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Evaluation of bronchial narrowing in coughing dogs with heart murmurs using computed tomography

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Abstract

Background: The origin of cough in dogs with heart murmurs is controversial, because the cough could be primary cardiac (eg, pulmonary edema, bronchi compression by left-sided cardiomegaly) or respiratory (eg, bronchomalacia, other bronchial or bronchiolar disease, interstitial lung disease) in origin.

Hypothesis/Objectives: To study the association between left atrium (LA) dilatation and cardiomegaly and bronchial narrowing in coughing dogs with heart murmurs using computed tomography (CT).

Animals: Twenty-one client-owned coughing dogs with heart murmurs and 14 historical control dogs.

Methods: Dogs with cough and murmur were prospectively recruited over 4 months. Cervical and thoracic radiography, echocardiography, and thoracic CT were performed in enrolled dogs. Control dogs, with no disease on thoracic CT and no records of heart murmur and coughing, were gathered from the institution's computerized database. Degree of bronchial narrowing was assessed using the bronchial-to-aorta (Ao) ratio, measured by 3 radiologists blinded to the clinical findings. After identifying bronchi that were significantly narrowed in dogs with murmur compared to controls, the relationship between degree of narrowing and LA/Ao ratio (measured echocardiographically) and vertebral heart scale (VHS) measured radiographically was studied in dogs with murmur using mixed-effects regression.

Result: Significant narrowing was identified for all left-sided bronchi and the right principal, middle, and caudal bronchi in the coughing dogs, compared with controls. Increasing LA size and VHS were significantly inversely associated with diameter for all left-sided and right-sided bronchi indicated above.

Abbreviations: Ao, aorta; B/A, bronchus to aorta ratio; BCS, body condition score; CT, computed tomography; FS, fractional shortening; LA, left atrium; LB1, left cranial bronchus; LB2, left caudal bronchus; LPB, left principal bronchus; MMVD, myxomatous mitral valve degeneration; PH, pulmonary hypertension; RB1, right cranial bronchus; RB2, right middle bronchus; RB3, accessory bronchus; RB4, right caudal bronchus; RPB, right principal bronchus; UIUC, University of Illinois Urbana-Champaign; VHS, vertebral heart scale.

Conclusion and Clinical Importance: Results indicate an association between LA enlargement and cardiomegaly and bronchial narrowing and support heart size-associated exacerbation of cough in dogs with murmurs.

KEYWORDS
bronchomalacia, canine, cardiomegaly, vertebral heart scale

1 | INTRODUCTION

Cough is governed by complex neural pathways, including multiple peripheral sensory pathways.[1] Most sensory nerve fibers are derived from vagal ganglia from 2 embryological lineages: the nodose ganglia, which terminate in distal airways and lung parenchyma, and the jugular ganglia, which terminate in proximal airways (ie, larynx, trachea, and main bronchi).[1] According to the "two pathway" model, sensors from the jugular ganglia are responsible for direct cough induction, whereas nodose-derived sensors cannot directly trigger cough, but facilitate or impede cough induction.[1] Despite sensory input mainly arising from the airways, coughing is encountered in a variety of underlying disease processes not exclusively associated with the airways (eg, lung interstitial and cardiac diseases), leading to diagnostic and therapeutic dilemmas.[2]

Cardiac cough is defined as a cough associated with cardiac disease.[2] Coughing is commonly observed in the course of cardiac disease,[3,4] and is associated with a negative prognosis in dogs with myxomatous mitral valve degeneration (MMVD).[5] Historically, cardiac cough has been reported as a sign of cardiogenic pulmonary edema and cardiomegaly.[2] Because cough receptors from the jugular ganglia are confined to the proximal airways, the presence of fluid in the alveoli or interstitium should not directly trigger cough in dogs with pulmonary edema, unless the amount of fluid is sufficient to affect the largest airways. This conclusion is corroborated by the lack of significant association between congestive heart failure and coughing in dogs with MMVD.[6] In this same study, left atrium (LA) enlargement however was associated with coughing.[6] Increased heart size could exert mechanical dorsal pressure on the main airways with subsequent stimulation of jugular ganglia sensors. On the other hand, most dogs with MMVD are small breeds and are predisposed to airway diseases such as tracheal collapse, bronchomalacia, and chronic bronchitis, which are well-recognized causes of coughing in dogs.[7,8] In a sample of dogs with MMVD divided into 2 groups according to absence or presence of overt LA enlargement, multiple bronchial collapse, most commonly involving left-sided bronchi, was observed in both groups, with no significant difference in site or severity of airway collapse between groups.[9] Nevertheless, the 2 groups were small, assessment of airway collapse severity was made by radiography, fluoroscopy, and bronchoscopy, and vertebral heart scale (VHS) was enlarged in both groups on thoracic radiography.[9] Hence, although the investigators failed to identify an association between cardiomegaly and airway collapse in these dogs, they concluded that the question as to whether or not the entity of cough secondary to airway compression from an enlarged heart existed remained open.[9]

Computed tomography (CT) is an accurate method to evaluate airway narrowing.[10] Especially, CT allows quantitative assessment of airway diameters.[11] Although most CT studies are done under general anesthesia, CT examinations now are reported in sedated dogs, eliminating the risk of anesthesia-associated bias when evaluating lower airway narrowing.[12-15] Hence, in our opinion, CT under sedation seems appropriate to explore the association between bronchial narrowing and cardiomegaly. Our aim therefore was to prospectively investigate the relationship between left atrial enlargement and cardiomegaly and bronchial narrowing using CT in sedated dogs with cardiac disease and cough. We hypothesized that there would be an inverse relationship between left-sided bronchi dimensions and LA and overall heart size in dogs with heart murmurs.

