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Systematic evaluation of evidence on Veterinary Viscoelastic Testing

Part 4: Definitions and Data Reporting

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Running title: PROVETS – Definitions and data reporting

Abbreviations:

α: alpha angle (TEG variable)

CFT: clot formation time (ROTEM variable)

CT: clotting time (ROTEM variable)

EPL: estimated percentage lysis (TEG variable)

G: shear elastic modulus or global clot strength (TEG variable)

K: kappa value (TEG variable)

LOE: level of evidence

LOT: lysis onset time (ROTEM variable)

LT: lysis time (ROTEM variable)

MA: maximum amplitude (TEG variable)

MCE: maximum clot elasticity or shear elastic modulus (ROTEM variable)

MCF: maximum clot firmness (ROTEM variable)

ML: maximum lysis (ROTEM variable)

R: reaction time (TEG variable)

ROTEM: rotational thromboelastometry

TEG: thromboelastography

Abstract

Objective: To systematically examine evidence surrounding definitions and reporting of data for viscoelastic testing in veterinary medicine.

Design**:** Standardized, systematic evaluation of the literature, categorization of relevant articles according to level of evidence and quality, and development of consensus on conclusions for application of the concepts to clinical practice.

Setting: Academic and referral veterinary medical centers.

Results: Databases searched included Medline, CAB abstracts, and Google Scholar.

Conclusions**:** All 4 standard thromboelastography (TEG) and rotational thromboelastometry (ROTEM) variables should be universally reported, and the reporting of shear elastic modulus in addition to maximum amplitude (MA) is encouraged. There is insufficient evidence to support universal usage of the coagulation index at this time. The K value and clot formation time are the most variable of the 4 parameters, with alpha angle, MA, and maximum clot firmness generally the least variable. Individual studies should report sufficient data on patients and institutional controls to enable definitions of hypo- and hypercoagulability to be evaluated post-hoc, and it is recommended that all studies specifically report how these conditions were defined. In reporting data relating to fibrinolysis, the TEG variables Ly30, Ly60, CL30, CL60 and the ROTEM variables LI30, LI60, ML, LOT and LT should be documented. Studies should report sufficient data on patients and controls to enable definitions of hyper- and hypofibrinolysis to be evaluated post-hoc, and we suggest that standard TEG/ROTEM assays may be unable to detect hypofibrinolysis in companion animals. We recommend that every center establish reference intervals, which are specific to either TEG or ROTEM. These reference intervals

should be established using veterinary clinical pathology guidelines, standardized protocols, and a minimum of 40 healthy animals. There is currently insufficient data in companion animals to suggest a utility for Vcurve variables beyond that of standard TEG variables.

Keywords: thromboelastometry, thromboelastography, dog, cat

Introduction

There are currently 2 main systems, the TEG and ROTEM, utilizing viscoelastic technology to evaluate hemostasis. Most current laboratory and clinical research in human and veterinary medicine has been generated using these systems. The differences between these methodologies and the influence of pre-analytical and analytical variables on these assays have been presented in the previous three domains. The focus of this domain is to define existing variables and summarize available evidence regarding the reporting of data.

Evidence Summary

Worksheet Question: Should the TEG derived MA value be converted into the G value?

Conclusions: All 4 standard TEG/ROTEM variables should be universally reported, enabling post-hoc calculation of G if required. The reporting of G in addition to MA is encouraged to allow authors to evaluate and compare the clinical utility of both variables.

Summary of evidence: The MA is the maximum amplitude, or width of divergence, of a tracing derived via TEG and represents the overall clot strength. The major contributors to MA are platelets, followed by fibrinogen, thrombin, factor XIII, and hematocrit. The shear elastic modulus, denoted by G, also represents the "global" clot strength and is derived from the MA using the following formula: G = (5000 X MA) / (100-MA). Since G is derived from the MA, it is a function of the same constituents. However, MA is a linear value expressed in mm, while G is an exponential transformation of MA expressed in dyn/cm^2. Consider that a change in MA from 55 to 70 mm (a 30% change) represents a change in G from 5,500 to 11,666 dyn/cm^2 (a 112% increase). This distribution has been proposed to be more sensitive to hemostatic changes, especially as MA increases in size.

