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Use of Thromboelastography in Clinical Practice



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KEYWORDS

• Coagulation • Hemostasis • Clinical pathology • Blood • Monitoring

KEY POINTS

- Viscoelastic testing with whole blood may provide information on in vivo hemostasis.
- Viscoelastic testing allows the identification of fibrinolysis, unlike many other assessments of hemostasis.
- The data achieved from viscoelastic tests can provide functional assessments of fibrin formation, clot strength, platelet function, as well as fibrinolysis.
- Many diseases are accompanied or identified by altered hemostasis. Viscoelastic tests can be an important adjunct for individualized clinical decision making.
- The use of activators and the introduction of point-of-care viscoelastic instruments is increasing the utility of these tests in clinical practice.

INTRODUCTION

Hemostasis is a complex physiologic process that culminates in the production of a fibrin clot. Classic models of hemostasis suggest that a cascade of coagulation factor interactions drive clot formation. However, the complex interactions between blood cells, platelets, endothelial cells, and soluble plasma factors described in the cell-based model of coagulation¹ highlight the potential limitations of standard plasma-based coagulation tests such as prothrombin time (PT) or activated partial thromboplastin time (aPTT). Viscoelastic testing, such as thromboelastography (TEG) or thromboelastometry, is performed on whole-blood samples, which include both soluble plasma factors as well as tissue factor and phospholipid-bearing blood cells and platelets. Therefore, viscoelastic tests may provide a closer representation of in vivo hemostasis. In addition, this methodology allows identification of fibrinolysis, and can provide analysis of platelet function.

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In recent years, viscoelastic testing has become increasingly accessible and popular in emergency and critical care settings and can provide important information for the diagnosis and management of patients with hemostatic disorders. This article discusses the principles and interpretation of viscoelastic testing, its application to small animal emergency and critical care medicine, and potential advantages and disadvantages of these tests.

METHODOLOGY

Samples

Original viscoelastic analyzers were designed as bedside tests, using nonanticoagulated (native) whole blood, and were analyzed within minutes of collection. This approach is impractical in a laboratory or clinical setting, and the use of citrated blood samples has been validated in dogs and cats.^{2,3} Importantly, a comparison study reported that results from TEG performed on citrated and native blood are not comparable.⁴

Instrumentation

The most common viscoelastic testing systems used in veterinary medicine include TEG (Haemonetics Corp., Haemoscope division, Niles, IL) and ROTEM (rotation thromboelastometry, Pentapharm GmbH, Munich, Germany). TEG and ROTEM systems use a pin, attached to a torsion wire, suspended in a cylindrical cup. An aliquot of 0.36 mL of blood is added to the cup (prewarmed to 37°C). In TEG systems, movement is initiated by the cup, which rotates around the static pin at an angle of 4.45° every 10 seconds. In contrast, in ROTEM systems, it is the pin that oscillates within a static cup. As a clot forms, the pin and cup are joined by fibrin strands. In the TEG system, this causes the pin and cup to rotate together, and the change in torque is transmitted through the torsion wire and converted to an electrical signal. In ROTEM systems, the formation of fibrin strands between the cup and pin reduce the pin's oscillation, which is measured by the angle of deflection of a light beam.⁵ In both systems, these changes are graphed as change in clot strength (measured in millimeters on the Y axis) against time (measured in minutes on the X axis).

Activators

In veterinary medicine, citrated samples are most frequently used for laboratory or clinic-based viscoelastic testing, using a contact activator such as kaolin or Celite. Recently, assays using tissue factor to assess the intrinsic pathway, or tissue factor with kaolin for more rapid analysis, have been used.⁶

Point-of-Care Testing

A novel, point-of-care viscoelastic device, viscoelastic coagulation monitor (VCM; VCM Vet, Entegriion, Inc, Research Triangle Park, NC) uses frosted glass discs held in parallel on flexible plastic arms within a cartridge. The narrow space between these discs holds the blood sample introduced via capillary action from a detachable sample cup. This surface triggers coagulation through contact activation. The plastic arms interact with optical sensors within the analyzer to assess the differences in proportional movement between stationary and oscillatory arms, and difference in these movements over time is calculated via device software and graphically displayed. Similar to the other viscoelastic technologies, the VCM measures fibrinolysis as the percentage decrease in the amplitude of the trace at various time points after the measurement of maximal clot strength (indicated as lysis parameters).

