NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.
I. BRONCHIAL CHALLENGE TESTING

INTRODUCTION

Patients with asthma and, to some extent, patients with obstructive lung diseases (e.g., chronic obstructive pulmonary disease, cystic fibrosis, endobronchial sarcoidosis, and congestive heart failure) have a tendency to exhibit variability over time in their degree of airway obstruction. The change in airway obstruction occurs either spontaneously or in response to environmental stimuli. This variability can be documented easily by performing serial spirometry.

Variability of airway obstruction has important diagnostic, therapeutic, and prognostic implications. Generally, increased variability in the degree of airway obstruction indicates increased susceptibility to bronchoconstrictive environmental stimuli. The potential of a given patient for exhibiting variability can be demonstrated in the pulmonary function laboratory by measuring their response to bronchoconstrictive agents.

Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness (BHR) is defined as the presence of an exaggerated bronchoconstrictive response to a given agent at a dose that would cause little or no response in a normal individual. (The terms hypersensitivity and hyperreactivity designate specific aspects of the dose-response curve to a given bronchoconstrictive agent and should not be used interchangeably with the term hyperresponsiveness.) BHR is a cardinal feature of asthma and a component of the operational definition of this disorder, but the mechanisms responsible remain largely unexplained.1

Bronchoprovocational Agents

A variety of agents have been employed to elicit BHR in diverse clinical and research applications. These range from pharmacologic agents to allergens, drugs, occupational sensitizers, exercise, and the inhalation of cold air. Specific agents such as drugs, allergens, or occupational sensitizers are utilized in specialized challenge tests. These procedures are available in few laboratories and require considerable experience in preparing challenge solutions and performing the tests.

This review addresses BHR testing that utilizes the two most commonly employed agents in clinical practice settings: the pharmacological bronchial challenge using commercially available methacholine and the challenge...
using exercise as a bronchoconstrictive agent. The American Thoracic Society (ATS) and the European Respiratory Society have published official statements on standards for the performance and interpretation of bronchial challenge tests.\textsuperscript{2,3}

**METHACHOLINE CHALLENGE TESTING**

Methacholine (acetyl-β-methylcholine chloride) is available in a United States Food and Drug Administration–approved formulation (Provocholine) as a dry powder from which solutions are prepared for aerosol inhalation in accordance to predetermined dilutional schemes. A variety of dosing protocols have been employed. Two techniques are widely used in North America: a 2-minute nebulizer tidal breathing dosing protocol recommended by the Canadian Thoracic Society and a 5-breath dosimeter protocol standardized by the National Institute of Allergy and Infectious Diseases. Both methods give similar results.

Both techniques begin with the inhalation of the lowest concentration of methacholine. Spirometry is performed following the inhalation of each successive concentration. If the forced expiratory volume in 1 second (FEV\textsubscript{1}) decreases by 20% or more compared to baseline, the test is terminated and the patient is given a bronchodilator. Otherwise, the test continues with the next higher concentration until the maximal concentration is given (16 mg/mL). The percent fall in FEV\textsubscript{1} relative to baseline is plotted on the ordinate and the concentrations of methacholine are plotted on the abscissa \textbf{(Figure 1)}. The result of the test is reported as PC\textsubscript{20}, the provocative concentration of methacholine associated with a 20% fall in FEV\textsubscript{1} in the plot. PC\textsubscript{20} is calculated by numerical interpolation of the last 2 data points.

Bronchial responsiveness to methacholine is graded according to the magnitude of the PC\textsubscript{20} into 4 levels according to \textbf{Table 1}. This categorization, when utilized in conjunction with methods of decision analysis, can be helpful in the diagnosis of asthma, as illustrated in case discussions presented later. It is important to bear in mind that the interpretation schema used in Table 1 is only valid if baseline spirometry shows no obstruction, and if there is substantial post-challenge reversal of bronchoconstriction.

Indications for the performance of a methacholine bronchial challenge are discussed in the context of discussions of the case reports that follow. Absolute and relative contraindications are listed in \textbf{Table 2}. Methacholine is a pregnancy category C drug (ie, no data are available on its effects on the fetus).

