

Hyperfibrinolysis diagnosed with rotational thromboelastometry and treated with tranexamic acid in a dog with acute traumatic coagulopathy

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Summary

A 4-year old male Australian Cattle Dog involved in a road traffic accident was presented with severe polytrauma to the Small Animal Clinic, University of Zurich. He was presented in hemorrhagic shock, with an initial lactate of 10.3mmol/l and ongoing bleeding from multiple injury sites. Acute traumatic coagulopathy diagnosed with ROTEM within one hour after accident showed marked hypocoagulation and hyperfibrinolysis. Treatment with a total dose of 40mg/kg of tranexamic acid intravenously resulted in successful elimination of hyperfibrinolysis in the following, serially measured ROTEM tracings.

Keywords: canine, ATC, trauma, fibrinolysis, ROTEM

Diagnose von Hyperfibrinolyse mittels Rotations-Thromboelastometrie und Behandlung mit Tranexamsäure bei einem Hund mit akuter traumatischer Koagulopathie

Ein 4-jähriger, männlicher Australian Cattle Dog wurde mit schwerem Polytrauma nach einem Verkehrsunfall an der Kleintierklinik der Universität Zürich vorgestellt. Er war in hämorrhagischem Schock, hatte mehrere blutende Wunden und ein Laktat von 10.3mmol/l bei Eintritt. Die akute Traumatische Koagulopathie (ATC) wurde mittels Rotationeller Thromboelastometrie (ROTEM) diagnostiziert und zeigte sich in markanter Hypokoagulabilität und Hyperfibrinolyse. Die Behandlung mit insgesamt 40mg/kg Tranexamsäure i.v. resultierte in einer erfolgreichen Therapie der Hyperfibrinolyse in den folgenden, seriell gemessenen ROTEM Untersuchungen.

Schlüsselwörter: Hund, ATC, Trauma, Fibrinolyse, ROTEM

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Introduction

Acute traumatic coagulopathy (ATC) describes a systemic coagulopathy following trauma. It is thought to result from tissue injury in combination with hypoperfusion and systemic inflammation, followed by a dynamic and complex process. Hypothermia, acidosis and hemodilution further impair the initiated coagulopathy (Brohi, et al., 2007; Frith, et al., 2010; Cohen, et al., 2013; Davenport, et al., 2016;). ATC can be characterized by hypercoagulation, hypocoagulation and hyperfibrinolysis, varying with increased injury severity and depending on time after injury (Dobson, et al., 2015). ATC occurs in up to 30% of the severely injured human

trauma patients and increases mortality at least fourfold (Brohi, et al., 2003; Maegele, et al., 2007; Frith, et al., 2010).

The diagnosis of ATC remains controversial, as there is no standardized and globally established test in human or veterinary medicine. Traditional coagulation tests like activated partial thromboplastin time (aPTT) and prothrombin time (PT) have been used along with platelet count and serum fibrinogen measurements to diagnose ATC (Cohen, et al., 2013). Viscoelastic tests such as rotational thromboelastometry (ROTEM) or thromboelastography (TEG) may be superior to assess coagulation in ATC, as they not only assess plasmatic coagulation,

Hyperfibrinolysis diagnosed with rotational thromboelastometry and treated with tranexamic acid in a dog with acute traumatic coagulopathy

B. Muri et al.

but also the formation and strength of the formed clot and its lysis (Frith, et al., 2010; Davenport, et al., 2011; Hagemo, et al., 2015; Rossaint, et al., 2016).

The ROTEM device (ROTEM delta, Pentapharm GmbH D-81829 München) measures the viscoelastic properties of whole blood under low shear conditions. The changes in viscoelasticity are visualized in a tracing and several parameters are automatically determined. The clotting time (CT) describes the time until fibrin formation starts and is comparable to PT and aPTT. The clot formation time (CFT) is determined by the kinetics of clot formation and depends mainly on fibrinogen concentration and thrombocytes numbers. The maximum clot firmness (MCF) describes the maximal strength of the fibrin/thrombocytes clot. Fibrinolysis can be assessed with the maximum lysis (ML). Several coagulation activators can be used. The ExTEM test measures clot formation by activation of the coagulation cascade through proprietary tissue factor (extrinsic pathway) while the InTEM uses phospholipids and ellagic acid and activates coagulation via intrinsic pathway. In the ApTEM test, fibrinolysis is inhibited by added aprotinin, an antifibrinolytic, to the ExTEM reagent. The FibTEM tracing enables determination of fibrinogen by added cytochalasin D, a platelet inhibitor, to the ExTEM reagent (Spiel, et al., 2006).

