CME CREDIT

AKSHAY BHATNAGAR, MD
Department of Internal Medicine, Cleveland Clinic

JONATHAN WIESEN, MD
Community Intensivists, Cleveland, OH; Ben Gurion University, Be'er Sheva, Israel

RAED DWEIK, MD
Interim Institute Chair, Respiratory Institute, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

NEAL F. CHAISSON, MD
Department of Critical Care Medicine, Respiratory Institute, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Evaluating suspected pulmonary hypertension: A structured approach

ABSTRACT

Pulmonary arterial hypertension (PAH) is a common consideration when patients have unexplained signs of cardiopulmonary disease. Guidelines have been issued regarding diagnosis and management of this condition. Since multiple conditions can mimic components of PAH, the clinician should think about the patient's total clinical condition before diagnosing and categorizing it. Proper evaluation and etiologic definition are crucial to providing the appropriate therapy. This review offers a case-based guide to the evaluation of patients with suspected PAH.

KEY POINTS

PAH has nonspecific symptoms, largely attributable to right ventricular dysfunction but seen in a host of other common cardiopulmonary ailments.

In a patient suspected of having pulmonary hypertension, it is important to take a methodic diagnostic approach to identify underlying contributors and minimize unnecessary testing.

Patients suspected of having PAH should be referred to a pulmonary hypertension center of excellence for evaluation and right heart catheterization.

Once testing is complete, therapy and management should be guided both by data obtained during the initial evaluation and by factors with prognostic significance. This approach has changed PAH from a disease with a grim outlook to one in which appropriate evaluation and guidance can improve patient outcomes.

doi:10.3949/ccjm.85a.17065

Pulmonary arterial hypertension (PAH) is a hemodynamic disorder that affects small and medium-size pulmonary arteries through cellular proliferation and luminal narrowing.[1] Increased pulmonary vascular resistance causes restricted blood flow in these arteries, leading to elevated pulmonary arterial pressure and afterload on the right ventricle. Despite advances in therapy, death usually occurs as a result of right ventricular failure.

However, PAH is neither the only form of pulmonary hypertension nor the most common. Pulmonary hypertension, defined as an elevated pulmonary arterial pressure (≥ 25 mm Hg) on right heart catheterization,[1] has a myriad of causes. The World Health Organization (WHO) classifies pulmonary hypertension into 5 separate groups based on the pathophysiologic mechanism (**Table 1**):

- Group 1—PAH, due to narrowed pulmonary arteries
- Group 2—due to left heart disease
- Group 3—due to lung disease or hypoxia, or both
- Group 4—due to chronic thromboembolism or other pulmonary artery obstruction
- Group 5—due to uncertain or multifactorial causes.

Experts recognize the morbidity and mortality associated with pulmonary hypertension now more than in the past, and they emphasize recognizing it early. Guidelines for its diagnosis and treatment were updated in 2015.[1]

Below, we use a case to discuss recommendations for initial evaluation and classification of pulmonary hypertension, particularly PAH.

TABLE 1

Updated World Health Organization classification of pulmonary hypertension

Group 1:
Pulmonary arterial hypertension
Idiopathic
Heritable
- *BMPR2* mutation
- Other mutations

Drug- and toxin-induced
Associated with:
- Connective tissue disease
- Human immunodeficiency virus (HIV) infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis

Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
- Idiopathic
- Heritable
  - *EIF2AK4* mutation
  - Other mutations
- Drug-, toxin-, and radiation-induced
- Associated with:
  - Connective tissue disease
  - HIV infection

Persistent pulmonary hypertension of the newborn

Group 2:
Pulmonary hypertension due to left heart disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital or acquired left heart inflow or outflow tract obstruction and congenital cardiomyopathies
Congenital or acquired pulmonary vein stenosis

Group 3:
Pulmonary hypertension due to lung diseases, hypoxia, or both
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases

Group 4:
Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
Chronic thromboembolic pulmonary hypertension
Other pulmonary artery obstructions
- Angiosarcoma
- Other intravascular tumors
- Arteritis
- Congenital pulmonary artery stenosis
- Parasites (hydatidosis)

Group 5:
Pulmonary hypertension with unclear or multifactorial mechanisms
Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with or without dialysis), segmental pulmonary hypertension

Reproduced with permission of the European Society of Cardiology and the European Respiratory Society. European Respiratory Journal Oct J 2015; 46(4):903–975. doi:10.1183/13993003.01032-2015

PAH is neither the only form of pulmonary hypertension nor the most common

A PATIENT SUSPECTED OF HAVING PULMONARY HYPERTENSION

A 63-year-old woman with a 25-pack-year history of tobacco use, as well as pulmonary embolism and coronary artery disease, presents to her primary care physician with exertional dyspnea. She had been a clerk at a hardware store and physically active until she took early retirement 8 months ago because of increasing fatigue. She initially felt the fatigue was simply "a sign of getting old."

Since retiring, she has noticed the slow onset of progressive dyspnea on exertion. She can no longer climb more than 1 flight of stairs or walk more than 1 block. She also complains of mild, fluctuating edema in her lower extremities over the past month. She quit smoking 8 years ago after undergoing placement of a drug-eluting stent in the mid-left circumflex artery. After this, she received

Diagnostic algorithm for evaluating a patient suspected of having pulmonary hypertension

