Myxomatous mitral valve degeneration (MMVD) is the most common cardiac disease in dogs in North America, accounting for 75% of all canine cardiac disease.¹ It is more prevalent in small dogs (< 20 kg), older animals, and female. Reportedly, 85% of small 13-year-old dogs exhibit evidence of a myxomatous mitral valve lesion,² though a valve lesion itself does not indicate clinical significance. The causes of MMVD are poorly understood, but it is assumed that there is a genetic factor. The onset of myxomatous degeneration on the valve leaflets or chordae tendineae results in incomplete coaptation, leading to mitral regurgitation (MR). The clinical presentation and progression of MMVD can vary heterogeneously, ranging from asymptomatic cases to potentially fatal cardiogenic pulmonary edema (CPE) depending on the severity of MR.³ The disease can be fatal or a life-long condition with little impact on the dog’s quality of life depending of its rate of progression.¹ In MMVD, estimates of cardiac-related death in dogs ranged from around 40% to 70% of cases.⁴ Prognosis is variable depending on the severity of the disease. Therefore, as with knowing the presence of the MMVD, assessment of the MMVD severity is also important in clinical practice.

OBJECTIVE
To evaluate the diagnostic value of pulmonary-vein-to-pulmonary-artery ratio (PV:PA) in dogs with myxomatous mitral valve degeneration (MMVD), classified according to the American College of Veterinary Internal Medicine (ACVIM) consensus guidelines.

ANIMALS
80 client-owned dogs with either MMVD (n = 65) or no cardiovascular disease (control group; n = 15) between August 5, 2020, and July 19, 2023.

METHODS
This is a retrospective study. Dogs with MMVD were classified according to ACVIM consensus guidelines. Echocardiograms, thoracic radiographs, and other measurements needed in this study were reviewed in all dogs. Spearman correlation was used to determine the correlation between the PV:PA and the following variables: vertebral heart size, vertebral left atrial size, left-atrium-to-aorta ratio, normalized left ventricular internal diameter, and peak transmitral early diastolic velocity. Receiver operating characteristic (ROC) curve analysis was used to evaluate the value of PV:PA in distinguishing between stages B1 and B2 and stages B2 and C.

RESULTS
All conventional indices showed correlations with PV:PA. The area under the ROC curve (AUC) for stages B1 and B2 was 0.83, and the cutoff value for differentiating stage B2 was 1.52. The AUC for stages B2 and C was 0.81, and the cutoff value for differentiating stage C was 2.09.

CLINICAL RELEVANCE
PV:PA was significantly different between control and the stage B1 group, stage B1 and B2 group, and stage B2 and C group. PV:PA can be an index that can be used in evaluating MMVD dogs.

Keywords: canine, echocardiography, myxomatous mitral valve degeneration, pulmonary artery, pulmonary vein

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Hemodynamically significant MR in dogs with MMVD can lead to cardiac remodeling, including left ventricular eccentric hypertrophy, enlargement of the left atrium (LA), and dilation of the pulmonary veins. Cardiac enlargement accelerates most rapidly 6 to 12 months before congestive heart failure (CHF) occurs. These days, veterinarians are classifying MMVD dogs according to MMVD classifications suggested by American College of Veterinary Internal Medicine (ACVIM) guidelines. Based on clinical trials, medical intervention starting at stage B2 onwards with pimobendan is recommended, so in practice, medical intervention with pimobendan is started in MMVD stage B2. Criteria suggested by ACVIM consensus guidelines for staging MMVD in dogs are murmur intensity, radiographic vertebral heart score (VHS), echocardiographic LA-to-artery ratio (LA:Ao) and left ventricular internal diameter in diastole normalized for body weight (LVIdDN), and clinical signs of heart failure. In addition to the indices mentioned above, the severity of MMVD needs to be assessed using various indices, and various studies have been conducted to evaluate the severity of MMVD.