In veterinary medicine there are only a few studies investigating ATC in canine trauma patients (Mischke, 2005; Abelson, et al., 2013; Holowaychuck, et al., 2014; Gottlieb, et al., 2016;) and most information regarding diagnosis and pathophysiology is derived from human medicine. To our knowledge, hyperfibrinolysis identified with ROTEM has not yet been described in canine trauma patients.

Case History

Physical examination

A 4-year old, male Australian cattle dog was presented to the emergency service of the Small Animal Clinic University of Zurich within fifteen minutes after being hit by bus. The dog was severely injured (Animal trauma triage score 13/18 (Rockar and 1994)) and presented in lateral recumbency. At presentation, the dog showed pale mucus membranes, a capillary refill time (CRT) of 3 seconds, a weak femoral pulse, a heart rate of 200 bpm and a rectal temperature of 39.2 °C. Respiratory rate (RR) was 24/min, with regular thoracic movements and unremarkable lung auscultation. There was a large area of anatomical degloving of the left abdominal wall, a ventral abdominal wall defect with evisceration of intestinal loops, a traumatic prepubic hernia with violation of the right vascular lacuna and laceration of the femoral artery and vein with active bleeding. Multiple, severe soft tissue lesions with muscular tear and diffuse bleeding of adductor muscles of the right thigh were noted.

Therapy

Oxygen was supplemented by face mask, a peripheral venous catheter was inserted and a stat acid-base analysis (RAPIDPoint 500, Siemens Schweiz AG) was performed. The dog received 4ml/kg of 7.2% NaCl (Natriumchlorid „Bichsel“ 7.2%, Dr. G. Bichsel AG, 3800 Interlaken), 10ml/kg of Ringer's acetate (Ringer-Acetat Fresenius i.v., Fresenius Kabi, 6370 Oberdorf) and 5ml/kg of hydroxyethyl starch (Voluven 6% balanced i.v., Fresenius Kabi, 6370 Oberdorf) as boluses over approximately five minutes each. The first detectable blood pressure during fluid resuscitation was 40mmHg measured by Doppler. The dog further received 20mg/kg of tranexamic acid (Cyclokapron®, Pfizer Corporation Austria, 1210 Wien), 0.2mg/kg of methadone (Metha-

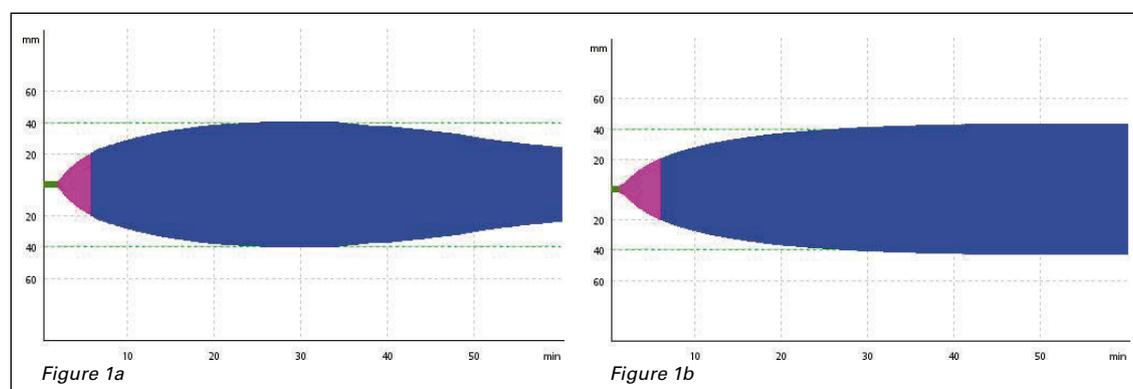


Figure 1: ExTEM (1a) and ApTEM (1b) profile of a dog with acute traumatic coagulopathy after initial therapy. Both profiles show hypocoaguability with a maximum clot firmness of 40 mm in ExTEM. The ExTEM profile shows hyperfibrinolysis, starting after 30 minutes. Lysis cannot be seen in the ApTEM, suggesting the identified lysis in the ExTEM profile represents true hyperfibrinolysis (Ganter, 2008)

Table 1: Blood Values (Blood gas, CBC and clinical Chemistry) at different time points during hospital stay.

