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The Shared Pathogenesis of Pulmonary Artery Hypertension

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ABSTRACT

Pulmonary artery hypertension is defined as an increased in pulmonary artery pressure exceeding 25 mmHg with normal pulmonary wedge pressure. The pathogenesis of pulmonary artery hypertension involves interaction among vascular, cellular and biomarker components in the pulmonary tissue; with eventual result is elevated pulmonary artery pressure. Vascular components are remodeling of intimal, medial and adventitial layers. Cellular components are played by apoptosis-resistant endothelial cells, proliferative-prone pulmonary artery smooth muscle cells, fibroblasts and inflammatory cells. The functional biomarkers are produced and mediated by these cellular changes, mainly endothelin-1, thromboxane, serotonin, nitric oxide, and prostacyclin. The pulmonary vascular remodeling in pulmonary artery hypertension are diverse and may present in various severity based on underlying etiology. Understanding the shared pathogenesis in pulmonary artery hypertension is of paramount importance in order to improve the disease management and treatment approach.

Keywords: pulmonary artery hypertension; pathogenesis; pulmonary vascular remodeling

INTISARI

Hipertensi arteri paru didefinisikan sebagai peningkatan tekanan arteri paru melebihi 25 mmHg dengan tekanan baji paru yang normal. Patogenesis hipertensi arteri paru melibatkan interaksi diantara komponen vaskular, sel dan biomarka dalam jaringan paru; dengan hasil akhir peningkatan tekanan arteri paru. Komponen vaskular berupa remodeling lapisan intima, media dan adventitia. Komponen sel dimainkan oleh sel endotel yang tahan-apoptosis, sel otot polos arteri paru yang mudah proliferasi, fibroblas dan sel radang. Biomarka fungsional diproduksi dan diperantarai oleh perubahan-perubahan sel ini terutama endothelin-1, tromboksan, serotonin, *nitric oxide*, dan prostasiklin. Remodeling vaskular paru pada hipertensi arteri paru beraneka dan bisa muncul dalam berbagai derajat keparahan tergantung etiologi yang mendasari. Memahami patogenesis bersama pada hipertensi arteri paru merupakan hal yang sangat penting untuk memperbaiki manajemen penyakit dan pendekatan terapi.

INTRODUCTION

Pulmonary artery hypertension is considered to be a progressive disease. It is defined as an increased in pulmonary artery pressure exceeding 25 mmHg with normal pulmonary wedge pressure.¹ Pathogenesis of pulmonary artery hypertension is hallmarked by pulmonary vascular remodeling.

Pulmonary vascular remodeling involves the cellular and molecular modification of the pulmonary vasculature, both reversible or irreversible. All three layers of pulmonary vasculatures, i.e. adventitial, medial and intimal layers, undergo physiological and morphological changes, both consecutively and concomitantly. Thickening of

all layers due to cellular growth and proliferation and pathological accumulation of certain cell types and products, such as cytokines, chemokines and matrix components, are interplayed in the microenvironment of pulmonary vasculature.²

In addition to structural remodeling from its native vascular cells, perivascular microenvironment played by surrounding cellular components, both from resident cells and migrated cells from remote origin, is supportive in the pathogenesis of pulmonary artery hypertension.³ These components release cellular products or biomarkers, in response to various stimuli. Release of functional biomarkers, mostly those related to maintenance of pulmonary vascular vasoconstriction and vasodilatation, is predominant. Inflammatory cytokines and chemokines, produced by inflammatory cells, are redundantly increased during development toward pulmonary hypertension.⁴ The aim of this review is to discuss the current shared pathogenesis prevailing in pulmonary artery hypertension.

DISCUSSION

Pulmonary Vascular Structural Remodeling

Increased pulmonary artery pressure is mainly due to increased resistance in pulmonary vasculature. In normal condition, pulmonary circulation is a high flow and low pressure circulation. The pulmonary arterioles are the

main regulator of pulmonary vascular resistance in a whole. These resistance vessels alter their anatomy and perivascular microenvironment in response to increased intraluminal shear stress.⁵ This pathological shear stress triggers abnormal pulmonary vascular tone, which is mediated by modulation of endothelial-derived relaxing factor and contracting factors.² Normally, pulmonary arterioles consist of single layer endothelial cell and lined by single non-continuous smooth muscle cells. In remodeling, these smooth muscle cells are hypertrophied and extend into distal part of arterioles, dubbed distal muscularization.² Whole layers of pulmonary artery, i.e intimal, medial and adventitial layers, undergo remodeling under persistent pathological shear stress.

