Coagulation and Anticoagulation in Pulmonary Arterial Hypertension

Gidon Berger MD[1,2], Zaher S. Azzam MD[2], Ron Hoffman MD[3] and Mordechai Yigla MD[1]

[1]Division for Pulmonary Medicine, [2]Department of Internal Medicine B, and [3]Thrombosis and Hemostasis Unit, Rambam Health Care Campus, and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: Pulmonary arterial hypertension is a complex pulmonary vascular disease with a broad range of abnormal vascular abnormalities. Vasoconstriction, remodeling and thrombosis contribute to some extent to increased pulmonary vascular resistance and pressure. This review presents current knowledge on the role of the thrombotic process in the pathogenesis of PAH and evaluates the rationale for anticoagulation therapy.

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Pulmonary arterial hypertension is a disease state characterized by an increase in pulmonary vascular resistance to blood flow across the pulmonary circulation, causing an increase in pulmonary artery pressure. The ensuing progressive right ventricular failure leads to progressive disability and in many cases, death. PAH can be idiopathic or associated with an underlying systemic disease.

Regardless of the etiology, thrombotic pulmonary vascular lesions are an integral part of pulmonary vascular pathology that includes, in addition, vasoconstriction and remodeling. Current evidence suggests that primary and/or secondary abnormalities of blood coagulation factors, antithrombotic factors and the fibrinolytic system all contribute to a prothrombotic state [1,2]. This review summarizes current knowledge on the thrombotic process regarding its contribution to the pathogenesis of pulmonary arterial hypertension and evaluates the rationale for anticoagulation therapy.

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension represents Group 1 (of five) within the World Health Organization pulmonary hypertension classification (Venice 2003 revision). This disease is characterized by an increase in pulmonary vascular resistance to blood flow across the pulmonary circulation with resultant elevation of pulmonary artery pressure. The ensuing progressive right ventricular dysfunction leads to progressive physical disability with a median survival in untreated patients of 2–3 years from the time of diagnosis. PAH is most commonly associated with an underlying systemic disease such as connective tissue disease, as well as congenital heart disease; however, PAH may be idiopathic [3].

Pulmonary arterial hypertension has three distinct pathological patterns:

- Plexiform lesion characterized by medial hypertrophy, eccentric or concentric-laminar intimal proliferation and fibrosis, fibrinoid degeneration, and arteritis with or without thrombosis.
- Thrombotic lesions characterized by the presence of thrombosis in different stages (fresh, organizing, or organized, and recanalized-collander lesions), varying degrees of medial hypertrophy, but without plexiform lesions.
- Veno-occlusive disease characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules [4].

The clinical presentation of patients with different histological subtypes of pulmonary arterial hypertension is remarkably similar and there are no distinctive features that would allow the clinician to differentiate among them based on clinical criteria only.

Thrombotic arteriopathy, a highly prevalent pathological pattern of PAH, is an important pathophysiological feature of the disorder

THROMBOTIC ARTERIOPATHY

The term thrombotic arteriopathy is applied to cases where a thrombotic lesion predominates. In two retrospective cohort studies evaluating histology in idiopathic PAH patients, the prevalence rates of isolated thrombotic arteriopathy were 56% and 57%, respectively [5,6]. In a detailed study [4] of pulmonary vascular histopathology from the National Institutes of Health Primary Pulmonary Hypertension Registry, 33% of 48 patients with pulmonary arteriopathy had thrombotic lesions.

