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Thrombelastographic Pattern Recognition in Renal Disease and Trauma

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Abstract

Introduction—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 to 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 upon these groupings, a taxonomical classification tree was constructed using MA and TEG ACT. Branch points were set at an ACT of 103 seconds, 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

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taxonomic categorization constitutes a rigorous system for the algorithmic interpretation of TEG based upon cluster analysis. This will form the basis for clinical decision support software for viscoelastic hemostatic assays.

Keywords

machine learning; pattern recognition; renal disease; trauma; coagulopathy; hypercoagulability; trauma induced coagulopathy; thrombelastography; viscoelastic hemostatic assay; classification tree analysis; taxonomy; hemodialysis

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) pre-operatively on end-stage renal disease (ESRD) patients undergoing hemodialysis access construction. These patients have been reported to be in various states of deranged coagulation which may impact their intraoperative care as well as their chance of graft survival. (1–6) Some authors have reported general hypercoagulability in uremic patients, while still others have noted paradoxical findings of either accelerated or delayed enzymatic initiation of coagulation in concert with super-normal 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 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.

Materials and Methods

Viscoelastic Hemostatic Assays and Parameters

Our standard VHA in use in our clinical laboratory is Rapid-Thrombelastography (Rapid-TEG®), which utilizes whole blood activated by a suspension of kaolin and tissue factor (TF), 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 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 utilized the basic parameters approved for clinical use in this analysis (figure 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 clotting time or TEG-ACT is a non-linear, stepwise transform of the R-time used to yield numeric values similar to the familiar and traditional ACT values used for many years for intra-operative 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 of both the platelet and fibrin contributions, with platelets contributing to approximately 80% of the observed amplitude. Other parameters we analyzed included the alpha-angle, which relates to the rate of the amplification phase of clot formation and which, under normal circumstances is largely a function of the concentration of fibrinogen.

Study Populations

De-identified data was obtained from the clinical hematology lab at Denver Health Medical Center. TEG data was abstracted by laboratory personnel on consecutive patients with ESRD undergoing initial hemodialysis access construction, from their routine pre-operative laboratory analysis. Rapid-TEG (tissue factor and kaolin activated) tracings were collected from blood samples of consecutive ESRD patients at the time of dialysis access construction (n=54), from May of 2012 through April of 2013. Rapid-TEG tracings were also obtained on admission blood samples from consecutive trauma patients during the same time period. This later patient group was restricted to those patients where Rapid-TEGs were performed on patients within one hour of injury, who had not received any blood products prior to sample collection. Trauma patients with pre-existing renal disease, coagulopathic disorder or on anticoagulant or antiplatelet drugs were excluded. This cohort was followed prospectively and subsequently further restricted to those patients went on to require a massive blood transfusion of at least 10 units of PRBCs in the first 6 hours after the time injury, which we use as a functional definition of clinically significant trauma induced coagulopathy (n=16). Lastly we compared both groups' Rapid-TEG to those tracings to those of healthy controls collected by the clinical hematology laboratory during the same calendar year for purposes of routine internal validation and maintenance of reference

ranges (n=22). These controls were performed in duplicate for each subject and the mean of each generated parameter utilized for the analysis.

Data Analysis

Plots of independent TEG parameters were analyzed for patterns coupled to disease state and compared to healthy controls. This analysis was empiric and consisted of initial qualitative cluster analysis of paired TEG parameters, followed by exclusion of parameter pairs exhibiting linear correlation in the pooled study group (figure 1B). TEG ACT, R, alpha-angle and MA were all compared empirically. Additionally, these parameters were compared to conventional coagulation assays and to physiologic parameters such as blood urea nitrogen and creatinine. Only TEG ACT and MA exhibited subjective clustering, without evidence of linear correlation.

