Heart or Lung Disease*

Determining the Primary Cause for Dyspnea on Exertion

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Abbreviations: \( C(a-v)O_2 = \) arteriovenous \( O_2 \) content difference; \( DCO = \) diffusion of carbon monoxide; \( PETCO_2 = \) end-tidal carbon dioxide pressure; \( Vd/VT = \) physiologic dead space/tidal volume; \( VE = \) minute ventilation; \( \dot{V}O_2 = \) oxygen uptake; \( \Delta \dot{V}O_2/\Delta WR = \) Change in oxygen consumption/change in work rate

CASE PRESENTATION

A 68-year-old woman was referred for evaluation of progressive dyspnea on exertion that had become especially troublesome for 2 months prior to the present examination. She experienced significant dyspnea with minimal walking and had been having difficulty performing her housework. She denied chest pain or discomfort with or without exertion.

She had been subjected to left upper lobe lobectomy for stage I bronchoalveolar cell carcinoma 1 year previously. She also had known rheumatic heart disease, acquired in childhood, and had manifested atrial fibrillation since her thoracotomy. There was no history of cigarette smoking. She had been maintained on a regimen of a combination of medications, including captopril, furosemide, digoxin, potassium, conjugated estrogens, and warfarin.

Physical examination disclosed a thin woman in no distress. BP was 130/70 mm Hg and the heart rate was irregular with a rate of 52 beats/min. The respiratory rate was 16 breaths/min and unlabored. Chest examination disclosed a left thoracotomy scar, and the breath sounds were equal bilaterally with no wheezes or rhonchi. Cardiovascular examination disclosed a slightly accentuated apical impulse located 1 cm lateral to the midclavicular line. There was a grade 3/6 pansystolic murmur at the apex and left sternal border. There also was a decrescendo diastolic murmur at the left upper sternal border. The carotid pulses were palpable with the suggestion of a delayed upstroke. There was no venous distention, liver enlargement, or peripheral edema.

An echocardiogram disclosed a mildly dilated left ventricle with mild generalized reduction of systolic wall motion. The mitral valve was thickened and moderately stenotic (valve area estimated to be 1.5 cm\(^2\)) together with moderately severe regurgitation. There was also a thickened aortic valve that was mildly stenotic (peak systolic pressure gradient estimated at 40 mm Hg by Doppler flow technique). Moderate tricuspid regurgitation was noted, and from its backward jet velocity, the right ventricular systolic pressure could be estimated in the range of 70 mm Hg.

A nuclear ventriculogram performed at rest disclosed a mildly dilated left ventricle with an ejection fraction of 44%. This value was augmented to 52% at peak exercise.

The patient’s pulmonary function tests are shown in Table 1.

At this point, the presumptive diagnosis was that of

<table>
<thead>
<tr>
<th>Table 1—Pulmonary Function Tests*</th>
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<tr>
<td></td>
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<tr>
<td>VC, L</td>
</tr>
<tr>
<td>FEV(_1), L</td>
</tr>
<tr>
<td>FEV(_1)/VC, %</td>
</tr>
<tr>
<td>TLC, %</td>
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<tr>
<td>DCO, %</td>
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*VC = vital capacity; TLC = total lung capacity.
obstructive and restrictive lung disease combined with valvular heart disease. It was not clear, however, how much of her dyspnea was attributable to her cardiac disorder as opposed to her pulmonary disease. She was thus referred for pulmonary consultation, and a noninvasive cardiopulmonary exercise test was then performed in which expired gas exchange was measured during continuous incremental cycle ergometry. The results of this test are given in Table 2 and Figures 1 and 2.

The ECG manifested atrial fibrillation throughout the test; nonspecific ST-T wave changes were present but showed no change with exercise.

Questions for Consultants:

1. How would you interpret the findings of the exercise test? Can they be explained best by cardiac or pulmonary disease?

