EDITORIAL

Advancements in Diagnosis of Pulmonary Arterial Hypertension in Scleroderma

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Scleroderma is defined on the basis of skin involvement, but internal organ damage is the primary cause of decreased survival. Until recently, scleroderma renal crisis was almost uniformly fatal but, in the past 20 years, angiotensin-converting enzyme (ACE) inhibitors have made this manifestation treatable (1). Renal crisis now accounts for only 8% of scleroderma-related deaths compared with 32% prior to the use of ACE inhibitors. At present, lung disease is the major cause of death in scleroderma. Pulmonary fibrosis and pulmonary arterial hypertension (PAH) result in 50% of all scleroderma-related deaths. Prior to the availability of new therapies, PAH, like renal crisis, was almost always fatal (2). The 2-year survival rate was 50%, and almost no one lived 5 years.

Dramatic advances in the treatment of PAH have occurred following the introduction of new drugs. In 2000, epoprostenol, a continuous intravenous infusion of prostacyclin, was shown to significantly improve function and quality of life in scleroderma patients with severe (New York Heart Association class III/IV) PAH (3). Additionally, treprostinil (a continuous subcutaneous prostacyclin infusion), bosentan (an oral dual-receptor endothelin antagonist), and an inhaled form of iloprost have all been demonstrated to improve 6-minute walk distances compared with placebo treatment (4). These agents are not only potent vasodilators, but their long-term use may reverse the vascular process by remodeling the vessels. In the near future, these and other drugs will likely significantly improve the long-term survival of scleroderma patients with PAH.

In the absence of an effective treatment for PAH, patient management did not necessitate an aggressive pursuit of the diagnosis. As described by Hachulla and colleagues in this issue of *Arthritis & Rheumatism* (5), ways to identify patients who have PAH need to be pursued more rigorously. Patients with class III disease already have significant right heart damage, and thus, if we wait until then to treat patients, improved survival and reversibility of the disease process are unlikely. Early intervention could prevent, delay, or at least alleviate the disease.

Unlike idiopathic PAH, scleroderma-related PAH develops in a known population of patients. We need to identify risk factors for PAH and then monitor these patients closely, treating them before the disease becomes irreversible. Patients with severe, isolated PAH have a long history of Raynaud’s phenomenon, limited scleroderma, anticientromere antibody positivity, an extremely low diffusing capacity for carbon monoxide (DLco) (mean 39% of predicted), near-normal forced vital capacity (FVC), minimal fibrosis, and an FVC:DLco ratio of >1.8 at the time of the diagnosis (6). Morphometry studies show that intimal proliferation of pulmonary arteries correlates with disease duration, indicating that PAH develops over a long period of time (7).

Recently, we investigated pulmonary function tests over a 15–20-year time period before patients developed PAH (6). In these patients, the DLco decreased linearly from 80% of predicted to 40% of predicted at the time of diagnosis, while the FVC remained close to normal. These findings also indicate that PAH develops slowly, over many years, in scleroderma. The availability of treatments for PAH has led to closer evaluation of all scleroderma patients. Since then, we have observed that PAH occurs more commonly in patients with diffuse systemic sclerosis and pulmonary interstitial fibrosis than previously recognized. Patients with antitopoisomerase antibody and severe interstitial fibrosis develop hypoxia-driven PAH. Such patients usually have a very low FVC and a DLco that is decreased to a similar degree, so the FVC:DLco ratio remains close to 1. Additionally, there are patients with an antinucleolar antibody who have moderate interstitial fibrosis and then later develop severe PAH out of proportion to the degree of fibrosis. These patients have
vasculopathy in addition to the fibrosis (8). The FVC:DLco ratio is similar to that seen in pure vasculopathy, i.e., >1.8.

