*J Vet Intern Med* 2013;27:286–292

# Risk Factors for Coughing in Dogs with Naturally Acquired Myxomatous Mitral Valve Disease

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**Background:** Cough often is reported as the primary clinical sign of congestive heart failure (CHF) in dogs with chronic degenerative myxomatous mitral valve disease (MMVD). Concurrent airway disease and compression of the left mainstem bronchus by a large left atrium also have been proposed as potential causes of coughing in these patients.

**Objectives:** To investigate the association between the presence of coughing and different potential causes of cough, including CHF, abnormal radiographic airway pattern, and cardiomegaly in dogs affected by naturally acquired MMVD.

**Animals:** Two hundred six client-owned dogs.

**Methods:** Retrospective analysis performed on medical records of dogs affected by MMVD that underwent full cardiac evaluation, including echocardiographic examination and thoracic radiography.

**Results:** Univariate analyses showed that CHF is not a predictor of coughing (OR = 1.369; 0.723, 2.594), whereas abnormal radiographic airway pattern (OR = 3.650; 2.051, 6.496) and increased left atrial size observed radiographically (OR = 3.637; 1.904, 6.950) or echocardiographically (OR = 2.553; 1.436, 4.539) were significantly associated with coughing in dogs with MMVD. The same risk factors were significant in multivariate analyses.

**Conclusions and Clinical Importance:** This study indicates that CHF is not significantly associated with coughing in dogs with MMVD. Instead, abnormal radiographic airway pattern and left atrial enlargement are associated with coughing in these patients. This important finding should be taken into account when considering diagnosis and clinical management of CHF in these dogs.

**Key words:** Airway disease; CHF; MMVD; Pulmonary edema.

Coughing is an important physiological function present in many mammalian species to remove or expel harmful substances, such as foreign bodies, mucus, or debris, from the airways and preserve the normal health of the respiratory tract.[1] Cough can be evoked by stimulation of coughing receptors localized in the larynx, trachea, or bronchi,[2,3] whereas irritation of smaller bronchi, bronchioles, and alveoli does not elicit coughing.[4] Furthermore, the luminal flow in the lower respiratory tract would be too low to generate sufficient shear forces to clear airway mucus and debris from such sites.[5] According to these observations, pulmonary edema should not be an expected cause of cough, unless fluid accumulation is severe enough to build up within the airways, producing a soft moist cough accompanied by blood-tinged sputum.[6]

**Abbreviations:**

| | |
|---|---|
| Ao | aorta |
| AOR | adjusted odds ratio |
| CHF | congestive heart failure |
| DSB | David S Biller |
| KSU | Kansas State University |
| LA/Ao | left atrial diameter and aortic root ratio |
| LA | left atrium |
| LC | Laura Crews |
| LF | Luca Ferasin |
| LVDd% | percent increase in left ventricular diameter in diastole |
| LVDD | left ventricular diameter in diastole |
| MB | Michele Borgarelli |
| MMVD | myxomatous mitral valve disease |
| SD | standard deviation |
| UMN | University of Minnesota |
| UOT | University of Turin |
| VHS | vertebral heart score |

Although there is a reported correlation between action potentials generated by coughing receptors and mean left atrial pressure in anesthetized rabbits, a direct association between resulting peribronchial edema and coughing is not reported.[7] Nevertheless, in many veterinary textbooks, cough commonly is associated with the presence of cardiogenic pulmonary edema in dogs.[8–13] Most dogs that develop congestive heart failure (CHF) are older small-breed dogs affected by chronic degenerative mitral valve disease (MMVD). This same group of patients also is prone to developing concomitant airway disease (eg, tracheal collapse, bronchomalacia, chronic bronchitis).[11,14–16] Moreover, cardiomegaly, and in particular left atrial (LA) enlargement, potentially may contribute to coughing in these patients by mechanical dorsal compression of the

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*Submitted March 22, 2012; Revised October 21, 2012; Accepted December 6, 2012.*