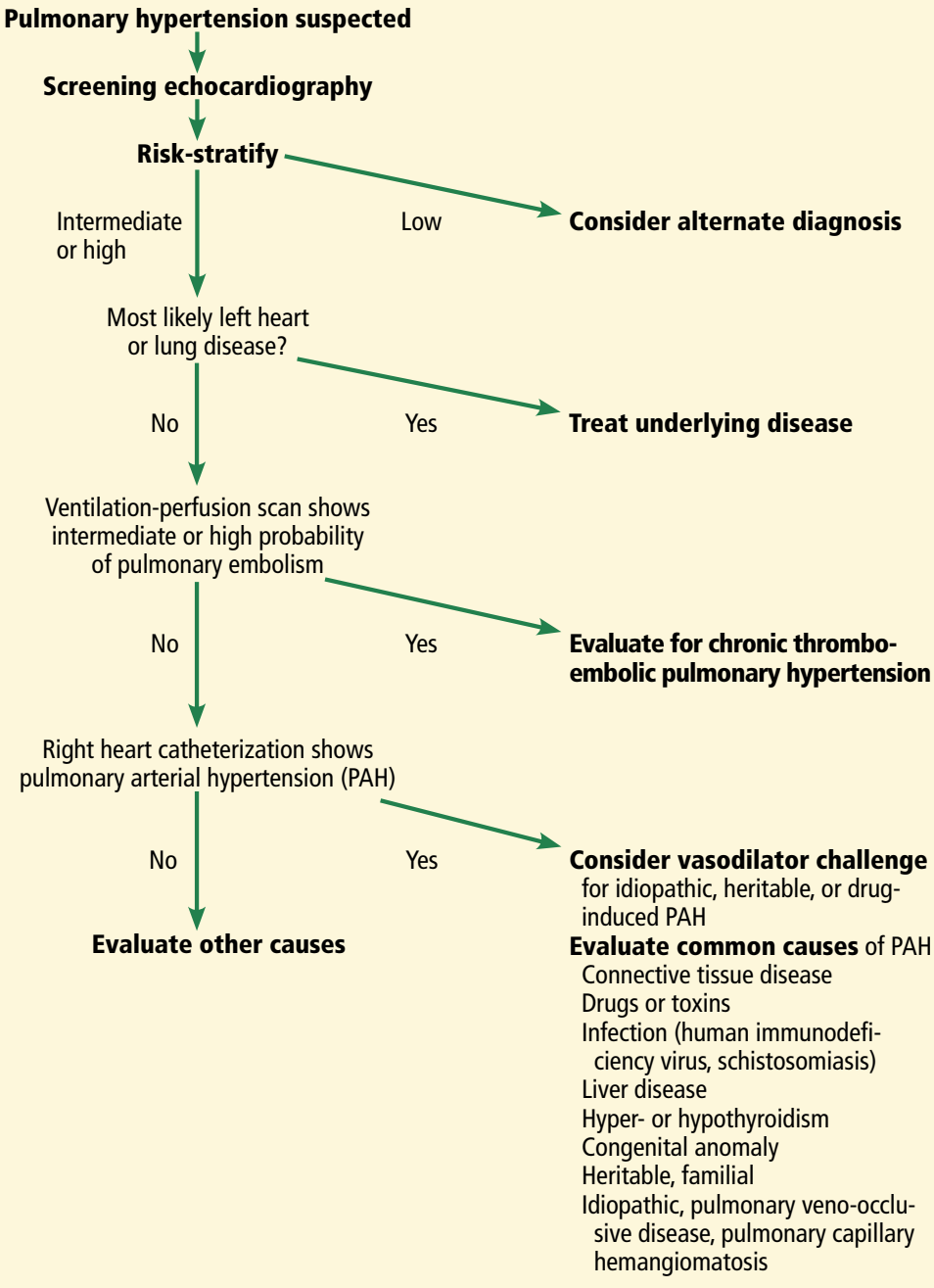

Figure 1.

Based on information in Galie et al, reference 1.

The patient initially felt the fatigue was simply 'a sign of getting old'

clopidogrel and was followed by a cardiologist for 2 years but stopped taking the medication because of bruising. She has not seen her cardiologist in more than 5 years.

She underwent elective right total knee arthroplasty 3 years ago, complicated by acute deep vein thrombosis in the right common femoral vein. Computed tomography

(CT) at that time did not reveal pulmonary emboli. She received warfarin therapy for 3 months.

She reports no current cough, chest pain, lightheadedness, or syncope. She has no orthopnea, and she feels normal at rest.

Her family history is unremarkable, and she has had no exposure to illicit substances, environmental toxins, or dietary supplements. She takes aspirin 81 mg daily, metoprolol 25 mg twice daily, lisinopril 10 mg daily, and simvastatin 40 mg at bedtime.

Her primary care physician detects a murmur in the left lower sternal border and sends her for transthoracic echocardiography, which demonstrates mild right ventricular dilation, right atrial dilation, and mildly reduced right ventricular function. The calculated right ventricular systolic pressure is 69 mm Hg. The left ventricle shows mild concentric hypertrophy; the left atrium is normal in size.

DIAGNOSTIC EVALUATION OF SUSPECTED PULMONARY HYPERTENSION

Accurate diagnosis and classification of pulmonary hypertension requires both a high level of suspicion for the disease and appropriate diagnostic testing. **Figure 1** depicts current recommendations for evaluating a patient suspected of having pulmonary hypertension. We will use this algorithm to guide proper risk stratification, classification, and invasive testing.

CLINICAL MANIFESTATIONS

Clinical manifestations of pulmonary hypertension are invariably related to right ventricular dysfunction. As pulmonary arterial pressure and pulmonary vascular resistance increase, the right ventricle initially compensates to preserve cardiac output through upregulation of sympathetic responses, dilation, and myocardial hypertrophy. For this reason, early clinical signs are either absent or nonspecific.[2] Eventually, however, the right ventricle can no longer compensate,[3] and cardiac output declines (**Figure 2**).

