

Are Coagulation Abnormalities Important in Pulmonary Arterial Hypertension?

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Commentary

Pulmonary arterial hypertension (PAH) is a multifactorial, progressive cardiopulmonary disorder characterized by increased pressures in the pulmonary circulation. PAH can be idiopathic, heritable, or it can be attributed to drugs/toxins or to disorders that produce lesions in the pulmonary arterioles (like connective tissue disease or portopulmonary hypertension). The reason why a disorder with such a diverse etiological background is classified in one Group (Group 1 of pulmonary hypertension) is mainly because these underlying conditions produce very similar pathophysiological changes in the pre-capillary pulmonary vascular bed, leading to a rise in the mean pulmonary arterial pressure, a functional decline, right heart failure and potentially death [1].

The main anatomical changes of the pulmonary vasculature which lead to the development of the disease are based on the sustained increase of the pulmonary vascular resistance, which comes as a result of a mechanical obstruction of the small to medium-sized pulmonary arteries and arterioles. This mechanical obstruction is the consequence of a number of different processes, like pulmonary vasoconstriction, irreversible remodeling, and in situ thrombosis. The anatomical changes of the pulmonary vascular bed are chronic and progressive, and they are associated with changes on the molecular and cellular level.

The molecular alterations observed in PAH can be traced, at least partly, to the dysfunction of the endothelial cells of the pulmonary vasculature. Irrespectively of the underlying cause of the disease, endothelial injury is considered a key player in the development of PAH's vascular pathology [2]. The involvement of the endothelium dysfunction in the development and the progression of the disease can be linked to vasoconstriction (induced for example by a decrease in nitric oxide and prostacyclin levels and an increase in endothelin-1 and serotonin levels), hyper-proliferation (induced by growth factors and pro-apoptotic proteins) and coagulation abnormalities [3].

The endothelium is a layer of endothelial cells, functioning like an organ which can regulate dynamically its micro-environment. Its main role is to ensure a normal blood flow, via the regulation of the coagulation process, vascular tone and angiogenesis. Therefore, in cases where the endothelium has become dysfunctional, the coagulation cascade could be dysregulated.

There is evidence indicating the existence of haemostatic abnormalities in patients with PAH. Post-mortem studies have revealed in situ thrombosis in the pulmonary vasculature of patients with idiopathic PAH (iPAH). Other studies have shown that the levels of tissue factor, von Willebrand factor and plasminogen activator inhibitor -1 were increased, which are indicators of endothelium dysfunction [4]. This pro-thrombotic state is further supported by findings of increased levels of substances like serotonin and thromboxane B2 [4]. On the other hand, platelets can, also, affect the pulmonary vasculature, through the excretion of substances like growth factors, serotonin and thromboxane A2, which could have vasoactive and mitogenic effects.

These data suggest that there is indeed a dysregulation of the coagulation process and a probable interaction of the vascular wall with the cellular and non-cellular blood components, but they offer no definite insight as to the nature of that interaction. PAH is a chronic, progressive disease, where its pathobiological and pathophysiological changes may predate by years the clinical manifestations and the diagnosis. The chronic structural and molecular alterations in the pulmonary arteries and arterioles can have variable and constantly changing effects to the endothelium, which in turn can affect the function of platelets and the coagulation process [5]. The altered hemostasis (e.g. platelets) could, then, affect in multiple ways the function of the endothelium.

Factors, like the patient's thrombophilic state, the etiology and the trajectory of the disease, could further complicate the above-mentioned interactions. In addition, there are no data regarding the coagulation process and any potential abnormalities in patients with genetic mutations. An increasing number of genetic mutations have been identified, many of which are associated with a clinical phenotype that includes coagulation abnormalities, but firm data are missing in this very interesting subset of patients.

In the current era, there are three main therapeutic pathways used in PAH: the endothelin-1, nitric oxide and prostacyclin pathway. Due to the specific molecular targets of the advanced PAH treatments, these medications can affect not only the pulmonary vasculature, but also the coagulation process, both directly (prostacyclin analogues inhibit platelet aggregation) and indirectly (e.g. the phosphodiesterase type 5 inhibitors can affect hemostasis through the nitric oxide pathway) [1]. The effects of those medications on the haemostatic equilibrium in PAH patients have not yet been explored.

The debate concerning the use of anticoagulants in PAH patients further stresses the importance of better understanding the role the coagulation plays in the PAH setting. Key parts of this debate are the facts that there are not clear guidelines regarding the use of anticoagulant medications in PAH patients and that there are not available data from large randomized control studies supporting or disputing the use of anticoagulants in this setting [6].

The above data show that there is a complicated relationship between coagulation and PAH. Even though, the exact mechanism of how the endothelium affects hemostasis, and vice versa, is not yet

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known, there are some key elements worth mentioning. The damaged endothelium of the pulmonary vasculature can release mediators, like nitric oxide and prostacyclin (substances that have been found decreased in PAH patients and are therapeutic targets), which can affect platelet activation and the initiation of the coagulation process. Most of the studies on the subject have provided direct and indirect evidence of hypercoagulability and defective fibrinolysis in PAH [7]. Based on these data, along with evidence of in situ thrombosis in iPAH patients, the current guidelines for the treatment of PAH from the European Society of Cardiology and European Respiratory Society (ESC/ERS) recommend the use of anticoagulation therapy as an adjunct treatment in some forms of PAH, like iPAH [1].

On the other hand, the data from the clinical setting seem controversial. Large observational studies have failed to prove a clinical benefit from the anticoagulation therapy in iPAH, while they demonstrated a potential risk for patients with connective tissue disease. In addition, there are increasing reports of hemorrhagic phenomena in these patients [6]. This controversy may be indicating that categorizing PAH patients only as “hypercoagulable”, may not be accurate.

The endothelium in PAH is subjected to a chronic and constant insult, that could lead to a chronic and constant activation of hemostasis. Since hemostasis can be better described as a dynamic equilibrium, such a chronic activation of the coagulation cascade can produce variable results. Depending on additional factors, like the etiology or the severity of the disease, the patient’s thrombophilic profile or the chosen treatment, this equilibrium could be tilted towards thrombosis or hemorrhage [5]. In addition, this chronic activation of haemostasis could have other consequences, like the functional “exhaustion” of the haemostatic process resulting in its further dysregulation [5]. These phenomena could have further (still unknown) impacts in PAH’s pathophysiology, since elements of the coagulation cascade (e.g.

platelets, serotonin and thromboxane) can affect key aspects of the disease, like vasoconstriction and angiogenesis.

In conclusion, there is a question repeating itself in many papers on the subject of coagulation and PAH are the coagulation abnormalities observed in PAH patients’ part of the cause of the disease, are they a consequence or just an epiphenomenon? With the available data, an answer would be difficult to provide. Nevertheless, taking into consideration the complex interplay between hemostasis and endothelium and the potential clinical implications, the relationship between coagulation and PAH could be considered important enough to be more actively explored.

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