Time after admission [h:min]	Reference interval	0:0	0:15	03:06*	9:40	15:00**	24:00	48:00
Blood Gas [V: venous; A:arterial]	V	V	V	V	V	V	A	A
pH	7,35-7,45	7,21	7,21	7,28	7,37	7,31	7,34	7,25
pCO ₂ [mmHg]	29-43	29,4	32,4	41,6	40,1	39,1	33,5	25,8
pO ₂ [mmHg]	30-53	72,4	135,8	58,3	54,1	33,9	100,2	95,7
HCO ₃ - std [mmol/l]	20-25	13,9	13,6	18,5	22,4	18,8	18,4	13
BE(B) [mmol/l]	-7 - 2	-14,5	-14	-7,1	-2,3	-6,2	-7,3	-14,6
Hct [%]	35-61	60	33	40	N/A	23	21	28
K ⁺ [mmol/l]	3,6-4,7	3,97	3,84	4,49	4,52	4,37	3,46	3,60
Ca ⁺⁺ [mmol/l]	1,21-1,41	1,23	1,03	1,09	1,45	1,21	1,23	1,24
Glu [mmol/l]	3,9-6,6	15	10,6	13,1	5,3	6,7	6,7	6,4
Lac [mmol/l]	0,42-2,13	10,36	6,53	3,35	2,61	1,48	1,18	2,94
CBC								
Hct [%]	42-55		30		29		19	
Leukocytes *10E3/ul	4,7-11,3		3,2				6,2	0,6
Thrombocytes *10E3/ul			108				64	
Clinical Chemistry								
Alb g/l	29-37		12		6	21	20	14

* Whole Blood Transfusion at 1:30h (22ml/kg); Surgery from approximately 3:00 to 8:30h;

** 20% Human Serum Albumin Transfusion (1g/kg) at 10:30h.

BE (B): Base Excess of Blood; Hct: Hematocrit; Glu: Dextrose; Lac: Lactate; Alb: Albumin; N/A: not available. CBC: Complete Blood Count, performed automatically on a Sysmex XT 2000i (Sysmex digitana, CH-Horgen). Clinical Chemistry was performed on a Cobas 6000 (Cobas 6000. Roche Diagnostics AG, CH-Rotkreuz)

Table 2: Different ROTEM Tracings (ExTEM, ApTEM, FibTEM) after 0:15h, 9:40h, 24h and 48h.

Parameter	EXTEM					APTEM				FIBTEM	
	A5 [mm]	CT [sec]	CFT [sec]	MCF [mm]	ML [%]	CT [sec]	CFT [sec]	MCF [mm]	ML [%]	CT [sec]	MCF [mm]
Reference interval*	N/A	26-57	53-153	46-62	0-10	31-59	67-164	52-65	0-3	35-108	3-9
0:15h	23	111	229	40	41	65	285	43	1	163	4
9:40h	25	47	210	48	1	54	228	46	1	154	5
24h	26	47	210	51	0	55	237	48	1	61	5
48h										135	4

* in-house references

A5: Amplitude 5min after CT; CT: Clotting Time; CFT: Clot Formation Time; MCF: Maximum Clot Firmness; ML: Maximum Lysis

don Streuli[®], Streuli Pharma AG, 8730 Uznach) and 20mg/kg of ampicillin-sulbactam (Ampicillin/Sulbactam 1000mg/500mg, Aurobindo Pharma GmbH, 81829 München). After this initial therapy, another blood sample was analyzed. Initial blood results are listed in Table 1.

Thromboelastometry

ROTEM analysis showed decreased clot strength and prolonged clotting time (Tab. 2). In the ExTEM tracing, hyperfibrinolysis with ML of 41% (reference interval 0-10%) was detected. The ApTEM tracing showed a ML

of 1% (reference interval 0-3%), confirming hyperfibrinolysis (Fig. 1). Fibtem MCF was 4mm (reference interval: 3-9mm). Based on these findings, tranexamic acid (20mg/kg) was repeated one hour after the first dose.

