Multicenter evaluation of signalment and comorbid conditions associated with aortic thrombotic disease in dogs

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OBJECTIVE
To assess signalment and concurrent disease processes in dogs with aortic thrombotic disease (ATD).

DESIGN
Retrospective case-control study.

ANIMALS
Dogs examined at North American veterinary teaching hospitals from 1985 through 2011 with medical records submitted to the Veterinary Medical Database.

PROCEDURES
Medical records were reviewed to identify dogs with a diagnosis of ATD (case dogs). Five control dogs without a diagnosis of ATD were then identified for every case dog. Data were collected regarding dog age, sex, breed, body weight, and concurrent disease processes.

RESULTS
ATD was diagnosed in 291 of the 984,973 (0.03%) dogs included in the database. The odds of a dog having ATD did not differ significantly by sex, age, or body weight. Compared with mixed-breed dogs, Shetland Sheepdogs had a significantly higher odds of ATD (OR, 2.59). Protein-losing nephropathy (64/291 [22%]) was the most commonly recorded concurrent disease in dogs with ATD.

CONCLUSIONS AND CLINICAL RELEVANCE
Dogs with ATD did not differ significantly from dogs without ATD in most signalment variables. Contrary to previous reports, cardiac disease was not a common concurrent diagnosis in dogs with ATD. (J Am Vet Med Assoc 2017;251:438–442)

Aortic thrombotic disease is a primary disease or secondary complication of a systemic disease state with devastating effects in dogs and cats.1-13 Cats with aortic thromboembolism often have severe concurrent cardiac disease associated with left atrial enlargement. Although most cats with aortic thromboembolism have cardiac disease, some conditions such as neoplasia or endocrinopathies can predispose cats to developing aortic thromboembolism.1

The reported prevalence of aortic thromboembolism ranges from 0.26% in cats evaluated in general practice14 to between 12% and 21% in cats with hypertrophic cardiomyopathy evaluated at tertiary centers.15 Although a substantial amount of information is available about cats with this disease process, ATD is not well characterized in dogs. In dogs, ATD is rare and thus previous reports6-13 involve small numbers of cases. The small number of dogs represented in these studies makes clinical characterization of ATD difficult. In addition, some of these reports provide conflicting information on signalment and common concurrent diseases.

Diagnosis of ATD can be difficult in dogs because of the nonspecific and insidious onset of clinical signs. Although clinical signs of an acute nature can exist, chronic ambulatory dysfunction of the pelvic limbs is a clinical sign often associated with ATD in dogs.11 Many of the comorbid diseases identified in dogs with ATD have important systemic consequences if left unaddressed, such as poor energy level, hypertension, hypercoagulability, platelet dysfunction, increased susceptibility to infections, and renal tubular and glomerular damage.6-10 Early diagnosis of ATD can have a beneficial effect on a patient’s quality of life if successful treatment is implemented. The purpose of the study reported here was to use data extracted from a large North American medical record database to characterize ATD in dogs.

Materials and Methods

Dogs and data collection
Data used in the study were obtained from the VMDB, which consists of an archive of medical re-
A case-control study design was used. Medical records were electronically reviewed to identify dogs for which a diagnosis of ATD had been recorded (case group). Multiple coding options for ATD were available when submitting information to the VMDB. Dogs were considered to have ATD if they had any of the following coded diagnoses: aortic thromboembolism, aortic thrombus, thrombus aorta, occlusion thrombus aorta, thromboembolism aorta, thrombus abdomen aorta, or thrombus abdomen aorta due to infection. Control dogs were randomly selected (5/ case dog) from among dogs admitted to the same teaching hospitals on the same dates as the case dogs. No exclusion criteria were applied to potential control dogs. Each dog was included only once.