The VCM has the potential to reach broader veterinary audiences because it does not require sample manipulation. As soon as a native whole-blood sample is loaded to the cartridge, the sample is monitored in real time in a self-contained automated system. It uses small amounts of fresh whole blood (0.25–0.5 mL) directly from the patient, and is less expensive and requires less technical skill compared with TEG and ROTEM. VCM reference intervals have been established for both dogs and cats.^{a,b}

INTERPRETATION OF VISCOELASTIC TEST RESULTS

Viscoelastic testing results in the formation of a trace of clot strength against time, from which multiple variables can be derived that allow for in-depth interpretation of coagulation status. The graph documents the progression from platelet aggregation, through clot formation, all the way to fibrinolysis and dissolution of the fibrin clot. Similar variables are measured by TEG and ROTEM; however, different terminology is used to describe these points in the tracing. These values are summarized in **Fig. 1** and **Table 1**, and are discussed in detail later.

Reaction Time/Clotting Time

The first stage of clot formation evaluated in viscoelastic testing is initial fibrin formation, reported as the reaction time (R) in TEG or clotting time (CT) in ROTEM systems. These values represent the point where fibrin polymers are first produced after clot initiation. R and CT can be expressed either in time (minutes) or distance (millimeters), and most commonly are reported as the time in minutes from clot initiation, to when the amplitude of the curve is 2 mm above baseline using citrated blood.

R and CT are affected by clotting factors within the intrinsic pathway including factor (F) VIII, FX, FXI, and FXII, as well as inhibitor activity. Prolongation of R or CT is associated with hypocoagulable states (eg, deficiencies in the aforementioned clotting factors), whereas a shortened R or CT is associated with a hypercoagulable state. The time at which R or CT are measured is the point at which standard plasma-based clotting assays such as PT or aPTT would end. Studies have shown variable correlation between results of R and CT from viscoelastic testing and results of standard coagulation assays. In a study that compared a control population with dogs admitted to an intensive care unit (ICU) with diseases known to affect coagulation status, there was a significant correlation between R and PT.⁷ In contrast, another study found that dogs with decreased PT and aPTT had significantly more thrombus formation, but there was no correlation with TEG variables, although 19 out of 25 (76%) dogs with shortened PT and aPTT also had a shortened R.⁸ In another study, there was also a trend toward shortened R times in patients with evidence of thrombosis on postmortem.⁹

Clot Kinetics/Clot Formation Time

After initial clot formation, the speed and strength of clot development is reported as clot kinetics (K) in TEG or clot formation time (CFT) in ROTEM systems. These values reflect the time taken to reach a predetermined level of clot strength, from initiation of

^a Buriko Y, Silverstein D. Establishment of normal reference intervals in dogs using viscoelastic coagulation monitor (VCM) and validation of the VCM device using thromboelastography (TEG). European Veterinary Emergency and Critical Care Congress, Venice, Italy, June 2018. *J Vet Emerg Crit Care* 2018; 28: S27.

^b Rosati T, Jandrey K, Burges J, et al. Establishment of a reference interval for a novel viscoelastic coagulometer and comparison to thromboelastography in healthy cats. European Veterinary Emergency and Critical Care Congress, Venice, Italy, June 2018. *J Vet Emerg Crit Care* 2018; 28: S34.