The dog was further stabilized and the right A. /V. femoralis were cross clamped with haemostats and ligated to control the ongoing bleeding. The eviscerated intestines and wounds were covered with sterile moist abdominal sponges.

Hyperfibrinolysis diagnosed with rotational thromboelastometry and treated with tranexamic acid in a dog with acute traumatic coagulopathy

B. Muri et al.

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B. Muri et al.

Diagnostic imaging and surgery

Fifty minutes after admission a whole body CT study was performed. The CT revealed multiple pelvic fractures, right fibula and tibia fractures, complete *musculus rectus abdominis* avulsion, free abdominal gas, but no detectable lesion of the skull, spine or thorax.

After receiving a unit of matched fresh whole blood (22 ml/kg), anaesthesia was co-induced with ketamin 5mg/kg (Ketanarkon 100, Streuli Pharma AG, 8730 Uznach) and midazolam 0.25mg/kg (Dormicum®, Roche Pharma (Schweiz) AG, 4153 Reinach) and maintained with sevoflurane in air/oxygen (1:1). Intra-operative analgesia was provided by lidocain (1.8 mg/kg/h) (Lidocain HCl „Bichsel“ 2%, Dr. G Bichsel AG, 3800 Interlaken), fentanyl (0,25ug/kg/h) (Fentanyl Sintetica, Sintetica AG, CH-6850 Mendrisio) and ketamin (0.6mg/kg/h). During the anaesthesia of about 8 hours, the dog was cardiovascularly stable with a mean arterial blood pressure (MAP) of >70mmHg throughout anaesthesia. Despite active warming following induction, rectal body temperature dropped to 34.4 °C during anaesthesia. During and after surgery, follow-up arterial blood gas analyses (Tab. 1) were performed and electrolyte abnormalities were corrected. Exploration of the abdomen was performed. The eviscerated intestinal bundle was copiously rinsed with warm Ringer's acetate before transferred back in the abdominal cavity. Resection and anastomosis of approximately 70cm of mid jejunum was performed due to avulsion of mesentery and associated vasculature and a partial omentectomy was performed. The complete avulsion of the tendo prepubicus was fixed to the pelvis with four drill holes and non-absorbable suture size 1 (Prolene®, Ethicon, Somerville, NJ 08876). The inguinal wound was lavaged and the right A./V. femoralis was sealed proximal to the ligation with an electrothermal bipolar tissue sealing system (LigaSure®, Covidien Medtronic plc, Dublin Ireland). The adductor muscles were debrided and repositioned and three active drains (Blake®, Ethicon, Somerville NJ 08876) were placed. Following closure of the abdomen, a vacuum assisted closure system (V.A.C®, KCI medical, San Antonio, TX 78265) was placed on the degloving defect on the flank. Intraoperatively, the bleeding from major vessels was controlled and diffuse bleeding from the peritoneal surface was noted.

Postoperative care

Approximately 10 hours after admission the dog was transferred to the intensive care unit, where another blood sample was taken from the indwelling central venous catheter for ROTEM analysis and determination of serum albumin concentration. At this time, the patient had received a total of 40mg/kg of tranexamic acid, 22ml/kg of whole fresh blood, 98ml/kg of crystalloids (Ringer's acetate) and 24ml/kg colloids (Voluven). The

FibTEM and ExTEM tracings were, except for the CFT and Alpha Angle of the ExTEM, within normal limits (Tab. 2). Hematocrit was 29% (reference interval 42-55%) and serum albumin concentration was 6g/l (reference interval 29-37 g/l). Subsequently, the dog was transfused with 1g/kg 20% human serum albumin (Albumin CSL 20%, CSL Behring AG, 3014 Bern), which increased serum albumin concentration to 21g/l. The dog additionally received paracetamol (10mg/kg, q8h) (Paracetamol Fresenius, Fresenius Kabi, 6370 Oberdorf) as an analgesic.