Twenty articles were identified which report G in addition to MA. Six studies were evaluated which reported both G and MA and included some comparison or discussion of the rationale for including the G value (LOE 3-6, Good-Poor).[1-6] Of these 6 however, none directly addressed the worksheet question. In the 2 veterinary studies, both found MA and G to be relatively equal in the dog at identifying patients with clinical bleeding (LOE 4),[6] or patients with hypercoagulability induced by the administration of steroids (LOE 3).[2] As such a recommendation for using G in addition to, or in place of, MA cannot be made.

Future Directions: Studies directly comparing the clinical utility of each value against a non-TEG outcome measure in companion animals are needed.

Worksheet Question: Which TEG/ROTEM clot formation values should be reported in publications?

Conclusions: We recommend that all 4 standard TEG/ROTEM variables are universally reported to enable meta-analyses to be conducted in future.

Summary of Evidence: Few studies compare the variability or predictive value of the 4 standard TEG/ROTEM variables. Evidence from 9 studies (4 canine, 3 equine, 2 feline) (LOE 2-3, Good),[7-15] generally suggests that K time / CFT is the most variable of the 4 parameters, with α and MA / MCF generally the least variable. This might influence the individual predictive utility of the 4 parameters and may need to be considered during construction of diagnostic or therapeutic algorithms. No studies specifically compared the predictive value of K/CFT versus α. A study on biological variation in coagulation parameters in dogs (LOE 3, Good),[15] suggests that all 4 TEG/ROTEM parameters provide useful information about hemostatic potential, as they have a low degree of individuality,

making population reference intervals useful for TEG variables.[16] This was in contrast to clotting times, antithrombin, fibrinogen, and D-dimers which all have a high degree of individuality, rendering decisions based on population based reference intervals insensitive for those analytes.

Future Directions: Research comparing the predictive ability of individual TEG/ROTEM parameters is required. Until such studies are available, it seems prudent to report all TEG/ROTEM parameters to facilitate post-hoc evaluation to be performed and comparisons between studies to be made.

Worksheet Question: How should hypercoagulability be defined?

Conclusions: There is insufficient evidence to recommend how hypercoagulability should be defined in companion animals based on TEG/ROTEM parameters at this time. We suggest that individual studies report sufficient data on patients and institutional controls to enable definitions of hypercoagulability to be evaluated post-hoc. We recommend that all studies specifically report how hypercoagulability was defined. We recommend that all 4 standard TEG/ROTEM variables are universally reported to enable meta-analyses to be conducted in future. We recommend that at minimum, contemporaneous values for hematocrit, fibrinogen concentration and platelet count be reported in addition to TEG/ROTEM results.

Summary of Evidence: By convention, shortened R (CF) or K (CFT), or increased α or MA (MCF), are considered consistent with hypercoagulability in companion animal species. Nine articles specific to veterinary companion animals were identified in which a clear definition for "hypercoagulability" was presented (LOE 2-6, Fair-Poor).[17-25] Two principle

strategies for assessing or defining hypercoagulability have been used in the companion animal literature to date: 1) comparison of the affected cohort with a control population, 2) use of a cut-off value in 1 or more TEG parameters to define hypercoagulability. Cut-off values used include the upper bound of the reference intervals for α and MA, the lower bounds of R and K times, G values >7200 Kdyn/cm^2 or values for these parameters >25% above or below the relevant reference interval boundaries. Although these values have been used to prognosticate in individual studies, no veterinary studies have compared these values with a reliable, independent and objective thrombosis endpoint. As such which TEG/ROTEM parameter (if any) should be used to identify hypercoagulability in companion animals remains unclear.

It is also evident from multiple studies in companion animals and humans (LOE 2-6, Good-Fair),[26-32] that several hematologic variables, in particular hematocrit, fibrinogen concentration and platelet count, significantly affect the results of TEG/ROTEM assays. As such, these values must be considered when defining hypercoagulability in particular patient populations, e.g. dogs with IMHA. Values for hematocrit, fibrinogen concentration and platelet count should be reported in addition to TEG/ROTEM values to enable the potential impact of these factors on the TEG/ROTEM results to be evaluated.

Future Studies: Further investigation, using a reliable thrombosis endpoint, in veterinary species to better define hypercoagulability based on TEG/ROTEM parameters is clearly required.

Worksheet Question: How should hypocoagulability be defined?

