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Hypercoagulability in Cats with Cardiomyopathy

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Background: Arterial thromboembolism (ATE) is a common complication of feline cardiomyopathy; however, the pathogenesis of ATE is unknown.

Hypothesis: Systemic activation of the coagulation cascade (hypercoagulability) and endothelial injury promote ATE in cardiomyopathic cats.

Animals: Healthy cats (n = 30) and 3 groups of cardiomyopathic cats: Group (1) left atrial enlargement only (LAE [n = 11]), ie, left atrial to aortic ratio >1.4; Group (2) LAE with spontaneous echocardiographic contrast, atrial thrombi or both (SEC-T [n = 16]); and Group (3) acute ATE with LAE (n = 16).

Methods: Hypercoagulability was defined by 2 or more laboratory abnormalities reflecting coagulation factor excess (high fibrinogen concentration or Factor VIII coagulant activity), inhibitor deficiency (low antithrombin activity), or thrombin generation (high thrombin-antithrombin complex [TAT] and D-dimer concentrations). High von Willebrand factor antigen concentration (vWF : Ag) was considered a marker of endothelial injury. Data were analyzed using nonparametric statistics.

Results: The 3 groups of cats with cardiac disease had higher median fibrinogen concentrations than did the healthy cats. Criteria of hypercoagulability were found exclusively in cats with SEC-T (50%) and ATE (56%). Hypercoagulability was not associated with left atrial size or congestive heart failure (CHF). ATE cats had significantly higher median vWF : Ag concentration than did the other groups.

Conclusinos and Clinical Importance: Systemic hypercoagulability is evident in many cardiomyopathic cats, often without concurrent CHF or overt ATE. Hypercoagulabilty may represent a risk factor for ATE. High vWF : Ag in ATE cats was attributed to downstream endothelial injury from the occlusive thrombus.

Key words: Aortic thromboembolism; D-dimer; Endothelial injury; Hemostasis; Spontaneous echocardiographic contrast; Thrombin-antithrombin complexes.

Arterial thromboembolism (ATE) is a common, frequently fatal, sequela of cardiomyopathy in cats.[1–3] Thromboemboli (TE) typically lodge in the aortic bifurcation, partially or completely restricting blood flow to the hindlimbs and inducing signs of severe pain, cold extremities, and caudal paresis. Thrombi also can occur in vessels supplying the mesentery, kidneys, brain, and lungs.[2,4,5] Many affected cats are euthanized, with reported fatality rates ranging from 61 to 100%; survivors of the initial episode frequently suffer rethrombosis.[2,3]

TE are believed to originate from fragmentation or dislodging of left atrial or left atrial appendage (LAA) thrombi. Formation of such thrombi is classically attributed to Virchow's Triad (endothelial injury, blood flow abnormalities, and hypercoagulability), all of which could contribute to TE in cardiomyopathic cats.[6] Patches of endomyocardial necrosis have been identified in the hearts of cats with cardiac disease on necropsy examination.[5] This could initiate thrombus formation by exposure of subendothelial tissue factor.[7] Decreased blood flow or stasis could promote the development of intracardiac thrombi by impaired clearance of activated coagulation factors and enhancement of platelet-endothelial interactions.[8] Decreased LAA flow and spontaneous echocardiographic contrast (SEC) have been documented in cardiomyopathic cats.[2,9] SEC is a "smoke-like" swirling blood flow pattern caused by erythrocyte aggregates in the left atrium and is thought to reflect localized blood stasis.[9–11] Decreased LAA flow is associated with SEC and left atrial enlargement (LAE) in cardiomyopathic cats[9] and humans.[10,11] Thus, SEC and, to a lesser extent, LAE are considered risk factors for atrial thrombosis and peripheral TE events in affected patients.[1–3,9–11]