Table 2—Cardiopulmonary Exercise Data*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Predicted</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate, W, maximum</td>
<td>88</td>
<td>29</td>
</tr>
<tr>
<td>Maximum VO(_2), L/min</td>
<td>1.1</td>
<td>0.52</td>
</tr>
<tr>
<td>Maximum VO(_2), mL/K/min</td>
<td>20</td>
<td>9.4</td>
</tr>
<tr>
<td>Maximum heart rate, beats/min</td>
<td>165</td>
<td>163</td>
</tr>
<tr>
<td>Maximum O(_2) pulse, mL/beat</td>
<td>6.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Anaerobic threshold, L/min</td>
<td>0.43</td>
<td>0.38</td>
</tr>
<tr>
<td>BP, rest, max</td>
<td></td>
<td>140/70, 150/70</td>
</tr>
<tr>
<td>Maximum VE, L/min</td>
<td>52</td>
<td>40</td>
</tr>
<tr>
<td>Breathing reserve, L/min</td>
<td>&gt;11</td>
<td>12</td>
</tr>
<tr>
<td>Pulse oximetry, rest, max ex</td>
<td></td>
<td>94%, 88%</td>
</tr>
<tr>
<td>VO(_2)/VT, rest, max ex</td>
<td>&lt;0.45 (rest)</td>
<td>0.31; 0.26</td>
</tr>
<tr>
<td>VO(_2)/W, mL/min/W</td>
<td>&gt;8.62</td>
<td>2.75</td>
</tr>
</tbody>
</table>

*Breathing reserve = maximum ventilatory volume – Ve at peak exercise; VO\(_2\)/VT=ratio of physiologic dead space (Vd) to tidal volume (VT). Note: VO\(_2\)=PaCO\(_2\)–PETO\(_2\)/PaCO\(_2\)

PETO\(_2\)=partial pressure of average expired CO\(_2\); PaCO\(_2\)=partial pressure of arterial CO\(_2\). max ex = maximum exercise.

Since an arterial catheter was not placed, PETCO\(_2\) is substituted for PaCO\(_2\) values. Due to the unpredictable relationship between PaCO\(_2\) and PETCO\(_2\) during exercise, however, especially in lung disease, the substitution of PETCO\(_2\) for PaCO\(_2\) in the noninvasive measurement of VO\(_2\)/VT reduces the reliability of this value.

Figure 2. VO\(_2\) is graphed with respect to increasing work rate. Predicted slope is represented by the straight dark line. The VO\(_2\) rise with a relatively flat slope during exercise.

2. What is the role for cardiopulmonary exercise testing in patients who complain of dyspnea?

3. Should measurement of exhaled gases during exercise be done primarily by pulmonologists or should it be employed widely by cardiologists as well?

4. This test was performed noninvasively, and thus an arterial catheter was not employed. Would the additional data obtained through this latter technique have changed the conclusions that might have been reached?

Comments by Consultants

Idelle M. Weisman, MD, FCCP, and R. Jorge Zeballos, MD

1. To set the stage for the interpretation of cardiopulmonary exercise test (CPET) results in this case, it is important to take into consideration that the subject is an elderly, thin, nonsmoking woman, functional class III NYHA, 1 year post left upper lobe lobectomy for alveolar cell carcinoma. Resting pulmonary function tests 1 year postthoracotomy demonstrated a marked reduction in VC (38%) and FEV\(_1\) (41%) with normal FEV\(_1\)/VC ratio as compared to prethoracotomy values. TLC was mildly reduced and DCO was markedly decreased (38%) compared to predicted values. These results are consistent with a restrictive ventilatory defect. There is no clear evidence for airway obstruction; a flow-volume loop contour may have been helpful. The
FVC and FEV₁ are disproportionately reduced compared to that which has been reported in the literature for lobectomy (VC usually decreases ≤20%). In this patient, the exaggerated reduction in lung volumes may possibly reflect exacerbation of her underlying cardiovascular disease with attendant pulmonary sequelae and/or respiratory muscle weakness. The DCO is strikingly abnormal, and most probably due to severe pulmonary hypertension with possible secondary parenchymal lung changes and reduced lung volume.¹ A restrictive defect with reduced DCO is well described in patients with mitral valve disease and severe pulmonary hypertension.¹

Cardiopulmonary exercise test: Additional information may have permitted a more meaningful interpretation (i.e., the ventilatory equivalent for CO₂ [Ve/Vco₂]), the breathing frequency, respiratory exchange ratio, the appropriate graphs with the submaximal to maximal responses, and Borg scale ratings of perceived exertion). With the available information, the results of the CPET may be interpreted as follows.