The pulmonary-vein-to-pulmonary-artery ratio (PV:PA) is an index measured using echocardiography. Pulmonary veins are more compliant than the pulmonary artery and enlarge with increases in left ventricular end diastolic pressure or increased pulmonary blood flow. In MMVD, left ventricular end diastolic pressure increases with MR severity. Therefore, as the left ventricular end diastolic pressure increases in progression of MMVD, an increase in PV:PA can be anticipated as supported by 2 studies. The primary objective of this study was to compare the PV:PA with other indices commonly used for evaluating MMVD to determine the diagnostic value of the PV:PA in evaluating MMVD. The secondary objective was to determine whether the PV:PA can differentiate between stages B1 and B2 and between stages B2 and C.

Methods

Animals

Eighty dogs were reviewed in this study. The owners’ consent was acquired for all dogs in this study to review their clinical data. This study included client-owned dogs and a healthy control group. Client-owned dogs presented to Jeonbuk National University Veterinary Medical Teaching Hospital (from August 5, 2020, to July 19, 2023) due to medical checkups or due to clinical signs associated with systemic cardiovascular disease except for mild to moderate pulmonary hypertension; > 70 mm Hg, severe pulmonary hypertension). In this study, there were a total of 26 dogs with pulmonary hypertension dogs (6 mild pulmonary hypertension dogs in stage B1, 5 mild pulmonary hypertension dogs and 6 moderate pulmonary hypertension dogs in stage B2, and 7 mild pulmonary hypertension dogs and 2 moderate pulmonary hypertension dogs in stage C). None of the healthy control dogs exhibited MR in echocardiography and other systemic cardiovascular disease through other tests. Dogs with MMVD were classified according to the consensus statement of ACVIM.

Thoracic radiography

All dogs underwent thoracic radiography to obtain right lateral and ventrodorsal views. For both VHS and vertebral left atrial size (VLS), right lateral view was used, and measurement was performed using digital calipers. VHS and VLS were measured following studies previously reported. The lung field was evaluated, along with clinical signs, such as tachypnea, to diagnosis CPE, which is important for classifying the MMVD stage. Additional evaluations of patients by thoracic radiography, such as blood vessels and heart shape, were also performed.

Echocardiography

The same ultrasound machine (Epiq 7C; Koninklijke Philips N.V.) was used to perform 2-D, M-mode, pulsed-wave Doppler, continuous-wave Doppler, and color-flow Doppler echocardiography on all dogs. All echocardiography was performed by 2 trained observers, directed by the corresponding author. The same machine also performed a concomitant electrocardiogram during echocardiography. LA:Ao was measured by the Swedish method from the right-sided parasternal short-axis view, end of systolic phase. Left ventricular internal diameter in diastole (LVIddd) was measured from the right-sided parasternal short-axis view using M-mode, and LVIdDDN was calculated using the formula LVIddd(cm)/Body weight(kg). Peak velocity of early diastolic transmitral flow (Peak E) was measured from the left-sided apical view using Doppler echocardiography with pulsed-wave sample volume (2.0 mm in width) placed at between the opening of the mitral valves. PV:PA was measured in all dogs routinely during echocardiography to evaluate the pulmonary vein and pulmonary artery. PV:PA was measured from the right-sided long axis 4-chamber view modified for pulmonary vein and pulmonary artery at end systole, 1 frame before the mitral valve opening, or end of the T wave. The pulmonary vein and pulmonary artery were measured in the trilling-edge-to-leading-edge method. PV:PA measurements were only performed in 2-D mode, and the zoom function was used where necessary (Figure 1). If regurgitation in the
Tricuspid valve was confirmed on color-flow Doppler, velocity was measured with continuous-wave Doppler under color-flow Doppler guidance and transformed into a pressure gradient according to the modified Bernoulli equation. All measurements are the mean of values measured over 3 consecutive cardiac cycles. As this study is retrospective, the researchers were not fully blinded to the patient information.

