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Thrombelastographic pattern recognition in renal disease and trauma

Michael P. Chapman, MD,[a,*] Ernest E. Moore, MD,[a,b] Dominykas Burneikis, BS,[a] Hunter B. Moore, MD,[a] Eduardo Gonzalez, MD,[a] Kelsey C. Anderson, BS,[a] Christopher R. Ramos, MD,[a] and Anirban Banerjee, PhD[a]

[a] Department of Surgery, University of Colorado-Denver, Aurora, Colorado
[b] Department of Surgery, Denver Health Medical Center, Denver, Colorado

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ABSTRACT

Background: Thrombelastography (TEG) is a viscoelastic hemostatic assay. We have observed that end-stage renal disease (ESRD) and trauma-induced coagulopathy (TIC) produce distinctive TEG tracings. We hypothesized that rigorously definable TEG patterns could discriminate between healthy controls and patients with ESRD and TIC.

Methods: TEG was performed on blood from ESRD patients ($n = 54$) and blood from trauma patients requiring a massive blood transfusion ($n = 16$). Plots of independent TEG parameters were analyzed for patterns coupled to disease state, compared with controls. Decision trees for taxonomic classification were then built using the "R-Project" statistical software.

Results: Minimally overlapping clusters of TEG results were observed for the three patient groups when coordinate pairs of maximum amplitude (MA) and TEG-activated clotting time (ACT) were plotted on orthogonal axes. Based on these groupings, a taxonomical classification tree was constructed using MA and TEG ACT. Branch points were set at an ACT of 103 s, and these branches subdivided for MA at 60.8 mm for the high ACT branch and 72.6 mm for the low ACT branch, providing a correct classification rate of 93.4%.

Conclusions: ESRD and TIC demonstrate distinct TEG patterns. The coagulopathy of ESRD is typified by a prolonged enzymatic phase of clot formation, with normal-to-elevated final clot strength. Conversely, TIC is typified by prolonged clot formation and weakened clot strength. Our taxonomic categorization constitutes a rigorous system for the algorithmic interpretation of TEG based on cluster analysis. This will form the basis for clinical decision support software for viscoelastic hemostatic assays.

1. Introduction

Thrombelastography (TEG) is a viscoelastic hemostatic assay (VHA) with a rapidly growing range of clinical applications. An example of this expanding applicability of TEG is the now ubiquitous practice of surgeons at our center of obtaining thrombelastograms (TEGs) preoperatively on end-stage renal disease (ESRD) patients undergoing hemodialysis access

* *Corresponding author*. Department of Surgery, Denver Health Medical Center, 777 Bannock St. Denver, CO 80204. Tel.: (443) 386-1307; fax: (303) 724-6310.
E-mail address: michael.chapman@ucdenver.edu (M.P. Chapman).
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construction. These patients have been reported to be in various states of deranged coagulation, which may impact their intraoperative care and their chance of graft survival [1–6]. Some authors have reported general hypercoagulability in uremic patients, whereas still others have noted paradoxical findings of either accelerated or delayed enzymatic initiation of coagulation in concert with supernormal final clot strength [7,8]. Unfortunately, these conflicting findings have yet to yield sound descriptive or explanatory models of the coagulopathy of ESRD and therefore have been of little clear diagnostic or prognostic value.

In contrast to the limited understanding of the patterns of coagulopathy present in ESRD, the trauma literature contains an abundance of studies of the utility of TEG and other VHAs for use in the diagnosis of trauma-induced coagulopathy (TIC), the goal-directed resuscitation of trauma patients with blood components and, most recently, as a prognostic tool for both early and late mortality in trauma as well as prediction of transfusion requirements [9–18]. It is our aim to extrapolate from our experience in applying TEG to TIC and apply machine learning and pattern recognition methodologies to the task of categorizing a broader population of patients with a variety of potential coagulation disorders.

Our eventual goals are to develop rigorous computational tools to model coagulopathic states as the sum of discreet contributory components whose relative magnitudes will serve to define unique clinical populations with unique management needs. Ultimately, we see such analyses as the basis for clinical decision support software to aid in the interpretation of complicated thrombelastograms (TEGs) in patients with multiple medical and surgical problems, much as software now aids in the interpretation of electrocardiograms [19]. We started by comparing two well-defined populations with a high likelihood of derangements of coagulation (ESRD and TIC patients) to healthy control subjects.

