

Review Article

The Hemostatic System in Arterial Thrombosis and Coronary Atherosclerosis

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Abstract

Thrombosis is the formation of a thrombus within a blood vessel, which partially or completely obstructs the blood flow. While venous thrombosis had much interest, arterial thrombosis needs more elucidations. The incidence of arterial thrombosis is increasing, worldwide, specifically in the form of coronary heart disease. Although venous and arterial thrombosis have traditionally been considered distinct pathophysiologic entities, the two disorders have many features in common, and there is evidence that persons with venous thrombosis may be at greater risk for arterial events, and vice versa. This review discusses the central pathogenic mechanisms of arterial thrombosis, particularly in atherosclerotic coronary heart disease. In addition, the roles of different hemostatic components in initiating atherosclerosis itself are discussed.

Keywords: Ischemic heart disease, Atherosclerosis, Arterial Thrombosis

1. Introduction

Thrombosis is the formation of a thrombus within a blood vessel, which partially or completely obstructs the blood flow, thus may be referred as "hemostasis in the wrong place". Thrombosis can occur both in veins (venous thrombosis) and arteries (arterial thrombosis). It is a major cause of morbidity and mortality in a wide range of arterial and venous diseases and patient populations. Arterial thrombosis is increasing, worldwide, specifically in the form of coronary heart disease¹.

As early as 1856, Virchow postulated, in his famous "Virchow's triad", that the pathogenesis of thrombosis is the result of at least one of the following three interrelated factors: (a) "decreased blood flow" (stasis), (b) "inflammation of or near the blood vessels" (vascular endothelial injury), and (c) "intrinsic alterations in the nature of the blood itself" (hypercoagulability)². Thrombosis occurs when the balance between thrombogenic factors and protective mechanisms is perturbed, whether due to an excess of pro-coagulatory factors or to a decline or defective functioning of anticoagulatory mechanisms. The protective mechanisms include the non-thrombogenic properties of intact endothelial cells, fluid-phase anti-proteases, and the dissolution of fibrin by the fibrinolytic system. Thrombogenic stimuli include injury or loss of endothelial cells and activation of platelets and blood coagulation³.

2. The Distinction between Arterial and Venous Thrombosis:

While many of the pathways regulating thrombus formation are similar to those that regulate hemostasis, the processes triggering thrombosis and, often, perpetuating the thrombus are distinct¹. Arterial atherothrombotic disease (i.e.,

acute myocardial infarction, ischemic stroke and peripheral artery disease) and venous thromboembolism (deep venous thrombosis and pulmonary embolism) are generally considered as separate entities from mechanistic and clinical points of view. While venous thrombosis has been traditionally associated with red blood cells enmeshed in fibrin (red thrombi), arterial thrombi are mainly composed of platelets with little fibrin or red cells, giving the appearance of white thrombi. Similarly, classic acquired risk factors for venous and arterial thrombosis are distinct, those for the former including cancer, surgery, immobilization, fractures, pregnancy and estrogen use, while risk factors for the latter include smoking, hypertension, diabetes, obesity and hyperlipidemia⁴.

The pathogenesis of arterial thrombosis appears to be different from that of venous thrombosis; activation of platelets under high shear flow play a major role in the former, whereas reduced blood flow and activation of blood coagulation are responsible for the latter⁴. Although there is overlap, both of venous and arterial thrombosis are initiated differently and clot formation progresses by somewhat distinct pathways. In the setting of stasis or states of hypercoagulability, venous thrombosis is activated with the initiation of the coagulation cascade primarily due to exposure of tissue factor; this leads to the formation of thrombin and the subsequent conversion of fibrinogen to fibrin. Arterial thrombus formation, on the other hand, is best presented as a complex interaction between platelets and coagulation proteins. In the artery, thrombin formation also occurs, but thrombosis is primarily promoted by the adhesion of platelets to an injured vessel, stimulated by exposed extracellular matrix, and additional platelets are recruited¹.

Although venous and arterial thrombosis have traditionally been considered distinct pathophysiologic entities, the two disorders have many features in common, and there is evidence that persons with venous thrombosis may be at greater risk for arterial events⁵. On the other side, the association of peripheral venous disease with arterial endothelial dysfunction was recently found^{6,7}. The pathogenesis of both disorders includes endothelial injury, platelet activation, elevated levels of intrinsic clotting factors and inflammatory markers, increased fibrinogen, and impaired fibrinolysis⁵.

3. Role of Hemostatic system in Coronary Atherothrombosis

Ischemic heart disease (IHD) remains a major cause of mortality and morbidity worldwide. Endothelial dysfunction, inflammation and increased coagulation all play a crucial role in the atherothrombotic process. Endothelial dysfunction is one of the earliest defects in atherosclerosis, leading to increased permeability of these cells to lipid particles and inflammatory molecules, consequently resulting in the formation of fatty streaks, which are collections of cholesterol laden macrophages. The fatty streak induces an inflammatory reaction in the vessel wall, with increased production of cytokines and chemo-attractant proteins, thereby intensifying the atherosclerotic process. Chronic inflammation and the deposition of fibrous tissue results in the slow conversion of fatty streaks, over many years, into mature atherosclerotic plaque⁸.