Because airway obstruction in itself is associated with increased responsiveness to bronchoconstrictive agents, it is difficult to interpret the significance of a decrease in PC\textsubscript{20} when this abnormality is present. In addition, the risk of precipitating an exaggerated fall in FEV\textsubscript{1} with methacholine is greater in subjects whose baseline spirometry shows airway obstruction. It is recommended that patients with baseline airway obstruction be given a bronchodilator instead of methacholine. A significant response, consisting of an increase in FEV\textsubscript{1} of 12% or more coupled with an absolute increase in FEV\textsubscript{1} of 200 mL or more, confirms the presence of BHR without having to risk using methacholine.

**Case 1 Presentation**

Patient 1 is a 27-year-old computer executive who presents with a complaint of reversible attacks of dyspnea and chest tightness lasting 20 to 40 minutes. The attacks

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occur mostly while he is at rest and occasionally while exercising on a treadmill. The most recent episode took place 10 days ago and prompted him to visit an emergency room, where the administration of aerosols of a β-adrenergic agonist was associated with gradual cessation of the attack. The patient denies cough or nocturnal awakenings with respiratory symptoms. The patient is afraid that he has developed asthma because both his mother and a sister have been diagnosed with this disorder.

The patient has a history suggestive of seasonal allergic rhinitis, but he does not recall having symptoms consistent with asthma during his childhood. Physical examination is normal except for the presence of a precordial systolic murmur and a mid-systolic click suggestive of mitral valve prolapse. Chest radiograph and electrocardiogram are within normal range. Results of pulmonary function tests and arterial blood gas analysis are normal. A methacholine bronchial challenge performed at a qualified medical center results in a 15% decrease in FEV₁ after a concentration of 16 mg/mL methacholine is inhaled.

### What is the correct interpretation of the results of patient 1’s methacholine challenge?

- **A)** There is mild BHR to methacholine consistent with a diagnosis of mild asthma
- **B)** There is normal responsiveness to methacholine, but this could be a false-negative result. The test should be repeated because false negatives are common.
- **C)** The results of the bronchial challenge rule out asthma in this patient
- **D)** The 10-day interval between the attack and the test is too long. The PC₂₀ may have returned to normal. The test should be repeated in closer proximity to an attack.
- **E)** The test is equivocal. It should be repeated using measurements of specific airways conductance (sGaw), because these measurements are more sensitive endpoints for methacholine challenge than the FEV₁ for distinguishing patients who have asthma from those who do not.

### Discussion

The answer is **C**. The primary clinical use of the methacholine challenge is to exclude the diagnosis of asthma. The negative predictive power of a methacholine challenge that results in a PC₂₀ greater than 16 mg/mL (ie, indicative of normal bronchial responsiveness; see Table 1) is 90% even if the prior probability of asthma was 70%. In a patient who has had symptoms suggestive of asthma less than 2 weeks before being tested and who is not taking anti-inflammatory medicines (eg, aerosol steroids), a normal bronchial responsiveness to methacholine essentially rules out asthma.

In patient 1, there is no suggestion that any of the conditions associated with a false-negative test are present.

### Table 1. Categorization of Bronchial Responsiveness to Methacholine

<table>
<thead>
<tr>
<th>PC₂₀ (mg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 16.0</td>
<td>Normal bronchial responsiveness</td>
</tr>
<tr>
<td>4.0–16.0</td>
<td>Borderline BHR</td>
</tr>
<tr>
<td>1.0–4.0</td>
<td>Mild BHR (positive test)</td>
</tr>
<tr>
<td>Less than 1.0</td>
<td>Moderate to severe BHR</td>
</tr>
</tbody>
</table>

BHR = bronchial hyperresponsiveness; PC₂₀ = provocative concentration of methacholine associated with a 20% fall in forced expiratory volume in 1 second.


