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Original Article

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Abstract

Feline arterial thromboembolism (ATE) is an acute condition that is usually associated with cardiomyopathy in cats. To date, there has been no report of factors associated with ATE in cats affected with hypertrophic cardiomyopathy (HCM) in Thailand. The purpose of this study was to find factors related to ATE in cats with HCM. A retrospective study was performed in 70 cats with HCM dividing them into two groups (26 ATE and 44 non-ATE groups) to analyze factors relating to ATE including sex, breed, age, weight, heart sounds, radiographic findings, echocardiographic findings and the environmental temperature. The result of univariable logistic regression analysis revealed that the factors significantly related to ATE in HCM cats were age, the presence of spontaneous contrast, percentage fractional shortening (FS), left atrial to aorta ratio (LA/Ao) and the environmental temperature. Multivariable logistic regression presented that age (OR: 7.503; 95%CI: 1.310-42.969; p = 0.024), the presence of spontaneous contrast (OR: 30.855; 95%CI: 4.298-221.487; p = 0.001), and the environmental temperature (OR: 1.616; 95%CI: 1.080-2.417; p = 0.019) were the factors related to ATE in HCM cats. The result of this study is valuable for the risk assessment of ATE in HCM cats.

Keywords: cats, hypertrophic cardiomyopathy, thromboembolism

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Introduction

Feline arterial thromboembolism (ATE) is an acute vascular obstruction secondary to thrombus formation or emboli occlusion (Borgeat *et al*., 2014). It is commonly found in cats affected by myocardial diseases. Thrombus occurs secondarily to factors called Virchow's triad consisting of hemostasis, endothelial injury and hypercoagulopathy. Most cats with ATE often show acute and progressive clinical signs due to thrombosis. ATE can lead to an increase in morbidity and mortality. A previous study has shown that 153 of 250 cases of ATE (61.2%) were euthanized at presentation and only 6 cases (2.4%) survived over 12 months (Borgeat *et al*., 2014).

The saddle thrombus, which causes a partial or complete obstruction of the distal aorta in cats, expectedly comes from emboli originating somewhere in the body. The most common clinical signs of ATE can be characterized by the 5Ps that include paralysis, pale or purple mucous membrane, pulseless, poikilothermia and pain (Borgeat *et al*., 2014).

Hypertrophic cardiomyopathy (HCM) is the primary myocardial disease affecting cats (Fuentes *et al*., 2020). Hypertrophic cardiomyopathy has accounted for 57% of all cardiomyopathies in cats (Ferasin *et al*., 2003). A previous study reported that approximately 21% of HCM cats were diagnosed with ATE (Fuentes, 2012). Cats affected with HCM and ATE had a 9% mortality rate (Payne *et al*., 2015).

As mentioned previously, HCM is the most common feline heart disease and a common cause of ATE. To our knowledge, there is no report of factors associated with ATE in cats affected with HCM in Thailand. The purpose of this study was to determine factors related to ATE in cats with HCM in Thailand.

Materials and Methods

Study Design: A retrospective study was performed. Electronic medical records of the Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University, Thailand from September 2014 to June 2019 were retrieved to identify cats diagnosed with HCM.

Inclusion and Exclusion Criteria: The diagnostic criteria for HCM consisted of an increase in the thickness of the left ventricular wall or interventricular septum at end-diastole (>5.5 mm) (Häggström *et al*., 2015) in cats with a weight range of 2.5-6 kg and aged more than 1 year old. Both females and males were included. Data from cats with systemic hypertension (systolic arterial blood pressure >160 mmHg) (Schober and Maerz, 2006), hyperthyroidism (total T4 >4 µg/dL) (Schober and Maerz, 2006) and other systemic diseases was excluded. HCM cats were divided into two groups (the ATE and non-ATE groups). ATE was defined by clinical signs including pain, poikilothermia, pallor, pulselessness and paralysis. Cats in the ATE group were HCM cats that had all the signs of ATE. The non-ATE group was HCM cats that had no clinical signs of ATE.

Statistical Analysis: Study variables included sex, breed, age, weight, heart sounds, vertebral heart score, the presence of spontaneous contrast, echocardiographic findings (i.e., left ventricular dimension at end-diastole and end-systole, interventricular septum thickness at end-diastole and end-systole, left ventricular posterior wall thickness at end-diastole and end-systole, fractional shortening (FS), the ratio of left atrial to aorta dimension (LA/Ao), the ratio of left atrial dimension at end-diastole to left atrial dimension at end-systole, and the environmental temperature on the first day that cats showed clinical signs of ATE. The average environmental temperature of the areas where the cats lived on the first day that cats had signs of ATE was retrieved from www.wunderground.com.