Conclusions: There is insufficient evidence to recommend how hypocoagulability should be defined in companion animals based on TEG/ROTEM parameters at this time. We suggest that individual studies report sufficient data on patients and controls to enable definitions of hypocoagulability to be evaluated post-hoc. We recommend that all studies specifically report how hypocoagulability was defined. We suggest that use of multiple TEG/ROTEM derived parameters in combination may increase specificity for identification of subsets of hypocoagulability. We recommend that all 4 standard TEG/ROTEM variables are universally reported to enable meta-analysis to be conducted in future. We recommend that values for hematocrit, fibrinogen concentration and platelet count be reported in addition to TEG/ROTEM results.

Summary of Evidence: Evidence from three studies in dogs (LOE 2 and 4, Good),[6, 20, 25] and 1 study in horses (LOE 2, Good),[8] suggest that a suitable universal definition for hypocoagulability cannot be determined at this time. Present literature provides evidence that trends in variables indicating hypocoagulability include increased R/CT or K/CFT values and/or decreased MA/MCF or G/MCE values. Studies in non-target species (LOE 6, Good-Fair),[33, 34] suggest that combinations of TEG/ROTEM parameters to identify hypocoagulability may provide superior predictive ability for bleeding; and that ROC curve analysis of individual parameters to identify cut-off points with associated sensitivity and specificity values may improve our quantification of bleeding risk. Only one of the aforementioned veterinary studies prospectively evaluated how tissue factor (TF) activated TEG correlated to clinical signs of bleeding in dogs compared to a routine coagulation profile.[6] TEG correctly identified dogs with clinical signs of bleeding with a positive predictive value (PPV) of 89% and a negative predictive value (NPV) of 98%. Whereas,

coagulation profiles had a PPV between 50-81% and a NPV between 92-93%, depending on the observer. It is noteworthy that underlying disease processes contributing to blood loss were varied. As previously mentioned, evidence from multiple studies in companion animals and humans (LOE 2-6, Good-Fair),[26-32] suggests that hematologic variables in particular hematocrit, fibrinogen concentration and platelet count significantly affect the results of TEG/ROTEM assays. As such, these values must be considered when defining hypocoagulability in particular patient populations, e.g. dogs with IMHA. Values for hematocrit, fibrinogen concentration and platelet count should be reported in addition to TEG/ROTEM values to enable the potential impact of these factors on the TEG/ROTEM results to be evaluated.

Future Directions: Further investigation is clearly needed to better define hypocoagulability using TEG/ROTEM parameters based on their correlation with signs of spontaneous or surgically induced hemorrhage.

Worksheet Question: Should the coagulation index, CI value, be reported and if so, what formula should be used?

Conclusions: There is currently insufficient evidence to make a recommendation regarding use of CI in companion animals. We suggest that the CI equation derived for humans is not used for companion animals ($CI = -0.245R + 0.0184K + 0.1655MA - 0.0241\alpha - 5.0220$). We suggest that the CI equation derived for dogs may be considered for use in that species ($CI = 0.1227R + 0.0092K + 0.1655MA - 0.0241\alpha - 5.0220$).[35] We recommend that all 4 standard TEG/ROTEM variables (R, K, α, MA / CT, CFT, α, MCF) are universally reported to enable calculation of a coagulation index post-hoc if required.

Summary of Evidence: Based on 5 articles reviewed (LOE 4-6, Fair-Poor),[32, 35-38] of which none completely addressed the worksheet question, recommendation for using CI in addition to, or in place of, other TEG parameters cannot be made. Two veterinary studies utilized CI as a variable. One study involving IMHA in dogs found an association between a normal CI and decreased survival but was retrospective in nature and necropsies were not performed.[35] The CI formula used was reported to be canine in origin, produced with recalcified, non-activated, citrated whole blood, and although a review paper was referenced, the derivation was not provided.[39] The second study documented hypercoagulability in patients with renal failure and protein-losing nephropathy, with increased CI as a supportive variable.[32] The CI formula used was the human derivation produced with recalcified, non-activated, citrated whole blood.

Thus, although a canine specific coagulation index equation has been generated, the methodology for this derivation was not reported and the applicability or potential benefits of this canine specific equation are unknown at this time. The extension of the CI equation derived for humans to canine patients has also not been validated and as such its use is not recommended. Provided all 4 standard TEG variables (R, K, α, MA) are reported in both healthy individuals and those under study the CI could be calculated post-hoc if necessary. It is prudent to keep in mind that, as discussed in other sections, TEG and ROTEM are affected by many variables and reference intervals are unique to the activator and laboratory protocol. Coagulation index is dependent upon these output variables and likely influenced by the same factors.

