Case Presentation
A 71-year-old man was evaluated for a chief complaint of progressive dyspnea on exertion over the previous 5 years. The patient’s medical history is significant for revascularized coronary artery disease, left diaphragmatic paresis, systemic hypertension, and obesity. His medications included aspirin 81 mg daily, metoprolol succinate 100 mg daily, lisinopril 10 mg daily, and simvastatin 20 mg daily. Over the 6 months before his presentation, the patient’s daily aerobic exercise tolerance performed on a stationary bicycle decreased from 30 minutes to 10 minutes in duration because of worsening dyspnea. Echocardiography demonstrated normal biventricular systolic and diastolic function, an estimated pulmonary artery systolic pressure of 43 mm Hg, and the absence of valvular disease or an intracardiac shunt. Pulmonary function testing revealed a moderate restrictive defect. Cardiopulmonary exercise testing was next considered to determine whether a cardiovascular or pulmonary limitation to exercise was present. Based on the available clinical data, we suspected exercise-induced pulmonary arterial hypertension (PAH) or exercise-induced heart failure with preserved left ventricular ejection fraction (HFpEF) as potential pathophysiological mechanism(s) by which to account for the patient’s symptoms. Thus, an invasive cardiopulmonary exercise test (iCPET) was performed (Figure 1), which uses intracardiac hemodynamic and arterial blood gas data generated during exercise from a pulmonary artery and radial catheter, respectively, to diagnose these and other select causes of exertional shortness of breath (Table).

Overview
Dyspnea is defined as an abnormal or uncomfortable awareness of breathing and may afflict up to one-quarter of the general population. Pathophysiological perturbations to normal breathing, cardiopulmonary function, or oxygen uptake by skeletal muscle cells modulate symptomatic expression of exertional dyspnea. Thus, exertional dyspnea is described universally across the spectrum of cardiopulmonary diseases, as well as in certain diseases of musculoskeletal and neuromuscular function, and in patients with significant anemia. This swath of dyspnea-associated comorbidities sets the framework for a diagnostic dilemma confronted commonly in cardiology and pulmonary practice: determining the contribution of cardiovascular disease to exertional dyspnea in the presence of competing comorbidities associated with breathlessness. iCPET affords the dynamic and simultaneous assessment of cardiovascular, respiratory, and metabolic function during exercise. In most cases, iCPET results inform clinicians regarding dyspnea pathophysiology to provide a definitive diagnosis, even in patients with comorbid cardiovascular and pulmonary disease. Thus, iCPET has evolved as the preferred diagnostic strategy for patients in whom the predominate mechanism of dyspnea is unresolved. Moreover, iCPET is a bona fide modality for determining treatment appropriateness or prognosis in patients with systolic heart failure, pulmonary hypertension, and hypoxic lung disease. However, despite these factors, iCPET remains underused. Therefore, we discuss the clinical application of...
iCPET and outline a practical approach to interpretation of iCPET results.

**Overview of Exercise Physiology**

Under normal physiological conditions, mitochondria in striated muscle cells consume O2 to synthesize adenosine triphosphate, which is the principal source of cellular energy and is required for normal skeletal muscle contraction. Increased muscle metabolism during graded exercise requires a commensurate increase in minute ventilation (VE) and pulmonary gas exchange. In a similar fashion, convective flow of O2 toward exercising muscle and efferent carbon dioxide (CO2) and hydrogen ion flow from exercising...
of which has been referred to as the anaerobic threshold (AT). The AT is often used in clinical practice as a key measure of overall fitness and cardiovascular function. Although anaerobic cellular metabolism affords continued functional activity during strenuous exercises, elevated levels of lactate quickly exceed endogenous buffering capacity, and minute ventilation (VE) must be increased to offset elevated circulating levels of CO₂ that are generated through the buffering of lactate by bicarbonate. Eventually, however, lactate concentration exceeds both buffering and ventilatory capacity, resulting in a drop in blood and muscle pH (ie, lactic acidosis) and, ultimately, cessation of physical activity.1 Thus, an abnormally low AT is generally associated with disorders of O₂ transport to, or subsequent uptake by, skeletal muscle mitochondrion (Figure 2).