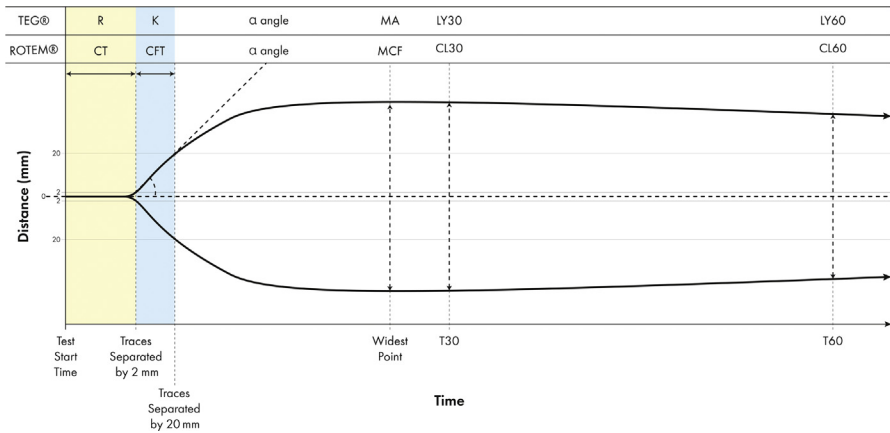


Fig. 1. A representative example of a viscoelastic trace showing the most common parameters and comparison between TEG and thromboelastometry (ROTEM). The X axis (time) shows critical points during the analysis where measurements are benchmarked. The Y axis is distance of the trace from baseline in millimeters (the amplitude). R (reaction time) or CT (clotting time) is reached when the amplitude reaches 2 mm. The K (clot kinetics) or CFT (clot formation time) is measured at 20-mm amplitude, a predetermined clot strength. The α (alpha) angle is formed from the line tangent between these first 2 points. The α angle represents the speed of fibrin formation and cross-linkage. Maximum amplitude (MA) or maximum clot firmness (MCF) is the widest point on the trace. The LY (lysis) or CL (clot lysis) times are measured at 30 minutes (T30) and 60 minutes (T60) after, and are indicated by the percentage of the MA/MCF.

clot formation at 2 mm, to when the curve reaches an amplitude of 20 mm. A shortened K or CFT is associated with hypercoagulability, whereas prolonged K or CFT is associated with hypocoagulability.

The K and CFT values are affected by platelet concentration and function, thrombin, fibrinogen, activity of FII and FVIII, and hematocrit (HCT). One study showed a significant increase in CFT after induction of in vivo reduced red cell mass (via phlebotomy), which was not confirmed by other coagulation variables, suggesting decreased HCT may artifactually result in hypercoagulable tracings using viscoelastic testing.¹⁰ This possibility is further supported by the results of a study whereby in vitro manipulation of blood to create different reductions in HCT (45%, 20%, and 10%) were either corrected for viscosity with alginate or diluted with equal volumes of saline. This method resulted in hypercoagulability (with a shortened K) when using saline to decrease viscosity, but hypocoagulability when using alginate to correct for changes in viscosity associated with reduced HCT.¹¹ This phenomenon has also been reported in a population of diseased dogs with naturally occurring anemia.¹²

Alpha Angle

The alpha angle (α) is the angle formed between the baseline and a line tangent to the curve at the point of R or CT. Both TEG and ROTEM systems use this terminology and definition. The α is a reflection of the speed of clot formation as well as the kinetics of fibrin formation and cross-linkage. It is therefore closely related to the K or CFT values, and thus is influenced largely by the same factors. An increased α is associated with hypercoagulability, whereas a decreased α is associated with hypocoagulability. In a study of human patients with trauma, the alpha angle from rapid TEG results (tissue