Hypercoagulability results from a systemic imbalance of coagulation factors and their inhibitors that favors pathological thrombin generation and, ultimately, thrombus formation. Such imbalance can be caused by excess coagulation factors (eg, fibrinogen and Factor VIII [FVIII]) and deficiency of inhibitors (eg, antithrombin [AT]) and is characterized by increased concentrations of products formed during thrombin generation (eg, prothrombin fragment 1 + 2) or as a consequence of thrombin activity (eg, fibrinopeptide A, thrombin-antithrombin complex [TAT] and D-dimer).[6,12,13] A systemic hypercoagulable state exists in many cardiomyopathic human patients, which might contribute to peripheral TE.[14–16] Two recent studies of feline cardiomyopathy also suggest that some cats (even if subclinical) are hypercoagulable, based on increased concentrations of TAT or D-dimer.[17,18]

We hypothesized that cardiomyopathic cats develop ATE because they are in a systemic hypercoagulable state

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or have underlying endothelial (arterial or endocardial) injury. For this study, we defined hypercoagulability as the presence of two or more of the following hemostatic abnormalities: hyperfibrinogenemia, increased FVIII coagulant activity (FVIII : C) (both of which are risk factors for TE in humans),[19–21] AT deficiency (also a risk factor for TE in humans and animals),[6,22] and markers of systemic or dysregulated thrombin formation (ie, high TAT or D-dimer concentration).[12,13,17] Endothelial injury was identified by high plasma von Willebrand factor antigen (vWF : Ag) concentration, an endothelial-specific marker.[20] von Willebrand factor is expressed in the endocardium of humans with cardiac disease, but not in healthy humans,[23] and is potentially also a marker of endocardial injury. We compared coagulation profiles among healthy cats, 2 groups of cardiomyopathic cats with echocardiographic "risk factors" for thrombosis—LAE only (Group LAE) and LAE with SEC, intracardiac thrombi or both (Group SEC-T), and cats with LAE and suffering from acute cardiogenic ATE (Group ATE).

Materials and Methods

Animals

Blood samples were prospectively obtained from healthy cats and cats with cardiac disease. Clinically healthy cats (determined by history and physical examination) were owned by veterinary students, faculty, or staff at the College of Veterinary Medicine, Cornell University. Client-owned cats with cardiac disease were admitted to the Cornell University Hospital for Animals or Foster Hospital for Small Animals at Tufts Cummings School of Veterinary Medicine. Cats with cardiac disease were separated into 3 groups, based on clinical signs, echocardiographic results, or both:

(1) LAE: These cats had LAE only, defined as a left atrial : aortic ratio (LA : Ao) > 1.4 on 2-dimensional ultrasonography[24];
(2) SEC-T: These cats had LAE and SEC with or without atrial thrombi; and
(3) ATE: These cats presented with clinical signs of acute (< 24 hours) ATE and had LAE.[1,2]

Medical Records were reviewed to compile the following information: signalment, history of prior cardiac disease, drug therapy, underlying disease, congestive heart failure (CHF; based on clinical signs of dyspnea or pleural effusion or pulmonary edema on radiographic examination), and echocardiographic findings, including final diagnosis (hypertrophic, dilated, or unclassified cardiomyopathy), LA : Ao, and presence of SEC or atrial thrombi. Client consent was obtained before sample collection and the study was approved by the Institutional Animal Care and Use Committee at each institution.

Sample Collection

Blood was collected on the day of admission by jugular venipuncture into potassium EDTA and 3.2% citrate anticoagulant tubes for CBC and coagulation profiles, respectively. Citrate blood samples were centrifuged at $3{,}000 \times g$ for 10 minutes and platelet poor plasma was frozen at or below $-20\,^{\circ}C$ until batch analysis. Samples from Tufts University were shipped monthly (on dry ice) to Cornell University for analysis.