The anticipated physiological changes to cardiopulmonary hemodynamics with exercise compared with rest include an increase in cardiac output up to 5-fold with an attendant increase in pulmonary artery systolic

Table. Cardiopulmonary Hemodynamic Criteria for Diagnosing Select Cardiac Limitations to Exercise

<table>
<thead>
<tr>
<th></th>
<th>mPAP (mm Hg)</th>
<th>Maximum PVR (dynes/s/cm²)</th>
<th>Additional Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH</td>
<td>&gt;30</td>
<td>&gt;120</td>
<td>± RV function</td>
</tr>
<tr>
<td>Exercise-induced PAH</td>
<td>&gt;30</td>
<td>&gt;120</td>
<td>Normal resting cardiopulmonary hemodynamics</td>
</tr>
<tr>
<td>Exercise-induced HFrEF</td>
<td>&gt;25</td>
<td>&lt;120</td>
<td>PCWP &gt; 20 mm Hg on exercise</td>
</tr>
<tr>
<td>Preload limitation to Exercise</td>
<td>&lt;25</td>
<td>&lt;120</td>
<td>Right atrial pressure maximum &lt; 8 mm Hg; Qt maximum and VO₂, maximum &lt; 80% predicted; all other central hemodynamics are normal.</td>
</tr>
</tbody>
</table>

Invasive cardiopulmonary exercise testing is required to diagnose exercise-induced pulmonary arterial hypertension (PAH), exercise-induced heart failure with preserved ejection fraction (HFrEF), and preload-dependent limitations to exercise according to these hemodynamic criteria. Although PAH may be identified at the time of IC PET during baseline hemodynamic assessment and is an important pulmonary vascular etiology to impaired exercise, the diagnosis of PAH may be achieved without IC PET according to hemodynamic abnormalities observed at rest. mPAP indicates mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; Qt, cardiac output; RV, right ventricle; and VO₂, maximum volume of oxygen consumption.

music is accomplished in a tightly regulated fashion. Cardiac output (abbreviated as Qt in CPET) is augmented through an early increase in stroke volume until maximum left ventricular contractility and preload recruitment are achieved. Further augmentation of cardiac output is modulated by increases in heart rate. Importantly, the efficiency of cardiovascular adaptations to exercise hinges, in part, on normal right ventricular–pulmonary circulatory coupling, because pulmonary vasodilation and recruitment are required to accommodate increases in right ventricular stroke volume.7

During strenuous exercise, adenosine triphosphate synthesis depends, in part, on the O₂-independent conversion of pyruvate to lactate, the onset

Figure 2. Anaerobic cellular metabolism and exercise physiology. A. Under physiological conditions, the metabolism of glucose to pyruvate by glycolysis occurs in the cytoplasm outside of mitochondrion. In the presence of molecular oxygen (O₂), pyruvate may enter into the citric acid cycle/electron transport chain (ETC) in mitochondrion. Alternatively, anaerobic cellular metabolism results in the conversion of pyruvate to lactic acid. Deprotonation of lactic acid is buffered by bicarbonate (HCO₃⁻) to form carbonic acid (H₂CO₃). Increased levels of carbon dioxide (CO₂) generated by the metabolism of H₂CO₃ are matched by an increase in minute ventilation (VE), which promotes the excretion of CO₂ as expired gas. By contrast, lactic acidemia occurs as a result of consumption of HCO₃⁻ that exceeds H⁺ buffering capacity despite increases in VE. B. The gas exchange anaerobic threshold (AT) is the point at which the volume of CO₂ output (VCO₂) abruptly increases relative to the volume of O₂ uptake (VO₂). Thus, factors that decrease O₂ delivery to peripheral tissue, such as decreased cardiac output and arterial O₂ desaturation attributable to pulmonary vascular disease, are associated with an early AT. ATP indicates adenosine triphosphate; CO₂, carbonic acid output; and NADH, nicotinamide adenine dinucleotide.

