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ORIGINAL STUDY

Prospective evaluation of platelet function and fibrinolysis in 20 dogs with trauma

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Abstract

Objectives: To determine platelet function and assess fibrinolysis in dogs following trauma using multiple electrical impedance aggregometry and a modified thromboelastographic (TEG) technique. To determine if the severity of trauma, as assessed by the Animal Trauma Triage (ATT) score and clinicopathological markers of shock, is associated with a greater degree of platelet dysfunction and fibrinolysis.

Setting: University teaching hospital.

Animals: Twenty client-owned dogs with trauma (occurring <24 h prior to admission and blood sampling) and ATT score of >4 were prospectively recruited. A control group of 10 healthy dogs was included.

Interventions: None.

Measurements and Main Results: Platelet function was measured using multiple electrode platelet aggregometry (MEPA) utilizing arachidonic acid, ADP, and collagen agonists. Fibrinolysis was assessed in citrated whole blood with the addition of tissue plasminogen activator (tPA; 50 U/mL) using kaolin-activated TEG. Conventional statistical analysis was performed to compare coagulation parameters between the groups and assess linear correlations. Median (interquartile range) ATT score was 5 (5–7), and 65% ($n = 13$) of dogs suffered polytrauma. Mean (± *SD*) time from trauma to blood sampling was 9 hours (± 6). Median (interquartile range) shock index and plasma lactate concentration were 1.1 (0.7–2.0, $n = 16$) and 2.9 mmol/L (0.9–16.0, $n = 18$), respectively. Four dogs did not survive to discharge (20%). There were no differences between the trauma and control group coagulation variables. A moderate negative

Abbreviations: AA, arachidonic acid; aPTT, activated partial thromboplastin time; ATC, acute traumatic coagulopathy; ATT, Animal Trauma Triage; AUC, area under the curve; COL, collagen; FFP, fresh frozen plasma; $Lysis_{30}$, 30-minute clot lysis; $Lysis_{60}$, 60-minute clot lysis; MEPA, multiple electrode platelet aggregometry; NIBP, noninvasive Doppler blood pressure; PAI-1, plasminogen activator inhibitor-1; RI, reference interval; SI, shock index; TEG, thromboelastography; TIC, trauma-induced coagulopathy; tPA, tissue plasminogen activator.

correlation between ATT score and area under the curve for ADP was found ($P = 0.043$, $r^2 = -0.496$).

Conclusions: Preliminary evaluation of platelet function measured by MEPA, and fibrinolysis measured by tPA-modified TEG, is not significantly different in this population of dogs with traumatic injury compared to healthy dogs.

KEYWORDS
acute traumatic coagulopathy, hyperfibrinolysis, platelet aggregometry, platelet dysfunction, thromboelastography (TEG)

1 | INTRODUCTION

Severe trauma is associated with derangements of coagulation status in people. Acute traumatic coagulopathy (ATC) is a coagulopathy that occurs in the immediate minutes following trauma prior to, or independent of, resuscitation efforts. It is a coagulopathy that is attributed primarily to the effects of tissue damage, hypoperfusion, and hemorrhage.[1] Hypocoagulability and hyperfibrinolysis are the hallmarks of ATC, which is reported to occur in up to 25% of severely traumatized people, and its presence is associated with a 4-fold increased risk of mortality and massive transfusion requirement.[2–4] Platelet hypofunction has also been shown to contribute to ATC in people and has been associated with a 10-fold increase in mortality despite normal platelet count.[5,6]

Resuscitation-associated coagulopathy occurs secondary to hemodilution with large fluid volumes, the administration of synthetic colloids, massive transfusion, and prolonged surgery, which contribute to the development of acidemia and hypothermia.[7–9] Trauma-induced coagulopathy (TIC) is a term used to describe the spectrum of coagulation changes that occur following severe traumatic injury due to endogenous ATC and resuscitation attempts.[4] There are multiple phenotypes of TIC, which may result in hypocoagulability or hypercoagulability and/or hypofibrinolysis or hyperfibrinolysis. The clinical manifestation is influenced primarily by the degree of change in thrombin production, platelet function, and fibrinolysis.[10] The accumulation of catecholamines and metabolites post injury, the extent of endothelial activation, and the host immune response also affect the phenotype of TIC.[10,11]