Coagulation Assays

All assays were performed on citrate plasma samples, thawed at $37\,^{\circ}C$, and chilled on ice until analysis. Cats were excluded if their samples contained gross clot fragments or if there was a history of difficult venipuncture, underlying disease (eg, neoplasia, infections),[25] or treatment (eg, urokinase, heparin)[26,27] that could independently affect test results. Assays included tests of hypercoagulability (fibrinogen, FVIII : C, AT, TAT, D-dimer) and endothelial injury (vWF : Ag). Fibrinogen was measured as Clauss fibrinogen[28] using a feline plasma calibration standard (fibrinogen content determined by gravimetric assay of clottable fibrinogen).[29] FVIII : C was measured in a modified 1-stage activated partial thromboplastin time (aPTT), using a canine FVIII-deficient substrate plasma, as described.[30] Antithrombin activity was measured based on its inhibition of thrombin with a chromogenic substrate kit.[a] Plasma vWF : Ag was measured by ELISA.[31] FVIII : C, AT, and vWF : Ag results were reported as a percentage of pooled feline plasma (prepared from 20 healthy cats). Reference intervals for these tests had been previously derived from minimum and maximum values of 30 healthy cats. D-dimer concentration was measured semiquantitatively in serially diluted samples by latex-agglutination[b] as described.[32] TAT concentrations were determined with an antihuman TAT ELISA,[c] which cross-reacts with several animal species[33] and has been used to document hypercoagulability in asymptomatic cardiomyopathic cats.[17] Results (ng/mL) were derived from a serially diluted human TAT standard curve. Reference intervals for TAT were established using the minimum and maximum results of the 30 healthy cats in this study (0–5.0 ng/mL), after removal of 1 outlier (9.5 ng/mL).

Coagulation screening tests, aPTT and prothrombin time (PT), also were performed, with an automated coagulation instrument[d] and commercial reagents.[e,f] Platelet counts were obtained from EDTA-anticoagulated blood with automated hematology analyzers.[g,h]

Statistical Analysis

Semiquantitative D-dimer results were converted to an ordinal scale (ascending order corresponding to increasing concentration) for analysis. Because data were non-Gaussian, differences between groups for each variable were compared with a Kruskal-Wallis analysis of variance, followed, where appropriate, by Bonferroni-adjusted Wilcoxon's rank sum tests (for pairwise comparisons).[i] Proportions were compared with Fisher's exact test.[i] $P < .05$ was considered significant. To preserve overall experimentwide error rate, we set α (2-tailed) for between-group comparisons to 0.008 for 6 tests and 0.006 for 9 tests.

Results

Patient Demographics

Samples from 66 cardiomyopathic cats were obtained, of which 23 were excluded (7 LAE, 8 SEC-T, 8 ATE) for these reasons: difficult venipuncture or clot fragments in the sample (9), urokinase (2) or low molecular-weight heparin therapy (8), and neoplasia (4). The remaining 43 cats enrolled in the study were primarily neutered male (79%, 34/43), domestic shorthair (65%, 28/43), or longhair (26%, 11/43) and middle-aged (median, 9 years; range, 2–15 years). Based on predefined clinical and echocardiographic criteria, 11 cats were classified as LAE, 16 cats were classified as SEC-T, and 16 cats as ATE.

Complete echocardiographic assessment was not performed in 3 ATE cats that were euthanized on admission. Hypertrophic or unclassified cardiomyopathy was the most common diagnosis (95%, 39/41). Atrial thrombi were detected in 3/16 SEC-T and 3/13 ATE cats. SEC was observed in 6/13 (46%) ATE cats. All cardiomyopathic cats had enlarged left atria (61% had severe enlargement [LA : Ao > 2.0]). Left atrial size did not differ among the 3 groups of cardiomyopathic cats ($P = .071$) (Fig 1).

Of the LAE cats, 46% (5/11) presented with CHF, whereas the remainder presented for reexamination of previously diagnosed cardiomyopathy (36%, 4/11) or cardiac murmur evaluation (18%, 2/11). One LAE cat was hyperthyroid. Most SEC-T cats (88%, 14/16) presented with CHF, of which 75% (12/14) had no prior diagnosis of cardiac disease. Two SEC-T cats (12%) presented for reexamination of previously diagnosed cardiomyopathy, one of which was coughing. All ATE cats presented with clinical signs of thromboembolism. Most (94%, 15/16) had hindlimb paralysis; 1 (6%) cat had fore- and hindlimb paralysis. Four cats (25%, 4/16) were in CHF. There was no prior history of cardiac disease in 88% (14/16) of ATE cats.

