Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

Yon K. Sung, MD[a], Lorinda Chung, MD, MS[b,c,*]

KEYWORDS

- Pulmonary hypertension • Pulmonary arterial hypertension
- Connective tissue disease • Systemic sclerosis • Systemic lupus erythematosus
- Mixed connective tissue disease

KEY POINTS

- Systemic sclerosis is the most common underlying disease associated with connective tissue disease–associated pulmonary arterial hypertension (CTD-PAH), and has the poorest prognosis.
- Patients with suspected PAH should undergo a complete evaluation, including right heart catheterization (RHC) and testing to rule out other possible causes of pulmonary hypertension.
- Patients with RHC-confirmed PAH should be treated with PAH-specific therapies. However, the role of immunosuppression for the treatment of CTD-PAH is unclear.
- The development of robust screening algorithms may lead to earlier diagnosis and improved survival in systemic sclerosis-PAH.

INTRODUCTION

Pulmonary hypertension (PH) is a disease that is strictly defined by having a resting mean pulmonary artery pressure (mPAP) of 25 mm Hg or greater as measured by right heart catheterization (RHC).[1] The causes of PH are diverse, but regardless of the cause, chronic elevation of pulmonary arterial pressures can lead to right ventricular

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[a] Division of Pulmonary and Critical Care Medicine, Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA; [b] Division of Rheumatology and Immunology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA; [c] Division of Rheumatology, VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, USA

* Corresponding author. VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304.

E-mail address: shauwei@stanford.edu

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strain, dilatation, dysfunction, and ultimately right heart failure. Historically, PH was classified as either primary or secondary PH. However, it was recognized that this classification scheme was insufficient for distinguishing between different types of PH. At the second World Symposium on PH in 1998, the causes of PH were categorized into 5 groups: group 1, pulmonary arterial hypertension (PAH); group 2, PH secondary to left heart disease; group 3, PH owing to chronic lung disease and/or hypoxia; group 4, chronic thromboembolic PH; and group 5, PH owing to unclear multifactorial mechanisms.[2] Over the years, the classification scheme has been updated to reflect the growing understanding of the pathophysiology of different types of PH (**Box 1**).

PAH (previously primary PH) is a subset of PH that is characterized by remodeling of the small to medium sized pulmonary arterioles. It is defined as a mPAP of 25 mm Hg or greater, a pulmonary artery wedge pressure of 15 mm Hg or less, and a pulmonary vascular resistance of 3 or more Wood units, as measured by RHC.[1] Pathologically, it is characterized by eccentric and obliterative thickening of the intima and media, which are composed of mainly smooth muscle cells and myofibroblasts. The hallmark of PAH is the plexiform lesion, a disorganized growth of endothelial cells that form false channels.[3] Before the development of PAH-specific therapies, the prognosis of PAH was poor with a 1-year survival of 69% and a 5-year survival of 38%.[4]

It is well-known that patients with connective tissue diseases (CTD) are at increased risk for developing group 1 PAH. As demonstrated in large cohort studies, the CTD that is most commonly associated with PAH is systemic sclerosis (SSc).[5,6] Other associated CTDs are systemic lupus erythematosus (SLE), mixed CTD (MCTD), and less commonly, inflammatory myopathies (polymyositis [PM] and dermatomyositis), primary Sjogren's syndrome (pSS), rheumatoid arthritis (RA), and undifferentiated CTD.

As a group, the survival of patients with CTD-PAH is poorer compared with patients with other types of PAH. With increasing awareness of the morbidity and mortality associated with PAH in CTDs, there have been an increasing number of studies examining the burden of disease, pathophysiology, and risk factors associated with developing PAH in CTDs. Furthermore, because SSc is the most common CTD associated with PAH, recent studies have investigated screening methods for early detection of PAH in SSc with the hopes of decreasing morbidity and improving survival.

In this review, we summarize the current understanding of the epidemiology, pathophysiology, and known risk factors for CTD-PAH. Clinical presentation, evaluation, treatment, and prognosis are also reviewed. Although the focus of this review will be on group 1 PAH, it should be noted that patients with CTD are also at risk for developing other forms of PH. In particular, patients with CTD often have interstitial lung disease (ILD) and thus may have group 3 PH. Left heart dysfunction is also common in CTD, especially in SSc, so group 2 PH should be considered. Also, although a rare entity, pulmonary venoocclusive disease can be seen in patients with CTD. It is important to distinguish between these groups because the categorization has implications for prognosis and treatment.

EPIDEMIOLOGY OF CONNECTIVE TISSUE DISEASE–ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

Much of the data on the epidemiology of PAH has been obtained through multicenter national and international registries. Registries that have included patients with CTD-PAH include the French, US REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management), US Pulmonary Hypertension Connection Registry, Spanish, new Chinese, and COMPERA (European). In these registries, the percentage of PAH patients with CTD-PAH ranges from 15% to 30%.[7] As stated, the majority of patients