During the following 12 hours, the dog was cardiovascularly stable. The diffuse bleeding from the inguinal space diminished clinically approximately one hour after surgical intervention and administration of 40mg/kg of tranexamic acid and no further clinical signs of bleeding were identified. 24h after admission another ROTEM analysis was performed (Tab. 2). Following ROTEM analysis, tranexamic acid was given one more time and was then discontinued, as hyperfibrinolysis was not detected anymore. The dog received 10ml/kg of cross matched concentrated red blood cells, increasing the hematocrit from 19% to 38%. 48h after admission, a CBC showed severe leucopenia and left shift (Tab. 1). The dog developed hypoglycaemia, MAP dropped to <60 mmHg and did not react to repeated fluid boluses with Ringer's acetate (total of 60ml/kg) and Voluven (3ml/kg). Cytological evaluation of abdominal fluid confirmed a septic abdomen with extra- and intracellular bacteria. At this time point, the owner elected for euthanasia. No post-mortem analysis was performed.

Discussion

Acute traumatic coagulopathy is a complication of trauma leading to coagulopathy and clinical bleeding diathesis followed by increased transfusion requirement and increased mortality (MacLeod, et al., 2003; Brohi, et al., 2003; Maegele, et al., 2007; Frith, et al., 2010; Davenport, et al., 2011). The coagulopathy is characterized by tissue damage through trauma and concurrent hypoperfusion, leading to a complex and dynamic activation and inhibition of several steps of haemostasis (Dobson, et al., 2015; Davenport and Brohi, 2016).

Hyperfibrinolysis is a common finding in people with severe trauma (Raza, et al., 2013; Cardenas, et al., 2014). The polytraumatised dog in our study showed marked hyperfibrinolysis which was identified by an increased ML starting 30 minutes after activation of the ExTEM tracing. Hyperfibrinolysis seen in the ExTEM tracing of our dog is supported by concurrent evaluation of the ApTEM profile, which did not show hyperfibrinolysis.

The comparison of the ApTEM to the ExTEM profile allows the diagnosis of hyperfibrinolysis in bleeding human patients, as lysis is inhibited in the ApTEM reagent by the addition of aprotinin, an antifibrinolytic (Ganter, 2008). To our knowledge, this is the first description of trauma-induced hyperfibrinolysis in a native blood sample and proven by concurrent ApTEM analysis. A previous case report suspected trauma-induced hyperfibrinolysis in frozen plasma samples that were activated with tissue plasminogen activator (Yoo, et al., 2016).

Hyperfibrinolysis is also not commonly identified in dogs with other diseases. It has been described in dogs with spontaneous (non-traumatic) haemoperitoneum (Fletcher, et al., 2015) and in dogs with *Angiostrongylus vasorum* infection (Sigrist, et al., 2017). The treatment of choice for hyperfibrinolysis is an antifibrinolytic drug, such as tranexamic acid (CRASH-2 trial collaborators, 2010). The presented dog initially received 20 mg/kg of tranexamic acid IV. The dose of tranexamic acid was empirically deduced from human data and own clinical experience. To our knowledge, no pharmacological evaluation of the minimal required dose to inhibit hyperfibrinolysis in dogs has been performed. As hyperfibrinolysis was still present on the first ROTEM analysis, despite administration of 20 mg/kg tranexamic acid five to ten minutes prior to blood sampling, we suspected that the patient needed more than 20mg/kg. While we cannot exclude that the maximal drug effect was not reached after 10 minutes, the finding of the need of higher dosages of tranexamic acid in dogs with overt hyperfibrinolysis and clinical signs of bleeding diathesis is in accordance with findings in dogs with hyperfibrinolysis for other reasons (Sigrist, et al., 2017). Potentially, the identified hyperfibrinolysis of this dog may have been even more significant prior to tranexamic acid administration. Hyperfibrinolysis was no longer detectable on ROTEM tracings after the second dose of tranexamic acid, however, no ROTEM analysis was available immediately after the second dose of tranexamic acid and prior to whole blood transfusion, which may have had an effect on hyperfibrinolysis as well. Additionally, no ROTEM analysis is available after weaning of the drug, so no conclusion can be drawn regarding the time frame of hyperfibrinolysis and the need for continued tranexamic acid supplementation in dogs with hyperfibrinolysis. The human European trauma guidelines recommend early (< 3h after injury) treatment with tranexamic acid until bleeding diminishes.

