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Pull-Out Clinical Algorithm
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Cover Photo: Chest x-ray depicts pulmonary hypertension and a Hickman catheter. In lower left, computed tomography shows interstitial lung disease and the dilated esophagus from scleroderma. (Courtesy of Victor F. Tapson, MD)
Driven to Find Cure for PH, Brundage Leads New Quest for Breakthrough in Therapy

Bruce Brundage, MD, has seen it all, from the first anecdotal cases when no treatment for pulmonary hypertension was available, to the landmark National Institutes of Health (NIH) registry, to the large scale clinical trials of today involving hundreds of patients. For anyone seeking to chart progress in the field, his career serves as a bridge, spanning milestones in the treatment of the disease. He has been associated with virtually every key development in the progress toward a cure, beginning in the 1970s when he served as the director of the cardiac catheterization laboratory at the University of California, San Francisco.

It was during his study of those early cases, when he inserted catheters into the pulmonary artery to measure the effects of various vasodilating drugs, that he began focusing on pulmonary hypertension. During the last 25 years, research has been his passion—leading him to serve on the steering committee of the national registry and to play a key role in the growth of the 5,000-member Pulmonary Hypertension Association (PHA), of which he is now president. “It was in the late 1970s that I discovered the NIH was starting its patient registry so I applied to have our center enrolled as part of the registry,” he said. “Soon afterward, I was invited to be on the steering committee for the patient registry at a time when we began collecting data in an organized manner.” Joining the faculty at the University of Illinois at Chicago, Dr Brundage teamed with Stuart Rich, MD, and Paul Levy, PhD, two leading investigators, as they explored the effects of high-dose calcium channel blockers in treating pulmonary hypertension. “This was the first breakthrough in the treatment because we found there was a percentage of patients who were helped.”

In 1990 Dr Brundage was named chief of the Department of Cardiology at Harbor-UCLA Medical Center and became involved in the early studies of intravenous prostacyclin therapy. Enrolling 300 patients to receive what was a new infusion therapy at the time, he was a coauthor of a major paper published in the Journal of the American College of Cardiology demonstrating the long-term survival benefits of prostacyclin. At that point (continued on page 20)
The Pulmonary Hypertension Association

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Visit us at www.phassociation.org

PHA’s website is a gateway to the PH community. With the active support of PHA’s Scientific Leadership Council, it is also a growing source of medical information (www.phassociation.org/Medical) about pulmonary hypertension:

• Complete copies of all issues of Advances in Pulmonary Hypertension
• Nine consensus statements adopted by PHA’s Scientific Leadership Council:
  - Summary and explanation of common PH tests
  - Flolan guidelines
  - Exercise recommendations
  - Sodium restriction recommendations
  - Recommendations on over-the-counter medications
  - Elective surgery
  - Travel recommendations
  - Referral recommendations
• Answers to Frequently Asked Questions
• PH physician listings
• On-line survey of medical interests
• New: Clinical Trials section
• New: Pulmonary Hypertension Resource Network (PHRN) information
• New: Bibliography of PH articles

Learn and teach with Pulmonary Hypertension: A Patient’s Survival Guide

Pulmonary Hypertension: A Patient’s Survival Guide is now in its second edition. Many physicians and nurses order this publication in quantity for their own information and to give to their patients. The author, Gail Boyer Hayes, is a professional writer who has lived with PH for almost 20 years. Bruce Brundage, MD, past chairman of PHA’s Scientific Leadership Council and a physician with a deep knowledge of PH, edited the book for medical accuracy.

Among the chapter headings in this 215-page book are:
• What Is PH?
• How Do I Know I’ve Really Got PH?
• Who Gets PH?
• PH Treatments
• Children and PH
• How to Take Your Medicine
• Living with PH

Also included: Resource section, Bibliography, and Glossary

Available for $25 per copy (or $15 for members), including shipping. Call 301-565-3004 or order on-line at www.phassociation.org (click on “Online Store”)
Scleroderma-Associated Pulmonary Hypertension: Who’s at Risk and Why

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Introduction
Pulmonary arterial hypertension is a life-threatening complication of several connective tissue diseases, including both diffuse and limited scleroderma (with a subgroup of limited scleroderma called the CREST syndrome), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and less commonly, rheumatoid arthritis, and dermatomyositis/polymyositis (Table 1). This review will discuss the incidence, potential etiologies, clinical presentation, and treatment options for patients with pulmonary hypertension and the scleroderma spectrum of diseases.

Epidemiology
Pulmonary hypertension complicates several of the connective tissue diseases (Table 1). Scleroderma is a progressive, multi-system disease manifested by connective tissue and vascular lesions in many organs, including lung, kidney, and skin. Pulmonary manifestations include interstitial fibrosis, pulmonary arterial hypertension, constriction of the chest wall due to skin thickening, diaphragmatic dysfunction, and chronic aspiration due to esophageal dysmotility.  

The incidence of pulmonary hypertension varies between 6% and 60% of patients with scleroderma. Up to 33% of patients with diffuse scleroderma have pulmonary hypertension, both isolated and in association with interstitial lung disease. In patients with limited scleroderma, formerly referred to as CREST (calcinosi cutis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias), up to 60% of patients have pulmonary hypertension. While not all patients have clinically significant pulmonary hypertension, two thirds of patients with pulmonary hypertension will have pathologic evidence of pulmonary vascular disease. Stupi et al reported two-year survival in patients with CREST without pulmonary hypertension to be greater than 80% while patients with pulmonary hypertension had a two-year survival of 40%. Sacks et al reported two-year survival of patients with pulmonary hypertension and either diffuse or limited scleroderma to be approximately 50%. Koh et al reported 40% survival in patients with scleroderma and pulmonary hypertension compared with higher survival in scleroderma patients without organ failure or with other lung involvement (i.e. interstitial lung disease) at two years.

Pulmonary hypertension has been reported in 4% to 14% of patients with systemic SLE with an overall mortality rate of 25% to 50% at two years from diagnosis of pulmonary hypertension. Patients with MCTD have features of several connective tissue diseases, including SLE, scleroderma, rheumatoid arthritis, and polymyositis. Most MCTD patients have either predominantly SLE or scleroderma with a myositis overlap. The behavior of the disease therefore follows either a predominantly SLE or a scleroderma pattern. The incidence of pulmonary hypertension in patients with MCTD is not certain but one report found two thirds of patients with MCTD had evidence of pulmonary hypertension and pulmonary hypertension has been frequently cited as a cause of death in patients with MCTD. The high incidence of pulmonary hypertension in MCTD is probably a result of the predominant scleroderma pattern of this disease in many patients with MCTD.

Rheumatoid arthritis affects 5% of the population over age 65 and pulmonary complications include interstitial pulmonary fibrosis, rheumatoid nodules, and pleural effusions. The incidence of isolated pulmonary hypertension is not known. In a recent report, 21% of patients with rheumatoid arthritis without evidence of other pulmonary or cardiac dis-

Table 1—Connective Tissue Diseases Associated with Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subgroup</th>
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<tbody>
<tr>
<td>Scleroderma</td>
<td>Diffuse</td>
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<tr>
<td></td>
<td>Limited</td>
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<tr>
<td></td>
<td>CREST</td>
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<tr>
<td>Systemic lupus erytematosus</td>
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<tr>
<td>Mixed connective tissue disease</td>
<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Dermatomyositis/Polymyositis</td>
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Advances in Pulmonary Hypertension 5
ease had mild pulmonary hypertension.\textsuperscript{16} The prognosis is not known. Other connective tissue diseases including dermatomyositis/polymyositis have been associated with pulmonary arterial hypertension but the incidence and prognosis are not known.\textsuperscript{17}