Future Directions: Studies directly evaluating the clinical utility of species and activator specific CI in animals compared to non-viscoelastic based outcomes are needed.

Worksheet Question: Which fibrinolysis parameters should be reported?

Conclusions: There is currently insufficient data in companion animals to recommend reporting of specific fibrinolytic variables. We suggest that the TEG variables Ly30, Ly60, CL30, CL60 and the ROTEM variables LI30, LI60, ML, LOT and LT be universally reported to enable meta-analyses to be conducted in the future.

Summary of Evidence: Few companion animal publications exist regarding the measurement of fibrinolysis using TEG or ROTEM.[40, 41] While numerous variables exist for the reporting of clot lysis, there does not appear to be consistency in the values reported in literature involving human subjects.[42-68]

In thromboelastography, the percentage reductions in the tracing amplitude at a specified amount of time (e.g. 30 or 60 minutes) after maximum amplitude is measured (Ly30 and Ly60) are commonly reported measures of fibrinolysis.[40, 41, 44, 47, 58, 69] Similar to these measurements, the clot lysis index (CL30 and CL60) is the amplitude of the tracing at a specific time point divided by the maximal amplitude, expressed as a percentage.[41, 49, 55] Another less commonly reported TEG value which describes fibrinolysis is the estimated percentage lysis at 30 minutes after MA (EPL), which is an estimated value based on the contour of the tracing immediately following the maximum amplitude.[47]

In comparison with these TEG measurements, ROTEM offers additional variables that describe fibrinolysis. The lysis index (LI30 and LI60) is the variable that represents the clot firmness remaining after a specified amount of time after the first appearance of a clot (CT) as a percentage of the maximum clot firmness (MCF).[52, 56] The variable ML indicates the maximum amount of lysis occurring throughout the ROTEM analysis,

expressed as a percentage of MCF.[52] Two additional variables that describe the rate of fibrinolysis are lysis onset time (LOT), the amount of time following MCF needed for clot firmness to decrease by 15%, and lysis time (LT), the time needed for clot firmness to decrease by 90% following the MCF.[52] Also, a separate assay called APTEM can be performed in which an inhibitor of fibrinolysis, aprotinin, is added to the sample. The results of this test can then be compared to standard assays (e.g. EXTEM) to verify recovered clot stability with the addition of aprotinin.[70]

Future Directions: Studies are needed in animals with true disease positive and disease negative status (hyper- or hypofibrinolysis) defined by non-viscoelastic methods to determine which, if any, TEG/ROTEM variables are clinically relevant. Studies are also needed which document normal values in healthy animals.

Worksheet Question: How should hyperfibrinolysis be defined?

Conclusions: There is insufficient evidence to recommend how hyperfibrinolysis should be defined in companion animals based on TEG/ROTEM parameters at this time. We suggest that individual studies report sufficient data on patients and controls to enable definitions of hyperfibrinolysis to be evaluated post-hoc. We suggest that the TEG variable (Ly30, Ly60, CL30, CL60) and the ROTEM variables (LI30, LI60, ML, LOT and LT) be universally reported to enable meta-analyses to be conducted in the future.

Summary of Evidence: Only 1 veterinary publication was identified that was able to demonstrate the utility of TEG to document hyperfibrinolysis in companion animals (LOE 5, Poor).[40] In contrast, there is a large body of human literature which focuses on identifying hyperfibrinolysis in patients with trauma, brain surgery, liver transplantation,

and other disease states using both TEG and ROTEM (LOE 6, Good-Poor).[42-63] Hyperfibrinolysis may be defined by changes in several TEG and ROTEM variables. It may be represented in TEG by an increase in Ly30 or Ly60, decrease in CL30 or CL60, or an increase in EPL. In ROTEM, hyperfibrinolysis may be detected by a decrease in LI30 or LI60, increase in ML, decrease in LOT, or decrease in LT. APTEM may also be beneficial for the confirmation of hyperfibrinolysis in standard INTEM or EXTEM assays. *Future Directions:* Studies are needed to correlate these variables with hyperfibrinolytic states, documented with non-viscoelastic based technology, to determine which are the most clinically relevant values.