Statistical analysis was performed using a commercial statistical program (SPSS software version 22.0, SPSS Inc., Chicago). Descriptive statistical analysis was used to identify the population characteristics. The normally-distributed data was presented as means ± standard deviation (SD) and the number of cats (%), respectively. The non-normally distributed data was illustrated as median (interquartile). Between-group comparisons of continuous variables were performed by the independent-samples t-test analysis for normally distributed data and the Mann-Whitney U test for nonparametric test. Categorical variables were compared by the Chi-square test. A p-value of $p<0.05$ was considered significant.

The Pearson correlation of variables was tested to prevent multicollinearity. If the correlation coefficient was greater than 0.8, only one variable was selected (Wang *et al*., 2019). The variable with higher biological plausibility was chosen for multivariable analysis. The Chi-square test was used to analyze the relationship between qualitative variables. Only one variable was selected, if a p-value was less than 0.05. Age was introduced into the analysis as a categorical variable based on 50th quartile frequency results from a previous study (Tantisuwat *et al*., 2018) and age for the separation of young and mature cats (AAFP, 2009).

A univariable logistic regression model was used to analyze selected candidate factors. Any associations with a p-value less than 0.05 were then included in the multivariable model. The multivariable model was constructed through both the likelihood method and the Pearson expected value approach (Hosmer *et al*., 1991). The multivariable logistic regression was performed using the backward elimination method. Quadratic terms were employed where there were non-linear trends and centering was used to avoid collinearity. A p-value less than or equal to 0.05 was considered significant.

Results

Data on 70 HCM cats was included in the study. The ATE and non-ATE groups consisted of 26 and 44 HCM cats, respectively. The population characteristics of the 70 cats affected by HCM are summarized in Table 1.

The Chi-square analysis of categorical data showed that age (p=0.009), the presence of abnormal lung sounds (p=0.006) and spontaneous contrast (p=0.029) were related to the presence of ATE in HCM cats. The

comparison between the ATE and non-ATE groups found that HCM cats with ATE had a younger age (p=0.043), decreased left ventricular dimension at end-systole (p=0.026), lower %FS (p=0.003), increased LA/Ao (p=0.004), and had been exposed to a higher average environmental temperature on the first day that they showed clinical signs (p=0.005).

Univariable Logistic Regression Analysis: Table 2 summarises the univariable association between ATE and potential risk factors. Factors associated with ATE (a p-value <0.05) including age, the presence of spontaneous contrast, left ventricular dimension during systole, FS, LA/Ao and the environmental temperature were selected for performing multivariate analysis.

Multivariable Logistic Regression Analysis: Table 3 summarises the multivariable analysis. Age, the presence of spontaneous contrast and environmental temperature were associated with ATE.

Table 1 Population characteristics of the 70 cats affected with hypertrophic cardiomyopathy

Variables	Category	ATE (n=26)	Non-ATE (n=44)	p-value
Sex	Male	16 (61.5)	28 (63.6)	0.861
	Female	10 (38.5)	16 (36.4)	
Breed	DSH	13 (50)	20 (45.5)	0.749
	Persian	9 (34.6)	19 (43.2)	
	Others	4 (15.4)	5 (11.4)	
Age (years)		2 (1.25-7)	8 (3-12)	**0.043**
Weight (Kg)		4.0 ± 1.0	4.1 ± 1.1	0.838
Heart sounds	Abnormal (Murmur / gallop)	14 (53.8)	25 (57)	0.988
	Normal	10 (38.5)	18 (43)	
Radiography				
Vertebral heart score		8.2 ± 1.0	8.6 ± 0.9	0.524
Echocardiography				
Spontaneous contrast	Presence	18 (69)	6 (14)	**<0.0001**
	Absence	8 (31)	38 (86)	
Septum-d (mm)		5.9 ± 1.2	6.3 ± 1.1	0.063
LV chamber-d (mm)		12.4 ± 3.2	12.6 ± 2.8	0.927
LV wall-d (mm)		6.1 ± 1.7	5.9 ± 1.7	0.531
Septum-s (mm)		6.4 ± 1.5	7.9 ± 1.4	0.218
LV chamber-s (mm)		5.2 ± 2.0	6.5 ± 2.5	**0.026**
LV wall-s (mm)		8.9 ± 1.9	8.5 ± 1.9	0.456
FS (%)		47.7 ± 12.0	57.4 ± 11.0	0.003
LA/Ao		2.3 ± 0.6	1.9 ± 0.6	**0.004**
Ao flow velocity (m/s)		1.1 ± 0.7	1.3 ± 1.0	0.246
PA flow velocity (m/s)		0.7 ± 0.2	0.8 ± 0.3	0.066
IVRT (ms)		47.7 ± 10.2	48.7 ± 9.7	0.702
MVE peak (ms)		0.8 ± 0.3	0.8 ± 0.3	0.964
MVA peak (ms)		0.5 ± 0.3	0.6 ± 0.3	0.148
MVE:A peak		2.0 ± 1.0	1.7 ± 1.0	0.176
LAD (mm)		18 ± 6	16 ± 6	0.124
LAS:D		0.9 ± 0.1	0.8 ± 0.2	0.184
Environmental factors				
Environmental temperature (°C)		30.2 ± 1.8	28.6 ± 2.3	**0.005**

