Respiratory phase can affect pulmonary vein-to-pulmonary artery ratio measured with CT

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OBJECTIVE
To evaluate pulmonary vein (PV)-to-pulmonary artery (PA) ratios obtained in healthy dogs by means of various CT protocols, accounting for the effects of the respiratory phase and contrast agent used.

ANIMALS
10 healthy Beagles.

PROCEDURES
Before and after contrast medium (600 mg iodine/kg) was injected IV, thoracic CT was performed with a positive-pressure breath-hold (inspiratory phase) and at the end of expiration (expiratory phase). After CT scanning, echocardiography was performed, and an optimized right parasternal long-axis view was obtained for measurement of PV and PA diameters. The PV and PA diameters were measured subsequently for each CT protocol.

RESULTS
Mean ± SD PV:PA values obtained from pre- and postcontrast inspiratory CT were 1.058 ± 0.072 and 1.020 ± 0.053, respectively, which were comparable to the echocardiographic value (P > .05). Mean PV:PA values obtained with pre- and postcontrast expiratory CT were 1.259 ± 0.094 and 1.239 ± 0.066, respectively, which were significantly (P = .005) greater than inspiratory CT measurements. There was a significant (r > 0.5, P < .05) linear relationship between PV:PA values obtained with pre- and postcontrast inspiratory CT and echocardiography.

CLINICAL RELEVANCE
PV:PA could be measured with thoracic CT in a manner similar to that for echocardiography. However, PV:PA values measured with expiratory CT were different from previously reported values. Therefore, the respiratory phase should be considered when evaluating pulmonary vascular size through CT, and measurements with the inspiratory CT protocol would be more accurate.

Pulmonary hypertension (PH) can be categorized as precapillary or postcapillary. The former type may be caused by heartworm disease, congenital shunts, and chronic respiratory disease, whereas the latter type may be caused by left-heart diseases such as myxomatous mitral valve degeneration and myocardial disease.1 PH may affect the cardiovascular system negatively and increases the likelihood of death.1,2

Right pulmonary artery (PA) catheterization is the gold standard for diagnosing PH.3 However, this procedure is invasive and associated with patient risks.4 Therefore, pulmonary arterial pressure is estimated indirectly by measuring tricuspid regurgitation (TR) and pulmonary regurgitation (PR) velocities with Doppler echocardiography. However, regurgitant flow may not be present or sufficient for measurement, and obtaining proper probe alignment is often difficult, leading to inaccurate measurements.5,6 To compensate for these limitations, several indexes have been developed, such as the main PA-to-aorta (AO) ratio and right PA distensibility index, which are noninvasive, straightforward to use, and not affected by Doppler ultrasonographic alignment restrictions.7,8 In recent studies,9-11 the pulmonary vein (PV)-to-PA ratio determined by means of echocardiography was described in healthy dogs and dogs with diseases such as myxomatous mitral valve degeneration and precapillary PH, and measuring PV:PA in this way was shown to be a noninvasive adjuvant tool in the diagnosis of PH in dogs with these diseases. Morphologic CT analysis of the pulmonary blood vessels in healthy dogs and dogs with diseases such as pulmonary thromboembolism has been undertaken previously.12-14 However, a quantitative comparison between the PV and PA measured by means of CT has not been performed. Moreover, several lung diseases, such as chronic obstructive
pulmonary disease, pulmonary thromboembolism, and pulmonary fibrosis, that can cause PH\textsuperscript{15} are common indications for thoracic CT, and clinical signs such as cough, exercise intolerance, and syncope in dogs with cardiopulmonary diseases are nonspecific. Therefore, thoracic CT is indicated along with echocardiography to differentiate between respiratory and cardiac disease. In light of this, it would be useful to determine the diagnostic utility of PV:PA measurements obtained by means of thoracic CT in the diagnosis of PH. In addition, it is known that changes in blood flow and diameter occur in pulmonary blood vessels according to the respiratory cycle\textsuperscript{16–18}; however, changes in PV:PA measurements associated with respiratory stage have not been reported.