**Pathogenesis**

The etiology of pulmonary hypertension in the scleroderma spectrum of diseases remains obscure. There appears to be direct involvement of the pulmonary circulation with intimal proliferation and medial hypertrophy, similar to that seen in primary pulmonary hypertension.\textsuperscript{6-9, 18} Some cases may also be related to severe pulmonary parenchymal disease, such as interstitial disease with hypoxemia. Additionally, diastolic dysfunction of the right and left ventricles has been seen in patients with scleroderma and may contribute to pulmonary hypertension.\textsuperscript{19}

Autoimmune processes have been implicated in the pathogenesis of pulmonary hypertension although the mechanism is not known. Positive antinuclear antibodies are frequently found in pulmonary hypertension patients without a diagnosis of connective tissue disease and pulmonary hypertension can occur before the onset of an identifiable connective tissue disease. In patients with scleroderma, anticentromere and antihistone antibodies have been associated with vascular disease. Anticentromere antibodies are primarily seen in the limited form of systemic sclerosis. Since patients with the limited form of systemic sclerosis have a higher incidence of pulmonary hypertension than do patients with diffuse disease, it is not surprising that anticentromere antibodies would be associated with a higher incidence of pulmonary hypertension. Antifibrillarin antibodies (anti-U3-RNP) are frequently found in patients with scleroderma and are more common with diffuse scleroderma-associated pulmonary hypertension.\textsuperscript{20} Anti-endothelial antibodies (aECA) are present in 40\% and 13\% of patients with diffuse scleroderma and CREST, respectively, and are associated with a higher incidence of pulmonary hypertension and digital infarcts.\textsuperscript{21} Antifibrillarin antibodies and aECAs are also associated with pulmonary hypertension in SLE.\textsuperscript{22} In patients with scleroderma and pulmonary hypertension, especially when accompanied by HLA-B35 antigen, antitopoisomerase II-alpha antibodies are more common, as are antibodies to fibrin-bound tissue type plasminogen activator.\textsuperscript{23}

Raynaud’s phenomenon, vasospasm of the arterioles in the distal systemic circulation, is commonly reported in patients with scleroderma. In one report, all patients with pulmonary hypertension and CREST had Raynaud’s, while 68\% without pulmonary hypertension had Raynaud’s.\textsuperscript{8} Raynaud’s is also common in patients with SLE and MCTD and pulmonary hypertension\textsuperscript{11, 24} but only 10\% to 14\% of patients with primary pulmonary hypertension have Raynaud’s.\textsuperscript{25} This observation has led to the “pulmonary Raynaud’s” hypothesis that vasospasm contributes to the development of pulmonary hypertension.\textsuperscript{26}

Acute hypoxic pulmonary vasoconstriction may be more pronounced in patients with pulmonary hypertension and scleroderma than in patients with primary pulmonary hypertension.\textsuperscript{27} However, another report found that pulmonary vasospasm was not present in patients with Raynaud’s and scleroderma without pulmonary hypertension.\textsuperscript{28} In support of this hypothesis, patients with scleroderma have defective endothelial-dependent vasodilation\textsuperscript{15} and this may be related to decreased endothelial nitric oxide synthase (eNOS).\textsuperscript{29} Although controversial, decreased lung eNOS has been reported in severe primary pulmonary hypertension.\textsuperscript{30} While the level of eNOS in connective tissue disease is not known, decreased production of lung nitric oxide has been found in patients with scleroderma and pulmonary hypertension.\textsuperscript{31} Similarly, expression of prostacyclin synthase in pulmonary endothelium may be decreased in patients with severe connective tissue disease-associated pulmonary hypertension.\textsuperscript{32}

Endothelin-1 is increased in serum of patients with both diffuse and limited scleroderma\textsuperscript{33} and while endothelin levels correlate with survival in patients with scleroderma, they are not higher in those with pulmonary hypertension.\textsuperscript{34} In contrast, higher serum endothelin levels are found in patients with SLE-associated pulmonary hypertension than in nonpulmonary hypertensive SLE patients.\textsuperscript{12} The role of endothelin-1 in pulmonary hypertension has led to the use of endothelin antagonists in treatment of patients with connective tissue disease-associated pulmonary hypertension.\textsuperscript{35} Serotonin may also play a role in the pathogenesis of pulmonary hypertension. In patients with systemic sclerosis and Raynaud’s, platelet serotonin concentrations are decreased and serum levels are increased.\textsuperscript{36, 37}

**Clinical Presentation and Evaluation**

Dyspnea is the most common presenting symptom of scleroderma-associated pulmonary hypertension. The clinical evaluation is similar to that of patients with primary pulmonary hypertension. History and physical examination often reveal findings of the underlying connective tissue disease (i.e., Raynaud’s, telangiectasias, rash, synovitis, interstitial lung disease, etc.). Decreased diffusing capacity of the lung is the most common pulmonary function abnormality and should prompt an evaluation for both pulmonary vascular and interstitial lung disease.\textsuperscript{38} A diffusing capacity of less than 40\% of predicted for lung volume places the patient in a poor prognostic category. Echocardiography may be helpful in the evaluation of patients suspected of having pulmonary hypertension as suggested by unexplained dyspnea or an isolated reduction in diffusing capacity. As previously discussed, patients with scleroderma should be considered an “at risk” group for the development of pulmonary hypertension, and echocardiography may reveal right ventricular hypertrophy and dilatation even before the onset of symptoms.\textsuperscript{39} Ultimately, as with primary pulmonary hypertension, right-heart catheterization is needed to confirm the diagnosis, assess hemodynamic severity, and exclude other possible contributing factors, such as an occult congenital heart defect. While it is generally thought that patients with scleroderma-associated pulmonary hypertension are less likely to demonstrate a favorable response to vasodilator therapy than patients with primary pulmonary hypertension (in whom the response rate is approximately 20\% to 25\%), a hemodynamically monitored assessment of vasoactivity is still advocated by some experts.
Table 2—Potential Therapeutic Options

<table>
<thead>
<tr>
<th>Vasodilators</th>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Angiotensin converting enzyme inhibitors</td>
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<tr>
<td>Alpha-adrenergic blockers</td>
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<tr>
<td>Prostaglandin preparations</td>
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<tr>
<td>Intravenous epoprostenol</td>
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<tr>
<td>Subcutaneous treprostinil</td>
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<tr>
<td>Inhaled iloprost</td>
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<td>Inhaled nitric oxide</td>
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<table>
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<tr>
<th>Phosphodiesterase inhibitors</th>
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<tr>
<td>Endothelin receptor antagonists</td>
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<td>Serotonin antagonists</td>
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<th>Immunosuppressive therapy</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Bone marrow transplantation</td>
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</table>

| Lung/Heart-lung transplantation   |

Therapy

Several therapeutic options are available for the treatment of scleroderma-associated pulmonary hypertension (Table 2). Oral vasodilators (calcium channel antagonists, angiotensin converting enzyme inhibitors, and alpha-adrenergic antagonists) have been used to treat pulmonary hypertension in patients with scleroderma. Although it has been reported that calcium channel blockers have improved survival in some patients with scleroderma-associated pulmonary hypertension, 40-42 it is generally acknowledged that only a small percentage of such patients respond favorably to these agents. Angiotensin converting enzyme inhibitors and an alpha-adrenergic blocker (prazosin) have also been used both acutely and over the long term in the treatment of connective tissue disease-associated pulmonary hypertension. 41, 43

In a randomized, multicenter study of continuously intravenously infused epoprostenol we reported short-term improvement in patients with pulmonary hypertension due to scleroderma. 44 111 patients with pulmonary hypertension and the scleroderma spectrum of disease (70% limited disease, 13% diffuse disease, 11% to 14% overlap syndrome, and 5% with features of scleroderma) were randomized to receive continuous infusion of epoprostenol vs. conventional treatment for 12 weeks. Epoprostenol improved exercise capacity, cardiopulmonary hemodynamics, New York Heart Association functional class, Borg dyspnea index, and likely Raynaud’s. However, there was no mortality benefit as had been seen in the same treatment duration with primary pulmonary hypertension, 45 possibly because of the multisystem nature of this disease. 44 It is important to point out that the study was not powered to detect a survival difference. Others have also found both short and long-term improvement with epoprostenol. 46, 47 Long-term follow-up of the patients in our study has suggested that epoprostenol may improve survival compared with historical controls. However, in general it appears as though survival/prognosis is worse for patients with scleroderma-associated pulmonary hypertension as compared with patients with primary pulmonary hypertension and needs further investigation. Treatment with epoprostenol in some patients has been associated with reports of pulmonary edema possibly resulting from pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. 48 Although very rare, pulmonary veno-occlusive disease may be more common in patients with connective tissue disease. 49