2 | MATERIALS AND METHODS

All protocols were approved by the Institutional Animal Care and Use Committee of the University of Illinois Urbana-Champaign (UIUC). A pilot study was performed using 10 normal dogs to estimate the mean and standard deviation of each bronchus/aorta (B/A) ratio and determine minimum sample size with α = 0.05, 1 − β = 0.8, and a 50% reduction of bronchial diameter in the case group. A minimum sample size of 12 dogs per group was obtained. Dogs used in the pilot study were not reused in the present study. All dogs with heart murmur and a history of coughing were prospectively recruited between February and May of 2014. Dogs were enrolled in the study if they had: (1) a heart murmur that was graded ≥3/6 by the attending clinician, and (2) if the owners reported ongoing coughing (> 2 weeks) at the time of presentation. All enrolled dogs had point-of-care venous biochemical, hematological, electrolyte, and blood gas analyses before sedation, 5-view cervical and thoracic radiographs, echocardiogram, and CT under sedation performed.

The 5-view cervical and thoracic radiograph series included thoracic right lateral, inspiratory left lateral, expiratory left lateral, ventrodorsal views, lateral neck view to evaluate VHS, presence of bronchial narrowing during expiration, and evidence of additional thoracic pathology. All radiographic interpretations, including VHS, were made by a radiology resident or a board-certified radiologist or both, blinded to the dog's clinical status, as previously described.[16] All VHS measurements were made on the right lateral view, unless ambiguity of the apex margin or concurrent disease required use of the left lateral view.

Echocardiography was performed using phased array probes by a radiology resident under the supervision of a board-certified radiologist. Images were obtained from routine right parasternal and left apical and parasternal short and long axis views. Evaluation included subjective assessment and objective measurements of the chamber sizes and wall thicknesses, measurement of LA/Ao ratio and fractional shortening (FS), and color Doppler evaluation of each outflow tract and valve, with continuous wave Doppler regurgitation velocities recorded to evaluate for pressure differential abnormalities. Tricuspid regurgitation velocities were converted to pressure differentials by using the modified Bernoulli equation.

Thoracic CT was performed under sedation using a 16-slice helical CT scanner. All enrolled dogs were sedated with IV butorphanol (0.4 mg/kg), except for 1 dog that received dexmedetomidine (2 μg/kg IV) because of fractious behavior. The dogs were placed in a transparent positioning device (VetMouseTrap, University of Illinois, Urbana, Illinois) in sternal recumbency, unless the dog was too large to fit in the VetMouseTrap device or if the dog was very sedated (ie, if the dog was not moving when placed in the trough outside of the VetMouseTrap). All dogs were scanned with a gantry rotation of 0.5 seconds using the following settings: 120 kVp, either 225, 280, or 380 mA, either 0.938 or 1.375 pitch, either 9.37 or 13.75 mm/s table speed, and either large or small field of view. These settings varied based on the size and movements of the dogs. If the patient moved during a series, then the series was repeated. No studies needed to be repeated more than once. The images were reconstructed for evaluation into dorsal and sagittal planes for complete evaluation for the tomographic abnormalities.

Enrolled dogs were compared with a control group composed of dogs with no history of coughing and no audible heart murmur. Data for control dogs were gathered from the UIUC radiology computerized database by searching for all dogs that underwent CT under sedation and had no pathological disease on thoracic CT examination (ie, no clinically relevant respiratory pathology). The CT images for the control group were anonymized and randomly mixed in with the case group during the single session interpretation. The CT images of both case and control groups were examined by 3 board-certified radiologists. The 3 radiologists examined all cases. Each radiologist was blinded to the dogs' underlying health status, history, and signalment, and to the results of the 2 other radiologists. All case and control dogs had age, sex, body condition score (BCS), body weight, and the presence or absence of a murmur including its grade recorded.

Assessment of CT images included measurements of the height of the left principal bronchus (LPB), left cranial bronchus (LB1), left caudal bronchus (LB2), right principal bronchus (RPB), right cranial bronchus (RB1), right middle bronchus (RB2), accessory bronchus (RB3), and right caudal bronchus (RB4).[17] Cycle of respiration was not accounted for, because no dogs were under general anesthesia. The bronchi were measured in a transverse plane at the smallest diameter. Measurements of the bronchi then were compared with the aorta in the same image to account for patient size variability. The aorta measurements were taken in a transverse plane to minimize the obliquity of the aorta. Thoracic height was measured at the level of LPB and from the sternum to the ventral midline of the thoracic vertebrae. A thoracic height-to-aorta ratio (TH/A) then was calculated by each radiologist for each dog using the aorta measurements at the level of LPB as an index of chest conformation. Subjective interpretation of the thorax also was recorded. Lung pathology was categorized as absent, mild, moderate, or severe. Type of lung pattern was categorized as alveolar, bronchial, or interstitial.

