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EDITORIAL COMMENT

Can We Use Viscoelastic Testing to Evaluate Microvascular Dysfunction in Acute Myocardial Infarction?*

Jerrold H. Levy, MD,[a] Kenichi A. Tanaka, MD[b]

The assessment and application of hypercoagulability characteristics in routine clinical practice continue to be important but poorly defined issues. It is a logical consideration that in the setting of acute vascular injury, a prothrombotic milieu resulting in occlusive clot generation will accelerate the progression and worsening of organ injury, especially for highly vascular organs. The current pandemic and increasing number of publications reporting hypercoagulability in the setting of microcirculatory and endothelial injury associated with SARS-CoV-2 viral infections has increased this recognition (1). In addition, the widespread use of laboratory testing and critical biomarkers to determine adverse thrombotic outcomes in COVID-19 has increased awareness of the role of hypercoagulability for clinicians, as prognostic tests that include D-dimer and fibrinogen levels, but also with increasing reports of viscoelastic testing (1).

Viscoelastic testing with the currently available point-of-care monitoring systems has also been increasingly reported as a diagnostic tool beyond bleeding management in surgery and trauma for its predictive value in patients with coronary artery disease. In this issue of *JACC: Basic to Translational Science*, Kang et al (2) explored the association between thrombogenicity and coronary microvascular dysfunction in Korean patients with acute myocardial infarction (MI). Between 2013 and 2017, the authors evaluated pre-procedural thrombogenicity using thromboelastography (TEG) (TEG 5000, Haemonetics), D-dimers, and fibrinogen levels in 114 patients. Coronary microvascular dysfunction was defined as an index of microcirculatory resistance of >40 U using an invasive physiologic test. The main hypothesis was a pre-procedural assessment of heightened thrombogenicity, defined as increased platelet-fibrin clot strength by thromboelastography is significantly associated with the risk of coronary microvascular dysfunction and major adverse cardiovascular events (MACE) over 3 years. As expected, age 75 years or older showed the strongest association with post-procedural coronary microvascular dysfunction at an odds ratio of 4.86, and with MACE at a hazard ratio of 7.0. Among the measured thrombogenicity parameters, a high platelet-fibrin clot strength of 68 mm or greater was significantly associated with coronary microvascular dysfunction (odds ratio: 3.16), and a higher rate of MACE (adjusted hazard ratio: 4.33). Furthermore, combined risk stratification with coronary microvascular dysfunction and platelet-fibrin clot strength increased the prognostic implication to predict the rate of long-term clinical outcomes. These observations are potentially important if platelet-fibrin clot strength could be used to diagnose and treat increased thrombogenicity with personalized antithrombotic therapy before long-term clinical events occur.

The microvascular circulation is a critical component of major organ viability, especially for such metabolically active organs as the cardiopulmonary and renal systems. The endothelium provides an extensive anticoagulant, anti-inflammatory,

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From the [a]Departments of Anesthesiology, Critical Care, and Surgery, Duke University School of Medicine, Durham, North Carolina, USA; and the [b]Department of Anesthesiology, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, USA.

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antiplatelet, and vascular regulatory ability to preserve blood flow and modulate vascular tone, especially in response to thromboinflammatory injury (3). With acute endothelial injury and plaque rupture in acute MI, the well-described procoagulant local vascular effects ensue, platelet activation occurs, and platelet-fibrin clot formation follows. The authors report that a high platelet-fibrin clot strength as determined by TEG in the setting of altered flow was associated with a higher rate of long-term ischemic event occurrences. Although viscoelastic testing does not reflect physiological platelet-centric thrombus formation under sheared flow, it includes interactions of platelets, red blood cells, leukocytes, coagulation, and fibrinolytic proteins in the whole blood. A clinically relevant thrombogenicity profile is based on all of the elements in whole blood and clot strength (also known as maximal amplitude on thromboelastography), and despite the limitations, may be considered as one such parameter that reflects in vivo clot generation at the site of vascular injury.