Increasing evidence has suggested the importance of endothelin-1 in the pathogenesis of pulmonary hypertension. In a multicenter, randomized, double-blinded placebo-controlled trial of the endothelin receptor antagonist bosentan (Tracleer®) for the treatment of pulmonary arterial hypertension, 213 patients with pulmonary hypertension, either primary or due to connective tissue disease (scleroderma and lupus), were randomized to receive placebo or bosentan at 125 or 250 mg orally twice daily. 35 After 16 weeks, distance walked in six minutes, functional class, Borg dyspnea index, and time to clinical worsening improved in patients receiving either dose of bosentan. In contrast to the improvement in patients with primary pulmonary hypertension, bosentan prevented the deterioration in six-minute walk compared with placebo. This suggested that patients with scleroderma did less well overall. Nevertheless, relative stability may represent a favorable outcome in a disease with an otherwise very poor prognosis. Bosentan has been associated with a dose-dependent increase in liver function tests, and monthly follow-up of these tests is required by the Food and Drug Administration. Other potential side effects are thought to include mild anemia, fluid retention, teratogenicity, and possibly testicular dysfunction and male infertility. Even in light of these potential adverse effects, the development of this oral therapy is thought to represent a significant advance.

Various prostacyclin analogues and delivery systems have been recently studied. Inhaled iloprost, a stable analogue of epoprostenol, was studied in a large placebo-controlled trial comparing inhaled iloprost with placebo in patients with severe pulmonary hypertension. Iloprost improved six-minute walk test results, functional status, and hemodynamics after 12 weeks of treatment. 50 The effect was greatest in patients with primary pulmonary hypertension. Combination with a phosphodiesterase inhibitor appears to increase the effectiveness of inhaled iloprost in patients with pulmonary hypertension. 51 Treprostinil, a stable prostacyclin analogue administered subcutaneously, was recently approved for use in patients with pulmonary arterial hypertension with efficacy at the highest doses of the drug. 52 Beraprost sodium, an orally bioactive prostacyclin analogue, improved six-minute walk distance in patients with primary pulmonary hypertension compared with patients with connective tissue disease. 53

Although nitric oxide has utility in acute pulmonary vasodilator testing in patients with scleroderma, there have not been any reports of its long-term use in the treatment of scleroderma-associated pulmonary hypertension. The selective serotonin receptor 2 antagonist ketanserin acutely improved pulmonary artery pressure and cardiac output in patients with scleroderma-associated pulmonary hypertension 54 while sar...
pogrelate, another receptor 2 antagonist, administered orally for 12 months, decreased mean pulmonary arterial pressure and increased right ventricular ejection fraction. These reports suggest a role for serotonin in the pathogenesis of scleroderma-associated pulmonary arterial hypertension, although a randomized, controlled trial has not been done.

Corticosteroids with and without cyclophosphamide have been reported to improve or stabilize pulmonary hypertension in patients with scleroderma. However, these represent case reports or retrospective case studies and no prospective study of immunosuppressive therapy has been completed in patients with connective tissue disease-related pulmonary hypertension. Use of immunosuppressive therapy may be more successful in patients with SLE than in those with scleroderma.

Surgical treatment, including atrial septostomy and lung or heart-lung transplantation may be considered for patients with severe pulmonary arterial hypertension in association with connective tissue disease. Survival in patients with connective tissue disease-associated pulmonary hypertension who undergo lung or heart-lung transplantation is not different from that in patients with primary pulmonary hypertension. Lung transplantation may also be of benefit in patients with severe fibrotic lung disease. Appropriate patient selection is important, though, and lung transplantation may be relatively contraindicated in patients with significant esophageal dysmotility or renal dysfunction.

Summary
Patients with scleroderma are at increased risk for the development of pulmonary hypertension, and the development of unexplained dyspnea or an isolated decrease in diffusing capacity should prompt evaluation. Echocardiography is often helpful in this situation. Because the prognosis of untreated pulmonary hypertension occurring in the setting of scleroderma is generally quite poor, vigilance is required on the part of physicians following this “at risk” group of patients. The past decade has seen important advances in the treatment of pulmonary arterial hypertension, including intravenous epoprostenol, oral bosentan, and subcutaneously infused treprostinil. As new therapies are developed for the treatment of pulmonary arterial hypertension, it is essential that patients with scleroderma-related disease are included in clinical trials.

Acknowledgement

Portions of this report are similar to upcoming articles written by the same authors in the 2nd Edition of Pulmonary Circulation edited by Drs Andrew Peacock and Lewis J. Rubin and in Progress in Cardiovascular Diseases.

References


This article will discuss several features of cardiac catheterization, specifically right-heart catheterization, as they relate to patients with pulmonary arterial hypertension (PAH).

The accepted gold standard definition of pulmonary hypertension is defined by most experts as a mean pulmonary arterial pressure of \( \geq 25 \) mmHg, with a concomitant pulmonary capillary wedge (PCW) pressure of \( \leq 15 \) mmHg, and pulmonary vascular resistance of \( >3 \) Wood units. These criteria are derived from the National Institutes of Health registry of patients with primary pulmonary hypertension.\(^1\) Thus, by definition, cardiac catheterization is required to definitively establish the diagnosis of PAH.

Cardiac catheterization should be considered essential for documenting hemodynamic severity, as well as completing a standard workup for pulmonary hypertension. The information obtained from cardiac catheterization in combination with clinical findings can be used to monitor therapeutic and adverse effects of medical interventions.

Measurement of hemodynamics in patients with PAH via cardiac catheterization can also provide added prognostic value. For example, in patients with primary pulmonary hypertension whose mean right atrial pressure was \( <10 \) mmHg, median survival was nearly 50 months without pulmonary vasodilator therapy, compared with less than 3 months in patients whose mean right atrial pressure was \( \geq 20 \) mmHg (Figure 1).\(^2\)

While echocardiography has been shown to be useful for estimating pulmonary arterial pressure, this modality has certain limitations that can ultimately lead to errors in diagnosing PAH without the use of cardiac catheterization to validate the measurements. Specifically, while echocardiographic estimates of pulmonary artery systolic pressures have been shown to correlate with pressures measured by catheterization,\(^3,4\) for individual patients, the error of measurement may be significant. This is especially important when making the initial diagnosis of PAH, since overestimates and underestimates may lead to an incorrect diagnosis.

In addition to limitations in pressure estimates, the lack of ability of echocardiography to measure PCW pressure (and thus left ventricular end diastolic pressure) bears important clinical significance, since it is essential to exclude pulmonary venous hypertension when making the diagnosis of PAH.

### The Catheterization Procedure

#### The Catheter

The pulmonary artery (right heart) catheter is designed for use in the ICU or in the cardiac catheterization laboratory to measure right-heart and pulmonary arterial hemodynamics, to estimate left ventricular end diastolic pressure, and to measure cardiac output. The catheter is usually 120 cm long and has multiple lumens so that pressure recordings and infusions can be made from various locations in the heart and pulmonary arteries. In addition, a small plastic balloon that is located at the tip of the catheter can be inflated and used to “float” the catheter in the direction of blood flow in order to facilitate catheter advancement. This balloon is also used to occlude the pulmonary artery in order to obtain estimates of left atrial pressure (see below). Finally, a thermistor (temperature indicator) is also located at the tip of the catheter; it is used to detect changes in blood temperature when performing thermodilution cardiac output measurements (see below).

