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Pulmonary arterial hypertension in systemic lupus erythematosus and systemic sclerosis

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Abstract

Pulmonary hypertension PH is a serious progressive condition associated with significant morbidity and mortality. Hemodynamically, it is defined by mean pulmonary arterial pressure (mPAP) of ≥ 25 mm Hg at restmeasured by right heart catheterization**.**

Keywords: Pulmonary hypertension, mPAP, SLE

INTRODUCTION

Pulmonary hypertension PH is a serious progressive condition associated with significant morbidity and mortality. Hemodynamically, it is defined by a mean pulmonary arterial pressure (mPAP) of ≥ 25 mm Hg at restmeasured by right heart catheterization**(1).**

According to WHO classification there are 5 groups of PH with shared pathophysiological and clinical characteristics: group 1, pulmonary arterial hypertension PAH; group 2, pulmonary hypertension associated with left sided heart disease; group 3, pulmonary hypertension associated with lung disease; group 4, chronic thromboembolic pulmonary hypertension (CTEPH); and group 5, with unclear mechanisms **(2).** Pulmonary arterial hypertension associated with underlying CTD (CTD–PAH) is now recognized as a distinct disease process. It may be seen in several CTDs likesystemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren's syndrome,mixed connective tissue disease (MCTD) and rheumatoid arthritis, but it is most commonly observed in systemic sclerosis (SSc–PAH) **(3).** CTD–PAH is considered to have pronounced underlying inflammatory component with significant differences in pathogenesis. Several studies have

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foundthat CTD–PAH is associated with a poor prognosis and worse response to therapy when compared to idiopathic PAH (IPAH); mortality noted is almost higher (four times)**(4).**

Epidemiology:

The prevalence of PAH in SScvaries between 5 and 12% in SSc patients and 50% in SSc-PH patients **(5).**SSc-PAH males had a shorter time for diagnosis and a shorter duration with a tendency towardspoor survival in males compared with females **(6).**The prevalence of PAH in SLE has been estimated to be between 0.5% and 17.5% **(7, 8).** The majority of patients with SLE-PAH are women (95% in the REVEAL registry).Female to male ratio was estimated to be 10: 1. Patients with SLE -PAH were younger when compared to other CTD patients. The mean age at PAH diagnosis wasaround 45 years **(9).**

Pathophysiology:

- **Autoimmunity and role of anti-endothelin1 receptor type A autoantibodies**:

Autoimmunity appears to have a central component of pulmonary artery vascular remodeling. Characteristic changes in the form of increased expression of adhesion molecules,endothelial cell apoptosis, inflammatory cell recruitment, intimal proliferation, a procoagulant state and adventitial fibrosis with vessel obliteration, has been found in early stages of PH**(10).**There is growing evidence suggestingthe pathogenic role of specific auto-antibodies in CTD-PAH. Auto-antibodies directed against endothelial cells in patients with CTD-PAH display a distinct reactivity profiles against antigens from micro and macro vascular beds **(11).** For example; in the serum of patients with SSc-PAH,anti-fibroblast antibodies, were found to cause fibroblast dysfunction leading to remodeling of the pulmonary vascular wall **(12).**

Activated endothelial cells secrete several vasoconstrictor mediators such as endothelin-1 (ET-1). ET-1 promotes leukocyte adhesion, vascular smooth muscle and endothelial cells' proliferation, fibroblast activation and irreversible vascular obliteration**(13).**It participates in the fibrotic pathway by inhibition of fibroblast matrix metalloproteinase-1 activity and stimulation of collagen production **(14).**There are two types of ET-1receptors: ET-A and ET-B.The ET-B receptorequally binds ET-1,ET-2, andET-3. The ET-A receptor is more selective for the ET-1. In humans, there is tendency of ET-A receptorfor differential binding to ET-1than ET-3 **(13).**.Hypoxia, cAMP, basicfibroblast growth factor (bFGF)and epidermal growth factor up-regulate the ET-Areceptor. Endothelins, platelet-derived growth factor, angiotensin II and transforming growth factor (TGF) down-regulateits production**(15).**

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ET-A receptors are located on the vascular smoothmuscle cells, where theyenhance vasoconstriction byincreasing release of intracellular calcium. Insome vessels, endothelin-inducedintracellular Ca elevation stimulate opening ofCa-activated K-channels with hyper-polarization and vasodilatation**(16).**

The net effect of endothelin activation is determined upon the state of the tissue.The number of these receptors and their sensitivity changeswithdifferent disease states.In normal tissue, the effect of ET-B is vasodilatation, but under pathologic processes, vasoconstriction predominates. This reversal may result fromincreasedendothelin levels or from thedown-regulation of ET-B receptors at the endotheliallevel and concurrent up-regulation of ET-B receptors on vascular smooth muscle cells **(16).**

Binding ofanti-ETAR auto-antibodies to their receptors triggers multiplecellular and systemic events that promote inflammation and fibrotic processeswith increased production of TGF-β,IL-8 and vascular cell adhesion molecule-1 (VCAM-1). They stimulate type I collagen production and induce T cell chemotaxis**(17).**

Another important consideration about theirroleis the intracellular pathways triggered by binding of anti-ETAR auto-antibodies to their receptors. They activate different signaling cascadesin which the extracellular signal-regulated kinase (ERK), the protein kinase C-α (PKC-α) and mitogen-activated protein kinase (MAP) pathways are involved **(18).**

Moreover, these auto-antibodies also trigger the activation of transcriptionfactors such as activator protein 1 (AP-1) and nuclear factor κB (NF-κB) in vascular cells which are involved in the canonicalpathways for important biological and pathological processes**(18).**

- **Inflammation:**

Inflammation isrecognizedas a pathological hallmark in PAH. It was suggested by the infiltration of inflammatory cells in pulmonary perivascular spaces within and around the plexi form lesions (**19**)**.**An increased level of pro-inflammatory markers suchasP-selectin, macrophageinflammatoryprotein-1a, IL-6 and IL-1b arealso observedinsevereformsofPAH **(20).**

- **Thrombosis:**

Thrombosis occurs more frequently in SLEpatients, usually in the presence of anti-phospholipidantibodies. Although antiphospholipid syndrome may lead to chronic thromboembolic PH,anti-phospholipid antibodies may have a role in mediating endothelial dysfunction andpromoting the secretionof adhesion molecules**(8).**In the existence of anti-endothelial cell antibodies, their binding toendothelial cells causes increased production of IL-8 andIL-6 **(21).**

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- **Pulmonary vasculopathy and vasculitis:**

Several pathways are implicated in the vascular remodeling such as; impaired apoptosis, up-regulation of anti-apoptotic mediators and abnormal proliferation of endothelial cells **(22).**Pulmonary vasculitisis shown to be more common in SLE-PAH whichis mainly mediated through immune complexesdeposition on the vessel wall**(23).**Pulmonary vasoconstriction alsomay lead to decreased oxygensaturation and hyper-expression of erythropoietin (EPO) andthe hypoxia-induciblefactor (HIF) which may promoteextensive vascularremodeling and smooth muscle cell proliferation**(24).**

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