*10.1111/jvim.12039*

trachea and mainstem bronchi. However, there seems to be no association between increased left atrial size and airway collapse in dogs.[17] Cardiomegaly, as assessed by vertebral heart score (VHS), has been identified as a diagnostic indicator for differentiating "cardiac cough" from "cough of non-cardiac origin" based on thoracic radiographs,[18] but the accuracy of VHS to identify dogs with echocardiographic evidence of cardiomegaly recently has been disputed.[17]

A study specifically addressing the relationship between coughing and canine MMVD has not been conducted to our knowledge. Therefore, the aim of this study was to investigate the association between coughing and potential causes of cough, such as cardiogenic pulmonary edema (CHF), airway disease, and cardiomegaly in dogs affected by naturally acquired MMVD.

## Materials and Methods

Data were collected retrospectively from the clinical records of 3 different institutions: University of Minnesota (UMN), University of Turin (UOT), and Kansas State University (KSU). Case selection was based on dogs that underwent a complete diagnostic evaluation of a heart murmur between 2005 and 2007 (UMN), 2003 and 2007 (UOT), and 2007 and 2009 (KSU). Inclusion criteria consisted of a definitive diagnosis of MMVD, full medical history, and full clinical investigation, which included echocardiographic examination and thoracic radiography performed on the same day. The diagnosis of MMVD was based on echocardiographic evidence of thickened mitral valve leaflets, mitral valve prolapse, and any degree of mitral valve regurgitation identified by color Doppler study. The presence or absence of cough, dyspnea, or both was based on observation of these signs by the clinician during clinical examination or by the owner or referring veterinarian in the preceding few days. Incomplete medical records, missing reference to clinical signs of cough and dyspnea, equivocal diagnosis, or the concomitant presence of other cardiac disease were considered criteria for exclusion. Dogs also were excluded from the study if they had received furosemide, antitussives, or anti-inflammatory drugs in the few days preceding the cardiology consultation.

Echocardiographic examinations were reviewed by 2 board-certified cardiologists (LF and MB). Left atrial size (LA) and aortic root diameter (Ao) were measured echocardiographically by the 2-dimensional method described by Hansson et al[19] and the LA/Ao ratio was used to identify left atrial enlargement (LA/AO >1.5). The left ventricular diameter in diastole (LVDd) was obtained by M-mode scanning of the left ventricle from the right parasternal short axis view. This value was used to calculate the percentage increase in LVDd (%increase = 100 × [(measured LVDd – expected normal LVDd)/expected LVDd]). Expected normal LVDd dimension was calculated according to Cornell's allometric scaling.[20]

Radiographic interpretation was performed by 2 board-certified radiologists (LC and DSB). Both radiologists were blinded to patients' history, clinical findings, and echocardiographic assessment. The presence of cardiomegaly accompanied by pulmonary venous congestion and interstitial or alveolar pattern was considered indicative of cardiogenic pulmonary edema (CHF). Heart size was measured by VHS on lateral views and subjects were deemed to have cardiomegaly if VHS was >10.7 (normal mean + 2 SD = 9.7 + 1.0 = 10.7).[21] Increased left atrial dimension was assessed subjectively on lateral projection as dorsal elevation of the distal portion of the trachea and carina, dorsal displacement of the left bronchus, loss of caudal cardiac waist with the dilated chamber extending dorsally and caudally. On dorsoventral view, increased left atrial size was defined as increased opacity of the heart base caused by summation of the enlarged chamber and bulging of the left heart border at the 2–3 o'clock position. Radiographic signs of tracheal collapse, bronchial collapse, bronchial pattern, and bronchiectasis were interpreted as concomitant airway abnormalities potentially responsible for coughing. Collected data were transferred onto an electronic spreadsheet[a] and verified by 2 of the investigators (LF and MB) for accuracy.

