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When the Chief Complaint Is (or Should Be) Dyspnea in Adults

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Dyspnea, "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity," is an important and challenging complaint associated with a wide variety of adverse clinical outcomes, including hospitalizations for chronic obstructive pulmonary disease and cardiac mortality. Although up to 85% of cases are caused by asthma, chronic obstructive pulmonary disease, interstitial lung disease, pneumonia, cardiac ischemia, congestive heart failure, or psychogenic disorders, a systematic approach can help to identity uncommon, but important, causes of dyspnea. In this review that includes clinical examples as well as a didactic review of currently available information, we suggest a step-wise approach to the evaluation of the adult patient with dyspnea. It is also important to avoid 3 possible pitfalls: accepting a cause for dyspnea in which the element identified is only part of a syndrome which includes that element; accepting a single cause for dyspnea when the cause is multifactorial; and failing to recognize a diagnosis and cause of dyspnea is incorrect and has been assumed without rigorous confirmation, when a patient with a specific diagnosis is referred for "failing to respond to treatment."   © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1: 129-36)

One of the most compelling, but often problematic, clinical challenges is to evaluate and treat the patient with dyspnea. Both communicating exactly what is meant by "dyspnea" or shortness of breath[1] and quantitating its severity are difficult because there are multiple approaches to these issues. In addition, the clinical problem of dyspnea can be hidden behind a diagnosis that has been assumed, but not rigorously established, when a specialist is consulted to assist with a patient who is "not responding to

appropriate therapy." This review uses a mixture of clinical vignettes, case presentations, and a didactic review of available information and literature to discuss this important problem and an approach to the patient with dyspnea, focusing mainly on adults. A detailed discussion of the neurophysiologic mechanisms of dyspnea is beyond the scope of this clinical review.[2]

CLINICAL VIGNETTE: LONG-AGO ASTHMA DIAGNOSIS DID NOT EXPLAIN BOY'S DIFFICULTY BREATHING

In an article published in *The Washington Post*,[3] Janice Lynch Schuster described the experience of her 10-year-old son Ian who, during a soccer game, collapsed on the field, unable to breathe. After 6 puffs of inhaled medication he was able to catch his breath and his father concluded, "Ian had an asthma attack during the game, but he was fine." A few years earlier Ian was given the diagnosis of asthma after an upper respiratory tract infection and, for several months, intermittently used an inhaler for symptom control. After his acute episode on the soccer field, a follow-up visit to a health care practitioner resulted in a diagnosis of "sports-induced bronchospasm" and instructions to use an inhaler as pretreatment before exercise. Only after severe episodes that resulted in multiple 911 calls, a pediatrician visit, and multiple emergency department visits, did an asthma specialist suggest the diagnosis of "larynx spasms triggered by acid reflux," because of the lack of wheezing on physical examination and Ian's previous history of acid reflux as an infant. Finally, after yet another episode, another emergency department physician finally made the correct diagnosis of "paradoxical vocal cord motion." In this case, the health care system failed Ian because a diagnosis not firmly established was assumed, and the real chief complaint, dyspnea, was not evaluated in a timely and appropriate manner. McFadden and Zawadski[4] have described vocal cord dysfunction masquerading as exercise-induced asthma, which is a physiologic cause for "choking" during athletic activities.

DYSPNEA: DEFINITION, DESCRIPTORS, AND QUANTITATION

An American Thoracic Society (ATS) consensus statement originally defined dyspnea as "sensations experienced by individuals who complain of unpleasant or uncomfortable respiratory sensations," and listed previous descriptors that included both patient-based sensations (an "awareness of respiratory distress," "the sensation of feeling breathless or experiencing air hunger," and "an uncomfortable sensation of breathing") and physician observations ("difficult, labored, uncomfortable breathing").[5] A 2012 update of the consensus statement referred to the original document and defined dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity."[6] Because this phenomenon is a symptom, we suggest that the description of dyspnea should be

Abbreviations used
        ATS- American Thoracic Society
        CBC- Complete blood count
    COPD- Chronic obstructive pulmonary disease
        CT- Computed tomographic
    DL_{CO}- Diffusing capacity of lungs for carbon monoxide
FEF_{25-75}- Forced expiratory flow rate at 25% and 75% of vital
            capacity
    FEV_1/FVC- FEV_1-to-forced vital capacity ratio
        FVC- Forced vital capacity
        RV- Residual volume
    RV/TLC- Residual volume-to-TLC ratio
        TLC- Total lung capacity

patient generated. Dyspnea is generally considered chronic when it lasts for longer than a month.

A diagnosis of dyspnea has important clinical implications. It has been estimated that up to one-half of patients admitted to tertiary care centers[7] and a quarter of ambulatory patients[8] have some element of dyspnea. Dyspnea is associated with a wide variety of adverse clinical outcomes, including hospitalizations for chronic obstructive pulmonary disease (COPD)[9] and cardiac mortality, even more so than angina.[10] Although it is not surprising that dyspnea is associated with mortality in patients with COPD,[11] many would not have predicted that it would be more predictive of 5-year survival than the forced expiratory volume in 1 second, the FEV_1.[12]

The latest ATS consensus statement lists a number of qualities that dyspnea may assume, including work/effort, tightness, air hunger/unsatisfied inspiration, and others.[6] Different disease entities can display different combinations of sensations associated with dyspnea. For example, Mahler et al[13] reported that among the most common descriptions of dyspnea (air hunger, chest tightness, breathing requires work, rapid breathing, and cannot get enough air) asthma was associated with work/effort and chest tightness, whereas interstitial lung disease was associated with work/effort and rapid breathing. Although a detailed history is important in evaluating the patient with dyspnea, describing dyspnea in such detail, although helpful, is often of limited benefit, because of the overlap of descriptors among a wide variety of clinical conditions.