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pressure by 2-fold up to a peak of ≈50 mm Hg and mean pulmonary artery pressure <30 mm Hg. Importantly, exercise-mediated increases in pulmonary circulatory flow are associated with both passive and active (eg, nitric oxide-dependent) pulmonary vasodilation and pulmonary vascular recruitment, with some reports estimating that pulmonary vascular resistance may decline during exercise by 60% in normal individuals.8,9

Noninvasive Cardiopulmonary Exercise Testing

Noninvasive (conventional) CPET is an appropriate initial test to evaluate exertional intolerance by defining the degree of exercise limitation, assessing for a pulmonary mechanical limit to exercise, and providing clues to the presence of a pulmonary vascular limit to exercise. This is accomplished in noninvasive CPET through the reporting of cardiac output, maximal volume of oxygen consumption (VO2) and carbon dioxide output (VCO2), minute ventilation (VE), and maximum voluntary ventilation (MVV). However, confirmation of pulmonary vascular disease, exercise-induced heart failure with preserved left ventricular ejection fraction (HFpEF), or preload-dependent causes of impaired exercise tolerance relies on interpreting changes in intracardiac hemodynamics with exercise, and, thus often requires iCPET (discussed in greater detail in the Interpreting iCPET Results section).

Both noninvasive and iCPET are usually performed with the patient on an upright or recumbent cycle ergometer. In contrast to traditional exercise treadmill tests, which use a graded, multi-stage approach to increase exercise workload (eg, Bruce protocol), changes to exercise workload in CPET are mediated by a gradual (and limitless) increase in pedal resistance by 10 Watts/min. The specific incremental increase in workload is individualized to each patient based on a pretest (and subjective) assessment of functional capacity. This continuous ramp strategy allows for the determination of the patient’s gas exchange and AT, and is maintained until patient exhaustion or objective evidence of hemodynamic instability or myocardial ischemia.7 Breath-by-breath pulmonary gas exchange and minute ventilation are measured by a metabolic cart (eg, MedGraphics, Sensormedics, others), and heart rate/rhythm and blood pressure are monitored by a 12-lead ECG and brachial sphygmomanometer (or radial arterial catheter transducer in the case of iCPET), respectively. In some centers, myocardial perfusion imaging may be included to enhance test sensitivity for detecting myocardial ischemia.

The final common pathophysiologic pathway to account for most organic causes of exertional dyspnea involves insufficient O2 supply to skeletal muscle or impaired uptake of O2 by skeletal muscle cells, which, collectively, may be attributable to abnormal cardiac, pulmonary vascular, or neuromuscular function. The integrated function of these systems is broadly assessed by measuring the maximum* oxygen uptake (VO2), which is calculated by the product of minute ventilation (VE) and the difference in inspired and expired fractions of O2. Thus, a fundamental objective of noninvasive (or invasive) CPET is quantification of maximum VO2, which is abnormal when observed to be ≈80% of predicted for the patient’s age, sex, and height.10

In patients with a low maximum VO2, it is necessary to determine whether a pulmonary mechanical limitation to exercise accounts for this finding. A pulmonary mechanical limit occurs when a patient’s peak ventilation during exercise approaches or exceeds the (resting) MVV, defined as the maximum volume of air that is voluntarily expired in 1 minute at rest. During constant load exercise, a normal individual and most patients with chronic obstructive lung disease are able to maintain a minute ventilation (VE) that is ≈70% of the maximum voluntary ventilation.11 Thus, an increase of VE: MVV >0.7 indicates a pulmonary mechanical limit to exercise. The most commonly encountered cause for this in clinical practice is severe chronic obstructive lung disease, and, to a lesser extent, interstitial lung disease and chest wall abnormalities.

If a pulmonary mechanical limitation to exercise is not observed or is not the initial limitation to exercise, then attention is directed next to CPET data that distinguish central cardiovascular dysfunction from impaired O2 extraction in peripheral tissue (collectively termed disorders of O2 flux) as a means by which to account for low maximal VO2. The (noninvasive) gas exchange AT is determined by the VO2 at which VCO2 abruptly increases relative to VO2 (Figure 2B). Thus, an early AT suggests a disorder of O2 flux from atmosphere to skeletal muscle mitochondrion. During a noninvasive CPET, a pulmonary vascular limit to exercise (either pulmonary arterial hypertension or pulmonary venous hypertension) is suggested by an elevated VE/VCO2 slope below the AT or an elevated ratio at the AT. Likewise, failure of the partial pressure of end-tidal CO2 to rise above resting baseline at the AT may suggest a pulmonary vascular abnormality that reflects both hyperventilation and ventilation/perfusion mismatch.12 Both of these scenarios require confirmation by iCPET, however, because there is a significant false-positive and false-negative rate reported for VE/VCO2 and partial pressure of end-tidal CO2 measurements.13,14