Table 1 Thromboelastography and thromboelastometry (rotational thromboelastometry) system variables and interpretation of results					
TEG	ROTEM	Units	Interpretation		Affected by
			Hypercoagulable	Hypocoagulable	
Reaction time	Clotting time	Minutes	Shortened	Prolonged	Clotting factors (FVIII, FIX, FXI, FXII)
Clot kinetics	Clot formation time	Minutes	Shortened	Prolonged	Platelet concentration, platelet function, FII, FVIII, fibrinogen concentration, HCT
Alpha angle	Alpha angle	Degrees	Increased	Decreased	Platelet concentration, platelet function, FII, FVIII, fibrinogen concentration, HCT
Maximum amplitude	Maximum clot firmness	Millimeters	Increased	Decreased	Fibrinogen concentration, platelet concentration and function, thrombin concentration FXIII, HCT
G (shear elastic modulus)	G (shear elastic modulus)	Dynes/cm ²	Increased	Decreased	Fibrinogen concentration, platelet concentration and function, thrombin concentration, FXIII, HCT
			Hyperfibrinolysis	Hypofibrinolysis	—
LY30/60	CL30/60	Percent	Increased	Decreased	Clot inhibitor concentration

Abbreviation: HCT, hematocrit.

factor activated) had the greatest single factor sensitivity (compared with other TEG parameters and conventional clotting tests) in predicting transfusion need in cases of moderate blunt trauma.¹³

Maximum Amplitude/Maximum Clot Firmness

The maximum height of the curve is referred to as the maximum amplitude (MA) in TEG or the maximum clot firmness (MCF) in ROTEM systems. MA depends on platelet concentration and function, as well as fibrinogen concentration and is

directly correlated to platelet and fibrin interactions, which determines the ultimate strength of the fibrin clot.

Shear Elastic Modulus

The shear elastic modulus (denoted by G in both TEG and ROTEM systems) measures overall coagulation status as hypocoagulable (decreased G), normocoagulable (normal G), or hypercoagulable (increased G). It is derived by the formula $G = 5000 \times MA / (100 - MA)$, and depends only on MA, but increases exponentially compared with MA, permitting more sensitive resolution at high amplitudes.

Clot Lysis

The final variable of the viscoelastic testing procedure reflects fibrinolytic-induced dissolution of the fibrin-platelet bonds formed between the pin and cup. The percentage return of MA to baseline is an indicator of this process, is evaluated either at 30 or 60 minutes, and is referred to as LY30/LY60 in TEG or CL30/CL60 in ROTEM systems.

Thromboelastography Platelet Mapping

Platelet mapping is available on the TEG platform to assess platelet function and measures percentage inhibition of platelet function compared with maximal uninhibited platelet function. The assay compares tracings obtained by cleaving and cross-linking fibrinogen (with reptilase and FXIIIa) inhibiting thrombin and platelets, with a tracing obtained by the addition of platelet agonists such that only thrombin is inhibited. The resulting MA is a function of platelet activation and offers a specific representation of platelet function.

Tracings

The following list includes tracing interpretations from TEG/ROTEM systems that are commonly encountered in emergency and critical care medicine. These are depicted visually in [Fig. 2](#).

- Normal
- Hypercoagulable
- Hypocoagulable
- Thrombocytopenia/thrombocytopenia
- Hyperfibrinolysis
- Disseminated intravascular coagulation (DIC) stage 1

VISCOELASTIC TESTING IN EMERGENCY AND CRITICAL CARE

The role of viscoelastic testing in veterinary emergency and critical care has grown rapidly over the last 20 years. It detects both hypocoagulable and hypercoagulable states, which has driven a large body of publications in the diagnosis and treatment of many disease states in the past decade. It has also been useful in the monitoring of anticoagulant therapy as well as evaluation of platelet function. A recent study used TEG to guide transfusion in dogs with hypocoagulable disorders.¹⁴ The important application of viscoelastic testing to veterinary emergency and critical care may also be emphasized by a study of dogs admitted to an ICU, which found abnormal TEG tracings in 14 of 27 (52%) patients in whom a wide array of disease states contributed to hemostatic dysfunction.⁷ A summary is given next of some important disease conditions in veterinary emergency and critical care medicine where viscoelastic testing has been shown to be helpful to evaluate hemostatic function, as well as to enhance diagnosis and treatment.