When performing right-heart catheterization specifically for patients with PAH, the catheter used often has several modifications that are designed to facilitate the catheterization process. The catheter is stiffer than the standard right-heart catheter and contains a blind-end port, which allows passage of a guidewire for additional stiffness, if desired. This extra stiffness is often needed because advancing the catheter into the pulmonary artery can be technically difficult in the presence of a dilated right ventricle, elevated pulmonary arterial pressure, and tricuspid regurgitation.
Precautions
When planning cardiac catheterization for a patient with suspected PAH, it is important to understand the risks associated with the procedure, and to have an emergency treatment plan in place should these risks occur. In addition, the desired measurements should be planned in advance, with careful consideration of the specific operational procedures that are to be done during the procedure.

Clinicians should be very familiar with how to interpret the measurements obtained at cardiac catheterization, and be able to troubleshoot suspected inaccuracies. Anticipation of complications and unexpected findings is essential, so that immediate action can be taken. Finally, the clinician must continuously scrutinize the findings and question the measurements for both accuracy and clinical relevance.

Patients with PAH may present with relatively few physical signs of PAH, yet have significant cardiovascular abnormalities. These patients, with “compensated right-heart failure,” can easily decompensate when subjected to the stressors of cardiac catheterization. Despite these risks, however, cardiac catheterization is safe if appropriate precautions are carried out.

• **Staff experience** – The physician and nursing and technical staff must all be familiar with the diagnosis and management of PAH and with the catheterization laboratory equipment. The staff must be meticulous about flushing and leveling the pressure transducers and flushing the catheter to ensure that accurate measurements are recorded.

• **Patient sedation** – It is generally recommended that adult patients be kept awake during catheterization. However, it is important that anxiety, which may induce tachycardia and hemodynamic embarrassment, be controlled. Small doses of benzodiazepines are useful for controlling anxiety. Close attention to continuous pulse oximetry is required, however, as hypoxemia during catheterization is not uncommon.

• **Atrial and ventricular ectopy** – As the catheter is manipulated into positions in the right atrium and ventricle, ectopic electrical activity is common. Usually, atrial premature beats and ventricular ectopic beats are brief and self-limited. Sustained activity including atrial and ventricular tachycardia may occur, however. Immediate repositioning or removal of the catheter is required in these instances, and antiarrhythmic therapy should always be available should the arrhythmia persist.

• **Bradyarrhythmias** – One of the most troublesome complications of cardiac catheterization in patients with PAH is the development of vagally mediated bradyarrhythmia and hypotension. Often, an anxious or sensitive patient may develop increased vagal tone 1) on viewing the catheterization instruments or during local anesthetic infusion; 2) on insertion of the catheter; or 3) on removal of the catheter. When these “vagal episodes” occur, profound bradycardia and hypotension often ensue within 30 to 60 seconds. It can be extremely difficult to resuscitate such a patient. Therefore, it is imperative that a vagal episode is anticipated in all patients, and that it is recognized and treated with atropine early in its course. This author always keeps an open vial of atropine at the bedside before, during, and after cardiac catheterization of a patient with pulmonary hypertension.

• **Reliability of measurements** – Cardiac catheterization measurements should be made preferably when the patient is supine, with anxiety minimized (see above), and at steady state. Spontaneous variation in hemodynamics over time is a known shortcoming of cardiac catheterization (**Figure 2**), and thus great care should be taken to ensure that all measurements are taken in close proximity of each other. In general, waiting at least 15 minutes after catheter insertion is advisable. Hemodynamic measurements should then be obtained as close together as possible.

Choice of Venous Access Sites
Commonly, the right internal jugular vein is used for insertion of a venous sheath through which the pulmonary artery catheter is passed. Other sites can be advantageous, depending on the situation (**Table 1**). For a patient’s initial catheterization, use of the femoral veins for catheterization may be preferred, because it allows the greatest flexibility with which the clinician can perform the most thorough evaluation. This is especially important for excluding left heart pathology when direct measurement of left ventricular end diastolic pressure is necessary.

Measurements to Record
Standard right-heart catheterization measurements (**Figure 3**) include:

- right atrial pressure (RAP)
- right ventricular pressure (RVP)
- pulmonary arterial pressure (PAP)
- pulmonary capillary wedge pressure (PCWP)
- systemic arterial pressure (BP) and heart rate
- cardiac output (CO)
- pulmonary arterial vasoreactivity

- pulmonary arterial (PA) (“mixed venous”) saturation
- superior vena cava (SV) saturation
- inferior vena cava (IVC) saturation
- right atrial (RA) saturation
- right ventricular (RV) saturation

*When indicated.

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**Figure 2**—Spontaneous variation in pulmonary arterial hemodynamics over time.
Normal pressure waveforms are shown in Figure 3. PCW pressure measurements are made when the balloon of the catheter is inflated after the catheter has been properly advanced into the pulmonary artery. The inflated balloon prevents the measurement of any pressure proximal to the balloon, and thus measurements recorded from the tip of the catheter reflect only left atrial pressure, which is commonly used as a surrogate for left ventricular end diastolic pressure.

The PCW pressure tracing should display three waveforms: the a wave represents contraction of the left atrium. The c wave is due to a rapid rise in the left ventricular pressure in early systole, causing the mitral valve to bulge backward into the left atrium, so that the atrial pressure increases momentarily. The v wave is produced when blood enters the left atrium during late systole, the time at which most filling of the left atrium occurs.

Hemodynamic calculations – The following formulas are used to calculate standard hemodynamic parameters derived from the above measurements:

\[
\text{Mean* systemic arterial pressure (mBP)} = \frac{\text{diastolic BP} + (\text{systolic-diastolic BP})}{3}
\]

\[
\text{Mean* pulmonary arterial pressure (mPAP)} = \frac{\text{diastolic PAP} + (\text{systolic-diastolic PAP})}{3}
\]

\[
\text{Pulmonary vascular resistance (PVR)} = \frac{(\text{mPAP-PCW pressure})}{\text{Cardiac output (CO)}}
\]

\[
\text{Pulmonary vascular resistance index (PVRI)} = \frac{\text{PVR}}{\text{Body surface area (BSA)}}
\]

\[
\text{Systemic vascular resistance (SVR)} = \frac{\text{mBP-RAP}}{\text{CO}}
\]

\[
\text{Systemic vascular resistance index (SVRI)} = \frac{\text{SVR}}{\text{BSA}}
\]

*Mean values may be more readily obtained by taking readings from bedside electronic monitoring equipment, which obviates the need for adjusting arithmetic means for extreme heart rates.

Cardiac output measurements – There are two standard methods for determining cardiac output. Both methods measure pulmonary blood flow, which in the absence of an intracardiac shunt is equal to systemic blood flow.

The thermodilution method for determining cardiac output uses the indicator dilution principle, where the indicator is cold saline infused as a bolus injection into the proximal port of the right-heart catheter. The thermistor at the distal end of the catheter then measures the appearance and disappearance of indicator over time, and a cardiac output is then calculated. This method can be inaccurate at very high or very low cardiac outputs, and can underestimate cardiac output when significant valve regurgitation is present.

When using this technique, the clinician must ensure that the proximal right atrial port for injection is actually in the right atrium, since the port can be in the right ventricle when the catheter is wedged.