2.1 | Statistical analysis

Statistical analyses were performed using STATA version 14.2 software (StataCorp LLC, College Station, Texas). Demographic continuous data (age and weight) were assessed for Gaussian distribution using histogram evaluation and the Shapiro-Wilk test (considered Gaussian if *P*-value >.05). Because none of the continuous variables were normally distributed, a Mann-Whitney test was used to compare them between cases and control dogs. An ordered logistic regression was used to compare BCS between the 2 groups. Absence of significant violation of the parallel regression assumption was assessed using the Brant test. A 2-tailed Fisher's exact test was used to compare the 2 groups in terms of sex.

For each dog, measurements of the height of each bronchus were divided by measurement of the aorta on the same image to provide B/A ratios. To determine which bronchi were significantly narrower in cases compared to control dogs and to take into account repeated measures by the 3 radiologists and the potential confounding effects of breed, age, weight, and BCS of the dogs, TH/A, and pulmonary arterial pressure estimation, a repeated-measures mixed-effects model analysis of covariance (ANCOVA) with unstructured random-effects covariance matrix was used, with the dependent variable being B/A and the independent variables being age, breed, weight, BCS, pulmonary arterial pressure estimation, TH/A, bronchi evaluated, radiologists, group (case or control), and second- and third-degree interactions among the bronchi evaluated, radiologists, and group. Both the fixed-effects and the random-effects parts of the model were reported. If significant differences in B/A were detected for the second-degree interaction between the bronchi evaluated and the group, the B/A was compared for each bronchus between the 2 groups by contrasts, and was considered narrower in the case group if B/A was significantly lower than in the control group with $P < .006$ (Bonferroni correction for 6 comparisons). Gaussian distribution and homoscedasticity of the residuals were assessed by graphical assessment of frequency distribution histograms and residual plots, respectively.

The remainder of the statistical analysis was restricted to coughing dogs with heart murmurs. To determine if a significant relationship between bronchial narrowing and LA/Ao (or VHS) existed, a repeated-measures mixed-effects model ANCOVA with unstructured random-effects covariance matrix was used, with the dependent variable being the square root of B/A and the independent variables being breed, age, weight, BCS, pulmonary arterial pressure estimation, TH/A, bronchial pattern category on CT, bronchi evaluated, radiologists, LA/Ao (or the VHS), and second- and third-degree interactions between the bronchi evaluated, radiologist, and LA/Ao (or the VHS) variables. A square root transformation was used on B/A to fulfill homoscedasticity requirements of the residuals.

Both the fixed-effects and the random-effects parts of the model were reported. A relationship between bronchial narrowing and LA/Ao (or VHS) was considered significant if the *P*-value associated with the variable LA/Ao (or VHS) or their interactions with the bronchi evaluated was <.05 and if the slope coefficient was negative. The random-effects part of the model was used to study dog-to-dog differences in this relationship.

3 | RESULTS

3.1 | Study population

Twenty-four dogs with heart murmurs and ongoing cough (cases) initially were enrolled in the study and compared to 14 control dogs with normal thoracic CT images. Because 3 case dogs did not have primary left-heart disease (ie, severe pulmonary hypertension [PH] resulting in heart remodeling, heart base tumor, degenerative tricuspid valve disease), they were excluded despite being presented for heart murmurs and ongoing cough, resulting in 21 dogs eventually included in the case group. Demographic data of the dogs of both groups are presented in Table 1.

The control group consisted of 9 breeds: 4 (29%) Shih Tzus, 3 (21%) Beagles, and 1 (7%) each of Cocker Spaniel, Miniature Dachshund, French Bulldog, Lhasa Apso, Maltese, mixed breed, and Poodle. The case group consisted of 15 breeds: 3 (14.3%) each of Chihuahuas, 2 (9.5%) Miniature Poodles, mixed breed dogs, and Cavalier King Charles Spaniels, and 1 (4.8%) each of American Pit Bull, Basenji, Beagle, Chinese Crested, Clumber Spaniel, Cocker Spaniel, Irish Terrier, Labrador Retriever, Miniature Pinscher, Rat Terrier, Shih Tzu, and Yorkshire Terrier. Based on the listed breeds, there were 6 (43%) and 2 (9.5%) brachycephalic dogs in the control and case groups, respectively, provided that no mixed breed dogs were brachycephalic.

No significant differences were identified between case and control groups regarding demographic data (Table 1).

In the case group, median VHS calculated from thoracic radiographs was 11.5 (range, 10.5-14.3). Only 1 dog had a VHS ≤10.5. Cardiac diseases diagnosed from echocardiogram included 17 (81%) dogs with MMVD (2/17 [12%] stage B1, 5/17 [29%] stage B2, 9/17 [53%] stage C, and 1/17 [6%] stage D), 3 (14%) with dilated cardiomyopathy, and 1 (5%) with mitral dysplasia. Median LA/Ao ratio measured by echocardiography was 2.0 (range, 1.5-3.5). Three dogs (14%) had a LA/Ao ratio < 1.6. Median FS was 41.3% (range, 5.5-64). Three dogs (12.5%) had FS < 20%. In dogs with tricuspid insufficiency (16 [76%] of the cases), the median peak tricuspid regurgitation gradient pressure was 39.1 mm Hg (range, 21.2-67.6). Seven of the 16 dogs (44%) had a peak tricuspid regurgitation gradient pressure <35 mm Hg.

