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Hipertrofik Kardiyomyopatiye Bağlı Arteriyel Tromboembolizmi Olan Üç Kedide Pıhtılaşma Durumunun Tromboelastografik Değerlendirilmesi

Thromboelastographic Evaluation of Coagulation Status in Three Cats
with Arterial Thromboembolism due to Hypertrophic Cardiomyopathy

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ÖZ

Arteriyel tromboembolizm (ATE) ile komplike olan veya olmayan hipertrofik kardiyomyopati (HCM) kedilerde tromboelastografi (TEG) kullanılarak pıhtılaşma ve fibrinolitik durumun nasıl değiştiğine dair bilgi eksikliği vardır. Bu nedenle burada HCM'ye bağlı ATE'li üç kedide koagülasyon durumu TEG ile değerlendirildi. Pıhtılaşma, protrombin zamanı (PT), aktive parsiyel tromboplastin zamanı (aPTT), d-dimer ve TEG parametreleri ile değerlendirildi. Bu klinik rapor, PT ve aPTT'nin hiper pıhtılaşmayı ve devam eden tromboz sürecini belirtmek için yeterli olmayabileceğini göstermiştir. TEG kullanılarak hiperkoagülabilitenin kedilerde tromboz tanısında bir kriter olarak kullanılabileceği düşünülmüştür.

ABSTRACT

There is lack of information on how coagulation and fibrinolytic status using thromboelastography (TEG) are altered in cats with hypertrophic cardiomyopathy (HCM) complicated with or without arterial thromboembolism (ATE). Thus, herein, coagulation status was evaluated with TEG in three cats with ATE due to HCM. Coagulation was evaluated by prothrombin time (PT), activated partial thromboplastin time (aPTT), d-dimer, and TEG parameters. This clinical report has showed that PT and aPTT may not be sufficient to indicate hypercoagulation and ongoing process of thrombosis. Hypercoagulability using TEG was thought to be able to use as a criterion for the diagnosis of thrombosis in cats.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) causes the thickening of heart muscle resulting in poor left ventricular relaxation and filling ability. HCM is the most common cardiac disease in cats, leading to arterial thromboembolism (ATE) with a high mortality rate.^{1,2} The most common factors predisposing to the ATE are endothelial dysfunction, blood stasis, and a hypercoagulable state (Virchow's triad) in cats with HCM.³

Thromboelastography (TEG) measures the global viscoelastic properties of whole blood clot formation and gives detail on hypocoagulable and hypercoagulable states.⁴⁻⁶ TEG parameters show platelet (PLT) functions and their interactions with each coagulation process such as clot time, clot kinetics, clot strength, clot elasticity, and fibrinolysis,⁵⁻⁷ thereby providing advantages to the prothrombin time (PT), activated partial thromboplastin time (aPTT), and d-dimer.⁷ There is no knowledge about TEG evaluation in cats with HCM and/or ATE. Also, the potential of TEG to describe hypercoagulation has not been reported in those cases yet. Thus, in this clinical study, coagulation status was evaluated by TEG, in conjunctive with the results of routine clinical and laboratory analysis in three cats with ATE due to symptomatic HCM.

CASE HISTORY

Three cats with different breeds, ages, and body weights were included (Table 1). These cats were presented to the small animal clinic with the main symptoms of sudden onset painful paralysis in one (Case 1) or both hind limbs (Case 2 and 3). The transthoracic echocardiography was performed to evaluate cardiac geometry and function (CarisPlus[®], Florence, Italy) (Table 2).⁷ Blood samples were collected for hematological and biochemical analysis (VetScan[®], Abaxis, USA). Serum levels of cardiac troponin (cTnI), pro-brain natriuretic peptide

(ProBNP), and an inflammatory marker serum amyloid A (SAA) were measured using specific kits (VCheck[®] V200, Bionote, USA). Coagulation status was evaluated by PT and aPTT (VsPro, Abaxis, USA) and d-dimer levels (VCheck[®] V200, Bionote, USA) (Table 3), and kaolin-activated TEG (TEG[®] 5000, MA, USA) (Table 4), as described in our^{5,7} and other previous studies.⁶ Computed tomographic angiography was performed to evaluate the blood flows of the arteries (Somatome Scope[®], Siemens, Germany).⁸

Table 1. Signalment, selected parameters of physical examination and hemato-biochemical analysis in three cats with arterial thromboembolism (ATE) due to hypertrophic cardiomyopathy (HCM).

