Hypercoagulability in Pulmonary Hypertension

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KEYWORDS

• Pulmonary arterial hypertension • Hypercoagulability • Thromboembolism • Anticoagulation
• Pulmonary hypertension • Pulmonary embolism • Right heart failure • Right ventricle

KEY POINTS

- Patients with pulmonary arterial hypertension are at increased risk of developing thrombi.
- There are known and suspected pathways that contribute to the hypercoagulability in patients with pulmonary arterial hypertension.
- The benefit of anticoagulation and antiplatelet therapy is not known in this patient population.
- Hypercoagulability is an etiology and a consequence of pulmonary hypertension.

INTRODUCTION

Pulmonary hypertension (PH) is defined as increased pressure in the pulmonary circulation, defined by convention and consensus as a mean pulmonary artery pressure of at least 25 mm Hg at rest.[1] The World Health Organization (WHO) has classified PH into 5 major groups: pulmonary arterial hypertension (PAH), PH caused by left heart disease, PH caused by lung disease or chronic hypoxia, PH caused by chronic thromboembolic disease, and a miscellaneous group.[2,3] PAH is a clinical condition that falls under WHO group 1, and can be idiopathic (IPAH), heritable (HPAH), caused by drugs and toxins (DTPAH), or associated with several other conditions (APAH) including connective tissue disease, congenital heart disease, HIV infection, or portal hypertension. PAH is characterized by molecular and pathologic alterations in the pulmonary circulation that result primarily in progressive vascular remodeling of the pulmonary arteries, increased pulmonary vascular resistance, and eventually right heart failure and death.[4,5] These alterations are caused by several inflammatory, metabolic, and cellular changes that ultimately result in occlusive lesions, in situ thromboses, and plexiform lesions, that are all representative of the pathologic findings of PAH.[4,6,7] There is evidence of pro-thrombotic pathobiology which suggests an increased hypercoagulable state in PAH patients. Based on limited evidence, anticoagulation therapy is recommended in certain PH patients; however, the degree of hypercoagulability and benefit of anticoagulant therapy are not known.

PATHOPHYSIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

PAH is characterized by excessive vasoconstriction of the distal pulmonary arteries (although the vasculopathy is not strictly limited to the pulmonary arterial system[8]). This is related to endothelial dysfunction and smooth muscle cell hypertrophy and proliferation (that at least in part is related to abnormal function or expression of potassium channels on smooth muscle cells), which leads to impaired production of vasodilator and

Disclosure Statement: The authors have no financial or commercial conflicts of interest to disclose. No funding was used for this article.
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Clin Chest Med 39 (2018) 595–603
https://doi.org/10.1016/j.ccm.2018.04.005

antiproliferative agents such as nitric oxide and prostacyclin, as well as overexpression of vasoconstrictor and proliferative substances such as thromboxane A2 and endothelin-1.[5] Other pathways and molecules, including serotonin,[9] have also been implicated in the pathogenesis of PAH. Activation of the endothelin pathway has been demonstrated in both plasma and lung tissue of PAH patients.[10] Although it is unclear whether increased endothelin-1 is a cause or consequence of PAH, it is known that endothelin-1 causes vasoconstrictive and mitogenic effects by binding to pulmonary vascular smooth muscle cells.[11] Endothelin receptor antagonists are efficacious in improving symptoms, exercise capacity, hemodynamics, and time to clinical worsening in PAH patients.[12,13]

The nitric oxide and cyclic guanosine monophosphate (cGMP) pathway is also important in the pathogenesis of PAH. Inhibition of cGMP destruction by phosphodiesterase type 5 (PDE-5) inhibitors results in pulmonary vasodilation. PDE-5 inhibitors also have antiproliferative effects.[14] PDE-5 inhibitors and guanylate cyclase stimulators are approved for the treatment of PAH and have shown to varying degrees benefits in hemodynamics, exercise capacity, and time to clinical worsening as with endothelin receptor antagonists.[2,15]

The third pathway that has been a major therapeutic target for PAH is the prostacyclin pathway. Prostacyclin is predominantly produced by endothelial cells, and it induces potent vasodilation. It also inhibits platelet aggregation, and has cytoprotective and antiproliferative effects.[16] PAH patients have a reduction in prostacyclin synthase expression in pulmonary arteries and prostacyclin urinary metabolites.[17] Synthetic analogs of prostacyclins have been developed that share similar pharmacodynamic effects of prostacyclin.[18–20] Efficacy of prostanoids is also seen in APAH and CTEPH (although currently not approved for CTEPH).[21–23]

A common feature in all forms of PAH is the vascular remodeling of the distal region of pulmonary arteries. This pathologic remodeling results in the formation of a layer of myofibroblasts and extracellular matrix between the endothelium and the internal elastic lamina, termed the neointima. The cellular processes underlying the muscularization of the usually nonmuscular distal arteries is incompletely understood, but the adventitial fibroblast is thought to be the first cell activated to proliferate and synthesize matrix proteins in response to a pulmonary hypertensive stimulus.[24] Upregulation of matrix metalloproteinases occurs, and these metalloproteinases are involved in the migration of the adventitial fibroblasts into the media layer. PAH is also associated with alterations of proliferation and apoptosis, resulting in thickened and obstructive pulmonary arteries.[5]

Endothelial cells also play a key role in vascular remodeling. Disorganized endothelial cell proliferation leads to the formation of plexiform lesions that are characteristic of PAH. The initiating stimulus that results in abnormal endothelial proliferation is not known, but may be hypoxia, shear stress, inflammation, response to drug or toxin, or a combination of these with a background genetic/genomic susceptibility. Defects in growth-suppressive genes have been reported in plexiform lesions, including growth factors such as platelet-derived growth factor, fibroblast growth factor, transforming growth factor beta (TGFβ), and bone morphogenic proteins.[2,25]

Inflammation also contributes to the pathogenesis of PAH. Pathologic specimens of patients with PAH show an accumulation of perivascular inflammatory cells including macrophages, dendritic cells, T and B lymphocytes, and mast cells. There is also an increased level of circulating cytokines and chemokines.[26–28] The role of inflammation is particularly noted in certain groups of PAH including HIV APAH and connective tissue disease APAH. Interestingly, patients with systemic lupus erythematosus APAH have improved on immunosuppressive therapy, emphasizing the role of inflammation in this subset of patients.[29–31] The pathogenesis of PH in patients with sickle cell disease (WHO group 5 PH) is also linked to inflammation, as elevated inflammatory markers and levels of cytokines and chemokines are associated with worse hemodynamics and poorer clinical outcomes.[32,33] Mitochondrial dysfunction has also been shown to be pathologic in PAH.[34]

Pathologically, PAH results in medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening, plexiform lesions, and thrombotic lesions in the distal pulmonary arteries. Thrombi are present in both the small distal pulmonary arteries and in proximal elastic pulmonary arteries.[2]

HYPERCOAGULABILITY IN PULMONARY ARTERIAL HYPERTENSION

There is a high prevalence of vascular thrombotic lesions found postmortem in patients with IPAH, as described in several studies.[35–38] These in situ thromboses may be caused by abnormalities in the coagulation cascade, endothelial cells, and/or platelets. Reduced plasma fibrinolysis was first reported in1973.[39] Since then, studies have shown that PAH patients have elevated plasma levels of fibrinopeptide A- and D-dimers,[5] and 1 study found