Worksheet Question: How should hypofibrinolysis / resistance to fibrinolysis be defined?

Conclusions: There is currently insufficient data in companion animals to recommend use of specific variables to define hypofibrinolysis. Standard TEG/ROTEM assays may be unable to detect hypofibrinolysis in companion animals.

Summary of Evidence: Changes in TEG variables indicative of hypofibrinolysis include: decreased Ly30 and Ly60, increased CL30 and CL60, and decreased EPL. Similarly, ROTEM values indicative of hypofibrinolysis include: increased LI30 and LI60, decreased ML, and increased or unmeasurable LOT and LT. Despite the widespread usage of TEG and ROTEM in veterinary medicine, variables describing fibrinolysis in canine and feline blood samples are infrequently reported. Three separate validation studies for thromboelastography in dogs (LOE 3, Good),[10, 14, 15] do not include data pertinent to fibrinolysis. A study comparing 3 methods of activation for TEG in healthy cats (LOE 3, Good),[12] described median and range values for Ly30 and Ly60. As described in this

manuscript, range values for Ly30 and Ly60 in normal cats reach as low as 0%. Similarly, reference intervals for Ly30 and Ly60 in dogs also reach 0% at the lower limit (LOE 5, Poor).[40] In the 1 study published in horses describing hypofibrinolysis in patients with acute gastrointestinal disease, reference intervals for Ly30 and CL30 extend to 0% and 100%, respectively (LOE 2, Fair).[41] As such, standard TEG and ROTEM assays appear to be unable to detect hypofibrinolysis in companion animals. The development of modified TEG models, which involve the addition of a fibrinolytic stress, e.g. tissue-plasminogen activator (t-PA), may better identify hypofibrinolysis.[66] A recent publication (LOE 2, Good) describes the usage of a t-PA-modified TEG analysis in a cohort of 20 dogs with diseases typically associated with thrombosis.[71] After applying t-PA, the lowest median lysis levels were in dogs with systemic inflammation and protein-losing disorders. Using a threshold below the lower end of the range of the healthy control group, more than 50% of the diseased dogs had Ly30 and Ly60 values consistent with hypofibrinolysis.

Future Directions: Studies are needed to correlate these variables with hypofibrinolytic states, documented with non-viscoelastic based technology, to determine the most clinically relevant data to report.

Worksheet Question: Should each center define its own TEG/ROTEM reference intervals? How should TEG/ROTEM reference intervals be defined?

Conclusions: We recommend that every center using TEG/ROTEM should establish its own reference interval using established veterinary clinical pathology guidelines. We recommend that reference intervals for TEG and ROTEM are not interchangeably used. We recommend that only appropriately trained operators be involved in establishing

reference intervals for TEG/ROTEM. We recommend that age and breed be considered when establishing reference intervals for TEG/ROTEM. We recommend that sample collection, sample handling and assay protocols be standardized when establishing reference intervals for TEG/ROTEM.

Summary of Evidence: Multiple studies (LOE 2-6, Good-Fair),[10, 11, 14, 15, 72-86] have reported methods for calculation of TEG/ROTEM reference intervals. No identified study specifically addressed the worksheet question, however, multiple analytical and pre-analytical factors have been shown to influence TEG results in companion animals and in people, suggesting that due consideration to such variables should be given when establishing reference intervals. The reader is referred to the first three sections of these guidelines for further information on this subject. Guidelines from non-target species (LOE 6, Good),[87] suggest that at least 40 individuals are required for accurate calculation of reference intervals based on the 2.5-97.5th percentiles. Evidence based guidelines for establishment of reference intervals in veterinary clinical pathology have recently been published by the American College of Veterinary Clinical Pathology and provide detailed guidance on methods for defining reference intervals.[a] Based on these guidelines, it is further recommended that direct sampling methods are used *a priori*, in which inclusion and exclusion criteria are established prior to selection of healthy reference animals, which should be deemed normal based on physical examination and blood work, including hematocrit, fibrinogen concentration and platelet count for reasons previously discussed. Data collected from less than 20 animals should not be reported as reference intervals.[88] Although data collected from between 20-40 animals may be used for reference interval

generation, they should be tested for normality and then appropriate robust or parametric methods used for RI calculation.[88]

Worksheet Question: What is the potential benefit of Vcurve data compared to conventional TEG parameters? Should TEG publications report Vcurve data and if so, which values?