Symptoms and signs. As in the patient described above, the first symptoms such as exertional dyspnea, fatigue, and lightheadedness usually arise in situations that call for increased cardiac output.[4] As right ventricular function worsens, symptoms start to occur at rest, and signs of increased right ventricular preload appear, such as abdominal and lower-extremity edema and pericardial effusion. Syncope is a sign of severe right ventricular dysfunction.[5]

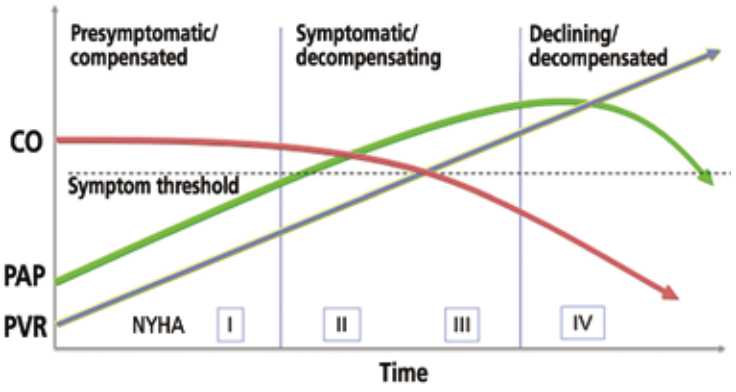

Figure 2. Natural progression of disease in patients with pulmonary arterial hypertension.

CO = cardiac output; NYHA = New York Heart Association functional class; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance

Physical examination. Look for signs of increased right ventricular loading and failure, eg:

- An accentuated intensity and persistent splitting of the second heart sound
- A prominent parasternal heave
- A prominent jugular "a" wave
- A systolic murmur along the left sternal border at the fourth intercostal space, which may worsen with breath-holding
- Pitting lower-extremity edema
- Hepatomegaly
- Hepatojugular reflux
- Hepatic pulsatility.[6]

Accurate diagnosis and classification require a high level of suspicion and appropriate diagnostic testing

ECHOCARDIOGRAPHY IN SUSPECTED PULMONARY HYPERTENSION

Since the early signs and symptoms of pulmonary hypertension are often nonspecific, the diagnosis is often delayed,[7] and it is first suspected when transthoracic echocardiography reveals signs of right ventricular dysfunction. Transthoracic echocardiography is relatively inexpensive, noninvasive, and reproducible, and it can give estimated values of several measures of right ventricular function, size, and pressure (**Figure 3**).

Many practitioners rely heavily on the es-

Figure 3. Echocardiographic views of a patient with pulmonary hypertension (left) and a patient without (right). Note the increased right ventricular-left ventricular ratio and right atrial enlargement in the patient with pulmonary hypertension.

LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle

timated right ventricular systolic pressure in diagnosing pulmonary hypertension. In theory, this number should be nearly the same as the pulmonary arterial systolic pressure. However, technical and patient-related aspects of transthoracic echocardiography often limit accurate measurement of the right ventricular systolic pressure, and readings often differ from those measured with right heart catheterization.[8]

The 2015 European Respiratory Society and European Society of Cardiology guidelines recommend using additional echocardiographic variables to determine the probability that a patient has pulmonary hypertension (**Table 2**).[1] While this recommendation is largely based on expert opinion, it supports the notion that right ventricular systolic pressure alone is not enough to determine the probability of pulmonary hypertension. Accordingly, patients with a right ventricular systolic pressure that is significantly elevated (> 50 mm Hg) or moderately elevated (> 40 mm Hg), along with other signs of right ventricular dysfunction (eg, a dilated right ventricle or atrium, septal flattening), should be considered for additional diagnostic testing.

Our patient had a markedly elevated right ventricular systolic pressure and signs of right ventricular dysfunction, suggesting a high probability of pulmonary hypertension.

More than 75% of cases of pulmonary hypertension are due to left ventricular dysfunction or to mitral or aortic valve disease (WHO group 2)

EVALUATING LEFT HEART DISEASE (WHO GROUP 2)

More than 75% of cases of pulmonary hypertension are directly related to left ventricular dysfunction or mitral or aortic valve disease (WHO group 2).[1] Since group 2 differs markedly from group 1 (PAH) in its pathophysiology and treatment, it is important to distinguish between them.

Compared with WHO group 1 patients, those in group 2 tend to be older, more of them are male, and more of them have comorbidities such as metabolic syndrome, hypertension, and coronary artery disease.[1,9] A combination of risk factors and clinical findings should be considered in identifying these patients.[10]

Transthoracic echocardiography is used to detect features of systolic and diastolic dysfunction. Left atrial enlargement is a clue that left heart disease may be present. In addition, signs of left ventricular or valvular dysfunction on electrocardiography or chest radiography are often helpful.

When estimated right ventricular systolic pressures are only minimally abnormal and no significant right ventricular dysfunction exists, further diagnostic evaluation is not warranted. However, because no single identifying feature or variable can readily distinguish group 2 from the other WHO groups, further

evaluation should be considered if the right ventricular systolic pressure is significantly elevated or right ventricular dysfunction exists.

Our patient had several risk factors for left heart disease, including a history of smoking and coronary artery disease. Nonetheless, findings consistent with severe right ventricular dysfunction necessitated further evaluation for other possible causes of her suspected pulmonary hypertension.

Postcapillary pulmonary hypertension

In patients for whom further evaluation is pursued, the diagnosis of WHO group 2 pulmonary hypertension is ultimately based on findings consistent with postcapillary or "passive" pulmonary hypertension on right heart catheterization. Although mean pulmonary arterial pressures must be at least 25 mm Hg to certify the diagnosis of pulmonary hypertension, a pulmonary artery occlusion pressure greater than 15 mm Hg (normal 6–12) and pulmonary vascular resistance of 3 Wood units or less (normal 0.3–1.6) suggests the pulmonary hypertension is due to elevated left atrial pressure (ie, postcapillary) rather than precapillary pulmonary arterial remodeling.

Mixed pre- and postcapillary pulmonary hypertension

Distinguishing pulmonary venous hypertension from PAH is important, since their management differs. In particular, PAH-specific therapies (ie, prostacyclin analogues, prostaglandin I2 receptor agonists, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and cyclic guanosine monophosphate stimulators) can have a detrimental effect in WHO group 2 patients by causing increased pulmonary capillary leakage with pulmonary edema.[11,12]

In some patients, chronic passive congestion in the pulmonary venous circulation causes additional disruption of the homeostatic milieu regulating precapillary smooth muscle and endothelial function. These changes result in structural remodeling of precapillary arterioles and increased precapillary vascular resistance, creating a "mixed" pulmonary hypertension with both pre- and postcapillary abnormalities.