Instruments used to measure or quantitate dyspnea typically evaluate one of several different domains: sensory-perceptual experience, affective distress, or symptom effect or burden (within Table 4 of Parshall[6]). Among the most common of the sensory-perceptual ("feels like") scales are visual analogue scales,[14] Borg ratings,[15] and Likert scales.[16] Many physicians find measures of symptom effect or burden such as the Medical Research Council breathlessness scale[17] most useful in practice; however, it must be acknowledged that such scales do not address what breathing feels like, the essence of dyspnea.

APPROACH TO THE PATIENT WITH DYSPNEA

It has been suggested that two-thirds of the causes of dyspnea are due to either a pulmonary or cardiac disorder[18] and that up to 85% of cases are caused by asthma, COPD, interstitial lung disease, pneumonia, cardiac ischemia, congestive heart failure, or psychogenic disorders (eg, anxiety, panic, or posttraumatic stress disorders).[19] Therefore, it is not surprising that much of the evaluation of the patient with dyspnea focuses on the cardiopulmonary systems. However, a systemic approach will not only lead to the correct diagnosis in these disorders but will also not overlook more uncommon causes of dyspnea.

CASE STUDY: A 68-YEAR-OLD WOMAN WITH COUGH AND DYSPNEA ON EXERTION

A 68-year-old woman was referred for evaluation of intermittent cough, occasional production of white sputum, and dyspnea on exertion. Cough and sputum production usually occurred in the setting of an upper respiratory infection, 2 to 3 times per year, with each episode lasting perhaps a week. Although the patient had no dyspnea at rest, she noticed dyspnea on exertion which had been gradually increasing over the past year, and especially during the past 2 months after an upper respiratory infection that has resolved. The patient had a 20 pack-year smoking history, having quit 10 years ago. She had no other significant medical problems and takes no chronic medication. She had allergies as a child and her mother had a history of asthma. Her physical examination revealed normal vital signs, a body mass index of 19, and an occasional wheeze and rhonchi on examination of the lungs, with no other abnormal findings.

First steps in evaluation of the patient with dyspnea

Although this patient's history and physical examination suggest a pulmonary cause for her dyspnea on exertion, we suggest that most adult patients with dyspnea, particularly those referred to a specialist by a primary care physician for the evaluation of this problem, would benefit from a comprehensive, step-wise approach to the problem. This would include a complete blood count (CBC) with differential cell count, a chemistry panel that includes renal and liver function tests, thyroid function tests, a chest radiograph, an electrocardiogram, and spirometry with pulse oximetry.[20] The purpose of these general screening tests is twofold: first, to discover uncommon, noncardiopulmonary causes of dyspnea such as unsuspected anemia, renal, hepatic, or thyroid disease; and second, to look for other significant disorders such as a pulmonary infiltrate or mass, or cardiac disease.

Role of pulmonary function testing

In this patient, after obtaining the initial tests on this list, it would be reasonable to skip spirometry and pulse oximetry and to proceed directly to complete pulmonary function testing. (If either the screening spirometry or pulse oximetry were abnormal, this would also be an indication for complete pulmonary function testing.) This would include spirometry before and after bronchodilator administration, measurement of lung volumes, and the diffusing capacity. This approach is suggested because the patient's history and physical examination suggest an obstructive lung disease, which if present, could represent either asthma or emphysema. (The patient's history is not compatible with the classic definition of chronic bronchitis.) The pulmonary function data, in addition to spirometry, could help to distinguish between asthma and emphysema. This woman's screening blood studies, chest radiograph, and electrocardiogram were all unremarkable. Her pulmonary function tests showed a FEV_1-to-forced vital capacity ratio (FEV_1/FVC) of 66% (predicted 76%; lower limit of normal, 63%), FEV_1 of 1.70 L (70% predicted; lower limit of normal 2.02 L), FVC of 2.57 L (81% predicted; lower limit of normal 2.66 L), and

a 10% improvement in FEV_1 and a 12% improvement in FVC after the inhalation of 4 puffs of albuterol.

What is the correct definition of airway obstruction?