### Table 2. Contraindications for Methacholine Challenge Testing

**Absolute contraindications**
- Severe airflow limitation (FEV₁ < 50% of predicted or < 1.0 L)
- Heart attack or stroke in the past 3 months
- Uncontrolled hypertension (systolic BP > 200 mm Hg or diastolic BP > 100 mm Hg)
- Known aortic aneurysm

**Relative contraindications**
- Moderate airflow limitation (FEV₁ < 60% of predicted or < 1.5 L)
- Inability to perform acceptable-quality spirometry
- Pregnancy
- Breast-feeding
- Current use of cholinesterase inhibitor medication (for myasthenia gravis)

BP = blood pressure, FEV₁ = forced expiratory volume in 1 second.

False-negative results are uncommon provided that the test is performed according to recommended technique. Another clinical indication of the methacholine test is to confirm the presence of BHR in patients suspected of having occupational asthma induced by a single specific sensitizer (eg, toluene diisocyanate). A small proportion of patients with this type of occupational asthma may only respond abnormally to challenges performed with the suspected specific agent, while continuing to respond normally to methacholine. This response pattern could be considered a false-negative result in an asthmatic patient.

Plethysmographic measurements of airways resistance (Raw) or of sGaw, when used as end-points for methacholine challenge, are less useful than the FEV₁ for identifying patients with asthma. The reason for this resides in a property of normal airway smooth muscle. The stretching of the airway that occurs with the obligatory full inspiration that precedes the measurement of the FEV₁ causes normal airway smooth muscle to relax, thus attenuating the contractile effect of methacholine. The airway smooth muscle of patients with moderate or severe asthma either loses this property or manifests it in an attenuated form. Because a deep inhalation is not required for measuring Raw or sGaw, there is no opportunity for blunting the bronchoconstrictive action of methacholine during a measurement in a normal subject. This effect may explain the diminished ability of these indices to distinguish normal and asthmatic responses to methacholine.

Case 2 Presentation

Patient 2 is a 35-year-old school teacher who presents with a complaint of productive cough and occasional wheezing for the past 4 weeks. The onset of these symptoms followed what appears to have been a short-lived upper respiratory infection (URI) with rhinorrhea, sore throat, and malaise. There is a strong prevalence of asthma and atopic disorders in her family. She has continued to smoke 1 pack of cigarettes per day throughout her illness, a habit she has had for 10 years. She denies the presence of sustained respiratory symptoms prior to the present episode. The patient is concerned about having developed asthma that is now being exacerbated by an episode of URI. She asks that you estimate the likelihood of such an occurrence.

The patient has begun taking 1 tablet daily of cetirizine, an antihistamine that had been prescribed for one of her brothers who has allergic rhinitis. The patient has experienced some relief of cough since starting this medication. Results of the physical examination, chest radiographs, and spirometry are all within normal range. You estimate, on clinical grounds, that the probability of asthma being present is low to moderate, approximately 30%. You request a methacholine challenge with the expectation that the results will help you improve this clinical estimate. The result of the methacholine challenge is a PC₂₀ of 6 mg/mL, which indicates borderline BHR (Table 1).

- To what extent should the results of the methacholine challenge affect your initial diagnostic impression for Patient 2?
  A) The post-test probability of asthma has been increased by the results of the methacholine challenge from 30% to approximately 70% to 80%
  B) The results of the test are essentially diagnostic of asthma in this patient
  C) The results of the test show only a low level of BHR and thus are not suggestive of the diagnosis of asthma
  D) The presence of a URI 4 weeks ago and the fact that the patient has not stopped smoking may account for the level of BHR demonstrated in the test. The test does not contribute to the diagnosis of asthma in patient 2.
  E) It is unlikely that the use of cetirizine has influenced the results of the test because antihistamines are known to have no bronchodilatory properties. The result of the test is confirmatory of asthma.

Discussion

The answer is D. This case exemplifies one of the most common expectations for the methacholine challenge test—that it can be used to assess the probability that a patient with asthmalike symptoms has the disorder.