The Fick method for determining cardiac output is based on the principle that consumption of a substance (oxygen in this case) must equal blood flow to the organ multiplied by the difference between the arterial and venous concentrations of the substance. For this method, the formula for cardiac output is as follows:

<table>
<thead>
<tr>
<th>Site</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right internal jugular vein</td>
<td>Facilitates pulmonary artery access; proximity to heart; may not need fluoroscopy</td>
<td>Cutaneous access can be difficult</td>
<td>Hematoma, pneumothorax, tracheal obstruction</td>
</tr>
<tr>
<td>Left subclavian vein</td>
<td>Facilitates pulmonary artery access; proximity to heart</td>
<td>Vascular control of bleeding difficult</td>
<td>Pneumothorax, hemothorax</td>
</tr>
<tr>
<td>Femoral veins</td>
<td>Easiest to cannulate; easiest for vascular control of bleeding</td>
<td>Most problematic for pulmonary artery access; small risk of infection; limits patient mobility; fluoroscopy required</td>
<td>Hematoma</td>
</tr>
</tbody>
</table>
has an extremely important role in the diagnosis and management of PAH. The initial (diagnostic) evaluation, to assure that all patients with suspected PAH as part of their clinical presentation exhibit pulmonary vasoreactivity, predict the response to long-term calcium channel blocker (CCB) therapy. Furthermore, patients with overt signs and symptoms of right-heart failure do not tolerate the high doses of a CCB required to produce hemodynamic benefit. The use of a CCB in these patients carries significant risk of worsening right ventricular failure and death.

This illustrates the complexities associated with vasodilator testing and the importance of understanding how to use CCB therapy. These agents should not be prescribed empirically for patients with PAH and should be reserved for patients with pulmonary vascular vasoreactivity who do not have signs of right ventricular failure (see below).

Vasodilator Testing: How It Is Done

The basics of pulmonary vasodilator testing in PAH include:

1. **Administration of appropriate pulmonary vasodilator.** The most commonly used pulmonary vasodilators for acute vasodilator testing are intravenous epoprostenol or adenosine and inhaled nitric oxide. These agents have been used by many PAH experts, and there is substantial documentation of their utility in PAH.

Initially, very low doses of the pulmonary vasodilator should be administered (Table 2). If at any time during up-titration of the vasodilator the systolic pressure falls below 85 mmHg or the patient complains of dyspnea or dizziness, the vasodilator should be discontinued, and the patient watched carefully until hemodynamics return to baseline.

Hemodynamic measurements should be repeated every 10 to 15 minutes as the dose of the vasodilator is increased. The dosing should continue until any one of the following criteria are met:

- drop in systolic pressure by 30% or < 85 mmHg systolic
- increase in heart rate by 40% or >100 bpm
- fall in heart rate to < 65/bpm with symptomatic hypotension
- intolerable side effects develop, such as headache, lightheadedness or nausea.
- target response achieved (see below)
- maximum dose of vasodilator agent given

2. **Recording the change in hemodynamics.** Focus on changes in mean pulmonary arterial pressure, PCWP, and cardiac output allows the quantitation of change in pulmonary vascular resistance.
Powerful Medicine.

That’s what we’ve created through the combination of Gentiva’s Specialty Pharmaceutical Services Division and Accredo Health, Incorporated. This alliance results in one of the country’s most extensive networks of pharmacies for the distribution of medications for pulmonary arterial hypertension.

Accredo Therapeutics, Inc. utilizes pharmacist-led clinical teams specializing in PAH therapies. Our focus on pulmonary arterial hypertension results in clinically advanced programs and services, including home nursing, to support the PAH community and their physicians. Our growth has also allowed increased access to managed care contracts making it easier for patients to receive the care they need.

One thing that remains constant is the friendly, caring team of professionals who will work with you day in and day out. We invite you to call them for answers to any questions you may have concerning PAH therapies.
vascular resistance (see above), however close attention must be
given to systemic blood pressure, heart rate, and oxygen
saturation as well, to ensure patient safety during up-titration
of the pulmonary vasodilator.

3. Interpreting the change in hemodynamics. Some PAH
experts regard a positive pulmonary vasodilator response as
one in which the mean pulmonary arterial pressure falls by at
least 22%, and others use a fall in pulmonary vascular resist-
ance of at least 26% to label a positive response. There is no
accepted standard for determination of pulmonary vasoreac-
tivity. However, a consensus statement prepared for the
Pulmonary Hypertension Association has recently been
released,\textsuperscript{16} and data exist that correlate a robust vasodilator
response with improved prognosis compared with patients
without such a response.

**Congenital heart disease** – A large number of alternative
etiologies of pulmonary hypertension should be entertained
when evaluating a patient with suspected PAH. Of particular
importance is the patient with congenital heart disease.
Because congenital heart disease can be easily overlooked
or missed, cardiac catheterization may be the only study to
uncover its existence. Thus, when planning catheterization
for PAH patients, careful consideration should be given to the
measurements that are to be obtained at the time of catheter-
ization. In particular, when the patient develops hypoxemia
with exercise, the clinician should take extra care not to miss
an intracardiac shunt, which may be due to an atrial septal
defect, especially of the sinus venosus type, which may be
missed at echocardiography, or may be due to the presence
of anomalous pulmonary veins. Standard measurements for
patients with suspected intracardiac shunts should always
include blood sampling at various sites to determine oxygen
saturation at all levels (SVC, IVC, RA, RV, and PA, see
Measurements to Record, above).

Dr Brundage's team at UCLA had enrolled more than 300
patients with pulmonary hypertension, one of the largest
groups in the country at one center.

Following his departure from UCLA in 1998,
Dr Brundage accepted the medical director's post at the
Heart Institute of the Cascades in Bend, Oregon. At that
point he began focusing more attention on the develop-
ment and financial resources of PHA. He had already
become chairman of the association's Scientific Advisory
Board in 1996, a position he held until 2001. The
Advisory Board has been renamed the Scientific Leader-
ship Council. This year he agreed to become president
of PHA and also serves as a member of the Board
of Trustees. As a key figure in PHA's growth, Dr Brundage
has seen the association's annual budget grow from about
$100,000 to $1.8 million in only five years. Gifts from
foundations, corporations, and individuals have spurred
the group's efforts in research and have helped it award
grants to young investigators seeking new therapies for
PH as they pursue a career in this field.

“I think PHA will encourage the formation of another
patient registry. Many things have changed since the for-
mation of the first NIH registry. We might be able to col-
lect data that will help us determine which patients are
candidates for lung transplantation. We may also investi-
gate the appropriate use of warfarin. The current recom-
mendation is that all patients with pulmonary hyperten-
sion receive warfarin, but this practice has never been
adequately evaluated in a randomized study. So we need
to determine in a randomized, placebo-controlled study
whether warfarin makes any difference in the long-term
outcome of patients with pulmonary hypertension. It has
been presumed that there is a thrombotic aspect of the
disease but the long-term beneficial effect of anticoagula-
tion has never been proven.

“This new registry will have thousands of patients in it
throughout the country. Since we have representatives on
the Scientific Leadership Council from Canada, Ireland,
Germany, and Italy, it could be an international registry,”
he added. “As president of PHA, my main focus will be to
raise revenues in support of all of these projects. I am
strongly committed to research to find a cure and raising
millions of dollars in this effort. This is the best way to get
to the cure. Pulmonary hypertension is multifactorial. The
more we study this disease the more clear it becomes that
it is a polyglot with many causes. Fortunately, many differ-
ent kinds of therapies are being developed.”

In recognition of his achievements, PHA has given
Dr Brundage its Physician of the Year Award. Widely
respected in the medical community for his commitment
to finding a cure for pulmonary hypertension, Dr Brundage
has also earned the respect of colleagues and patients
alike for his compassionate attitude and the quality of
patient care he provides.
results in “over-wedging.” Prolonged over-wedging will yield a falsely high PCW pressure and may result in pulmonary infarction.

If an accurate PCW pressure cannot be obtained during right-heart catheterization, it is prudent to consider direct measurement of left ventricular end diastolic pressure via left-heart catheterization.

Summary
Cardiac catheterization should be considered for definitive diagnosis in all patients suspected of PAH. It is the only reliable method for this purpose, it can be used for determining vasodilator responsiveness of the pulmonary vasculature, and if is part of a standard diagnostic workup for patients with suspected congenital heart disease. For patients with suspected secondary forms of PAH, it is especially important to be certain that the diagnosis is accurate, as many of these patients have concomitant left heart and lung disease that could confound the diagnosis.