Intimal layer of pulmonary artery is lined by single layer endothelial cells and thin basal membrane. The thickening of intimal layer is occurred in pulmonary artery hypertension due to the deposition of matrix protein and collagen. The matrix protein and collagen are generated by fibroblasts and myofibroblasts, which are recruited in subintimal area. They form regular and concentric or irregular and eccentric thickening of the subintimal and intimal layers.⁶ The thickening of this intimal layer is called neointima. This neointima cause occlusive or almost occlusive of luminal artery. The histopathology examination of neointimal shows concentric laminar and/or nonlaminar fibrosis.⁶ The

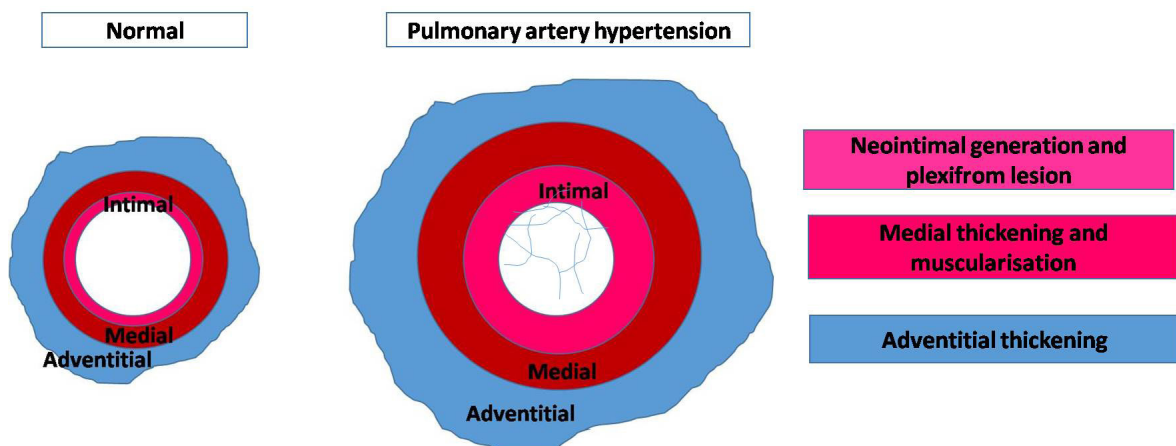


Figure 1. The pulmonary vascular remodeling

disorganized proliferation of endothelial cells leads to formation of the plexiform lesion, an important sign of severe pulmonary hypertension.² The cells in the plexiform lesion consist of angiogenesis-expressing endothelial cells and supported by a stroma containing matrix proteins and myofibroblasts.⁷ This lesion will transform into an intraluminal concentric obstruction composed of endothelial cells, recruited myofibroblasts, fibrous scar and foci of thrombosis.⁶

Medial layer of pulmonary artery mostly consists of smooth muscle cells. In the early changes during pathophysiology of pulmonary artery hypertension, vascular smooth muscle cells increase its size (hypertrophy) and change into proliferative state (hyperplasia). The hypertrophied smooth muscle cells usually in the proximal branch of pulmonary artery, whereas the hyperplasia occurs in the more distal vessel. The phenotype of vascular smooth muscle is altered into hyperproliferative smooth muscle cells which release matrix protein and collagen.⁷ Increased medial thickness in pulmonary vasculature is due to smooth muscle cell hypertrophy and hyperplasia, matrix protein and collagen accumulation, and myofibroblast differentiation from fibroblast.² Not only anatomical changes, the functional changes in remodeled medial layers also contribute to pulmonary artery hypertension.⁴

The adventitia layer of pulmonary artery is compiled by connective tissues that surround the airways and pulmonary arteries. It contains lymphatic vessels and vasa vasorum, therefore a channel for inflammatory cells and rich source of cytokines/chemokines.⁴ The adventitial fibroblast is activated under hypoxia, strenuous shear-stress or cytokine/chemokine stimuli.³ This activation produces matrix protein and promotes thickening of adventitial layer. It also produces pro-inflammatory cytokines/chemokines and recruits macrophages and leukocytes which induce perpetual inflammatory state and neovascularisation which supply inflammatory components in the more inner vascular layers, i.e. medial and intimal layers.³ In addition to inflammation conduit, adventitial layer also an entrance for endothelial progenitor cells and mesenchymal and bone marrow-derived stem cells in which involve in the pathogenesis of pulmonary artery hypertension.^{8,9} Figure 1 depicted pulmonary vascular remodeling.