Upon study entry, 2 cats (1 LAE, 1 SEC-T) were being treated with aspirin (80 mg PO q48h), 1 cat in each group with clopidogrel (18.75 mg PO q12h), and 15 cats (6 LAE, 8 SEC-T, 1 ATE) with various combinations of ACE-inhibitors, diuretics, calcium channel blockers, and β-blockers.

Tests of Hypercoagulability: Fibrinogen, FVIII : C, AT, TAT, and D-Dimer

Median fibrinogen concentration was higher for the 3 groups of cardiomyopathic cats than the group of healthy cats, although all median values were within reference intervals (Fig 2). Hyperfibrinogenemia occurred in a significantly greater proportion of ATE (44%, 7/16) than healthy cats (3%, 1/30) ($P = .003$). ATE cats had significantly higher median FVIII : C than LAE cats ($P = .007$) (Fig 3). Median AT, TAT, and D-dimer concentrations did not differ among groups ($P > .008$) (Figs 4–6); however, more ATE and SEC-T cats (50%, 8/16) had high TAT concentrations compared with healthy cats (3%, 1/30) ($P = .007$).

Cats in each group then were subcategorized by the number of abnormal test results of hypercoagulability; those with ≥2 abnormal results were classified as hypercoagulable. Because no cats had low AT, this test did not contribute to the classification. Significantly more ATE (56%, 9/16) or SEC-T (50%, 8/16) cats were hypercoagulable compared with LAE (0/11, 0%) cats (ATE: $P = .005$; SEC-T: $P = .012$). Similar numbers of ATE and SEC-T cats were hypercoagulable ($P = 1.000$). None of the healthy cats were hypercoagulable (Figs 2–7).

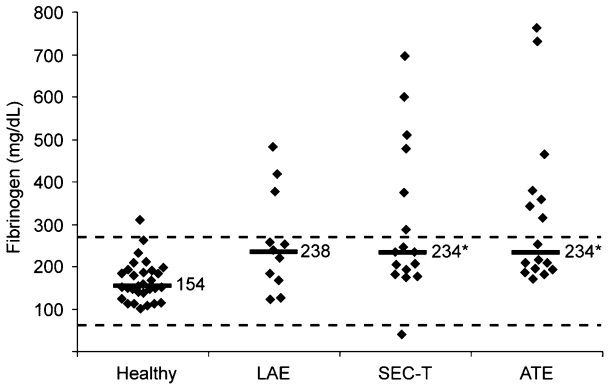

Fig 2. Dotplot of fibrinogen concentration in healthy cats and 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values; dotted lines encompass the reference interval. *Median significantly different from healthy cats ($P < .008$).

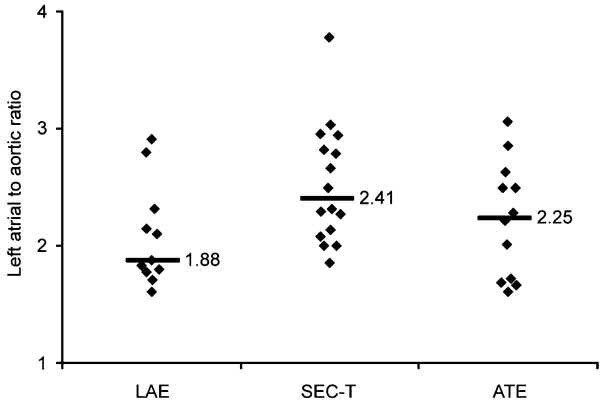

Fig 1. Dotplot of left atrial to aortic ratios in 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values. Median values were not significantly different ($P = .071$).

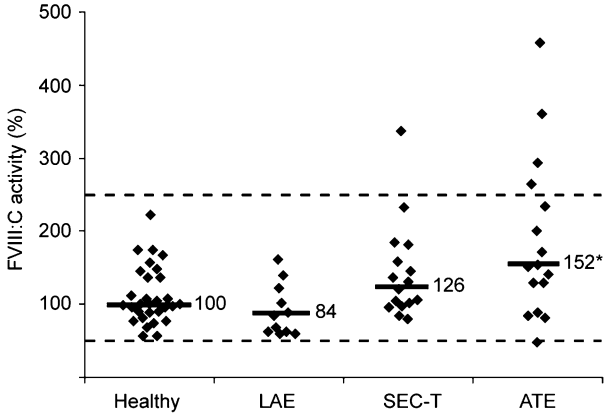

Fig 3. Dotplot of FVIII : C activity in healthy cats and 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values; dotted lines encompass the reference interval. *Median significantly different from LAE cats ($P < .008$).

