Olgu sunumu
Case report

Hipertrofik Kardiyomiyopatiye Bağlı Akut Aortik Tromboembolisi Olan Bir Kedide Doku Plazminojen Aktivatörü Tedavisinin Tromboelastografi ile Değerlendirilmesi

Thromboelastography Evaluation of Tissue Plasminogen Activator Therapy in a Cat with Acute Aortic Thromboembolism due to Hypertrophic Cardiomyopathy

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ÖZ

Akut arteriyel tromboembolizm (ATE), trombusun aortun trifürkasyonuna yerleştiği, hemen tedavi edilmezse ölüme veya organlarda ciddi hasara yol açan çok ağrılı ve ölümcül ciddiyetli bir durumdur. ATE tedavisinde ilk seçenek olarak doku plazminojen aktivatörü (tPA) gibi trombolitik ajanlar tercih edilmektedir; ancak insan ve hayvanlarda spontan kanama gibi olası yan etkileri nedeniyle dikkatli kullanılmaları gerekir. Bu nedenle pıhtılaşma durumunun izlenmesi, çözünen intravasküler pıhtıların yönetimi ve tedavisinde önemli bir rol oynar. Pıhtı oluşumu, gücü ve lizis dinamiklerini ölçen ve pıhtı tutarlılığı hakkında bilgi sağlayan tromboelastografi (TEG), pıhtılaşma durumunu ve trombolitik tedaviye yanıtı değerlendirmede yararlı bir araç olarak kabul edilmiştir. Kedilerde intravenöz tPA ile uygulanan trombolitik tedavinin tromboelastografik takibini gösteren bir çalışma bulunmamaktadır. Bu nedenle burada hipertrofik kardiyomiyopatiye (HCM) bağlı ATE'li bir kedide tPA kullanılarak başarılı bir tromboliz rapor edilmiş ve ilk kez TEG ile trobolitik tedavi izlenmiştir.

ABSTRACT

Acute arterial thromboembolism (ATE) is an extremely painful and fatal serious condition in which the thrombus lodges in the trifurcation of the aorta, resulting in death or severe damage to organs if not treated immediately. Thrombolytic agents such as tissue plasminogen activator (tPA) are preferred as a first choice of the treatment for ATE; however, they should be used carefully because of their possible side effects such as spontaneous bleeding in human and animals. Therefore, monitoring coagulation status plays an important role in the management and treatment of dissolving intravascular clots. Thromboelastography (TEG) that measures the dynamics of clot formation, strength, and lysis, and provides information of clot consistency has been accepted as a useful tool for assessing coagulation status and response to thrombolytic therapy. There is no study showing the thromboelastographic monitoring of the thrombolytic therapy with intravenous tPA in cats. Therefore, we reported here thrombolysis by using tPA successfully in a cat with ATE due to hypertrophic cardiomyopathy (HCM) and for the first time monitoring the lytic treatment by TEG.

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INTRODUCTION

Aortic thromboembolism (ATE) is a condition in which a large blood clot (thrombus) has traveled and lodged itself in a location that cuts off the blood supply to parts of the body such as legs, kidneys, and brain.[1] Possible reasons for ATE include heart diseases, kidney diseases (renal failure and nephrotic syndrome), endocrine diseases (hypothyroidism and hyperadrenocorticism), neoplasia and pancreatitis.[2] ATE is one of the most common complications of hypertrophic cardiomyopathy (HCM) in humans[3,4] and cats.[5]

In the case of HCM, enlarged left atrium (LA) that promotes smoke-like stagnant or turbulent blood flow activating the coagulation pathway and promote clot formation. The cats suffering from ATE (FATE) are presented in general with an acute and distressing presentation with hyperventilation and severe pain, and are suddenly unable to use their hind legs appropriately. Physical examination shows absence of pulse in the affected legs and cold paws with cyanotic (blue-tinged) pads and nail beds confirming loss of blood supply along the extremity.[7]