The ATS statement on methacholine testing discusses the relative merits of two interpretative strategies: (1) a method grounded in principles of decision analysis, which combines the prior probability of having the disease with the categorization of BHR shown in Table 1; and (2) a dichotomous method that views the results of the test as either negative or positive, with a PC₂₀ of 8 mg/mL or greater indicating a negative result.

An extensive discussion of this subject exceeds the scope of this review. In brief, according to the first interpretive strategy, when a patient with symptoms suggestive of asthma has a PC₂₀ of less than 1 mg/mL, the diagnosis of asthma is basically established. A PC₂₀ between 1 and 8 mg/mL can contribute to the refinement of a prior probability of asthma, but cannot corroborate or refute the diagnosis. (Options B and C are therefore
incorrect.) This interpretive strategy utilizes the family of curves depicted in Figure 2, which illustrate how, for any level of BHR, a pre-test probability of having asthma can be translated into a post-test probability. The most obvious limitation of this approach is the current lack of uniform, valid clinical criteria to estimate the pre-test probability of asthma in a given patient.

The dichotomous strategy for interpretation of the results of methacholine testing has the advantage of not requiring a prior estimate of the clinical likelihood of asthma. The weakness of this strategy lies in the relatively large rate of false-positive test results. For example, 30% of patients with allergic rhinitis have a PC20 for methacholine in the range of 4 to 16 mg/mL.6

Factors that may decrease bronchial responsiveness include asthma medications, antihistamines, and foods containing caffeine-like compounds. Bronchial responsiveness is increased by acute exposure to specific agents (eg, antigens, occupational sensitizers), nonspecific agents (eg, pollutants, irritants, cigarette smoke), and respiratory infections. The categorization of BHR to methacholine in the range of 4 to 16 mg/mL depends on the patient's medical history and the presence of symptoms suggestive of asthma. This approach assumes that other factors that are known to alter airway responsiveness have been excluded. Patient 2 has conditions that may alter bronchial responsiveness (ie, smoking,8 recent respiratory infection,9 and administration of the antihistamine cetirizine3). Therefore, option A, in which a post-test probability is derived using the curves presented in Figure 2, is incorrect.

EXERCISE BRONCHIAL CHALLENGE

Exercise challenge in clinical settings is indicated when the identification of exercise-induced bronchoconstriction (EIB) is of diagnostic or therapeutic interest. Typically, the test has been used in children with symptoms suggestive of asthma because EIB is present in virtually all patients with asthma in the pediatric age group and because it mimics a “real-life” inciting stimulus for bronchoconstriction.10 Another indication for exercise challenge is to investigate the cause of asthma-like symptoms occurring during exercise in adults whose occupation requires them to perform physically demanding work.11 Under these conditions, a reduced PC20 to methacholine is not sufficient to establish that the symptoms experienced during exercise are, in fact, due to EIB.

Exercise challenge is contraindicated by the same conditions that abrogate the performance of methacholine challenges (Table 2). In addition, patients with evidence of myocardial ischemia or arrhythmia should not be tested. Exercise challenge testing may not be helpful in patients with significant orthopedic disorders involving the lower limbs who are unlikely to achieve the required exercise intensity.
Case 3 Presentation

Patient 3 is a 21-year-old military recruit who presents with a complaint of dyspnea and wheezing while engaged in high-intensity exercise during boot camp. He has no history of recent URI, atopy, nocturnal awakenings with asthma symptoms, or productive morning cough. He has never smoked cigarettes.

Results of the physical examination are normal. Results of pulmonary function testing and arterial blood gas analyses are within normal range. The result of methacholine challenge testing is a PC_{20} of 12 mg/mL.

An exercise challenge test is performed on an ergometric bicycle with the patient breathing room air from a medical-grade compressed air tank at ambient temperature. The duration of the test is 8 minutes. During the last 5 minutes of the test the patient’s heart rate ranges between 160 to 170 bpm (approximately 85% of maximum predicted). The respiratory technician administering the test reports that toward the end of the test the patient could be heard wheezing, with the sound audible at a distance. The wheezing disappears shortly after cessation of exercise. Serial spirometry obtained 5, 10, 15, 20, and 30 minutes following the cessation of exercise shows a decrease in FEV_{1} of 8% in comparison to baseline.