Atherothrombosis refers to the occurrence of thrombosis on atherosclerotic lesions, the typical setting for arterial thrombosis. It represents the acute event that converts chronic atherosclerosis, a silent, asymptomatic, progressive disease into symptomatic, life-threatening clinical complications, including acute myocardial infarction (AMI) and stroke. Intravascular thrombogenesis, the main pathogenic mechanism of coronary artery disease (CAD), is influenced by a complex interplay of procoagulant, anticoagulant, fibrinolytic, endothelial damage/dysfunction and inflammatory processes⁹.

3.1. Atherosclerosis:

Atherosclerosis is a continuum of lesions resulting from the deposition of cholesterol in the arterial wall, favored by circulating oxidized LDL cholesterol. In turn, cholesterol deposition triggers an inflammatory reaction resulting in arterial wall thickening and luminal narrowing or total occlusion. Atherosclerosis may be chronic, by gradually increasing cholesterol and inflammatory cells deposits, smooth muscle proliferation, and fibrosis, or acute (thrombosis on the surface of a fissured or ruptured plaque)¹⁰. The association between cardiovascular risk factors and atherosclerotic disease is well documented. However, the mechanism by which these risk factors induce lesion formation and lead to cardiovascular events is not entirely defined¹¹.

Endothelial dysfunction plays an important role in the initiation, progression, and clinical complications of various forms of inflammatory and degenerative vascular diseases. In a healthy environment, there is a balanced expression of these products which maintains the integrity of the luminal surface, ensuring protection of the vessel wall and providing a healthy blood flow. Endothelial damage upsets this balance to initiate events that play a pivotal role in the progression of the atherosclerotic process³. Changes in endothelial structure and function, provoked by pathophysiological stimuli, can result

in alterations in the interactions of endothelium with the cellular and macromolecular components of circulating blood and of the blood vessel wall. These alterations can include: functional imbalances in local prothrombotic and anti-thrombotic factors, growth stimulators and inhibitors, and vasoactive (dilator, constrictor) substances, enhanced permeability to (and subsequent oxidative modification of plasma lipoproteins), and hyperadhesiveness for blood leukocytes¹².

The pathogenesis of coronary atherosclerosis is multifactorial. Briefly, endothelial injury results in the adhesion and transmigration of leukocytes from the circulation into the arterial intima and the migration of smooth muscle cells from the media into the intima. Macrophages recruited into the artery wall become lipid laden foam cells by engulfing modified lipoproteins. As the lesion progresses, inflammatory mediators cause the expression of procoagulant factors and matrix degrading proteinases that can weaken the fibrous cap of the plaque. If the fibrous cap ruptures, coagulant factors in the blood can access the thrombogenic lipid core, causing thrombosis on a previously nonocclusive atherosclerotic plaque. This process diminishes coronary artery perfusion through stenosis or by distal embolisation of the thrombus¹³.

3.2. Coronary Thrombogenesis

Damage to the endothelium and/or external stimuli activates platelets that adhere to the exposed subendothelial von Willebrand factor and collagen. These initial adhesive interactions induce intracellular signaling pathways that activate platelets. High shear stress also activates platelets both directly and indirectly by lowering the threshold of platelet activation by chemical agonists to which platelets are exposed in the microenvironment of the arterial thrombus. Thus, following adhesion, platelets are activated explosively by several interacting pathways; intracellular signaling initiated by the adhesion event itself, direct action of locally increased shear stress, and agonists released (e.g., ADP, TxA₂) and generated (e.g., thrombin) at the site of vascular injury¹⁴.

A cell-based model of arterial thrombosis identifies tissue-factor-bearing cells (monocytes and endothelial cells) as the initiating site of coagulation. The complexing of tissue factor with factor VIIa (from plasma) leads to thrombin generation. Thrombus maturation and growth takes place on platelet surfaces. Inflammatory cytokines, including tumor necrosis factor (TNF) α and interleukin-1, facilitate thrombin generation by stimulating the release of tissue factor (TF) from monocytes and vascular endothelial cells. A systemic "prothrombotic state" is recognized among patients with risk factors for atherosclerotic disease. This supports priming for coagulation responses that precedes clinical events¹⁵.

In arterial thrombosis, mainly located on atheroma, inflammation promotes plaque rupture¹⁶, and increases TF expression in endothelial cells and monocytes¹⁷. The amount of TF bound to FVII (TF/FVIIa complex) is several times greater than that of TF/FVIIa complex formed in a wounded vascular wall¹⁸, and with platelet it causes a burst of thrombin formation. Partial or total occlusion of the blood vessel, stasis and activation of blood clotting proteins and platelets and artery diameter, are parameters that prevent dilution of activated factors and generated thrombin. These parameters together with platelet-erythrocyte interactions promote thrombus growth¹⁹.