Next, this parameter pair, which exhibited subjective evidence of clustering underwent statistical taxonomic analysis to generate classification “trees”. Classification trees are computational models that relate categorical response or output variables to continuous predictor or input variables. They are similar in principle to, but mathematically and computationally distinct from regression trees, which relate continuous variable to continuous variables. Decision trees for taxonomic classification of our patients were built empirically using the “R-Project” freeware statistical software, and underwent one round of “pruning” (modification by successive optimization of terminal branches), as described below, to improve classification accuracy. (21) The principle figure of merit for this type of classification task is overall correct categorization (or classification) rate. In this case, this task refers to categorization of the patients into their known disease or wellness states: ESRD, TIC or healthy controls, using only the two TEG parameters provided to the software. Additionally, we report the residual mean deviance, which is a metric of the degree of detail of the leafing pattern of the tree, and gives insight into potentially missed sub-categorizations as well the variance within groups. (22)

Results

Exploratory analysis revealed three distinct clusters of patients when maximum amplitude (MA) values were plotted against activated clotting time (ACT) values. Each cluster appeared subjectively to correspond to a particular study group with minimal overlap, as seen in figure 2. In order to rigorously define these clusters, we turned to a statistical analysis technique to create a taxonomic scheme known as a known as classification tree, wherein all individuals are segregated in bins or clades by decisions made based upon the value of a given independent variable at a “branch point” which defines the structure of the “tree”. Classification trees can provide rules for categorization, especially when the interaction between variables is complex and non-linear. This method allowed us to select a specific set of values for MA and ACT variables that best predicts the clinical group to which the patient belongs, in this case a simplified case wherein the clinical distinction between the three groups in unambiguous and without overlap: patients with ESRD, trauma patients in hemorrhagic shock but with preexisting renal disease and healthy controls.

The software was programmed to derive branch points by successive approximation and the resulting categories were compared to the observed minimally overlapping clusters of TEG results for the three patient groups when coordinate pairs of maximum amplitude (MA) and TEG activated clotting time (ACT) were plotted on orthogonal axes. Based upon these groupings, a taxonomical decision tree was constructed using MA and TEG ACT. Initially the software concluded that seven terminal nodes or “leaves” existed. This yielded a misclassification error rate of 6.5%. Pruning to four terminal nodes increased the residual mean deviance from 0.395 to 0.491 and the overall correct categorization rate remained unchanged at 93.4%, (figure 3).

A set of rules was derived from this classification tree to describe the clustering pattern we observed, which are applied as consecutive classification decisions or branch points of the tree: (1) Initially segregate the patients with an ACT <103 only (i.e. normal or super-normal rate of enzymatic coagulation) from those with an ACT ≥ 103 (relative prolonged enzymatic phase). (2) If a patient has an ACT <103 and MA < 72.55, they likely belong to the control group. (3) If a patient has an ACT <103, but MA ≥ 72.55, they likely belong to the ESRD group. (4) If a patient has an ACT ≥ 103, and MA < 60.8, they likely belong to the ACOT group. (5) If a patient has an ACT ≥ 103, but MA ≥ 60.8, they likely belong to the ESRD group. These rules, yield a simple scheme with 3 branch points and 4 terminal nodes or leaves. Stated differently, branch points for cluster definition were set at an ACT of 103 seconds, and these branches subdivided by setting branch points for MA at 60.8 mm for the high ACT branch and 72.6 mm for the low ACT branch. This is shown graphically in relation to the actual clinical categories in figure 4. This scheme provided a correct classification rate of 93.4%.

Discussion

ESRD and TIC demonstrate clearly distinct TEG patterns, a finding which has both mechanistic and practical implications for our understanding of derangements of coagulation in surgical patient populations. 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 both prolonged clot formation and weakened clot strength. Most importantly, for future application in pattern recognition software for clinical decision support, these patterns are distinguishable by the use of very simple binary decision algorithms.