Categorical data presented as the number of cats (%) and compared using the Chi-square test.

The normally distributed data is presented as mean ± standard deviation (SD) and compared using the independent t-test. The non-normally distributed data is expressed as median (interquartile) and compared using the Mann-Whitney U test.

ATE= arterial thromboembolism; Septum-d = interventricular septal thickness at diastole; LV chamber d = left ventricular diameter in diastole; LV wall d = left ventricular free wall thickness in diastole; Septum-s = interventricular septal thickness at systole; LV chamber-s = left ventricular diameter in systole; LV wall-s = left ventricular free wall thickness in systole; FS = fractional shortening; LA/Ao = left atrial to aortic ratio; Ao flow velocity = aortic flow velocity; PA flow velocity = pulmonary artery velocity; IVRT = isovolumic relaxation time; MVE peak = mitral valve peak velocity of early diastolic transmitral flow wave (E wave); MVA peak = mitral valve peak velocity of early diastolic transmitral flow wave (A wave); MVE : A peak = mitral valve peak velocity ratio between peak E and peak A; LAD = left atrium at end-diastole; LAS :D = left atrium systole to diastole ratio; kg = kilogram.

Table 2 The univariable logistic regression analysis for evaluating the association between potential risk factors of arterial thromboembolism and hypertrophic cardiomyopathy in cats

Variables	Odds ratio (95%CI)	p-value
Age (years)		
> 7	1.000	-
≤ 7	4.370 (1.379-13.844)	**0.012**
Weight (Kg)	0.950 (0.587-1.537)	0.835
Heart sounds		
Normal	1.000	-
Abnormal (Murmur/gallop)	1.008 (0.360-2.732)	0.988
Radiography		
Vertebral heart score	1.147 (0.753-1.745)	0.523
Echocardiography		
Spontaneous contrast		
Absence	1.000	-
Presence	14.250 (4.301-47.212)	**<0.0001**
LV septum-d	0.712 (0.454-1.116)	0.138
LV chamber-d	0.985 (0.835-1.163)	0.860
LV wall-d	1.058 (0.799-1.401)	0.694
LV septum-s	0.806 (0.572-1.135)	0.218
LV chamber-s	1.290 (1.017-1.637)	**0.035**
LV wall-s	0.906 (0.699-1.173)	0.452
FS (%)	0.926 (0.881-0.974)	**0.003**
LA/Ao	3.349 (1.410-7.954)	**0.006**
Ao flow velocity	0.692 (0.364-1.313)	0.260
PA flow velocity	0.097 (0.009-1.042)	0.054
IVRT	0.989 (0.940-1.040)	0.661
MVE peak	0.691 (0.140-3.406)	0.649
MVA peak	0.314 (0.040-2.461)	0.270
MVE:A peak	1.357 (0.828-2.225).	0.226
LAD	1.984 (0.801-4.914)	0.139
LAS:D	12.065 (0.250-581.389)	0.208
Environmental factors		
Environmental temperature	1.692 (1.176-2.437)	**0.005**

Septum-d = interventricular septal thickness at diastole; LV chamber-d = left ventricular diameter in diastole; LV wall-d = left ventricular free wall thickness in diastole; Septum-s = interventricular septal thickness at systole; LV chamber-s = left ventricular diameter in systole; LV wall-s = left ventricular free wall thickness in systole; FS = fractional shortening; LA/Ao = left atrial to aortic ratio; Ao flow velocity = aortic flow velocity; PA flow velocity = pulmonary artery velocity ; IVRT = isovolumic relaxation time; MVE peak = mitral valve peak velocity of early diastolic transmitral flow wave (E wave) ; MVA peak = mitral valve peak velocity of early diastolic transmitral flow wave (A wave) ; MVE : A peak = mitral valve peak velocity ratio between peak E and peak A ; LAD = left atrium at end-diastole; LAS :D = left atrium systole to diastole ratio; kg = kilogram.