- **How do you interpret the results of patient 3’s exercise challenge test?**
  A) Serial FEV_{1} should have been tested during exercise, not after cessation. The test is therefore invalid.
  B) The result of the test is diagnostic of exercise-induced bronchoconstriction (EIB) in this patient.
  C) The temperature of inhaled air should have been cooler than the ambient air. The test is invalid.
  D) A repeat test is recommended using full inspiratory-expiratory flow-volume loops.
  E) The combination of reduced PC_{20} for methacholine and a decrease in FEV_{1} during exercise is highly suggestive of the diagnosis of asthma.

Discussion

The answer is D. The mechanisms causing bronchoconstriction during exercise involve rapid water loss from the airway. The extent of water loss is directly related to the magnitude of the ventilation achieved during exercise, the duration of exercise, and to the water content of the inspired air. The ATS recommends using a compressed air source for inhaled air. The inhaled air should be at ambient temperature (which should not exceed 25°C) and should contain less than 10 mL of water/L.

Patients should exercise for a total of 8 minutes, during 4 to 6 minutes of which the patient should reach a heart rate of 80% to 90% of the maximum predicted or a ventilation rate of 40% to 60% of the maximum predicted. These conditions were met in the test performed on patient 3.

There is still disagreement on the relative importance of the various intermediary mechanisms of water loss that lead to bronchoconstriction. Dehydration, cooling, osmotic effects, and rewarming of the airways are all believed to be involved. However, because EIB occurs in the absence of airway cooling, it is not necessary in testing to lower the temperature of the inspired air below the usual ambient temperature of a typical air-conditioned pulmonary function laboratory.

Exercise-induced bronchoconstriction develops after cessation of an 8-to10-minute period of exercise. The expected response of the airways during exercise of this duration is bronchodilation, not bronchoconstriction (Figure 3), and therefore spirometry should be performed following, not during, exercise.

A decrease in FEV_{1} of 10% relative to baseline is considered evidence suggestive of EIB. A fall of 15% is diagnostic of EIB. The results of the test on patient 3 fall short of these values. The presence of borderline BHR to methacholine in patient 3 with no symptoms suggestive of asthma other than wheezing during intense exercise challenge is associated with a low post-test probability for the diagnosis of asthma.

Vocal cord dysfunction is a disorder that is often confused with asthma. A subset of patients with vocal cord dysfunction has been described whose symptoms appear predominantly or exclusively during intense physical activity. Because patient 3’s symptoms appear under such circumstances but his clinical presentation and test results are not consistent with a diagnosis of asthma, a repeated exercise challenge test with full inspiratory-expiratory flow-volume loops recorded should be considered.

Case 3 Follow-up

Patient 3 undergoes a repeat exercise challenge using the same protocol. Flow-volume loops show that an inspiratory flow cut-off occurred at a time when wheezing was present (Figure 4). Direct laryngoscopy confirms a diagnosis of vocal cord dysfunction by showing paradoxical vocal cord adduction during inspiration. (Stridor in patient 3 had evidently been mistaken for wheezing by the laboratory personnel—a common clinical occurrence.)
II. CARDIOPULMONARY EXERCISE TESTING IN LUNG DISEASE

INTRODUCTION

The diagnostic or prognostic use of cardiopulmonary exercise testing (CPET) for patients with lung diseases is an area of growing clinical interest, and the clinical applicability of this technique is quickly evolving. Two factors have contributed to this rapid growth. An understanding of basic concepts of exercise physiology has increased in recent years. Moreover, because of advances in computer technology, complex physiologic data can now be easily collected, processed, and analyzed in a routine pulmonary function laboratory.