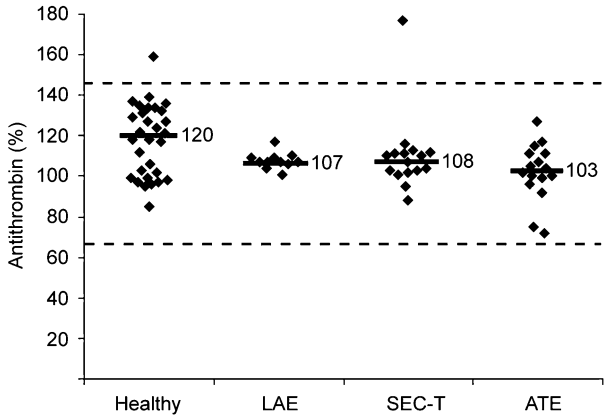

Fig 4. Dotplot of AT activity in healthy cats and 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values; dotted lines encompass the reference interval. Medians did not differ significantly ($P = .049$).

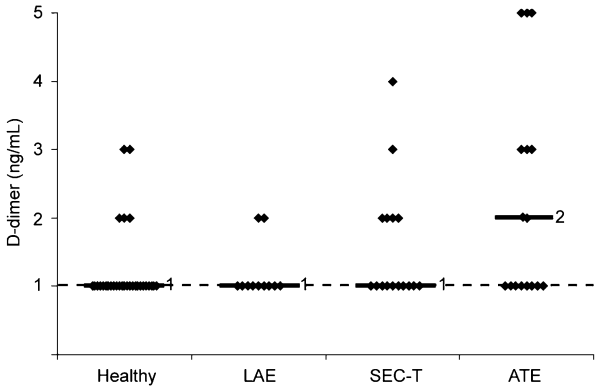

Fig 6. Dotplot of D-dimer concentration in healthy cats and 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values; the dotted line represents the upper limit of the reference interval. Medians did not differ significantly ($P = .035$).

von Willebrand Factor Antigen: Test of Endothelial Injury

ATE cats had significantly higher median vWF : Ag than any other cat group ($P < .008$) (Fig 7). Furthermore, only ATE cats (50%, 8/16) had high vWF : Ag.

Examination of Risk Factors

Because the degree of LAE is considered to be a risk factor for ATE in cardiomyopathic cats by some investigators, we compared LA : Ao between hypercoagulable and nonhypercoagulable cardiomyopathic cats to assess any influence of atrial size on hemostatic balance. There was no significant difference in left atrial size between hypercoagulable (median LA : Ao, 2.29, range, 1.66–2.94) versus nonhypercoagulable (median LA : Ao, 2.14, range, 1.61–3.8) cats ($P = .644$). Hypercoagulable cats were no more likely to have severely enlarged left atria (LA : Ao > 2.0) (87%; 13/15) than nonhypercoagulable cats (58%; 14/24) ($P = .126$). Median values for all hemostatic tests were similar in cats with or without severely enlarged left atria (Table 1).

To determine if cats in CHF were more likely to be hypercoagulable, as suggested previously,[j] we compared the proportions of hypercoagulable and nonhypercoagulable cats with cardiac disease in CHF and median coagulation results between cardiomyopathic cats with or without CHF. Similar proportions of hypercoagulable and nonhypercoagulable cats had CHF (65 versus 46%,