In cases, alveolar lung pattern, mostly mild to moderate, was considered present on CT in 14% to 48% of dogs, interstitial lung pattern, mostly mild to moderate, was considered present on CT in 60% to 76% of dogs, and bronchial pattern, mostly mild, was considered present on CT in 24% to 33%, depending on the radiologist.

3.2 | Comparison of bronchial diameter between case and control groups

Median B/A (ie, LPB/Ao, LB1/Ao, LB2/Ao, RPB/Ao, RB1/Ao, RB2/Ao, RB3/Ao, and RB4/Ao ratios) in coughing dogs with heart murmurs and in controls are presented in Table 2. Based on the mixed-effects ANCOVA model and contrasts results, LPB (*P* < .0001), LB1 (*P* = .0001), LB2 (*P* = .0001), RPB (*P* = .001), RB2 (*P* = .001), and RB4 (*P* < .0001) were significantly narrower in the case group compared to the control group. The contrasts were lowest for LB2 (−0.28, 95% confidence interval [CI], −0.36 to −0.19) and LPB (−0.26; 95% CI, −0.35 to −0.17), followed by RB4 (−0.22; 95% CI, −0.39 to -0.13), LB1 (−0.15; 95% CI, −0.24 to −0.06), RPB (−0.14; 95% CI, −0.23 to −0.06), and RB2 (−0.14; 95% CI, −0.22 to −0.05). According to the random-effects part of the model, the between-dog (0.004) and within-dog (0.02) variances were low in the metrics of B/A.

Significant differences in B/A measurement were detected among radiologists for LPB and LB2 (Table 2). The difference was between

TABLE 1 Demographic data for the coughing dogs with heart murmur (case group) and the controls (control group). Table entries represent median values (minimum-maximum) for continuous and ordinal variables and number of dogs (percent of dogs) for categorical variables

Variable	Case group (n = 21)	Control group (n = 14)	*P* value
Age (years)	10 (5-14)	9.6 (6.8-16.3)	.45
Weight (kg)	8.6 (2.6-33)	7.4 (5.1-13.4)	.87
BCS (9-point scale)	5 (2-5)	5 (2-7)	.84
Sex			.67
Neutered males	6 (28%)	7 (50%)	
Intact males	1 (5%)	0	
Spayed females	13 (62%)	7 (50%)	
Intact females	1 (5%)	0	
TH/A	7.05 (3.79-9.51)	7.79 (5.38-10.87)	.22

Abbreviations: BCS, body condition score; TH/A, thoracic height-to-aorta ratio.

TABLE 2 Bronchus-to-aorta ratio measured from computed tomography images of coughing dogs with murmur (case group) and controls (control group) by the 3 board-certified radiologists. Results are presented as median value (minimum-maximum). The bronchus to aorta ratio (B/A) was compared for each bronchus between the two groups by contrasts, and was considered narrower in the case group if B/A was significantly lower than in the control group with $P < .006$ (bolded)

	Case group (n = 21)			Control group (n = 14)			
Bronchus/Ao ratio	Radiologist 1	Radiologist 2	Radiologist 3	Radiologist 1	Radiologist 2	Radiologist 3	*P* value
LPB/Ao	0.35 (0-0.72)	0.55* (0-0.89)	0.47 (0-0.87)	0.54 (0.39-0.81)	0.74* (0.64-0.92)	0.65 (0.50-0.98)	**<.0001**
LB1/Ao	0.20 (0-0.47)	0.24 (0-0.46)	0.17 (0-0.43)	0.30 (0.12-0.59)	0.32 (0.11-0.51)	0.27 (0.12-0.59)	**.001**
LB2/Ao	0.25 (0-0.71)	0.40* (0-0.78)	0.23 (0-0.58)	0.53 (0.08-0.81)	0.54 (0.11-0.88)	0.53 (0.07-0.83)	**<.0001**
RPB/Ao	0.60 (0-1.01)	0.68 (0-0.97)	0.67 (0.43-1.03)	0.70 (0.41-0.85)	0.80 (0.60-1.07)	0.71 (0.50-0.97)	**.001**
RB1/Ao	0.37 (0-0.61)	0.38 (0.11-0.66)	0.37 (0-0.69)	0.40 (0.21-0.54)	0.38 (0.33-0.60)	0.43 (0.29-0.61)	.02
RB2/Ao	0.20 (0-0.45)	0.22 (0-0.42)	0.22 (0-0.96)	0.29 (0.20-0.46)	0.35 (0.13-0.041)	0.30 (0.13-0.44)	**.001**
RB3/Ao	0.30 (0-0.55)	0.31 (0.16-0.69)	0.35 (0.13-0.68)	0.37 (0.10-0.64)	0.32 (0.18-0.53)	0.35 (0.24-0.52)	.06
RB4/Ao	0.52 (0-0.90)	0.51 (0-0.95)	0.52 (0.31-0.92)	0.69 (0.32-1.02)	0.77 (0-0.96)	0.68 (0.42-1.09)	**<.0001**

Abbreviations: Ao, aorta; LB1, left cranial bronchus; LB2, left caudal bronchus; LPB, left principal bronchus; RB1, right cranial bronchus; RB2, right middle bronchus; RB3, accessory bronchus; RB4, right caudal bronchus; RPB, right principal bronchus.
*Indicates a significant difference ($P < .003$) in B/A measurement between radiologist 2 or 3 and radiologist 1.