Invasive Cardiopulmonary Exercise Testing

In contrast to noninvasive CPET, iCPET involves the additional insertion of pulmonary artery and radial artery catheters before exercise (Figure 3). This critical distinction affords complete cardiopulmonary hemodynamic and peripheral tissue O2 extraction analyses, without which only the degree of impairment (maximum VO2)
and the identification of a pulmonary mechanical limitation to exercise are possible. In this way, iCPET expands broadly over conventional CPET the range of data acquired during exercise to include key physiological measures that are required to diagnose 3 under-recognized causes of exertional dyspnea: exercise-induced PAH, exercise-induced heart failure with preserved left ventricular ejection fraction (HFpEF), and preload-dependent limitations to cardiac output (preload failure), as well as quantifying functional limitations to exercise, and thus prognosis, in patients with established PAH at rest. Additionally, arterial and mixed venous blood sampling in iCPET (1) increases oxyhemoglobin saturation measurement accuracy compared with cutaneous pulse oximetry used in noninvasive CPET, which may generate erroneous results at peak exercise resulting from probe displacement, peripheral hypoperfusion or vasoconstriction, or calloused skin among other causes, and (2) allows for the direct measurement of changes to mixed venous blood O₂ content with exercise, thereby enhancing the accuracy of peripheral tissue O₂ extraction measurements and the diagnosis of mitochondrial myopathy.

Performing iCPET

The safety profile and contraindications to invasive CPET are akin to those reported for noninvasive stress testing, although factors that influence the safety of pulmonary or radial artery catheter placement must be considered before patient enrollment and include thrombocytopenia, anticoagulated status, limitations to central venous access, or an abnormal Allen’s test. At our institution, a collaborative effort among cardiologists, pulmonologists, and exercise physiologists is preferred to minimize iCPET complications. An interventional cardiologist or pulmonologist performs pulmonary artery catheter placement under ultrasound guidance and fluoroscopy, followed by radial artery catheter placement. A supervising physician, registered nurse, and 2 exercise physiologists monitor the patient’s clinical status throughout the duration of the test.

Mean systemic arterial pressure, end-expiratory right atrial pressure, and systolic/diastolic and mean right ventricular and pulmonary arterial pressures are recorded continuously (CALYSTO Series IV, Witt Biomedical Corp, Melbourne, FL). The mean end-expiratory pulmonary capillary wedge pressure (PCWP), arterial and mixed venous blood gases, and lactate concentrations are sampled every minute. A recent study performed in supine patients at rest suggested that recording mean end-expiratory PCWP values is critical, as PCWP averaged over the duration of the respiratory cycle may underestimate the left ventricular end-diastolic pressure in ≤30% of patients. This observation holds particular importance for patients in whom a diagnosis of exercise-induced HFpEF is considered, because any negative bias in PCWP estimation will lead to underdetection of impaired diastolic function as a potential pathophysiological mechanism by which to account for exertional dyspnea (see below for a discussion of cardiopulmonary hemodynamics in exercise-induced HFpEF). If the end-expiratory PCWP approaches 20 mm Hg, it is our practice to instruct the patient to voluntarily decrease respiratory rate near completion of exercise to minimize the (potentially) confounding effect of respiratory variation on biventricular filling pressure measurements.

Interpreting iCPET Results

One potential model for clinical interpretation of iCPET results is provided in Figure 4. It is important to note
that in iCPET, cardiac output (Qt) is measured by dividing the volume of O₂ (VO₂) by the difference in O₂ content between arterial and venous blood (C[a–v]O₂), collectively expressed as Qt=VO₂/C(a–v)O₂, and thus cardiac output is not measured directly, but rather via the true Fick principle. Additionally, published normal values for maximum exercise cardiac output (and other cardiopulmonary hemodynamic measures) are extrapolated from relatively small data sets (some in well-trained athletes) and therefore may not account fully for individual patient characteristics that influence exercise tolerance independently. An estimate of maximum predicted cardiac output can be derived from VO₂ predicted for a given individual (based on age, sex, and height) divided by an estimate of the normal maximum exercise C[a–v]O₂ (ie, normal is 140 mL/L). A decrease in the maximum cardiac output (Qt) <80% commensurate with a decrease in maximum VO₂ defines a cardiac limitation to exercise.