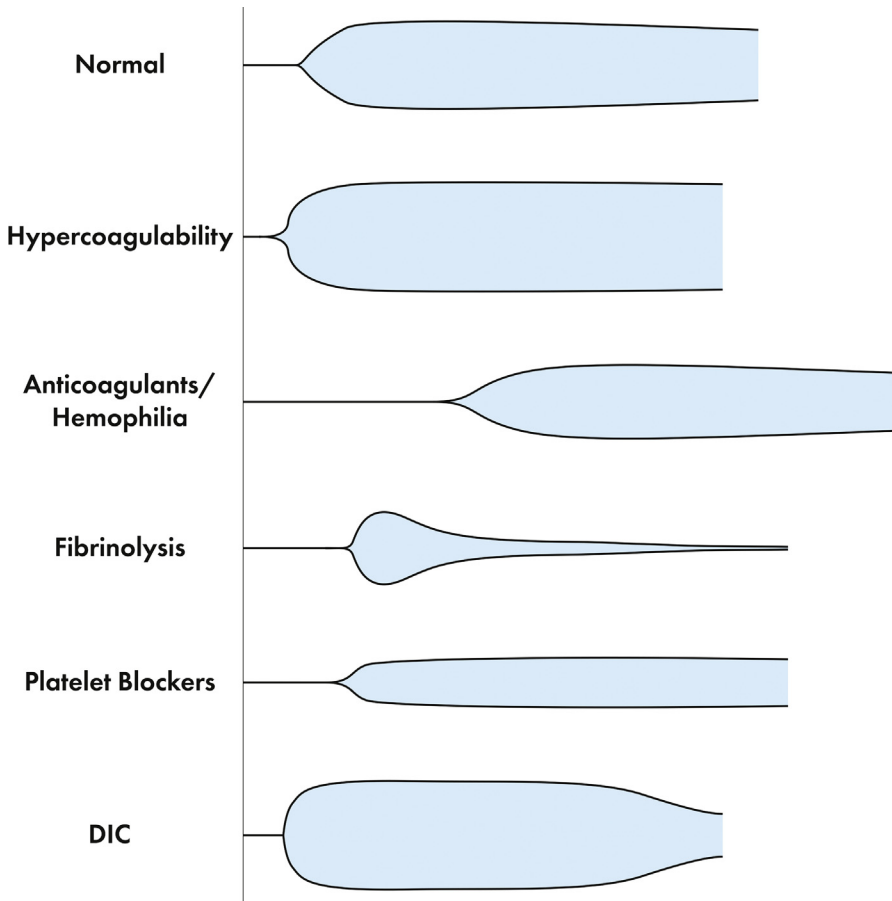


Fig. 2. A series of viscoelastic traces in health and disease shown for comparison and pattern recognition.

Disseminated Intravascular Coagulation

DIC represents a complex and dynamic hemostatic disorder. The classic progression of disease is characterized by early hypercoagulability caused by activation of tissue factor and inhibitor consumption by inflammatory mediators, followed by hypocoagulability caused by consumption of coagulation factors and increased fibrinolysis.^{15,16} The ability of TEG to assess global coagulation status, including hypocoagulability, hypercoagulability, and fibrinolysis, makes it a powerful tool for the diagnosis and management of patients with DIC.

Reflecting the pathophysiology outlined earlier, the results of a prospective study of 50 dogs with DIC showed hypercoagulability in 22 of 50 (44%), hypocoagulability in 11 of 50 (22%), and normocoagulability in 17 of 50 (34%) based on G values from recombinant human tissue factor–activated TEG¹⁷. Dogs with hypocoagulability had 2.38 increase in relative risk of death compared with hypercoagulable dogs. In another study, an increased risk of mortality associated with hypocoagulability based on thromboelastometry (TEM) in dogs with DIC was also found, with an odds ratio of 4.800 compared with

dogs with hypercoagulability, and odds ratio of 3.429 compared with dogs with normocoagulability.¹⁸