PAH = pulmonary arterial hypertension

Since these changes were found in the absence of clinical or pathological evidence of pulmonary embolism, they were considered as *in situ* thrombosis, as originally proposed by Bjornsson and Edwards [6]. Thrombotic lesions have also been described in pathological samples from patients with PAH associated with exogenous toxins (e.g., aminorex) and with portal hypertension [7]. Taken together, these observational studies indicate a relatively high prevalence of thrombotic lesions in PAH. Furthermore, these studies suggest that the presence of thrombotic lesions are related to age and disease duration but are not specific with regard to the etiology of PAH. The exact role of thrombosis in the pulmonary arteries and the microvasculature is controversial. One theory holds that thrombotic arteriopathy is an epiphenomenon of the underlying hypertensive pulmonary vascular state and endothelial dysfunction of PAH. Another view is that chronic organized thrombotic pulmonary vascular lesions are integral aspects of pulmonary vascular remodeling, luminal narrowing and increased pulmonary vascular resistance that contribute to the progression of PAH. Irrespective of whether thrombotic arteriopathy is a cause or consequence of PAH, thrombotic arteriopathy may alter the progression and prognosis of the disease.

Pulmonary vascular endothelial dysfunction might lead to local thrombosis

THROMBOSIS

As stated above, pulmonary intravascular thrombosis and thrombotic arteriopathy are common pathological findings in PAH. Indeed, in the study by Eisenberg et al. [8], the level of fibrinopeptide, a byproduct and a marker of fibrin degradation and generation, was elevated in all 31 PAH patients and markedly so in 19 of 31 patients (61%). Other studies showed increased expression of von Willebrand factor antigen [9,10], a pivotal glycoprotein in primary hemostasis that functions as an adhesive protein for platelets to the vessel wall in PAH, either idiopathic or associated with congenital heart disease. These patients also exhibit abnormal vWF multimer pattern [11], possibly due to degradation of the vWF main subunit [12].

Thrombosis is a complex process characterized by interaction of endothelial cells with both soluble elements (e.g., plasma coagulation proteins) and cellular elements of blood (e.g., platelets). In a healthy state, a balance exists between ongoing thrombosis and prevention of clot formation by both antithrombotic and fibrinolytic systems.

THE ROLE OF ENDOTHELIUM IN PAH

Endothelial cells regulate the thrombotic-antithrombotic balance and participate actively in the process of coagulation by activating factor X, facilitating the formation of the thrombin-activating prothrombinase complex and activating the extrinsic pathway of coagulation via release of tissue factor. In addition, endothelial cells produce and release von Willebrand factor.

Endothelial cells not only facilitate the thrombotic process but also actively inhibit thrombosis and promote fibrinolysis. Production and release of nitric oxide and prostacyclin, two potent inhibitors of platelet aggregation, by the endothelial cells are important mechanisms in the prevention of intravascular thrombosis [13]. In addition, expression of thrombomodulin, a high affinity receptor for thrombin, on the surface of endothelial cells prevents cleavage of fibrinogen to fibrin. Endothelial cells are also a source of tissue plasminogen activator, a key activator of plasminogen in the fibrinolytic cascade. On the other hand, endothelial cells also synthesize and release plasminogen activator inhibitor-1, an inhibitor of t-PA, highlighting the role of the endothelium in regulating the fine balance of prothrombotic and antithrombotic processes.

There are several lines of evidence indicating that endothelial cell dysfunction might interfere with the normal balance between prothrombotic and antithrombotic mechanisms and contribute to the pathophysiology of PAH.

Thrombomodulin, produced by endothelial cells, is a membrane-bound co-factor with a high affinity for thrombin that renders the capacity of endothelium to cleave fibrinogen, or activates platelets. Furthermore, thrombomodulin rapidly activates protein C. Abnormalities of the thrombomodulin/protein C anticoagulant system, evidenced by a decrease in soluble thrombomodulin in patients with idiopathic PAH, may initiate or play a role in perpetuation of pulmonary hypertension [14].

The endothelium, as mentioned earlier, also has an important role in the fibrinolytic process. Endothelial cells of pulmonary arteries release t-PA both continuously and acutely in response to triggering factors. Since t-PA has only limited activity on a preexisting fibrin clot, acute and local production of t-PA plays a major role in fibrinolysis and, thus, maintains the antithrombotic state in the pulmonary circulation. On the other hand, endothelial cells also synthesize and release PAI-1, which inhibits t-PA by rapid formation of enzyme inhibitor complex. Indeed, increased levels of PAI-1, supporting ongoing thrombosis, were found in the plasma of 17 of 29 idiopathic PAH patients [8].

