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Global assays of fibrinolysis

Sir, With interest, I have read the recent review of Ilich and co-workers on global assays of fibrinolysis.1 Although I agree with the general conclusions of the review, including the conclusion that there is no gold standard test for assessing fibrinolytic capacity, I would like to comment on some aspects of the review.

First, although the review extensively discusses plasma-based clot lysis assays, it is not mentioned that one of the variants has been extensively clinically validated in large epidemiological studies. We and others have used a plasma-based clot lysis assay using tissue factor to induce coagulation and exogenous tissue-type plasminogen activator (tPA) to induce lysis. Hypofibrinolysis as assessed by this assay has been shown to increase the risk for both venous and arterial thrombosis in the general population and may be associated with an increased risk for post-thrombotic syndrome (reviewed in 2). Additionally, we have shown that the combination of hypofibrinolysis and hypercoagulability synergistically increases the risk for venous thrombosis.3 We have shown that the test is sensitive for all known fibrinolytic components (except for tPA), and have shown that levels of plasminogen activator inhibitor type 1 (PAI-1), plasminogen, thrombin activatable fibrinolysis inhibitor (TAFI), α2-antiplasmin, fibrinogen, factor (F) VII, FX, FIX, and FII explained 77% of the variation in the clot lysis time.4 The increased risk of venous thrombosis associated with plasma hypofibrinolysis appears primarily driven by elevated plasma levels of PAI-1 and TAFI,5 whereas the increased risk of arterial thrombosis associated with hypofibrinolysis appears primarily driven by α2-antiplasmin.5

Second, it is proposed that assays aimed at detecting hyperfibrinolysis should not contain exogenous tPA. Whereas (acute) overwhelming release of tPA may be a cause of a hyperfibrinolytic state, hyperfibrinolysis unrelated to excess tPA release also occurs. In general terms, it is still unclear what the contribution of circulating tPA in regulating endogenous fibrinolysis is compared with tPA acutely released following vascular injury. It can be argued that the circulating tPA concentrations in most individuals is so low that its effects will be readily overruled by the tPA released from endothelial cells acutely following clot formation. Therefore, a test with exogenously added tPA may be appropriate, also for detection of hyperfibrinolysis. Indeed, our plasma-based test detects hyperfibrinolysis during liver transplantation,6 the hyperfibrinolytic state of patients with hemophilia,7 and α2-antiplasmin deficiency,8 for example.

Finally, despite the clear association between hypofibrinolysis and risk of venous thrombosis, there is likely little need to develop whole blood or plasma-based assays to diagnose hypofibrinolysis as it clearly increases the risk for a first event, but not for a recurrence.9 As laboratory assessment of hypofibrinolysis will generally only be considered in patients that already suffered a thrombotic event, a diagnosis will not have clinical consequences, similar to the lack of clinical consequences of thrombophilia testing in the majority of patients.10 Diagnosis of hyperfibrinolysis may be useful in selected cases. However, it is unclear what exactly defines clinically relevant hyperfibrinolysis, which should be taken into account when new tests will be developed for clinical purposes. As antifibrinolytic agents are also effective prohemostatics in patients without overt hyperfibrinolysis (e.g., patients with mild von Willebrand disease), the clinical consequences of a diagnosis of hyperfibrinolysis may also be limited as one would consider treatment of a bleeding patient with antifibrinolytics regardless of a positive hyperfibrinolysis diagnosis. On the other hand, the controversy on the hyperfibrinolytic state in patients with trauma and controversy on whether all patients with trauma benefit from antifibrinolytic therapy11,12 may indicate that diagnostic tests for hyperfibrinolysis may have clinical applications.

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REFERENCES