Trauma is a leading cause for admission in small animal veterinary hospitals and is associated with significant morbidity and mortality.[12–14] Intracavity bleeding is reported in up to 38% of veterinary trauma patients.[12,15,16] Furthermore, up to 36% of dogs may require a packed red blood cell transfusion following severe trauma.[12,17] Hemostatic derangements are reported in cats and dogs following trauma; however, a consensus defining features of TIC and ATC in veterinary species has not been reached.[18–21] Evidence of the presence of ATC, characterized in people within a clinical setting by hypocoagulation and hyperfibrinolysis based on viscoelastic tests, is limited in canine trauma patients. Two separate case reports have documented hypocoagulation and hyperfibrinolysis using rotational thromboelastometry and tissue plasminogen activator (tPA)-challenged thromboelastography (TEG) in dogs with severe polytrauma.[22,23] A study using rotational thromboelastometry to assess coagulation status in 33 dogs presenting within 6 hours of trauma reported hypocoagulability in 33% of dogs, of which 9% were also hyperfibrinolytic.[24]

Viscoelastic techniques are currently considered superior to traditional methods of coagulation testing for assessing fibrinolysis, predicting transfusion requirement, and predicting outcome in people.[25–28] However, viscoelastic tests are insensitive to mild/moderate fibrinolysis when compared to increased plasmin–antiplasmin and D-dimer concentrations.[29] Modification of TEG assays with recombinant tPA can uncover the fibrinolytic potential of whole blood and aid detection of fibrinolytic dysfunction.[22,30–33] In human trauma patients, the use of viscoelastic techniques to guide goal-directed therapeutic interventions improves survival and results in reduced utilization of plasma and platelet transfusion products.[34] Diagnosis of ATC in traumatized dogs, by interrogating platelet function and fibrinolysis, could guide therapeutic interventions and potentially improve clinical outcomes. Currently, there are no studies that have assessed platelet function and fibrinolysis in dogs following traumatic injury.

The aims of this study were to assess platelet function, via arachidonic acid (AA)-, ADP-, and collagen (COL)-induced whole blood electrical impedance platelet aggregometry, and to assess the degree of fibrinolysis using citrated whole blood kaolin-activated TEG with tPA challenge in dogs following trauma. We hypothesized that dogs with severe traumatic injury and evidence of hypoperfusion would have decreased ADP-, AA-, and COL-induced platelet aggregation and hyperfibrinolysis compared to healthy control dogs. We also hypothesized that higher degrees of traumatic injury, as assessed by the Animal Trauma Triage (ATT) score and markers of hypoperfusion, would be associated with greater platelet dysfunction and fibrinolysis.

2 | MATERIALS AND METHODS

This was a single-center observational prospective study with client-owned dogs. Ethics approval (URN 2017 1688-3) was granted by the Royal Veterinary College's Clinical Research and Ethical Review Board to enroll a cohort of 30 dogs into the study: 20 dogs with trauma and 10 healthy dogs as a control population. Dogs were included in the study population if they had sustained either penetrating or blunt traumatic

injury within the preceding 24 hours resulting in an admission ATT score of >4. An ATT score of >4 was chosen as this has been associated with moderate trauma and has been reported to have a 22% mortality rate.[35] Polytrauma was defined as injuries to 2 or more areas including the head, thorax, abdomen, or extremities. Dogs were excluded from the study population if they were <6 months old, weighed <5 kg, had a known congenital coagulopathy, had a manual platelet count of $<100 \times 10^9$/L or a PCV <20% on admission, and if colloids (synthetic or natural), blood products, nonsteroidal anti-inflammatory drugs, antifibrinolytic medication, or anticoagulants were administered prior to sampling.[36–39] Due to the uncharacterized hyperfibrinolytic syndrome reported in Greyhounds, all pure and crossbred sighthounds were excluded from the study and control populations.[40] Dobermans were also excluded from the study due to the higher prevalence of von Willebrand factor deficiency in this breed.[41]

To ensure consistency, all samples were collected and platelet aggregometry and tPA-TEG assays were run by the same investigators (RB and SC). In the study population, all samples were collected from the same venipuncture site when blood was sampled for other clinical purposes. Samples were obtained following clean venipuncture using a 21-Ga butterfly catheter[i] and vacutainer[ii]. The first 1 mL of blood was discarded, as recommended by veterinary viscoelastic guidelines, or used for clinical diagnostic testing, and the remaining blood was collected in 1.5 mL 3.2% citrate anticoagulated tubes and 1.5 mL of hirudin anticoagulated tubes.[42] The control population comprised healthy blood donor dogs >1 and <10 years of age. Blood donor dogs were deemed healthy following assessment by a clinician not associated with the study based on their history, physical examination findings, and results of CBC, serum biochemistry panel, and infectious disease screening required for being a blood donor. Samples were collected as per the study population protocol during blood draw for routine health screening prior to donation.