Data were extracted from the medical records of included dogs regarding reproductive status (sex and neuter status), age, body weight, breed, and diagnoses. Age was categorized as ≤ 12 months, > 1 to 2 years, > 2 to 4 years, > 4 to 7 years, > 7 to 10 years, > 10 to 15 years, and > 15 years. Body weight was categorized as 0.45 to 2.27 kg (1 to 5 lb), > 2.27 to 6.81 kg (> 5 to 15 lb), > 6.81 to 13.64 kg (> 15 to 30 lb), > 13.64 to 22.73 kg (> 30 to 50 lb), > 22.73 to 34.09 kg (> 50 to 75 lb), > 34.09 to 45.45 kg (> 75 to 100 lb), and > 45.45 kg (> 100 lb). For the dogs with a recorded diagnosis of ATD, data were extracted regarding all other diagnoses entered into their VMDB records. Diseases were considered as concurrent if they were recorded at the same visit as when ATD was recorded. During this process, diseases were not judged as to whether they may be a predisposing factor for ATD development. Dogs were considered to have PLN if they had a coded diagnosis of PLN, amyloidosis, glomerulonephropathy, or glomerulonephritis.

### Statistical analysis

Data were analyzed by use of statistical software. Descriptive statistics and ORs for ATD diagnosis were calculated for each exposure variable (reproductive status, age category, body weight category, and breed). Tests of homogeneity were performed to determine whether the odds of ATD diagnosis differed by exposure variable category. For the exposure variables age and body weight, a test for linear trend of the log odds against the exposure variable categories was performed to evaluate whether the odds of ATD diagnosis increased or decreased with increasing age or body weight. All exposure variables were then included in development of a multivariable logistic regression model to investigate their association with ATD diagnosis. A backward stepwise approach to model building was used, with variables removed from the full model on the basis of Wald test results. The Hosmer-Lemeshow test was used to assess model fit. Values of $P \leq 0.05$ were considered significant.

### Results

Of 984,973 dogs with records in the VMDB during the study period, 291 (0.05%) had a recorded diagnosis of ATD and were included in the case group; 1,445 dogs were included in the control group. Characteristics of dogs in each group were summarized (Table 1). Fifty-two percent of all dogs with ATD diagnosis were male, and 48% were female. Dogs with ATD included 57 breeds, the most common of which were mixed (21.6%), Labrador Retriever (10.0%), Shetland Sheepdog (6.2%), Golden Retriever (5.5%), and Toy Poodle (3.1%). All other breeds were represented by < 3% of case dogs.

For 99 (34.0%) dogs with an ATD diagnosis, no concurrent diseases were recorded. The most commonly recorded concurrent conditions were PLN (n = 64 [22.0%]), neoplasia (35 [12.0%]), hyperadrenocorticism (15 [5.2%]), systemic hypertension (15 [5.2%]), and hypothyroidism (15 [5.2%]). Other types of concurrent diseases were recorded for < 5% of case dogs. Various forms of neoplasia included adrenal carcinoma, prostatic carcinoma, transitional cell carcinoma,
osteosarcoma, lymphosarcoma, primary lung carcinoma, pancreatic carcinoma, aortic chondrosarcoma, soft tissue sarcoma, hepatocellular carcinoma, pheochromocytoma, small intestinal adenocarcinoma, mammary carcinoma, gastric adenocarcinoma, thyroid carcinoma, and pituitary carcinoma.

Tests of homogeneity revealed that the odds of ATD diagnosis did not differ significantly by reproductive status \((p = 0.06)\), age category \((p = 0.98)\), or body weight category \((p = 0.78)\). The test for linear trend revealed no significant increase or decrease in the odds of ATD diagnosis with increasing age \((p = 0.84)\) or body weight \((p = 0.88)\). The test of homogeneity indicated that the odds of ATD diagnosis differed significantly \((p < 0.001)\) by breed.

Multivariable modeling revealed that only breed had a significant association with ATD diagnosis. Specifically, compared with mixed-breed dogs, Shetland Sheepdogs had a significantly \((p = 0.003)\) higher odds of ATD diagnosis \((OR, 2.59; 95\% CI, 1.40 to 4.82)\).