The submaximum data should be interpreted cautiously as the graphs may be misleading. In Figure 1, the HR response appears to be flat with a peak heart rate between 135 to 140 per minute; however, during the physical examination the heart rate was 52 per minute and the peak heart rate reported in Table 2 is 163, indicating that the heart rate could increase in response to the exercise stress. Likewise, although Figure 2 clearly demonstrates the markedly reduced aerobic capacity, the flat response may be more apparent than real, resulting from an artificially high resting value for VO₂. It is difficult to accept a resting VO₂ of 500 mL in a 55-kg female whose resting VO₂ should be around 200 mL (1 met×55 kg). If the latter situation were the case,VO₂ would double with exercise. This in turn would reflect an increase in cardiac output and/or in O₂ extraction. Weber and Janicki² have shown that patients with severe valvular heart disease (VO₂ of less than 10 mL/kg) can double their resting cardiac output with exercise. Regardless of these corrections, the O₂ pulse response to the increasing work rate (WR) would be flat or decreasing. Since O₂ pulse is the product of SV and C(a-V)O₂, and assuming that maximum C(a-V)O₂ has been achieved at peak exercise, it is likely that in this patient the abnormal O₂ pulse response reflects an abnormal stroke volume.³⁴

Although the patient achieved her maximum predicted heart rate, this may not be a reliable indicator of maximal cardiovascular response, as she was in atrial fibrillation. The significant reduction in peak VO₂ is consistent with a severe reduction in functional aerobic capacity. The O₂ pulse response is flattened and only 51% of predicted at peak exercise; the ΔVO₂/ΔWR is also notably abnormal. The reduced O₂ pulse and ΔVO₂/ΔWR, and achievement of maximum HR at low WR (contributed to by atrial fibrillation) are all consistent with cardiovascular limitation.²³⁴ This is probably due to a combination of factors, including valvulopathies (mitral, aortic), heart failure, atrial fibrillation, and chronic pulmonary hypertension. The low AT is also consistent with cardiovascular limitation, but may also reflect deconditioning and peripheral muscle dysfunction. In patients with heart failure, even though reduced aerobic power is primarily due to decreased cardiac output (reduced O₂ delivery), peripheral factors, which include abnormalities in the peripheral circulation and skeletal muscle metabolism/function (O₂ utilization), also contribute to the reduced aerobic power.

The respiratory system in this patient was evaluated only by the comparison of the maximum Ve achieved with the predicted value. The patient had a borderline breathing reserve of 12 L/min (23% of Ve maximum predicted, normal ≥25%) and, therefore, does not appear ventilatory limited. The breathing reserve is usually normal in patients with heart disease.²³⁴ The high Ve/VO₂ reported at peak exercise is commonly observed in patients with pulmonary disease, but has also been reported in patients with mitral valve disease.¹ In this patient, the reported physiologic dead space to tidal volume ratio (VD/VT) is unreliable and cannot be used,⁵ because end-tidal CO₂ pressure (PetCO₂) was used rather than PaCO₂. Vd/VT calculated using PaCO₂ is abnormal in pulmonary patients due to high dead space ventilation, but may also be abnormal in patients with advanced heart disease usually in association with an increased Ve/VO₂ as a reflection of reduced cardiac output and increased V/Q abnormalities.³⁴

A pulmonary gas exchange abnormality in this patient is suggested by a 6% reduction in oxygen saturation by pulse oximeter (94% to 88%) with minimal exercise. Although valuable as a trending indicator, pulse oximetry (accuracy of ±4%) cannot replace arterial blood gas measurements.⁵ In this patient, pulse oximetry desaturation may reflect actual arterial desaturation. Patients with resting DCO of less than 50% and those with severe pulmonary hypertension are likely to desaturate with exercise. Additionally, reduced mixed venous O₂ caused by the decreased cardiac output and/or increased O₂ extraction in the presence of V/Q mismatching as a consequence of parenchymal changes due to mitral stenosis, can also be responsible for the O₂ desaturation.¹

