

EDITORIAL COMMENT

Is Endogenous Fibrinolysis a Major Player in Occurrence of Atherothrombotic Events Following Acute Myocardial Infarction?*



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An arterial atherothrombotic event is a finely regulated process involving a complex interplay between vulnerable blood, vulnerable vessel, and blood stasis. Following exposure of prothrombotic components by rupture or erosion of the vulnerable plaques, the formation of obstructing intraluminal thrombus is one of the most important pathomechanisms in clinically relevant presentation with acute myocardial infarction (AMI). Vulnerable blood (thrombogenicity) comprises complex interactions between cellular components (eg, platelet and inflammatory cells) and plasma factors (inflammatory, procoagulant, anticoagulant, and fibrinolytic factors).¹

Endogenous fibrinolysis is a powerful natural defense mechanism against arterial thrombotic occlusion. Multiple clinical studies have shown that impaired endogenous fibrinolysis (or hypofibrinolysis) can be detected in a significant number of patients with acute coronary syndrome (ACS), which

is a recently recognized risk factor for developing a recurrent cardiovascular (CV) event.¹ In addition, patients with spontaneous ST-segment elevation resolution before percutaneous coronary intervention had more rapid and potent fibrinolysis than those without. However, the mechanistic determinants of the endogenous fibrinolytic system have not been well understood, and translational research in this area is required to assess its prognostic implication in a diverse spectrum of CV diseases.

In this issue of *JACC: Basic to Translational Science*, Kanji et al² investigated the determinants of endogenous fibrinolysis with the prespecified subgroup analysis of the RISK-PPCI (RISK model to predict adverse outcomes after Primary Percutaneous Coronary Intervention) cohort including patients with ST-segment elevation myocardial infarction (STEMI) (n = 129).² In these patients, the level of whole blood endogenous fibrinolysis measured by global thrombosis test was modestly related to fibrinogen (r = 0.300, P = 0.001), high-sensitivity C-reactive protein (r = 0.236, P = 0.011), and shear-induced platelet reactivity. This indicator was only weakly related to plasma clot lysis in response to tissue plasminogen activator, indicating an important role for cellular components in determining fibrinolytic status. In addition, patients with a lysis time ≥2,500 seconds showed a 3.6-fold higher risk of clinical events, predominantly driven by CV death, compared with those with a lysis time <2,500 seconds. The investigator found that whole blood lysis time was superior to other hemostatic parameters in predicting clinical outcomes among these STEMI patients. Whole blood occlusion time was not able

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to predict the risk of clinical events in this study. The investigators insisted on the evidence for bidirectional crosstalk between coagulation and inflammation, and mechanistic insights to guide pharmacological strategies to treat hypofibrinolysis.

Another large-scale clinical study from the PLATO (Study of PLATelet Inhibition and Patient Outcomes) trial showed a similar finding in 4,354 ACS patients.³ In this study, a validated turbidimetric assay was employed to evaluate plasma clot lysis time and maximum turbidity (a measure of clot density). After adjusting for CV risk factors, each 50% increase in lysis time and maximum turbidity was associated with an increased risk of CV death by 1.36-fold and 1.24-fold, respectively. After adjustment with other prognostic biomarkers, the association with CV death remained significant for lysis time (HR: 1.20; 95% CI: 1.01-1.42; $P = 0.042$) but not for maximum turbidity. These observations would be another clinical evidence to support prognostic implication of endogenous fibrinolytic activity in AMI patients.

Attempts to prevent atherothrombotic events have mainly focused on diminishing the formation of a thrombus through control of platelet and coagulation activity. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ receptor inhibitor is a standard strategy to control the activated platelet reactivity in ACS patients, and the prognostic implication of high platelet reactivity measured by platelet function test has been suggested to introduce a potent P2Y₁₂ receptor inhibitor.⁴ The limited clinical benefit of this strategy has been observed according to the disease acuity and phase. In addition, maintained hypercoagulability and impaired endogenous fibrinolysis appeared to be unaffected by the current DAPT strategy. In addition, the inflammatory activity has been identified to increase the residual ischemic risk in patients presented with ACS. Therefore, both the inflammation and coagulation pathways may contribute to increase the risk of atherothrombotic events through the cross-over interaction between the 2 pathways.