References
16. www.phassociation.org/medical

Pitfalls of Measurements
Incorrect recordings of PCW. A common pitfall when measuring PCW pressure in patients with PAH involves incorrect interpretation. This occurs when the right-heart balloon flotation catheter is not in proper position, yielding an inaccurate pressure tracing (Figure 5). The most common cause of this error is the recording of a dampened pulmonary arterial pressure rather than a true occlusion pressure. This error results in a falsely elevated pressure measurement, often misleading the clinician into believing that the patient has pulmonary venous hypertension rather than PAH.

This author frequently employs two techniques for avoiding this measurement error:

1) Partially inflating the balloon and gentle forward advancement of the catheter, in order to better seat and seal the catheter against the walls of the pulmonary artery branch.

2) Validating an abnormally elevated measurement by gently withdrawing a blood sample from the distal port of the right-heart catheter during balloon inflation and PCW pressure recording, to ensure that the saturation of the sample matches systemic arterial (left atrial) saturation, ie, if the catheter is correctly placed in the wedge position, the oxygen saturation of the blood distal to the catheter should be very high (see text, Figure 5).

Another problem with PCW pressure measurements is over-inflation or excessive advancement of the balloon, which

Fig. 5—Left panel: Balloon flotation catheter recordings of pulmonary arterial (PA) and right ventricular (RV) pressure in a patient with pulmonary hypertension. Right panel: Recording of the same PA pressure after inflation of balloon, mistakenly labeled as pulmonary capillary wedge pressure (PCW). Note the dashed vertical lines depicting the peak PA and purported PCW pressure tracings, which occur at the same time in the cardiac cycle. Also note the lack of a and v waves in the purported PCW recording. Measurement of arterial saturation from blood withdrawn from the distal catheter port demonstrated a saturation of 74%, with simultaneous arterial sample measured at 99%. If this had been an actual PCW recording, oxygen saturation from the distal catheter port would also have been 99%. Also, since the v waves in a true PCW recording are transmitted waves, the peaks in v waves would have occurred later than the peak PA pressure waves. (I, AVF, V = electrocardiogram leads.) (Images courtesy of Blaufuss Multimedia Laboratories, San Francisco, CA.)
pulmonary arterial hypertension, recognizing that in some patients they do occur simultaneously?

**Dr Badesch:** I would suggest looking for physical exam findings that suggest pulmonary hypertension or pulmonary fibrosis, and then using echocardiography to support or refine the diagnosis of pulmonary hypertension. A right-heart catheterization can be done to confirm the presence of pulmonary hypertension. The diffusing capacity can fall in either pulmonary fibrosis or pulmonary hypertension, but if it falls in isolation, meaning that the lung volumes are normal, it may suggest the presence of pulmonary hypertension.

**Dr McLaughlin:** Would the pulmonary function test then be an appropriate screening tool to perform on an annual basis in the scleroderma population?

**Dr Badesch:** I think it is very reasonable to follow the PFTs regularly. If you see an isolated fall in the diffusing capacity this should raise the possibility and lead to further evaluation, perhaps with an echocardiogram.

**Dr Seibold:** The pearls are that virtually all scleroderma patients who have pulmonary arterial hypertension have a diffusing capacity less than 55% of predicted. There are a couple of data sets that argue that when the percent of forced vital capacity (FVC) is compared with the percent of DLCO, if that ratio is elevated, it also enriches for the diagnosis of pulmonary arterial hypertension. One published series suggests a ratio of greater than 1.4. Our own data at our center shows a ratio of greater than 1.8.

**Dr McLaughlin:** Is there a population that should have echocardiography on a regular basis?

**Dr Badesch:** Yes. We might want to step back a step. Before I said that pulmonary arterial hypertension patients are typically dyspneic and sometimes clinical dyspnea on exertion is missed in rheumatologic practice. Scleroderma patients have a chronic catabolic disease; they tend to have ambulation difficulties, they tend to become very sedentary for orthopedic and musculoskeletal and peripheral vascular reasons, complicating their scleroderma. So they don’t typically present complaining of dyspnea on exertion. And I think that rheumatologists probably as a rule tend to back into this diagnosis through regular performance of pulmonary function testing. And it seems quite reasonable to recommend annual pulmonary function testing as a minimum interval, across the board for all scleroderma patients, probably more frequently, if you were following someone early with active inflammatory fibrotic disease. It also follows that if the best screening test for pulmonary arterial hypertension is a Doppler echocardiogram, it is appropriate to obtain a baseline study in all patients with scleroderma, and that this test might also be repeated at some minimum interval. I don’t think that we have the trial data that exactly validate what the standard of clinical practice should be. One argument should be that if you are doing pulmonary function testing and you see changes in the diffusing capacity, that might trigger repeat of the Doppler echocardiogram. Another argument might be that repeat Doppler echocardiograms might be done at about the same interval as repeat pulmonary function tests.

**Dr McLaughlin:** What do you do in your practice, Jim?

**Dr Seibold:** I look at the pulmonary function test as the outcome and turn to the Doppler echo as a measure of process. We get baseline echoes on as many patients as we can, but the decision to repeat is usually not triggered by time interval but by some index of suspicion, either clinical dyspnea or a change in the pulmonary function test.

**Dr McLaughlin:** And Ginny, what do you do in your practice?

**Dr Steen:** I think that is exactly what I do. I probably do not repeat the PFT yearly in everyone if they have normal diffusing capacity or only mildly decreased DLCO. On the other hand, if they already have a diffusing capacity of 60 to 65% and they have had 10 years of disease, then following PFT’s on a yearly basis would be helpful at least to detect changes that would precipitate doing an echocardiogram. Many patients have echocardiograms that show mild pulmonary hypertension, which is in the range where the echo is difficult to interpret. Since we don’t know how many of those are real pulmonary hypertension versus false positives, I think it is important to keep that in mind and to proceed to catheterization when you find mild pulmonary hypertension rather than jumping ahead and making a diagnosis of this deadly disease. I know we all have had experiences where we have an echo that says that the pulmonary artery pressures are 40 and you get all worried and nervous and you do a cath and the results are totally normal.

**Dr Badesch:** My impression is that follow-up and screening for pulmonary hypertension in the rheumatology and internal medicine community are probably not as stringent as what we have heard from Jim and Ginny. My sense is that by the time patients get referred to us for the evaluation and treatment of pulmonary hypertension they often have relatively advanced disease.

**Dr Seibold:** I agree. I think there is a disconnect between the way the true scleroderma expert approaches this and the way the community rheumatologist/internist approaches this. Lacking a pharmacoeconomic or costs of care study to actually validate it, I tend to come down in favor of a recommendation of a minimum annual interval. I agree that there are subsets of patients who don’t change much over time. But if we are looking at a rate of transition from nonpulmonary hypertension to pulmonary hypertension of any level that may approach 5% of patients per year, that is a rather high incidence and I think that would justify a blanket recommendation for annual pulmonary function testing.

**Dr McLaughlin:** And I think this is all more an issue now that we have effective therapies. Perhaps 10 or 15 years ago rheumatologists were not screening because frankly there was...
Dr Badesch: That’s a good question. Our experience mimics you want to comment on that?

Dr McLaughlin: I’d like to talk about proceeding with a heart catheterization to further evaluate patients who have pulmonary hypertension on an echocardiogram. One thing that is always important in looking at pulmonary hypertension patients is testing for vasoreactivity. And the scleroderma population, at least in my experience, is very rarely vasoreactive and so I am frequently asked by rheumatologists “Why do we have to cath in the first place?” Dave, do you want to comment on that?

Dr Badesch: That’s a good question. Our experience mimics yours somewhat in that I think the likelihood of acute vasoreactivity is lower in the population with scleroderma than in primary pulmonary hypertension. I still think that cardiac catheterization plays an important role in evaluation of these patients. I think that establishing their baseline hemodynamics, or ruling out the rare patient with an intercardiac shunt or some other lesion that is contributing to their development of pulmonary hypertension, is important. Furthermore, in patients who are failing despite the best available medical therapy, it may be important to repeat the cardiac catheterization to confirm that it is worsening of their pulmonary hypertension that is accounting for their symptoms. In that situation, comparing the current hemodynamics to their baseline results can be very helpful. So, I still feel that right-heart catheterization plays a role in these patients, but it may not be so much in terms of evaluating vasoreactivity as in establishing a baseline, ruling out other contributing factors, and then having that information available for future comparison.