Patients with a central cardiovascular limitation to exercise discovered on iCPET may be categorized further into 1 of 4 diagnoses based primarily on cardiopulmonary hemodynamics (Table). Exercise limitation attributable to resting pulmonary arterial hypertension is strongly suspected in patients that (1) meet conventional hemodynamic criteria for PAH at rest, (2) demonstrate a mean pulmonary artery pressure >30 mm Hg and pulmonary vascular resistance >120 dynessecxcm⁻⁵ at peak exercise, and (3) demonstrate evidence of right ventricular remodeling/systolic dysfunction on transthoracic echocardiography or cardiac MRI. Although PAH is an important cause of exercise limitation, diagnosing PAH does not require iCPET per se, and may be confirmed by resting hemodynamics alone. Patients with exercise-induced PAH, which is believed to represent an early PAH phenotype, generally present with normal cardiopulmonary hemodynamics at rest, but on iCPET demonstrate increased mean pulmonary artery pressure >30 mm Hg, pulmonary vascular resistance >120 dynessecxcm⁻⁵, and PCWP <20

![Diagram of a diagnostic algorithm for interpreting iCPET results.](http://circ.ahajournals.org/)

**Figure 4.** A diagnostic algorithm for interpreting iCPET results. A, Assessment of functional capacity is determined by calculating the maximum volume of oxygen consumed (VO₂), which may be performed during conventional or invasive cardiopulmonary exercise testing (iCPET). B, An increase in the minute ventilation relative to ventilatory capacity (VE: MVV) indicates a pulmonary mechanical limitation to exercise. Alternatively, early achievement of the anaerobic threshold (AT) suggests disordered oxygen (O₂) flux that may be a consequence of: (C) decreased cardiac output (ie, abnormal O₂ delivery) or (D) impaired O₂ extraction by skeletal muscle tissue from arterial blood. This determination, and subsequent analyses presented in the diagnostic algorithm, require iCPET and cannot be performed by conventional exercise stress testing alone. In patients with a central cardiovascular limit to exercise, specific cardiopulmonary hemodynamics profiles observed during exercise are suggestive of (E) exercise-induced PAH, (F) exercise-induced heart failure with preserved ejection fraction (HFpEF), or (G) a preload limitation to exercise. COPD indicates chronic obstructive pulmonary disease; mPAP, mean pulmonary artery pressure; MVV, maximum voluntary ventilation; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; and VCO₂, volume of exhaled carbon dioxide.
mm Hg.9 In patients with normal biventricular function, an increased mean end-expiratory PCWP >20 mm Hg at peak exercise in the absence of elevations to pulmonary vascular resistance suggests exercise-induced HFpEF.21 Finally, exertional dyspnea may be associated with preload-dependent limitations to cardiac output.16,17 In this patient population, failure to augment right atrial pressure or PCWP on exercise is observed in the presence of abnormally decreased cardiac output. It is hypothesized that this phenomenon reflects hypovolemia, neurocardiogenic disease, or both.

**Clinical Follow-Up**

**Interpretation of the iCPET Results**

In the case vignette patient, iCEPT was performed to determine an etiology of progressive dyspnea (Figure 1). Functional performance data indicates a significant limitation to exercise tolerance, which is reflected by a diminished maximal exercise VO\(_2\) of 59% predicted. These findings were observed despite a respiratory exchange ratio of 1.07; when present, a respiratory exchange ratio >1.05 indicates a sufficient level of effort was performed by the patient to identify a potential limitation to exercise through interpretation of iCPET. Exercise performance data demonstrate that volume of oxygen consumption (VO\(_2\)) at the AT was 30% predicted VO\(_2\) max. Collectively, these findings suggest impaired O\(_2\) delivery to peripheral tissue in the setting of diminished exercise tolerance.

To explore a pathophysiological mechanism by which to account for this observation, the patient’s pulmonary function and respiratory data were analyzed next, which indicate decreased forced vital capacity (42% predicted) and forced expiratory volume in one second (FEV1; 44% predicted), and a normal FEV1/forced vital capacity ratio (99% predicted). The VE:MMV was >0.7, but only at maximum exercise, indicating that an initial pulmonary mechanical limit to exercise was not present. In turn, key findings from analysis of gas exchange data at maximal exercise include an oxyhemoglobin saturation of 88.4% (predicted >97%), which was associated with an abnormal increase in the alveolar-arterial oxygen gradient (P[A–a]O\(_2\)) from 35.9 mm Hg to 61.6 mm Hg (predicted P[A–a]O\(_2\) gradient is <30 mm Hg). Taken together, these data suggest the presence of a restrictive lung disease pattern sufficient to induce a mild and secondary pulmonary mechanical limit to exercise, while failure to maintain a normal alveolar-arterial oxygen gradient on exercise suggests associated pulmonary vascular disease.

