# Implementing a shared-care approach to improve the management of patients with pulmonary arterial hypertension

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## ABSTRACT

Patients with pulmonary arterial hypertension (PAH) may present to internists, rheumatologists, cardiologists, or pulmonologists. This breadth of clinicians who encounter PAH patients, together with the complicated nature of PAH as a disease entity, argues for a shared-care approach to the management of these patients. This review describes the contributions of several key specialties to PAH management and outlines the collaborative PAH management model in place at our institution.

Successful approaches to pulmonary arterial hypertension (PAH) are typically collaborative approaches. Patients with PAH may present to general internists, rheumatologists, cardiologists, or pulmonologists. Moreover, centers of excellence in PAH across the United States bring together the expertise of pulmonologists in pulmonary and pulmonary vascular physiology, respiratory function testing, and pathology; the expertise of cardiologists in cardiovascular physiology, cardiac imaging, and pathology; and the expertise of rheumatologists in systemic autoimmune diseases.

These factors argue for a shared-care team approach to optimize the care of patients with PAH. An ideal way to embody this team approach is to form a pulmonary hypertension center, although the principles of this approach can apply even without such a formal center in place.

Most centers of excellence in PAH across the United States are run by either pulmonologists or cardiologists, with members of the other specialty playing a prominent role. This is natural, given that PAH has long been an area of interest for pulmonologists and cardiologists, since most patients with PAH present to these specialists by the very nature of their typical symptoms, including dyspnea on exertion and chest pain.

Nevertheless, the roles of specialists vary at different pulmonary hypertension centers, and every center needs more than just the expertise of a pulmonologist, a cardiologist, and a rheumatologist. The comprehensive care of patients with this complicated disease requires input from such team members as a pathologist with experience in pulmonary vascular diseases, an active interventional radiology program, an experienced thoracic transplant team, laboratory support, and nurses with expertise in PAH.

This article describes the contributions of key specialists to the management of patients with PAH and outlines the collaborative model for PAH patient management at the Cleveland Clinic Foundation.

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## ■ SCREENING AND DIAGNOSIS

At our institution, patients with PAH are referred to our pulmonary hypertension center, where their care is directed by a pulmonologist, who performs the initial evaluation. Input is sought from other specialists, including cardiologists and rheumatologists (whose roles are outlined below), if the workup reveals the possibility of a secondary etiology.

Pulmonary arterial hypertension may occur as a primary disease or as a complication of various systemic, cardiac, or pulmonary conditions,[1,2] as described earlier in this supplement. Some of these underlying diseases may be suspected on clinical grounds, but the nonspecific nature of the symptoms makes recognizing an underlying disease difficult unless the extrapulmonic symptoms or findings are evident. In most patients PAH has an underlying etiology, and the possibility of secondary causes should be vigorously explored. Because of the insidious onset and progression of PAH, its nonspecific symptoms, and its varied underlying causes, a high index of suspicion is needed for a correct and timely diagnosis.

Conditions associated with PAH should be identified to allow a focused screening strategy and effective treatment. Most patients are identified during evaluation of symptoms or incidentally during evaluation for unrelated problems. A transthoracic echocardiogram is currently the preferred screening test for PAH. Screening may be appropriate in any group of patients believed to be at increased risk of developing PAH. The biggest challenges that PAH centers and physicians who manage PAH face today are deciding whom and how to screen for this rare yet lethal disease and determining the cost-effectiveness of such a screening process. This is especially pertinent given the relative nonspecificity of the presenting symptoms and the fact that patients are typically in later stages of the disease by the time the diagnosis is finally made.

### Role of the rheumatologist

Given the high incidence of PAH in patients with systemic autoimmune diseases,[3] the rheumatologist is an integral member of the PAH management team. This is especially true since many patients with systemic autoimmune diseases typically present with symptoms or findings related to their underlying rheumatologic disease long before they develop PAH. A high index of suspicion and careful attention to the patient's complaints may allow for earlier diagnosis and intervention.

**TABLE 1**
Systemic autoimmune diseases associated with pulmonary arterial hypertension

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| Scleroderma |
| • Diffuse[7] |
| • Limited (CREST syndrome)[9] |
| Systemic lupus erythematosus[13,14] |
| Mixed connective tissue disease[15] |
| Rheumatoid arthritis[16] |
| Dermatomyositis/polymyositis[17,18] |
| Behçet disease |
| Takayasu arteritis |
| Antiphospholipid antibody syndrome |