Echocardiography has been the primary tool for identification of patients who potentially have PAH. Screening demonstrates that 20–65% of patients have elevated echo Doppler pressures. This variability relates primarily to differences in the patient population studied and the definition of a “positive” echocardiography result (9). Hachulla and colleagues prospectively studied echocardiograms in 709 systemic sclerosis patients from centers in France (5). Using an algorithm that included velocity of tricuspid regurgitation (VTR) from the echo Doppler, dyspnea, and right heart catheterization, they identified 8% of their patients who were not previously known to have PAH. The use of the right heart catheterization is absolutely necessary to confirm the presence of PAH.

The patients studied by Huchalla et al fulfilled the formal “definition” of PAH with a mean pulmonary artery pressure (PAP) of >25 mm Hg at rest or >30 mm Hg with exercise on right heart catheterization. However, the level of the mean PAP on right heart catheterization was <30 mm Hg in two-thirds of the patients, and 5 of the patients had increased PAP only with exercise. Since patients who die from PAH usually present with PAP >50 mm Hg, the significance of these low-level pressures is unclear. In our retrospective case-matched controlled study of 106 patients with PAH, the mean of the echo Doppler pulmonary artery systolic pressure (PASP) 4 years prior to the diagnosis of severe PAH was only slightly increased, with a mean value of 34 mm Hg (6). This value was not significantly different from the value of 29 mm Hg in the control patients. Some of the patients studied had normal echocardiographic results 6 months prior to the diagnosis of severe PAH. Thus, while the DLco is slowly decreasing for many years prior to PAH, it is not clear whether the PAP is increasing slowly or whether there is some trigger that causes a relatively sudden increase in the pressure.

Hachulla et al used exercise during the right heart catheterization to diagnose PAH in 5 patients. In our investigations, we found increased PASP with exercise in half of the high-risk patients studied by echocardiography. Grunig et al showed that almost all patients with the gene for familial PAH had exercise-induced PAH, but there is incomplete penetrance of the gene for PAH (10). Is scleroderma similar? Do patients have abnormal increases in PAP at rest or with exercise and yet fail to develop severe PAH? We do not yet know the combination of findings, such as dyspnea, very low DLco, high FVC:DLco ratio, increased VTR at rest, increased PASP at rest, or exercise, that results in the greatest risk for developing future severe, fatal PAH. MacGregor et al followed up a group of systemic sclerosis patients and found that 65% with a PASP >35 mm Hg on echocardiography did not have any deterioration at 3 years (11). Twenty percent of the patients who had increasing pulmonary pressures died during this time period. Hachulla and colleagues agree that the outcome of their patients is still not known, and they plan to follow up these patients closely in the future (5).

These studies confirm that scleroderma patients with “pre,” “early,” or “mild” PAH can be identified, and such cases are probably more common than previously recognized. However, the most important issues are the natural history of the disease in these patients and whether treatment with new medications will prevent, delay, or alleviate the severe, irreversible, and deadly forms of PAH. It is important that we identify the most informative risk factors for severe disease so that a controlled, early-intervention study with high-risk patients can be performed. At this point, it is premature to assume that all patients with mild increases in PAH, such as those described in the report by Hachulla et al, require treatment. These patients may have deterioration or improvement in their symptoms and 6-minute walk distance, since we do not yet know the natural history of their disease.

Like Hachulla and colleagues, we have initiated a multicenter study to investigate these issues. The Pulmonary Hypertension Assessment Registry Of Scleroderma (PHAROS) is a multicenter study that will further characterize high-risk patients. In the PHAROS study, patients with very low DLco, increased PASP, or increased FVC:DLco ratio will be followed up to determine who develops definite PAH by right heart catheterization and what the best predictors are. Patients will also be followed up after the initiation of treatment to determine the long-term outcome, morbidity, and mortality of patients treated with the new therapies.

We have not yet developed therapy for the overall treatment of scleroderma, but we can work toward improving outcome in patients with severe lung disease. If we can be as successful with the treatment of PAH as we have been with the treatment of scleroderma renal crisis, we will significantly improve the overall outcome of this difficult disease.

REFERENCES
1. Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of


