**Assessment of coagulation utilizing thromboelastometry in dogs undergoing orthopedic surgery**



*Published version:*

DOI:10.1111/vec.12300



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# Assessment of coagulation in dogs undergoing orthopedic surgery utilizing thromboelastometry

**Abstract**

**Objective** – Evaluation of blood coagulation by means of thromboelastometry in dogs after orthopedic surgery.

**Design** – Longitudinal observational study.

**Setting** – University Veterinary Teaching Hospital.

**Animals** – Thirty-four adult, client-owned dogs.

**Interventions** –Whole blood from each dog was collected by jugular venipuncture (20-gauge needle) using minimum stasis. The blood was then placed into tubes containing 3.8% trisodium citrate (1 part citrate: 9 parts blood) and stored at 37°C.

**Measurements and Main Results** – Dogs undergoing orthopedic surgery were enrolled and whole blood was collected before (T0), at 24 hours (T1) and 1 week (T2) after surgery. Statistically significant differences ($p < 0.05$) between the values of the thromboelastometry parameters were noted: an increase in maximum clot firmness (MCF) from T0 to T1 in the in-TEM and fib-TEM profiles (both $p = 0.0001$), and from T0 to T2 in the in-TEM, ex-TEM, and fib-TEM profiles ($p = 0.012$, $p = 0.037$ and $p = 0.0001$, respectively), and in the $\alpha$ angle in the in-TEM and ex-TEM profiles ($p = 0.019$ and $p = 0.036$, respectively), and in the fib-TEM profile from T1 to T2 ($p = 0.039$). All parameters were, however, within our institutional reference ranges.

**Conclusions** – This is the first study to assess changes in coagulability by means of thromboelastometry and platelet function analysis in dogs following orthopedic surgery. Our results show that, unlike the increased hypercoagulation observed in human orthopedic patients, a hypercoagulable state did not develop in dogs undergoing orthopedic surgery.

Key words: small animal, hemostasis, surgery, thromboelastometry.

aPTT activated partial thromboplastin time

CFT clot formation time

CT clotting time

MCF maximum clot firmness

PT prothrombin time

TEG thromboelastography

TEM thromboelastometry

THR total hip replacement

## Introduction

Hypercoagulable states are frequent in human patients undergoing surgery. According to a study by McCrath *et al.* (2005), hypercoagulabilty following non cardiac surgeries develops in 40% of patients .[1] Such conditions, associated with other factors of Virchow's triad (i.e., venous stasis and vessel wall damage), may lead to thrombotic complications, including myocardial infarction, ischemic stroke, deep vein thrombosis and pulmonary embolism.[1]

Numbering among the categories of surgical patients considered at risk for thrombotic complications are those undergoing major orthopedic surgery (new and revision total hip replacement, total knee replacement or fractured neck of femur repair).[2] Studies conducted in human medicine have shown a prothrombotic state in surgical patients; for example, Wilson *et al.* (2001) evaluated hemostasis in 250 patients undergoing surgery for proximal femoral fracture and found hypercoagulability to be correlated with the development of deep venous thrombosis;

Okamura *et al.* (2008) observed hypercoagulability in 30 human patients undergoing total knee, total hip arthroplasty, and other lower extremity orthopedic surgeries.[3,4] The hypothesized causes for the hypercoagulability were surgical trauma with tissue factor expression, systemic inflammation, platelet activation, blood loss, and fluid administration.[1,3] Because of the risk of thrombosis, all human patients receive antithrombotic prophylaxis after orthopedic surgery. Hypercoagulability in dogs after orthopedic surgery has not yet been investigated. In veterinary medicine, a few studies in dogs have described pulmonary embolic complications following cemented total hip replacement (THR).[5,6,7] The pathogenic hypothesis for this event is the elevated femoral intramedullary pressure during stem insertion , ensuing in fat or bone marrow embolization.[8] Pulmonary embolism was not reported in a study on non cemented THR in 11 dogs, where other surgical techniques were applied and pulmonary embolism was diagnosed differently.[9]

Hypercoagulability in postsurgical human patients has been investigated by thromboelastography. Thromboelastography (TEG)/thromboelastometry (TEM) measure the viscoelastic properties of whole blood during the various different phases of clot formation, stabilization and eventual lysis. This complete view of the entire hemostatic process makes the techniques a good instrument to study hypercoagulability. In veterinary medicine, hypercoagulabilty has been investigated and demonstrated by means of TEG in a variety of disorders, including parvoviral infection, neoplasia, protein-losing enteropathy, hemolytic anemia, disseminated intravascular coagulation and protein-losing nephropathy.[10-15] Recently, Smith *et al.* validated TEM also for the canine species. [16]

Knowing the hemostatic status and its related potential complications is important, especially in intensive care unit patients. In brief, TEM/TEG are new tools for the complete assessment of coagulation.