With mixed-breed dogs as the referent group, non-significant ORs for other breeds were as follows: Labrador Retriever, 0.90 \((95\% CI, 0.54 to 1.49; p = 0.67)\); Toy Poodle, 1.52 \((95\% CI, 0.67 to 3.43; p = 0.32)\); and Golden Retriever, 0.99 \((95\% CI, 0.52 to 1.87; p = 0.97)\). The odds for all other breeds combined were also significantly \((p = 0.001)\) higher than the odds for mixed-breed dogs \((OR, 1.73; 95\% CI, 1.25 to 2.41)\). Half of Shetland Sheepdogs with ATD \((9/18)\) had no concurrent disease recorded.

**Discussion**

The study reported here revealed no association between ATD diagnosis and dog age, reproductive status, and body weight. Approximately one-third \((34.0\%)\) of dogs with an ATD diagnosis had no recorded concurrent disease. When a concurrent disease was recorded, PLN was the most common. Shetland Sheepdogs had approximately twice the odds of ATD diagnosis as mixed-breed dogs \((OR, 2.44)\), and this finding may warrant further investigation. The reported prevalence of systemic hypertension in that breed is 13%.\(^1\) It remains unknown whether subclinical systemic hypertension may predispose Shetland Sheepdogs to ATD.

Data for the present study were obtained through an electronic search of the VMDB. Data from all patient visits, both routine and nonroutine, are used to populate the database, and there are no restrictions on the type of information that can be entered. Five control dogs were randomly selected from the VMDB population for every case dog during the study period. Use of 4 to 5 control subjects/case subject is known to increase the statistical power of a case-control study.\(^1\) Considering that the VMDB includes information from a wide range of patients, hospitals, and clients, the information obtained in the present study may constitute a more accurate representation of dogs with ATD than information obtained in previous studies,\(^6\) which lacked a control group and provided conflicting information about signalment and other diagnoses.

In a postmortem study involving 36 dogs, no age, sex, or breed predilection for ATD was identified.\(^6\) Five \((14\%)\) of these dogs had PLN, and for 7 \((19\%)\) dogs, the source of thromboembolism was the heart (endocarditis or atrial thrombi). In a case series involving 6 dogs, mean age was 9.3 years \((6, 14\text{ years})\) and mean body weight was 20.9 kg \((46 \text{ lb})\), similar to findings of the present study in which the largest proportions of dogs were in the 10- to 15-year and \(>22.73\)- to 34.09-kg categories. No breeds were overrepresented in that case series,\(^7\) but 3 of the 6 dogs had concurrent hyperadrenocorticism.

Findings in another case series involving 13 dogs, which highlighted neurologic abnormalities secondary to ATD, included more males \((n = 10)\) than females \((3)\) and a high number of Cavalier King Charles Spaniels \((6)\). In 2 of those dogs, PLN was identified as a concurrent condition. In a retrospective study involving 26 dogs with ATD, median age was 10.3 years and median body weight was 26.8 kg \((59 \text{ lb})\). Of all dogs with ATD in that study, 58\% had no concurrent conditions, whereas 35\% had PLN. Despite the variations in age, sex, breed, and comorbid conditions in the aforementioned reports, dogs with ATD consistently appear of be of advanced age and PLN is a common concurrent diagnosis.

No conclusions regarding breeds other than those specifically evaluated in the present study could be drawn because those breeds were represented by < 3\% of dogs and consequently grouped together in the statistical analysis. Although this group containing all other breeds had a significantly greater odds of an ATD diagnosis than mixed-breed dogs \((OR, 1.73)\), it remains unclear whether certain breeds within this other category were of greater odds than others.