CREST = calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias

Patients with scleroderma, systemic lupus erythematosus, and certain other systemic autoimmune diseases **(Table 1)** are considered to be at high risk for developing PAH.[3] Ungerer et al[4] estimated the prevalence of PAH to be as high as 33% in patients with scleroderma. Although early retrospective studies[5,6] based on autopsy or surgical pathology specimens reported a higher prevalence of PAH among patients with limited scleroderma, or the "CREST syndrome" (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias), more recent clinical studies have indicated a prevalence of PAH closer to 30% to 35%.[7–9] Pulmonary arterial hypertension may occur as an isolated complication of scleroderma or secondary to interstitial fibrosis. Studies show a significant increase in mortality in scleroderma patients with PAH compared with those without PAH.[10–12]

Pulmonary arterial hypertension has been reported in a smaller proportion of patients with systemic lupus erythematosus, 4% to 14%, but is associated with a 2-year mortality rate of 25% to 50% among these patients.[13,14]

As many as 66% of patients with mixed connective tissue disease have been said to develop PAH.[15] The incidence of PAH in patients with mixed connective tissue disease may be high because this entity represents a specific clinical subset of patients with a predominant sclerodermatous pattern of disease.

Causes of elevated pulmonary artery pressure in

**TABLE 2**
Evaluation for pulmonary arterial hypertension in patients with systemic autoimmune disease

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| **History and review of symptoms**<br>Raynaud phenomenon, esophageal reflux, digital ulcers, vascular bruits, rash, oral ulcers, alopecia, thyroid examination, lymph node examination, fever/sweats, edema |
| **Laboratory studies**<br>Complete blood count, coagulation profile, liver enzyme tests, creatinine phosphokinase, urinalysis (with fresh sediment examination), autoantibody screen directed by history and physical examination |
| **Chest radiograph** |
| **Electrocardiogram*** |
| **Pulmonary function tests***<br>Spirometry, lung volume tests, diffusion capacity |
| **Ventilation-perfusion lung scan** |
| **Echocardiogram*** |
| **Right heart catheterization** |

*Performed routinely at diagnosis and at routine follow-up intervals as discussed in the text.

patients with rheumatoid arthritis include chronic interstitial fibrosis and arterial intimal proliferation.[16] Polymyositis[17] and dermatomyositis[18] also are associated with fibrointimal proliferation and obliteration of small pulmonary arteries.

It is important to remember that patients with these diseases, especially scleroderma, may curtail their activities on account of musculoskeletal or peripheral vascular involvement and therefore may not present with dyspnea on exertion or chest discomfort. It is also extremely difficult to define the role of interstitial fibrosis as opposed to PAH in these patients, especially since a subgroup of patients may present with both.

It is critical to follow patients with limited scleroderma closely since these patients tend to present late in the course of PAH and have lower survival rates than those with coexistent interstitial fibrosis and restrictive lung disease.[12] On initial evaluation and subsequent visits, this subgroup of patients should be asked specifically about cardiopulmonary complaints, including cough, exertional dyspnea, pedal edema, chest pain, orthopnea, syncope, and presyncope.

Findings and symptoms of underlying systemic autoimmune diseases should regularly be looked for, including Raynaud phenomenon, telangiectasias, synovitis, gastroesophageal reflux disease, dysphagia, and others **(Table 2)**.

**Screening tests and recommendations.** All patients with scleroderma should undergo a chest radiograph, an electrocardiogram, and complete pulmonary function testing (spirometry, lung volume tests, and diffusion capacity) at baseline.[1] Ungerer et al[4] showed that, among a number of noninvasive tests studied, a diffusion capacity of lung for carbon monoxide (DLCO) below 43% of the predicted value had the greatest sensitivity (67%) for PAH and a dilated right descending pulmonary artery on chest radiograph had the greatest specificity (100%) for PAH. Both interstitial fibrosis and PAH may be associated with a decline in DLCO, but a disproportionate fall in DLCO relative to forced vital capacity should prompt an evaluation for PAH in patients with the CREST syndrome.[10,12] A DLCO less than 40% of predicted also portends a worse prognosis.[19]

Patients with scleroderma should be considered at high risk for PAH, and a transthoracic echocardiogram is recommended at baseline regardless of whether they have symptoms of PAH. Dyspnea on exertion or a declining DLCO in the absence of an alternate explanation, especially in a patient with an autoimmune disease of 10 years' or more duration, should trigger PAH evaluation with repeated transthoracic echocardiography.

There are no clear literature-based recommendations on who should be screened for PAH or how frequently, but we believe that all patients with scleroderma should have yearly pulmonary function tests and those with a declining DLCO should have a transthoracic echocardiogram. Some authorities have recommended yearly transthoracic echocardiography for all scleroderma patients.[20] In view of the lower incidence of PAH in patients with systemic lupus erythematosus, rheumatoid arthritis, and other systemic autoimmune diseases, transthoracic echocardiography is recommended only if the patient has otherwise unexplained symptoms compatible with PAH.

