

REVIEW TOPIC OF THE WEEK

# Endogenous Fibrinolysis

## An Important Mediator of Thrombus Formation and Cardiovascular Risk



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### ABSTRACT

Most acute cardiovascular events are attributable to arterial thrombosis. Plaque rupture or erosion stimulates platelet activation, aggregation, and thrombosis, whilst simultaneously activating enzymatic processes that mediate endogenous fibrinolysis to physiologically maintain vessel patency. Interplay between these pathways determines clinical outcome. If proaggregatory factors predominate, the thrombus may propagate, leading to vessel occlusion. However, if balanced by a healthy fibrinolytic system, thrombosis may not occur or cause lasting occlusion. Despite abundant evidence for the fibrinolytic system regulating thrombosis, it has been overlooked compared with platelet reactivity, partly due to a lack of techniques to measure it. We evaluate evidence for endogenous fibrinolysis in arterial thrombosis and review techniques to assess it, including biomarkers and global assays, such as thromboelastography and the Global Thrombosis Test. Global assays, simultaneously assessing proaggregatory and fibrinolytic pathways, could play a role in risk stratification and in identifying impaired fibrinolysis as a potential target for pharmacological modulation. (J Am Coll Cardiol 2015;65:1683-99) © 2015 by the American College of Cardiology Foundation. Open access under [CC BY-NC-ND license](#)

Cardiovascular disease is the leading cause of morbidity and mortality in developed countries. The common pathological process responsible for the majority of these disorders, including acute coronary syndrome (ACS) and ischemic stroke, is the development of an occlusive arterial thrombus.

Disruption of an atherosclerotic plaque through rupture or erosion creates a prothrombotic environment to circulating platelets and procoagulant factors. The major thrombogenic components contained within the atherosclerotic plaque include tissue factor and collagen (1-3). Exposure to this thrombotic milieu provides a potent stimulus for platelet activation, aggregation, and thrombosis (Figures 1A and 1B).

Activation of the coagulation cascade also leads to direct activation of the enzymatic processes that mediate endogenous fibrinolysis (Figure 1C). This interaction is important to ensure that thrombosis is controlled and vessel patency is maintained.

The interplay between these opposing pathways is likely to determine the occurrence and clinical outcome of a resulting thrombus. If proaggregatory and procoagulant factors predominate, an intraluminal thrombus may propagate and lead to complete vessel occlusion, with subsequent lasting downstream tissue damage (Figure 1B). If, in contrast, the prothrombotic factors are balanced by a healthy fibrinolytic system, then a thrombus may not develop or may not cause lasting vessel occlusion (Figure 1C).

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## ABBREVIATIONS AND ACRONYMS

<b>ACS</b>	= acute coronary syndrome(s)
<b>AMI</b>	= acute myocardial infarction
<b>GTT</b>	= Global Thrombosis Test
<b>MACE</b>	= major adverse cardiovascular event(s)
<b>PAI</b>	= plasminogen activator inhibitor
<b>ROTEM</b>	= rotational thromboelastometry
<b>SR</b>	= spontaneous reperfusion
<b>STEMI</b>	= ST-segment elevation myocardial infarction
<b>TAFI</b>	= thrombin-activatable fibrinolysis inhibitor
<b>TEG</b>	= thromboelastography
<b>t-PA</b>	= tissue-type plasminogen activator

## IMPORTANCE OF THE ENDOGENOUS FIBRINOLYTIC SYSTEM IN ACS

An intact endogenous fibrinolytic system serves to actively prevent the buildup of formed thrombi through dissolution of an arterial thrombus (**Central Illustration**). Despite a wealth of evidence supporting its role in preventing lasting arterial occlusion, this pathway has been relatively overlooked as compared with the understanding, monitoring, and pharmacological modulation of platelet reactivity. This may have occurred due to limitations of earlier methods to robustly measure the activity of the fibrinolytic system. Additionally, besides the use of plasminogen activators to achieve acute thrombolysis in the setting of acute myocardial infarction (AMI) and stroke, pharmacological options available to manipulate the fibrinolytic state have been very limited.

Evidence from clinical, histopathologic, and autopsy studies (4-9), as well as clinical observations, support the proposal that AMI may represent a failure of timely, spontaneous endogenous thrombolysis. In 585 patients presenting with ST-segment elevation myocardial infarction (STEMI), spontaneous reperfusion (SR), evidenced by electrocardiographic resolution of ST-segment changes, was observed in 14.9%, and normal coronary flow on angiography was observed in 14.7% of patients (10). In 1,667 patients assigned to the primary percutaneous coronary intervention arm of the ASSENT 4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction) trial (11), SR was associated with a lower composite of death, heart failure, or shock compared with those with persistent ST-segment elevation. In 710 STEMI patients undergoing primary percutaneous coronary intervention, SR was observed in 22%, and these patients had a lower incidence of death, congestive heart failure, and recurrent ACS at 30 days than those without SR (12). Furthermore, histopathologic studies evaluating aspirated coronary thrombi from patients with STEMI have demonstrated significant heterogeneity in the composition and age of the culprit thrombi (4-7). Among 1,362 STEMI patients, up to 40% demonstrated lytic or organized thrombi, signifying that thrombus formation occurred days to weeks before final vessel occlusion (7). This underpins the notion that thrombus generation is an active and dynamic process, where constant thrombosis and thrombolysis may occur in concert.

Autopsy studies of healed plaque disruptions also provide evidence of thrombus formation as a dynamic process (8,13). Plaque instability appears to be present for some time before an occlusive thrombus is formed, and may be asymptomatic. Nonocclusive mural thrombi may form over plaque disruptions, leading to phasic progression of atherosclerotic lesions, but without presenting as ACS (13,14).

Despite the fact that plaque rupture represents a common unifying event for coronary thrombosis, there is significant variability in clinical manifestation and outcome. This variability may be explained, in part, by the role of endogenous fibrinolysis in limiting the propagation of formed thrombi and preventing total coronary occlusion (**Central Illustration**). In this paper, we review the methods currently available to assess endogenous fibrinolysis and evaluate the evidence for the role of endogenous fibrinolysis as a mediator of arterial thrombus formation in coronary disease.

## FACTORS DETERMINING RESISTANCE OF THROMBUS TO LYSIS

Whole blood clots are more resistant to lysis than plasma clots, implying that blood cells and fibrin are responsible for the resistance (15) (**Central Illustration**). Platelets play the main role in resistance, but red cell-derived microparticles can also contribute to thrombin generation, whereas elastase released from leukocytes trapped or adherent to the thrombus exerts a plasmin-independent fibrinolytic effect. Arterial (platelet-rich) thrombi are much more resistant to lysis than erythrocyte-rich venous thrombi (16). The mechanisms through which platelets contribute to thrombolysis resistance are 3-fold (**Central Illustration**):

1. Platelets contain >90% of the circulating plasminogen activator inhibitor (PAI)-1. During aggregation, in response to thrombin, PAI-1 is released from platelets into the thrombus mass and is the major determinant of arterial thrombolysis resistance (17).
2. The procoagulant activity or contribution of platelets to thrombin generation is extremely important, not only in the generation of, but also in the lysis of the formed thrombus. A high shear stress milieu, such as that found in an artery with a severe stenosis, will trigger microparticle release from activated platelets, resulting in a burst of thrombin generation. In addition to PAI-1, thrombin-activatable fibrinolysis inhibitor (TAFI) also contributes to thrombolysis resistance.

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