2. Materials and methods

2.1. VHAs and parameters

Our standard VHA in use in our clinical laboratory is Rapid-Thrombelastography (Rapid-TEG), which uses whole blood activated by a suspension of kaolin and tissue factor, supplied as a standardized reagent by the instrument manufacturer. Samples for Rapid-TEG are collected by fresh venipuncture with a 21-gauge needle into evacuated, preservative-free sample tubes (Vacutainer; Becton–Dickinson, Franklin Lakes, NJ). Samples are run according to the manufacturer's instructions on a TEG 5000 Thrombelastograph Hemostasis Analyzer (Haemonetics, Niles, IL) [20]. The raw output of the TEG assay is a graphical tracing with time after activation on the *x*-axis and amplitude (equivalent to clot strength) as the dependent variable on the *y*-axis. TEG output parameters consist of various mathematical transforms of this Cartesian coordinate data. We used the basic parameters approved for clinical use in this analysis (Fig. 1A). The R-time is the time required after activation to reach an amplitude of 2 mm and is indicative of the rapidity of the enzymatic processes of the initiation phase of coagulation. The TEG-generated activated

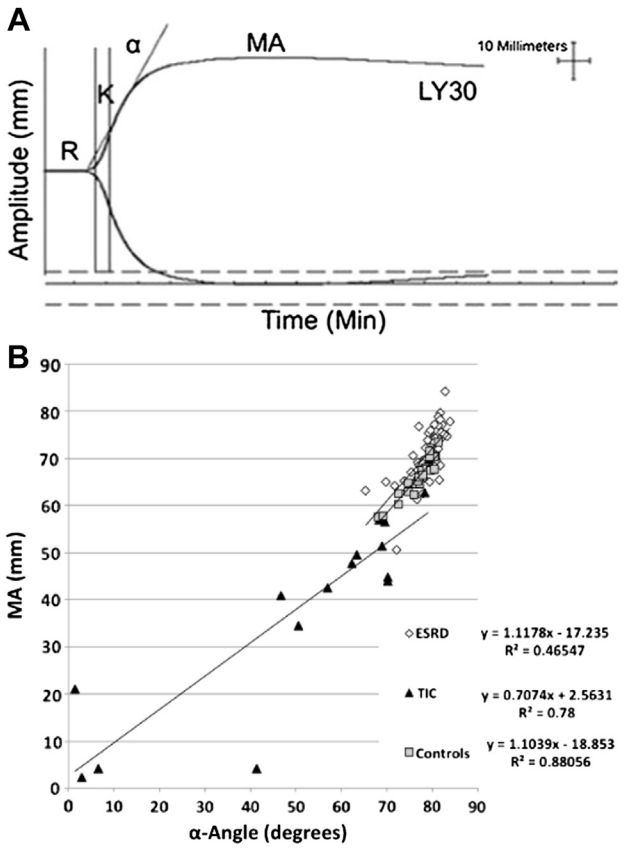

Fig. 1 – (A) Features of a typical thrombelastogram (TEG) with routinely reported parameters. R: reaction time to clot initiation, which reflects soluble enzyme activity and platelet-mediated catalysis; TEG ACT (not shown in this diagram) a calculated parameter based on R, normalized to correspond to traditional ACT values; K: clot kinetics parameter defined as time until 20-mm amplitude is achieved; α-angle: the angle from the baseline to the rising curve's tangent ray α, drawn from the splitting point of the tracing from baseline, which serves as another metric of clot kinetics; MA: (clot strength) reported in units arbitrarily defined as millimeters; LY30: percentage of clot lysis (generally from enzymatic degradation of fibrin) 30 min after MA. (B) Linear correlations between TEG parameters exclude their use for the next phase in analysis. As illustrated herein, a linear correlation exists between α-angle and MA, both within and among the three patient populations. This indicates that the two parameters are linked in such a way (either causally or otherwise) that confounds their utility as independent inputs to our classification scheme.

clotting time (ACT) or TEG-ACT is a nonlinear, stepwise transform of the R-time used to yield numeric values similar to the familiar and traditional ACT values used for many years for intraoperative monitoring of heparin efficacy. Prolongation of the TEG ACT is indicative of impairment of the enzymatic phase of coagulation. The other key parameter in TEG is the maximum amplitude (MA), which is indicative of the final overall clot strength, comprised both the platelet and fibrin contributions, with platelets contributing to approximately