Cellular Activation and Modification

In addition to vascular structural remodeling in the pathogenesis of pulmonary hypertension, cellular activation and subsequent modification are also an integral part of the pathogenesis. The cellular components are

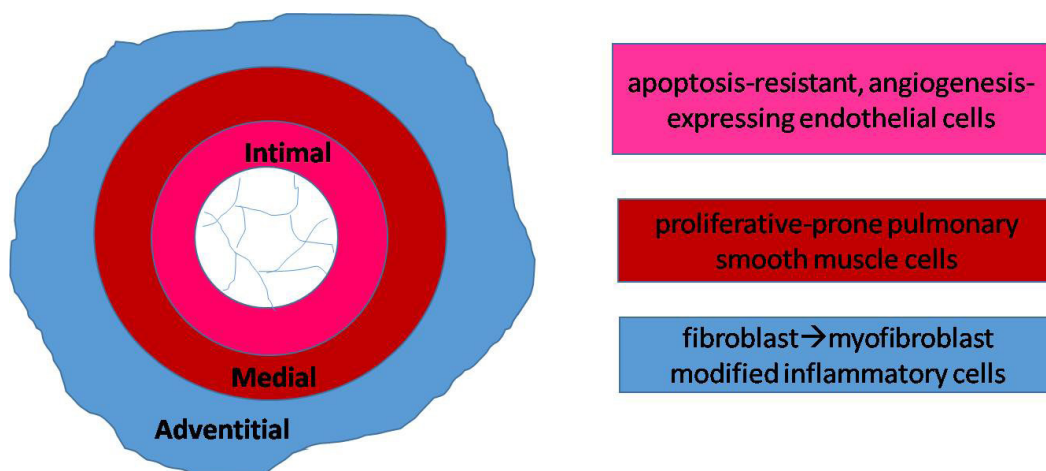


Figure 2. Cellular components of pulmonary vascular remodeling

played by apoptosis-resistant and angiogenesis-expressing endothelial cells, proliferative-prone pulmonary smooth muscle cells, myofibroblasts and modified inflammatory cells. The source of these cells are resident endothelial, smooth muscle, and fibroblast/ myofibroblast progenitors as well as derived from circulating progenitor cells which are recruited by chemokine signaling in pulmonary microenvironment.⁹

Endothelial cells in the plexiform lesion excessively express angiogenic factor, vascular endothelial growth factor (VEGF). It suggests that certain endothelial cells generate self growth signals to which they are reactive. The net effect is the growth-responsive and apoptosis-resistant cells resembling neoplastic phenotype.¹⁰ Resident fibroblasts, mostly reside in adventitial layer, are activated and differentiated into myofibroblasts which are capable of producing matrix protein and collagen, gaining mobility to inner vascular layer and recruiting inflammatory cells.³ The inflammatory cells, which consist of macrophages, monocytes, T lymphocytes and dendritic cells, are abundant in perivascular layer and scattered in adventitial layers.⁵ Figure 2 depicted cellular components in pulmonary vascular remodeling.

Biomarker Release and Alteration

The role of biomarkers in the pathogenesis of pulmonary hypertension has been widely investigated. The functional biomarkers are produced during pulmonary vascular remodeling and cellular changes, mainly endothelin-1, thromboxane, serotonin, nitric oxide, prostacyclin and adrenomedulin. Endothelin-1 is a potent vasoconstrictor. It stimulates smooth muscle cell proliferation, nitric oxide and prostacyclin release and fibroblast activation.⁸ Vasoconstriction is also mediated by thromboxane which is overproduced in pulmonary vascular remodeling. Because of the stimuli of chronic hypoxia, pathologic shear stress and various injuries, endothelial cells in the pulmonary circulation generate extensively vasoconstrictor and pro-proliferative mediators, mainly endothelin-1, angiotensin-II and thromboxane A2.¹¹ On the other hand, they produce less vasodilator and anti-proliferative mediators, i.e. nitric oxide and prostacyclin. This imbalance state may serve to maintain vessel wall tension and favors to the remodeled pulmonary vascular under hypertensive state. The abnormal endothelial cells are a principal initiator of pathologic pulmonary vascular remodeling, through released and altered