Conclusions: There is currently insufficient data in companion animals to suggest a utility for Vcurve variables beyond that of standard TEG variables. We suggest that universal reporting of Vcurve parameters of the TEG curve in companion animals is not required at present. We suggest however, that authors consider reporting Vcurve data in addition to standard TEG variables in order to increase the amount of data available for review.

Summary of Evidence: Thrombus velocity curves (Vcurve) are plotted from the first derivative of the waveform generated by the TEG system and are expressed as changes in clot tensile strength per unit of time (dynes/cm^2/s), representing the maximum velocity of clot formation.[b] Vcurve derivatives include the 'time to maximum rate of thrombus generation' (TMRTG), 'maximal rate of thrombus generation' (MRTG), 'total thrombus generated' (TG), 'time to maximal rate of lysis' (TMRL), 'maximum rate of lysis' (MRL) and 'total lysis' (L). These computed parametric derivatives enable quantification of the kinetics of clot propagation and they have been suggested to represent surrogate markers of thrombin generation (LOE 6, Good-Poor).[89, 90] Vcurve parameters cannot be calculated from the standard TEG parameters but only obtained by analysis of the velocity curve generated at the time the TEG was performed. Therefore, if a study does not report Vcurve parameters, that information (if later shown to be useful) would involve authors going back

to the original output generated by the TEG analyzer, which would prove logistically difficult.

Twenty-one peer-reviewed manuscripts (LOE 2-6, Good-Poor) [3, 25, 86-103] fulfilled the search criteria by reporting TEG Vcurve data. Several of the studies (LOE 6, Good-Poor), [3,25, 86,87,91-95,99,102,103] all in non-target species, provide evidence in support of using Vcurve variables to further delineate the hemostatic abnormalities. Support for using these data occur in the context of direct thrombin inhibitor administration,[99] antiplatelet drug administration,[92] liver transplantation,[91] transfusion effectiveness,[91] parturition,[93,94] critical illness,[3] and hemophilia.[103] Some studies were more methodological and showed a correlation between Vcurve variables and platelet count,[25] and one study demonstrated that both standard TEG and Vcurve variables are, not surprisingly, affected by timing of initiation of analysis.[102]

Several studies (LOE 2-6, Fair-Poor)[88-90,97,98] were neutral in support of using Vcurve data in addition to standard TEG variables. One veterinary study (LOE 2, Fair)[88] evaluated the ability of TEG Vcurve variables to highlight deficiency in procoagulant activity in Scott syndrome. Although the TMRTG was prolonged in dogs with the defect, there was too much overlap with unaffected dogs for this to be considered useful from a diagnostic standpoint, and other methods, such as flow cytometry, were superior in their diagnostic capability. A second study in dogs (LOE 2, Fair)[89] examined standard TEG and Vcurve variables in dogs with primary immune-mediated hemolytic anemia. Although there were some significant changes, conflicting data were generated that cannot be easily explained. The third canine study (LOE 3, Poor)[90] sought to determine if dogs with carcinoma had Vcurve evidence of hypercoagulability by evaluating the TTG variable.

While dogs with tumors did have higher mean TTG compared with controls, there appeared to be much overlap in values with control dogs. Furthermore, thrombin-antithrombin complexes were not significantly different between the groups, which would suggest that thrombin generation was not increased, if this is considered the gold standard.

The time from sample collection to onset of testing, mode of activation, and sample matrix, all vary dramatically between the aforementioned studies making it difficult to draw any conclusions. Based on evidence from 3 studies performed in dogs (LOE 2-3, Fair-Poor),[92-94] universal reporting of Vcurve parameters in publications reporting TEG analysis cannot be supported at the present time. As regards the specific Vcurve parameters that may prove to be most useful MRTG, TMRTG and TG were identified.

Future Directions: Investigations are needed to test the aforementioned Vcurve parameters against validated, independent (i.e. not TEG-derived) markers of clot formation kinetics such as the calibrated automated thrombogram.[95]

Footnotes

[a] http://www.asvcp.org/pubs/pdf/RI%20Guidelines%20For%20ASVCP%20website.pdf

[b] TEG 5000 User's Manual, Haemoscope, part of Haemonetics Corporation, Braintree, MA.

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