ABNORMALITIES OF PLATELET FUNCTION IN PAH

Platelets not only participate in clot formation but are capable of releasing many vasoactive substances that promote vaso-

vWF = von Willebrand factor

t-PA = tissue plasminogen activator
PAI-1 = plasminogen activator inhibitor type-1

constriction (e.g., thromboxane-A_2, serotonin) and thrombosis (e.g., TxA_2), as well as growth factors that stimulate proliferation of smooth muscle cells, endothelial cells, and fibroblasts (e.g., serotonin, platelet-derived growth factor). Increased platelet aggregation is enhanced by the altered balance of vasoactive mediators in idiopathic PAH, such as increased TxA_2 (pro-aggregatory) and decreased nitric oxide and prostacyclin (anti-aggregatory).

The role of activated platelets in PAH in thrombi formation in the pulmonary vasculature was investigated in experimental models. There is an emerging role of platelet-selective release of mediators, such as serotonin, TxA2 and growth factors occurring in patients with severe PAH.

One of the key mechanisms by which platelets are involved in the pathophysiology of PAH may be the production and release of serotonin, a vasoactive substance with important effects on cell growth and proliferation [15]. Idiopathic PAH patients were found to have a markedly elevated plasma serotonin level while the serotonin content of platelets, the major source of blood serotonin, was significantly reduced [16].

Interruption of ongoing thrombosis is expected to improve the prognosis of patients with idiopathic PAH

INHERITED THROMBOPHILIC STATES IN PAH

Deficiencies of the classical inhibitors of coagulation (e.g., antithrombin, protein C, protein S) and abnormal procoagulant factors (e.g., factor V Leiden) are well-recognized risk factors for thrombosis. With the rare exception of PAH associated with antiphospholipid antibodies, there is no evidence to suggest an increased tendency to PAH in inherited thrombophilic states [17].

ANTICOAGULATION IN PULMONARY ARTERIAL HYPERTENSION

The American College of Chest Physicians clinical guidelines [18] support the use of anticoagulation with a grade "B" recommendation (a moderate recommendation) based on observational studies that indicate a survival benefit in anticoagulated idiopathic PAH patients, and weak recommendation based on expert opinion only for other PAH types. However, due to the small number of patients and the methodological limitations of these studies, the power of these recommendations is weak.

The role of anticoagulation in PAH was reviewed by summarizing seven observational studies [2]. One case series [19], three retrospective cohort studies [5,20,21] and one prospective cohort study [22] demonstrated a survival benefit of anticoagulation therapy in 488 idiopathic PAH patients. In contrast to these five studies suggesting that anticoagulation therapy may be an effective intervention, two retrospective cohort studies did not support these findings [23,24]. In the study by Frank et al. [23], improved 5 year (63% versus 38%) and 10 year survival (39% versus 20%) were reported in warfarin-treated versus warfarin-naive PAH patients associated with systemic diseases. However, warfarin-treated and warfarin-naive idiopathic PAH patients had similar outcome as manifested by the 5 year survival rate.

SUMMARY

Available evidence suggests that thrombotic arteriopathy is an important pathophysiological feature of PAH and may alter the progression and prognosis of idiopathic PAH patients. The pulmonary vascular endothelium plays an important role in maintaining blood fluidity through the lung. Studies have shown that an impairment of this function in patients with idiopathic PAH or severe secondary pulmonary hypertension leads to local thrombosis. Interruption of ongoing thrombosis with effective systemic anticoagulation therapy is expected to improve the prognosis, especially for patients with disease not responsive to vasodilators.

Correspondence:
Dr. G. Berger
Division of Pulmonary Medicine, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096, Israel
Phone: (972-4) 854-2650
Fax: (972-4) 854-2031
email: g_berger@rambam.health.gov.il

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TxA_2 = thromboxane-A_2

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