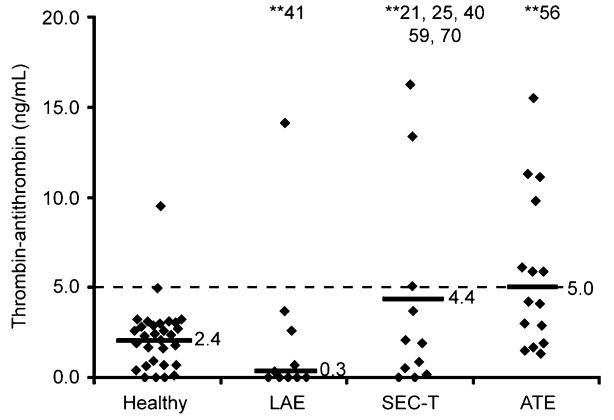

Fig 5. Dotplot of thrombin-antithrombin complex (TAT) concentration in healthy cats and 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values; the dotted line represents the upper limit of the reference interval. The *y*-axis is truncated (20 ng/mL); higher values are represented by the asterisks. Medians did not differ significantly ($P = .010$).

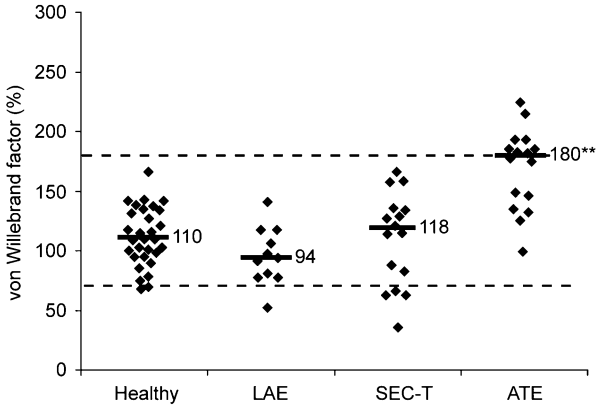

Fig 7. Dotplot of von Willebrand factor antigen (vWF : Ag) concentration in healthy cats and 3 groups of cardiomyopathic cats: LAE, left atrial enlargement; SEC-T, spontaneous echocardiographic contrast, atrial thrombi, or both; ATE, arterial thromboembolism. Bars, median values; dotted lines encompass the reference interval. **Median significantly different from all other groups of cats ($P < .008$).

$P = .380$). Coagulation test results did not differ between cats with or without CHF (Table 1).

Discussion

Our study provides evidence of hypercoagulability and endothelial injury in at least 50% of cats with overt ATE. We also found evidence of hypercoagulability in 50% of cardiomyopathic cats with SEC, but not in cats with LAE alone. Hypercoagulability was not associated with CHF, in contrast to a previous report in which D-dimer was increased only in cats with CHF.[j] Unlike that report, the classification of hypercoagulability was based on an increase in at least 2 of 4 parameters (fibrinogen, FVIII : C, TAT, D-dimer), because no single abnormal hemostatic test is considered diagnostic of hypercoagulability. We reasoned that a concomitant increase in procoagulant factors and markers of thrombin generation provided stronger evidence of hemostatic imbalance favoring fibrin deposition, as suggested previously.[17]

Hypercoagulable cats were no more likely to have severe LAE (LA : Ao > 2.0) than nonhypercoagulable cats. Although 45% of LAE cats had LA : Ao > 2.0, none were hypercoagulable. This finding suggests that LAE is not sufficient for development of a hypercoagulable state in cardiomyopathy and additional factors are required. These factors are likely to include decreased atrial function, blood stasis, enhanced erythrocyte aggregability, and hyperviscosity.[9–11,15,34] Thrombi in cats with ATE, like thrombi in deep vein thrombosis (DVT) in humans, consist of aggregates of erythrocytes and fibrin (red thrombi), suggesting that decreased flow or stasis or both (considered necessary but not sufficient for DVT) also contributes to the pathogenesis of ATE in cats.[5,10,34] Although some ATE cats may be hypercoagulable as a consequence of metabolic derangements secondary to occlusive thrombi (eg, metabolic acidosis, tissue hypoxia), SEC-T cats were similarly hypercoagulable in the absence of systemic thromboembolism. This observation suggests that hypercoagulability is a contributing factor to, rather than consequence of, ATE.