There is controversy over the ideal way to identify these patients but little disagreement that they face a worse prognosis than those without precapillary remodeling.[13] In light of this, efforts have been made to characterize this cohort.

Historically, mixed pre- and postcapillary pulmonary hypertension was defined as the combination of all of the following:

- Mean pulmonary arterial pressure ≥ 25 mm Hg
- Pulmonary artery occlusion pressure > 15 mm Hg
- Transpulmonary gradient (the mean pulmonary arterial pressure minus the pulmonary artery occlusion pressure) > 12 mm Hg.[14]

However, the utility of the transpulmonary gradient for distinguishing mixed pulmonary hypertension has been questioned because of concerns over its susceptibility to variations in stroke volume and loading conditions.[15]

The diastolic pulmonary gradient (the pulmonary arterial diastolic pressure minus the pulmonary artery occlusion pressure) has been proposed as an alternative to the transpulmonary gradient under the theory that it is less sensitive to fluctuation from variations in flow or loading.[15]

Current guidelines[1] suggest that a patient who has all of the following should be considered to have mixed pulmonary hypertension:

- A mean pulmonary arterial pressure > 25 mm Hg

TABLE 2

Echocardiographic features supporting pulmonary hypertension

Right atrial dilation (area > 18 cm^2)
Elevated right atrial pressure based on inferior vena cava (IVC) assessment (IVC > 21 mm and collapses < 50% with inspiratory sniff)
Ratio of right ventricle to left ventricle basal diameter > 1
Interventricular septal flattening or bowing towards the left ventricle
A "mid-systolic notch" across the right ventricular outflow tract
Reduced right ventricular outflow Doppler acceleration time < 105 msec
Increased early diastolic pulmonary regurgitation velocity > 2.2 m/sec
Pulmonary artery diameter > 25 mm

Based on information in Galiè et al, reference 1.

All patients with suspected pulmonary hypertension should also be assessed for underlying pulmonary parenchymal or physiologic disease

- A pulmonary artery occlusion pressure > 15 mm Hg
- A diastolic pulmonary gradient > 7 mm Hg or a pulmonary vascular resistance > 3 Wood units, or both.

Occult group 2 pulmonary hypertension

Currently, the diagnosis of WHO group 2 pulmonary hypertension is based on elevated resting pulmonary artery occlusion pressure. However, some patients with WHO group 2 pulmonary hypertension and transiently low preload from aggressive diuresis or fasting may have a low pulmonary artery occlusion pressure during right heart catheterization and be misdiagnosed as having WHO group 1 PAH.[12,16]

This concern was acknowledged in the 2015 Ambrisentan and Tadalafil in Patients With Pulmonary Arterial Hypertension (AMBITION) study after investigators changed the protocol to exclude patients who technically met the criteria for WHO group 1 PAH, but had borderline-elevated pulmonary artery occlusion pressure and additional risk factors worrisome for left heart disease and occult WHO group 2 pulmonary hypertension.[17,18]

Up to 70% of patients with obstructive sleep apnea have pulmonary hypertension

Several strategies, including passive leg-raising, fluid challenge, and exercise during diagnostic right heart catheterization, have been proposed to better classify these patients.[19] Unfortunately, due to a lack of standardization of normal values and methodology for executing these maneuvers, consensus is lacking over their routine use, and recommendations for their use have not been provided.[1]

EVALUATION OF LUNG DISEASE (WHO GROUP 3)

All patients with suspected pulmonary hypertension should also be assessed for underlying pulmonary parenchymal or physiologic disease.

WHO group 3 consists of pulmonary disorders that, over an extended time, can lead to pulmonary hypertension. The most common of these disorders include chronic obstructive pulmonary disease, interstitial lung disease, and combined pulmonary fibrosis and emphysema.[1]

Pulmonary hypertension in these patients is precapillary, and changes in pulmonary vascular resistance are influenced by multiple factors, the most significant of which is alveolar hypoxia. Hypoxia induces pulmonary artery vasoconstrictionn (in contrast to the reflexive hemodynamics seen in peripheral tissues, where systemic vascular tone is generally lower in states of hypoxia) as a mechanism to divert pulmonary blood flow to well-ventilated portions of the lung and maintain ventilation-perfusion matching.

Repeated chronic hypoxia also alters cellular structure and function of pulmonary vessels and leads to medial hypertrophy and increased vascular tone, thus contributing to the development of pulmonary hypertension in many of these patients.[20]

Obstructive sleep apnea. Up to 70% of patients with obstructive sleep apnea have pulmonary hypertension.[21] Chronic repetitive hypoxia throughout the night increases the levels of reactive oxygen species and alters cellular and molecular signaling, thus inducing vascular remodeling. In addition, apneic events during sleep promote catecholamine-driven elevations in systemic blood pressure. Over time, patients are at higher risk of developing left ventricular dysfunction and concomitant postcapillary group 2 pulmonary hypertension.[22] Because typical methods of obstructive sleep apnea screening (eg, the Epworth Sleep Scale) have been historically poor at discriminating PAH patients with obstructive sleep apnea from those without, patients diagnosed with PAH should be considered for formal sleep testing.[23,24]

Pulmonary function tests, chest imaging

Pulmonary function tests and high-resolution computed tomography are essential to any PAH evaluation and help to exclude WHO group 3 pulmonary hypertension.[1]

An abnormal result on CT or spirometry can help point toward parenchymal lung disease. Normal spirometry and lung volumes with an isolated reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) is typical of patients with WHO group 1 PAH.