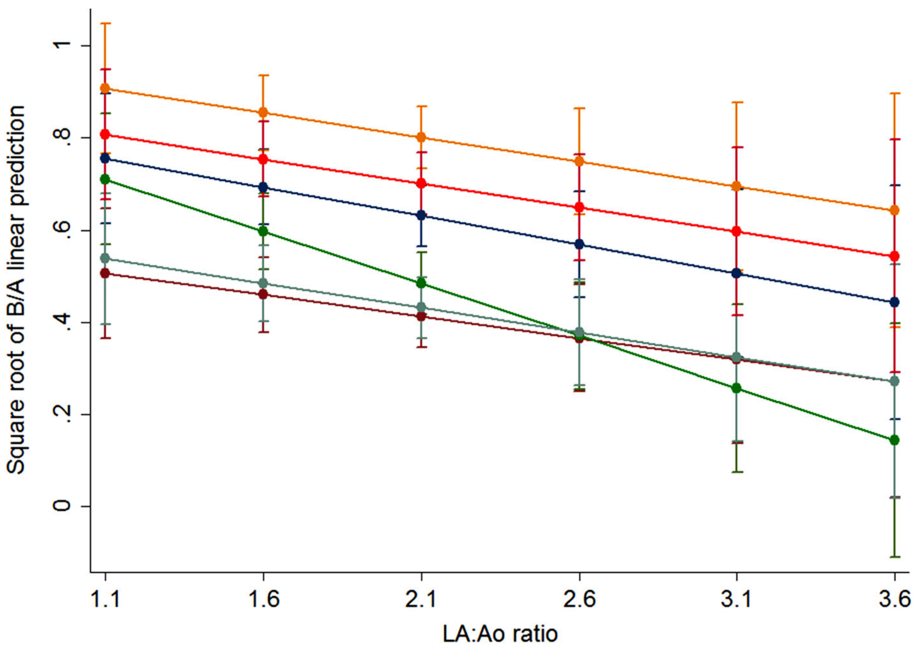

FIGURE 1 Graph plots showing predictive margins of the relationship between square root of bronchus-to-aorta (B/A) ratios (on the y axis) and left atrium-to-aorta (LA:Ao) ratio (on the x axis) in the 21 dogs with a cough and a murmur at the left principal bronchus (LPB, blue), left cranial bronchus (LB1, maroon), left caudal bronchus (LB2, green), right principal bronchus (RPB, orange), right middle bronchus (RB2, teal) and right caudal bronchus (RB4, red). The relationship did not significantly differ among the 3 radiologists. Error bars represent 95% confidence intervals

radiologists 1 and 2, with radiologist 2 usually measuring higher B/A compared to radiologist 1.

3.3 | Relationship between LA/Ao ratio and bronchus/Ao ratio in coughing dogs with heart murmurs

The relationships between LA/Ao ratio measured by echocardiography and the square root of B/As in coughing dogs with heart murmurs are depicted in Figure 1. Only bronchi that were identified as significantly narrower in the case group (ie, LPB, LB1, LB2, RPB, RB2, and RB4) were included in the analysis. The association between LA/Ao ratio and the square root of B/A was significant for all bronchi ($P = .01$). The higher the LA/Ao ratio, the lower the square root of B/A (coefficient, −0.22; 95% CI, −0.39 to −0.05). The relationship between LA/Ao ratio and the square root of B/A did not differ significantly among radiologists. According to the random-effects part of the model, the slope of the relationship between LA/Ao ratio and the square root of B/A did not vary substantially from 1 dog to another (variance of the coefficient, 0.002). The between-dog (10^{-20}) and within-dog (0.02) variances were low in the metrics of the square root of B/A. No significant associations were found between the square root of B/A and TH/A ($P = .99$) or bronchial patterns on CT ($P = .48$).