ATC is further characterized by hypocoagulation, which was identified in our dog as well. Decreased MCF, prolonged CT and prolonged CFT were identified in the first ExTEM. Since the dog received fluid therapy prior to blood sampling for ROTEM analysis at presentation,

we cannot exclude a dilutional or hypocoagulable effect seen with colloids and hypertonic saline. However, doses were lower than those administered in studies that showed significant effect on ROTEM parameters compared to dilution alone (Adamik, et al., 2015; Reuteler et al., 2017). As described above, tissue trauma in combination with hypoperfusion are the main causes for developing ATC. Rising injury severity is associated with the severity of hypocoagulation and hyperfibrinolysis (Brohi, et al., 2008; Frith, et al., 2010). In a study with 40 dogs (Holowaychuck, et al., 2014), the finding of ATC, defined as two or more abnormal coagulation tests, was more common in dogs with higher injury severity. The presented dog was severely polytraumatised, with an ATT score of 13/18 (Rockar, et al., 1994), and also severely hypoperfused at presentation, with a serum lactate of 10.3mmol/l and clinical signs of hypovolaemic shock in addition to a non measurable blood pressure. In addition to tissue trauma and hypoperfusion leading to development of ACT, several factors are known to contribute to the coagulopathy: acidosis, hypothermia and hemodilution. Mild acidosis was present at admission with a pH of 7.21, which might have had a worsening effect on coagulation measured by ROTEM (Engstrom, et al., 2006; Dirkmann, et al., 2008) and, as discussed above, the dog received fluid therapy prior to determination of ROTEM parameters. Hypothermia however was not present. Unfortunately, the dog did not survive to discharge. However, the dog was euthanized due to development of a septic abdomen 48 hours after presentation and not due to apparent signs of coagulopathy.

In humans, the incidence of ATC is more than 25% in severely injured trauma patients (Brohi, et al., 2003; Maegele, et al., 2007; Frith, et al., 2010). Studies evaluating ATC in dogs are limited, with a single study describing ATC in 15% of 40 dogs with severe trauma (Holowaychuck, et al., 2014), whereas another study of 30 dogs with acute trauma did not find any signs of hypocoagulopathy at all (Abelson, et al., 2013). The most recent study described ATC in only one out of 18 dogs sustaining blunt force trauma (Gottlieb, et al., 2017). However, the incidence and outcome of ATC depends on how ATC is defined. In human medicine, several definitions of ATC exist (Brohi, et al., 2007; Frith, et al., 2010; Cohen, et al., 2013; Gonzalez, et al., 2016). Previous studies evaluating ATC in dogs have used different definitions, since there is no formal definition. Palmer suggested that every dog who sustained severe trauma with the presence of severe hypoperfusion (MAP < 60mmHg, Base Excess < - 6mmol/l, Lactate > 5 mmol/l), haemorrhagic shock with uncontrollable bleeding and viscoelastic tracing displaying decreased clot strength (<40% of mean reference value) or prolonged traditional coagulation assays (>1.5 the labora-

Hyperfibrinolysis diagnosed with rotational thromboelastometry and treated with tranexamic acid in a dog with acute traumatic coagulopathy

B. Muri et al.

Hyperfibrinolysis diagnosed with rotational thromboelastometry and treated with tranexamic acid in a dog with acute traumatic coagulopathy

B. Muri et al.

tory mean) is highly suggestive of ATC (Palmer and Martin, 2014). Our dog showed the clinical signs of hypoperfusion described by Palmer but only a 13% reduction in MCF. However, it showed hyperfibrinolysis, which seems to be an important factor in the pathogenesis of ATC which is not included in Palmer's definition. Diagnosing hyperfibrinolysis using ROTEM is not very sensitive, but if it is diagnosed in trauma patients, mortality ranges up to 60-70% (Schöch, et al., 2009). Based on human data we strongly believe that the combination of hypocoagulability and hyperfibrinolysis in thromboelastometry is a distinct if not unique sign of ATC.

Conclusion

This case report describes a severely polytraumatised dog with thromboelastographic signs of hypocoagulability and hyperfibrinolysis, which resembles thromboelastographic signs of ATC in humans. Hyperfibrinolysis and hypocoagulability was successfully treated with the described management including administration of tranexamic acid. Further studies investigating hyperfibrinolysis in dogs with trauma and with suspected ATC are needed.

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Hyperfibrinolysis diagnosed with rotational thromboelastometry and treated with tranexamic acid in a dog with acute traumatic coagulopathy

B. Muri et al.