The aim of this study was the perioperative evaluation of blood coagulation by means of TEM in dogs undergoing orthopedic surgery. Our hypothesis was that in dogs, as in humans, orthopedic surgery may cause hypercoagulability.

## Materials and methods

### Animals

The study was conducted according to animal welfare considerations and regulations of the Ministry of Health. Dogs undergoing orthopedic surgery between January and September 2009 were enrolled into this prospective clinical study after informed consent was obtained from the owners. The dogs underwent THR, THR revision, double pelvic osteotomy, tibial plateau leveling osteotomy, femoral fracture repair or elbow fracture repair.

The exclusion criteria were: presence of neoplasia, history of a tendency to spontaneous bleeding; positivity to serologic tests for *Leishmania infantum* (titer >1:40; immunofluorescence antibody test), for *Ehrlichia canis* [a], *Borrelia burgdorferi* [a], *Anaplasma phagocytophilum* [a] or *Dirofilaria immitis* [a]; administration of corticosteroids in the 4 weeks before surgery.

The patients underwent preoperative evaluation including: physical examination; complete blood count [b]; biochemical profile [c] including albumin, total protein, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, cholesterol, trygliceride and urinalysis (dipstick test [d] and sediment analysis).

Dogs were premedicated with eptadone (0,2 mg/Kg IM) and anesthesia was induced with propofol (2 to 4 mg/Kg IV, to effect). Dogs then were intubated, and anesthesia was maintained by administration of isoflurane in oxygen and air. All dogs were administrated lactated Ringer's solution at a rate of 10 ml/ Kg/h IV. All surgeries were performed by one experienced surgeon (LP) and standardized surgical protocols were used. After the extubation standard postoperative care included the administration of buprenorfine (10 µg/Kg/6-hourly, IV) and carprofen (2 mg/kg/12-hourly, SC or orally with food).

The sample size had been determined using the Kastenbaum, Hoel e Bowman tables for ANOVA;[17] A minimum sample size of 25 animals, repeated for three measurements, was calculated, taking into account: a) a power of the study equal to 80%; b) a significance level of 0.05; c) a standardised range (max-min/sigma) equal to 0.8.

**Hemostasis**

Thromboelastometry,[e] PFA-100 [f] and platelet count (CBC)[b] were performed at three time points: 1 hour before the surgery (T0), 24 hours after the conclusion of the surgery (T1), and 7 days after surgery (T2).

Blood specimens were collected by jugular venipuncture with a 20 gauge needle by exerting minimal hemostasis on the vessel. Samples obtained with difficulty (e.g. venipuncture requiring numerous attempts, repositions of the needle or interruption in blood flow into the tube) were discarded and the collection was repeated in the contralateral jugular. Samples were stored at 37°C in 3.8% trisodium citrate tubes.[g]

For the thromboelastometry assay, analyses were performed within 30 minutes after blood collection according to the manufacturer's instructions, and the analyses were run for 60 minutes. Three different profiles were tested for each sample: in-TEM, ex-TEM and fib-TEM assays. In the in-TEM assay, the sample is recalcified by the star-TEM[h] reagent and the intrinsic pathway is activated by the in-TEM reagent[i], whereas in the ex-TEM profile, after recalcification, the extrinsic pathway is triggered by the ex-TEM reagent[l]. In the fib-TEM assay, the extrinsic pathway is activated by tissue factor in the presence of a platelet inhibitor[m] to assess the functional fibrinogen level. The following parameters were assessed for each profile: clotting time ([CT], s); clot formation time ([CFT], s); maximum clot firmness ([MCF]; mm) and α angle (α, °).

**Statistical analysis**

The data were entered into an *ad hoc* database and analyzed using commercial statistical software[h]. A test for normality based on skewness and on kurtosis was performed to test data distribution. Levene's robust test was used to evaluate the homogeneity of variances. ANOVA was applied to the data to compare the lengths of coagulation time. The Bonferroni's correction was applied. When the data did not fulfill the assumptions of the parametric method, Friedman's two way analysis of variance was performed. The significance level was set at $p < 0.05$.