Dr McLaughlin: The other important measurement on the right-heart cath, particularly in this patient population, is wedge pressure or left ventricular end-diastolic pressure. This patient population tends to be older than the primary pulmonary hypertension population, they tend to have more concomitant illnesses, such as hypertension, and they may in fact have mild pulmonary hypertension on an echocardiogram that is really the result of systemic hypertension and left ventricular hypertrophy and elevation of LVEDP causing their pulmonary hypertension. So it is also crucial in securing the correct diagnosis and subsequently the correct treatment for these patients.

Dr Seibold: If I had to make a quick list about why one should be willing to do right-heart catheterization in scleroderma it would be 1) to confirm and to precisely quantify the diagnosis; 2) to exclude the possibility of occult left ventricular diastolic failure; and 3) to exclude a component of concomitant cardiac problems. In around 20% of the caths that we do here, we frequently find that the aortic valvular lesions are a little bit worse than was suspected, or we find mitral valve pathology, or something along those lines that truly influences our approach to therapy. Fourth on the list would be that the echo is not a perfect test. It is relatively imprecise in those that have estimated pulmonary artery systolic pressures less than 40. And there is a relatively substantial group of patients, maybe as many as 20%, who lack a tricuspid jet and one cannot get a reliable estimate of pulmonary artery systolic pressure by Doppler. So, that would be the complete list. There is no question that rheumatologists are not requesting right-heart catheterizations by their consultants frequently enough.

Dr McLaughlin: Why don’t we move along to those therapies? David, you were the principal investigator of the first trial of Pulmonary Arterial Hypertension in the Scleroderma Spectrum of Diseases with Flolan. Do you want to summarize the very impressive results of that trial for the group?

Dr Badesch: As you know, prostacyclin was initially developed for patients with primary pulmonary hypertension and we saw an improvement in exercise capacity, cardiopulmonary hemodynamics, and survival in a 12-week study. We attempted to replicate that study in the scleroderma population and what we found was that prostacyclin did in fact improve the exercise capacity and cardiopulmonary hemodynamics similarly to the way that it had in the population with primary pulmonary hypertension. We did not see a survival benefit over the three-month course of that study, but the study was not powered to detect a survival benefit. I believe that the study of prostacyclin in patients with scleroderma-associated pulmonary hypertension has led to the inclusion of such patients in the subsequent trials of therapeutic agents for pulmonary hypertension.

Dr McLaughlin: It is important to point out what the prognosis is of scleroderma complicated by pulmonary hypertension in the absence of any treatment at all. It is a horrific survival curve.

Dr Badesch: In looking at several studies done prior to the use of prostacyclin in these patients, it appears as though the two-year survival rate was in the range of 40 to 55% or so, in patients who developed pulmonary hypertension as a complication of scleroderma disease.

Dr Steen: That has certainly been our experience. But we have to remember that previously the diagnoses have been made so late that the only time the diagnosis was made really was when patients had right-heart failure and clear-cut classic clinical pulmonary hypertension. Without treatment, even to survive two years for many patients was just unheard of. With the use of prostacyclin, my patients have had a much better survival rate and quality of life, even when the diagnosis is not made until the patient has right-heart failure.

Dr McLaughlin: One of the problems that the scleroderma population sometimes has with prostacyclin is difficulty mix-
ing. Because many of them have severe Raynaud’s and digital ulcers and sometimes even amputations, this can be problematic. That is one of the reasons why the subcutaneous prostacyclin analogue, treprostinil, which has recently been FDA-approved, may be useful in those patients. The scleroderma patients were included in the double-blind placebo-controlled randomized study of subcutaneous treprostinil and indeed benefited. Sometimes, however, that drug is difficult to use because of pain at the infusion site. Jim, you mentioned that there were three FDA-approved drugs. The third one is an oral therapy, bosentan. Would you like to comment on your experience with that so far? And perhaps even how the advent of an oral therapy has changed practice patterns that lead to earlier screening and diagnosis?

**Dr Seibold:** There is no question that the logistical convenience of an oral therapy really revolutionizes the clinical approach. Prostacyclin is expensive, it is relatively cumbersome, it has more than a certain level of day-to-day adverse effects that impact the quality of life. I agree with you that the administration of treprostinil in the whole scheme of things will be more convenient for scleroderma patients and they will be a little bit better able to handle that.

**Dr Badesch:** The other important thing to point out is that the mechanism of action of bosentan is considerably different from that of prostacyclin. Endothelin levels may be increased in some patients with scleroderma, and using an endothelin receptor antagonist in that situation may make particular sense, beyond even what you might expect in patients with pulmonary hypertension. So, it is particularly attractive on a theoretical basis to block endothelin in patients with scleroderma and scleroderma-related pulmonary hypertension. In a randomized and placebo-controlled study involving over 200 patients with primary pulmonary hypertension and pulmonary hypertension occurring in association with collagen vascular disease, bosentan-treated patients demonstrated better activity tolerance, as assessed by the 6-minute walk test, than patients receiving placebo. The drug seems to be relatively well tolerated although it is important to mention the side effects that have been seen to date. It can cause an elevation in liver function tests and this mandates following liver function tests on a regular basis. In fact, the FDA has mandated testing at least monthly. The drug has the potential to be teratogenic and therefore contraception is very important. It may cause male infertility and young male patients should be informed of that prior to beginning the treatment. And finally, it can cause some mild anemia and at times some fluid retention.

**Dr McLaughlin:** Those are important points. Dave, would you like to speculate on the results in the scleroderma subpopulation BREATHE-1 trial, compared with the scleroderma population in your trial? Granted, it was a much smaller number in the BREATHE-1 trial, but they didn’t seem to obtain as much benefit in terms of exercise tolerance over the 16 weeks of that trial as the scleroderma patients treated with intravenous epoprostenol did in your trial. Any thoughts on that?

**Dr Badesch:** The data suggest that in the study of intravenous prostacyclin in patients with scleroderma-associated pulmonary hypertension, there was both an improvement in the treatment group and a decline in the control group that accounted for the difference between study groups. In the BREATHE-1 study, when looking at the subgroup of patients with scleroderma-associated pulmonary hypertension, it appears as though bosentan may have contributed to the maintenance of stability while patients in the placebo arm continued to deteriorate. Now as you’ve mentioned, whether or not we can take away much of a message from that is a little in doubt because the relatively small number of patients with scleroderma included in the BREATHE-1 study. Whether or not bosentan can contribute to the same amount of symptomatic improvement or improvement in exercise capacity as prostacyclin in this population I think is still just little bit up in the air.

**Dr McLaughlin:** So, the drug has been commercially available for 7 or 8 months. Jim, Ginny, would you like to share your experience with it so far?

**Dr Seibold:** We were somewhat concerned when we saw the failure to improve in the scleroderma subset that was incorporated in the BREATHE-1 study, but suspect from our clinical use of the drug that that was an artifact of the relatively small sample size. We have about 65 scleroderma patients who are receiving bosentan currently. A large percentage of those patients, somewhere in the 80% range, have substantial, measurable, clinical improvement and improved exercise capacity. So we believe that more widespread use of the drug will validate that there is a positive clinical benefit from bosentan therapy.

**Dr McLaughlin:** That is an important point. The scleroderma population made up a very small percentage of these included in the BREATHE-1 trial and a much larger experience such as yours, Jim, is very important to delineate how effective this therapy is in this subpopulation.