Several studies suggest the use of thrombolytic as a gold standard therapy for ATE since surgical removal of the clot have risks (anesthesia, spontaneous reperfusion, and sepsis, etc.) in patients with heart disease.[1,5-7] However, there are limited clinical experience with thrombolytic agents such as streptokinase and recombinant tissue plasminogen activators (tPA) in dogs[8] and cats.[9-11] It was reported that tPA achieved better lysis rate than streptokinase in humans[13]. Drugs of tPA (alteplase, reteplase and tenecteplase) are one of the key components of the dissolution of blood clots. Primary function of tPA includes catalyzing the conversion of plasminogen to plasmin, the primary enzyme involved in the dissolution of blood clots.[9] The common points of the studies performed about thrombolytics are that close monitorization of coagulation during tPA therapy due to bleeding tendency and its intravenous administration as early as possible following diagnosis of ATE have been needed.[9]

Thromboelastography (TEG) is a viscoelastic hemostatic assay evaluating primary, secondary and tertiary hemostasis in whole blood. A major advantage of TEG compared to traditional methods evaluating hemostasis such as platelet count and global clotting times (prothrombin time – PT and activated partial thromboplastin time - aPTT) is the ability to assess clot formation from its initiation to fibrinolysis. TEG is also able to assess the interactions between platelets and clotting proteins, as well as other blood cells, a feature of coagulation that cannot be assessed by other currently clinically available methods.[9,14,16-19] To the best of the authors' knowledge, there is no information yet on the use of TEG in monitoring coagulation status in cats receiving tPA therapy. In this report, therefore, the effect of tPA treatment was evaluated using TEG in a cat with ATE due to HCM, before and 24 hrs after administration.

Case Description

A 3-year-old intact female domestic shorthair cat was presented to the animal hospital with a history of acute onset of dyspnea / tachypnea (84 respiration per minute [rpm]), hypothermia (36.5 °C), lameness and severe pain in hind legs. First clinical examination was performed at 6 hrs after initial of the symptoms and revealed the severe pain and loss of sensation in the hind legs, bruising on the extremity pads and ischemic purple color at the nail base. The cat was placed to oxygen cage after administering of furosemide (2 mg/kg, IV, bolus, and then two times at the same dose with 2 hrs. intervals; Lasix 20 mg/2 ml, Sanofi, İstanbul) and buthorphanol (0.25 mg/kg, SC; Butomidor 10 mg/ml, Interhas, Turkey) for the treatment of respiratory distress (possibly due to pulmonary edema) and pain stabilization, respectively.

Just before furosemide administration, blood samples were collected to evaluate complete blood cell count (CBC; HM5, Abaxis, USA), serum biochemistry profile (VetScan VS2, Abaxis, USA) and coagulation status (TEG 5000, Haemoscope Hemostasis Analyser, USA). Results revealed a hemoconcentration and increases in serum total protein, albumin, alanine aminotransferase, and blood glucose levels. Serum NT-ProBNP level of 75 pmol/L (Vcheck, Bionote, USA) was compatible with the suspicious of a heart disease (Table 1). The immunochromatographic tests for FeCoV, FIV and FeLV were negative, as well.

Right after the patient stabilization (meaning that respiration rate was reduced from 84 rpm to 52 rpm with resolving in dyspnea), radiological examination was performed. Latero-lateral (A) and ventro-dorsal (B) x-ray of the thorax revealed pulmonary edema (just like in the first physical examination), mild pulmonary artery enlargement and elongation of the heart (cardiomegaly) with noticeable aerophagia due to dyspnea (Figure 1). Electrocardiographic (ECG) examination revealed sinus arrhythmia, QS complexes (absence of R waves and presence of deep S waves in lead II and III), right axis deviation, and a wide complex ventricular extra systole (VES), with a heart rate of 136 bpm (CareWell 1103L, China) (Figure 2).

