ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

CONNECTIVE TISSUE DISEASES AND PULMONARY HYPERTENSION

Amal A. Hassan[a], Zainab H. Saeid[c] , Huda Talaat[a], Nadia F. Muhammed[b], Rasha A. Abdel-Magied[a]

[a] Rheumatology and Rehabilitation Department, Minia University, Egypt
[b] Radiology Department, Minia University, Egypt

[c] Chest Department, Minia University, Egypt

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

According to WHO classification there are 5 groups of PH : group 1, pulmonary arterial hypertension PAH; group 2, pulmonary hypertension associated with left heart disease; group 3, pulmonary hypertension associated with lung disease; group 4, chronic thromboembolic pulmonary hypertension (CTEPH); and group 5, miscellaneous with unclear mechanisms **(2).** PAH associated with underlying CTD (CTD–PAH) is being increasingly recognized as a distinct disease process. It may be seen in several CTDs such as systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjogren's syndrome and rheumatoid arthritis but is most commonly seen in systemic sclerosis (SSc–PAH) **(3).** Though histologically indistinguishable, CTD–PAH is thought to have significant differences in pathogenesis with a pronounced underlying inflammatory component. Several studies have established that CTD–PAH is associated with a worse prognosis and poor response to therapy compared to idiopathic PAH (IPAH); mortality noted is almost 4 times higher **(4).**

Epidemiology:

The prevalence of PAH in SSc has been estimated to be between 5 and 12% in SSc patients and 50% in SSc-PH patients **(5).** Gender differences have also been observed in SSc-PAH. SSc-PAH males had a shorter time to PAH diagnosis and shorter PAH duration with a trend toward worse survival in males compared with females **(6).**

The prevalence of PAH in SLE varies widely between 0.5% and 17.5% **(7, 8).** The majority of patients with SLE-PAH are women (95% in the REVEAL registry with RHC confirmed disease) with a female to male ratio of 10: 1. Patients with SLE -PAH were younger compared to other CTD-PAH patients with mean age at PAH diagnosis of 45 years **(9).**

Pathophysiology:

- **Autoimmunity and role of anti-endothelin 1 receptor type A autoantibodies**:

Characteristic vascular changes, in the form of endothelial cell apoptosis, increased expression of cell adhesion molecules due to endothelial cell activation, inflammatory cell recruitment, a procoagulant state, intimal proliferation and adventitial fibrosis leading to vessel obliteration, has been described in early stages of PH **(10).** IgG antibodies directed against endothelial cells and obtained from patients with IPAH and SSc-PAH display distinct reactivity profiles against antigens from micro-and macro-vascular beds **(11).** Anti-fibroblast antibodies, found in the serum of patients with SSc-PAH, are suspected of causing fibroblast dysfunction leading to pulmonary vascular wall remodeling **(12).**

Activated endothelial cells secrete various vasoactive mediators such as endothelin-1 (ET-1). ET-1, the most potent vasoconstrictor, promotes leukocyte adhesion, endothelial cells' proliferation, vascular smooth muscle cell proliferation, induces fibroblast activation and irreversible vascular obliteration **(13).** ET-1 participates in fibrotic cascade by stimulation of fibroblast collagen production and inhibition of matrix metalloproteinase-1 activity **(14).** There are two types of receptors to ET-1: ET-A and ET-B which produce differing, and sometimes opposing effects. While the ETB receptor binds ET-1, ET-2, and ET-3 equally, the ETA receptor is most selective for ET-1. In fact, for humans, there is a 1,000-fold differential binding affinity of ETA receptor for ET-1 versus ET-3 **(13).** Cell membranes may contain one or both types of receptors. The regulation of ETA and ETB receptor production is similar to that of endothelin itself. Hypoxia, cAMP, epidermal growth factor, and basic

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

fibroblast growth factor (bFGF) up-regulate the ETA receptor in some tissues, while endothelins, angiotensin II (ATII), platelet-derived growth factor, and TGF down-regulate its production. In contrast, ATII and perhaps (bFGF) up-regulate, and cAMP and catecholamines downregulate, ETB receptors **(15).**

ETA receptors predominate on vascular smooth muscle cells, where they induce vasoconstriction by increasing intracellular calcium. In some vascular smooth muscle cells, endothelin-induced intracellular Ca elevation opens Ca-activated K-channels, leading to hyperpolarization and perhaps vasodilation. Vessels with a large number of these types of cells may dilate in response to endothelin. ETB receptors located on vascular smooth muscle cells similarly stimulate vasoconstriction, but those located on endothelial cells induce vasodilation by stimulating the release of NO and prostacyclin **(16).**

The net effect of endothelin activation depends upon the state of the tissue, because both the number of receptors and their sensitivity change in disease states. In normal tissue, the effect of ETB is vasodilatory, but under pathologic conditions, vasoconstriction predominates. This reversal of effect may result from an increase in endothelin levels as well as from the localized down-regulation of ETB receptors at the endothelial level and the concurrent up-regulation of ETB receptors on some vascular smooth muscle cells **(16).**

Binding of stimulating anti-ETAR autoantibodies to their receptors can trigger multiple cellular and systemic events that affect inflammation and fibrotic processes such as production of TGF-β by human dermal microvascular endothelial cells, inducion of IL-8, vascular cell adhesion molecule-1 (VCAM-1). They induce T cell chemotaxis and stimulate type I collagen production by skin fibroblasts **(17).**