The following data were collected on admission for the trauma group: time and cause of trauma, patient signalment, weight, mentation, respiratory rate and effort, heart rate and rhythm, noninvasive Doppler blood pressure (NIBP), rectal temperature, evidence of pleural or peritoneal effusion on point-of-care-ultrasound, ATT score, PCV, total plasma protein concentration, automated[iii] and/or manual estimation of platelet count, blood pH, base excess, and plasma lactate concentration[iv]. Further information regarding the patient's injuries was collated from diagnostic imaging and surgical reports. The administration of blood products and antifibrinolytic medication after sampling was recorded. The duration of hospitalization and outcomes were also recorded. Presence of shock was noted if shock index (SI) was >1 or at least 2 of the following if SI could not be calculated: hyperlactatemia (>2 mmol/L) and either tachycardia (>140/min) or hypotension (<100 mm Hg).[43] Cavitary effusions were classified as hemorrhagic, as defined by a fluid sample PCV of >10%[44]; uroperitoneum with confirmed urinary tract rupture on retrograde positive contrast radiography; and septic effusions diagnosed if phagocytosed bacteria were evident on fluid cytology. The following data were collected for the control group: signalment, body weight, PCV, and automated[c] and manual estimation of platelet count.

Multiple electrode platelet aggregometry (MEPA)[v] was performed on hirudin anticoagulated blood samples utilizing AA[vi], ADP[vii], and COL[viii] agonists. Testing was performed in duplicate according to a previously published protocol within 30–120 minutes of sample collection.[45] Results were excluded from analysis if the coefficient of variation was >20% and insufficient sample remained to repeat measurements.

TEG was performed between 30 and 60 minutes of sampling.[42] The citrate anticoagulated blood sample was kept at room temperature and reconstituted with thawed tPA[x] stored at −80°C to a concentration of 50 U/mL of blood (0.09 mg/mL) as per a previously described method utilizing tissue factor rather than kaolin as an activator.[33]

Statistical analysis was performed using a commercially available software package[ix]. Categorical data were compared with chi-square or Fisher's exact tests. Continuous data were assessed for normality using the Shapiro–Wilk Test and visual inspection of histograms. Median and 25th–75th percentiles (interquartile ranges) were reported for skewed data, and mean ± *SD* were reported for normally distributed data. Normally distributed continuous data were analyzed using an independent samples *t*-test, and skewed data were analyzed with a Mann–Whitney *U* test for independent samples. Significance was set at $P < 0.05$ (2-tailed). Pearson's correlation coefficient was used to assess for correlation between the time from trauma and ATT score with tPA-TEG or MEPA coagulation variables. A value of $r^2 > 0.90$ was considered an excellent correlation, $r^2 > 0.70$–0.89 was considered a very strong correlation, $r^2 > 0.50$–0.69 was considered a strong correlation, $r^2 > 0.20$–0.49 was considered a moderate correlation, and $r^2 < 0.20$ was considered a poor correlation.[46]

3 | RESULTS

3.1 | Study population

During the study period (January 2018 to December 2020), a total of 54 dogs presented following trauma; 1 or more of the exclusion criteria were present in 34 dogs. The following breeds were included in the trauma group ($n = 20$): American Bulldog ($n = 1$), Boston Terrier ($n = 1$), Chihuahua ($n = 1$), English Cocker Spaniel ($n = 2$), German Shepherd ($n = 1$), Golden Retriever ($n = 1$), Irish Setter ($n = 1$), Jack Russell Terrier ($n = 1$), Labrador Retriever ($n = 2$), Miniature Schnauzer ($n = 1$), West Highland White Terrier ($n = 1$), Yorkshire Terrier ($n = 2$), and mixed-breed dogs ($n = 5$). The following breeds were included in the control group: German Shepherd ($n = 2$), Labrador ($n = 6$), and mixed-breed dogs ($n = 2$).

Within the trauma group, 3 dogs were entire females (15%), 6 neutered females (30%), 4 entire males (20%), and 7 neutered males (35%). Within the control group, 2 dogs were entire females (20%), 2 neutered females (20%), 3 entire males (33.3%), and 3 neutered males (33.3%). Sex was not significantly different between the 2 groups ($P = 0.914$).

The median age of dogs in the trauma group (41 months, 23.5–52.5) was significantly lower than those in the control group (63 months,

57–71; $P = 0.019$). The median weight of dogs in the trauma group (13.5 kg, 8.7–23.6) was significantly lower than dogs in the control group (39.5 kg, 26.3–34.9) ($P < 0.001$).

Medical treatment and stabilization prior to referral were performed at the primary care practice in 16 of 20 (80%) dogs. Witnessed causes of trauma were road traffic accidents ($n = 12$; 60%), high-rise falls ($n = 2$; 10%), dog attacks ($n = 2$; 10%), collision with a tree ($n = 1$; 5%), and falling from a stationary vehicle ($n = 1$; 5%). Unwitnessed trauma occurred in 2 dogs (10%) and was suspected to be related to road traffic accidents.

