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Distinct Mechanism between Arterial and Venous Thrombosis: Impact for Clinical Manifestations

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Introduction: basic mechanism of hemostasis and thrombosis

Hemostasis is a complex physiological process aiming to keep the integrity of a closed circulatory system after an occurrence of vessel wall injury. Hemostasis involving the role of circulating platelets and coagulation cascade.[1] There are two major pathways that act independently to activate the platelet. The first pathway is mediated by collagen and the other by tissue factor. After intimal layer injury, platelets are recruited through the interaction between platelet's surface glycoprotein (GPVI and GPIb/V/IX) with collagen and von Willebrand factor. This process results in adhesion of platelets in the site of injury. Further recruitment of platelets is achieved by secretion of aggregatory mediators such as thromboxane A2 and adenosine diphosphate.[1,2]

The formation of three dimensional platelet clot involving the activation of GPIIb/IIIaintegrins. In the setting of deeper tissue damage, the activation of platelet is mediated by tissue factor released predominantly from medial and adventitial layer of vessel wall. This process generates thrombin from prothrombin and activates coagulation cascade resulting in fibrin generation.[1]

In the physiologic condition, blood is maintained in the fluid state by certain mechanism. The endothelium of vessel wall plays a major role in this process by producing antithrombotic mediators such as nitric oxide, prostacyclin, and the ectonucleotidase CD39.[1]

The balance of prothrombotic and antithrombotic properties of blood and vessel wall has to be regulated to maintain the closed circulatory system but prevent pathologic formation of thrombus at the same time. The alteration of this balance leads to some forms of disease entities. Thrombosis is a group of disease characterized by pathologic formation of thrombus resulting in occlusion of blood vessel.[1,3] Traditionally, the patho- genesis of thrombosis is originated from interdependent factors: blood stasis, vessel wall injury, and hypercoagulable state.[4]

A. Mechanism of arterial thrombosis

Arterial thrombosis frequently occurs in the setting of preexisting atherosclerotic plaque.[2,5,6] Although considered as different process, it is proposed that the mechanism responsible for the formation of atherosclerotic plaque is also responsible for arterial thrombogenesis and vice versa. The formation of atherosclerotic plaque is a result of interaction between endothelium,

leukocyte, smooth muscle of vessel wall, and certain component of adaptive immune response such as macrophage. Contrarily, it is traditionally accepted that thrombosis is a result of activation of platelet and coagulation cascade.[1,7]

There are evolving concepts that propose the mechanism responsible for thrombosis involving the role of interaction between endothelial cell and leukocyte. Furthermore, it has been proposed that platelet and certain factors of coagulation cascade are associated with the progression of atherosclerotic plaque.[7]

The formation of atherosclerotic plaque is a chronic process taking years to develop but it is an insidious event of plaque rupture that leads into an arterial thrombotic episode. After an event of plaque rupture or fissuring, platelets interact with subendothelial matrix which support platelet adhesion.[7] The adhesion of platelet to the site of injury is obtained through ligand-receptor binding. Some of subendothelial matrix proteins that act as ligand are collagen, von Willebrand factor, laminin, and fibronectin. Each of these ligands bind the specific platelet's surface glycoprotein. [1,5,7]

There is a unique property of the ligand favoring the formation of thrombus. In arterioles or stenotic arteries where the shear stress is high, von Willebrand factor has an increasing affinity resulting higher amount of platelet that can be recruited and activated.[7,8] Similarly, on the site of ruptured atherosclerotic plaque the flow is turbulent thus increases the shear stress and the affinity of von Willebrand factor that in turn activates the platelet. Once platelet is activated, it recruits more platelet to form a platelet-rich white thrombus. Following thrombus propagation, the flow is decreased at the distal part of thrombus creating local condition of stasis. It explains the formation of erythrocyte-rich red thrombus in the tail of the clot.[7]

B. Mechanism of venous thrombosis

The clinical background of venous thrombosis often differs from arterial thrombosis.[9] A study involving patients with spinal cord injury revealed that blood stasis plays a major role in the formation of venous thrombus. Valvular sinus of lower extremity vein is the most common site where the thrombus originated. A slow blood flow state in the valves activates the coagulation cascade by allowing the accumulation of procoagulant mediator such as thrombin.[4] In the physiologic state, venous valves produce antithrombotic proteins such as thrombomodulin and endothelin protein C receptor (EPCR) to prevent thrombus formation. Venous stasis alters this balance by providing a microenvirontment favoring thrombus formation. Venous stasis is associated with decreasing level of oxygen and increasing hematocrit. Hypoxic state in this microenvirontment halts the expression of antithrombotic proteins.[10]