The diagnosis of airway obstruction is based on a reduced FEV_1/FVC. However, several definitions of an abnormally reduced FEV_1/FVC exist:

- A fixed percentage below the predicted FEV_1/FVC (eg, 5% or more below the predicted FEV_1/FVC; if the predicted FEV_1/FVC is 72%, a value of ≤67% would be considered abnormal).
- Below relatively arbitrary aged-based norms (eg, a "normal" FEV_1/FVC for a person 8 to 19 years of age ≥85%; 20 to 39 years of age ≥80%; 40 to 59 years of age ≥75%; and 60 to 80 years of age ≥70%). These criteria have been suggested by the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines.[21]
- An FEV_1/FVC <70% after administration of a short-acting bronchodilator (eg, 4 puffs of albuterol through a spacer). This criterion has been put forth by the Global Initiative for Chronic Obstructive Lung Disease consortium.[22]
- An FEV_1/FVC (or FEV_1-to-VC ratio) less than the lower limits of normal defined as less than the fifth percentile predicted. This statistical approach is suggested by ATS/European Respiratory Society Task Force on the Standardisation of Lung Function Testing.[23]

For clinical management, unlike a formal interpretation of a set of pulmonary function tests, we suggest that the clinician be given wide latitude in tentatively assigning a diagnostic disease category. Therefore, we suggest that this patient has an obstructive lung disease, having met the first 3 definitions of airway obstruction, even though a formal evaluation of her spirometry, based on the ATS/European Respiratory Society Task Force statement, might not label her as such. (Please also note that her FEV_1 and FVC are both below her lower limits of normal.) After acute administration of a bronchodilator, the patient's FEV_1 improved 10% and her FVC improved 12%. Although this degree of improvement does not meet the most commonly used standard for a bronchodilator response in patients with asthma (a 12% improvement in FEV_1 *and* at least 200-mL increase in FEV_1),[24] we again suggest giving the clinician wide latitude in assigning a tentative bronchodilator response. We suggest that a 10% improvement in *either* FEV_1 *or* FVC is sufficient to suggest the presence of a positive response to a bronchodilator and to warrant a trial of bronchodilator therapy. Although widely maligned, we suggest that a 20% to 30% improvement in an abnormal FEF_{25-75} (forced expiratory flow rate at 25% and 75% of vital capacity, with an abnormal FEF_{25-75} ≤70% predicted) could also be used to suggest a positive bronchodilator response.

Value of additional pulmonary function testing: lung volumes and diffusing capacity

With the data available, we conclude that the patient has an obstructive lung disease which could either be asthma or COPD (emphysema). Measurement of lung volumes and diffusing capacity can be helpful in distinguishing asthma from emphysema. The patient's total lung capacity (TLC) was 5.00 L (96% predicted), her residual volume was 2.51 L (114% predicted), and her residual volume-to-TLC ratio (RV/TLC) was 50%

(117% predicted). Therefore, she has normal lung volumes (does *not* have a restrictive lung defect) and appears to have an element of air trapping (increased RV and RV/TLC). Her diffusing capacity of lungs for carbon monoxide (DL_{CO}) was 17.34 mL/min/mm Hg (82% predicted; lower limit of normal, 16.92 mL/min/mm Hg), "normal" based on both being ≥80% predicted and above her lower limit of normal, but slightly reduced.

Although both asthma and emphysema are characterized by airway obstruction, the diffusing capacity should be normal in asthma, and most patients will not show signs of air trapping when not having an acute exacerbation. Conversely, both a decreased diffusing capacity and air trapping are common in emphysema. Therefore, in this clinical setting, even though many lung function tests are technically "normal," we have made a clinical diagnosis of mild emphysema. Our initial therapeutic approach would include a long-acting bronchodilator (tiotropium) with albuterol to be used as rescue. An alternative could be a long-acting β-agonist with albuterol rescue; we have chosen tiotropium because of its potent effect as a bronchodilator in COPD and its once-a-day dosing schedule. We will also consider a future prescription for pulmonary rehabilitation, because this is one of the most effective interventions for patients with COPD.[25] Finally, because the patient's arterial blood gas was normal (pH 7.45; pCO_2, 38; pO_2, 83), supplemental oxygen is not indicated.

Could this patient have asthma instead of COPD/emphysema? Yes.

Does it matter? Probably not.

It is certainly possible that this woman has asthma instead of mild emphysema. Methacholine bronchoprovocation that showed a high degree of bronchial hyperresponsiveness would be consistent with a diagnosis of asthma, although patients with COPD, particularly those with abnormal baseline lung function, have also been reported to be hyperresponsive to methacholine. Making a diagnosis of asthma would have likely altered the initial therapeutic approach by making it prudent to include an inhaled corticosteroid in her therapeutic regime. Whether to use an inhaled corticosteroid could depend on whether the patient has had (or develops) exacerbations that require systemic corticosteroids, because these agents are indicated for patients with both asthma and COPD in whom such exacerbations occur.

PULMONARY FUNCTION AND OTHER FINDINGS IN PULMONARY CAUSES OF DYSPNEA

Common pulmonary causes of dyspnea and some of their characteristic features are listed in Table I. As noted, among the obstructive lung diseases, asthma is characterized by airway obstruction that is at least partially reversible. Both the diffusing capacity and imaging studies (chest radiograph and chest computed tomographic [CT] scan) should be normal (or minimally abnormal with acute hyperinflation and occasionally subtle peribronchial findings). Chronic bronchitis is a clinical diagnosis of productive cough,[26] which can occur in the absence of airflow obstruction. Emphysema is often characterized by air trapping, especially with exercise (dynamic hyperinflation) and a decreased diffusing capacity, in addition to airway obstruction. Bronchiectasis is also characterized by chronic sputum production with the diagnosis being confirmed by typical findings on chest radiograph and/or chest CT scan. Airway obstruction, often with