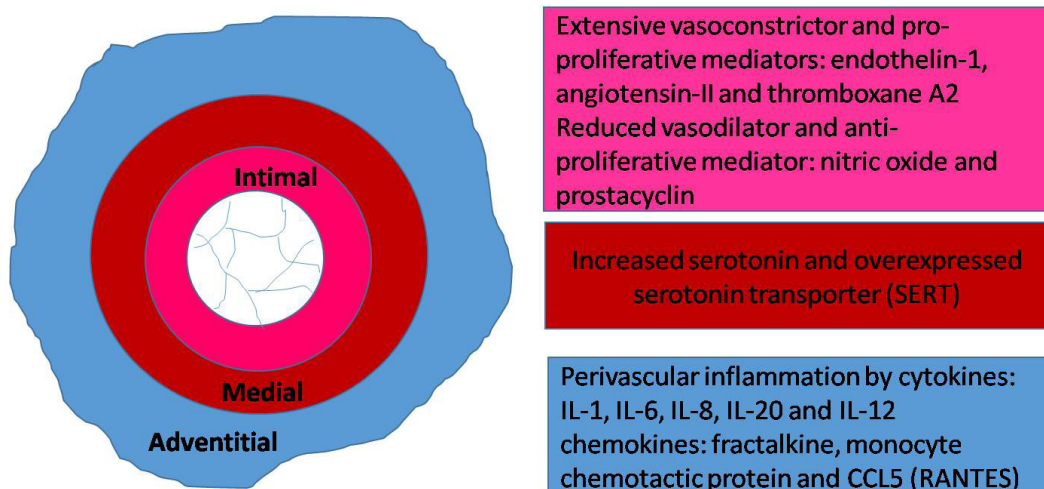


Figure 3. Biomarkers involve in pulmonary vascular remodeling

biomarker functionality.¹¹

Inflammation is a stimuli of pulmonary vascular remodeling. Cytokines and chemokines are contributors for developing perivascular inflammation. Interleukin-1 (IL-1), IL-6, IL-8, IL-20 and IL-12 are major cytokines correlate with severity of pulmonary hypertension.⁴ Elevated plasma level of tumor necrosis factor α is also prevailed in pulmonary artery hypertension.¹² Increased chemokines level is identified such as fractalkine, monocyte chemotactic protein and CCL5 (RANTES), which contribute toward developing pulmonary artery hypertension.¹²

Platelet and plasma level of serotonin are increased in pulmonary hypertension. Increased bioavailability of serotonin, a vasoconstrictor and profibrotic biomarker, due to increased serotonin release from platelets and endothelial cells is prevailing in pulmonary hypertension.⁸ The effect of increased serotonin level in pulmonary circulation is hyperplasia and hypertrophy of pulmonary artery smooth muscle cells.¹¹ Serotonin transporter (SERT) overexpressed by pulmonary artery smooth muscle cells is responsible for the upregulated mitogenic activity of serotonin by these cells.⁸ SERT increased expression enhances serotonin transport into pulmonary smooth muscle cells and induces medial thickening and distal muscularisation.¹³ In patients with idiopathic pulmonary artery hypertension, the expression of SERT is increased which is associated with susceptibility to plasma serotonin mitogenic activity.¹¹ Figure 3 depicted the associated biomarkers and pulmonary vascular remodeling.

CONCLUSION

Pathophysiology of pulmonary artery hypertension involves complex mechanisms consisting delicate interaction among pulmonary vascular structures, cellular modification and biomarker alteration. Understanding each component of mechanisms is of paramount

importance in order to improve the disease management and treatment approach.

DISCLOSURE

This article had been presented in Jogja Cardiology Update 2017, Yogyakarta, Indonesia. Part of the review article had been published in its proceedings.

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