Another important consideration about the role of stimulating autoantibodies, are the relatively new and preliminary studies on characterization of intracellular pathways triggered by binding of anti-ETAR autoantibodies to their receptors. They have been shown to activate different downstream signaling cascades in which the protein kinase C-α (PKC-α) and the extracellular signal-regulated kinase (ERK)1/2 mitogen-activated protein (MAP) kinase pathways are involved **(18).**

Moreover, anti-ETAR autoantibodies also trigger the activation of transcription factors such as nuclear factor κB (NF-κB) and activator protein 1 (AP-1) in vascular cells. These signaling molecules and transcription factors are involved in canonical pathways that have a myriad of roles in important biological and pathological processes **(18).**

- **Inflammation:**

Inflammation is increasingly recognized as a pathological hall mark in PAH as suggested by infiltration of inflammatory cells in pulmonary perivascular spaces within and around plexiform lesions (**19).** In addition, increased levels of inflammatory markers such as macrophage inflammatory protein-1a, IL-1b and IL-6, and P-selectin are observed in severe forms of IPAH **(20).**

- **Thrombosis:**

Occurs more frequently in lupus patients, particularly in the presence of antiphospholipid antibodies. Although antiphospholipid syndrome per se may lead to chronic thromboembolic pulmonary hypertension, antiphospholipid antibodies have been shown to mediate endothelial dysfunction and induce the secretion of adhesion molecules **(8).** This may also occur in the presence of anti-endothelial cell antibodies – their binding to endothelial cells results in increased production of IL-6 and IL-8 **(21).**

References:

1. **Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, et al., (2013):** Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol.; 62(l): D42–D50.
2. **Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, et al., (2014):** Updated clinical classification of pulmonary hypertension. Turk Kardiyol Dern Ars.; 42(1):45-54.
3. **Shahane A (2013):** Pulmonary hypertension in rheumatic diseases: epidemiology and pathogenesis. Rheumatol Int.; 33:1655–1667.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

4. **Fisher MR, Mathai SC, Champion HC, Girgis RE, et al. (2006):** Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 54(9):3043–3050.
5. **Morrisroe K, Huq M, Stevens W, Rabusa C, et al. (2016):** Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. BMC Pulm Med.;16(1):134.
6. **Pasarikovski CR, Granton JT, Roos AM, Sadeghi S, et al. (2016):** Sex disparities in systemic sclerosis-associated pulmonary arterial hypertension: a cohort study. Arthritis Res Ther.;18(1):30.
7. **Arnaud L, Agard C, Haroche J, Cacoub P, et al., (2011):** Pulmonary arterial hypertension in systemic lupus erythematosus. Rev Med Interne.; 32:689–697.
8. **Tselios K, Gladman DD, Urowitz MB (2016):** Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies. Open Access Rheumatol.; 9:1-9.
9. **Chung L, Liu J, Parsons L, et al. (2010):** Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest.; 138:1383–1394.
10. **Kherbeck N, Tamby MC, Bussone G, Dib H, et al. (2013):** The role of inflammation and autoimmunity in the pathophysiology of pulmonary arterial hypertension. Clin Rev Allergy Immunol.; 44:31-8.
11. **Dib H, Tamby MC, Bussone G, Regent A, et al. (2012):** Targets of anti- endothelial cell antibodies in pulmonary hypertension and scleroderma. Eur Respir J; 39:1405-14.
12. **Tamby MC, Humbert M, Guilpain P, Servet- taz A, et al. (2006):** Antibodies to fibroblasts in idiopathic and scleroderma- associated pulmonary hypertension. Eur Respir J; 28:799-807.
13. **Hosoda K, Nakao K, Arai H, Suga S, et al. (1991):** Cloning and expression of human endothelin-1 receptor cDNA. FEBS Lett.; 287:23–6.
14. **Viswanath V, Phiske MM, Gopalani VV (2013):** Systemic Sclerosis: Current Concepts in Pathogenesis and Therapeutic Aspects of Dermatological Manifestations. Indian J Dermatol.; 58(4): 255–268.
15. **Rubanyi GM, Polokoff MA (1994):** Endothelins: molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. Pharmacol Rev.; 46:325–415.
16. **Maureen D, Mayes MD (2003):** Endothelin and Endothelin Receptor Antagonists in Systemic Rheumatic Disease. Arthritis & Rheumatism; 48(5):1190–1199.
17. **Kill A, Tabeling C, Undeutsch R, Kühl AA, et al. (2014):** Autoantibodies to angiotensin and endothelin receptors in systemic sclerosis induce cellular and systemic events associated with disease pathogenesis. Arthritis Res Ther.; 16: R29.
18. **Cabral-Marques O, Riemekasten G (2016):** Vascular hypothesis revisited: role of stimulating antibodies against angiotensin and endothelin receptors in the pathogenesis of systemic sclerosis. Autoimmun. Rev.; 15, 690–694.
19. **Voelkel NF, Gomez-Arroyo J, Abbate A, Bogaard HJ, et al. (2012):** Pathobiology of pulmonary arterial hypertension and right ventricular failure. Eur Respir J.; 40: 1555-65.
20. **Cracowski JL, Chabot F, Labarere J, Faure P, et al. (2014):** Proinflammatory cytokine levels are linked with death in pulmonary arterial hypertension. Eur Respir J.; 43:915-7.
21. **Arends SJ, Damoiseaux JG, Duijvestijn AM, Debrus-Palmans L, et al. (2013):** Functional implications of IgG anti-endothelial cell antibodies in pulmonary arterial hypertension. Autoimmunity.; 46(7):463–70.