On arrival to the hospital, all trauma dogs included in this study were assessed in the emergency room and promptly admitted to the hospital. Triage and delayed admission did not occur in this patient population due to injury severity and adequate staffing levels to facilitate concurrent client communication and patient care. Blood samples were collected at the time of admission in 10 dogs. In the other 10 dogs, blood sampling was performed shortly after admission; 4 patients presented in a stable condition and did not require any resuscitation fluids, while 3 patients received 10 mL/kg of isotonic crystalloids and 2 patients received 30 and 40 mL/kg, respectively, of isotonic crystalloids between admission and blood sampling. One patient suffered cardiopulmonary arrest on arrival due to pneumothorax and severe hypoxemia; however, return of spontaneous circulation was achieved following cardiopulmonary resuscitation. This patient had sampling performed 6 hours following return of spontaneous circulation; resuscitative fluids were not administered. The mean time from trauma to blood sampling was 9 (± 6) hours.

3.2 | Injury severity

The median respiratory rate was 38 (26–51) breaths per minute. Panting was recorded in 3 of 20 dogs (15%). In the absence of increased respiratory effort or abnormal lung sounds, panting was attributed to nonrespiratory causes. One dog arrived cyanotic and gasping for breath; this dog subsequently respiratory arrested and required rapid intubation due to the presence of a large pneumothorax.

The mean heart rate was 137 (± 53) per minute. Cardiac arrhythmias were detected in 5 dogs (29.4%) and included ventricular premature complexes ($n = 5$), accelerated idioventricular rhythms ($n = 5$), and ventricular tachycardia ($n = 1$). One dog was inappropriately bradycardic and hypertensive, at 56/min and 160 mm Hg systolic, respectively, deemed consistent with a Cushing's reflex, and was subsequently diagnosed with a depressed skull fracture and subdural hemorrhage.

Temperature was measured in 19 of 20 dogs (95%) on admission, with median temperature of 37.2°C (36.5–37.8°C). NIBP was recorded on admission in 16 of 20 dogs (80%); the mean systolic NIBP was 113 mm Hg (± 42). Severe hypotension (systolic NIBP <60 mm Hg) was documented in 3 of 20 dogs (15%). Blood pressure readings could not be obtained in 2 of these dogs due to severe shock, indicated by marked tachycardia combined with hyperlactatemia—224/min (lactate 2.8 mmol/L) and 200/min (4.3 mmol/L).

Assessment of admission blood pressure was not attempted in 2 of 20 (10%) dogs presented in extremis requiring immediate resuscitation and therapeutic interventions. Of these 2 dogs, 1 was peri-arrest on arrival due to a large volume pneumothorax; this dog had a heart rate of 34/min and lactate of 4.6 mmol/L. The other dog had an inappropriately low heart rate of 120/min, lactate of 16 mmol/L, and peritoneal effusion. The SI was calculated for 16 of 20 dogs (60%), with a median SI of 1.1 (0.7–2.0).

Dogs in the trauma group had a mean PCV of 45% (± 8). Dogs in the control group had a mean PCV of 49% (± 5%). PCV was not significantly different between the 2 groups ($P = 0.142$). Platelet count (manual and/or automated) was $>100 \times 10^9$/L (reference interval [RI], $150–900 \times 10^9$/L) for all dogs within the trauma and control groups. The median automated platelet count was 234×10^9/L (150–253) for the trauma group ($n = 16$). The median automated platelet count in the control group ($n = 10$) was 228×10^9/L (187–279). Platelet count was not significantly different between the 2 groups ($P = 0.638$).

Within the trauma group, blood pH and plasma lactate were measured at admission ($n = 18$). Median blood pH was 7.317 (7.276—7.361) (RI: 7.35–7.47). Median plasma lactate concentration was 2.9 mmol/L (0.9–16 mmol/L) (RI: <2 mmol/L). Base excess was reported in 14 dogs at admission (70%), with a median of −3.25 (−6.2 to −1.5).

The injuries sustained were variable, and 65% of dogs ($n = 13/20$) sustained polytrauma with injuries to 2 or more areas including the head, thorax, abdomen, or extremities (Table 1). The median ATT score was 5 (5–7), with the highest being 10/18. Diagnostic imaging (ultrasound and/or computed tomography) revealed pleural effusion in 4 dogs (20%) and peritoneal effusion in 10 dogs (50%). The pleural effusion was uncharacterized in all 4 dogs. In 3 of the dogs (30%) with peritoneal effusion, the fluid was too scant to sample and therefore remained uncharacterized. In the remaining 7 dogs, the following effusions were documented: hemoabdomen ($n = 4$; 40%), hemoabdomen with evidence of blue–black cytoplasmic granules within neutrophils and macrophages consistent with bile peritonitis ($n = 1$; 10%), uroabdomen ($n = 1$; 10%), and septic neutrophilic exudate with hemorrhagic component ($n = 1$; 10%).