This review provides examples and discussion of interpretative approaches to a few characteristic patterns of response to exercise in some lung disorders. For a comprehensive overview of the use of CPET in the evaluation of lung diseases, the reader is referred to the European Respiratory Society's position document on indications, standardization, and interpretation of exercise testing in lung diseases.15

It is important to note that no studies have yet successfully demonstrated a predictive value for these patterns of measurement in the diagnosis of various clinical disorders. However, each pattern of response to exercise constitutes a set of appropriate physiologic expectations for a given lung disorder. There is usually sufficient concordance between clinical expectations and the findings of CPET to reinforce the clinical diagnosis. However, when the observed findings during exercise do not fit the expectations of the model, the clinical diagnosis may be challenged. A context is thus provided in which to proceed with further testing.

The simplest protocol for exercise testing involves imposing on the subject progressively incremental workloads using either an ergometric bicycle or a motor-driven treadmill. The magnitude of the increments in workload is individually tailored to yield an exercise duration of approximately 10 minutes, terminating with the subject's inability to continue because of limiting symptoms. Continuous noninvasive measurements are obtained of exhaled carbon dioxide and oxygen concentrations (end-tidal pressures of CO₂ [PETCO₂] and O₂ [PETO₂]) while the subject breathes room air from a mouthpiece or a loose-fitting mask. Air flow, respiratory rate, external work rate, electrocardiogram, arterial oxygen saturation by pulse oximetry (SpO₂), and systemic blood pressure are also continuously measured. Data are processed to yield derived variables, including oxygen utilization (˙VO₂), carbon dioxide production (˙VCO₂), respiratory exchange ratio (RER), lactate or "anaerobic" threshold (LT), ventilation (˙VE), and tidal volume (VT).

Primary and derived variables are then combined in basic trend plots. These trends are put to use to gain further insight into aspects of exercise performance in the patient, either during submaximal or near-peak performance. The review by Younes16 provides additional information on interpretative strategies using selected basic plots.
For the sake of simplicity and to provide an introduction to the subject, the interpretation of the tests in the cases that follow are based only on changes in a limited number of variables, which are listed in Table 3.

Peak oxygen utilization (\(\dot{V}O_2\)peak) is the oxygen utilization rate at peak exercise (ie, the highest level of exercise achieved before symptoms cause a patient to cease exercising). LT is the rate of oxygen utilization during exercise above which a sustained increase in blood lactate occurs. LT can be measured directly by serial determinations of blood lactate. More commonly, it is estimated noninvasively from the relationship between \(\dot{V}O_2\) and \(\dot{V}CO_2\). In this approach, LT is the value of \(\dot{V}O_2\) associated with an accelerated increase in \(\dot{V}CO_2\) relative to \(\dot{V}O_2\), determined graphically as the intersection of 2 linear slopes (Figure 5).

Ventilatory reserve (VR) is defined as the difference between the ventilatory capacity and the minute ventilation at peak exercise, expressed as a percentage of the ventilatory capacity. The VR represents the potential of the minute ventilation to increase. (Ventilatory capacity is difficult to estimate. It can be approximated grossly from spirometric measurements taken at rest of maximum voluntary ventilation or by multiplying the FEV\(_1\) by 40.)

The heart rate reserve (HRR) is the difference between the predicted maximum heart rate and the heart rate at peak exercise, expressed as a percentage of the maximum predicted heart rate. The HRR represents the potential of the heart rate to increase.

### CASE 4 PRESENTATION

Patient 4 is a 57-year-old man who presents with a complaint of worsening exertional dyspnea. He has a history of ethanol abuse and 60 pack-years of cigarette smoking. He is currently taking ipratropium by metered-dose inhaler and a systemic corticosteroid (20 mg of prednisone daily) for his dyspnea. In spite of these medications, however, for the past 6 months he has been unable to walk for more than half a block because of shortness of breath.

Patient 4's FEV\(_1\) is 1.7 L (45% of predicted). The ratio of FEV\(_1\) to forced vital capacity (FVC) is 50%. Arterial blood gas analysis at rest, breathing air, is as follows: pH, 7.43; PCO\(_2\), 39 mm Hg; PO\(_2\), 65 mm Hg. These results are comparable to assessments obtained 1 year ago. Chest radiograph shows hyperinflation. Results of a complete blood count are normal.