**Results**

Of 34 eligible adult dogs candidates for orthopedic surgery, 29 were included at T0 and T1 and 25 at T2 (4 animals were lost to follow-up because the owners did not return for the second visit), and 5 were excluded (1 because of neoplasia, 1 because of filariasis and 3 because of Leishmaniasis). Seven dogs underwent THR, 1 THR revision, 1 double pelvic osteotomy, 16 tibial plateau leveling osteotomy, 3 femoral fracture repair and 1 elbow fracture repair.

Of these 29 dogs, 13 were males and 16 females, aged from 1 to 11 years (age, 3.64 ± 2.77). Four dogs were crossbreed, 6 were Labrador Retriever, 2 were Beagle, 1 Cane Corso and 1 German Shepherd; the other breeds included: Boxer, Bull Mastiff, English Bull Dog, Dobermann Pinscher, Dogue de Bordeaux, Drahthaar (German wire-haired pointer), Golden Retriever, Maremma sheepdog, American Pit Bull Terrier, Setter Gordon, and Sharpei. The CBC, biochemical and urinalysis values were all within our institutional reference ranges.

The results of the comparisons of the TEM tracings at the three time points (T0 vs T1, T1 vs T2 and T0 vs T2) are listed in Tables 1-3, respectively. Significant differences ($p < 0.05$) were found between T0 and T1, where there was an increase in MCF in the in-TEM and fib-TEM profiles at T1; between T0 and T2, where there was an increase in MCF (in all profiles) and the $\alpha$ angle (in the in-TEM and ex-TEM profiles) at T2; between T1 and T2, where MCF was increased in the fib-TEM profile at T2. All parameters were within our institutional reference ranges, however (Table 4).[18]

**Discussion**

Orthopedic surgery is known to increase the risk for hypercoagulability and thromboembolic complications during the postsurgical period in human patients.[3,4]

To the best of the authors' knowledge, coagulation in perioperative dogs has been assessed in a few studies and with different methods. Two studies evaluated the blood coagulation profile after ovariohysterectomy in female dogs: Millis *et al.* (1992) performed standard coagulation profiles (PT, aPTT and fibrinogen), fibrin degradation product, antithrombin III and platelet count; Sobiech *et al.* (2011) carried out standard coagulation profiles, thrombin time, D-dimer and antithrombin activity.[19,20] The first study revealed only a postoperative increase in fibrinogen level, whereas the second showed a prolonged aPTT, higher fibrinogen and D-dimer concentrations and lower levels of antithrombin activity in the postoperative patient.[19,20] Another study in dogs after gonadectomy evaluated the bleeding tendency in greyhounds according to platelet count, PFA-100, von Willebrand factor, factor VIII, PT, aPTT, fibrinogen, D-dimer, plasminogen, antiplasmin and antithrombin. The results showed a post-operative increase in the fibrinogen level and antiplasmin activity.[21] Altered fibrinolysis was reported by Lanevschi *et al.* (1996) who evaluated plasminogen, tissue plasminogen activator and alpha 2-antiplasmin in dogs after different surgical procedures. Finally, a recent study by Villar *et al.* (2011) showed that aPTT and PT are not predictors of bleeding in greyhounds undergoing gonadectomy, while thromboelastography parameters representing fibrin cross-linking (α angle) and clot strength (maximum amplitude) were considered predictors of bleeding. Indeed, postsurgical TEG showed a decrease in the α angle in the bleeder dogs and an increase in the maximum amplitude and α angle in the non-bleeder dogs.[22]

Thromboelastometry/thromboelastography are useful tools to identify hypo- and hypercoagulable conditions in dogs.[10,11,14,23,24] In the thromboelastometric profiles, CT represents the first phase of fibrin formation, from activation of the test to a clot amplitude of 2 mm; this parameter is mainly affected by the concentration of plasma coagulation factors and coagulation inhibitors (e.g., antithrombin or drugs).[25,26] CFT expresses the velocity of clot formation and is affected predominantly by platelet number and function and by fibrinogen activity. MCF, the maximum firmness reached by the clot, is determined by both platelet number and function and fibrin formation in the presence of factor XIII.[25,26] The α angle corresponds to the slope of the tangent on the elasticity curve, where a decrease indicates a tendency towards hypocoagulability and an increase a hypercoagulable condition.[25,26]