Blood products were administered to 4 dogs (20%) post-sampling. Two dogs each received packed red blood cells and fresh frozen plasma (FFP); packed red blood cell volumes administered were 11 and 12 mL/kg, respectively; the FFP volume administered was 14 mL/kg for 1 dog and not recorded for the other dog. Two dogs received only FFP (13 and 44 mL/kg). One dog received 2 dosages of intravenous tranexamic acid[xi] (15 mg/kg, q 8 h).

The mean duration of hospitalization was 8 days (± 4.3). In total, 4 dogs did not survive to discharge from the hospital (20%); of these dogs, 3 were euthanized due to the severity of their injuries. Cardiac arrest occurred in the other dog, and return of spontaneous circulation was not achieved despite attempts at cardiopulmonary resuscitation.

3.3 | Coagulation

Within the trauma group ($n = 20$), machine error resulted in missing data for area under the curve (AUC) of ADP ($n = 1$), AA ($n = 2$), and

TABLE 1 Summary of injuries sustained by 20 dogs with trauma and an Animal Trauma Triage (ATT) score >4.

Head	Thorax	Abdomen	Axial skeleton	Appendicular skeleton	Soft tissues/ocular
Traumatic brain injury ($n = 2$) Seizures ($n = 1$) Avulsion of canine tooth ($n = 1$)	Cardiac arrhythmias ($n = 5$) Pulmonary contusions ($n = 8$) Pneumothorax ($n = 10$) Traumatic pulmonary bullae ($n = 1$) Thoracic body wall rupture ($n = 1$) Puncture wounds to diaphragm ($n = 1$) Pleural effusion—presumed hemorrhage ($n = 4$)	Septic peritonitis ($n = 1$) Renal parenchymal rupture ($n = 1$) Pre-pubic tendon rupture ($n = 1$) Urethral tear ($n = 1$) Abdominal wall rupture ($n = 3$) Hemoabdomen ($n = 4$) Uroabdomen ($n = 1$) Hemoabdomen/Bile peritonitis ($n = 1$)	Skull fractures ($n = 3$) Vertebral body fracture/subluxation ($n = 4$) Vertebral transverse process fracture ($n = 1$) Coccygeal fracture ($n = 1$) Pelvic fracture ($n = 6$) Rib fracture ($n = 4$) ANNPE ($n = 1$) T13/L1 hydrated disc extrusion with spinal cord oedema or contusion ($n = 1$)	Coxofemoral luxation ($n = 2$) Open femoral fracture ($n = 1$)	Skin abrasions ($n = 9$) Lameness ($n = 1$) Corneal ulceration ($n = 1$) Transection of sciatic nerve ($n = 1$) Sciatic neuropathy ($n = 1$) Brachial plexus injury ($n = 1$)

Abbreviation: ANNPE, acute noncompressive nucleus pulposus extrusion.

TABLE 2 Multiple electrical impedance aggregometry area under the curve for ADP-, AA-, and COL-induced aggregation for dogs with trauma and healthy control dogs.

Group	ADP AUC RI: 10.1–103.7	AA AUC RI: 13.6–74.9	COL AUC RI: 6.2–105.3
Trauma	58.16 (± 27.34) ($n = 19$)	52.61 (± 25.13) ($n = 18$)	58.61 (± 29.08) ($n = 18$)
Control	47.70 (± 25.76) ($n = 10$)	41.70 (± 18.75) ($n = 10$)	44.50 (± 15.79) ($n = 10$)
P-value	0.164	0.121	0.084

Note: Means (± *SD*s) are reported.
Abbreviations: AA, arachidonic acid; ADP, adenosine diphosphate; AUC, area under the curve; COL, collagen; RI, reference interval.

COL ($n = 2$). There was no difference in MEPA and tPA-TEG variables between the trauma and control groups (Tables 2 and 3).

Within the trauma group, there was no correlation between the time from trauma and MEPA or tPA-TEG variables. There was a significant moderate negative correlation between ATT score and AUC of ADP, with an increased ATT score correlated with lower AUC of ADP, indicating a reduction in platelet function due to altered ADP activity at P2Y1 and P2Y12 receptors ($P = 0.043$, $r2 = -0.496$).[47]

Shock was detected in 13 of 20 dogs on presentation. Within the trauma group, there was no statistically significant difference in coagulation variables between dogs with and without shock. There was no statistically significant difference in MEPA and tPA-TEG when comparing dogs within the trauma group with shock and the control group (Tables 4 and 5).

