Endogenous Thrombolysis
A Hidden Player in Acute Coronary Syndromes?*

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Arterial thrombosis is a major cause of morbidity and mortality worldwide. Rupture or erosion of an atherosclerotic plaque stimulates platelet adhesion and aggregation and activation of the coagulation cascade, which result in thrombus formation. The fate of an evolving thrombus is largely determined by the balance between proaggregatory and procoagulant factors, on the one hand, and the fibrinolytic system, on the other (1). If the former prevail, thrombus growth may result in complete arterial occlusion with potentially devastating consequences.

The global thrombosis test (GTT) (Montrose Diagnostics, London, United Kingdom) is a recently developed point-of-care test aimed to assess simultaneously platelet reactivity and spontaneous thrombolysis in non-anticoagulated blood (12). In this test, blood is allowed to flow through a conic plastic tube containing 2 steel ball bearings, a flat segment on the inner wall of the tube preventing the balls from occluding the lumen. Platelets become activated by high shear stress by their passing through the narrow gap between the larger ball bearing and the wall. Activated platelets aggregate and initiate coagulation in the space downstream, and fibrin-stabilized platelet aggregates occlude the second gap, stopping blood flow. If spontaneous thrombolysis occurs, blood flow is restored. The test measures the occlusion time (OT) and the lysis time (LT), which have been shown to reflect, respectively, thrombus formation and spontaneous thrombolysis (12).

Recognition of the importance of platelet activation and the coagulation cascade in this process has fueled the development of a large number of drugs targeting different mechanisms of platelet aggregation and thrombin generation. These drugs have become one of the mainstays of the prevention and treatment of acute coronary syndromes (ACS) and other vascular events (2). In addition, several bedside platelet function assays have recently been developed that have been able to predict thrombotic complications and could be useful for tailoring antiplatelet therapy (3,4).

In contrast with the wealth of information on prothrombotic factors, the role of endogenous fibrinolysis in arterial thrombosis has often been neglected. This may have occurred, on the one hand, because of the lack of specific drugs that enhance fibrinolysis—apart from plasminogen activators in the setting of acute myocardial infarction or ischemic stroke—available for clinical use (1). On the other hand, studies that have investigated the association between fibrinolytic status—by assessing genetic variants related to the activity of the individual molecules involved or by directly measuring their plasma levels—with the risk of thrombotic events have obtained conflicting results (5–8). In addition to the varying methodologies, these inconsistencies have been attributed to the marked variation of plasma levels of fibrinolytic proteins both between and within subjects (1) and to nonfibrinolytic properties of these proteins with opposing effects on atherothrombosis (8). Despite these shortcomings, the evidence of early spontaneous reperfusion in 15% to 20% of patients with ST-segment elevation myocardial infarction (9) or ischemic stroke (10), and the finding in the former that the culprit thrombus is often heterogeneous in composition and age (11), support the concept of arterial thrombosis as a dynamic process in which endogenous fibrinolysis may play a prominent role.

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In this issue of the Journal, Saraf et al. (13) assessed the value of the GTT in predicting major adverse cardiac events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or stroke, after a 12-month follow-up of 300 ACS patients on dual-antiplatelet therapy. A control sample of 100 healthy people was also tested. As compared with untreated controls, ACS patients had more prolonged OT and LT, indicating less thrombogenicity and impaired thrombolysis. Whereas OT was not associated with outcome, a prolonged LT was predictive of MACE even after adjusting for some baseline predictors. Receiver-operating characteristics curve analysis showed that LT significantly discriminated between patients with and without MACE (area under the curve = 0.63). A cutoff of LT ≥3,000 s provided the best discrimination, and the risk increased...
further as LT increased. The net reclassification improvement attained by including LT ≥3,000 s in a model with other predictors was estimated at 0.26 (p < 0.001). In a subset of 100 patients, OT was weakly associated with the results of the VerifyNow P2Y12 assay (Accumetrics, San Diego, California), which were also not predictive of MACE. The authors concluded that impaired endogenous thrombolysis measured with GTT is an independent risk factor for recurrent thrombotic events.

This is the first study addressing the prognostic usefulness of a global assessment of endogenous thrombolysis in patients with coronary artery disease, and the authors are to be credited for their original approach. The results should prompt renewed interest in the role of endogenous fibrinolysis in the pathophysiology of ACS and in the potential utility of assessing thrombolytic status in patients with this and other clinical conditions. Nevertheless, owing to these potential important implications, some issues should be discussed.

First, the variability of LT measurements was relatively high (coefficient of variation of about 20%) both in control subjects and ACS patients. Although this variability concurs with previous studies with the same technique and with that observed by biochemical determinations of individual markers of fibrinolysis (1), it might compromise the interpretation of the results in a given patient, particularly if they are close to the proposed cutoff value.

Second, as the authors acknowledged, that GTT was performed only once during the acute phase represents a limitation. A residual effect of the antithrombotic regimens used in the initial management of patients on platelet function could have affected OT and its relation to MACE. Similarly, the value of LT in predicting complications might have been different had patients been tested at a later stage. In this respect, significant changes in the levels of fibrinolytic markers have been described during the first days after an ACS (14).

Finally, but not less important, the sample size was relatively small for a study of this nature. The low number of events obliged the authors to restrict the multivariable adjustment to a reduced number of predictors. Ejection fraction was not systematically recorded, and no adjustment was intended for heart failure, a variable with a strong association with adverse events in ACS patients (15,16). This is a significant limitation because the incremental prognostic value of LT might have been substantially lower after adequate adjustment for all the clinical predictors.

Hopefully, future studies will shed light on these issues. Meanwhile, the present results should encourage reassessment of the role of endogenous thrombolysis not only in ischemic heart disease but also in other conditions suspected to be influenced by the fibrinolytic status such as deep vein thrombosis or bleeding disorders. To date, no specific modulators of the fibrinolytic status are available for chronic use in humans (1). However, a more precise knowledge of its role in these clinical conditions, to which the study of Saraf et al. (13) has contributed significantly, is a prerequisite for the future development of effective therapies targeting endogenous thrombolysis.

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REFERENCES


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