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Editorials

Assessing Thrombin Generation at the Point of Care

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Point-of-care testing (POCT)[2] draws vitality from the invention of new biosensors and, in this issue of *Clinical Chemistry*, takes a major step forward with the introduction of an amperometric test strip that assesses thrombin generation *(1)*. Historically, on-site whole-blood measurements, such as the activated coagulation time *(2, 3)* and ionized calcium, improved our understanding of the complex pathophysiology occurring during surgery and massive transfusion *(4)*. Gaps have persisted, however, in our ability to decipher hemostasis events. Fortunately, we now have an opportunity to improve bedside decision-making.

Potential applications include hemostatic treatment for hemophilias, inflammation and vascular remodeling, surgical microvascular bleeding, disseminated intravascular coagulation, thrombosis, drug therapy (e.g., hirudin and activated protein C), and severe sepsis, where previous insight into hyper- or hypocoagulable states has been difficult, if not impossible, with nonintegrative tests such as prothrombin time (PT) and activated partial thromboplastin time, and impractical with reagent- and labor-intensive thrombin assays requiring time-consuming processing steps and large sample volumes. Of course, we still must gain clinical experience with this new electrochemical thrombin biosensor and its benefits at the point of care (POC), whether hospital or home.

Miniaturized technologies developed and implemented for use in handheld POC instruments now cover a broad range of analytes. For example, handheld devices are capable of delivering rapid results for blood gases (P_{CO_2}, P_{O_2}), pH, hematocrit, electrolytes (potassium, ionized calcium, sodium, and chloride), metabolites (glucose, creatinine, and urea nitrogen), coagulation (PT), and cardiac biomarkers (troponin I, creatine kinase MB, and B-type natriuretic peptide). Multiplexing of tests in cartridges and other preanalytic packaging provides evidence of substantial progress in the past 3 decades *(5)*.

In 1962, Clark and Lyon introduced the first amperometric biosensor for measurement of blood glucose *(6)*. Now, strip-based glucose sensors have been adopted for use with numerous glucose meters. Test strips offer several advantages, including minimal sample volume, simple operation, and rapid results. When provided with a constant driving potential, the analyte bound to the receptor will undergo an oxidation-reduction reaction that can be quantified by measuring the electron exchange from the working electrode (anode) to the counterelectrode (cathode). This electron exchange, or current, is limited by the diffusion of the analyte through a selectively permeable membrane and various boundary layer phenomena, but in a well-designed test strip will be linearly proportional to the concentration of target analyte *(5)*.

Any new amperometric test strip, however, must be validated and ideally should meet all laboratory medicine standards for accuracy, imprecision, and quality. Clinical trials will be necessary to validate manufacturer specifications and to provide multivariate evidence that establishes clinical utility. Validation protocols must involve testing the device in the presence of potential confounding factors found in blood, such as drugs. Significant difficulties, even with well established POC devices, arise from the lack of reference materials for comparing and reporting results. As well, licensing authorities, such as the FDA, have not published exacting standards, certainly not for test strip–based thrombin assays. Thuerlemann et al. *(1)* are encouraged to pursue additional studies for clinical validation.

At this point in time, no single reference method or calibration material for whole-blood analyte measurement has been adopted universally among manufacturers, indicating a lack of harmonization that can adversely impact diagnoses, treatment decisions, and patient outcomes *(7)*. Inconsistency in coagulation test results based on different instrument–reagent combinations yields different diagnostic sensitivities to coagulation factor deficiencies. The international normalized ratio (INR) attempts to remedy deviations in

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[2] Nonstandard abbreviations: POCT, point-of-care testing; PT, prothrombin time; POC, point of care; INR, international normalized ratio.

prothrombin time results, but discrepancies persist *(8)*. Despite challenges, every effort should be made to thoroughly validate this new amperometric test strip for thrombin to achieve high reproducibility in assessing thrombin generation.

Thuerlmann et al. present a novel logic for assessing hemostasis by using an amperometric biosensor that focuses downstream in the coagulation cascade to thrombin generation *(1)*. No hemostatic event comprises solely either extrinsic or intrinsic coagulation pathways, which heretofore were assessed independently by conventional coagulation assays, but still will represent some combination of the two. We anticipate that placing the analytical focus downstream will yield a more predictive measurement indicative of coagulation potential. Thrombin, a coagulation protein generated in the common pathway, offers a natural choice since it converts circulating fibrinogen (factor I) to insoluble fibrin (factor Ia), thereby forming the truss work of a clot *(9)*.

Clinically, assessing thrombin generation will find utility in several settings, including management of hemostasis therapeutics. Early studies indicate that antithrombotic-targeted therapy can reduce morbidity and mortality in patients with sepsis *(10)*. Coagulation suppression and amplification therapies associated with surgery and hemophilia, respectively, which require multiple empirical measurements to assess therapy efficacy, have shown strong correlation between thrombin generation measurement and therapeutic effectiveness *(11, 12)*. Early evidence indicates that increased thrombin generation is associated with increased risk of recurrence, a fatal complication affecting approximately 5% of patients with venous thromboembolism *(13)*. Unfortunately, the development of an evidence-based approach to thrombin generation has been impeded by lack of clinical data to validate efficiency in patient diagnosis *(14)*. We now have the opportunity to obtain evidence that will allow clinicians to understand thrombin generation where it will be the most useful—for decisions at the point of care.

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