Decreased potential in the ability to naturally dissolve or lyse a developing thrombus may be responsible for a major part of the residual ischemic risk in ACS patients on an optimal antiplatelet regimen. The Global Thrombosis Test measures the time taken for shear-induced occlusive thrombus formation (occlusion time) and the time to achieve spontaneous lysis of thrombi in the second phase of the test (lysis time).¹ Lysis time of whole blood may reflect in vivo clot generation at the site of vascular injury. Contrary to other hemostatic measurements, the thrombogenic stimulus of the Global Thrombosis

Test is high shear rate alone, and no chemicals (platelet agonists or procoagulants) are added.

The investigators reported that a prolonged fibrinolysis time ($\geq 2,500$ seconds) as determined by Global Thrombosis Test was associated with a higher rate of a long-term ischemic event, which is in line with earlier observations.¹ A higher level of creatinine was only an independent predictor of prolonged lysis time ($\geq 2,500$ seconds: OR: 1.02; 95% CI: 1.00-1.03; $P = 0.035$), which may indicate the limited association with coagulation and inflammation. Furthermore, being a substudy of a small, single-center clinical study with only 36 patients who experienced clinical events, meticulous caution in interpretation is warranted. The follow-up period was limited to 1 year, and that the adverse event occurred mainly at a very early period may also be a limitation. Whether impaired endogenous fibrinolysis is a modifiable risk factor can be an important issue. DAPT regimen reduces platelet reactivity over time, whereas lysis time appears unaffected by oral antiplatelet medications. Previous data have suggested that lysis time could be reduced by direct oral anticoagulants and the protease-activated receptor (PAR)-1 inhibitor. Direct oral anticoagulants or the PAR-1 inhibitor in addition to antiplatelet therapy may reduce the risk of recurrent ischemic events in ACS. Testing an endogenous fibrinolysis could identify those who may benefit most from additional anticoagulation in ACS patients.

Global hemostasis tests such as TEG (Haemonetics) or ROTEM (Tem International) use citrated whole blood to measure clot formation under low shear, by transducing changes in the viscoelastic properties of blood.¹ Clotting is initiated with kaolin, and a transducer detects changes in clot viscoelastic properties that reflect clot formation and lysis. Our group has suggested the close association between platelet-fibrin clot strength (maximal amplitude ≥ 68 mm) and coronary microvascular dysfunction (index of microcirculatory resistance of >40 U) in AMI patients⁵ and the prognostic implication of platelet-fibrin clot strength (maximal amplitude ≥ 68 mm) in patients presenting with stable angina.⁶ From this analysis, we could not find any association between endogenous fibrinolysis activity (lysis time at 30 minutes) and clinical events. The level of platelet-fibrin clot strength was modestly related to prothrombin time ($r = 0.154$, $P = 0.001$), fibrinogen ($r = 0.334$, $P < 0.001$), hemoglobin ($r = 0.279$, $P < 0.001$), and platelet count ($r = 0.301$, $P = 0.011$). In addition, the level of lysis time was modestly associated with fibrinogen ($r = 0.102$, $P < 0.001$). These data also showed the linkage of clot strength and fibrinolysis

time with other hemostatic measurements. Furthermore, exploring the association between coagulability and fibrinolysis is an interesting issue in predicting clinical outcomes. Future studies regarding combined phenotype with hypercoagulability and impaired fibrinolysis are needed in various clinical events.

In summary, the investigators are to be congratulated for their novel study that investigates the determinants of endogenous fibrinolysis in patients with STEMI. Important considerations from Kanji et al are that the effectiveness of endogenous fibrinolysis in whole blood is related in part to fibrinogen levels, inflammation, and shear-induced platelet reactivity. Their findings provide evidence for bidirectional crosstalk between coagulation and inflammation and support the importance of cellular components. It is difficult to generalize the causality due to a retrospective design and a small sample size in a single-center population. In conclusion, it is important to consider endogenous fibrinolysis and its determinants that affects to clinical outcomes in AMI patients. The impaired endogenous fibrinolysis related with increased thromboinflammatory state is

appreciated as a key influencer of clinical events, which might be a modifiable risk factor in ACS patients. Given the perspectives, assessing an endogenous fibrinolysis using the Global Thrombosis Test may enhance risk stratification and facilitate future targeting of adjunctive antithrombotic therapies.

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