If the thrombus is non-occlusive and blood flow remains rapid, the thrombi may organize and become incorporated into the atherosclerotic plaque. With more marked arterial narrowing, shear rates increase and promote more extensive platelet and fibrin deposition, which can result in the formation of an occlusive thrombus²⁰. Indeed, the thrombotic response to plaque disruption is dynamic. In this respect, thrombosis, repeat thrombosis, and thrombolysis along with embolization all occur simultaneously in many patients with acute coronary syndrome, and this is considered responsible for intermittent flow obstructions²¹.

4. The Link between Inflammation – Atherosclerosis and Thrombosis:

The hemostatic components; platelets, coagulation, and fibrinolysis may be key factors in inflamed blood vessel wall. Atheroma evolution is not only a proliferative process but also involves thrombosis. Thrombosis is not simply the final occlusive event. It also contributes to atherosclerosis lesion development¹³.

4.1 Role of Platelets in Atherosclerosis:

Platelets play important role in atherosclerosis formation. Platelets can interact with both leukocytes and endothelial cells and secrete various inflammatory factors and promote inflammation. On the other hand, inflammation inhibits anti-thrombotic effect on endothelial cells²². Activated platelets firmly adhere to vascular endothelium via β_3 integrins, release pro-inflammatory compounds (IL-1 β , CD40L), and induce a proatherogenic phenotype of endothelial cells (chemotaxis, MCP-1; adhesion, ICAM-1). Subsequently, adherent platelets recruit circulating leukocytes, bind them, and inflame them by receptor interactions, thereby initiating leukocyte transmigration and foam cell formation. Thus,

platelets provide the inflammatory basis for plaque formation before physically occluding the vessel by thrombosis upon plaque rupture²³. Actually, platelet P-selectin expression and the number of platelet-derived microparticles (PMPs) levels showed positive associations with abnormal carotid intima-media thickness (IMT), suggesting a critical role of enhanced platelet reactivity in atherosclerotic wall alteration²⁴.

4.2 Role of Tissue Factor:

One of the potentially important mechanisms of atherosclerotic cardiovascular risk is the expression of TF on the cell membrane surface and/or the release of TF as the soluble form or microparticle-bound from stimulated cells or disrupted atherosclerotic plaque. Apart from its known effects on blood coagulation, TF can also function as a signaling receptor, which activates an intracellular signaling pathway that leading to cell proliferation, angiogenesis, and inflammation. This may play a key role in the link between the inflammation–atherosclerosis–thrombosis trilogy^{25,26}.

4.3 Role of Thrombin in Atherosclerosis:

In addition to its physiological roles in the hemostatic system, thrombin has an array of effects on endothelial cells as a trigger of endothelial dysfunction, regulation of vascular tone and permeability, VSMC proliferation, and recruitment of monocytes into the atherosclerotic lesions. Moreover, thrombin has an important role in platelet-mediated pro-inflammatory cascades, resulting in stimulation of ICAM-1, VCAM-1, E-selectin, and MMPs. Furthermore, α -Thrombin is a potent mitogen and stimulates cell division and promotes angiogenesis, possibly through vascular endothelial growth factor. All of these mediators are involved in the pathophysiology of atherosclerosis and contribute to the initiation, formation, progression and destabilization of coronary atherosclerotic plaques. Its signaling mechanisms with a pro-atherogenic impact on the arterial vessel wall are mostly established via Proteinase-activated receptors (PARs)^{27,28}.

4.4 Interaction of Fibrinolytic System with Atherosclerosis Formation:

PAI-1 may be involved in CAD as a result of the initialization and progression of atheromatosis with enhanced fibrin accumulation, either by a fibrinolysis impaired effect or by enhancing the feedback synthesis response²⁹. Cells in the advanced atherosclerotic plaques express high levels of urokinase-type plasminogen activator (uPA) and its receptor (uPAR). Apart from being a regulator of fibrinolysis, uPA mediate the extracellular matrix (ECM) degradation, and plays a pivotal role in cell adhesion, migration and proliferation, during tissue remodeling³⁰.

5. Conclusions

While it is used to refer the hemostatic system as being involved in atherothrombosis, it was meant particularly the second phase (thrombosis). Currently, it can be said that it may be involved in both processes, perhaps equally. More research areas are opened now to elucidate these hidden roles of the hemostatic system in atherosclerotic ischemic heart disease.

The immediate goals in atherosclerosis management are to relieve symptoms and to improve organ perfusion. Aggressive risk factor modification to retard or prevent ongoing atherosclerosis is among the most important parts of long-term management. Smoking cessation, meticulous control of hypertension and diabetes, weight management, and lipid-lowering therapy should all be advised. While anticoagulant therapy is one of remarkable therapeutics in the clinical consequences of atherosclerosis, proper use of anticoagulant (type, route, and dose), may be included among atherosclerosis risk factor modification, however, further intensive studies should be carried out.

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