Echocardiographic examination was performed as suggested.[20] Briefly, interventricular septum (IVSd) and left ventricular free wall thickness at diastole (LVFWd) and left atrial to aortic root diameter ratio (LA/Ao) were measured at right parasternal short axis view (RPSAx) of the LV at the papillary muscles and aortic levels, respectively (Caris Plus, Color Doppler, Esoate, Italy). Aortic flow was assessed by color Doppler at left apical 5 chamber view. Results showed asymmetrically thickened IVS (6.5 mm; reference ≤ 6 mm) and LVFW (7.1 mm; reference ≤ 6 mm), and increased LA/Ao (2.8, reference < 1.5), indicating a moderate asymmetric concentric LV hypertrophy and marked dilation of the LA, respectively. Severe spontaneous smoke echocardiographic contrast (SEC) in the enlarged LA was observed, as well.

In addition to these findings, that LV outflow tract diameter (LVOT: 7.0 mm) and Ao maximal pressure gradient (Ao-maxPG: 6.7 mmHg) were found within reference ranges showed the presence of non-obstructive HCM.[21] Doppler ultrasonography revealed the absence of pulse and flow in the femoral arteries bilaterally. The findings were clinically indicative of ATE due to HCM.[22]

Table 1. Hematologic and serum biochemistry panel of the patient presented with feline references.

Hemogram	Patient	Reference	Serum Biochemistry	Patient	Reference
WBC (K/µL)	6.16	5-12	ALB (G/dL)	4.9	2.2-4.4
Nötrofil (K/µL)	4.01	2.50-12.50	ALP (U/L)	42	10-90
Lenfosit (K/µL)	2.09	0.4-6.8	ALT (U/L)	733	20-100
Monosit (K/µL)	0.04	0.15-1.70	AMY (U/L)	1191	300-1100
Eozinofil(K/µL)	0.01	0.1-0.79	TBIL (mg/dL)	0.3	0.1-0.6
Bazofil (K/µL)	0.00	0.00-0.10	BUN (mg/dL)	29	10-30
RBC (M/µL)	12.50	5.5-8.5	Ca (mg/dL)	10.3	8.0-11.8
HCT (%)	60.9	30-45	Phos (mg/dL)	3.7	3.4-8.5
HGB (G/dL)	18.9	9-15	Crea (mg/dL)	2.2	0.3-2.1
MCV (fL)	49	41-58	Glu (mg/dL)	284	70-150
MCH (pg)	15.2	12-20	Na^+ (mmol/L)	153	142-164
MCHC (G/dL)	31.1	29-37.5	K^+ (mmol/L)	4.2	3.7-5.8
RDW (%)	19.2	17.3-22	TP (G/dL)	9.7	5.4-8.2
PLT (K/ µL)	269	200-500	GLOB (G/dL)	4.8	1.5-5.7
MPV (fL)	14.4		NT-ProBNP	75	<100 pmol/L
PDW (%)	37.3				
PCT (%)	0.39				

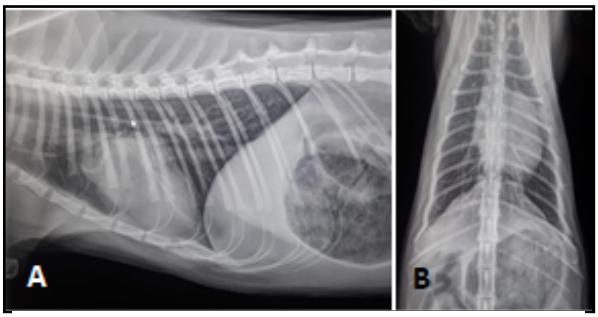

Figure 1: Laterolateral (A) and ventrodorsal (B) x-ray of the thorax revealed broncho-alveolar pattern and elongation of the heart with noticeable aerophagia due to dyspnea.

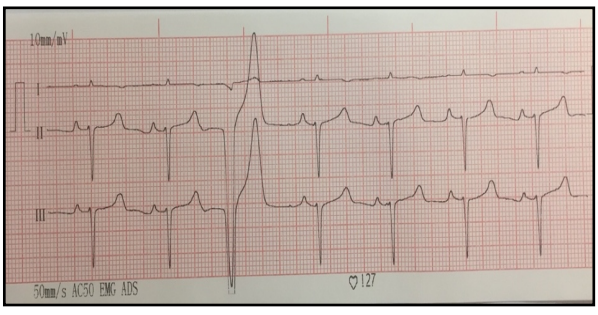

Figure 2: Electrocardiographic examination of the cat revealed sinus arrhythmia, QS pattern, and a wide complex ventricular extra systole (50 mm/sec., 10 mm/1 mV).