Serologic studies for patients with systemic autoimmune diseases should be ordered selectively on the basis of the history and physical examination. Anticentromere antibody is seen predominantly in patients with limited scleroderma and may indicate an increased risk for PAH.[3] The presence of antibodies to U3 small nucleolar ribonucleoprotein (U3 snRNP) has been associated with PAH in patients

with scleroderma[21] and may be diagnostically useful in patients suspected of having PAH. The presence of antiendothelial cell antibodies has been suggested to predict PAH in patients with systemic lupus erythematosus[22]; this is an area of ongoing study. Patients with antiphospholipid antibodies, with or without systemic lupus erythematosus, may develop PAH on the basis of occult, chronic thromboembolic disease. Some of these antibodies will also bind to endothelial cells. Many patients with primary pulmonary hypertension have elevated titers of antinuclear antibodies.[23] Debate continues on whether this represents a forme fruste of systemic lupus erythematosus or scleroderma or whether it is just a laboratory feature of primary pulmonary hypertension.

### Role of the cardiologist

The cardiologist has an important role in screening and managing patients with PAH by excluding cardiac causes of secondary pulmonary hypertension **(Table 3)** and treating any that are identified.

Pulmonary arterial hypertension associated with heart disease can be caused by increased pulmonary blood flow (precapillary pulmonary hypertension) or by increased pulmonary venous pressure (postcapillary pulmonary hypertension). Eventually, the pressure or flow abnormalities cause pulmonary vascular remodeling, which perpetuates increased vascular resistance by further narrowing the pulmonary arterial tree (mixed pulmonary hypertension).[24] The category of increased blood flow includes the congenital heart defects with left-to-right shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus, transposition of great vessels, and partial anomalous pulmonary venous drainage) and conditions associated with an increase in total blood volume, cardiac output, or both, such as thyrotoxicosis and chronic renal failure.

Left ventricular failure is the most common cause of pulmonary venous hypertension in both adults and children. The more common causes of left ventricular dysfunction include coronary artery disease, cardiomyopathy, mitral valve disease, and diastolic dysfunction. Some patients with left-to-right shunts may be clinically asymptomatic, although they usually complain of fatigue, palpitations, and dyspnea on exertion and may show signs of cyanosis and cardiac failure. In contrast, patients with left ventricular dysfunction present with signs and symptoms predominantly arising from acute or subacute pulmonary edema. Examination of the heart and systemic vessels may provide valuable clues about the nature of the shunt and valvular heart diseases.

**TABLE 3**
Role of the cardiologist in the assessment for pulmonary arterial hypertension

Exclude cardiac causes of secondary pulmonary hypertension:
- Systolic left ventricular failure
  - —Dilated cardiomyopathy
  - —Ischemic cardiomyopathy
  - —Other (alcohol-related, peripartum, familial, etc)
- Diastolic dysfunction
  - —Hypertensive heart disease
  - —Constriction
  - —Restriction
- Valvular heart disease
- Congenital heart disease

Perform diagnostic imaging studies to assess for cardiac secondary causes of pulmonary hypertension:
- Echocardiography, including transesophageal
- Right heart catheterization (hemodynamics)
- Computed tomographic scanning or magnetic resonance imaging (used selectively)
- Adjunctive ischemia evaluation, including stress testing or coronary angiography (used selectively)

Following a thorough history and physical examination, selected cardiac studies are performed. Echocardiography, including a transesophageal echocardiogram, is an effective means of screening for the presence of valvular diseases, left ventricular dysfunction, and septal defects. When appropriate, computed tomographic scanning or magnetic resonance imaging of the pericardium may be performed to exclude restrictive and constrictive heart diseases. Right heart catheterization is recommended for all patients undergoing evaluation for PAH and is necessary to confirm the presence of PAH and to establish responsiveness to vasodilator agents. The right atrial pressure, cardiac index, and mean pulmonary artery pressure should be noted carefully because of their prognostic significance.[25]

## ■ A COLLABORATIVE TREATMENT MODEL

At our institution, the treatment and follow-up of patients with PAH is usually performed by the pulmonologists, cardiologists, and nurse PAH coordinators who make up the PAH team. Once PAH is diagnosed, the severity of hypertension and the underlying cause dictate further management. Most pulmonary hypertension centers manage and make treatment recom-

**TABLE 4**
Web sites for patient education on pulmonary arterial hypertension

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| **Sites specific to pulmonary hypertension** |
| www.phassociation.org<br>(Pulmonary Hypertension Association) |
| **General health care sites** |
| www.nhlbi.nih.gov/health/public/lung/other/pph.htm<br>(National Heart, Lung, and Blood Institute) |
| www.who.int<br>(World Health Organization)* |
| www.americanheart.org<br>(American Heart Association)* |
| www.clevelandclinic.org/health<br>(Cleveland Clinic Foundation)* |
| www.MayoClinic.com<br>(Mayo Clinic)* |

*To obtain relevant information, patients should do a site search for "pulmonary hypertension."

mendations for patients with various forms of PAH, thromboembolic pulmonary hypertension, and PAH due to inflammatory causes.[1] Pulmonary hypertension caused by most other diseases (chronic obstructive pulmonary disease, sleep apnea, etc) is treated by treating the underlying disease.