Systemic hypercoagulability is unlikely to be the primary force initiating thrombus formation, because approximately half of the SEC-T and ATE cats did not fulfill our criteria of hypercoagulability. Procoagulant imbalance may be restricted to the atrium of these cats, as reported for human patients with mitral stenosis (where there is left atrial hypercoagulability without spillover into the systemic circulation)[35] or other factors (eg, platelet activation) may contribute to ATE in cardiomyopathic cats.[36] Alternatively, our laboratory criteria for hypercoagulability may be too stringent or the tests we employed may be insensitive to this hemostatic state.

The most direct indicator of hypercoagulability in this study was high TAT,[12,13,17,33,37] which forms when free thrombin is neutralized by AT (in a 1 : 1 molar ratio). In the absence of sustained thrombin generation, TAT is rapidly cleared from the circulation. Half of the ATE and SEC-T cats had high TAT, compatible with excess local or systemic thrombin generation and likely a procoagulant state. However, TAT is currently unsuitable as a clinical assay because of the need for batching samples (ie, unstable reagents, ELISA methodology) and expense.

D-dimer concentration was high in 50% of ATE cats, which contrasts to a preliminary report in which no ATE cats had high D-dimer.[j] Furthermore, unlike previous

Table 1. Median (range) hemostatic test results in cats with cardiac disease categorized by severity of left atrial enlargement (severe = LA : Ao > 2.0) and by the presence or absence of congestive heart failure (CHF).

	LA : Ao > 2.0		Congestive Heart Failure		Clinically Healthy
Test	No (n = 11)	Yes (n = 28)	No (n = 20)	Yes (n = 23)	(n = 30)
Fibrinogen (mg/dL)	216 (123–483)	254 (38–760)	213 (123–760)	247 (38–697)	154 (101–311)
FVIII : C (%)	151 (63–294)	113 (59–458)	146 (48–458)	106 (59–337)	120 (85–159)
AT activity (%)	96 (92–112)	107 (75–177)	104 (75–117)	107 (72–177)	100 (56–223)
TAT (ng/mL)	0.7 (0–59.2)	3.9 (0–70.3)	3.0 (0–56.2)	3.7 (0–70.3)	2.0 (0.0–9.5)
D-dimer (ng/mL)	<250 (<250 to 1000–2000)	<250 (<250 to >2000)	<250 (<250 to >2000)	<250 (<250 to >2000)	<250 (< 250 to 500–1000)
vWF : Ag (%)	117 (66–182)	129 (36–224)	132 (36–224)	127 (52–193)	110 (68–166)
Platelet count ($\times 10^9$/L)	255 (135–350)	350 (83–550)	350 (135–550)	286 (83–350)	274 (140–499)
aPTT (seconds)	16 (14–24)	16 (11–29)	16 (12–29)	17 (11–34)	15 (12–18)
PT (seconds)	20 (16–27)	20 (15–28)	20 (16–28)	20 (15–34)	18 (16–24)

Results for clinically healthy cats are provided as an internal reference interval.

Medians (comparing yes/no within each separate category, i.e., LA : Ao or CHF) were not significantly different ($P > .006$).

aPTT, activated partial thromboplastin time; AT, antithrombin; FVIII, factor VIII; PT, prothrombin time; TAT, thrombin-antithrombin complex; vWF : Ag, von Willebrand factor antigen concentration.

reports,[k,18] D-dimer was increased in some healthy cats. These differences may be partly explained by the use of different reagents and assay methods.[32,38] Unlike TAT, D-dimer is an indirect indicator of thrombin generation. It is a specific degradation product of cross-linked fibrin produced by thrombin-mediated cleavage of fibrinogen followed by plasmin-mediated lysis of the resultant fibrin clot.[38] D-dimer appears to be a sensitive test for thrombosis in dogs,[38] and thus it was unexpected that relatively few ATE cats had high D-dimer. Possible explanations for this observation are that cats may rapidly clear D-dimer or a localized thrombus (in the aorta) may not result in high systemic D-dimer concentrations,[13] particularly with concurrent diminished blood flow beyond the occlusion site.