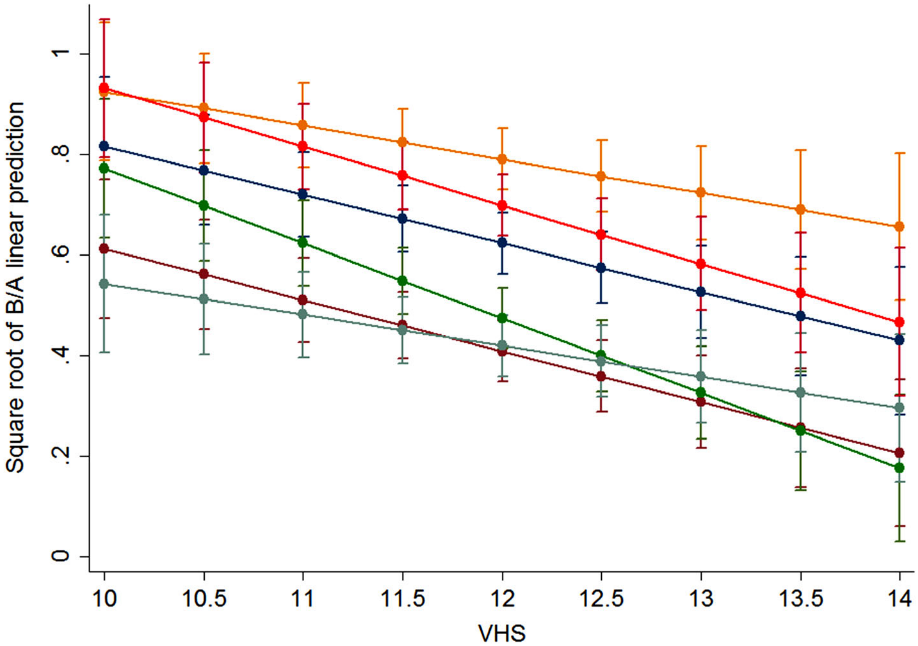

FIGURE 2 Graph plots showing predictive margins of the relationship between square root of bronchus-to-aorta (B/A) ratios (on the y axis) and vertebral heart scale (VHS; on the x axis) in the 21 dogs with a cough and a left principal bronchus (LPB, blue), left cranial bronchus (LB1, maroon), left caudal bronchus (LB2, green), right principal bronchus (RPB, orange), right middle bronchus (RB2, teal) and right caudal bronchus (RB4, red). The relationship did not significantly differ among the 3 radiologists. Error bars represent 95% confidence intervals

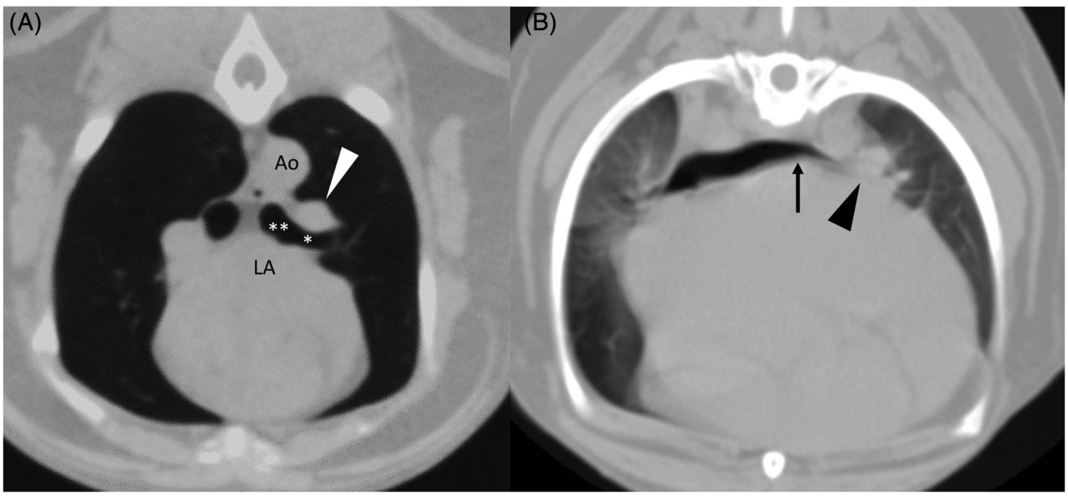

FIGURE 3 Transverse plane survey CT images of normal control group (A) and coughing dog group (B) dogs. In a control group Shih Tzu dog (A), note the normal appearing diameter of the left principal (**) bronchus LPB located between the aorta (Ao) and left atrium (LA), and of the left caudal lobar primary (*) bronchus LB2 located between the left caudal lobar pulmonary artery (white arrowhead) and left atrium (LA). In a Cavalier King Charles spaniel dog from the coughing group, note attenuation of the luminal diameter of left principal (black arrow) bronchus LPB and left caudal lobar primary (black arrowhead) bronchus LB2. The dog in "B" had moderate interstitial infiltrate consistent with interstitial pulmonary edema, severe left atrial enlargement secondary to myxomatous mitral valve degeneration with increased LA:Ao (2.3) and VHS (14.0), and pulmonary hypertension based on tricuspid regurgitation gradient pressure (66.6 mm Hg)

3.4 | Relationship between VHS and bronchus/Ao ratio in coughing dogs with heart murmurs

The relationships between VHS measured radiographically and the square root of B/As in coughing dogs with heart murmurs are depicted in Figure 2. Only bronchi that were identified as significantly narrower in the case group (ie, LPB, LB1, LB2, RPB, RB2, and RB4) were included in the analysis. The association between VHS and the square root of B/A was statistically significant for all bronchi (P = .001). The higher the VHS, the lower the square root of B/A (coefficient, −0.14; 95% CI, −0.22 to −0.05). The relationship between VHS and the square root of B/A did not differ significantly among radiologists. According to the random-effects part of the model, the slope of the relationship between VHS and the square root of B/A did not vary substantially from 1 dog to another (variance of the coefficient: 10^{-4}). The between-dog (0.05) and within-dog (0.02) variances were low in the metrics of the square root of B/A. No significant associations were found between the square root of B/A and TH/A (P = .85) or bronchial patterns on CT (P = .06).

4 | DISCUSSION

We aimed to assess the association between cardiomegaly (defined by increased VHS on radiography) and LA enlargement (defined by increased LA/Ao ratio on echocardiography) and bronchial narrowing in a group of coughing dogs with heart murmurs using CT imaging under sedation. Because our objective was not to focus on MMVD only but to assess the effect of any increase in heart size on airway diameter, other cardiac diseases characterized by cardiomegaly, such as dilated cardiomyopathy, were included in the case group.[2] According to our results, significant narrowing of all left-sided bronchi, RPB, RB2, and RB4 was identified in coughing dogs with heart murmurs compared to controls.