Other study involving animal model suggested similar mechanism in stenotic and compressed vein. This may explain thrombosis of the upper extremity in the absent of valves. In stenotic vein, other mechanism has been proposed in terms to explain the formation thrombus.[11] Endothelial cell in stenotic vein is activated and producing certain mediators favoring the formation of thrombus, a similar mechanism to the formation of arterial thrombus. Activated endothelium expresses von Willebrand factor and P-selectin that interact with platelet and

leukocyte respectively through ligand-receptor binding.[1,12]

Hypercoagulable state is the second factor contributing to the formation of venous thrombus. Certain conditions are associated with the increasing level of coagulation factors thus providing a hypercoagulable state.[10,11] Familial thrombophilia is a group of rare disease increasing the tendency of thrombosis.[3,12] More epidemiologically significant causes of hypercoagulable state are age, cancer, major surgery, pregnancy, hormone contraceptive and hormone replacement therapy, and obesity. In elderly, there is a shifting proportion of procoagulant and anticoagulant mediator. An increasing level of fibrinogen, factor VIII, and factor X is not followed by a proportional increment of blood anticoagulant level.[12] Inflammation is thought to be the source of procoagulant surge following a major surgery beside the direct impact to the vascular integrity. The expression of tissue factor on monocyte and lymphocyte membrane is significantly increased 1 day following a total knee replacement. Pregnancy is also a significant cause of hypercoagulable state.[12,15] In pregnant women, there are increasing fashion of factor VII, factor VIII, factor X, fibrinogen, and von Willebrand factor. Physiogically, this state is providing a protection from hemorrhage at the time of peripartum and miscarriage. In certain cancer, a hypercoagulable state is created by secreting a procoagulant mediator such as tissue factor or by activating signaling pathway through lymphocyte or monocyte.[12]

Although traditionally proposed that venous thrombosis is mainly a result of venous stasis and hypercoagulable state, current evidence shows that vascular injury is an important factor in pathogenesis of venous thrombosis. Following the injury of the intimal layer, von Willebrand factor is exposed to the platelet similar to the mechanism of arterial thrombus formation.[12] In the fibrotic vein, this process could occur without the actual intimal tear. Endothelial cell activation could be a consequence of intimal injury on cellular and molecular level. The causes of intimal injury are the placement of central venous catheter, hemodyalisis catheter, radiation, trauma, and extrinsic compression.[10,12]

C. Arterial vs. venous thrombosis: from structure to clinical impact

On cellular and molecular level, it has been traditionally proposed that there is a distinct structure between arterial and venous thrombus. Arterial thrombus is suggested to be white thrombus meanwhile venous thrombus is thought to be red thrombus.[13,14] In the past few years, there is an evoking evidence that the differentiation of arterial and venous thrombus is much like a matter of proportion rather than discrete entities. The structure of both thrombi is composed of complex structure of fibrin network and cellular component such as erythrocyte, platelet, and leukocyte.[13] Although the dichotomy of arterial and venous thrombus is important, it has been proposed that specific condition which the thrombus originated plays major role in composition of thrombus.[13,14,15] For instance, older arterial thrombus is shown to contain less amount of platelet compared to relatively fresh thrombus. Similarly as the effect of endothelial activation, thrombus formed in stenotic upper extremity vein is suggested to contain more platelets

compared to thrombus originated from lower extremity which stasis is the main contributing factor.[10,13,14]

However, the mechanism is clear that high shear augments the recruitment of platelet thus promoting the formation of platelet-rich white thrombi and slow flow is associated with the generation of erythrocyte-rich red thrombi.[13]

From the understanding that arterial and venous thrombosis shares some pathogenesis and pathological features albeit the distinct mechanism, there are several implications in prevention and treatment of patients with arterial and venous thrombosis.[13,14,15] For instance, although aspirin is drug of choice in treating patient with arterial thrombosis, there are well established evidence that supports the role of anticoagulant. Similarly, there are increasing amount of evidences supporting the usage of antiplatelet in venous thrombosis.[15]

The understanding of thrombus structure may also impact clinical outcome of fibrinolysis. The mediators released by activated platelet lead to a more compact fibrin aggregate. It is also proposed that those mediators inhibit the binding of serine protease to fibrin causing the decreasing of its activity in degrading fibrin. Those mechanism could explain the tendency of platelet-rich thrombus to be less vulnerable to fibrinolytic agent.[16] Finally, although there are emerging knowledge of pathogenesis and structure of arterial and venous thrombus, it is still needed to build a better approach in managing patient with arterial and venous thrombosis.

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