Statistical analysis

All statistical analyses were performed using a commercial program (IBM SPSS statistics, version 29.0.0.0 (171); SPSS Inc). Continuous data were examined for normality using the Kolmogorov-Smirnov test. Based on the data distribution, the results were reported as the median and IQR. Continuous data among the 4 study groups were compared using the Kruskal-Wallis test. Pairwise comparisons between the control and B1 groups, the B1 and B2 groups, and the stage B2 and C groups were conducted using the Mann-Whitney U test. No correction for multiple comparisons was performed. Spearman correlations were used based on the data distribution to assess the correlations between the PV:PA and the other continuous variables (VHS, VLAS, LA:Ao, LVIDdN, Peak E). Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic value of the PV:PA and to define the cutoff values to diagnose MMVD stage B2 and C. The cutoff is determined by the highest sum of sensitivity and specificity. A P value < .05 was considered statistically significant.

Results

In the present study, 80 dogs were reviewed. The age, weight, sex, and breed data for the groups were summarized (Table 1). Dogs were reported as Maltese.

Table 1—Summary characteristics for 80 client-owned dogs reviewed in this study designed to evaluate the diagnostic value of pulmonary-vein-to-pulmonary-artery ratio, grouped based on whether they were healthy (control group; n = 15) or had myxomatous mitral valve degeneration classified according to the American College of Veterinary Internal Medicine (ACVIM) guidelines as stage B1 (n = 30), B2 (n = 19), or C (n = 16) between August 5, 2020, and July 19, 2023.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>ACVIM stage B1</th>
<th>ACVIM stage B2</th>
<th>ACVIM stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n= 80)</td>
<td>15</td>
<td>30</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Age (y)</td>
<td>7.0 (5–11.5)</td>
<td>11.0 (10.0–11.0)</td>
<td>11.0 (10.0–12.5)</td>
<td>12.0 (10.0–13.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.0 (3.9–10.2)</td>
<td>5.3 (4.2–8.5)</td>
<td>5.0 (3.6–7.5)</td>
<td>3.9 (2.4–5.0)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5:10</td>
<td>11:19</td>
<td>10:9</td>
<td>9:7</td>
</tr>
</tbody>
</table>

Median (IQR) for continuous data.
F = Female, M = Male.
All of the dogs with myxomatous mitral valve degeneration in this study were classified according to ACVIM guidelines. Median (IQR) for continuous data.

ACVIM = American College of Veterinary Internal Medicine. LA:Ao = Left-atrium-to-aorta ratio. LVIDdN = Normalized left ventricular internal diameter in diastole. Peak E = Peak transmural early diastolic velocity. PV:PA = Pulmonary-vein-to-pulmonary-artery-ratio. VHS = Vertebral heart size. VLAS = Vertebral left atrial size.

(a) Difference from ACVIM stage B1. (b) Difference from ACVIM stage B2. (c) Difference from control group. (d) Difference from ACVIM stage B2.

The results of Spearman correlation (ρ) analyses indicated significant (P < .001) positive correlations between the PV:PA and VHS (ρ = 0.398), VLAS (ρ = 0.607), LA:Ao (ρ = 0.712), LVIDdN (ρ = 0.753), and Peak E (ρ = 0.668). All measurements related to left ventricular filling pressure or LA pressure correlated positively with the PV:PA.

Figure 2—Box plot illustrating the pulmonary-vein-to-pulmonary-artery-ratio (PV:PA) ratio in 80 dogs reviewed in this study between August 5, 2020, and July 19, 2023. Dogs with myxomatous mitral valve degeneration (MMVD) were classified according to the American College of Veterinary Internal Medicine guidelines. The box contains the 25th to 75th percentiles. The line inside the box indicates the median, the cross inside the box indicates the mean value, and the circle outside the box indicates the outliers. Pairwise comparisons between the control and stage B1 groups, the stage B1 and B2 groups, and the stage B2 and C groups were conducted, and all the results were found to be significant. *P = .004; **P < .0001; ***P = .002.
Currently, MMVD is diagnosed and classified according to the ACVIM consensus guidelines, utilizing methods such as clinical signs, thoracic radiography, and echocardiography. To evaluate the progression of MMVD in dogs, veterinarians utilize conventional indices such as VHS and VLAS from thoracic radiography as well as LA:Ao, LVIDdN, and Peak E from echocardiography. The PV:PA, investigated in this study, is easy to measure, like other conventional indices. In this study, we assessed the PV:PA as an evaluation tool for MMVD by comparing it with other conventional indices; comparing the PV:PA between the control and stage B1 groups, the stage B1 and stage B2 groups, and the stage B2 and stage C groups; and conducting ROC curve analysis between the stage B1 and B2 groups and the stage B2 and C groups, respectively.