TABLE I. Common pulmonary causes of dyspnea

	FEV$_1$/FVC	TLC (FVC)	DL$_{CO}$	Other findings
Obstructive lung diseases				
Asthma	D/(N)*†	N*/(I)†	N*	Normal imaging* (hyperinflation acutely)†
COPD				
Chronic bronchitis	D/N	N	N	Clinical diagnosis*, Normal imaging or increase (bronchial)† markings
Emphysema	D*	I/(N)†	D*	Emphysema on imaging*
Bronchiectasis	D*	N/I	N/D	Chronic sputum production; bronchiectasis on imaging*
Cystic fibrosis	D*	N/D	N/D	Multisystem disease; cysts and infiltrates on imaging*
Upper airway disease	N/D	N	N	Abnormal flow-volume curves; imaging can be helpful*
Restrictive lung diseases				
Interstitial lung disease	N/I	D*	D*	Increased interstitial markings on imaging
Occupational (eg, asbestosis)	N/I	D*	D*	Increased interstitial markings on imaging
Hypersensitivity pneumonitis	N/D	N/D	N/D	Antigen exposure, systemic symptoms (acutely), Imaging with infiltrates and ground glass on CT scan*
Neuromuscular diseases (pseudo-restriction)	N	N*/D	N	Decreased maximum inspiratory pressure/force (MIP/MIF)* Decreased maximum voluntary ventilation (MVV)*
Pulmonary vascular diseases				
Pulmonary embolism	N	N*	N/D	CT arteriography for diagnosis; increased dead space*
Pulmonary hypertension	N	N*	D	Echocardiography highly suggestive; cardiac catheterization is definitive*

D, Decreased; *I*, increased; *MIP/MIF*, maximum inspiratory pressure/maximum inspiratory force; *MVV*, maximum voluntary ventilation; *N*, normal.
*Most common and/or most important findings.
†Findings, although they occur, are less common.

FIGURE 1. Chest CT arteriography in a 59-year-old-woman with chronic dyspnea, acutely worsening. The *red arrow* points to the trachea that has been severely compressed by a mass, apparently arising from the thyroid gland.

progressive declines in FEV$_1$, is common in cystic fibrosis, which is frequently recognized because of the multisystem nature of the disease. Upper airway diseases, either with a normal or abnormal FEV$_1$/FVC, often present as an apparent obstructive lung disease. Flow volume curves and imaging studies are the most useful techniques for establishing this diagnosis.

Restrictive lung diseases are characterized by a decreased TLC. Although a decreased vital capacity (either FVC or slow vital capacity) in the presence of a normal or increased FEV$_1$/FVC can suggest restriction, the "gold standard" requires a measurement of the TLC. Interstitial lung disease such as sarcoidosis and certain occupational exposures such as asbestosis often present with a decreased TLC, abnormal gas exchange (decreased diffusion capacity), and interstitial changes on chest imaging. Hypersensitivity pneumonitis involves the inhalation of an antigen, often organic, with acute systemic symptoms (fever and leukocytosis), dyspnea with more chronic disease, and abnormal findings on imaging studies (infiltrates on chest radiographs, often ground glass on chest CT scan). Neuromuscular diseases can present with a pseudo-restrictive pattern on pulmonary function testing (normal or increased FEV$_1$/FVC, decreased FVC but normal TLC) with preserved gas exchange (normal DL$_{CO}$). The diagnosis is made by measuring muscle function (maximum inspiratory pressure/maximum inspiratory force). A low maximum voluntary ventilation on spirometry can also suggest neuromuscular impairment.

Finally, common pulmonary vascular causes of dyspnea include chronic thromboembolic disease (pulmonary embolism) and pulmonary hypertension. Characteristic of these disorders are abnormalities in gas exchange. In addition, the defining physiologic characteristic of pulmonary embolism, increased dead space, can be observed on cardiopulmonary exercise testing. A number of resources are available for guiding the interpretation of pulmonary function tests.[23,27]