4 | DISCUSSION

We investigated TIC in dogs and found a significant negative correlation between high ATT score and AUC of ADP. However, in contrast to previously published studies in people,[1,2,5,10] platelet function as measured by MEPA and tPA-TEG to assess fibrinolysis remained within the RI in the trauma group, with no difference between trauma and control groups. In addition, severity of shock in dogs with trauma was not correlated with platelet function or fibrinolysis.

Platelet dysfunction in people with trauma is well recognized; however, the mechanism is incompletely understood.[6,48] A proposed mechanism suggests platelet activation is increased immediately following tissue injury, evidenced by increased circulating platelet-derived microparticles, expression of CD62 P-selectin, and increased levels of the active conformation of glycoprotein IIb/IIIa.[49] However, reduced platelet function and subsequently decreased aggregation can also occur.[49]

It is hypothesized that severe trauma causes widespread activation and degranulation of circulating platelets, resulting in depletion of adenine nucleotides and serotonin levels.[50] These "exhausted" platelets are no longer able to aggregate or contract and cannot effectively contribute to clot formation. This theory is supported by the finding that CD62 P-selectin, which is a marker of platelet activation, is decreased following ex vivo ADP challenge in traumatized people compared to healthy controls.[6] It has also been proposed that severe traumatic injury and hypoperfusion result in widespread ADP release and direct systemic platelet activation.[51] Trauma-induced platelet dysfunction is correlated with markers of injury severity and may persist for up to 120 hours following injury in people.[5]

This is the first study to assess platelet function using MEPA in dogs with trauma. Platelet function has been measured in canine models of atraumatic hemorrhagic shock following induction of severe hypotension (<60 mm Hg systolic).[52] Significantly increased markers of endothelial activation, autoheparinization, and inflammation have been documented following severe traumatic injury.[11] Although atraumatic shock does not cause the same degree of endothelial activation and damage as traumatic injury, available evidence suggests that platelet hypofunction does occur in dogs with hypovolemic shock.[52–54] In this study, systolic blood pressure at hospital admission was <60 mm Hg in only 3 dogs; however, data were unavailable for

TABLE 3 Kaolin-activated thromboelastography with tPA parameters for calcified citrated whole blood samples for 20 dogs with trauma and 10 healthy control dogs.

Group	*R* (min) RI 1.7–5.1	*K* (min) RI 0–6.1	Angle (°) RI 35–85	MA (mm) RI 34–69.3	*G* (d/sc) RI 1.4–9.5	$Lysis_{30}$ (%) RI 0–51.4	$Lysis_{60}$ (%) RI 0–75.2
Trauma	2.8 (2.4–3.5)	2.0 (1.4–2.8)	65.9 (58.7–68.7)	55.5 (49.5–60.5)	6.2 (4.9–7.7)	1.0 (0–20.2)	13.8 (0–44.6)
Control	3.7 (2.7–3.9)	2.4 (2–3.1)	60.8 (57.8–64.1)	47.7 (46.2–50.3)	4.6 (4.3–5.1)	10.2 (0–29.3)	38.7 (2.5–58.1)
P-value	0.154	0.293	0.222	0.104	0.067	0.304	0.191

Note: Median (IQR) reported.
Abbreviations: *G*, clot strength; *K*, clot strength; $Lysis_{30}$, 30-minute clot lysis; $Lysis_{60}$, 60-minute clot lysis; MA, maximum amplitude; *R*, reaction time; RI, reference interval; tPA, tissue plasminogen activator.

TABLE 4 Multiple electrical impedance aggregometry area under the curve for ADP-, AA-, and COL-induced aggregation for dogs with trauma in shock and healthy control dogs.

Group	ADP AUC RI 10.1–103.7	AA AUC RI 13.6–74.9	COL AUC RI 6.2–105.3
Trauma (shock)	58.50 (± 28.45) (*n* = 12)	52.35 (± 29.46) (*n* = 11)	64.83 (± 30.44) (*n* = 12)
Control	47.70 (± 25.76) (*n* = 10)	41.70 (± 18.75) (*n* = 10)	44.50 (± 15.79) (*n* = 10)
P-value	0.390	0.484	0.139

Note: Means (± *SDs*) are reported.
Abbreviations: AA, arachidonic acid; ADP, adenosine diphosphate; AUC, area under the curve; COL, collagen; RI, reference interval.

TABLE 5 Kaolin-activated thromboelastography with tPA parameters for calcified citrated whole blood samples for 13 dogs with trauma in shock and 10 healthy control dogs.