Left-sided bronchi are most commonly narrowed in dogs both with and without heart disease or cardiomegaly.[18-21] This could explain why a previous study did not find any differences in terms of bronchial collapse distribution between dogs with and without cardiomegaly.[9] The reasons for the left-sided distribution of bronchial collapse in dogs without cardiomegaly are unclear and might include thoracic conformation (especially brachycephalic dogs and small breed dogs), obesity, or concurrent respiratory disorders.[18,19,21] No significant association was found in our study between thoracic conformation (as assessed by TH/A) and bronchial narrowing. The suggestion that barrel-shaped chest conformation is a factor contributing to bronchial compression in dogs therefore should be questioned based on our results. In dogs with cardiomegaly, it could be explained by the anatomical relationship between the left bronchi and the heart and large vessels. The LPB is located directly between the aorta and the LA. The left caudal lobar bronchus is located between the left caudal lobar artery and the LA. Increased size or pressure or both within the LA dorsally displaces the LPB and caudal lobar bronchi, whereas the enlarged left pulmonary artery tends to prevent this deviation in position. The initial effect is compression of LB2, followed by compression of LPB (Figure 3).[22] Interestingly, the LPB and LB2 were the most narrowed bronchi in our study, which fits with a previous hypothesis.[22] Furthermore, the left cranial pulmonary artery traverses the thorax dorsal to the LB1, and hence also can compress LB1.[23] This may be because of compression of an airway at risk (eg, weakened by bronchomalacia) by the adjacent vascular structures ("rock and hard place"). When enlarged, the LA causes variable degrees of attenuation of the LPB and left caudal lobar bronchi. This attenuation (loss of a distinct tubular gas opacity) was subjectively thought to be more severe on ventrodorsal compared with dorsoventral or lateral images, possibly exacerbated by the weight of the heart on the dependent (dorsally located) airways. Interestingly, RPB, RB2, and RB4 also were significantly narrowed in dogs with cardiomegaly in our study.

Heart size was measured using 2 variables (LA/Ao ratio and VHS) in our study. Despite imperfect correlation between VHS and LA/Ao ratio in dogs, increases in LA/Ao ratio and VHS both were significantly associated with narrowing of all bronchi described above.[24] The VHS measurement has been described previously as an objective and reliable method for assessing cardiomegaly in dogs using thoracic radiographs, with minimal interobserver variability.[16] Although LA/Ao ratio only estimates the size of the LA, VHS is particularly useful for evaluating overall cardiac enlargement.[25,26]

The association between increasing LA/Ao ratio measured echocardiographically and VHS measured radiographically and narrowing of the left bronchi, RPB, RB2, and RB4 could be causal (ie, heart enlargement compresses the bronchi and results in bronchial narrowing) or confounded. Potential confounding factors include age, breed and body size and conformation, obesity, and concurrent respiratory diseases.[18,19,21]

Indeed, bronchomalacia and MMVD both are more prevalent in older small breed dogs.[19,27] Bronchomalacia has been reported in Yorkshire Terriers, Pugs, Shih-Tzus, Chihuahuas, and Miniature Poodles. Two poodles, 3 Chihuahuas, 1 Shih-Tzu, and 1 Yorkshire Terrier were included in our study as cases, representing 33% of our study sample. However, among the predisposed breeds listed above, only the Pug has higher VHS reference range values.[28,29] Larger relative heart volume and smaller distance from principal bronchi to vertebra has been identified by CT in small breeds and barrel-chested dogs.[30] Dogs with bronchomalacia also have lower body weight and higher BCS.[19] High BCS might cause VHS overestimation.[29] Body condition score also may add to respiratory effort, thereby exacerbating airway dynamics in an airway weakened by bronchomalacia. To investigate these potential confounders, multivariate analysis was performed in our study and disproved a confounding effect of age (within the age range of the dogs included in the study), breed, body weight, body conformation (as estimated by TH/A), and BCS on the association between LA/Ao ratio and VHS and bronchial narrowing. Concurrent respiratory diseases such as chronic bronchitis or bronchomalacia were possible in our study sample. No significant association was found in our study between bronchial pattern on CT and B/A ratio, suggesting that a confounding effect of bronchial disease on the association between heart size estimators and bronchial narrowing was unlikely. Chronic respiratory diseases might cause PH, resulting in right ventricular enlargement and increased VHS.[31,32] Right heart enlargement is present in 43.5% of dogs with PH caused by a respiratory disease or hypoxia or both.[33] Fifty-six percent of the dogs with heart murmurs had detectable PH (>35 mm Hg) in our study, which could be secondary to heart disease or to a concurrent respiratory disorder.[33] However, a PH confounding effect was not supported by our multivariate analysis. These results support a direct association between heart size and bronchial narrowing, which might explain why airway narrowing is more prevalent in dogs with heart murmurs, and cardiac enlargement measured by VHS is significantly associated with cough.[19,34] Our results also could explain the significant improvement of cough in dogs with preclinical MMVD receiving pimobendan, as decreased heart size also was observed in these dogs.[35] Finally, our results suggest a possible role for bronchial stenting as a therapeutic option in coughing dogs with cardiomegaly and airway collapse that are not responding to medical treatment.[36] However, careful patient selection will be needed because of the narrowing of multiple airways seen in the dogs of our study. Additional studies are required to investigate bronchial stenting in these dogs, because the therapeutic benefit of this approach on long-term outcome currently is unknown.[36]