CASE STUDY: A 59-YEAR-OLD WOMAN WITH CHRONIC DYSPNEA, ACUTELY WORSENING

A 59-year-old woman presented to the emergency department with acute worsening of her chronic dyspnea. She had been followed and treated by an otolaryngologist for a unilateral vocal cord dysfunction. Over the course of this illness her voice decreased in intensity. In addition, she had a 30 pack-year smoking history and continued to smoke intermittently. On the day of presentation she noted a marked increase in her baseline dyspnea that was now moderately severe at rest. Her physical examination was notable for her speaking in a whisper and
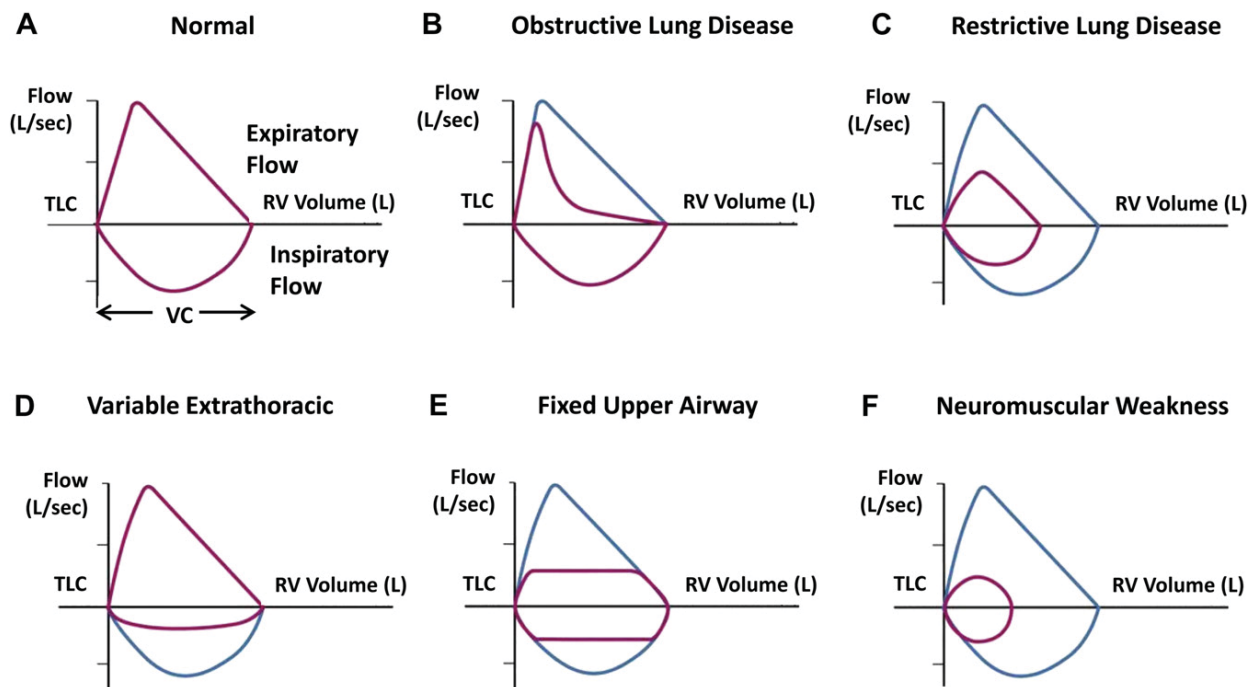
FIGURE 2. Flow volume curves for a number of common clinical conditions (modified from Gildea and McCarthy[28]). **A,** Normal flow volume curve. **B,** Flow volume curve characteristic of intrathoracic airway obstruction (eg, asthma or emphysema). **C,** Flow volume curve characteristic of restrictive lung disease (eg, interstitial lung disease). **D,** Flow volume curve characteristic of variable extrathoracic obstruction (eg, vocal cord paralysis). **E,** Flow volume curve characteristic of fixed upper airway obstruction (eg, large airway or tracheal tumor). **F,** Flow volume curve characteristic of neuromuscular disease/weakness (eg, Guillain-Barre syndrome).

markedly decreased breath sounds throughout all lung fields. Because of the sudden onset of dyspnea and a concern for pulmonary embolism in this patient who smoked, a CT thoracic arteriogram was performed. The CT scan showed marked intrathoracic compression of the trachea, apparently from a thyroid mass (Figure 1). She was immediately moved to an intensive care unit and within 24 hours developed airway compromise that required surgical intervention.

This patient's clinical course again stresses the importance of a thorough and systematic investigation of dyspnea, which, in many cases, can be multifactorial. This patient's dyspnea could have been due to a COPD exacerbation, as well as her vocal cord dysfunction, and/or her intrathoracic mass compressing the trachea. Comprehensive pulmonary function testing, including flow volume curves, could have helped to identify this problem in a more timely fashion.

VALUE OF FLOW VOLUME CURVES IN THE EVALUATION OF DYSPNEA

Complete pulmonary function testing should not only include spirometry before and after bronchodilator administration, measure of lung volumes, and diffusing capacity but also flow volume curves. Flow volume curves cannot only help to confirm a diagnosis that is suspected (ie, obstructive or restrictive lung disease) but also suggest a diagnosis that has not been suspected (eg, variable airway obstruction associated with vocal cord paralysis or fixed airway obstruction associated with an anatomic abnormality or tumor).

The flow volume curves for a number of common clinical conditions are shown in Figure 2 (modified from Gildea and McCarthy[28]). A normal pattern is shown (Figure 2, A) with the inspiratory portion of the curve below the x-axis and the expiratory portion above it. Also shown is the typical finding in a patient with an intrathoracic obstructive lung disease such as asthma or emphysema, that is, low expiratory flow rates at low lung volumes (Figure 2, B). The pattern in restrictive lung diseases (Figure 2, C) is qualitatively the same shape as normal, just smaller. The pattern shown in Figure 2, D, is associated with variable extrathoracic obstruction that can be seen in vocal cord paralysis, as well as in at least some cases of vocal cord dysfunction,[4,29] such as that in the clinical vignette of the boy with paradoxical vocal cord motion.[3] Figure 2, E, shows the pattern observed in a patient with fixed upper airway obstruction, often because of an anatomic abnormality or tumor. We predict that the 59-year-woman with chronic dyspnea, acutely worsening, would have shown such a pattern, if these tests had been performed. Finally, Figure 2, F, shows the pattern often observed in a patient with neuromuscular weakness, which is similar to that observed in restrictive lung diseases (smaller in all dimensions than normal), but with softer, more rounded contours.