Group	*R* (min) RI 1.7–5.1	*K* (min) RI 0–6.1	Angle (°) RI 35–85	MA (mm) RI 34–69.3	*G* (d/sc) RI 1.4–9.5	$Lysis_{30}$ (%) RI 0–51.4	$Lysis_{60}$ (%) RI 0–75.2
Trauma (shock)	2.9 (± 1.11)	2.7 (± 1.99)	59.05 (± 14.18)	51.78 (± 9.75)	5.72 (± 1.80)	16.23 (± 23.31)	29.66 (± 28.43)
Control	3.7 (± 0.91)	2.4 (± 0.85)	60.8 (± 10.52)	47.7 (± 6.49)	4.6 (± 1.47)	10.2 (± 17.26)	38.7 (± 27.63)
P-value	0.149	0.477	0.401	0.270	0.196	0.489	0.375

Note: Median (IQR) reported.
Abbreviations: d/sc, dynes/sec; *G*, clot strength; *K*, clot strength; $Lysis_{30}$, 30-minute clot lysis; $Lysis_{60}$, 60-minute clot lysis; MA, maximum amplitude; *R*, reaction time; RI, reference interval; tPA, tissue plasminogen activator.

a further 2 dogs. The absence of severe hypovolemic shock may have resulted in a lack of platelet dysfunction in the trauma group.

Increased injury severity is associated with platelet dysfunction in people.[55,56] The median ATT score was 5/18 (5–7) in our trauma group and the highest score was 10/18. Our study inclusion criteria set the ATT score of >4 as a score of 5 has been associated with moderate trauma and 22% mortality.[35] In addition, for each point increase in the ATT score, a 2.3–2.6 decreased likelihood of survival is reported, as such the ATT score is an indicator of injury severity.[35] Given the low median ATT score of dogs in this study, it is possible that the trauma sustained was not severe enough to cause platelet dysfunction. There was, however, a moderate negative correlation between a higher ATT score and AUC for ADP, although AUC for ADP remained above the lower reference limit. This may suggest platelet hypofunction worsens with increased injury severity. This finding warrants further investigation in a larger study population, ideally with higher ATT scores.

Hyperfibrinolysis is well documented in people following trauma.[1,2,57,58] Severe traumatic injury results in massive tPA release, which overwhelms the neutralizing capacity of fibrinolytic inhibitors, particularly plasminogen activator inhibitor-1 (PAI-1). This profibrinolytic imbalance is eventually counteracted by upregulation of PAI-1, which occurs within hours of injury.[59] This initial imbalance between activation and inhibition of fibrinolysis following severe trauma could explain why administration of tranexamic acid (TXA) within 3 hours of injury has been associated with reduced mortality in people.[60]

Hyperfibrinolysis resulting in hemorrhage that resolved with antifibrinolytic treatment has been reported following traumatic injury in dogs.[22,23] However, this current study did not demonstrate a statistically significant difference in clot lysis times between the trauma and control groups as assessed by tPA-TEG. Blood samples were obtained within 3 hours of injury in only 4 dogs (20%), and 12 dogs (60%) were sampled >6 hours from the time of trauma. Herrero et al[24] reported

that 33% of dogs were hypocoagulable <6 hours from trauma, of which 9% had evidence of hyperfibrinolysis. However, the authors reported that all hypocoagulable dogs were normocoagulable at 6 and 24 hours following trauma. Given the protracted time from trauma to sampling in our study, it is possible that upregulation of PAI-1 may have already occurred, resulting in resolution of a hyperfibrinolytic phase. The median $Lysis_{30}$ (30-minute clot lysis) in the trauma group was 1% (0–20.2) compared to a $Lysis_{30}$ of 10.2% (0–29.3) in the control group. Although not statistically significant, hypofibrinolysis or fibrinolytic shutdown within the trauma group could have contributed to the lower median $Lysis_{30}$.

Despite not reaching statistical significance, high $Lysis_{30}$ times of 60.4% and 68.5% were observed in 2 dogs within the trauma group. Furthermore, the dog with $Lysis_{30}$ of 60.4% had ongoing hemothorax following thoracic wound debridement and chest drain placement. This dog was subsequently treated with a single dose of tranexamic acid (15 mg/kg IV), following which hemorrhage resolved. TEG was not repeated after administration of tranexamic acid; it is not possible to determine whether a reduction in fibrinolysis was achieved and contributed to hemostasis. Within the control group, high $Lysis_{30/60}$ times were also observed, with 1 apparently healthy dog having a $Lysis_{60}$ of 76.1%. It is interesting that similarly high $Lysis_{60}$ times were observed in both a healthy dog and the traumatized dog with ongoing hemothorax attributed to hyperfibrinolysis. Within the control group, the dogs with increased lysis times were all Labradors ($n = 6$); the maximum $Lysis_{60}$ time observed in non-Labradors was 6%. This may represent a breed-specific variation and tendency toward increased fibrinolysis; the significance of this is unknown and further investigation is warranted.

