Editorial

Screening for Pulmonary Hypertension in Scleroderma: How and When to Look?

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a clinical-physiologic syndrome characterized by elevated pulmonary artery pressure (PAP), as defined by mean PAP > 25 mm Hg, or a systolic PAP > 35 mm Hg. PH most commonly arises due to underlying cardiopulmonary disease, but may also be due to pulmonary thromboembolic disease, or to intrinsic disease of the pulmonary microcirculation, which is termed pulmonary arterial hypertension (PAH)[1]. Regardless of the clinical setting, PH is often a severe illness that manifests symptoms of dyspnea, fatigue, and peripheral edema; progresses to right heart failure; and is associated with a high risk of mortality. Indeed, in many types of PAH, including idiopathic (IPAH, formerly known as primary PH) and PAH associated with connective tissue disease (CTD) such as scleroderma, average survival in the absence of therapy is only 2 to 3 years.

Pulmonary complications of scleroderma contribute importantly to the morbidity and mortality of scleroderma. Indeed, pulmonary disease has become the major cause of mortality in patients with scleroderma[2,3]. Among pulmonary complications, scleroderma-associated PAH is the most common. Although PAH may be present pathologically in perhaps half of scleroderma patients, PAH clinically affects 10–20%[4-7]. Most studies[7], including the report by Chang and colleagues in the current issue of *The Journal*[8], suggest PAH is more common in limited versus systemic scleroderma. PAH most commonly arises in patients with longstanding, established scleroderma, the clinical onset of PAH typically being delayed 10–15 years after onset of the more common clinical features of Raynaud's phenomenon and esophageal dysmotility. Most importantly, PAH in scleroderma is often associated with significant and disabling dyspnea, as well as significant mortality[9,10]. Besides isolated PAH, patients with scleroderma can also develop PH due to other conditions, including pulmonary fibrosis, pulmonary thromboembolic disease, and heart disease.

THERAPY OF PAH

Over the past 10 years, an increasing number of novel therapies for PAH have been studied in randomized clinical trials, and many are available for clinical use in the treatment of patients with PAH, including IPAH and scleroderma-associated PAH. Current therapeutic options for PAH include prostacyclin derivatives, such as intravenous epoprostenol, subcutaneous and intravenous treprostinil, and inhaled iloprost, as well as oral therapies, such as the nonselective endothelin-receptor antagonist, bosentan, and the phosphodiesterase V inhibitor, sildenafil[11,12]. Therapy with many of these agents is associated with improvements in pulmonary hemodynamics, symptoms, and exercise capacity[11,12]. Moreover, therapy with intravenous epoprostenol and oral bosentan is associated with improved survival in patients with IPAH[13], although a survival benefit has not been shown for other patients with PAH, including scleroderma-associated PAH.

DIAGNOSIS OF PH IN SCLERODERMA

Given the availability of safe, effective therapeutic options for patients with PAH, the accurate and timely diagnosis of PAH in patients with scleroderma has assumed greater importance. However, it remains uncertain how best to identify these patients. Can patients with scleroderma depend on their physicians to recognize the clinical manifestations of PH and to make a clinical diagnosis of PH? Unfortunately, the answer appears to be "No." A clinical diagnosis of PH is often delayed 12–18 months because of the nonspecific nature of the symptoms. As well, physical examination findings suggestive of PH, such as increased intensity of the pulmonic component (P2) of the 2nd heart sound, a left parasternal right-ventricular heave, and elevated jugular venous pressure, can be subtle and easily overlooked. In addition, scleroderma patients are often limited on exertion by other manifestations, including pulmonary

See Natural history of mild-moderate pulmonary hypertension and the risk factors for severe pulmonary hypertension in scleroderma, *page 269*

fibrosis and arthritis, and other common conditions, e.g., ischemic heart disease and asthma. Indeed, many patients with PAH have historically been diagnosed at more advanced, World Health Organization functional class III and IV stages of their disease.