In summary, the patient had an abnormal cardiopulmonary exercise test with severe reduction in functional capacity. Exercise limitation was most probably multifactorial with cardiovascular/pulmonary vascular factors quantitatively the most impor-

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tant. In the absence of atrial fibrillation, the patient may have exercised longer, and ventilatory factors contributing to exercise limitation may have been more apparent. Moreover, respiratory (ie, hypoxemia), and deconditioning contributing to exercise limitation appears likely but of lesser magnitude.

2. CPET is very helpful in the evaluation of dyspnea, especially in patients with combined cardiopulmonary disease, in order to determine the greater contributing factor to exercise limitation, and in patients with unexplained dyspnea.6

3. CPET can be performed by pulmonologists and cardiologists. Optimal use of CPET in clinical practice requires that physicians who perform and interpret CPET should be properly trained in this discipline. Accurate interpretation and meaningful application of CPET results requires knowledge of a patient’s clinical status and history, as this may have direct impact on the results.

4. The placement of an arterial line with arterial blood gas analysis and pulmonary gas exchange measurements would have been very helpful in more clearly diagnosing/characterizing the pulmonary gas exchange response to exercise and its contribution to exercise limitation in this patient. The patient had borderline breathing reserve with significant desaturation with pulse oximetry during exercise. The limitations of pulse oximetry have been noted. The magnitude of arterial desaturation, wasted dead space ventilation, and reduced values of PaO2 and alveolar-arterial oxygen pressure difference would better define the role of pulmonary vascular disease or possibly even parenchymal lung disease secondary to mitral valve dysfunction.

REFERENCES
1 Bates DV, Macklem PT, Christie RW. Respiratory function in disease. 2nd ed. Philadelphia: WB Saunders, 1971
6 Weisman IM, Zeballos RJ. Clinical evaluation of unexplained dyspnea. Cardiologia 1996; 41:621-34

COMMENTS BY CONSULTANTS
Adrian Hall, MB, BS, and Karlman Wasserman, MD, PhD, FCCP

The case presented describes a woman who had a very significant decrease in exercise tolerance over a 2-month period. She had a left upper lobectomy 1 year previous to the current evaluation. While no prethoracotomy exercise data are presented, her resting lung function deteriorated beyond that predicted from removal of a lobe of a lung. Also, her diffusing capacity was lower (38% of predicted) than expected solely from a lobe resection.

In response to the questions posed by the editor: 1. The patient’s exercise test shows that the major parameters of aerobic function, including peak VO2, anaerobic threshold (Table 2), and ΔVO2/ΔWR (Fig 2) are very abnormal. These findings indicate that the patient is suffering from inability to transport adequate O2 from the lungs to the metabolically active muscle. This usually occurs because of cardiovascular abnormality, although reduced O2 carrying capacity (anemia and increased carboxyhemoglobin) might exaggerate the extent of the underlying pathophysiologic condition.

The failure for VO2 to increase indicates that pulmonary blood flow and therefore cardiac output are not increasing despite increasing work rate (Fig 2). Thus, high-energy phosphate must be regenerated anaerobically with lactic acid increasing rapidly in the muscle. If VCO2 measurements were provided in Figure 2, it should be increasing rapidly relative to VO2 since the lactic acid is buffered almost totally by HCO3− (22 mL of extra CO2 for each mmol of lactic acid buffered by HCO3−). The extra CO2 produced from buffering and the net increase in arterial H+ are powerful stimuli to breathe, and along with an increased VD/VT ratio, are the likely mechanisms for the patient’s symptom of dyspnea.