The patient’s exercise hemodynamic data demonstrate a decreased maximum cardiac output (Qt) of 55% predicted, which is calculated according to the equation VO\(_2\)/C(a–v)O\(_2\) (see above), and, in the current case patient, is derived by 1208 mL/min + 140 mL/L. Diminished maximum cardiac output occurred in the setting of a significantly diminished chronotropic response to exercise (57% of maximum predicted heart rate), and was associated with a substantial increase in right atrial pressure from 6 mm Hg to 18 mm Hg (normal is <10 mm Hg), mean pulmonary artery pressure from 23 mm Hg to 59 mm Hg (normal is <30 mm Hg), and pulmonary vascular resistance from 170 dynes×sec×cm\(^5\) to 370 dynes×sec×cm\(^5\). Importantly, a normal increase in PCWP on exertion was noted (<20 mm Hg) thereby excluding exercise-induced HFpEF. The functional consequence of these abnormal cardiopulmonary hemodynamic changes to exercise on tissue oxygenation (ie, circulatory performance) is reflected by a robust decline in mixed venous oxygen saturation (SvO\(_2\)) from 55.4% to 21.0%.

**Synthesizing a Differential Diagnosis and Treatment Plan Based on the iCPET Data**

During incremental exercise, an initial central cardiac limitation to exercise was identified by an early AT and confirmed by the patient’s low maximum cardiac output. At 6 minutes of exercise, a secondary pulmonary mechanical limitation to exercise was discovered owing to an increase in the ratio of minute ventilation (56 L/min) to maximum ventilatory volume (49 L/min) (VE:MMV =1.3; normal is ≤0.7). Therefore, to establish a diagnosis, features of the iCPET study pertaining to causes of low cardiac output were emphasized. Specifically, significant arterial oxyhemoglobin desaturation (with a P[A–a]O\(_2\) difference >30 mm Hg), increased mean pulmonary arterial pressure (>30 mm Hg), and blunted fall in pulmonary vascular resistance (>120 dyne×sec×cm\(^5\)) at peak exercise compared with rest were the central diagnostic data for this case. Thus, the most appropriate differential diagnosis for the patient’s exertional shortness of breath was decreased cardiac output attributable to (1) exercise-induced PAH or (2) a blunted chronotropic response to exercise.

To improve the patient’s blunted heart rate response, his β-receptor antagonist dose was decreased from 100 mg to 25 mg daily. Additionally, pulmonary vasodilator therapy with a phosphodiesterase type-V inhibitor or endothelin receptor antagonist was considered for the treatment of exercise-induced PAH. Because of the patient’s history of coronary artery disease and the associated potential for long-acting nitrate therapy in the future, which is contraindicated in the setting of concurrent phosphodiesterase type-V therapy, treatment with an endothelin receptor antagonist was preferred. Endothelin receptor antagonism is an established pharmacotherapeutic strategy for the management of PAH, although the efficacy of these drugs in patients with exercise-induced PAH is less well established. Nevertheless, owing to severely decreased functional capacity in the setting of a cardiopulmonary hemodynamic profile consistent with exercise-induced PAH, the patient was eligible for enrollment into an FDA-approved clinical trial assessing the selective endothelin type-A receptor antagonist ambrisentan (5 mg daily).
in patients with exercise-induced PAH (clinicaltrials.gov, NCT01051960).

The patient reported substantial recovery of exercise tolerance at 6 months after β-receptor antagonist dose reduction, ambrisentan therapy initiation, and voluntary weight loss. At least monthly clinical follow-up is advised to monitor side effects and changes in clinical status in all patients on endothelin receptor antagonist therapy over the initial 12 weeks of treatment. In addition, repeat iCPET may be performed in the setting of clinical worsening despite continued optimal medical therapy to determine therapeutic tolerance or the development of an alternative pathophysiological mechanism to impaired exercise tolerance.

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