Parameters	Case 1	Case 2	Case 3	References*
Breed	Scottish fold	Mix	Mix	NA
Age – years	1	7	16	NA
Sex	Male	Male	Male	NA
Body weight Kg	3.5	5.2	4.3	NA
Temperature °C	38.6	39.1	38.7	38.1 – 39.2
Heart rate bpm	240	230	246	<220
Respiratory rate rpm	64	80	140	<40
WBC x10 ³ /uL	29.9	26.1	17.5	5.5 – 19.5
Hct %	32.9	22.8	31.0	30-45
PLT count x10 ³ /uL	106	68	246	300-800
ALT IU/L	112	563	187	22 – 84
ALP IU/L	84	68	142	9 - 53
BUN mg/dL	112.7	45.4	52.0	17.6-32.8
Cr mg/dL	2.8	0.8	1.8	0.8 – 1.8
cTnI ng/mL	3.8	3.5	1.3	0.00 – 0.16
Pro-BNP pmol/L	>1500	>1500	1496	<50
fSAA ug/ml	4.2	3.8	3.0	<5.0

*www.msddvetmanuel.com WBC: White blood cell count, Hct: Hematocrit, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, Cr: Creatinine, Pro-BNP: Pro-brain natriuretic peptide, fSAA: Feline serum amyloid ANA: Not applicable

Table 2. Some echocardiographic parameters obtained from three cats with arterial thromboembolism (ATE) due to hypertrophic cardiomyopathy (HCM).

Parameters	Case 1	Case 2	Case 3	References*
IVSd mm	6.2	6.5	6.2	4.6 ± 0.6*
LVIDd mm	18.9	10.7	15.7	15.9 ± 2.3*
LVPWd mm	6.0	11.0	9.6	4.3 ± 0.7*
IVSs mm	8.1	7.3	7.7	7.4 ± 1.3*
LVIDs mm	9.9	6.0	11.0	8.1 ± 1.8*
LVPWs mm	6.7	12.1	9.7	7.5 ± 1.1*
FS %	47.6	43.9	29.7	49 ± 7*
LA/Ao	2.9	1.8	2.9	0.9 ± 0.1*
AoVmax m/s	0.8	2.8	1.0	1.1 ± 0.2*
Mitral E/A	1.7	1.9	1.9	1.5 ± 0.3*
LA vol ml A2Ch	11.9	9.7	8.9	1.8 – 2.1**
LAA Vmax m/s	0.18	0.17	0.21	0.24-1.0***

IVSD: Interventricular septum diastole; LVIDd: Left ventricular internal diameter diastole; IVSs: Interventricular septum systole; LVIDs: Left ventricular internal diameter systole; LVPWd: Left ventricular post wall diastole; LVPWs: Left ventricular post wall systole; FS: Fractional shortening; LA/Ao: Left atrium/ aorta ratio; AoVmax: Aort maximal velocity; Mitral E/A: Mitral early ventricular filling (E) and late atrial contraction (A); LA vol ml A2Ch: Left atrial volume at apical 4-chamber view; LAA Vmax: Left atrial appendage maximal flow velocity. References were collected from *Boon JA (Veterinary Echocardiography, 2nd ed., Wiley-Blackwell, USA, 2010), **Rauch et al. (BMC Vet. Res. 16: 263, 2020), and ***Schober and Maez (J Vet Intern Med, 20:120-30, 2006).

Table 3. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and d-dimer in three cats with arterial thromboembolism due to hypertrophic cardiomyopathy.