Table 3 The multivariable logistic regression analysis for evaluating the association between potential risk factors of arterial thromboembolism and hypertrophic cardiomyopathy in cats

Variables	Odds ratio (95%CI)	p-value
Age (years)		
> 7	1.000	-
≤ 7	7.503 (1.310-42.969)	**0.024**
Echocardiography		
Spontaneous contrast		
Absence	1.000	-
Presence	30.855 (4.298-221.487)	**0.001**
LV chamber-s	1.157 (0.747-1.792)	0.514
FS (%)	0.935 (0.867-1.008)	0.079
LA/Ao	0.375 (0.091-1.545)	0.175
Environmental temperature	1.616 (1.080-2.417)	**0.019**

LV chamber-s = left ventricular diameter in systole; FS = fractional shortening; LA/Ao = left atrial to aortic ratio

Discussion

This study found that age, the presence of spontaneous contrast and environmental temperature were associated with ATE in HCM cats. This study shows that HCM cats presenting with factors including age equal to or less than 7 years and the presence of spontaneous contrast in the left atrium assessed by echocardiography had a greater chance to develop ATE. In addition, every 1 °C increase in the environmental temperature was associated with 1.6 times of developing ATE in HCM cats.

The present study found that HCM cats of an age less than 7 years old tended to have ATE approximately 7.5 times more than HCM cats with an age greater than 7 years old. A previous study found that the mean age of cats with ATE from all causes of both HCM and non-HCM was twelve years old (range 1-21 years) (Borgeat *et al*., 2014). The median age of cats in the ATE group in the present study was 2 years, which was younger than that in the non-ATE group. The majority of cats in the ATE group (19/24; 73.1%) had an age equal to or less than 7 years. In addition, the number of HCM cats that had an age equal to or less than 7 years (n=39) was higher than those that had an age more than 7 years (n=23). These findings might reflect the result of the logistic regression. However, the Fisher's exact test showed the independence of age and ATE (p=0.089). HCM cats of a younger age may have more concurrent abnormalities that may induce the development of ATE. A previous study found that cats with systolic anterior motion (SAM) of the mitral valve were younger than cats without SAM (Payne *et al*., 2015). Interestingly, HCM cats of an age less than 7 years old had increased LA/Ao (2.18 ± 0.56) compared to those in HCM cats aged more than 7 years old (1.86 ± 0.69) (p=0.042). Most cats affected with ATE have atrial enlargement (Smith *et al*., 2003). An enlargement of the left atrium might be one of the factors inducing ATE in younger cats in this study.

This study showed that the presence of spontaneous contrast in HCM cats was significantly associated with an occurrence of ATE. Spontaneous contrast caused by ultrasonic backscatter from red blood cell aggregates or thrombus is commonly formed under low flow and low shear conditions (or blood stasis) in the left atrium (Schober *et al*., 2006). The result of this study suggests a protocol for the management of cats with HCM by monitoring the presence of spontaneous contrast within the left atrium. Therefore, whenever the spontaneous contrast is found, anti-platelet agents should be supplemented to the cat to prevent ATE.

The result of the present study revealed that the higher temperature cats were exposed to, the more the opportunity to develop ATE was considered (OR: 1.616). At present, the explanation of the mechanism between ambient temperature and the risk of ATE has not yet been reported. A study in humans demonstrated that platelet counts, platelet activity and thrombin-antithrombin (TAT) coagulation complexes increased in response to hyperthermic environmental conditions resulting in increasing the risk of clot formation (Kupchak *et al*., 2017). Whether an increase in platelet function and coagulation activity occurs in cats exposed to a high-temperature environment needs further investigation to be confirmed.

The limitation of this study resulted from the retrospective design. Missing data may affect the statistical analysis. Another limitation was the unbalanced number of the ATE and non-ATE groups that may also affect the statistical analysis.

In conclusion, this study demonstrates that HCM cats with an age equal to or less than 7 years old and the presence of spontaneous contrast in the left atrium are associated with the development of arterial thromboembolism. The increase in environmental temperature in Thailand is also associated with ATE in HCM cats. These findings could support veterinarians in evaluating the risk of ATE and may be helpful to prevent or monitor the occurrence of ATE in HCM cats.

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