CASE STUDY: A 40-YEAR-WOMEN WHOSE ASTHMA FIRST MARKEDLY IMPROVED THEN WORSENED

This case study is abstracted from Wechsler et al.[30] A women developed new onset asthma and sinusitis at age 40 which was
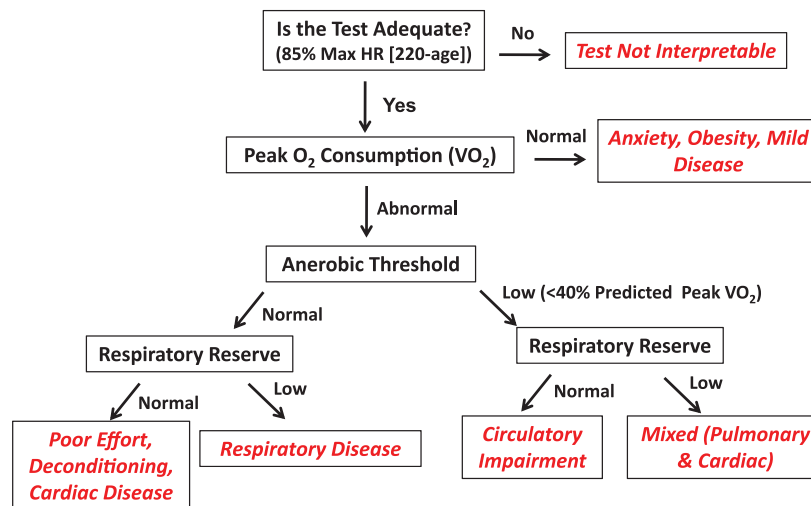
FIGURE 3. Simplified algorithm for interpretation of cardiopulmonary exercise tests (simplified from Milani et al[34] and modified from Peters[35]). Other information is also available from this test such as the O_2 pulse that is a measure of cardiac function (a surrogate for cardiac output), and the pulmonary dead space volume-to-tidal volume ratio (V_D/V_T), which is increased in patients with pulmonary emboli after exercise. *HR*, Heart rate (measured in beats/minute); *Max*, maximum; *VO_2*, peak oxygen consumption.

uncontrolled with inhaled corticosteroids, theophylline, and rescue β-agonist, requiring frequent burst of systemic corticosteroids. The addition of a leukotriene modifier markedly improved her asthma control, permitting her to discontinue the use of systemic corticosteroids over several months. Two to 3 weeks after discontinuing systemic corticosteroids she developed first an erythematous rash, followed by fever, nausea, anorexia, and loose stools. Her white blood cell count was 18.8×10^9/L with 36% eosinophils. The leukotriene modifier was stopped, and high-dose systemic corticosteroids were begun. Her respiratory status deteriorated, and a chest radiograph showed patchy alveolar infiltrates and an echocardiogram showed global biventricular hypokinesis with and ejection fraction of 35% to 40%. Skin biopsy showed perivascular lymphocyte infiltrate with eosinophils and a lung biopsy showed organizing pneumonitis, granuloma formation, multifocal necrosis, and a necrotizing vasculitis. Treatment with cyclophosphamide in addition to systemic steroids resulted in a clinical improvement.

This report was one of the first to describe a Churg-Strauss-like syndrome, possibly associated with the administration of a leukotriene modifier and systemic corticosteroid withdrawal. It reminds us that the airway obstruction characteristic of asthma can be part of a number of other distinct syndromes. These include the following:

- Churg-Strauss syndrome, a multisystem (often involving the skin, gastrointestinal tract, heart, and nervous system) vasculitis characterized by a necrotizing, granulomatous vasculitis.[30]
- Allergic bronchopulmonary aspergillosis, characterized by an immunologic reaction to *Aspergillus* with a positive skin test for *Aspergillus*, high total IgE levels (typically >1000 IU/mL), and often fleeting pulmonary infiltrates. Chronic disease can progress to bronchiectasis (which may be central) and a mixed obstructive and restrictive pattern on pulmonary function testing.[31]
- Anaphylaxis, characterized by sudden onset and multisystem disease (upper airway, respiratory, skin, and cardiovascular

systems, less often gastrointestinal or genitourinary involvement), which can be confirmed by an elevated serum tryptase level.[32]
- Pulmonary eosinophilic syndromes, a diverse group of disorders that also usually include radiographic abnormalities.[33]

CASE STUDY: A 60-YEAR-OLD MAN WITH SHORTNESS OF BREATH AND MULTIPLE MEDICAL PROBLEMS

A 60-year-old man was referred for specialty evaluation because of shortness of breath. His conditions had been diagnosed as congestive heart failure, asthma, possible COPD (30 pack-year history of cigarette use), gastroesophageal reflux disease, and hypertension. His medications included a diuretic, β-blocker, angiotensin-converting enzyme inhibitor, inhaled corticosteroid/long-acting β-agonist combination, albuterol as needed, proton pump inhibitor, and aspirin. Physical examination showed both wheezes and crackles. A chest radiograph showed an enlarged heart. Spirometry results included FEV_1/FVC of 69%, FEV_1 of 72% predicted, and FVC of 76% predicted. TLC was 80% predicted and the DL_{CO} was 75% predicted. Echocardiogram showed an ejection fraction of 35% with diastolic dysfunction. The conclusion of the cardiologist who saw him in consultation was that his dyspnea is not due to cardiac disease.

