Abnormal fibrinolysis identified by viscoelastic tests in relation to clinical outcomes

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EDITORIAL

Abnormal fibrinolysis identified by viscoelastic tests in relation to clinical outcomes: Last call to harmonize criteria for future studies on promising associations

With the broad use of whole blood viscoelastic tests in bedside monitoring of hemostasis, the impact of abnormal fibrinolysis on adverse clinical outcomes is increasingly reported in various patient groups, including trauma, sepsis, and liver disease.[1–3] Starting from the hypothesis that liver transplant (LT) recipients with postoperative fibrinolysis resistance would have a greater risk for developing early graft dysfunction (EAD), Moore and coworkers studied the relationship between EAD and fibrinolysis resistance on postoperative day-1 (POD-1) in a paper published in this issue of *Liver Transplantation*.[4]

Viscoelastic tests are poorly suitable to detect decreased fibrinolytic activity because 0% lysis is part of the normal range for both rotational thromboelastometry (ROTEM) and thromboelastography (TEG).[5,6] The authors elegantly overcome this handicap by performing a tPA-modified TEG (tTEG), by the addition of tissue plasminogen activator (tPA) to a kaolin-induced TEG test to reach a final concentration of 75 ng/mL, which allows for adequate detection of a hypofibrinolytic status.[7]

The authors identified the tTEG LY30 < 0.0% on POD-1 as the best inflection point for the risk of EAD, with an area under the ROC curve of 0.64 (95% CI 0.56–0.73, $p = 0.002$). These data indicate that patients with ex vivo generated clots that do not lyse within 30 minutes even in the presence of generous amounts of tPA appear to be in trouble, although it is unclear whether the hypofibrinolytic state directly or indirectly links to EAD. Although the area under the ROC curve does not have a spectacular discriminatory value, the rate of EAD was substantially higher in patients with fibrinolysis resistance compared with those without (42% vs. 17%, $p < 0.001$, respectively). The odds of having EAD were 2.43 times (95% CI: 1.07–5.50, $p = 0.03$) higher in recipients with fibrinolysis resistance. The authors therefore suggest that a tTEG LY30 on POD-1 = 0.0% should be used to identify patients with a higher risk of EAD.

This study defines for the first time a liver transplant–specific inflection point for fibrinolysis resistance that can identify patients with a higher risk of developing EAD. Although it is unclear whether the treatment or prevention of the hypofibrinolytic state will reduce the risk for EAD, identifying patients at risk may have clinical utility. However, there are some methodological aspects that we would like to highlight.

Since LY30 0% means no lysis even in the presence of exogenous tPA, it could be interesting to assess whether there would be additional merit in testing higher tPA doses to further stratify the level of fibrinolysis resistance. Alternatively, the delta tTEG LY30, obtained by subtracting the POD-1 LY30 from the anhepatic LY30 (the time when tPA usually reaches the highest values during LT), as done previously by this group, may give additional information about graft function.[8]

In addition, patients with fibrinolysis resistance were further divided in this study into those who show a fibrinolysis shutdown or a hypofibrinolytic phenotype. The definitions of these fibrinolysis resistance subtypes are complex and rely on whether patients generate an LY30 > 3.0% during surgery or not. When patients have an LY30 > 3.0% and thus show a certain degree of lysis in a TEG assay that was not modified by tPA, they are classified as hyperfibrinolytic. When patients subsequently develop fibrinolysis resistance, they are categorized as having a fibrinolysis shutdown phenotype. Native TEG and tTEG were performed at baseline, during LT, and on POD-1, using the criteria for hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown defined by a citrate kaolin TEG test that had been described in a trauma population.[9] It is not quite clear whether the use of these trauma-derived criteria in the liver transplant population is fully justified, particularly given the profound changes in the fibrinolytic

Abbreviations: EAD, early graft dysfunction; LT, liver transplant; POD-1, postoperative day-1; ROTEM, rotational thromboelastometry; TEG, thromboelastography; tPA, tissue plasminogen activator; tTEG, tPA-modified TEG.