The mechanism for the failure of cardiac output to increase in response to exercise, in this case, is most likely heart failure. The increase in VO2 during exercise is dependent on an increase in heart rate, stroke volume, and arteriovenous O2 content difference (C(a-v)O2). Heart rate increased immediately at the start of exercise but then remained constant despite increasing work rate. The O2-pulse (stroke volume × C(a-v)O2) is 3 mL/beat at the start of exercise and remains unchanged as work rate is increased (Fig 1). This means that C(a-v)O2 has reached a maximal value (approximately 15 mL/dL assuming a normal hemoglobin concentration) at the lowest work rate, or that stroke volume is decreasing as C(a-v)O2 is increasing at submaximal work rates. At maximal exercise, stroke volume calculated from O2-pulse with an assumed C(a-v)O2 = 15 mL/dL would be quite low at about 20 mL (the calculated stroke volume would increase inversely with the degree of anemia because C(a-v)O2 would decrease proportionately). Since the patient had physical and echocardiographic evidence of mitral insufficiency, part of the low effective stroke volume might be due
to regurgitation of part of the left ventricular stroke into the left atrium. The tricuspid insufficiency is probably related to the pulmonary vascular changes that accompany mitral valve disease.

Pulmonary vasoconstriction commonly takes place in chronic heart failure as might be found in patients with mitral valve disease. This might serve as a protective mechanism in preventing frank pulmonary edema when pulmonary vascular pressures are high as observed in functionally important mitral valve disease. The pulmonary vasoconstriction reduces the size of the pulmonary capillary bed resulting in a reduced DCO and an increased Vd/Vt ratio (decreased perfusion to ventilated lung). The low DCO in this patient cannot be accounted for by a lobectomy and is most likely attributable to the vasoconstriction that takes place in the lungs in patients with mitral valve disease.

It should be noted that the ventilatory equivalent for O₂ (Ve/Vo₂) at maximal exercise is very high (76) and suggests that Vd/Vt is also high. Arterial sampling is essential for determination of Vd/Vt, a value that is very likely to be abnormal in the case under discussion. It should be appreciated that Vd/Vt calculated by substituting PETCO₂ for PaCO₂, as was done in this case, is invalid. The same mechanism that increases Vd/Vt lowers PETCO₂. Thus, substitution of PETCO₂ for PaCO₂ gives a falsely normal value.

Heart failure might have caused the restrictive changes in lung function that apparently developed since the prethoracotomy study. The normal FEV₁/FVC suggests that there is no important obstructive lung disease.

2. Dyspnea on exertion precedes dyspnea at rest in the course of developing cardiovascular or pulmonary diseases. Therefore, it is difficult to imagine a more specific and appropriate test for directly addressing the cause of a patient’s dyspnea symptom than a cardiopulmonary exercise test. The challenge is for the examiner to know what to measure and to understand the difference between a physiologic and a pathophysiologic response.

3. Cardiopulmonary exercise testing should be employed to evaluate any organ that plays a role in the coupling of external to cellular respiration. Because both heart and lung diseases cause abnormal gas exchange at the airway, albeit different in pattern, it is appropriate for both cardiologists and pulmonologists to be interested in the gas exchange response to exercise. Cardiopulmonary exercise testing also has application in other specialties; for instance, anesthesiologists have applied cardiopulmonary exercise testing in preoperative evaluation of risk for major surgery in patients older than 60 years. In addition, the contribution of obesity to exercise intolerance in both cardiovascular and lung diseases would best be evaluated by cardiopulmonary exercise testing. Thus, exercise testing with measurement of exhaled gases should not be regarded as “turf” for any specialty, in our opinion.

4. Ordinarily, noninvasive cardiopulmonary exercise testing provides all of the information required for most clinical applications. However, arterial blood sampling for blood gases, pH, and possibly for lactate measurements during exercise has considerable diagnostic value and to have had these performed in this case would have been advantageous. To support the evidence that oxygen transport to the exercising muscles was impaired in the patient under study would be confirmed by a metabolic (lactic) acidosis at a very low work rate. As pointed out above, the Vd/Vt measurement provided in the report is undoubtedly erroneous because PETCO₂ rather than PaCO₂ was used to calculate dead space.