This is an all too common patient with a number of possible causes of dyspnea, including an obstructive lung disease, with COPD/emphysema more likely than asthma, congestive heart failure, and/or possible deconditioning. Airway obstruction is suggested by the FEV_1/FVC of 69%, and the presence of emphysema by a decreased diffusing capacity of 75% predicted. The TLC of 80% may be at the lower limit of normal (depending on the predicted norm used) and could suggest either the present of another (restrictive) pulmonary disorder or perhaps congestive heart failure with interstitial edema. The echocardiogram does confirm some degree of cardiac dysfunction. A high-resolution

TABLE II. Stepwise approach for the evaluation of the patient with dyspnea

Step 1	The purpose of these screening tests is twofold.

1. CBC with differential cell count, a chemistry panel that includes renal and liver function tests, thyroid function tests
  2. Chest radiograph
  3. Electrocardiogram
  4. Spirometry with pulse oximetry
	1. To rule out important, but uncommon, causes of dyspnea such as anemia, renal, liver, or thyroid dysfunction
	  2. To uncover important overt causes of dyspnea such as pneumonia, lung mass or tumor, or significant cardiac disease

Step 2	These tests are typically the heart of the dyspneic work-up and are often the most revealing, and will be used according to the findings of the initial evaluation.

1. Complete pulmonary function tests (spirometry before and after administration of a bronchodilator, measurement of lung volumes, diffusing capacity, and flow volume curves)
  2. Chest CT scan (high resolution and/or CT arteriography)
  3. B-type natriuretic peptide measurement and transthoracic echocardiography	

Step 3	If steps 1 and 2 have been unrevealing, the clinician usually has 2 choices.
Cardiopulmonary exercise testing	1. A therapeutic trial (which will often have been tried in the past with limited success) 2. Cardiopulmonary exercise testing

chest CT scan might be able to help differentiate between an interstitial lung disease and interstitial edema/mild volume overload. Although all of these abnormalities individually are mild, in combination they could explain the clinical picture, or it is possible that one disorder may predominate.

Perhaps the best way to differentiate among a variety of cardiopulmonary causes of dyspnea is through cardiopulmonary exercise testing. Such an approach not only allows the physician to examine cardiopulmonary physiology but also to look for evidence of cardiac ischemia, similar to a cardiac stress test. A simplified algorithm for analyzing a cardiopulmonary exercise test is shown in Figure 3 (simplified from Milani et al[34] and modified from Peters[35]). After determining that an adequate test has been performed (ie, reaching the target heart rate), an examination of the peak oxygen consumption, anaerobic threshold, and respiratory reserve can help differentiate among respiratory, cardiac, and other causes of dyspnea. Other information is also available from this test such as the O_2 pulse, which is a measure of cardiac function (a surrogate for cardiac output), and the pulmonary dead space volume-to-tidal volume ratio, which is increased in patients with pulmonary emboli after exercise.

The patient reached a maximal heart rate of 140 beats/minute; therefore, the test was adequate (ie, his predicted maximal heart rate was 85% of 220 − his age [60] or 136 beats/minute). With a low peak oxygen consumption and normal anerobic threshold and respiratory reserve, the patient is most likely to have either poor effort, deconditioning, or cardiac disease. Therefore, his cardiologist may have underestimated the significance of his cardiac disease. In any case, after consultation with the cardiologist, a decision to prescribe a low-intensity exercise program was made. Collaboration and consultation with the pulmonary physician/physiologist in the cardiopulmonary exercise laboratory can provide many benefits when faced with such confusing clinical data.

CONCLUSION

The evaluation of a patient with dyspnea can be challenging. However, a stepwise approach can both usually identify the cause(s) of dyspnea and avoid missing important contributing factor(s) (Table II). Step 1 includes a routine history, physical examination, and laboratory testing that includes a CBC with differential cell count, a chemistry panel that includes renal and liver function tests, thyroid function tests, chest radiograph, electrocardiogram, and spirometry with pulse oximetry. The purpose of these tests is to both rule out important but uncommon causes of dyspnea such as anemia, renal, liver, or thyroid dysfunction and uncover important overt causes of dyspnea such as pneumonia, lung mass or tumor, or significant cardiac disease. Step 2 includes tests that are most likely to correctly identify the cause(s) of dyspnea: complete pulmonary function tests (spirometry before and after administration of a bronchodilator, measurement of lung volumes, diffusing capacity, and flow volume curves); chest CT scan (high-resolution and/or CT arteriography), and/or B-type natriuretic peptide measurement and transthoracic echocardiography. If the diagnosis is still in doubt, step 3, a cardiopulmonary exercise tests, can more clearly define the pathophysiology involved.

