Clinical and Research Applications of Markers of Thrombosis

Manesh R. Patel, MD
and Richard C. Becker, MD

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Summary

We provide a brief overview of vascular thrombosis as applied to the arterial circulatory system. This background serves as a template for understanding potential biomarkers of thrombosis. Additionally, the integrated relationship between genotype and phenotypic expression of disease, measurable as circulating (soluble) proteins and cell-based products, including fibrinogen, thrombin, thrombomodulin, tissue factor, tissue factor pathway inhibitor, platelet surface markers, and others, is highlighted. Finally, the role of endothelial cell and endothelial cell-surface markers as biomarkers of thrombosis is discussed. As applicable, the clinical and potential research applications of specific biomarkers of thrombosis are provided.

Key Words: Thrombosis; biomarker; coagulation; endothelial cell.
INTRODUCTION

Hemostasis is the physiological process that maintains blood in a fluid state within circulation (2). Under normal physiological circumstances, blood components do not interact with an intact vascular endothelium. Arterial thrombosis, like venous thrombosis, as described by Virchow, occurs when there is alteration in blood flow, change in the hemostatic protein composition of blood, or change in the vessel wall. The activation of coagulation leads to a series of cell-surface-based events that result in the activation of multiple proteins. These proteins not only function to increase the clotting ability of blood, but they simultaneously activate anticoagulant processes as well. In this manner, the exquisite balance of hemostasis is restored with both thrombin and fibrin generation and degradation all occurring at any given moment.

Thrombosis within the coronary vascular bed is a dynamic process, with clot formation and dissolution occurring simultaneously at many sites. Occlusive thrombus and circulatory compromise occur when there is a shift in the balance between these processes (1). Recent advances in understanding the pathobiology of atherothrombosis have demonstrated a finely orchestrated interplay among inflammation, thrombosis, and oxidative stress. As the fundamental properties of atherogenesis, endothelial cell injury/dysfunction, plaque metamorphosis, and thrombogenesis are elucidated, measurable biological markers representing the natural history of disease that can be used for diagnosis, risk assessment, and the management of patients with coronary atherothrombosis are likely to emerge.

INITIATION OF THROMBOSIS

The initiation of thrombosis is dependent on two critical steps: vessel wall injury and the adherence of platelets on this disrupted surface. When there is a dysfunctional surface or a breach in the endothelial surface, a series of biochemical events is triggered that leads to the rapid deposition of platelets and insoluble fibrin as an initial plug that is the start of the repair process. In a cell-based model of arterial thrombosis, the integrity and state of the endothelium are the basis for the initiation of thrombosis (3). The pivotal step in transforming the endothelium into a procoagulant surface is the production of tissue factor (4,5) (Fig. 1). Tissue factor is an integral membrane glycoprotein that must be anchored to a phospholipid membrane to be active (6). Activated monocytes, attracted to sites of vascular injury by tumor necrosis factor (TNF)-α and interleukin-1, also elaborate tissue factor (7,8). Tissue factor forms a complex with factor VII and activated factor VII (VIIa), a powerful procoagulant complex that cleaves its substrates, factor IX and factor X, and starts the coagulation cascade (6,9).

In addition to elaborating tissue factor when activated, the endothelium participates in the second component of thrombus initiation—platelet deposition. The primary molecule responsible for platelet adhesion is von Willebrand factor (vWF), especially in vessels with high shear stress such as coronary vessels (10,11). This molecule is synthesized by the endothelium. Activated or injured endothelial cells (ECs) can also release vWF and P-selectin, molecules also involved in platelet and leukocyte adhesion (12). Storage granules, called Weibel-Palade bodies, contain P-selectin and vWF within the EC and fuse with the cell membrane on activation to present these molecules on the EC surface (13,14). In this manner, through either activation or severe injury leading to deendothelialization, the molecular signals for both the initiation of coagulation and platelet adhesion are initiated at the vessel wall.