Coagulation changes are associated with the degree of injury sustained in people. While considerable variation can occur, normal coagulation status is expected with mild injuries; hypercoagulability is associated with moderate injury and progression to hypocoagulability and finally a hyperfibrinolytic state with severe injury.[57,58] In traumatized dogs, a moderate correlation has been demonstrated between disease severity, as assessed by APPLE-fast score, and increased activated partial thromboplastin time (aPTT).[20] In addition, increased ATT score has been correlated with prolonged prothrombin time (PT)/aPTT and decreased maximum amplitude in dogs following trauma.[21] In contrast to these findings, Abelson et al did not demonstrate any correlation between ATT and *G* value; however, other coagulation parameters were not assessed.[19] As previously stated, the median ATT score in our study was 5/18 (5–7), which represents comparatively mild injury, and the highest score was 10 ($n = 1$).[35] Hyperfibrinolysis has been associated with severe trauma in 2 dogs with ATT scores of 8/18 and 13/18.[22,23] It is possible that the degree of traumatic injury sustained by most dogs in this study did not result in sufficient endothelial activation and tPA release to induce a hyperfibrinolytic state.

Limitations of this study include the in vitro activation and assessment of coagulation using MEPA and tPA-TEG, sample size, and lack of standardized patient treatment. Furthermore, serial assessment of coagulation would have been optimal given the reported dynamic nature of coagulation derangement in human trauma patients. Although dogs were excluded if they had received drugs or fluids known to alter coagulation, variable volumes of crystalloids were utilized during resuscitation efforts and could have affected coagulation status by contributing to hemodilution, acidosis, and hypothermia.[61,62] In addition, although no correlation was found between the time from trauma and clot lysis, the low number of dogs presenting and having blood sampled within 3 hours of trauma, when endogenous inhibitors of fibrinolysis are yet to be upregulated, may have resulted in type II error.[59,60] Similarly, the low number of patients enrolled in this study might have resulted in a type II error when exploring associations with fibrinolytic or platelet function variables. Delayed blood sampling post admission occurred because ethical approval restricted sampling solely for the purpose of clinically justified reasons with residual blood permitted to be used for study coagulation tests.

The use of the ATT score as an inclusion criterion could also have resulted in confounding factors. Dogs with traumatic injury can have dynamic disease and may progress through various stages of shock. Thus, it is possible that patients in the emergency room had ATT scores that were not representative of their injury severity. Conversely, the use of the ATT scoring system meant that dogs with relatively minor soft tissue injury met the inclusion threshold.

Finally, in a study of 3,599 dogs, an ATT score >10 was rare, with <1% of observations in any group.[63] Low median ATT scores of 1 (1) and 2 (2) have also been reported for a cohort of 2583 toy breed dogs and 116 giant breed dogs, respectively.[64] This suggests that severe injury is uncommon in dogs or underreported, or that those with a high ATT score succumb to their injuries before receiving veterinary care.[13,19,35] It is possible that dogs that do survive trauma and present to a veterinarian may not have sustained injuries severe enough to incite coagulation derangement.

5 | CONCLUSION

This study did not demonstrate decreased platelet function or increased fibrinolysis in traumatized dogs compared to healthy controls, which may be due to insufficient trauma severity in this patient population. Our study did document a moderate negative correlation between a higher ATT score and AUC for ADP, which may suggest decreased platelet function with increased injury severity.

CONFLICT OF INTEREST STATEMENT

Daniel Chan is the editor of the Journal but only participated as an author in the peer review process. The authors declare no other conflicts of interest.

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ENDNOTES

[i] Hirudin, S-Monovette, Sarstedt AG&Co, Sarstedtstr, Germany.
[ii] BD Vacutainer, Plymouth, UK.
[iii] Siemens Advia 2120.
[iv] ABL800 Flex blood gas analyser, Radiometer Medical ApS, Denmark.
[v] Multiplate, Roche Diagnostic International Limited.
[vi] ASPItest, Roche Diagnostic International Limited.
[vii] ADPtest, Roche Diagnostic International Limited.
[viii] Collagen, Helena-Biosciences, UK.
[ix] Actilyse, Boehringer Ingelheim Ltd., UK.
[x] SPSS IBM Statistics version 20.
[xi] Tillomed Laboratories Ltd, UK.

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