Conversely, whole blood coagulation testing poses certain limitations. First, hematocrit is an important modifier of platelet-fibrin clot strength, and the lower hematocrit becomes, the greater is platelet-fibrin clot strength (3). The predictors of coronary microvascular dysfunction in this study included advanced age and female gender, which are strong risk factors for anemia, and thus it is possible that their high platelet-fibrin clot strength cohort might have represented a high-risk population with anemia (4).

It is notable in the demographic data that Korean patients had much lower rates of metabolic syndrome compared with those reported in North America. For example, Mahla et al (5) reported the mean body mass index (BMI) of 31 kg/m^2, and the rate of hypertension and diabetes as 85% and 41% in a similar patient population in the United States. These were in contrast to the mean BMI of 24.1 kg/m^2, and the prevalence of 40.5% and 22.4% for hypertension and diabetes in the Korean study. The trend for patients with lower BMI to have coronary microvascular dysfunction is important, as it might be a reflection of frailty associated with advanced age. Collectively, these data suggest that a high platelet-fibrin clot strength, which is often used as a marker of abnormal hemostasis, can be a negative predictor in the setting of acute MI.

A number of studies have previously shown the positive association between elevated fibrinogen level and the extent of myocardial injury. In the present study, plasma fibrinogen levels were similar between coronary microvascular dysfunction and noncoronary microvascular dysfunction cohorts, but the interaction between thrombin-activated platelets and fibrin(ogen) was more robust based on the high platelet-fibrin clot strength. The activator used in this assay is kaolin, a type of clay that commonly speeds the reaction and activates coagulation via the intrinsic pathway, and platelets via thrombin generation. The kaolin-activated TEG test is not influenced by $P2Y_{12}$ inhibitors or von Willebrand factor, and its major determinants are platelet count and fibrinogen level. The authors demonstrated enhanced in vivo coagulation in the D-dimer levels in the coronary microvascular dysfunction cohort (787 ± 646 vs control, 473 ± 345 ng/mL; upper limit, 500 ng/mL). Conversely, there were trends of lower platelet count as well as platelet reactivity in the noncoronary microvascular dysfunction group (195 ± 89 vs 235 ± 110 platelet reaction unit [PRU]) on the VerifyNow $P2Y_{12}$ test (Instrumentation Laboratory). The lower PRUs were also associated with more frequent ticagrelor use, and thus patient selection might have been confounded. As the authors mentioned, ticagrelor treatment is considered to pose a higher bleeding risk following post-MI cardiac interventions in Korean patients. Collectively, lower D-dimer levels in the noncoronary microvascular dysfunction group likely reflect a small, localized thrombotic burden, and perhaps the differences also could be accounted for by the increased number of ticagrelor-treated patients.

Taken together, the authors are to be congratulated for their novel study that suggests a close relation of hypercoagulability assessed by TEG to coronary microvascular dysfunction after reperfusion in patients with acute MI. Important considerations for this study by Kang et al (2) are that high platelet-fibrin clot strength (≥68 mm) is associated with a significantly elevated risk for coronary microvascular dysfunction and MACE in older and potentially more frail patients. The causal relationship cannot be established due to a retrospective design and a small sample size in a single ethnic population. In addition, the pre-procedural parameter of platelet-fibrin clot strength does not specifically detect platelet reactivity or thrombin generation in vivo, and different viscoelastic test reagents and devices may increase the variability of the measurement.

In conclusion, it is important to consider multiple underlying factors that lead to coronary microvascular

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dysfunction and MACE following post-MI cardiac interventions. The thromboinflammatory state is increasingly appreciated as a key influencer of microvascular health, and perhaps the use of viscoelastic testing could be considered as a potential tool to identify patients with microvascular dysfunction. Viscoelastic testing may enhance risk stratification and facilitate future targeting of adjunctive antithrombotic therapies. A further prospective study is warranted to test if viscoelastic testing can predict such risks in a racially diverse population.

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ADDRESS FOR CORRESPONDENCE: Dr Jerrold H. Levy, Departments of Anesthesiology, Critical Care, and Surgery, Duke University Medical Center, 2301 Erwin Road, 5691H HAFS Box 3094, Durham, North Carolina 27710, USA. E-mail: jerrold.levy@duke.edu.

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