SEE ARTICLE ON PAGE 724

system in patients with cirrhosis. For future studies, it will be important to link fibrinolytic phenotypes to clinical data. A laboratory definition of hyperfibrinolysis, for example, may be irrelevant if patients with such a laboratory anomaly do not excessively bleed.

Several fibrinolytic profiles based on TEG or ROTEM tracings have been defined during the last years: hyperfibrinolysis, hypofibrinolysis, fibrinolysis shutdown, persistent fibrinolysis, delayed fibrinolysis, occult fibrinolysis, fibrinolysis resistance, and a combination of them.[10] Fibrinolysis that is clinically correlated with bleeding and thrombosis in some studies, has been previously investigated using plasma-based tests performed under relatively well-standardized conditions.[7,11] In contrast, the spectrum of reagents used to perform the viscoelastic test is more extensive. In the case of the TEG, different reagents have been used to characterize fibrinolytic profiles: native TEG (unmanipulated depiction of clot formation), kaolin TEG (contact activation with aluminum silicate), rapid TEG (tissue factor)—each one with their own reference ranges.[10] On the other hand, fibrinolytic parameters of TEG and ROTEM are marginally (but significantly) different but not interchangeable in patients or in healthy subjects.[12] The use of different tests may thus lead to a different classification of the same patient. In addition, most of these studies do not include the assessment of fibrinogen function (that is, a functional fibrinogen assay in the case of TEG and a FIBTEM test in the case of ROTEM), which is relevant as it has been demonstrated that a fibrinolysis-like tracing may also occur as a result of platelet-mediated clot retraction.[13] Specifically, under certain conditions, a TEG or ROTEM tracing can be erroneously interpreted as a fibrinolytic phenotype.

Most importantly, the normal range of fibrinolysis is tight in both TEG and ROTEM, which as mentioned before makes it difficult to define hypofibrinolysis but conversely, relatively small increases already result in a hyperfibrinolytic state. According to the variability reported in these tests, it is not clear that this technology, based on the decrease of a movement signal over time, can supply a degree of accuracy and reproducibility that accurately allows the detection of abnormal fibrinolytic phenotypes.[14,15]

Finally, different from patients who face an acute event (trauma, sepsis, and surgery) and suffer an acute fibrinolysis imbalance, patients with chronic liver disease develop a reset of their fibrinolytic balance over time without a clear fibrinolytic bleeding phenotype in most patients. In healthy controls, tTEG LY30 has been reported as 7.6% (5.0%–12.7%) (median [IQR])[10] whereas in the 158 LT candidates reported in the present study, tTEG was LY30 17.6% (4.2%–35%) before LT, which is a mild fibrinolytic phenotype. However, based on a definition derived from trauma-induced fibrinolysis,[9] the same authors reported in a previous study a fibrinolytic shutdown profile in 72% of LT recipients before LT,[2] which is in contrast to the 2 theories most prevalent in literature, which are that a substantial proportion of patients with cirrhosis have hyperfibrinolysis, or that the average patient with cirrhosis is normo-fibrinolytic.[16] In order to correctly interpret potential changes in fibrinolytic profiles during and after liver transplantation, we should take the rebalanced hemostatic status of patients with the chronic liver disease into account and perhaps reconsider the reference ranges and specific cutoffs derived from other patient populations.

Despite the aforementioned concerns, viscoelastic tests can help the clinical management of patients with abnormal fibrinolysis in the acute setting, where time matters, and may be helpful to predict complications such as EAD. Future studies should assess whether the link between EAD and fibrinolysis resistance is direct (ie, linked to microvascular or macrovascular complications) or indirect. Finally, we really need to agree on the methods of measurements and definitions to appropriately label the different fibrinolytic profiles. Then we can conduct studies, ideally using clinical parameters, whole blood viscoelastic tests, plasma-based functional tests, and assays on markers of in vivo activation of fibrinolysis, to better understand underlying mechanisms of abnormal fibrinolysis and the link to clinical outcome. With such information, we will ultimately be able to provide targeted treatment to those patients with abnormalities on viscoelastic testing.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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