RA pressure are more likely to develop lung congestion during exercise, because of the combined effects of increased fluid filtration caused by high PAWP and reduced pulmonary lymphatic drainage due to central venous hypertension.[19]

As compared with patients with HFpEF and isolated postcapillary PH, patients with cpc-PH are more likely to display this pattern of RA hypertension and pericardial restraint, because of the inability of the RV to pump blood through the lungs in the setting of significant pulmonary vascular disease.[43] These patients display low LV transmural distending pressure, flattening of the interventricular septum, and underfilling of the LV, resulting in failure to augment

CO through failure of Frank Starling reserve.[43] In some patients there may even be reduction in PAWP during exercise related to pulmonary vascular disease and secondary abnormalities in RV-PA coupling.[44] In the presented case, even as there was elevation in PVR at rest and with exercise, RA pressure did not increase nearly as dramatically as PAWP. This suggests that RV functional reserve with exercise may still be relatively preserved.

The patient presented in the case displayed marked systemic hypertension, with a hypertensive response to exercise. This is related to systemic vascular stiffening and is quite typical of HFpEF.[45] The prominent V wave in the PAWP tracing (Fig 2, asterisk) is also common in HFpEF and is most often related to poor left atrial compliance, although one also must consider mitral regurgitation. For this reason, we often perform concurrent echocardiography. The absence of significant mitral regurgitation in this case suggests that the large V wave was more a reflection of increased left atrial stiffness, as is commonly observed in HFpEF.[46]

According to the Fick principle, VO_2 is equal to the product of CO and AVO_2diff. During exercise, a slight increase in arterial oxygen content occurs because of hemoconcentration, but most of the increase in AVO_2diff is related to a decrease in mixed venous oxygen content due to enhanced distribution of blood and extraction in skeletal muscle. Like CO reserve impairments, many patients with HFpEF also display abnormalities in the ability to augment AVO_2diff.[47-49] Normally, the AVO_2diff (in mL/dL) should approach the value of hemoglobin (in g/dL), and in this case, the AVO_2diff "reserve" was severely impaired (10.2 mL/dL vs 15.1 g/dL). This is also reflected by the higher than expected PA saturation at peak exercise (50%), which normally should decrease to less than 30%.[27,30] This suggests a peripheral impairment in oxygen distribution, extraction, or utilization that could be related to inadequate distribution of blood flow or primary problems in skeletal muscle. However, possibly the PA saturation was higher than expected because the patient discontinued exercise because of severe discomfort from dyspnea rather than from reaching a limitation in perfusion of blood to the leg muscles.

Patients with disorders of skeletal muscle, such as mitochondrial myopathies, display an increase in CO that greatly exceeds the value predicted based on observed changes in VO_2.[9] Like the patient described in the case, they typically display a higher than expected PA saturation and low AVO_2diff at peak exercise, with a high arterial lactate indicating anaerobic glycolysis (Table 3). However, unlike the case presented, these patients typically display a CO reserve that is greater than 150% predicted, rather than being depressed. Other patients may display a phenotype of inadequate peripheral oxygen extraction in the absence of a demonstrable mitochondrial myopathy or elevation in filling pressures, often with a coexisting diagnosis of chronic fatigue syndrome.[50] Some patients may display a CO reserve limitation in the setting of normal or low RA and PAWP. In these patients, the problem lies in an inability to augment venous return rather than in the ejection of blood from the heart. This preload failure is seen in patients with autonomic disorders or postural orthostatic tachycardia syndrome, where there is an inability to augment venous return during exercise, and they also may display higher PA saturations as well.[8,50] When clinical suspicion is higher for preload failure, upright exercise may be preferred to supine, because venous return is lower in the upright position.

Conclusion

Invasive CPET combines the expired gas analysis capabilities of CPET with the definitive assessments of pressure, flow, and resistance from cardiac catheterization, providing the most robust evaluation of exertional intolerance available in clinical practice. This review summarizes the performance and proper interpretation of invasive CPET, which relies on careful integration of pressure waveforms, blood gas data, expired gas analysis, and assessments of oxygen transport. Given the comprehensive nature of these assessments and excellent safety profile, invasive CPET has emerged as the gold standard method to evaluate patients with unexplained dyspnea.

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References

1. Borlaug BA. Diagnosis and treatment of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2020; in press.
2. 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.
3. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart

failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation*. 2017;135(9):825-838.

4. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. *Circulation*. 2013;127(10):1157-1164.
5. Huang W, Resch S, Oliveira RK, Cockrill BA, Systrom DM, Waxman AB. Invasive cardiopulmonary exercise testing in the evaluation of unexplained dyspnea: insights from a multidisciplinary dyspnea center. *Eur J Prev Cardiol*. 2017;24(11):1190-1199.
6. Kovacs G, Herve P, Barbera JA, et al. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J*. 2017;50(5).
7. Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013;128(13):1470-1479.
8. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. *Pulm Circ*. 2016;6(1):55-62.
9. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. *Brain*. 2003;126(Pt 2):413-423.
10. Eisman AS, Shah RV, Dhakal BP, et al. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail*. 2018;11(5):e004750.
11. Herve P, Lau EM, Sitbon O, et al. Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J*. 2015;46(3):728-737.
12. Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40(40):3297-3317.
13. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1).
14. Chomsky DB, Lang CC, Rayos GH, et al. Hemodynamic exercise testing: a valuable tool in the selection of cardiac transplantation candidates. *Circulation*. 1996;94(12):3176-3183.
15. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):861-870.
16. Nauta JF, Hummel YM, van der Meer P, Lam CSP, Voors AA, van Melle JP. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2018;20(9):1303-1311.
17. Obokata M, Kane GC, Sorimachi H, et al. Noninvasive evaluation of pulmonary artery pressure during exercise: the importance of right atrial hypertension. *Eur Respir J*. 2020;55(2):1901617.
18. Picano E, Pellikka PA. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. *Eur Heart J*. 2016;37(27):2097-2104.
19. Reddy YNV, Obokata M, Wiley B, et al. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J*. 2019;40(45):3721-3730.
20. Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary exercise testing: what is its value? *J Am Coll Cardiol*. 2017;70(13):1618-1636.
21. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2016;133(24):e694-e711.
22. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. *JACC Heart Fail*. 2016;4(8):607-616.
23. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018;6(8):665-675.
24. Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail*. 2015;8(1):41-48.
25. Mizumi S, Goda A, Takeuchi K, et al. Effects of body position during cardiopulmonary exercise testing with right heart catheterization. *Physiol Rep*. 2018;6(23):e13945.
26. Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. *Am J Cardiol*. 1978;41(1):52-59.
27. Stampfer M, Epstein SE, Beiser GD, Braunwald E. Exercise in patients with heart disease: effects of body position and type and intensity of exercise. *Am J Cardiol*. 1969;23(4):572-576.
28. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013;15(7):776-785.
29. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37(43):3293-3302.
30. Epstein SE, Beiser GD, Stampfer M, Robinson BF, Braunwald E. Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. *Circulation*. 1967;35(6):1049-1062.
31. Borlaug BA, Obokata M. Is it time to recognize a new phenotype? Heart failure with preserved ejection fraction with pulmonary vascular disease. *Eur Heart J*. 2017;38(38):2874-2878.
32. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39(30):2810-2821.
33. Dorfs S, Zeh W, Hochholzer W, et al. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35(44):3103-3112.
34. McCallister BD, Yipintsoi T, Hallermann FJ, Wallace RB, Frye RL. Left ventricular performance during mild supine leg exercise in coronary artery disease. *Circulation*. 1968;37(6):922-931.
35. Parker JO, Thadani U. Cardiac performance at rest and during exercise in normal subjects. *Bull Eur Physiopathol Respir*. 1979;15(5):935-949.
36. Esfandiari S, Wolsk E, Granton D, et al. Pulmonary arterial wedge pressure at rest and during exercise in healthy adults: a systematic review and meta-analysis. *J Card Fail*. 2019;25(2):114-122.
37. Guyton AC, Lindsey AW. Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. *Circ Res*. 1959;7(4):649-657.
38. van Empel VP, Kaye DM, Borlaug BA. Effects of healthy aging on the cardiopulmonary hemodynamic response to exercise. *Am J Cardiol*. 2014;114(1):131-135.
39. Wolsk E, Bakkestrom R, Thomsen JH, et al. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. *JACC Heart Fail*. 2017;5(5):337-346.
40. Pandey A, Kraus WE, Brubaker PH, Kitzman DW. Healthy aging and cardiovascular function: invasive hemodynamics during rest and exercise in 104 healthy volunteers. *JACC Heart Fail*. 2020;8(2):111-121.
41. Ho JE, Zern EK, Lau ES, et al. Exercise pulmonary hypertension predicts clinical outcomes in patients with dyspnea on effort. *J Am Coll Cardiol*. 2020;75(1):17-26.
42. Borlaug BA, Reddy YNV. The role of the pericardium in heart failure: implications for pathophysiology and treatment. *JACC Heart Fail*. 2019;7(7):574-585.
43. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J*. 2018;39(30):2825-2835.

44. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. *J Am Coll Cardiol*. 1999;34(6):1802-1806.

45. Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017;70(2):136-148.

46. Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;21(7):891-900.

47. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. *J Am Coll Cardiol*. 2011;58(3):265-274.

48. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail*. 2015;8(2):286-294.

49. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. *Circulation*. 2018;137(2):148-161.

50. Melamed KH, Santos M, Oliveira RKF, et al. Unexplained exertional intolerance associated with impaired systemic oxygen extraction. *Eur J Appl Physiol*. 2019;119(10):2375-2389.