As a result, screening for the PH in patients with scleroderma has been advocated in clinical practice guidelines[1]. The definitive diagnostic test for PH is right heart catheterization and invasive measurement of PAP. However, this is neither practical nor cost-effective as a screening test. The pulmonary diffusing capacity for carbon monoxide (DLCO) is a reproducible test of pulmonary gas exchange that is cheap, simple to perform, and widely available. In patients with scleroderma, a markedly reduced DLCO is common at the time of the diagnosis of isolated PAH[5,14]. Moreover, reduced DLCO on serial testing in scleroderma patients may anticipate the onset of clinical PAH. For example, the incidence of PAH was 20% within 5 years in patients with limited scleroderma and reduced DLCO, and increased to 35% in patients with DLCO < 55% of the predicted level[15]. In another study, scleroderma patients with PAH at 5 years prior to diagnosis of PAH had DLCO (mean 52% of predicted) lower than scleroderma patients who did not subsequently develop PAH (mean DLCO > 80% of predicted)[16]. Moreover, in some scleroderma-PAH patients followed for 15 years prior to diagnosis of PAH, DLCO declined progressively from 80% of predicted 15 years before PAH to 45% of predicted at the time of diagnosis of PAH, while remaining stable at > 80% in scleroderma patients not developing PAH. As a result, serial DLCO testing in scleroderma patients has been recommended for early detection of PAH[1]. It should be noted that a reduced DLCO is not specific for significant PH, as parenchymal disease, e.g., pulmonary fibrosis or emphysema, can also be associated with reduced DLCO.

Doppler echocardiography has been proposed as a noninvasive screening test for PH in scleroderma. Indirect signs of hemodynamically significant PH include right ventricular (RV) hypertrophy and enlargement, right atrial enlargement, paradoxical motion of the interventricular septum, and diastolic left ventricular compression. PAP cannot be directly measured by echocardiography, but RV systolic pressure (RVSP), a surrogate for systolic PAP, can be estimated by echo. A moderate-high correlation (0.57–0.93) has been reported between transthoracic echo estimation of RVSP and systolic PAP measured via right heart catheterization[14]. RVSP is calculated using the formula: RVSP = 4V2 + RAP, based on measurement of velocity (V) of the systolic tricuspid regurgitation (TR) jet. The right atrial pressure (RAP) can be clinically assessed from jugular venous distension, or estimated based on respiratory variation of the inferior vena cava during echocardiography, or a standardized value can be used. Unfortunately, estimated RAP can vary widely, from 5 to 25 mm Hg. In addition, whereas a TR jet can be detected in the majority (74%) of patients with PH, absence of a detectable Doppler TR jet did not rule out significant PH[17].

Among a broad population of healthy male and female control subjects aged from 1 to 89 years, average RVSP was 28 ± 5 mm Hg, but values ranged from 15 to 57 mm Hg, being higher in older subjects with higher body mass index[18]. The European Society of Cardiology has published guidelines for the definition and classification of PH severity on echocardiographic criteria[19]. Based on their definition of normal RVSP (< 35 mm Hg, or TR velocity < 2.7 m/s), a number of patients may be falsely diagnosed with PH. Moreover, the definitions of mild PH (RVSP 36–50 mm Hg, TR velocity 2.8–3.4 m/s), and moderate-severe PH (RVSP > 50 mm Hg, TR velocity > 3.4 m/s) remain poorly validated against clinical features or prognosis. As well, there are few data on intraobserver and interobserver variability and reproducibility of RVSP assessment over time. This limitation is significant, as brought out in the report by Chang, *et al*, in which 17% of patients with "mild-moderate" PH (defined by the authors as RVSP 36–55 mm Hg) progressed to "severe" PH (RVSP > 55 mm Hg), but 16% showed "improvement" with either normal RVSP or undetectable TR on repeat echocardiography. Although these findings may indicate worsening or improvement over time, they more likely highlight the lack of data on (1) reliable echocardiographic criteria defining the presence of hemodynamically significant PH, (2) the clinical correlates of echocardiographically determined PH, and (3) the natural history of PH over time.

As a final caveat, echocardiography may indicate the presence of PH, but does not diagnose PAH, which requires a systematic clinical and laboratory assessment for underlying causes of PH. As such, echocardiographic studies of the prevalence of PH in patients with scleroderma[20] should not be mistakenly used as indications of the number of patients who will benefit from pharmacologic therapy for PAH.

In summary, isolated PAH is an important complication of scleroderma, for which safe and effective, novel therapies are available. Recent clinical practice guidelines suggest both serial DLCO measurement and routine echocardiography in order to screen for PH in scleroderma. However, such a strategy remains poorly validated and subject to many limitations. New echocardiographic methods are emerging that will likely facilitate the future noninvasive assessment of patients with PH. For example, novel contrast agents may improve the accuracy and reproducibility of the TR Doppler signal. Real-time 3-dimensional echocardiography, tissue Doppler assessment, and strain rate imaging may increase the sensitivity for detection of RV dysfunction. As experience with newer imaging modalities increases and they are rigorously assessed in future clinical studies, novel noninvasive technologies for the assessment of PH and RV function will help clinicians determine when and how scleroder-

ma patients should be screened for PH, and how that information should be used in therapeutic decision-making.

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