Editorial

Early Detection of Pulmonary Hypertension in Connective Tissue Disease

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Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic state that is defined by an increase in mean pulmonary arterial pressure ≥25 mmHg at rest measured with right heart catheterization (RHC) [1].

PH can be classified into 5 main subgroups by the clinical and pathophysiological characteristics: group 1 - pulmonary arterial hypertension (PAH); group 2 - PH due to left heart disease; group 3 - PH due to chronic lung disease and/or hypoxemia; group 4 - PH due to chronic thromboembolism or other pulmonary artery obstruction; and group 5 - PH due to uncertain or multifactorial mechanisms [2].

Group 1 PH, PAH, is characterized by a pre-capillary PH in the absence of other causes, such as lung disease, left heart disease, chronic thromboembolism, etc. Connective tissue disease (CTD)-associated PAH belongs to group 1 PH [3]. The European Society of Cardiology (ESC) and European Respiratory Society (ERS) define PAH as a mean pulmonary artery pressure of ≥25 mmHg at rest and pulmonary artery wedge pressure/left ventricular end diastolic pressure of ≤15 mmHg and pulmonary vascular resistance of more than 3 wood units by RHC [4].

The reported prevalence of PAH is 5～25 cases/million with an incidence of 2～5 cases/million [5]. The most common etiology of PAH in adults is idiopathic, followed by CTD, congenital heart disease or portal hypertension [6].

In a UK study in 2005, the prevalence of CTD-PAH was 4.23/million and the incidence was 1.55/million [7]. The frequency of PAH among patients with CTD is increasing, which may be due to the increased awareness of the subtypes of the disease and the use of non-invasive screening diagnostic tests [6,8]. Among CTDs, systemic sclerosis (SSc) is the most prevalent cause of CTD-PAH, comprising 75% and followed by systemic lupus erythematosus (8%～19%), mixed connective tissue disease (8%～9%), rheumatoid arthritis (3%～5%), dermatomyositis/polymyositis (4%), unclassified CTD (2%), and Sjögren's syndrome (1%). The prevalence of PAH in SSc patients has been estimated to be 8%～12% [9].

Regarding the survival of subgroups of PAH, patients with CTD have more severe symptoms and a poorer prognosis than other groups in the absence of therapy [10]. The survival of PAH is improved significantly after early detection of the disease, the application of vasodilator therapy, and improved therapeutic strategies [5]. The data from PAH trials shows that earlier intervention may improve the treatment efficacy and delay the time to clinical deterioration [3].

Unfortunately, most patients with PH are diagnosed late. The initial phase of PAH is clinically silent and detectable signs and symptoms usually appear when the pathological changes are fully developed. The length of this preclinical phase of the disease is currently unknown [3]. Furthermore, nonspecific symptoms of PH-CTD usually overlap with other common medical conditions, such as musculoskeletal disease or anemia, and contribute to delayed diagnosis [3,11]. Considering the limitations of reliance on exertional dyspnea, other tools for early detection are required.

In the past issue of *Journal of Rheumatic Diseases*, Jung et al. [12] examined the prevalence of PH in patients with CTD and evaluated the various clinical manifestations

and biomarkers as potential tools to detect PH early. The results of the pulmonary function test, total cholesterol, red cell volume distribution width, alkaline phosphatase, and New York Heart Association functional class III or IV differed significantly according to the presence of PH. On the other hand, there was no difference in the incidence of PH according to the presence of interstitial lung disease (ILD). However, the study should be interpreted with caution because PH was diagnosed with echocardiography without confirmation of RHC. In addition, while the incidence of ILD was compared between groups with PH or without PH, the extent of ILD was not considered in the analysis.

Several clinical risk factors for the development of PAH in SSc have been suggested: advanced age, post-menopausal state, degree of skin involvement, disease duration of more than 5 years, severe peripheral vascular disease, presence of pulmonary fibrosis, microstomia, gastro-esophageal reflux and dysphagia, telangiectasia, and abnormal nail fold capillaroscopy [9,13-15].

SSc-ILD is a frequent manifestation of SSc, occurring in up to 75% of patients [16]. Coexistent ILD and PAH may be identified in 2%~18% of SSc patients [17]. SSc-PH can occur in isolation or in combination with ILD as a direct consequence of severe ILD (group 3 PH) or just co-occurrence with ILD (PAH and mild ILD insufficient to cause PH). The discrimination of the two conditions has been defined variably according to the extent of chest involvement on high-resolution computed tomography together with lung function testing abnormalities [18]. On the other hand, the causality and contribution of ILD on the significance of PH are uncertain in some cases [14,15,19]. Mild ILD has been suggested as a risk factor for the subsequent development of PAH [16,20]. Furthermore, the combination of ILD and PH shows a dismal prognosis with 3-year survival rates of 35% [21].

Although echocardiography is the most widely used noninvasive modality to screen for PAH, other noninvasive markers have been studied for the detection of SSc-PAH. A low diffusing capacity for carbon monoxide (DLCO) can also predict the occurrence of PAH in SSc patients. Patients with SSc-PAH typically have moderate-to-severe reductions in DLCO at the time of diagnosis, and a predicted DLCO of <60% is associated with a markedly increased probability of PAH [13,22-25].

B-type natriuretic peptide (BNP) is released from ventricular myocytes when the wall tension increases. In patients with PAH, BNP and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) correlate with the disease severity and is also highly predictive of SSc-PAH [13,26–28].

Several biomarkers are also considered as a tool for the early diagnosis and screening of PAH, but a few of them have been tested in prospective studies [29,30]. Subtypes of antinuclear antibody, such as anti-nucleosome antibodies, anti-centromere antibodies, anti-U3-ribonucleoprotein (anti-U3-RNP), and Anti-Th/To are associated with PAH while anti-U1-RNP is associated with a reduced risk [29,30].

Anti-angiotensin receptor type-1 antibody and anti-endothelin receptor type A, which affect the inflammation and fibrotic process by direct receptor activation, are also considered diagnostic markers for CTD-PAH, particularly in SSc [29,31,32].

Chemokines, growth differentiation factor-15, and markers of vascular injury, such as von Willebrand factor, endothelin-1, and vascular endothelial growth factor, are also suggested for use in the early detection of PAH in CTDs, especially SSc [29,31].

Longitudinal observational studies have shown that systematic screening for SSc-PAH can improve the outcomes [33]. Moreover, the accuracy of screening algorithms for SSc-PAH can be improved by combining different tests that are predictive of the presence of PAH [33]. The DETECT (early, simple and reliable detection of pulmonary arterial hypertension in SSc) protocol is a two-step scoring algorithm based on forced vital capacity, DLCO, telangiectasia, anti-centromere antibody, NT-pro BNP, serum urate, electrocardiogram, and subsequent echocardiography to determine the need for RHC in systemic sclerosis. The protocol results in fewer false negatives than an approach using echocardiography alone [34]. The new 2015 ESC/ERS guidelines also recommend a combined screening approach (using biomarkers, lung function, and echocardiography) to predict the presence of PAH in SSc [4].

In conclusion, an evaluation of the clinical risk factors, biomedical markers, and their combinations are valuable tools for the early detection of CTD-PH, thereby enabling prompt intervention to improve the survival of patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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