At our institution, cardiologists from the section of heart failure perform most right heart catheterizations for PAH patients. Afterwards, patients are admitted to the heart failure unit if they are deemed to require continuous intravenous epoprostenol. The physician directing the PAH team (at our institution, a pulmonologist or sometimes a cardiologist) makes treatment decisions on the basis of the type of PAH, the patient's functional class, and the hemodynamic measurements obtained from right heart catheterization. All treatment decisions are made in consultation with the other physicians who are participating in the patient's care.

## Treatment considerations

Treatment of PAH should include attempts to reverse any identified contributing factors, which often brings substantial clinical improvement. For instance, PAH associated with obstructive sleep apnea may improve with nasal continuous positive airway pressure, thromboendarterectomy may be helpful in treating accessible thromboemboli,[26] and patients with marked right ventricular dysfunction and edema often respond symptomatically to salt restriction and diuretics.

The potential therapeutic and survival benefits of oxygen supplementation in patients with chronic hypoxemia should never be overlooked. Supplemental oxygen should be prescribed for patients with chronic lung disease and arterial oxygen pressure measured below 55 to 60 mm Hg, and for patients with significant sleep-induced or exercise-induced hypoxemia.[27–29] Warfarin administration has also been associated with improved survival in patients with primary pulmonary hypertension.[30–32]

Surgical treatment, including atrial septostomy and lung or heart-lung transplantation, may be considered for patients with severe PAH who do not respond to other interventions.[33–35] In general, the need for lung transplantation in patients with primary pulmonary hypertension has declined with the newer drug therapies (epoprostenol, bosentan, treprostinil, calcium channel blockers, etc) discussed by Gildea et al earlier in this supplement. Choosing the appropriate patient as a transplant candidate and the correct time to refer to a transplant center are the crucial first steps, taken by the pulmonary hypertension center, in the transplantation process.

## Pulmonary hypertension center referral and management

The PAH coordinator is usually the first contact in the referral process. While most referrals come from physicians, many patients call the pulmonary hypertension center directly. The PAH coordinator receives the medical records, reviews test results, and creates a schedule to complete the evaluation process in consultation with the pulmonologist. After the initial physical assessment, the coordinator arranges any additional testing, a cardiology consultation, and right heart catheterization, if appropriate. At our institution, patients with PAH, especially those receiving epoprostenol infusion, are assigned beds in select cardiac wards where the nurses are adept at caring for patients with cardiovascular diseases and are familiar with epoprostenol infusions.

When treatment has been determined, the PAH coordinator offers on-site teaching about the disease to the patient and his or her family, providing them with the most recent information **(Table 4)**. The coordinator also submits information for insurance verification for PAH treatments and arranges home nursing and follow-up appointments.

Patients with PAH require ongoing monitoring of their medication dosages and screening for side effects. For instance, intravenous epoprostenol has been associated with a number of adverse effects that should be monitored for, and patients receiving bosentan require liver function tests before therapy is started and monthly thereafter. The PAH coordinator keeps a log of every event and medication change, as well as a log of right heart catheterization results.

As long as patients are on therapy, they return to our pulmonary hypertension clinic every 2 to 3 months for clinical examination and a 6-minute walk test. Echocardiography and right heart catheterization are performed every 6 and 12 months, respectively, as long as patients are progressing as expected (see article by Gildea et al in this supplement). Patients' complaints and concerns are triaged over the phone by the PAH coordinator in consultation with the pulmonologist. Patients who need further attention are seen in the pulmonary hypertension clinic for evaluation.

The PAH coordinator provides an invaluable communication link between the patient and the various physicians involved in his or her care, preventing redundancy and ensuring that care is timely. The coordinator also serves a crucial function by coordinating the two essential components of PAH patient management: (1) the pulmonary hypertension center physicians and ancillary support (nursing, pathology, radiology), and (2) the patient's support network at home, consisting of local physicians, home care agencies, and family members. Keeping these two components mutually informed and working together is a key to continuing optimal care for the patient.

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