The principal finding of this study is that the PV:PA has significant correlation with other conventional indices (VHS, VLAS, LA:Ao, LVIDdN, and Peak E) and that there were significant differences in the PV:PA between the control and stage B1 groups, the stage B1 and stage B2 groups, and the stage B2 and stage C groups. We also suggested cutoff values to differentiate stage B1 from stage B2 and stage B2 from stage C based on our results.

In the previous studies, research had been conducted on PV:PA in normal dogs and MMVD dogs classified based on International Small Animal Cardiac Health Council (ISACHC) guideline. Comparisons were made between all groups, and significant differences were observed only between groups IB, II, and III compared to the control group and between groups II and III compared to group IA. However, to the best of the authors’ knowledge, investigation based on the stages specified in the ACVIM consensus guidelines had not been undertaken yet. Enlargement of the pulmonary veins reflect an increase in pulmonary venous pressure and can serve as a predictive index for CPE. In this study, research on PV:PA was conducted according to the groups classified in the ACVIM consensus guidelines. Previous studies evaluated and demonstrated satisfactory reproducibility; therefore, we did not assess reproducibility. In this study, the PV:PA measurement were taken solely from 2-D images.

In the comparison between the control and stage B1 group, unlike other indices, only the PV:PA was found to be statistically significant. According to the ACVIM consensus guidelines in MMVD dogs, stage B1 is defined as asymptomatic dogs with mitral valve regurgitation not severe enough to meet the criteria related to LA and left ventricle (LV) enlargement, for using medical treatment to delay the onset of heart failure.

Unlike the ISACHC guidelines, which classify ISACHC IB in subjective terms (findings of left heart enlargement), the ACVIM consensus guidelines suggest specific standards to classify the dog as stage B2. Based on the echocardiographic measurements from a previous study, it can be speculated that some dogs classified as ISACHC IB should be classified as stage B2. In clinical practice, there are dogs with MMVD with mild to moderate left heart enlargement who do not fulfill the criteria of stage B2. This could explain the difference between the control and stage B1 groups in this study but the lack of difference between the control and ISACHC IB groups in Merveille et al. From the authors’ experience,
it has been observed that pulmonary vein enlargement precedes LA and LV enlargement in cases of acute CHF caused by chordae tendineae rupture of the mitral valve. Pulmonary vein enlargement might precede LA enlargement because the pulmonary vein consists of smooth muscle, which is replaced by myocardium as the pulmonary vein connects to the LA. The PV:PA may be more sensitive and reflect changes more rapidly in response to alterations in intracavitary pressure compared to other conventional indices. Our results potentially demonstrate this. More prospective studies comparing the PV:PA in dogs with stage B1 MMVD and healthy dogs are needed. In the comparison between the stage B1 and B2 groups, all of the measurements, including the PV:PA, were found to be statistically significant as expected (P < .001). Various attempts have been made to assess the severity and prognosis of MMVD in dogs, and these results suggest that the PV:PA may also be helpful in evaluating MMVD severity and prognosis.\textsuperscript{3,6–10,13,15,22} In the comparison between the stage B2 and C groups, the PV:PA and LA:Ao were found to be statistically significant. Our findings indicate that LA:Ao and the PV:PA can be used as diagnostic indices in dogs with preexisting left heart remodeling due to MMVD (MMVD stage B2). In previous studies,\textsuperscript{30} LA:Ao has been utilized as a predictor of CHF in dogs with MMVD, and our study demonstrated similar results.