A magnetic resonance angiography (MRA) was performed to confirm the presence of ATE, as reported in a previous study.[23] MRA images showed that the contrast medium (Iohexol, 10 ml, iv.; Omnipaque, Opakim, Türkiye) did not progress caudally at the level of femoral arteries (data not shown).[23] Based on the results of clinical and laboratory examinations, another risk factor for the development of ATE was not found.

Coagulation status was evaluated by TEG (TEG 5000, Haemoscope Hemostasis Analyser, USA), using anticoagulated blood samples (Vacuette®, sodium citrate 3.2% Greiner Bio-One, Germany). TEG analyses were performed before (baseline) and 6 and 24 hrs after the treatment, within 30 minutes following the blood collection[24]. TEG analysis included reaction time (R time) and kinetic time (K time) of clot kinetic, alpha angle (α-angle) of clot strengthening, maximum amplitude (MA) of platelet function, and lysis rate (LY30, the percentage of lysis 30 min after MA) of clot stability.[16]

For thrombolytic treatment, tPA was preferred because of achieving better lysis rate as compared with other well-known agents such streptokinase.[9,10] Central venous catheter (CVC) was placed and then tPA therapy was started as suggested in a previous study.[25] Briefly, alteplase (Actilyse®, Boehringer Ingelheim, Germany), a recombinant tPA, was administered at 1 mg/kg IV via cephalic veins over 1 hr with the first 10% of the infusion administered as an IV bolus over 10 min.[9] Right after the drug administration, the cat was evaluated by physical examination and abdominal and thoracic ultrasonography for any evidence of external or cavitary hemorrhage, respectively.

TEG analysis showed that R time, MA and LY30 values were found to be normal, but K time and α-angle were out of the reference ranges at admission (Table 2 and Figure 3A). R time increased dramatically from 6.2 min of pre-treatment value to 112.7 min at 6 hrs after tPA treatment (Figure 3B), with value returning to normal at post-treatment 24 hrs. K time, α-angle, MA and LY30 could not be measurable at 6 hrs following the tPA administration, and then while K and LY30 values were normalized, α-angle and MA values increased at 24 hrs compared to those of their initial values (Figure 3c). In this period, clinically a significant decrease in pain perception, along with the patient's starting to step on his hind legs, and an increased perception of deep pain were observed in the neurological examination. Bruised extremity pads and ischemic nail bases returned almost to their healthy colors and respiration rate returned below 30 rpm.

The cat was discharged home with a medical protocol of thromboprophylaxis; clopidogrel (18.75 mg, PO, SID; Plavix 75 mg tb., Sanofi, Türkiye) and aspirin (5 mg/kg, PO, once every 72 hr, Coraspin 100 mg tb., Bayer Türk Kimya, Türkiye), and cardiomyopathy (HCM); furosemide (1 mg/kg, PO, BID, Lasix 40 mg tb., Sanofi, Turkey) and benazepril (0.25 mg/kg, PO, SID, Cibacen 5 mg tb., MEDA, Türkiye)[21]. An echocardiographic follow up was applied seven days later to re-evaluate the health status. At the time of writing, the cat was still living with drugs with reducing dosage of furosemide (1 mg/kg, once a day) and close contact with the owner was established to control the drug regimen and patient wellness. Also, the periodical controls including ECG, thoracic x-ray, CBC and renal panel (serum BUN and Cr) as well as serum electrolytes such as Na and K were carried out to observe possible side effects of medicals in every 3 months during the patient monitorization. The cat received thromboprophylaxis but did not need thrombolytic treatment after the first admission.

Table 2. Thrombolestographic evaluation of the cat.