### *Statistical Models*

Univariate logistic models were used to assess the patient's likelihood of exhibiting coughing. The radiographic variables considered in the analysis were cardiogenic pulmonary edema (CHF), increased LA size, cardiomegaly (VHS >10.7), VHS (continuous variable), bronchial pattern, tracheal collapse, bronchial collapse, and combined presence of radiographic airway abnormalities (thereafter indicated as "pattern of airway disease—all causes", which is a composite category including any of the preceding 3 variables). Two continuous variables (LVDd% and LA/Ao) and 2 categorical echocardiographic variables (LVDd >10% normal and LA/AO >1.5) were included in the analysis of echocardiographic variables. Age and body weight were analyzed both as continuous and categorical variables (greater than or less than 8.5 years and 8.6 kg for age and body weight, respectively). Such threshold values were arbitrarily extrapolated from a recently published study showing that dogs with airway collapse were significantly older (mean age, 8.5 years) and had lower body weight (mean body weight, 8.6 kg).[16] All of these variables are referred to as "cough model specific variables" hereafter.

Multivariate models were generated using statistically significant variables from the univariate analysis. Two different multivariate models relating to radiographic (model 1) and echocardiographic (model 2) variables were chosen in an effort to avoid potential multicollinearity. Furthermore, to avoid collinearity and overfitting, highly significant pattern of airway disease (all causes) and pulmonary edema were retained from model 1 and placed in conjunction with the continuous variables from the multivariate model 2, to create model 3.

Finally, to address modifying effects, 2-way adjusted interaction models were generated to address the interaction of left atrial (LA) enlargement (increased LA size assessed by radiography and LA/AO >1.5 measured echocardiographically) and the presence or absence of abnormal airway pattern. A 2-way adjusted interaction also was used to assess the interaction of increased LA size on thoracic radiographs with age measured as a continuous variable.

All analyses were conducted using SAS[b] and a type 1 error probability of 0.05 was utilized as an indication of statistical significance.

Normally distributed data in the results are expressed as mean ± standard deviation (SD) and nonparametric data are expressed as median (25th – 75th percentile).

## Results

The database query identified 206 cases of dogs (49.5% female, 50.5% male) with an echocardiographically confirmed diagnosis of MMVD, which fulfilled all of the inclusion criteria. These dogs belonged to 49 different breeds, with mixed breeds being the most frequently represented group (12.9%), followed by

Miniature Poodles (7.1%), Yorkshire terriers (6.7%), and Cocker spaniels (6.7%). Their mean age was 10.7 ± 2.5 years (range, 3.8–16.6), with a median body weight of 9.0 (6.0–16.7) kg (range, 1.8–52.0).

Seventy-two dogs (34.9%) were asymptomatic. Ninety-nine dogs (48.5%) had a clinical observation of coughing and 27 of these dogs had radiographic evidence of cardiogenic pulmonary edema (27.3%). Sixty-seven coughing dogs had a concomitant radiographic airway abnormality (32.5%) and only 6 (6.1%) had radiographic evidence of pulmonary edema in the absence of an abnormal airway pattern. Fifteen dogs (7.3%) had tachypnea or dyspnea not associated with CHF. Finally, all dogs with radiographic evidence of pulmonary edema had a clinical presentation compatible with tachypnea or dyspnea (100%), with or without coughing.

Left atrial size was increased in 143 (69.4%) dogs on radiographic examination and in 124 (60.2%) on echocardiographic examination (LA/Ao >1.5) with a median LA/Ao ratio of 2.0 (1.8–2.4) (range, 1.51–3.6). Cardiomegaly, interpreted as increased VHS (>10.7), was observed in 143 dogs (69.4%) on radiographic examination. Left ventricular size was increased in 140 dogs (67.8%) on echocardiographic examination (LVDd >10%).

