Pulmonary Circulation on the Crossroads Between the Left and Right Heart in Systemic Sclerosis

A Clinical Challenge for Cardiologists and Rheumatologists

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KEYWORDS

• Pulmonary hypertension • Systemic sclerosis • Right heart • Pulmonary circulation

KEY POINTS

- Pulmonary hypertension is frequent in systemic sclerosis and is associated with poor prognosis.
- Pulmonary hypertension occurs as a result of a pulmonary arteriopathy but also can be a consequence of interstitial lung disease and/or left heart involvement.
- These phenotypes may be difficult to differentiate and often overlap, complicating both the diagnosis and the follow-up.
- An integrated multidisciplinary approach, including a rheumatologist, cardiologist, and pulmonologist, is mandatory to improve patients' management.

INTRODUCTION

Systemic sclerosis (SSc) is a complex multiorgan immune-mediated disease characterized by fibrosis of the skin and internal organs and by vasculopathy.[1,2] Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mm Hg at rest, as assessed by right heart catheterization

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(RHC).[3] In patients with SSc, PH can be the result of an isolated pulmonary arteriopathy, determining a condition of pulmonary arterial hypertension (PAH), a relevant cause of morbidity in SSc.[4] It is included in the first group of the new clinical classification of PH, characterized by precapillary PH with pulmonary artery wedge pressure (PAWP) less than or equal to 15 mm Hg.[3]

Elevated pulmonary artery pressure (PAP) in SSc also may occur, however, as a consequence of interstitial lung disease (ILD) or left ventricular (LV) systolic and/or diastolic dysfunction.[5] In these situations, the term PAH is not correct and the more generic term PH should be used. It is also true that an overlap between the different etiologies of PH is possible and likely frequent in SSc patients; therefore, it is important to distinguish the hemodynamic contribution of the diverse mechanisms, which are linked to different therapeutic and prognostic correlates.

DIFFERENT ETIOLOGIES OF PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

The pathophysiology of the mechanisms leading to the onset of PH is complex, with interplay between inflammation process, autoimmunity, and systemic vasculopathy. Some overlap within different subtypes of PH may exist, because this condition shows a pathophysiologic continuum,[6] which is particularly evident in SSc patients, who can present with several forms of PH during the course of the disease. The most typical form was traditionally believed PAH, group I, according to the most recent European and American guidelines.[3,7] Group II (PH due to left heart disease) and group III (PH due to lung disease and/or hypoxia), however, also can be present in SSc patients. In the Pulmonary Hypertension Assessment of Recognition of Outcomes Registry of Scleroderma (PHAROS), SSc patients with PH were classified as group I PAH in 69% of cases, group II PH in 10% of cases, and group III PH in 21% of patients.[8] Rarely, pulmonary veno-occlusive disease (PVOD) may also be present in SSc patients.[9]

Pulmonary Arterial Hypertension

According to the 2015 European Guidelines[3] on PH, PAH is defined by a mean PAP (mPAP) of greater than or equal to 25 mm Hg with a PAWP of less than or equal to 15 mm Hg at RHC and a pulmonary vascular resistance (PVR) of greater than 3 Wood units with either normal or reduced cardiac output (CO)[10] in absence of other forms of precapillary PH. The prevalence of PAH in SSc is reported as 8% to 12% in the European League Against Rheumatism (EULAR) Scleroderma Trials and Research Group database.[2] Nevertheless, a recent study confirms a lower prevalence of PH in Italy compared with Anglo-Saxon cohorts.[11] Moreover, it ranges from 0.5% to 15% based on RHC diagnosis in different studies.[12–14] PAH greatly affects morbidity and mortality in these patients, responsible for almost 30% of SSc-related deaths.[2] SSc patients with PAH have a significantly worse 3-year survival compared with SSc patients without PAH.[15] It is debated whether SSc-PAH is less responsive to specific vasoactive therapies than patients with idiopathic PAH,[16–18] because data from randomized trials indicate that more intensive treatments—especially combination therapy—would gain similar benefits in SSc-associated PAH compared with other forms of PAH.[19–23] One of the reasons given to explain the suboptimal efficacy of PAH treatment, highlighted in some studies, is that drugs are started too late in the course of the disease, due to delay in diagnosis. Signs and symptoms of PAH are generally nonspecific and underestimated, because they are often not discriminated from general SSc symptoms, postponing the diagnosis to more advanced phases of the disease, characterized by structural and irreversible damage of the pulmonary vasculature. It has been shown that patients identified with PAH via an active screening program have a better prognosis than those diagnosed in the course of routine clinical practice,[24] underlining the potential benefit of early diagnosis and early intervention in the course of the pathologic process.

PVOD is a rare form of PH, with a prevalence of 0.1 to 0.2 per million persons per year. From a histologic point of view it is characterized by fibrotic occlusion of postcapillary venules. In the 2015 European Society of Cardiology Guidelines[3], PVOD has been classified, together with pulmonary capillary hemangiomatosis, in a specific subgroup next to PAH, because of the similar pathologic, genetic and clinical features.[3] PVOD may complicate SSc,[25,26] although a recent study showed that radiological signs of PVOD seem less common in SSc-PAH than previous reports suggest. They correlate, however, with a worse prognosis, and clinicians should be aware of the risk of noncardiogenic pulmonary edema induced by PAH-specific therapy.[9] Portal hypertension can also occur in patients with hepatobiliary involvement, which is not infrequent in SSc.[5,27]

Pulmonary Hypertension Due to Lung Disease

ILD is common in both diffuse and limited cutaneous SSc, with clinical manifestations in approximately 40% of patients.[28] When ILD is