Thirty-four percent of dogs reported to have ATD in the present study had no concurrent disease recorded that could predispose them to development of ATD, and this finding of ATD diagnosed without a concurrent disease was also obtained in other studies.\(^1\) Some humans with ATD of the distal portion of the aorta reportedly have abnormal aortic diameters, and this is believed to cause ATD.\(^1\) It is possible that a similar condition predisposes dogs to ATD development, but this could not be determined from the available data in the present study.

Recorded concurrent diseases in dogs with ATD in the present study included PLN, hyperadrenocorticism, hypothyroidism, systemic hypertension, and neoplasia. Previous studies\(^6\) have also shown PLN to be associated with ATD. Protein-losing nephropathy is associated with glomerular lesions that allow a loss of proteins, including antithrombin. With substantial antithrombin loss in addition to platelet hyperreactivity, a prothrombotic state develops, predisposing dogs to ATD.\(^2\)
Endocrine diseases such as hyperadrenocorticism and hypothyroidism have also been associated with ATD in dogs and humans.5,7,9,23–29 Dogs with hyperadrenocorticism have high blood coagulation factor concentrations and low blood antithrombin concentrations, creating a prothrombotic state. They are also predisposed to systemic hypertension, which can increase the likelihood of thromboembolic complications.23–25 Hypothyroidism has been associated with both hypercoagulable and hypofibrinolytic states, both of which predispose dogs to ATD.26–29 Hypofibrinolytic states are associated with a 2-fold increase in the risk of arterial thrombosis in humans.30 Systemic hypertension can affect endothelial function, platelet function, and the coagulation system, resulting in a prothrombotic state.31 A state of hypofibrinolysis can also occur with systemic hypertension.31,32 In 12.0% of dogs with ATD in the present study, neoplasia was a concurrent disease, and this finding may warrant further investigation.

Cardiac diseases such as endocarditis were uncommon in dogs with ATD in the present study, despite a strong association identified between cardiac disease and aortic thromboembolism in cats.1,2 The lack of dogs with a cardiac-related diagnosis could have been related to insufficient testing, or it could be that the association identified in cats does not apply to dogs, suggesting different disease processes for the 2 species. If disease processes do indeed differ, this could influence diagnostic and therapeutic decisions for dogs with ATD.

The present study had several limitations. All data were obtained from historical records in the VMDB. Full medical records from individual institutions were available for evaluation in some but not all cases. Diagnoses were retrospectively confirmed by the authors for some but not all dogs with ATD. Some diagnoses could have been missed, and some could have been incorrect. In addition, some legitimate diagnoses may simply not have been entered into the VMDB. For instance, if disseminated intravascular coagulopathy and ATD were both diagnosed in a given dog, then only the ATD diagnosis might have been entered. No information was available regarding medications administered or how well controlled certain concurrent diseases were in the dogs with ATD, and the chronicity of clinical signs associated with ATD was not available for analysis.

Another important limitation was that the VMDB includes only records of animals evaluated at veterinary teaching hospitals. Consequently, dogs evaluated solely at primary care hospitals were omitted. Dogs evaluated at veterinary teaching hospitals, with or without referral from primary care hospitals, may represent more severely diseased patients. In addition, some of the concurrent diseases recorded for the dogs in the present study may simply be more prevalent in older versus younger dogs; the study was not designed to control for this possibility. No inferences can be made regarding causality with respect to any factor considered in the study.

Regardless of the aforementioned limitations, inclusion of dogs from multiple hospitals over several decades allowed the most representative characterization of ATD in dogs to date. Aortic thromboembolic disease causes fairly nonspecific clinical signs in dogs, and the findings reported here may help clinicians in the diagnosis of this condition. Any dog with a confirmed or suspected diagnosis of ATD should be further evaluated for other common concurrent diseases, namely PLN, neoplasia, systemic hypertension, hyperadrenocorticism, and hypothyroidism.

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Footnotes

a. Intercooled Stata, version 13, StataCorp, College Station, Tex.

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