TEG was shown to be helpful in the diagnosis of the hyperfibrinolytic phase of DIC in a dog with metastatic hemangiosarcoma, with increased K, decreased α , decreased MA, and markedly increased LY30 and LY60.¹⁹

Sepsis

Coagulopathy associated with sepsis can range from mild activation of the coagulation system to DIC, as discussed previously. Viscoelastic testing has proved useful in human septic patients for assessment of fibrinolytic activity, hypercoagulability, and diagnosis of DIC, as well as prediction of relative risk of mortality.²⁰ In a study of dogs with naturally occurring septic peritonitis, preoperative values of MA and α were significantly greater (more hypercoagulable) in nonsurvivors than survivors, with normal MA a specific predictor of survival (100%).²¹ In contrast, in a study of experimental endotoxemia in dogs, there was a significant decrease in α angle and MA relative to a control population, consistent with hypocoagulability.²²

Trauma

Trauma-induced coagulopathy is a common phenomenon in patients with trauma, and, in human medicine, the concurrent findings of coagulopathy, acidosis, and hypothermia are collectively termed the lethal triad.²³ Acidemia is thought to contribute to hemostatic dysfunction in patients with trauma, and in vitro acidification of blood in dogs resulted in progressive hypocoagulability as measured by some TEG parameters, including α and MA.²⁴ In an experimental rabbit-based model of trauma, hemodilution and hypothermia resulted in decreased α and MA, and a decreased rate of clot formation (measured by Vmax) consistently predicted coagulopathic bleeding and death in animals better than plasma-based clotting assays.²⁵

In a clinical, prospective study investigating coagulation abnormalities in dogs with severe acute trauma, decreased α and decreased MA were associated with nonsurvival relative to control dogs.²⁶ In contrast, in another study of dogs with severe trauma (with an animal trauma triage [ATT] score >5), 10 out of 30 (33%) dogs had an increased G, suggesting hypercoagulability.²⁷ No dogs in this study were hypocoagulable based on TEG or standard coagulation test results. Hypercoagulability was also found in a population of dogs (4 out of 18 [22%]) and cats (1 out of 19 [5%]) following blunt trauma.²⁸ This study also documented hypocoagulability, and, in dogs, decreased MA was significantly associated with injury severity based on ATT scores.

Trauma also importantly affects clot degradation. Hyperfibrinolysis is reported commonly in human studies of acute trauma and in animal models of hemorrhagic shock; however, inhibition of fibrinolysis (fibrinolysis shutdown) is also reported and has been documented in animal studies of tissue injury.^{29,30}

The complex hemostatic disorders associated with trauma may be influenced by acid-base status, effective circulating volume, inflammatory mediators, body temperature, and therapeutic interventions. Viscoelastic testing may play an increasingly important role in global evaluation of the coagulation status of veterinary patients with trauma.

Immune-Mediated Hemolytic Anemia

Immune-mediated hemolytic anemia (IMHA) has been associated with many hemostatic disorders, including DIC, hypercoagulability, and a predisposition for thromboembolism, including pulmonary thromboembolism (PTE).³¹ Viscoelastic testing is

therefore a valuable tool in this disease condition for global assessment of coagulation status, and numerous clinical studies have been conducted.

A prospective study of 11 dogs with primary IMHA found a hypercoagulable state relative to a control population, based on lower median K, higher median α , higher median MA, and increased G.³² A subsequent study with greater numbers of dogs (n = 30) with primary IMHA also reported that dogs were significantly hypercoagulable versus controls, with significantly shorter K, greater α , and greater MA. Interestingly, this study also found that MA was significantly higher at hospital admission in survivors than nonsurvivors, with increased odds of 30-day survival of 1.13 with each unit increase in MA.³³ This counterintuitive finding was also supported by a study whereby no dogs with a normal coagulation index survived, suggesting that dogs that were not hypercoagulable had an increased risk of death.³⁴

As noted previously, there is an inverse correlation between HCT and TEG variables K and MA, which may result in artifactual hypercoagulable tracings, possibly hampering interpretation of results in a study of IMHA. As noted in the Goggs and colleagues³³ study, if the MA, for example, were affected solely by the decreased HCT, then it would be expected that the packed cell volume would have been associated with outcome, which was not the case in that study. In addition, IMHA is associated with an inflammatory state, which is a known possible cause of hypercoagulability, and other possible causes may include hyperfibrinogenemia, increased contact pathway activation, platelet hyper-reactivity, or hemolysis. In addition, IMHA can be a secondary disease process to an underlying cause such as neoplasia or infectious disease, which may also affect coagulation.