As in WHO group 2 pulmonary hypertension, patients with significant obstructive sleep apnea or underlying parenchymal lung disease who exhibit only features of mild pulmonary hypertension usually do not require further pulmonary hypertension evaluation, as management of the underlying lung disease

is the preferred treatment in these patients.[1] However, since the diagnostic accuracy of echocardiography (**Figure 4**) is lower in patients with advanced lung disease,[25] those who have inconclusive echocardiographic results, who have symptoms consistent with advanced pulmonary hypertension or right ventricular dysfunction, or who are planning to undergo a surgical procedure (eg, transplant, lung volume reduction) should undergo further testing and be evaluated at a pulmonary hypertension referral center.[1]

In our patient, CT of the chest did not show any evidence of parenchymal lung disease, and pulmonary function tests showed no evidence of obstruction or restriction. There was a moderate decrease in DLCO, which did not reach normal limits when adjusted for lung volumes. In this setting, further evaluation of her PAH was warranted.

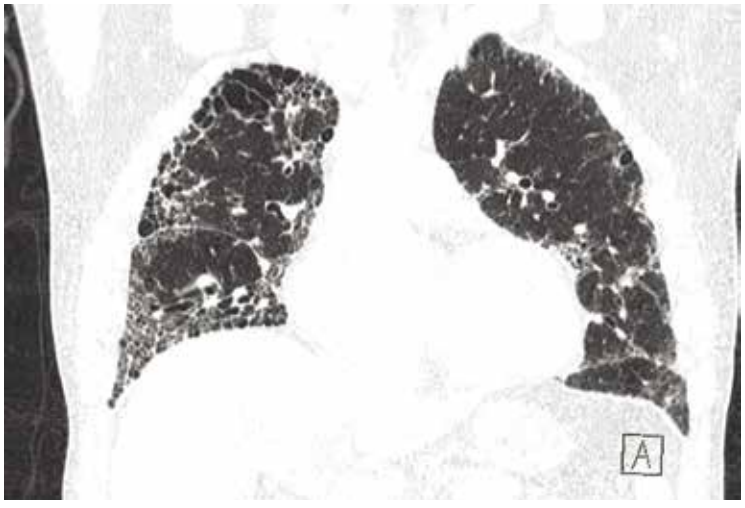

Figure 4. A patient with combined pulmonary fibrosis and emphysema. In patients with findings consistent with underlying structural lung disease, further diagnostic testing for pulmonary arterial hypertension may not be warranted.

EVALUATION OF THROMBOEMBOLIC DISEASE (WHO GROUP 4)

Once pulmonary hypertension due to underlying left heart disease or parenchymal lung disease has been excluded, testing for chronic thromboembolic pulmonary hypertension is necessary, even in the absence of prior known pulmonary embolism. Identifying these patients is paramount, as chronic thromboembolic pulmonary hypertension (WHO group 4) is the only type of pulmonary hypertension for which a definitive cure is available.[26]

Up to 9% of patients who survive acute pulmonary embolism exhibit features of chronic proximal thrombosis and remodeling of distal pulmonary arteries.[27]

It remains unknown exactly why some patients develop chronic thromboembolic pulmonary hypertension and others do not, but the pathophysiology involves inappropriate thrombus resolution after venous thromboembolic events. Monocyte recruitment (which plays an important role in thrombus resolution) is reduced, angiogenesis is impaired (preventing effective vascular collateralization), and abnormal fibroblast proliferation leads to distal pulmonary vascular wall thickening.[28] There is some evidence of increased thrombophilic risk in this population, and approximately 10% to 20% of patients are positive for antiphospholipid antibodies or lupus anticoagulant.[29,30]

Patients with chronic thromboembolic pulmonary hypertension usually present with symptoms similar to those of WHO group 1 PAH. Up to one-quarter of patients have no recollection of prior pulmonary embolism.[31] As the disease progresses, signs and symptoms related to elevated pulmonary vascular resistance and right ventricular dysfunction are common.[32,33]

Chronic thromboembolic pulmonary hypertension (WHO group 4) is the only type for which a definitive cure is available

Although thrombi usually resolve quickly, the diagnosis of chronic thromboembolic pulmonary hypertension should be made only after at least 3 months of appropriate anticoagulation to avoid treatment of transient hemodynamic changes often seen after an acute pulmonary embolism.[1]

Radiographic changes associated with chronic thromboembolic pulmonary hypertension are distinct from the intraluminal filling defects seen with acute thromboembolism, since chronic thrombi tend to become organized and eccentric. On imaging, one may see features of rapid luminal narrowing or eccentric filling defects rather than the conventional central filling defects of acute pulmonary embolism. These changes are often overlooked by radiologists who are not specifically looking for chronic thromboembolic pulmonary hypertension.[34] For this reason,

the sensitivity and specificity of identifying chronic thromboembolic disease using radionuclide ventilation-perfusion lung scanning is superior to that of CT angiography.

All patients with suspected PAH should undergo a ventilation-perfusion scan.[1,35] In patients with ventilation-perfusion mismatch on radionuclide scanning, pulmonary angiography can fulfill multiple goals of measuring pulmonary arterial pressures, identifying the extent and location of chronic thromboemboli, and can determine whether surgical thromboendarterectomy is feasible.

If chronic thromboembolic pulmonary hypertension is identified, it is imperative that patients be referred to a center of excellence specializing in its management regardless of symptom severity, as surgery can be curative and may prevent development of progressive right ventricular dysfunction.[36]

Our patient's ventilation-perfusion scan was normal, effectively ruling out the possibility of chronic thromboembolism as a cause of her pulmonary hypertension.

