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REVIEW TOPIC OF THE WEEK

Arterial Thrombus Stability

Does It Matter and Can We Detect It?

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ABSTRACT

The spontaneous lysis of a coronary thrombus is a natural protective mechanism against lasting occlusion and downstream infarction. Thrombus stability is thus a direct determinant of clinical outcome. Compared with the extensive study of the crucial role of platelets, coagulation, and flow in arterial thrombosis, little attention has been paid to factors affecting thrombus stability, despite evidence linking impaired spontaneous fibrinolytic activity with acute coronary events. We summarize experimental evidence for the importance of thrombus stability and highlight the need for physiologically relevant tests to assess spontaneous disintegration/fibrinolysis of platelet-rich thrombi under arterial flow conditions, review techniques to assess thrombus stability in vitro, and describe novel imaging techniques to characterize thrombosis in vivo. Such techniques may allow tailoring of pharmacotherapy to potentiate thrombus instability, through fragmentation of platelet thrombi and/or enhanced endogenous fibrinolysis, to reduce infarct size. (J Am Coll Cardiol 2017;70:2036–47) © 2017 by the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

The stability of an arterial thrombus, specifically the strength of its attachment to the vessel wall and its resistance to dislodgment by flowing blood, will determine the clinical sequelae of the thrombotic occlusion, namely the extent of subsequent downstream tissue damage (1) (**Central Illustration**). Understanding the crucial role of platelets, coagulation, and flow conditions in the mechanism of coronary thrombus formation has translated into the application of potent antiplatelet and anticoagulant agents for the treatment and prevention of thrombosis. In contrast, the determinants of thrombus stability, namely factors that confer stability on an arterial thrombus and impart resistance to arterial flow and shear conditions, have been far less well explored and have resulted in no new pharmacologic approaches or better targeting of currently available treatments.

In vitro studies of thrombus stability have been largely confined to the assessment of fibrinolysis (plasma or whole blood clot lysis) under low-flow conditions, to the assessment of the structure and density of the fibrin meshwork, and to the study of the effects of various fibrinolysis inhibitors (2,3). It is increasingly recognized that the in situ generation of thrombin from within the platelet thrombus, as well as platelet- and leukocyte-derived integrins and plasma coagulant proteins, exert a profound effect on thrombus stability (4,5). Because thrombin generation is inhibited by citrate, the contribution of thrombin to stability cannot be assessed by using anticoagulated blood (6). Thrombus instability results

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in the formation of macroemboli or microemboli, whose susceptibility to lysis in the circulation will determine the downstream clinical sequelae. Currently available antiplatelet medications inhibit thrombus formation by preventing platelet activation and/or aggregation in response to specific agonists, but the in vivo antithrombotic effects, including the specific effects of such medications on thrombus stability and endogenous fibrinolysis, are largely unknown.

Since the last review of this subject in 2006 (7), significant advances have been made in understanding the mechanisms that confer stability on an arterial thrombus. The aim of the present review was to assess the relevance of key mediators of thrombus stability in determining clinical outcome and to discuss techniques currently available for assessing this subject. The importance of the assessment of coronary thrombus stability is 2-fold. First, there is a need to assess the "thrombotic status" of an individual to predict the likelihood of occlusive thrombus formation and to assess the likely response to different medications, using in vitro or ex vivo techniques. Second, there is a need to detect and image the state of the coronary thrombus in vivo, whether stable or unstable, when a coronary thrombotic event occurs, and to visualize downstream myocardium and assess response to pharmacotherapy by using noninvasive imaging modalities.

FACTORS INFLUENCING THE STABILITY AND FATE OF ARTERIAL THROMBI

FIBRIN. Activation of the coagulation system consolidates the developing platelet aggregate, such that the resultant thrombus can resist arterial pressure and ultimately grow to fully occlude the arterial lumen. The contribution of the coagulation process to arterial thrombus formation is shown in **Figure 1**. Regardless of the whether the intrinsic or extrinsic pathway of coagulation predominates, thrombin plays a key role. Activated platelets initiate the contact (intrinsic) phase of coagulation by expressing phosphatidylserine on their surface membrane, which leads to in situ thrombin generation on the platelet surface.

Among factors that affect or modulate the structure and the stability of an arterial thrombus, thrombin perhaps plays the key role (**Central Illustration**). Thrombin concentration modulates fibrin structure, and the resultant fibrin architecture directly affects the stability of the thrombus. At low concentrations of thrombin, porous clots with thick fibrin fibers are formed, whereas at high thrombin concentrations, a dense network of thin fibers is formed. Thrombus comprising thicker fibrin fibers is more susceptible to lysis than thrombus composed of thinner, more dense fibrin fibers (8). Electron microscopy has shown that thrombin generated in situ, on the surface of activated platelets, produces a significantly denser fibrin fiber network than the addition of exogenous thrombin, and this increased fibrin density translates into greater resistance to lysis closer to the cell surface (9). When fibrin polymerization was blocked in whole blood perfused over a collagen surface, thrombus growing to cause 90% luminal obstruction was unstable and embolized at very low shear rates; thrombus formed in whole blood in which fibrin formation was not inhibited could withstand extremely high shear without embolization (10).

Although thrombin has a key role, other components of the coagulation system, in particular factors XIIIa and XIIa and von Willebrand factor (vWF), also modulate the 3-dimensional structure of the fibrin meshwork (**Figure 1**).

Evaluation of intracoronary thrombi aspirated during primary coronary angioplasty from patients presenting with ST-segment elevation myocardial infarction, using electron microscopy and clot permeability studies, showed that the content of fibrin and vWF within the thrombus were predictors of thrombolysis resistance (11).

FLOW. In addition to the effects of thrombin and fibrin, the effects of blood flow—which both delivers platelets to the site enabling thrombus growth and also subjects the growing thrombus to shearing forces that remove individual or small groups of platelets or causes large-scale embolization—have an impact on clot stability. To evaluate the independent contributions of thrombin and fibrin generation on clot growth and stability, Gly-Pro-Arg-Pro (GPRP) was used to block fibrin polymerization in vitro; the goal was to determine the effects of thrombin independent of fibrin formation (10). The fibrin mesh was shown to confer a 12- to 28-fold increase in shear resistance on a growing clot. Under arterial wall shear rates (1,000 s^{-1}) at constant flow, the nonocclusive platelet and fibrin deposits (without GPRP) could withstand maximum shear rates of approximately 29,000 s^{-1} at about 95% of full channel occlusion, whereas embolization was marked with GPRP present when shear forces were as low as approximately 2,900 s^{-1}. The very high shear rates that exist in stenosed coronary arteries have great impact not only on the growth rate

ABBREVIATIONS AND ACRONYMS

ADP = adenosine diphosphate

DTI = direct thrombus imaging

GPRP = Gly-Pro-Arg-Pro

MR = magnetic resonance

MRI = magnetic resonance imaging

NET = neutrophil extracellular trap

t-PA = tissue type plasminogen activator

vWF = von Willebrand factor

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