The TEM profiles in our study showed changes indicating an increase towards a prothrombotic state in dogs undergoing orthopedic surgery; nonetheless, all parameters were within our institutional reference ranges.[18] These changes, as indicated by the increase in MCF and the $\alpha$ angle, are similar to those Villar *et al.* (2011) reported for the TEG profile after gonadectomy in non-bleeder greyhounds. Also in human studies, TEG showed a greater increase in maximum amplitude (the TEG parameter corresponding to MCF) and $\alpha$ angle, indicating a condition of hypercoagulability. Wilson *et al.* (2001) identified, in patients following surgery for proximal femoral fracture, a period of hypercoagulability that persisted for 6 weeks, despite the use of antithrombotic prophylaxis. More recently, McCrath *et al.* (2005) reported that the incidence of thrombotic complications in patients undergoing a wide variety of surgical procedures was significantly more frequent, with a maximum amplitude >68 mm.[1,3]

MCF results from the interaction between platelets and fibrinogen activation in the presence of factor XIII, and it does not depend on the presence of procoagulant factors. An increase in this parameter can be due to an increase in fibrinogen concentration, in platelet activity or in the level or activity of factor XIII. Finally, alterations in TEG parameters (prolonged clot formation time and decreased $\alpha$ angle) following carprofen administration, previously reported by Brainard *et al.*, were not identified in the present study.[27]

This is the first study to assess coagulation status by means of thromboelastometry in dogs following orthopedic surgery. Contrary to what happens in human orthopedic patients, hypercoagulability did not develop in our study population. In human medicine, the mechanisms thought to cause hypercoagulability are surgical trauma with tissue factor expression, systemic inflammation, platelet activation, blood loss and fluid administration.[1,3] Further studies are needed to explain why a hypercoagulable state does not occur in dogs, despite the presence of at least some of such predisposing factors.

Our results could mean that healthy dogs after orthopedic surgery might be less predisposed than human patients to thrombus formation.[28,29] Venous studies with contrast (e.g., angiography or computed tomography angiography) might be one way to exclude the presence of thromboembolic events, obviating the need antithrombotic prophylaxis in orthopedic postoperative dogs admitted to an intensive care unit.

Finally, further studies are needed to compare the impact of different orthopedic surgeries, the changes in coagulability in a population of older dogs, and the interaction of concomitant pathologies or other predisposing factors (e.g., patients with multiple trauma).

***Footnotes***

[a] Snap 4 DX, IDEXX Laboratories, Westbrook, ME, USA.

[b] ADVIA 120 Hematology, Siemens Healthcare Diagnostics, Tarrytown, NY, USA.

[c] ILAB 300 plus, Clinical Chemistry System, Instrumentation Laboratories, Milan, Italy.

[d] Multistix 10 SG Reagent Strips, Siemens Healthcare Diagnostics, Tarrytown, NY, USA.

[e] ROTEM, TEM innovation GmbH, Munich, Germany.

[f] Venosafe 3.8% buffered sodium citrated, Terumo, Leuven, Belgium.

[g] Stata Statistical Software: Release 11. StataCorp LP, College Station, TX, USA.

[h] Star-TEM 10 (0.2 mol/l $CaCl_2$ in HEPES buffer pH 7.4 and 0.1% sodium acide in glass vials), TEM innovations Gmbh- Munich-Germany.

[i] In-TEM (partial thromboplastin phospholipid made of rabbit brain (chloroform extract), ellagic acid, buffer, preservatives in small glass vials), TEM innovations Gmbh- Munich-Germany.

[l] Ex-TEM (recombinant tissue factor and phospholipids, CaCl2, preservatives and buffer in small glass vials), TEM innovations Gmbh- Munich-Germany.

[m] Fib-TEM (Cytochalasin D / DMSO solution 0.2 mol/l $CaCl_2$ in HEPES buffer pH 7.4, preservative in glass vials), TEM innovations Gmbh- Munich-Germany.

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**Table 1:** Comparison between thromboelastometry values obtained at T0 (n=29) and T1 (n=29).

| | CT[§] s | | CFT[||] s | | MCF[¶] mm | | α** degree | |
|---|---|---|---|---|---|---|---|---|
| | **T0** | **T1** | **T0** | **T1** | **T0** | **T1** | **T0** | **T1** |
| **in-TEM** | 178.8 (118-390) | 176.03 (134-263) | 96.83 (52-202) | 78.67 (47-145) | 63.23 (53-74) | 68.8* (59-86) p=0.0001 | 72.27 (55-80) | 75.5 (62-81) |
| **ex-TEM** | 49.59 (31-81) | 48.59 (32-66) | 111.34 (60-215) | 95.59 (53-223) | 61.48 (48-75) | 67.86 (49-78) | 69.03 (55-79) | 71.48 (51-80) |
| **fib-TEM** | 48.7 (25-77) | 48.26 (26-84) | na | na | 15.76 (5-36) | 18.4* (6-35) p=0.0001 | 68.29 (50-82) | 73.85 (63-81) |

Values are expressed as median (minimum-maximum); na, not applicable.