RIGHT HEART CATHETERIZATION

All patients with suspected PAH should undergo ventilation-perfusion scanning

Once the above-mentioned conditions have been evaluated, patients with suspected PAH should be referred to a pulmonary hypertension center of excellence to undergo right heart catheterization. If this test reveals PAH, further vasoreactivity testing should be performed if the etiology of the PAH is considered to be idiopathic, heritable, or drug-induced.[1]

Vasoreactivity is most commonly tested using 20 ppm of inhaled nitric oxide, but alternative formulations including intravenous epoprostenol, intravenous adenosine, or inhaled iloprost are acceptable. Patients who have a positive vasoreactive test usually respond well to high-dose calcium channel blocker therapy and have a significantly better prognosis than other patients with PAH.[37]

Patients with WHO group 1 PAH who do not have idiopathic, heritable, or drug-induced PAH have not been shown to have favorable outcomes using calcium channel blockers even if they have a positive vasoreactive response. A positive vasoreactive response is defined as a drop in mean pulmonary arterial pressure of at least 10 mm Hg to an absolute level of 40 mm Hg or less. Cardiac output should be preserved or elevated compared with baseline values during the challenge.[1]

In reality, only 10% to 15% of patients with idiopathic PAH have a positive vasoreactive response, and half of these patients stop responding within 1 year.[38] Therefore, clinicians should not assume that calcium channel blockers will be successful in the long term in a vasoreactive patient, and these patients should have follow-up right heart catheterization after 3 to 6 months and annually thereafter to ensure continued vasoreactivity.[1]

In patients who are no longer vasoreactive or whose functional status is worse than New York Heart Association functional class I or II, conventional PAH-specific therapy should be started.

LOOKING FOR CAUSES OF 'IDIOPATHIC' PAH

Pulmonary hypertension is considered the final common pathway of many varied diseases and syndromes, and therefore one cannot say it is idiopathic without making a robust effort to identify features of alternative causes and rule out other contributing factors.

Although the exact etiology of idiopathic PAH is unclear, well-characterized imbalances in vascular homeostasis have been identified. These include processes that promote vasoconstriction, cell proliferation, and thrombosis (thromboxane A2, endothelin-1, and serotonin) and those that suppress prostacyclin, nitric oxide, and vasoactive intestinal peptide-mediated vasodilation.[1] Furthermore, an abnormal angiogenic response to hypoxia and vascular endothelial growth factor has been observed.[39]

Before considering a diagnosis of idiopathic PAH, a careful history is essential. Other causative agents include appetite-suppressing medications, such as fenfluramine derivatives or stimulants such as amphetamines. Human immunodeficiency virus (HIV) or hepatitis, a history of splenectomy, and prior thyroid or liver disease are also common causes of PAH. Joint pain, myalgias, Raynaud features, or a rash characteristic of connective tissue disease can be identified on history and physical examination. Worldwide, chronic exposure to high-altitude climates and exposure to schis-

tosomiasis are significant causes of PAH, but are rarely seen in developed nations. Confirmatory serum tests for HIV, antinuclear antibody, scleroderma antibody, and thyroid function are essential.[1]

Genetic factors

If patients report having relatives with possible or probable PAH, genetic counseling is recommended, particularly for rare but causative gene mutations.

BMPR2, the gene that codes for the bone morphogenetic protein receptor type 2, can carry mutations with variable penetrance over the patient's lifetime depending on other genetic polymorphisms, concurrent inflammation, and the patient's sex.[40]

The population carrier estimates of *BMPR2* mutations are only 0.001% to 0.01%, but mutations in this gene are identified in approximately 25% of nonfamilial PAH patients and in over 75% of those with a familial inheritance pattern. The BMPR2 protein is a part of the transforming growth factor beta family and is partially responsible for control of vascular cell proliferation. Mutations in this gene lead to PAH at a younger age than in those with mutation-negative idiopathic PAH and to a more severe clinical phenotype in terms of pulmonary vascular resistance and cardiac function.[40]

Other mutations. Although *BMPR2* is the most commonly identified gene mutation in patients with PAH, other gene mutations within this family have also been recognized. These include mutations in the genes for activin receptor-like kinase 1 and endoglin, which, although better known for their association with hereditary hemorrhagic telangiectasia, can lead directly to PAH.[40]

More recently, a novel autosomal recessive gene mutation in eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*) has been identified in patients with pulmonary veno-occlusive disease[41] and pulmonary capillary hemangiomatosis,[42] which are specific subclasses of WHO group 1 PAH. The mechanistic parallels between *EIF2AK4* and these diseases are not clear, but the prevalence of disease in those with a familial inheritance pattern and an *EIF2AK4* mutation is nearly 100%.[41] Thus, identification of this mutation has been accepted as a way to confirm pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis in patients suspected of PAH with features of these diseases.[43,44]

GROUP 5: MISCELLANEOUS FORMS OF PULMONARY HYPERTENSION

WHO group 5 pulmonary hypertension encompasses disorders whose pathophysiology does not fit neatly within the context of the other pulmonary hypertension subtypes. Nonetheless, appreciation of these disorders is important in determining the etiology and appropriate therapy for patients with pulmonary hypertension. The mechanism driving abnormal pulmonary arterial pressures in patients with group 5 pulmonary hypertension is not always clear and may involve intrinsic or extrinsic factors.[1]

Diseases within group 5 include those that cause extrinsic compression of the pulmonary arteries (ie, fibrosing mediastinitis) or intrinsic elevations in pulmonary vascular resistance (sarcoidosis, pulmonary Langerhans cell histiocytosis, sickle cell anemia, polycythemia vera, and malignancy).

The most common cause of pulmonary hypertension in this category is sarcoidosis. Current theories suggest that, for most patients, invasion of granulomatous inflammation within the arterial walls induces PAH via fibrotic or inflammatory vascular occlusion. Extrinsic compression due to lymphadenopathy, right or left ventricular dysfunction due to cardiac myocite infiltration, and endothelin-induced pulmonary vasoconstriction are other possible links between the PAH and sarcoidosis.[45]

If patients report having relatives with possible or probable PAH, genetic counseling is recommended

PROGNOSTIC RISK STRATIFICATION IN THE PATIENTS WITH PAH

The final challenge in evaluating patients with suspected PAH is to estimate their risk of death. Although nonmodifiable risk factors including age, sex, and associated comorbidities play a significant role in determining prognosis, several potentially modifiable risk factors should be used to estimate the 1-year mortality risk (**Table 3**). These include features on physical examination consistent with right heart failure, New York Heart Association functional class, 6-minute walking distance or cardiopulmonary exercise capac-