Univariate logistic regression analysis consisted of 16 independent variables modeling the presence of cough. All cough model specific variables were associated with a greater incidence of cough with the exception of cardiogenic pulmonary edema. Based on radiography, 8 variables (increased left atrial size, VHS, cardiomegaly [VHS >10.7], bronchial pattern, tracheal collapse, bronchial collapse, and all causes of radiographic airway abnormalities) were found to be significantly associated with cough. Based on echocardiography, 4 variables (LVDd%, cardiomegaly [LVDd >10%], LA/Ao ratio, and increased left atrial size [LA/AO >1.5]) were associated with cough. Finally, both old age and small body weight were associated with coughing (Table 1).

Two multivariate models were generated to assess the validity of the univariate models in the presence of other variables. Analyzing radiographic variables using model 1, 2 of the cough model specific variables (increased LA size and radiographic indication of abnormal airway pattern) were statistically significant. In assessing echocardiographic cough model specific variables significant in univariate analysis and expressed continuously (model 2), LA/Ao remained significant. Interestingly, in model 3, abnormal radiographic airway pattern (all causes) exhibited an even greater adjusted odds ratio (AOR) as did LA/Ao, whereas pulmonary edema and LVDd% showed similar results (Table 2).

The first 2-interaction analysis exhibited approximately a 4-fold greater odds ratio for dogs that presented with radiographically enlarged left atrium in the presence of abnormal radiographic airway pattern as opposed to those with enlarged left atrium without a radiographically detectable abnormal airway pattern (Fig 1A). A similar phenomenon was observed with echocardiographic LA/AO ratio >1.5, for which a 2-fold increase was observed (Fig 1B). A divergent interaction effect may be present for 2 variables, but the interaction terms were nonsignificant for the enlarged LA (radiographic finding) by abnormal airway pattern ($P = .458$) as well as the interaction of LA/AO >1.5 by abnormal airway pattern ($P = .307$), suggesting that both of these main effects might act independently of each other. An additional interaction was analyzed between age as a continuous variable and the presence or absence of enlarged LA. Although increased age, especially in the presence of an enlarged LA (radiographic finding), would be expected to exhibit a larger AOR, the interaction again was nonsignificant ($P = .856$) despite the significant effect reported in univariate analysis for the respective variables reported in Table 1 (Fig 2).

**Table 1.** Result of the univariate analyses showing the association between the risk of developing cough and radiographic/echocardiographic variables, as well as signalment, in 206 dogs with naturally acquired mitral valve disease.

| Variables | Odds Ratio | Lower 95% CI | Upper 95% CI | *P* Value |
|---|---|---|---|---|
| Radiographic assessment | | | | |
| Cardiogenic pulmonary edema (CHF) | 1.369 | 0.723 | 2.594 | .3350 |
| Increased left atrial (LA) size | 3.637 | 1.904 | 6.950 | <.0001 |
| VHS >10.7 | 2.653 | 1.421 | 4.955 | .0022 |
| VHS value | 1.658 | 1.262 | 2.179 | .0003 |
| Pattern of airway disease (all causes) | 3.650 | 2.051 | 6.496 | <.0001 |
| Bronchial pattern | 8.776 | 2.519 | 30.579 | .0006 |
| Tracheal collapse | 3.310 | 1.831 | 5.983 | <.0001 |
| Bronchial collapse | 3.332 | 1.400 | 7.926 | .0065 |
| Echocardiographic assessment | | | | |
| LVDd >10% | 2.220 | 1.211 | 4.068 | .0099 |
| LVDd% | 1.021 | 1.008 | 1.034 | .0012 |
| Left atrial enlargement (LA/Ao >1.5) | 2.553 | 1.436 | 4.539 | .0014 |
| LA/Ao | 2.510 | 1.498 | 4.206 | .0005 |
| Signalment | | | | |
| Elderly dog (>8.5 year) | 3.263 | 1.536 | 6.930 | .0021 |
| Age | 1.144 | 1.024 | 1.279 | .0177 |
| Small dog (body weight <8.6 kg) | 1.795 | 1.033 | 3.115 | .0381 |
| Body weight | 1.036 | 1.007 | 1.067 | .0156 |

CHF, congestive heart failure; VHS, vertebral heart score; LVDd >10%, percent increase in left ventricular diameter in diastole greater than 10%; LVDd%, percent increase in left ventricular diameter in diastole; LA/Ao >1.5, ratio between left atrial diameter and aortic root diameter greater than 1.5; LA/Ao left atrial diameter and aortic root ratio.