In the correlation analysis, all of the conventional indices demonstrated in this study showed a significant correlation with the PV:PA (P < .001). This was expected based on prior research.\textsuperscript{14} This finding suggests that the PV:PA can function as a useful echocardiographic index with which to evaluate and monitor dogs in MMVD, similar to other conventional indices.

ROC analysis was conducted between stage B1 and stage B2 and stage B2 and stage C using the PV:PA as the index. The comparison between stage B1 and stage B2 revealed an AUC of 0.83, with a calculated cutoff value of 1.52 (sensitivity, 90%; specificity, 65%). Currently, according to ACVIM consensus guidelines, the indices to diagnosis stage B2 include VHS and VLAS from thoracic radiograph and LA:Ao and LVIddN from echocardiography.\textsuperscript{1} Considering the results from this study, the PV:PA can offer additional information with which to evaluate MMVD stage B2 in dogs. The comparison between stage B2 and stage C revealed an AUC of 0.81, with a calculated cutoff value of 2.09 (sensitivity, 81%; specificity, 73%). Currently, diagnosing CHF in dogs with MMVD involves identifying the clinical signs, confirming pulmonary edema through thoracic radiograph, performing an echocardiographic examination using Doppler studies, and measuring serum N-terminal pro-B-type natriuretic peptide.\textsuperscript{1,9,23–26} Considering the result from this research, the PV:PA exhibits potential as a diagnostic tool for CHF in dogs with MMVD. Other Doppler measurements can also be used to diagnose CHF in dogs with MMVD. However, these measurements require a considerable level of experience in echocardiography.\textsuperscript{5,26,27} On the contrary, the PV:PA is an accessible index that can be measured in 2-D mode, similar to LA:Ao and LVIddN.

This study has several limitations. First, left atrial pressure was not directly measured by heart catheterization due to the procedure’s invasiveness, risk of complications, and requirement for general anesthesia. Consequently, the precise quantification of congestion due to MR was not feasible. Instead, this study employed alternative conventional indices related to the severity and prognosis of MMVD in dogs.\textsuperscript{1,3,7,10,11,13} A second limitation is in the population of this study; Malteses were overrepresented (22/80 [27%). A third limitation is that treatments were not controlled in the stage B2 and C groups. Some of dogs were administered pimobendan if they had been diagnosed with MMVD stage B2 previously. However, if dogs were presented to veterinary hospital for the first time due to CPE caused by MMVD, they had not been administered any cardiovascular treatment prior to the veterinary hospital presentation. The administration of pimobendan during MMVD stage B2, prior to the onset of CPE, may have impacted the outcomes. Additionally, some patients in MMVD stage C were administered furosemide for stabilization before echocardiography. Furosemide can reduce congestion in the LA and pulmonary veins, potentially influencing the results.\textsuperscript{28} A further study on the impact of furosemide on the pulmonary veins is needed. In order to indirectly determine the level of congestion through the PV:PA, it is essential for the pulmonary artery to remain constant. However, in the case of pulmonary hypertension, pulmonary artery enlargement occurs.\textsuperscript{29–33} In this study, we excluded dogs with severe pulmonary hypertension; however, those with mild to moderate pulmonary hypertension, which are part of pathophysiology of MMVD, were not excluded.\textsuperscript{4,31} There is a potential for the PV:PA to be underestimated in dogs with pulmonary hypertension. Lastly, while previous studies\textsuperscript{8,14} assessed the reproducibility of the PV:PA, we did not.

In conclusion, in dogs with MMVD, the PV:PA increases at each stage of the disease. The PV:PA can be utilized in diagnosing and staging dogs with MMVD, along with other conventional indices. Furthermore, in this study, there was a statistically significant difference between the stage B1 and B2 groups, meaning it could be used to distinguish between and monitor progression from stage B1 and to stage B2. The PV:PA can also serve as a diagnostic index of CHF in cases where left ventricular remodeling has already occurred. The respective cutoff values have been proposed as 1.56 and 2.09. Further study with a larger population and prospective design of PV:PA in dogs with MMVD is warranted.

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Disclosures

The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.
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