Neoplasia

Malignant neoplasia has been associated with an increased risk of pulmonary thromboembolism (PTE), although the condition is often diagnosed postmortem.³⁵ Viscoelastic testing can be helpful to diagnose hypercoagulability, which in turn may predispose to PTE formation; however, this modality has not proved helpful as a stand-alone test in the prediction of PTE formation.^{36,37}

One study using tissue factor-activated TEG found hemostatic dysfunction in 28 of 49 dogs (57%) in a cross-section of different neoplasms.³⁸ Hemostatic dysfunction was significantly more likely in dogs with malignant neoplasia, and most dogs in the study were hypercoagulable (22 out of 49 [45%]). It was interesting to note that all dogs with hypocoagulability (6/ out of 49 [12%]) had malignant neoplasia with evidence of metastatic disease, although patient numbers were small. Another study of 71 dogs with malignant neoplasia also found that hypercoagulability was the most common TEG abnormality, present in 47 out of 71 (66%) patients.³⁹ In a study of dogs with multicentric lymphoma, 17 out of 27 (63%) were found to be hypercoagulable based on TEG findings of decreased R, shortened K, increased α angle, or increased MA, and these alterations did not resolve in some patients for up to 1 month following clinical remission.⁴⁰

Hemostatic dysfunction is common in veterinary patients with neoplasia, including hypercoagulability, and viscoelastic testing is an important test modality for evaluation of coagulation status in these patients. Further studies may be helpful to investigate any possible prognostic significance to these results.⁴¹

ADVANTAGES AND DISADVANTAGES OF VISCOELASTIC TESTING

Viscoelastic testing offers numerous advantages for the diagnosis and monitoring of coagulation status in emergency and critical care patients. There are also some

Box 1**Advantages and disadvantages of viscoelastic monitoring in small animal critical care**

Advantages

- More global assessment of hemostasis that better reflects the complex physiology of in vivo coagulation.
- Rapid turnaround time.
- Small volume of blood required.
- Possible to evaluate both hypercoagulability and hypocoagulability.
- Able to evaluate hypofibrinogenemia and fibrinolysis.
- TEG system can analyze platelet function.
- Results reported in both graphical format and numerical measurements, aiding in rapid interpretation of results.

Disadvantages

- Does not evaluate contribution of endothelium to coagulation.
- Requirement for close access to machine.
- Variability in results, especially based on use of different activators.⁴¹
- Poor reproducibility, even with the same analyzer subject to standardized testing.⁴²
- Results may be affected by HCT of the patient.
- May be affected by hypothermia.⁴³
- Low sensitivity to mild coagulation factor deficiencies or mild defects in primary hemostasis.

disadvantages to this test modality that should be considered. These considerations are summarized in **Box 1**.

SUMMARY

Viscoelastic testing offers unique insight into the process of clot initiation, amplification, propagation, and termination through fibrinolysis. The graphical and numeric outputs from these tests are easy and rapid to interpret, and results can be used for both diagnosis and management of disease. However, although viscoelastic testing may provide a more global assessment of coagulation status, it is not intended to replace standard coagulation tests, or be interpreted as a stand-alone test. Viscoelastic testing is most powerful when used in conjunction with other tests of hemostasis. The use of these tests in veterinary emergency and critical care medicine continues to increase and likely will continue to expand with ongoing clinical use and research.

DISCLOSURE

The authors have nothing to disclose.

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