## Discussion

In this study, there was no statistical association between coughing and CHF, identified by radiological evidence of cardiogenic pulmonary edema, in dogs with naturally acquired MMVD. Several observations support this finding. Primarily, it has been clearly dem-

**Table 2.** Multivariate models relating to radiographic and echocardiographic variables that were significant in the univariate analyses reported in Table 1.

| Significant Variables | Adjusted Odds Ratio | Lower 95% CI | Upper 95% CI | *P* Value |
|---|---|---|---|---|
| *Model 1* | | | | |
| Radiographic assessment | | | | |
| Cardiogenic pulmonary edema (CHF) | 0.663 | 0.317 | 1.385 | .2739 |
| Increased left atrial (LA) size | 3.477 | 1.605 | 7.537 | .0016 |
| VHS >10.7 | 1.462 | 0.702 | 3.046 | .3100 |
| Pattern of airway disease (all causes) | 3.505 | 1.905 | 6.450 | <.0001 |
| *Model 2* | | | | |
| Echocardiographic assessment | | | | |
| LVDd% | 1.011 | 0.996 | 1.027 | .1501 |
| LA/Ao | 1.900 | 1.010 | 3.573 | .0463 |
| *Model 3* | | | | |
| Radiographic/echocardiographic assessment | | | | |
| Pulmonary edema | 0.685 | 0.322 | 1.485 | .3267 |
| Pattern of airway disease (all causes) | 4.255 | 2.285 | 7.925 | <.001 |
| LVDd% | 1.015 | 0.999 | 1.032 | .692 |
| LA/Ao | 2.062 | 1.022 | 4.159 | .0432 |

VHS, vertebral heart score; LVDd%, percent increase in left ventricular diameter in diastole; LA/Ao >1.5 indicates a ratio between left atrial diameter and aortic root diameter greater than 1.5.

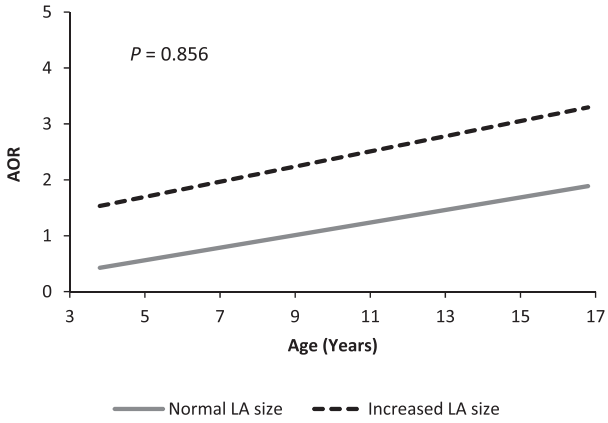


**Fig 2.** Interaction modelling presence or absence of increased left atrial (LA) size by age as a continuous variable.

onstrated that stimulation of cough receptors does not occur at an alveolar or interstitial level, but only in the proximal parts of the respiratory tree (eg, larynx, trachea, bronchi) in different animal models, including dogs.[4] Therefore, the presence of fluid in the alveolar or interstitial spaces should not trigger cough in patients with pulmonary edema, unless the amount of fluid is sufficient to flood the upper airways. In such an event, the fluid would be expected to produce a soft moist cough accompanied by blood-tinged foamy sputum, as observed in human patients.[6] However, this phenomenon usually is observed only in dogs with very severe or peracute cardiogenic pulmonary edema. Another important observation that emerges from our study is that dogs with pulmonary edema inevitably presented with dyspnea or tachypnea, supporting the fact that isolated coughing (without dyspnea or tachypnea) is a very unlikely sign of CHF in dogs. This observation would be compatible with observations in human patients, in whom common symptoms of CHF include fatigue, dyspnea, peripheral edema, and exercise intolerance, whereas cough is only considered a minor sign.[22] Interestingly, a recent study on the evaluation of clinical and echocardiographic variables to determine the presence of heart failure in dogs indicated that increased respiratory rate is one of the most independent predictors of CHF in dogs with dilated cardiomyopathy and MMVD.[23]