Time / TEG parameters	R minutes	K minutes	α angle degrees	MA mm	LY30 %
Pre-treatment	6.2	11.4	21.8	58.3	0.0
6 hrs after the treatment	112.7	-		--	-
24 hrs after the treatment	7.2	3.8	41.4	77.6	0.0
References*	2.4-9.5	1.2-3.9	45.5-73.5	46.8-66.1	0.0-9.0

R: reaction time; K: clotting time; α angle: alpha angle; MA: maximum amplitude; LY30: clot lysis 30 min after MA is reached.

* Marschner C.B., Bjørnvad C.R., Kristensen A.T., Wiinberg B.: Thromboelastography results on citrated whole blood from clinically healthy cats depend on modes of activation. Acta Vet Scand. 2010, 52(1):38.

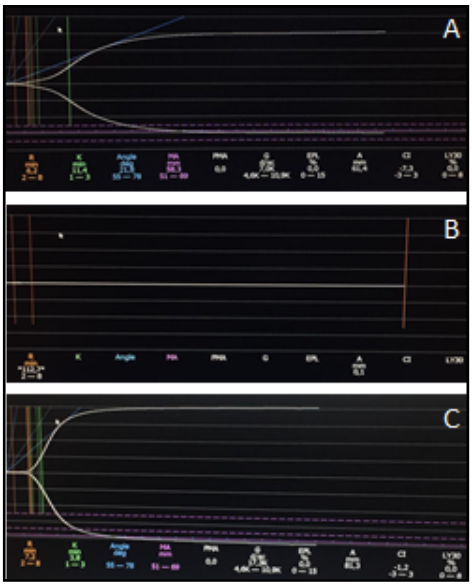

Figure 3: Thrombolestographic evaluation of the cat before (A), 6 hrs (B) and 24 hrs after (C) the tPA treatment.

DISCUSSION

This case report represents the therapeutic effectiveness of administration of intravenous tPA for thrombolysis, and how the coagulation status could be monitored using TEG in a cat with ATE due to HCM in practice. Considering the operative and anesthetic risks of thrombectomy, we have shared this case report stating that using tPA in the elimination of thrombus at the dose described here can lead to success with a much cheaper and risk-free method, and for the first time, TEG may be a useful and practical tool in monitoring the safe management of the thrombolysis in the first 24 hrs. of the treatment.

ATE, a very painful and fatal serious condition, affects approximately 25-30 percent of cats with heart disease such as HCM.[26] In this case, HCM as a causative factor for ATE was diagnosed based on the clinical, radiographic, and echocardiographic examinations, and the presence of ATE was confirmed using the MRI as reported previously.[22,23] Based on the imaging techniques and the comprehensive clinical and laboratory examinations, there were no other underlying disease for the development of ATE was found.

In cats with HCM, SEC and/or thrombus formation occurred especially in enlarged LA are associated with the blood stasis leading to increase in platelet activity (hypercoagulation) and endothelial damage.[1,5-7] Formatted thromboses may remain mobile or adhered to a wall of the LA, become enlarged and block the exit to the LV, or may break apart as an emboly and pass from the Ao to femoral arteries.[1,5-7] Arterial occlusion and impaired collateral circulation may explain the presence of the bruising on the

extremity pads and ischemic purple color at the nail base in the presented cat.

If the thrombus can be surgically removed or medically resolved within a short time, survival time may be longer and life quality may be increased.[27] However, the surgical treatment (embolectomy) is not recommended because of the high risk of death during and potential re-embolization after the procedure.[6] In human medicine, after an acute ischemic stroke, intervention with intravenous tPA for up to 6 hrs can provide complete cure.[3,4,28,29] Thus, thrombolytic therapy is suggested as a standard practice for acute thromboembolism in humans, as well as dogs and cats.[9-11,25] On the other hand, there are limited clinical experience with thrombolytic agents such as streptokinase and tPA in dogs[8] and cats.[9-11] In this case, we decided to use the tPA to resolve the thrombus and improve the tissue perfusion since the timing of starting thrombolytic therapy seemed appropriate, and it achieves better lysis rate than streptokinase.[12]