A cardiac evaluation is undertaken in view of a strong family history of atherosclerosis and because the degree of patient 4's dyspnea seems out of proportion with the severity of airway obstruction. The electrocardiogram (EKG) is equivocal, demonstrating nonspecific changes to the ST-T segment in the lateral leads. An echocardiogram obtained during dopamine infusion fails to reveal evidence of myocardial or valvular dysfunction.

Data from CPET of patient 4 are summarized in Table 4.

- **How does this test contribute to an understanding of the mechanisms of decreased exercise tolerance in patient 4?**

A) The pattern of response seen in patient 4 is typical of patients with COPD. The test adds nothing to what is already known clinically regarding this case.
B) An increased HRR in a patient with COPD indicates concomitant cardiac disease.

C) Patients with COPD are not expected to be limited by leg discomfort during exercise. This finding in patient 4 suggests that cardiovascular dysfunction is present.

D) The presence of a normal VR and the magnitude of the observed fall in SpO\textsubscript{2} are unusual for COPD patients. Further investigation is warranted.

E) The test is inconclusive without LT data. The test should be repeated with serial blood samples for determination of the lactate threshold.

**Discussion**

**The answer is D.** The results of CPET in patient 4 have many features characteristic of the response of patients with COPD to exercise. Decreased peak oxygen utilization invariably accompanies moderate or severe airway obstruction. Patients with COPD tend to be physically deconditioned and often have a low LT when it can be assessed directly; however, it is usually not possible in these patients to assess LT indirectly by measuring the intersection of 2 slopes as illustrated in Figure 5. VR is typically absent or severely reduced in patients with COPD owing to decreased ventilatory capacity together with a large physiologic dead space. It is unusual for VR to be normal, as in patient 4. HRR is typically normal or increased in patients with COPD. A reduction in SpO\textsubscript{2} during CPET does not always occur in patients with COPD. When it does occur, however, it is rarely as severe as in patient 4. Finally, although most patients with COPD are limited by dyspnea during CPET, some patients terminate exercise because of leg discomfort. When this occurs, VR is typically not yet fully exhausted.

**Case 4 Follow-up**

The magnitude of decrease in oxygen saturation during exercise in patient 4 is confirmed by repeating CPET while sampling arterial blood via an indwelling radial cannula. A patent foramen ovale is ruled out as a cause of exercise hypoxemia. Subsequently, liver function tests and a liver biopsy are found to be consistent with cirrhosis. The excessive exercise-related hypoxemia seen in patient 4 could be a manifestation of the type of gas exchange dysfunction that occurs in patients with liver cirrhosis. The administration of...

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**Table 4. Parameters Measured During Exercise Testing in Patient 4**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak oxygen utilization</td>
<td>30% of predicted (reduced level)</td>
</tr>
<tr>
<td>Lactate threshold</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Ventilatory reserve</td>
<td>50% (normal level)</td>
</tr>
<tr>
<td>Heart rate reserve</td>
<td>5% (normal level)</td>
</tr>
<tr>
<td>SpO\textsubscript{2}</td>
<td>Reduction to 65%</td>
</tr>
<tr>
<td>Reason for stopping test</td>
<td>Leg discomfort</td>
</tr>
</tbody>
</table>

\(\text{SpO}_2\) = arterial oxygen saturation as measured by pulse oximetry.
oxygen during exercise corrects patient 4’s hypoxemia and allows him to pursue a pulmonary rehabilitation program.

Case 4 illustrates the use of CPET to resolve an apparent clinical inconsistency. The low level of exercise tolerance experienced by this patient was believed to be disproportional to the severity of airway obstruction indicated by an FEV₁ of 1.7 L. The results of the CPET showed excessive hypoxemia that, in turn, directed the expansion of the work-up, leading to the discovery of cirrhosis.