Another important consideration is that cough is an uncommon finding in other domestic species affected by CHF, such as the cat or horse, whereas tachypnea or dyspnea represents the most commonly reported finding.[11,24] Similarly, the major clinical finding in dogs affected by noncardiogenic pulmonary edema is tachypnea or dyspnea, rather than coughing.[25,26]

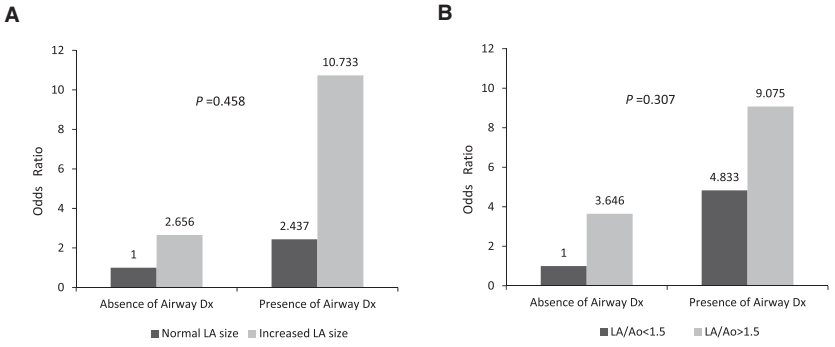


**Fig 1.** Interaction between the presence of abnormal radiographic airway pattern and the presence of left atrial enlargement assessed radiographically (A) and echocardiographically (B) for the risk of coughing in 206 dogs with naturally acquired mitral valve disease. LA/Ao indicates the ratio between left atrial diameter and aortic root diameter. Both interactions were not statistically significant at $\alpha = 0.05$ confidence level.

Finally, recent studies on prognostic characteristics in dogs with MMVD do not report coughing as a significant variable affecting survival, indicating that coughing, unlike respiratory effort and exercise intolerance, is not an important indicator of CHF severity in these patients.[27,28] If coughing was a strong indicator of CHF, survival of patients would have been affected by the cough score in these 2 studies.

The concomitant presence of airway disease suggested by an abnormal radiographic pattern represents the higher risk factor for coughing in dogs with MMVD. This result can be explained by the fact that the anatomical localization of the observed underlying pathology is expected to be associated with stimulation of cough receptors. Furthermore, the reported odds ratio may have been underestimated, given the lack of sensitivity of standard radiographic examination in identifying dynamic airway collapse when compared with fluoroscopy and bronchoscopy.[16,29] Traditional radiography also has poor sensitivity to detect infectious tracheobronchitis ("kennel cough"), which is a common cause of coughing in dogs.[10] Similarly, parasitic infection by *Dirofilaria immitis* or *Oslerus osleri* might cause cough without necessarily showing clinically relevant radiographic changes. Neoplastic lesions were not observed in the selected cases of this study, but they could represent another differential diagnosis in older dogs affected by MMVD. Coexisting diseases also have been reported in humans, in whom comorbidities, such as chronic obstructive pulmonary disease, are observed in many CHF patients.[30]

Left atrial size represents another potentially important cofactor for the presence of coughing in dogs affected by MMVD, and this is supported by the increased risk in dogs with increased LA size, observed on thoracic radiography or echocardiography. This finding supports previous observations that bigger than normal hearts can exert a mechanical dorsal pressure on the airways with subsequent stimulation of coughing receptors.[18] Such pressure, however, may not be the primary cause of bronchial collapse, as indicated in a study in which the association between LA enlargement and airway collapse was not confirmed in dogs with MMVD.[17]