TABLE 3

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis	Estimated 1-year mortality		
	Low-risk (< 5%)	Intermediate risk (5%–10%)	High risk (> 10%)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO functional class	I, II	III	IV
6-minute walk distance	> 440 m	165–440 m	< 165 m
Natriuretic peptide levels	BNP < 50 ng/L NT-proBNP < 300 ng/mL	BNP 50–300 ng/L NT-proBNP 300–1,400 ng/L	BNP > 300 ng/L NT-proBNP > 1,400 ng/L
Imaging (echocardiography, CMRI)	RA area < 18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamics	RA pressure < 8 mm Hg CI ≥ 2.5 L/min/m^2 Svo_2 > 65%	RA pressure 8–14 mm Hg CI 2.0–2.4 L/min/m^2 Svo_2 60%–65%	RA pressure > 14 mm Hg CI < 2.0 L/min/m^2 Svo_2 < 60%

CI = cardiac index; CMRI = cardiac magnetic resonance imaging; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RA = right atrium; Svo_2 = saturation of venous oxygen; WHO = World Health Organization. Reproduced with permission of the European Society of Cardiology and the European Respiratory Society. European Respiratory Journal Oct 2015; 46(4):903–975. doi:10.1183/13993003.01032-2015

ity, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and findings on echocardiography and right heart catheterization.[1]

Cardiac magnetic resonance imaging (MRI) has gained popularity as a noninvasive and reproducible alternative to echocardiography. Image fidelity and characterization of right ventricular function and right ventricular ejection fraction are all more accurate than with echocardiography, and serial MRI has proven valuable in its ability to guide patient prognosis.[46]

However, MRI is more expensive than echocardiography, and some patients cannot tolerate the procedure. In addition, for those who can tolerate it, MRI is not a suitable alternative to right heart catheterization, since it cannot accurately estimate pulmonary artery occlusion pressure or pulmonary arterial pressures.[1] For these reasons, cardiac MRI use varies across pulmonary hypertension centers.

A goal of treatment is to reduce a patient's risk. While no consensus has been achieved over which PAH-specific therapy to start with, evidence is robust that using more than 1 class of agent is beneficial, capitalizing on multiple therapeutic targets.[17,47]

In our patient, right heart catheterization revealed PAH with a mean pulmonary arterial pressure of 44 mm Hg, pulmonary artery occlusion pressure 6 mm Hg, and a cardiac index of 2.1 L/min/m^2. Ancillary testing for alternative causes of PAH was unrevealing, as was vasoreactivity testing. Our patient could walk only 314 meters on her 6-minute walk test and had an initial NT-proBNP level of 750 ng/L.

Based on these and the findings during her evaluation, she would be classified as having intermediate-risk PAH with an estimated 1-year mortality risk of 5% to 10%.[1] Appropriate therapy and follow-up would be guided by this determination. Specific therapy is beyond the scope of this article but we would start her on dual oral therapy with close follow-up to reassess her 1-year mortality risk. If there were no improvement over a short period of time, we would add further therapy.