Finally, be aware of 3 common pitfalls with evaluating the patient with dyspnea. First, accepting a cause for dyspnea in which the element identified is only part of a syndrome which includes that element (eg, making a diagnosis of simple asthma in a patient with Chrug-Strauss syndrome or bronchopulmonary aspergillosis). Second, accepting a single cause for dyspnea when the cause might be multifactorial (eg, failing to uncover a mediastinal mass in a patient with coexisting vocal cord dysfunction). Third, failing to recognize that a diagnosis and cause of dyspnea is incorrect and has been assumed without rigorous confirmation, when a patient with specific diagnosis is referred for "failing to respond to treatment."

REFERENCES

1. Dyspnea. Wikipedia. Accessed November 5, 2012.
2. Nishino T. Dyspnoea: underlying mechanisms and treatment. Br J Anaesth 2011;106:463-74.
3. Schuster JL. Long-ago asthma diagnosis didn't explain boy's difficulty breathing. Mother's frightening episode trying to find out why her 10 year old couldn't breathe. Published July 23, 2012. The Washington Post. Available from: http://articles.washingtonpost.com/2012-07-23/national/35487468_1_inhaler-ian-asthma-diagnosis. Accessed November 5, 2012.
4. McFadden ER Jr, Zawadski DK. Vocal cord dysfunction masquerading as exercise-induced asthma. a physiologic cause for "choking" during athletic activities. Am J Respir Crit Care Med 1996;153:942-7.
5. American Thoracic Society. Dyspnea. Mechanisms, measurement, and management: a consensus statement. Am J Respir Crit Care Med 1999;159: 321-40.

6. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012;185:435-52.

7. Desbiens NA, Mueller-Rizner N, Connors AF, Wenger NS. The relationship of nausea and dyspnea to pain in seriously ill patients. Pain 1997;71:149-56.

8. Kroenke K, Arrington ME, Mangelsdorff AD. The prevalence of symptoms in medical outpatients and the adequacy of therapy. Arch Intern Med 1990;150: 1685-9.

9. Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. Chest 2005;128:3810-6.

10. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. N Engl J Med 2005;353:1889-98.

11. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350: 1005-12.

12. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121: 1434-40.

13. Mahler DA, Harver A, Lentine T, Scott JA, Beck K, Schwartzstein RM. Descriptors of breathlessness in cardiorespiratory diseases. Am J Respir Crit Care Med 1996;154:1357-63.

14. Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. Rehabil Nurs 1989;14:323-5.

15. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-81.

16. Guyatt GH, Townsend M, Berman LB, Keller JL. A comparison of Likert and visual analogue scales for measuring change in function. J Chronic Dis 1987;40: 1129-33.

17. Fletcher CM, Elmes PC, Fairbairn MB, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959;2:257-66.

18. Gillespie DJ, Staats BA. Unexplained dyspnea. Mayo Clin Proc 1994;69: 657-63.

19. Michelson E, Hollrah S. Evaluation of the patient with shortness of breath: an evidence based approach. Emerg Med Clin North Am 1999;17:221-37, x.

20. Karnani NG, Reisfield GM, Wilson GR. Evaluation of chronic dyspnea. Am Fam Physician 2005;71:1529-37.

21. NAEPP Guidelines. National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma Full Report. 2007. Available from: http://www.nhlbi .nih.gov/guidelines/asthma/. Accessed November 5, 2012.

22. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Revised 2011. Available from: http://www.goldcopd.org/. Accessed November 27, 2012.

23. Pellegrino R, Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, et al. ATS/ERS Task Force: Standardisation of Lung Functiom Testing. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.

24. Tepper RS, Wise RS, Covar R, Irvin CG, Kercsmar CM, Kraft M, et al. Asthma outcomes: pulmonary physiology. J Allergy Clin Immunol 2012;129(3 Suppl): S65-87.

25. Troosters T, Gosselink R, Janssens W, Decramer M. Exercise training and pulmonary rehabilitation: new insights and remaining challenges. Eur Respir Rev 2010;19:24-9.

26. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. Lancet 1965;1:775-9.

27. Al-Ashkar F, Mehra R, Mazzone PJ. Interpreting pulmonary function tests: recognize the pattern, and the diagnosis will follow. Cleveland Clin J Med 2003; 70:866-81.

28. Gildea TR, McCarthy K. Pulmonary Function Testing. Cleveland Clinic. Center for Continuing Education. Publications: Disease Management Project. Available from: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/ pulmonary/pulmonary-function-testing/. Accessed November 27, 2012.

29. Leggit J. Case Resport. Vocal Cord Dysfunction. Am Fam Physician 2004;69: 1045-6.

30. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 1998;279: 455-7.

31. Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2002;110:685-92.

32. Simons FE. Anaphylaxis. J Allergy Clin Immunol 2008;121(2 Suppl):S402-7.

33. Katz U, Shoenfeld Y. Pulmonary eosinophilia. Clin Rev Allergy Immunol 2008; 34:367-71.

34. Milani RV, Lavie CJ, Mehra MR, Ventura HO. Understanding the basics of cardiopulmonary exercise testing. Mayo Clin Proc 2006;81:1603-11.

35. Peters SP. Special considerations in adults for diagnoses that may coexist with or masquerade as asthma. Ann Allergy Asthma Immunol 2010;104:455-60.