The increased risk for coughing in dogs with radiographic suggestion of airway disease and increased LA size also emerges from the results of the multivariate analysis, suggesting that these 2 variables are the most important morbidity factors causing coughing in dogs with MMVD. The statistical analysis, however, also suggests that both of these main effects are statistically independent. Nevertheless, previous reports of young dogs affected by congenital cardiac abnormalities accompanied by substantial cardiomegaly do not mention cough as a presenting complaint.[31,32] Because airway disease is more commonly observed in older dogs, cardiomegaly may be a more likely cause of cough in patients with pre-existing airway disease as compared with young individuals with a healthy respiratory system. This hypothesis, however, does not seem to be statistically supported by the results of the interaction analysis presented in this study.

A confounding factor for the understanding of the coughing mechanisms in dogs with MMVD is the positive clinical response observed after administration of furosemide, the so-called "furosemide therapeutic trial", often performed in small animal practice to determine if a cough could be the result of pulmonary edema.[11] However, furosemide also can exert several anti-inflammatory and antitussive effects, which may result in a satisfactory inhibition of coughing, regardless of the possible presence (or absence) of CHF in a patient.[33,34] Another confounding factor in this context is the common self-limiting nature of infectious tracheobronchitis, suggesting that some of the perceived antitussive effects may not actually be caused by furosemide administration itself. Obviously, all of the above hypotheses would require additional studies.

A major limitation of this study is its retrospective design. Patients were seen by different clinicians at different institutions and therefore clinical and echocardiographic assessment may have varied. Furthermore, the type of coughing was not characterized in these patients, nor was its frequency and severity. Although resting or sleeping respiratory rate measured at home would have added important information, these data were not available in all patients.[23,35]

Another important limitation is represented by the fact that some patients may have already received diuretic treatment before their cardiology evaluation. Although we tried to exclude all patients that had received diuretics in the 24 hours before referral, some residual therapeutic effects cannot be completely excluded. However, we believe that if diuretic treatment was sufficient to resolve the radiographic signs of pulmonary edema in these cases, the clinical presentation would be expected to have changed accordingly. Conversely, a persistence of cough after successful diuretic treatment would have suggested an alternative underlying cause rather than pulmonary edema. Specific investigations of the airways, such as fluoroscopy or bronchoscopy, were performed in only a small number of patients. Therefore, the presence or absence of airway disease was only assessed radiographically, with the technical limitations described above. However, this is also true for detecting radiographic signs of CHF, which means that a proportion of dogs in this study may have had mild undetected CHF, despite thoracic radiography being considered the clinical "gold standard".[23] Furthermore, it has been reported in other studies that radiographic diagnosis of CHF in dogs is associated with relatively high observer variability.[23,36] Finally, only a relatively low number of dogs had radiographic changes consistent with CHF and this may have affected the strength of statistical results.

In conclusion, this study shows that coughing is not associated with CHF attributable to cardiogenic pulmonary edema in dogs with naturally acquired MMVD, whereas abnormal radiographic airway patterns and increased left atrial size showed a significant association with coughing in these dogs. The study also demonstrates that patients with radiographic

evidence of pulmonary edema typically are tachypneic or dyspneic, indicating that cough, in the absence of dyspnea or tachypnea, rarely should be considered as a sole clinical indication of CHF in dogs.

## Footnotes

[a] Microsoft Office Excel XP 2003, Microsoft Corporation, Redmond, WA
[b] SAS v.9.2, Cary, NC

## Acknowledgments

The authors thank all the clinicians working at their institutions who contributed to the diagnostic investigation and clinical management of the patients examined in this study. Special thanks also are attributable to Heidi Ferasin and Mark Rishniw for their detailed and constructive review of the manuscript. This study was not supported by any grants.

*Conflict of Interest*: Authors disclose no conflict of interest.

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