Parameters	Coagulation cascade	Case 1	Case 2	Case 3	References*
PT sec	Extrinsic system	18.5	15.9	16.7	15-21
aPTT sec	Intrinsic system	100.7	110.5	97.0	94-125
D-dimer ug/mL	Fibrinolytic system	0.1	0.1	0.2	<0.3

*according to suggested reference values by manufactures; PT and aPTT (VsPro, Abaxis, USA) and d-dimer (VCheck V200, Bionote, USA).

Table 4. Thromboelastographic analysis in three cats with arterial thromboembolism due to hypertrophic cardiomyopathy.

Parameters	Case 1	Case 2	Case 3	References
Clot time				
– R time min	0.7	1.2	1.8	1.4 – 9.5 [#]
– SP min	ND	1.0	1.6	2.4 – 15.8 [*]
Clot kinetics				
– K time min	0.8	0.8	0.8	1.2 – 3.9 [#]
– α-angle degree	83.9	80.7	81.6	45.5 – 73.5 [#]
Clot strength				
– MA mm	76.3	76.8	80.3	46.8 – 66.1 [#]
– PMA	1.0	0.0	0.0	RI
– TMA min	ND	15.4	13.0	13.4 – 39.4 ^ψ
– G Dyn/sc	16.1	16.6	20.4	7.1 ± 2.4
– E Dyn/sc	ND	331.2	407.1	92 – 217
– TPI sec	ND	198.8	244.3	5-90 ^β
Clot stability				
– A30 mm	69.5	76.8	76.3	36.3 +/- 17.9
– A60 mm	68.2	73.6	71.1	30.3 +/- 17.0
Clot lysis				
– EPL %	0.1	0.0	2.0	0 – 15 ^β
– Ly30 %	0.1	0.0	2.0	2.4 – 15.8 [*]
– Ly60 %	1.2	1.1	5.0	1.1 – 13.1 [#]
– CLT min	ND	60.6	60.6	RI
Overall assessment				
– CI	7.2	6.7	6.7	-4.6 – 2.5 [*]

References were collected from [#] Marschner et al. (2010); ^{*} Engelen et al. (2017); ^ψ Çöl et al. (2013); and ^β Liu et al. (2016).

ND: Not determined; RI: Reference intervals could not be found for related parameters.

RESULTS and DISCUSSION

Our observations such as acute onset of paralysis, weak (Case 1) or undetectable pulses (Case 2 and 3) of the femoral artery in the affected legs, and pale (Case 1) or cyanotic paw pads (Case 2 and 3) were typical signs for representing ATE compatible with the previous studies.^{2,3} HCM was suspected on the clinical and radiological findings, and was confirmed by interventricular septum and left ventricular (LV) wall thickness, and different severity of left atrial (LA) dilation (Table 2), as reported earlier.^{1,2} HCM was sub-classified as an obstructive form (HOCM) due to a high velocity of aortic flow in Case 2. Micro-clot and thrombus formation were characterized by the spontaneous echo contrast in dilated LA using M-mode echocardiography. The micro (Case 1 and 2) and large clots (Case 3) may move from the LA to the aortic trifurcation, right iliac artery (Case 1), and the caudal part of the abdominal aorta (Case 2 and 3; Figure 1). Increased cardiomyocyte necrosis and LV wall stress (represented by increased cTnl and pro-

BNP levels) with pleural and pulmonary edema, were suggestive for congestive heart failure in cats studied³ (Table 1).



Figure 1. Computed Tomography (CT) Angiography shows the blockade of blood flow (red arrow) at the level of abdominal aorta in a cat (Case 2).