This accomplishment of this relatively simple computational task demonstrates the potential amenability of TEG to analysis by machine learning tools. Machine learning, in this case refers to the construction of the type of limited artificial intelligence algorithms known as “expert systems” which can learn to analyze and find patterns in complex data of high dimensionality (i.e. multiple variables) in much the same way as the human mind does, but faster and more reproducibly and with less limitation on the number of variables that the system is capable of comprehending.

Ultimately, we aim to build layers of such algorithms into a clinical decision support software system, which can report the probabilities of a particular patient having particular

patterns of coagulopathy that associates with an underlying disease state or states. The most obvious applications of such a tool is either as (1) a safety system, catching potential missed diagnoses in the manual interpretation of the TEG, or (2) in the setting of trauma and emergent surgery where a patient's history and comorbid conditions (e.g. renal or liver disease) or medications impacting coagulation are unknown, but which information could potentially be extracted from the complex multidimensional data space of the TEG tracing.

In our particular machine learning task, we sought to answer the question of whether there are recognizable pattern in the TEG tracing which can be used to distinguish patients of a known state of disease or health from each other. This is known as "supervised learning" as the computational engine is given the task or inferring an algorithm, which describes data that is already labeled as belonging to known categories. This is contrasted with "unsupervised learning" (e.g. principle component analysis) which relies solely on the characteristics of the data itself. In our case, we used this "training data" to develop a decision/taxonomic tree algorithm and then mapped this back onto the apparent clusters. While this "bootstrapping" approach is valid for determining the feasibility of classification by a particular pattern recognition algorithm, it does not necessarily indicate that this method is generalizable to a larger population. Therefore, the next logical step in our development of this algorithm will be application to a larger group of unknown "test data", preferably from other centers, for validation of generalizability.

It is worth noting that there is a certain amount of subjectivity to the way an algorithm is developed in a supervised learning scenario. For example, the acceptable value for correct classification rate depends, in the case of medical diagnostics, on the clinical scenarios involved. This is analogous to the simple relation of sensitivity and specificity of a diagnostic test with a binary outcome, which may be varied along its existence curve, known as the receiver operating characteristic curve. The desire to optimize sensitivity versus specificity in actual application depends on a number of factors, including prevalence of the disease entity in question and whether the test is intended as a screening or definitive diagnostic test. In our case, we merely sought to attain the best possible overall correct classification rate (93.4%).

Another subjective factor involves giving guidance or feedback to the computational system as it develops the algorithm. In decision tree analysis, one form of this guidance is "pruning" of the developing tree. We suspected that the tree may have been "over-fitted", a routine complication of using a relatively small number of observations. As over-fitting can cause dithering (and indeed misclassification with larger groups of future data, input as unknowns) we attempted to prune the classification tree to four terminal nodes. Pruning may be done to optimize the misclassification error rate or to simplify the algorithm. In our case, reducing from seven to four terminal nodes avoided undue complexity and did not alter the misclassification error rate, and therefore represented an optimization. Pruning increased the residual mean deviance from 0.395 to 0.491. This is arguably a non-optimal change, but in the case of this sort of classification tree, the residual mean deviance is not a key metric of error, but rather describes how detailed or granular the classification is. Overly detailed classification is, in fact not desirable, not only because it is computationally expensive, but because it may create distinctions based upon noise where none exist in physical reality.

Moreover, in our case, with pruning the overall correct categorization rate remained unchanged at 93.4%, there is no negative impact on categorization accuracy, given our predetermined clinical groups. Ideally, pruning is carried out both at the training stage to remove nodes that have no intuitive or physical reality, and at the generalization stage, wherein the algorithm is observed for unstable or non-optimized features when applied to unlabeled test data.