**Dr Badesch:** I think it is important as we look toward the future to mention that we might begin to combine some of these different therapies in patients with pulmonary hypertension due to scleroderma and perhaps we will be using some form of prostacyclin preparation in combination with an endothelin receptor antagonist, a phosphodiesterase inhibitor, and perhaps oral L-arginine or a nitric oxide donor. Multimodality therapy that mimics the way we treat systemic hypertension or cancer might have a greater likelihood of a positive effect in patients with pulmonary hypertension due to scleroderma. It is important to note that my comments in this regard are speculative, and not yet supported by clinical studies.

**Dr McLaughlin:** I agree with that, David, and certainly combination therapy is where we are going. The scleroderma
patients were included in the BREATHE-2 trial, which looks at the combination of bosentan and prostacyclin in patients with severe pulmonary hypertension. Scleroderma patients are also being included in other clinical trials, specifically with the PDE5 inhibitor sildenafil and selective endothelin receptor antagonists. Dave, you also mentioned L-arginine; there is an international trial looking at L-arginine supplementation in patients with pulmonary arterial hypertension that also includes the scleroderma spectrum of diseases.

Dr Seibold: It should be emphasized that there is a level of scientific enthusiasm/optimism about the specificity of all these drugs in the scleroderma vascular lesion. We all recognize that scleroderma starts with vascular injury frequently expressing as dysfunctional vascular change, ie, Raynaud’s phenomenon, but the endothelial injury is important very early on. One consequence is diminished nitric oxide production. A second consequence is diminished prostacyclin synthase activity and lower prostacyclin levels. A third and potentially very important tissue response is increased endothelial production of endothelin, which has vasoconstrictive effects and a variety of proliferative and proinflammatory effects that may perpetuate and worsen the structural vascular injury. So all of these agents that are being discussed, from L-arginine through prostacyclin delivery systems through endothelin antagonists may have some level of specifically addressing a key pathophysiologic derangement of scleroderma.

Dr McLaughlin: We focus so much on the existence of pulmonary arterial hypertension in the scleroderma spectrum of diseases. Are there other rheumatologic diseases that are associated with pulmonary hypertension? I have seen patients with some different rheumatologic diseases, lupus, even just Sjögren’s syndrome, or polymyositis, present with pulmonary hypertension. Is that rare, or is that something rheumatologists should keep their eye out for?

Dr Steen: Well, certainly they are significantly less common than in scleroderma, but I think in the lupus population and the mixed connective disease population it is becoming more and more of a problem. In the other diseases, Sjögren’s and myositis and even rheumatoid arthritis, pulmonary hypertension is well documented and we have all had these patients, but the frequency is much less.

Dr McLaughlin: Dave, have you treated a number of patients with pulmonary hypertension and interstitial lung disease? Clearly that population exists. One thing we always worry about is the potential for a worsening in V-Q mismatch, and then sometimes we just tend to treat them for their pulmonary hypertension because there is nothing else to do. I have treated a number of patients like that and I can’t say that I have seen anyone develop worsening hypoxemia because of the V-Q mismatch. How about yourself?

Dr Badesch: Initially, we excluded patients with more than mild interstitial lung disease from the prostacyclin study, because of the concern that we would worsen ventilation perfusion mismatching. I have continued to be relatively cautious in my approach to those patients, but, as I am sure other centers have done, we have broadened the group of patients we will try to treat aggressively with prostacyclin and now bosentan. I agree with you that the worsening of ventilation perfusion mismatching is probably not as much of a problem as we expected it might be early on. I would add that in the population with both interstitial lung disease and pulmonary hypertension, the early consideration of the possibility of lung transplantation is an important aspect of their care. Some of these patients may not prove to be good candidates for lung transplantation because of esophageal dysmotility and reflux and the risk of aspiration, but in the group of patients with both pulmonary hypertension and interstitial lung disease, it may be particularly important to consider the possibility of lung transplantation early on. What do you think, Jim, do you end up referring those patients for a transplant evaluation?

Dr Seibold: Dave, I really agree, but I can’t find a program that will accept my patients. The problem is that somewhere between 85% and 90% of these patients have esophageal dysmotility. So there are very few centers in the United States that are doing single lung transplantation in scleroderma at all, and there is a long list of centers that have automatically excluded scleroderma from consideration.

Dr McLaughlin: Would anyone like to make any closing remarks before we finish up?

Dr Badesch: I am pleased to see that patients with scleroderma-related pulmonary hypertension are being included in most of the studies now. And as Jim mentioned earlier, the level of enthusiasm for treating these patients has increased over time. I hope that we will continue to work collaboratively on clinical trials and toward improving the timely diagnosis of pulmonary hypertension and prompt initiation of appropriate therapy.

Dr Steen: I hope that in future studies we look for patients who have what I’d term pre-pulmonary hypertension, or are borderline, or at high risk, or whatever you want to call them, and see whether by very early aggressive treatment we might totally prevent or allay or delay the dangerous deadly consequences of this.

Dr Seibold: I would just like to express my appreciation and admiration to the group of collegial, high-quality investigators in cardiology and pulmonary medicine who have pushed the field of management options in pulmonary hypertension so far and so fast, and have made available so many different options for patients with scleroderma. It has been an astounding several years of productivity.

Dr McLaughlin: The one thing I want to emphasize from our discussion is that recognizing these patients is critical. We now have something that we can do for them. Early detection of pulmonary arterial hypertension in the scleroderma population might allow us to really have an impact on this devastating disease.
Vallerie McLaughlin, MD, Associate Professor of Medicine, Rush Presbyterian-St. Luke’s Medical Center, Chicago, Illinois, conducted this roundtable discussion. The panel included James R. Seibold, MD, Professor and Director, UMDNJ Scleroderma Program, New Brunswick, New Jersey; David B. Badesch, MD, Professor of Medicine and Clinical Director, Pulmonary Hypertension Center, University of Colorado Health Sciences Center, Denver, Colorado; and Virginia Steen, MD, Professor of Medicine, Georgetown University Medical Center, Washington, DC.

**Dr McLaughlin:** What do we think is the true incidence of pulmonary arterial hypertension in the scleroderma population?

**Dr Steen:** We first have to separate the different kinds of pulmonary hypertension that occur in scleroderma. Patients with limited scleroderma, or the CREST syndrome, as it is referred to, get primarily what we call vasculopathy or an isolated pulmonary hypertension unrelated to interstitial fibrosis, and it can occur in the very serious deadly form in up to as many as 20% of patients. Other patients, and it’s anywhere from 10% to 30%, will have some evidence of either potential pulmonary hypertension or mild pulmonary hypertension as evidenced by abnormal findings on pulmonary function tests (PFTs) or echocardiograms. Another patient population, those with diffuse scleroderma, is more likely to have the interstitial fibrosis and they can have pulmonary hypertension related to that. And then there is the group of patients sort of in between, those who have a little bit of pulmonary fibrosis and a little bit of pulmonary hypertension, and depending on the nuances of their disease, one seems to predominate.

**Dr Seibold:** Scleroderma generally segregates into a rapidly evolving widespread form called diffuse scleroderma. These patients have a fairly high risk of having an inflammatory pulmonary process that looks a lot like nonspecific interstitial pneumonitis and the early onset of interstitial fibrosis. These patients develop dyspnea and impaired exercise capacity that is a mixture of their established interstitial lung disease but is clinically exacerbated by the evolution of the pulmonary vascular lesion. At the other end of the spectrum, you have limited scleroderma patients who seem to be relatively spared, although not completely, from this whole dynamic of interstitial inflammation and fibrosis but who develop an isolated vasculopathy that really starts to become clinically relevant somewhere around the 10th year or so of disease. The educated guess here is that the pulmonary vascular or arteriolar lesion is universal, and it can progress slowly and show up as pulmonary arterial hypertension alone at later stages of limited scleroderma, but it is a cofactor in the morbidity of patients with interstitial lung disease, including diffuse scleroderma.

**Dr McLaughlin:** David, do you have any pearls on how one might differentiate pulmonary fibrosis from (continued on page 22)