Our study had several limitations. Coughing dogs with heart murmur were compared to controls without a history of cough and audible heart murmur. Control dogs underwent CT evaluation for other reasons than respiratory conditions (eg, metastasis screening). Dogs were included as controls only if the CT examination was considered to be free of pathological disease by a board-certified radiologist. Although considered healthy, some degrees of bronchial and alveolar patterns were diagnosed by the different radiologists in these dogs. Bronchial pattern could be explained by age-related changes in control dogs, such as in a previous study.[37] Some degrees of atelectasis could explain the alveolar pattern seen in a few control dogs, because there was no breath hold before image acquisition.[38]

Computed tomography was used in sedated animals to objectively measure the size of the bronchi in the most physiological condition possible. We created a B/A ratio to evaluate airway narrowing. This measurement might have been influenced by the respiratory cycle. Because dogs were unanesthesized, images were acquired at a random time during the breathing cycle. Bronchial lumen diameter differs when measured with positive pressure ventilation technique and during end expiration in dogs.[39] In healthy dogs, bronchial collapsibility is greatest for dorsal segmental bronchus, LB2 and RB2, reaching up to 50% diameter reduction during expiration compared to maximal inspiration.[10] Natural bronchial collapsibility however is likely lower during tidal breathing. Furthermore, the change in bronchial diameter owing to natural collapsibility during the breathing cycle should be randomly distributed into our sample rather than systematic, and is therefore unlikely to confound the relationship between heart size and airway narrowing.

Phase of breathing also might have affected aorta diameter measurement to an extent that is undetermined.[40] Because of the large variation in body size and conformation among dog breeds, aortic diameter commonly is accepted as a reliable landmark for ratio studies to assess the size of thoracic or abdominal structures, including kidneys, adrenal glands, LA, and main pulmonary artery.[40-42] Thoracic width was not measured and therefore could not be used to assess the confounding effect of chest conformation on the association between LA/Ao ratio (and VHS) and B/A. A TH/A ratio was created as a surrogate of the thoracic width-thoracic depth ratio.

Echocardiography, used to measure LA/Ao ratio, was performed by a supervised radiology resident; the measurements therefore might have been less accurate than those made by a board-certified cardiologist.

Bronchial-to-aorta ratio was selected over the bronchoarterial ratio to minimize effects of concurrent diseases such as PH, dehydration, and effect of mass lesions on the size of the bronchial artery, and to minimize the number of measurements, because having a single norm on which to compare (ie, the aorta) likely limited the variability of measuring many smaller vascular structures. Our study was not designed to validate B/A for clinical use but rather to use B/A to test our hypothesis of airway compression by cardiomegaly. Because this index has not been validated previously, 3 radiologists were involved in the study to take into account interobserver variability of B/A measurement in the association between B/A and heart size and to ensure that the association was consistent among radiologists. No differences among radiologists were detected for the relationships between LA/Ao ratio and VHS and the square root of B/A.

Because bronchoscopy and airway sampling were not performed in the coughing dogs with murmurs, no definitive respiratory diagnosis was achieved for these dogs. Hence, bronchial narrowing in the case group could be the result of an underlying respiratory disease, such as chronic bronchitis or bronchomalacia, rather than compression by an enlarged heart. However, the significant inverse linear relationship between the square root of B/A and LA/Ao ratio and VHS (ie, the higher the LA/Ao ratio or the VHS, the more narrowed the bronchi) strongly supports implication of cardiomegaly in the airway narrowing. Whether or not a respiratory disease is necessary for the heart to exert a physical effect on the bronchi remains unknown. Our study was not designed to answer this question.

Repeated-measures mixed-effects ANCOVA models were used to study the associations between heart size and B/A. Both fixed effects and random effects were reported. The fixed effects part provides the linear relationship between heart size and airway narrowing for an average coughing dog with a heart murmur, and the random-effects part gives the between-dog and within-dog variance of this relationship. No significant between-dog and within-dog variance was detected for the association between heart size and airway narrowing.

Ours is the first study to evaluate the diameter of the large airways in sedated (but unanesthetized) dogs. Previous studies have evaluated the airway diameter of anesthetized dogs. The effects of positive pressure ventilation on the diameter of normal and affected large airways are not known. We suggest that CT imaging of sedated spontaneously breathing patients provides a closer correlation to the awake patient than CT imaging of a patient undergoing positive pressure ventilation. Artifactual dilatation of the airways, thereby underestimating collapse, may be possible with positive pressure ventilation. The effect of sternal versus dorsal recumbency during radiography (or CT) similarly may affect bronchial diameter, with heart weight being an additive effect on the ventrodorsal view. Additional studies are required to investigate these possible effects.

In conclusion, our study identified a relationship between LA/Ao ratio measured echocardiographically and VHS measured radiographically and bronchial narrowing, supporting the contribution of cardiomegaly on airway collapse and heart size exacerbation of cough in dogs with heart murmur and cardiomegaly. This relationship is not restricted to the LPB as previously suspected, and especially involves LB2 and RB4. The anatomical relationship of these large airways between the LA and adjacent intrathoracic arterial structures is thought to exacerbate conditions for collapse.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the IACUC of the University of Illinois College of Veterinary Medicine.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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