In order for the patterns recognized by either a human operator or an expert computer system to have validity, they must ultimately tied back to plausible physical and biological mechanisms that explain the distinction between clusters of individuals adhering to various patterns. For this reason, we chose to compare three types of patient (healthy, TIC and ESRD) with manifestly different physiology, whose patterns of coagulation could reasonably be expected to be distinct, even without a complete understanding of the underlying molecular pathophysiology. Coagulopathy of ESRD likely represents a very specific combination of enzymatic phase failure of multifactorial origin (nutrition, consumption, organic acids) and activated platelets possibly with some degree of hyperfibrinogenemia. (7, 23) TIC, on the other hand, is known to be a polymorphous entity that presents heterogeneously, but which archetypally consists of a pan-coagulopathy with a prolonged enzymatic phase, platelet dysfunction, fibrinogen dysfunction and frequently a component of hyperfibrinolysis. (24–27) This heterogeneity is likely the result of global systemic insults stemming from the inflammatory response to tissue injury and (by unknown intermediaries) global ischemia.

While the de-identified nature of our study data prevents our collection of a detailed clinical history and blood samples with which to investigate the molecular mediators of coagulation in these patients, the overall clustering of the observable phenomena of coagulation is nevertheless illuminating. The important understanding which our findings support, is that the enzymatic initiation of clotting (kinetic clotting behavior) and the propagation/ amplification phase are indeed functionally distinct and can be analyzed in a reductionist manner, as separate processes or phases of clot formation.

Conclusions

Our findings emphasize the importance of pattern recognition in the interpretation of the thrombelastogram and the viability of machine learning as a means to generate clearly defined taxonomic groups based upon these patterns. Such taxonomic categorization is the foundation for the development of a rigorous system for algorithmic interpretation of TEG based upon cluster analysis. Such a system could serve as the basis for clinical decision support software for viscoelastic hemostatic assays. (28, 29)

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Figure 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: activated clotting time (not shown in this diagram) a calculated parameter based upon 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: maximum

amplitude (clot strength) reported in units arbitrarily defined as millimeters; LY30: percentage of clot lysis (generally from enzymatic degradation of fibrin) 30 minutes after MA. **(B) Linear correlations between TEG parameters exclude their use for the next phase in analysis.** As illustrated herein, a linear correlation that exists between α -angle, 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.

Figure 2. Subjective clustering of ESRD versus TIC patients versus healthy controls with respect to TEG ACT and MA

In a three-dimensional existence space wherein the classifying TEG parameters ACT and MA comprise two orthogonal, continuous dimensions and the patient's actual clinical category (ESRD, TIC or healthy control) is the third orthogonal, categorical variable, we observe three evident clusters with minimal overlap, clearly corresponding the patients' actual clinical categorization. *ESRD* $\equiv$ end stage renal disease; *TIC* $\equiv$ trauma induced coagulopathy; *TEG* $\equiv$ thrombelastography; *ACT* $\equiv$ activated clotting time; *MA* $\equiv$ maximum amplitude (refer to figure 1A for detailed descriptions of these parameters).

Figure 3. Optimization of classification trees

The initial tree proposed by the computational method had six branch points seven terminal nodes or leaves (A). This was successively pruned to three branch points and four terminal nodes (B), with a resultant loss of detail as represented by an increase in the residual mean deviance from 0.395 to 0.491, but no loss in the accuracy of the categorization at 93.4%. As this change represents in a simpler algorithm with no decrement in the correct categorization rate, it represents a positive step in optimization of our classification tree.

Figure 4. Rigorous clustering of ESRD versus TIC patients versus healthy controls with respect to TEG ACT and MA

In the same three-dimensional existence space shown in Figure 2 (wherein the classifying TEG parameters ACT and MA comprise two orthogonal, continuous dimensions and the patients' actual clinical category is the third orthogonal, categorical variable) we here see the explicit relationship of the 4 terminal nodes to their actual spatial clusters. The correct categorization rate is 86/92 or 93.4%. *ESRD* $\equiv$ end stage renal disease; *TIC* $\equiv$ trauma induced coagulopathy; *TEG* $\equiv$ thrombelastography; *ACT* $\equiv$ activated clotting time; *MA* $\equiv$ maximum amplitude (refer to figure 1A for detailed descriptions of these parameters).