REFERENCES

1. **Galiè N, Humbert M, Vachiery JL, et al**. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46(4):903–975. doi:10.1183/13993003.01032-2015
2. **Galiè N, Rubin LJ, Hoeper M, et al**. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomized controlled trial. Lancet 2008; 371(9630):2093–2100. doi:10.1016/S0140-6736(08)60919-8
3. **Howard LS**. Prognostic factors in pulmonary arterial hypertension: assessing the course of the disease. Eur Respir Rev 2011; 20:236–242. doi:10.1183/09059180.00006711
4. **Brown LM, Chen H, Halpern S, et al**. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. Chest 2011; 140:19–26. doi:10.1378/chest.10-1166
5. **Elliot CG, Farber H, Frost A, Liou TG, Turner M**. REVEAL Registry: medical history and time to diagnosis of enrolled patients. Chest 2007; 132(4):631a. doi:10.1378/chest.132.4_MeetingAbstracts.631a
6. **Minai OA, Budev MM**. Diagnostic strategies for suspected pulmonary arterial hypertension: a primer for the internist. Cleve Clin J Med 2007; 74(10):737–747. pmid:17941295
7. **Badesch DB, Raskob GE, Elliott CG, et al**. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. Chest 2010; 137(2):376–387. doi:10.1378/chest.09-1140
8. **Fisher MR, Forfia PR, Chamera E, et al**. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179(7):615–621. doi:10.1164/rccm.200811-1691OC
9. **Robbins IM, Newman JH, Johnson RF, et al**. Association of the metabolic syndrome with pulmonary venous hypertension. Chest 2009; 136(1):31–36. doi:10.1378/chest.08-2008
10. **Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiery JL**. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016; 37(12):942–954. doi:10.1093/eurheartj/ehv512
11. **Opitz CF, Hoeper MM, Gibbs JSR, et al**. Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. J Am Coll Cardiol 2016; 68:368–378. doi: 10.1016/j.jacc.2016.05.047
12. **Robbins IM, Hemnes AR, Pugh ME, et al**. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. Circ Heart Fail 2014; 7(1):116–122. doi:10.1161/CIRCHEARTFAILURE.113.000468
13. **Gerges C, Gerges M, Lang MB, et al**. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 2013; 143(3):758–766. doi:10.1378/chest.12-1653
14. **Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT); Galiè N, Hoeper MM, Humbert M, et al**. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009; 34(6):1219–1263. doi:10.1183/09031936.00139009
15. **Naeije R, Vachiery JL, Yerly P, Vanderpool R**. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013; 41(1):217–223. doi:10.1183/09031936.00074312
16. **Frost AE, Badesch DB, Miller DP, Benza RL, Meltzer LA, McGoon MD**. Evaluation of the predictive value of a clinical worsening definition using 2-year outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. Chest 2013; 144(5):1521–1529. doi:10.1378/chest.12-3023
17. **Galiè N, Barberà JA, Frost AE, et al; AMBITION Investigators**. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015; 373(9):834–844. doi:10.1056/NEJMoa1413687
18. **Farr G, Shah K, Markley R, Abbate A, Salloum FN, Grinnan D**. Development of pulmonary hypertension in heart failure with preserved ejection fraction. Prog Cardiovasc Dis 2016; 59(1):52–58. doi:10.1016/j.pcad.2016.06.002
19. **Hoeper MM, Barberà JA, Channick RN, et al**. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009; 54(suppl 1):S85–S96. doi:10.1016/j.jacc.2009.04.008
20. **Chaouat A, Naeije R, Weitzenblum E**. Pulmonary hypertension in COPD. Eur Respir J 2008; 32(5):1371–1385. doi:10.1183/09031936.00015608
21. **Minai OA, Ricaurte B, Kaw R, et al**. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am J Cardiol 2009; 104(9):1300–1306. doi:10.1016/j.amjcard.2009.06.048
22. **Kholdani C, Fares WH, Mohsenin V**. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ 2015; 5(2):220–227. doi:10.1086/679995
23. **Prisco DL, Sica AL, Talwar A, et al**. Correlation of pulmonary hypertension severity with metrics of comorbid sleep-disordered breathing. Sleep Breath 2011; 15(4):633–639. doi:10.1007/s11325-010-0411-y
24. **Dumitrascu R, Tiede H, Eckermann J, et al**. Sleep apnea in precapillary pulmonary hypertension. Sleep Med 2013; 14(3):247–251. doi:10.1016/j.sleep.2012.11.013
25. **Arcasoy SM, Christie JD, Ferrari VA, et al**. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003; 167(5):735–740. doi:10.1164/rccm.200210-1130OC
26. **Pepke-Zaba J, Jansa P, Kim NH, Naeije R, Simonneau G**. Chronic thromboembolic pulmonary hypertension: role of medical therapy. Eur Respir J 2013; 41(4):985–990. doi:10.1183/09031936.00201612
27. **Guérin L, Couturaud F, Parent F, et al**. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost 2014; 112(3):598–605. doi:10.1160/TH13-07-0538
28. **Lang IM, Pesavento R, Bonderman D, Yuan JX**. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 2013; 41(2):462–468. doi:10.1183/09031936.00049312
29. **Pepke-Zaba J**. Diagnostic testing to guide the management of chronic thromboembolic pulmonary hypertension: state of the art. Eur Respir Rev 2010; 19(115):55–58. doi:10.1183/09059180.00007209
30. **Bonderman D, Turecek PL, Jakowitsch J, et al**. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb Haemost 2003; 90(3):372–376. doi:10.1160/TH03-02-0067
31. **Pepke-Zaba J, Delcroix M, Lang I, et al**. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011; 124(18):1973–1981. doi:10.1161/CIRCULATIONAHA.110.015008
32. **Kim NH, Delcroix M, Jenkins DP, et al**. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013; 62:(suppl 25):D92–D99. doi:10.1016/j.jacc.2013.10.024
33. **Moser KM, Auger WR, Fedullo PF**. Chronic major-vessel thromboembolic pulmonary hypertension. Circulation 1990; 81(6):1735–1743. pmid:2188751
34. **McNeil K, Dunning J**. Chronic thromboembolic pulmonary hypertension (CTEPH). Heart 2007; 93(9):1152–1158. doi:10.1136/hrt.2004.053603
35. **Tunariu N, Gibbs SJ, Win Z, et al**. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007; 48(5):680–684. doi:10.2967/jnumed.106.039438
36. **Fedullo P, Kerr KM, Kim NH, Auger WR**. Chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2011; 183(12):1605–1613. doi:10.1164/rccm.201011-1854CI
37. **Rich S, Kaufmann E, Levy PS**. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992; 327(2):76–81. doi:10.1056/NEJM199207093270203

38. **Sitbon O, Humbert M, Jaıs X, et al**. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005; 111(23):3105–3111. doi:10.1161/CIRCULATIONAHA.104.488486
39. **Chin KM, Rubin LJ**. Pulmonary arterial hypertension. J Am Coll Cardiol 2008; 51(16):1527–1538. doi:10.1016/j.jacc.2008.01.024
40. **Soubrier F, Chung WK, Machado R, et al**. Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 2013; 62(suppl 25):D13–D21. doi:10.1016/j.jacc.2013.10.035
41. **Eyries M, Montani D, Girerd B, et al**. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. Nat Genet 2014; 46(1):65–69. doi:10.1038/ng.2844
42. **Best DH, Sumner KL, Austin ED, et al**. *EIF2AK4* mutations in pulmonary capillary hemangiomatosis. Chest 2014; 145(2):231–236. doi:10.1378/chest.13-2366
43. **Best DH, Sumner KL, Smith BP, et al**. *EIF2AK4* mutations in patients diagnosed with pulmonary arterial hypertension. Chest 2017; 151(4):821–828. doi:10.1016/j.chest.2016.11.014
44. **Hadinnapola C, Bleda M, Haimel M, et al; NIHR BioResource–Rare Diseases Consortium; UK National Cohort Study of Idiopathic and Heritable PAH**. Phenotypic characterization of *EIF2AK4* mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. Circulation 2017; 136(21):2022–2033. doi:10.1161/CIRCULATIONAHA.117.028351
45. **Diaz-Guzman E, Farver C, Parambil J, Culver DA**. Pulmonary hypertension caused by sarcoidosis. Clin Chest Med 2008; 29(3):549–563. doi: 10.1016/j.ccm.2008.03.010
46. **Mauritz GJ, Kind T, Marcus JT, et al**. Progressive changes in right ventricular geometric shortening and long-term survival in pulmonary arterial hypertension. Chest 2012; 141(4):935–943. doi:10.1378/chest.10-3277
47. **Galie N, Palazzini M, Manes A**. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. Eur Heart J 2010; 31(17):2080–2086. doi:10.1093/eurheartj/ehq152

***ADDRESS**: Neal F. Chaisson, MD, Respiratory Institute, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; chaissn@ccf.org*