Hyperfibrinogenemia occurred in 37% of cardiomyopathic cats, and median fibrinogen concentrations were higher in all 3 groups of cardiomyopathic cats as compared with healthy cats. This finding suggests that cardiac disease stimulates fibrinogen synthesis in an acute phase response, perhaps related to underlying inflammation[5] or rheologic abnormalities. Hyperfibrinogenemia is an independent risk factor for arterial[19] and venous[39] thrombosis in humans and may contribute to hypercoagulability in dogs with hyperadrenocorticism[37] and immune-mediated hemolytic anemia.[40] Of particular relevance to ATE in cats, rouleaux formation and blood viscosity are enhanced by fibrinogen,[41] and hyperfibrinogenemia has been associated with increased blood viscosity and SEC in cardiomyopathic humans.[11,15]

No cats in this or previous studies[17,18] were AT deficient. Thus, a lack of AT does not appear to be involved in the pathogenesis of ATE. We also found a marked increase in FVIII : C in several ATE cats. This increase could be attributable to an acute phase response or endothelial injury, and might conceivably contribute to the hypercoagulable state in these cats.[21,42]

In this study, we hypothesized that endothelial injury (involving the heart, arteries, or both) contributes to the development of ATE in cats and used vWF : Ag as a marker for this injury. Only cats with acute ATE had high vWF : Ag, despite SEC-T cats being similarly hypercoagulable and having similar degrees of LAE and incidence of left atrial thrombi. The simplest interpretation of this result is that vWF : Ag is increased as a consequence of downstream endothelial injury from the occlusive thrombus. However, we cannot exclude the possibility that prethromboembolic endothelial or endocardial injury occurs in ATE cats, resulting in increased vWF : Ag before the ATE event.

Limitations of our study include relatively low numbers of cats in each disease group and conservative statistical testing (which decreases power and increases risk of a type II error). Cats were not excluded because of CHF medication; however, none of the drugs used are known to impact the hemostatic parameters we examined. This study was designed to identify putative risk factors for ATE rather than providing a basis for designing treatment regimens. Finally, our screening strategy may have missed SEC or atrial thrombi in some cats[1,34] and some healthy cats may have had occult cardiomyopathy.[l]

In conclusion, we found evidence of hypercoagulability in approximately half of the cats with more severe forms of cardiomyopathy (ie, those with SEC or ATE). Our cross-sectional study design cannot define causal factors for ATE, but our data are compatible with results of trials in humans that link cardiac syndromes such as mitral stenosis,[35] nonvalvular atrial flutter,[43] and nonrheumatic atrial fibrillation[44,45] with systemic hypercoagulability. Furthermore, human patients with left atrial and aortic SEC reportedly have a higher incidence of TE, attributable to hypercoagulability.[43]

Prospective studies are needed to evaluate whether the echocardiographic findings of SEC or left atrial flow dynamics and laboratory evidence of hypercoagulability are indeed predictive of future TE or are useful for guiding prophylactic therapies. As in previous studies, our data suggest that the pathogenesis of ATE is multifactorial and therefore treatment and prevention of this syndrome might involve drug combinations modulating hemostasis (ie, platelets and coagulation factors) and inflammatory pathways.

Footnotes

[a] STAchrom ATIII, Diagnostica Stago, Parsippany, NJ
[b] Biopool D-dimer Latex, Trinity Diagnostics, Wicklow, Ireland
[c] Enzygnost TAT micro, Dade-Behring, Deerfield, IL
[d] STACompact, Diagnostica Stago
[e] Dade Actin FS, Dade-Behring
[f] Thromboplastin LI, Helena Laboratories, Beaumont, TX
[g] ADVIA 120, Bayer, Tarrytown, NJ (Cornell University)
[h] Technicon H-1, Bayer (Tufts University)
[i] Analyse-it for Excel, Analyse-it Software Ltd, Leeds, UK
[j] Hoolihan C. Plasma D-dimer concentrations in cats with left atrial enlargement. J Vet Intern Med 2006;20:775–776 (abstract)
[k] Fox LE, Portillo E, Crum H, et al. D-dimer concentrations in healthy and clinically ill cats. J Vet Intern Med 2005;19:447 (abstract)
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