tPA, a 69 kD glycoprotein and an enzyme of serine protease family, shows thrombolytic activity by catalyzing the conversion of plasminogen to plasmin, the primary enzyme involved in the dissolution of blood clots.[30] Thus, while thrombolytics are used, close monitorization of coagulation is needed due to spontaneous bleeding tendency.[6] In this cat, TEG, a whole blood coagulation analyzer, was used to evaluate coagulation status because it is accepted as a sensitive and useful method to evaluate coagulation abnormalities such as hypercoagulopathy, hypocoagulapathy and disseminated intravascular coagulation in dogs[14,19,31] cats[15,17,18,24], and humans.[32] Additionally, that TEG is used to characterize the whole clotting cascade from initiation of clot formation to fibrinolysis provides it a great advantage as compared with the traditional coagulation tests such as PT and aPTT.[31]

In veterinary medicine, TEG analysis has been used to evaluate coagulation status in health and disease in dogs and cats. Yilmaz et al.[19] evaluated the hemostatic function by TEG in dogs with dilated cardiomyopathy (DCM) in which majority of the dogs showed a hypercoagulation rather than hypocoagulation state. In another study, Bae et al.[32] used TEG to therapeutically monitor the use of rivaroxaban (anticoagulant) in dogs, and the usefulness of TEG in determining the individual dose regimen and monitoring the treatment was noted. TEG analysis was performed in healthy[15,34,35] or diseased cats such as obesity[36], acute trauma[37], hyperthyroidism[38], infection[39], liver disease[18], and was used to monitor feline anticoagulant therapy.[34] In a study conducted in healthy cats, significant changes in the TEG parameters after an anticoagulant (factor Xa inhibitor) administration was found compatible with hypocoagulable state.[40] However, there is no study yet showing the thromboelastographic monitoring of the thrombolytic therapy with intravenous tPA in cats with heart disease.

In this cat, TEG values before the treatment showed an abnormal clot kinetic and strengthening based on the prolonged R time and decreased α-angle compared to the references reported for healthy cats[15], although we expected to see a hypercoagulation state. Six hours after the tPA administration, prolonged coagulation time was revealed by a straight line, and TEG analysis was thus truncated at 112 min., which was most probably due to thrombolytic activity of tPA relating with catalyzing the conversion of plasminogen to plasmin. Following the tPA treatment, at 24 hrs, all TEG parameters measured in this cat were within reference ranges, indicating that coagulation cascade was returned to normal coagulation status from hypocoagulation due to thrombolytic.

Although intravenous alteplase (tPA) is cleared primarily by the liver with an initial half-life of fewer than 5 min. and a terminal half-life of 72 min.[41], in our case thrombolytic activity/hypocoagulation state in response to tPA was stable till 6 hrs. This may be due to species differences, and/or long-lasting elimination of tPA clearance in cats. In addition to the normalization of TEG parameters, cat improved clinically and started to step on his hind limbs. In this period, bruised extremity pads and ischemic nail bases returned almost to their healthy colors and respiration rate returned into the reference range at rest. The cat was discharged home with a medical protocol of thromboprophylaxis (clopidogrel and aspirin) and cardiomyopathy (furosemide and benazepril). Cats receiving tPA therapy could be monitored on the possible tPA-related side effects such as reperfusion injury and acute kidney injury.[25,42] We couldn't observe any side effects and/or replaces of ATE during 3 months, based on the comprehensive diagnostic approaches.

As a result, the case report presents the advantages of clinical therapeutic monitoring of tPA treatment with TEG include the following: (i) prevention of possible over-dose drug administration; (ii) gives chance to safely monitor the thrombolytic process created during the treatment; (iii) assesses the effectivity of anticoagulant drug regimen immediately during the monitorization of tPA treatment in cats with ATE. Clinicians should be kept in mind that coagulation should be closely monitored in both HCM and thrombolytic treatments in cats with ATE, and TEG may be considered as a useful and practical tool to evaluate coagulation status and to monitor tPA treatments in cat practice.

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