As seen in Table 3, our results were compatible with the previous studies reporting that PT and aPTT might be better for identifying hypocoagulability rather than hypercoagulability², and that plasma d-dimer were within the reference ranges in cats with HCM.² TEG provides a comprehensive overview of the clotting process, from initial thrombin generation to fibrinolysis.⁴ Observed decreases in the reaction (R), split (SP), and kinetic times (K), and an increase in α -angle (Table 4) revealed the shortened duration required for initial fibrin formation, meaning the increased tendency of blood to coagulate (hypercoagulability).⁹ Among TEG parameters, maximum amplitude (MA) and G values are widely used to evaluate clot strength. An increase in MA means that the patient's blood is in a hypercoagulable state and is prone to thrombosis.¹⁰ In this study, while MA increased, time to MA (TMA) was detected at a low normal level, showing that the ultimate strength of the fibrin clot might be increased in cats with ATE due to HCM. G value is the single most important value of the entire assay because of representing the overall function or effectiveness of the clot.¹⁰ In addition to higher G value, clot elasticity parameters (E and thrombodynamic potential index-TPI) were found higher than their references, indicating the presence of a thrombotic state in cats with ATE, as suggested.⁹

Clot stability and fibrinolysis were evaluated by TEG amplitude (A), lysis (Ly), and estimated percent lysis (EPL).^{6,7} Herein, observed changes in these parameters may be associated with an increase in clot stability (represented by increased A values), decreased fibrinolysis (represented by low Ly values), and increased resistance to lysis (represented by prolonged clot lysis time) in the cats studied.¹¹ TEG CI value is a unique parameter providing an overall global assessment of the clotting process, from fibrin formation to clot lysis, in real-time.¹⁰ The usefulness of the CI value for identifying hypercoagulability and predicting thromboembolic events was published in patients with prostate cancer¹² and gynecological oncology patients.¹³ In this study, the observed increase in CI value was compatible with the changes in other TEG parameters representing hypercoagulability in three cats (Figure 2).

This is a pilot study, and thus, included the limited number of cases with ATE. Coagulation status is evaluated by a comprehensive coagulation panel. Some parameters such as plasma thrombin-antithrombin complex (TAT), fibrinogen level, clotting factors, and natural anticoagulant levels in this panel were not analyzed in our cases. These cats were discharged 5 days (Case 1), 10 days (Case 2), and 7 days (Case 3) after the admission, with a minimal restriction of walking in the affected legs, with a standard treatment protocol for ATE and HCM.¹⁴

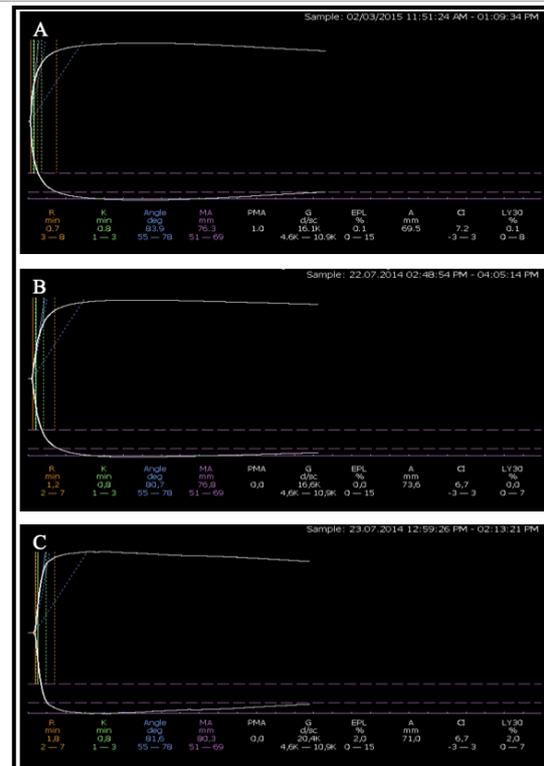


Figure 2. Thromboelastography tracings in Case 1 (A), 2 (B) and 3 (C).

Another limitation may be that coagulation status could not be reassessed before the cats were discharged from the hospital.

This case series showed that PT and aPTT may not be enough to indicate hypercoagulation and the ongoing process of thrombosis. Hypercoagulability using TEG may be used as a criterion for the diagnosis of thrombosis. Faster initiation of blood clotting, increased clot strength, and stability, and low clot lysis rate should be kept in mind to develop new diagnostic, and potential prophylactic and therapeutic strategies in HCM cats with ATE.

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