* statistically significant differences between the control and the postsurgical group (p <0.05);

§clotting time; || clot formation time; ¶ maximum clot firmness; **α angle.

**Table 2:** Comparison between thromboelastometry values obtained at T1 (n=29) and T2 (n=25).

| | **CT§ s** | | **CFT|| s** | | **MCF¶ mm** | | **α** degree** | |
|---|---|---|---|---|---|---|---|---|
| | **T1** | **T2** | **T1** | **T2** | **T1** | **T2** | **T1** | **T2** |
| **in-TEM** | 176.03 (134-263) | 160.54 (118-224) | 78.67 (47-145) | 62.38 (37-92) | 68.8 (59-86) | 69.07 (56-79) | 75.5 (62-81) | 78.38 (73-82) |
| **ex-TEM** | 48.59 (32-66) | 43.84 (33-55) | 95.59 (53-223) | 70.56 (41-129) | 67.86 (49-78) | 69.6 (55-78) | 71.48 (51-80) | 76.04 (65-82) |
| **fib-TEM** | 48.26 (26-84) | 41.57 (33-55) | na | na | 18.4 (6-35) | 25.96* (13-36) p=0.039 | 73.85 (63-81) | 75.34 (61-83) |

Values are expressed as median (minimum-maximum); na, not applicable.

* statistically significant differences between the postsurgical groups (p <0.05);

§clotting time; || clot formation time; ¶ maximum clot firmness; **α angle.

**Table 3:** Comparison between thromboelastometry values obtained at T0 (n=29) and T2 (n=25).

| | CT§ s | | CFT|| s | | MCF¶ mm | | α** degree | |
|---|---|---|---|---|---|---|---|---|
| | **T0** | **T2** | **T0** | **T2** | **T0** | **T2** | **T0** | **T2** |
| **in-TEM** | 178.83 (118-390) | 160.54 (118-224) | 96.83 (52-202) | 62.38 (37-92) | 63.23 (53-74) | 69.08* (56-79) p=0.012 | 72.26 (55-80) | 78.38* (73-82) p=0.019 |
| **ex-TEM** | 49.59 (31-81) | 43.84 (33-55) | 111.34 (60-215) | 70.56 (41-129) | 61.48 (48-75) | 69.6* (55-78) p=0.037 | 69.03 (55-79) | 76.04* (65-82) p=0.036 |
| **fib-TEM** | 48.7 (25-77) | 41.58 (33-55) | na | na | 15.76 (5-36) | 25.96* (13-36) p=0.0001 | 68.29 (50-82) | 75.34 (61-83) |

Values are expressed as median (minimum-maximum); na, not applicable.

* statistically significant differences between the control and the postsurgical group (p <0.05);

§clotting time; || clot formation time; ¶ maximum clot firmness; **α angle.

**Table 4**: Comparison of our institutional reference ranges for ROTEM tests (n=45) and values measured atT0, T1 and T2.

| **Test** | | **CT s** § | **CFT s** ‖ | **MCF mm** ¶ | **α °** ** |
|---|---|---|---|---|---|
| **in-TEM** | T0 | 178.83 | 96.83 | 63.23 | 72.26 |
| | T1 | 176.03 | 78.67 | 68.8 | 75.5 |
| | T2 | 160.54 | 62.38 | 69.08 | 78.38 |
| | Range | 126-363 | 47-224 | 50-75 | 55-81 |
| **ex-TEM** | T0 | 49.59 | 111.34 | 61.48 | 15.76 |
| | T1 | 48.59 | 95.59 | 67.86 | 71.48 |

| | | fib-TEM | | | |
|---|---|---|---|---|---|
| T2 | Range | T0 | T1 | T2 | Range |
| 43.84 | 29-92 | 48.7 | 48.26 | 41.58 | 14-102 |
| 70.56 | 54-275 | na* | na* | na* | na* |
| 69.6 | 36-73 | 15.76 | 18.4 | 25.96 | 6-26 |
| 76.04 | 47-79 | 68.29 | 73.85 | 75.34 | 48-78 |

T0, T1and T2 values are expressed as median; Range values are expressed as 5th-95th percentile (95% confidence intervals); * not applicable;

§clotting time; || clot formation time; ¶ maximum clot firmness; **α angle.