The fact that lower limb discomfort, rather than dyspnea, was the exercise-limiting symptom in this patient suggests that efforts directed at improving ventilatory function probably would not result in improved exercise tolerance. Steroid-induced myopathy or malnutrition associated with cirrhosis may explain patient 4’s apparent lower limb weakness.

CASE 5 PRESENTATION

Patient 5 is a 27-year-old woman who presents with a complaint of progressive dyspnea on exertion and fatigue of 6 months’ duration. She recently experienced an episode of dizziness during an aerobics class and became alarmed. She had been in good health prior to the onset of these symptoms, and denies tobacco or recreational drug use. Results of arterial blood gas analysis are as follows: pH, 7.44; PCO₂, 34 mm Hg; PO₂, 85 mm Hg. Lung function tests show normal spirometry and lung volumes. The carbon monoxide diffusion in the lungs (DLco) is 81% of predicted. Chest radiograph and EKG findings are normal. Data from CPET of patient 5 are summarized in Table 5.

- **The results of CPET in patient 5 are consistent with which of the following conditions?**
  A) Interstitial lung disease or COPD
  B) Congestive heart failure or COPD
  C) Congestive heart failure or interstitial lung disease
  D) Chronic pulmonary hypertension or interstitial lung disease
  E) Chronic pulmonary hypertension or COPD

Discussion

The answer is D. Patterns of response to exercise in the conditions listed in the question are contrasted in Table 6. The greatest prevalence of primary pulmonary hypertension occurs in young women. This case illustrates a frequent dilemma of differential diagnosis that occurs when a young woman complains of dyspnea and pre-syncope during exercise, but routine assessments fail to provide evidence of an abnormality. The results of CPET in patient 5 strongly suggest that either an interstitial lung disease (accompanied by normal chest radiographic findings) or chronic pulmonary hypertension is present.

Patients with chronic pulmonary hypertension tend to demonstrate decreases in peak oxygen utilization that are roughly proportional to their decrease in cardiac output response to exercise. The lactate threshold is decreased. The development of acidosis early in exercise, coupled with the tendency of patients with chronic pulmonary hypertension to have a low PCO₂, contributes to increased ventilation during exercise. However, this is usually not of a magnitude that would cause an abnormal reduction in VR.³⁰ VR is generally normal in these patients largely because the ventilatory capacity remains intact. Characteristically, patients with chronic pulmonary hypertension have a significant decrease in oxygenation during exercise, which is brought about primarily by a decrease in oxygen content of mixed venous blood.²¹

Case 5 Follow-up

On the basis of the results of CPET, patient 5’s work-up is expanded. Arterial blood gas analysis confirms the presence of hypoxemia during exercise that was suggested by pulse oximetry. A high-resolution computed tomographic scan shows no evidence of interstitial lung disease. Results of a ventilation/perfusion scan are normal. A right-sided cardiac catheterization demonstrates normal wedge pressure and moderate elevation of the pulmonary arterial pressure (mean, 50 mm Hg). A diagnosis of primary pulmonary hypertension is made. Subsequent review of patient 5’s history reveals that the patient had used appetite suppressant drugs for the preceding 6 months, suggesting a possible etiology for the disorder.
Table 6. Selected Patterns of Abnormal Response to Cardiopulmonary Exercise Testing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interstitial Lung Disease</th>
<th>Chronic Pulmonary Hypertension</th>
<th>Congestive Heart Failure</th>
<th>Chronic Obstructive Pulmonary Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak oxygen utilization</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Lactate threshold</td>
<td>Normal or low</td>
<td>Low</td>
<td>Low</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Ventilatory reserve</td>
<td>Normal or reduced</td>
<td>Normal</td>
<td>Normal or reduced</td>
<td>Absent or reduced</td>
</tr>
<tr>
<td>Heart rate reserve</td>
<td>Normal or reduced</td>
<td>Normal</td>
<td>Normal or reduced</td>
<td>Normal or reduced</td>
</tr>
<tr>
<td>Reduction of Spo₂</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Spo₂ = arterial oxygen saturation as measured by pulse oximetry.


REFERENCES