Finally, the pulse oximetry study suggests a decrease in arterial oxyhemoglobin saturation during exercise. Because pulmonary blood flow did not increase, evident from the nonchanging Vo₂ with increasing work rate (Fig 2), but ventilation did increase, it is not likely that oxyhemoglobin desaturation did, in fact, take place during exercise. Thus, this indirect measure of oxyhemoglobin saturation provided by pulse oximetry might be erroneous and deserves confirmation by direct arterial blood measurement. To understand the contributions of the exercise metabolic acidosis, hypoxemia, and increased Vd/Vt to the patient’s symptoms, arterial blood gases and pH measurements were necessary.

References

Case Follow-up and Editorial Comments
Steven R. Mohnssen, MD, FCCP, and Morton E. Tavel, MD, FCCP

The noninvasive CPET was interpreted as showing a primary cardiovascular limitation to exercise, with a secondary pulmonary vascular disorder due to the underlying valvular heart disease.

It is well known that a noninvasive cardiopulmo-
nary exercise test has limitations, including inaccurate \( V_d/V_t \) values and a lack of blood gas data. The interpreting physician, however, was of the opinion that the data obtained by this test were strong enough in this case to support the diagnosis, and, therefore, a second test with an arterial catheter, although supportive, was not believed necessary.

The patient was, therefore, referred back to her cardiologist for cardiac catheterization and consideration of valvular heart surgery. The hemodynamic data confirmed the presence of severe mitral regurgitation and aortic stenosis, combined with pulmonary hypertension (pulmonary arterial pressure of 100/55 mm Hg). Mitral stenosis was present but considered mild, and the coronary arteries were normal.

The degree to which atrial fibrillation and the rapid ventricular response contributed to the cardiac limitation is worthy of mention. Significant mitral stenosis is capable of impairing filling of the left ventricle during diastole, a portion of the cycle which is disproportionately shortened by tachycardia. In this context, rapid ventricular responses associated with atrial fibrillation, therefore, not only markedly impair left ventricular filling, but also may produce a pronounced elevation of left atrial and pulmonary capillary pressure, factors which in themselves may contribute to dyspnea and reduced exercise capacity. Thus, in the presence of significant mitral stenosis, one should always attempt whenever possible to control pharmacologically the ventricular rate response to exercise (preferably to less than 130/min).

On the other hand, the degree of mitral stenosis noted in this instance was believed not of sufficient magnitude to have played a major role in the limitation described earlier. Although effective mechanical atrial contraction is absent, the atrial fibrillation *per se* is generally not an important factor in limiting cardiac performance, except in conditions associated with reduced left-ventricular compliance, as encountered in hypertrophic cardiomyopathy, etc.

A double valve replacement at the aortic and mitral valve positions was performed successfully. Although she suffered a minor embolic cerebral infarction in the perioperative period, she recovered quite nicely. Subsequent follow-up demonstrated significantly improved exercise tolerance and no further complaints of dyspnea. Atrial fibrillation persisted. An echocardiogram performed 3 years postoperatively showed normal function of the mitral and aortic prosthetic valves, concentric hypertrophy of the left ventricle, mild tricuspid regurgitation, and mild left atrial dilatation.

This case demonstrates the clinical value of CPET in determining the primary organ system limitation in those individuals afflicted with combined cardiac and pulmonary disorders. In addition, this test is useful in the treatment of patients with heart failure, and in the evaluation of those being considered for cardiac transplant, preoperative evaluation of patients being considered for thoracotomy and other major surgical procedures, as well as in the evaluation of patients with various pulmonary disorders, which includes assessment before and during pulmonary rehabilitation.

It is important to stress that “cardiac exercise testing” and “pulmonary exercise testing” are not necessarily separate tests and that gas exchange at the cellular level requires coordination of the heart, lungs, pulmonary, and peripheral circulations.

Abnormal respiratory patterns and gas exchange can occur from cardiac disorders and, likewise, pulmonary disease can cause abnormal cardiac function. CPET, therefore, provides useful clinical information both to pulmonologists and cardiologists alike and should not be considered the “domain” of any specialty.