The objectives of our study were to compare PV:PA values obtained by means of thoracic CT in healthy dogs with those obtained by means of echocardiography, and to evaluate the effect of contrast injection and respiratory phase on PV:PA values measured with thoracic CT.

**Materials and Methods**

**Animals**

Ten purpose-bred healthy Beagles (8 sexually intact females and 2 sexually intact males) with a mean weight of 10 kg (range, 7.5 to 11 kg) were used in the study. Dogs were housed at Seoul National University and were used for noneuthanasia research. All dogs were considered healthy on the basis of the results of a physical examination, thoracic radiography, and echocardiography performed prior to anesthesia. The study protocol was approved by the Seoul National University Institutional Animal Care and Use Committee (SNU-210818-3).

**CT**

Acepromazine (0.02 mg/kg, IV, once) was administered as a premedication. For anesthetic induction, alfaxalone (2.0 mg/kg, IV, once) was administered. Dogs were then intubated, and anesthesia was maintained with isoflurane in oxygen. Noninvasive blood pressure, oxygen saturation, heart rate, and end-tidal carbon dioxide (CO\textsubscript{2}) concentration were monitored during anesthesia.

All CT scans were performed with a 64-slice scanner (Aquilion 64; Toshiba Medical Systems) by a veterinarian with expertise in diagnostic imaging (JL). All dogs were positioned in sternal recumbency, and helical transverse images were acquired with the following parameters: 1.0-mm slice thickness, 120 kVp, 200 mAs, 512 X 512 matrix, 0.75 s/rotation, and a spiral pitch factor of 1.484. Both pre- and postcontrast CT scans were performed for all dogs with a positive-pressure breath-hold (inspiratory phase) and at the end of expiration (expiratory phase). Inspiratory-phase CT scans were performed with a positive-pressure breath-hold of 15 cm H\textsubscript{2}O. Then, expiratory-phase scans were obtained after confirming that end-tidal CO\textsubscript{2} concentration was 0. Although the time it took for end-tidal CO\textsubscript{2} concentration to reach 0 varied for each individual, it was less than 10 seconds. The scan time, including both the inspiratory and expiratory phases, was less than 60 seconds. Subsequently, iodinated contrast medium (2 mL/kg, IV; Omnipaque 300, GE Healthcare) was injected through a preloaded IV catheter at a rate of 2 mL/s with an injector (Stellant, Medrad Inc.). Because the dogs weighed 7.5 to 11 kg, contrast injection took about 10 seconds (range, 7.5 to 11 s). Immediately after contrast administration, CT scans were performed in the inspiratory and expiratory phases in the same manner. Scans were examined to determine that the PVs and PAs of all dogs had sufficient contrast enhancement.

**Echocardiography**

CT and echocardiographic examinations were performed on the same day in all dogs. After CT scanning, echocardiography was performed while each dog was still anesthetized, so that measurements obtained with the 2 modalities under the same conditions could be compared. All echocardiographic examinations were performed with a 2- to 9-MHz sector transducer (Arietta 850, Hitachi Ltd). The dog was positioned in right lateral recumbency, and electrocardiographic leads were connected. The presence of TR and PR was confirmed in the standard right parasternal long-axis and short-axis views. Subsequently, as described previously,\textsuperscript{9,11} the optimized right parasternal long-axis view for the measurement of PV and PA diameters was obtained. To obtain the optimized right parasternal long-axis view, the transducer was moved apically and angled dorsocranially, visualizing the ostium of the right PV longitudinally and the right PA transversely (Figure 1). All images were acquired by a veterinarian with expertise in diagnostic imaging (JL).

**CT and echocardiographic measurement of PV and PA**

Anonymized data were assigned to 3 veterinarians with expertise in diagnostic imaging (JL, JC, LB) and were evaluated independently with DICOM viewer software (RadiAnt DICOM Viewer, Medixant). Measurements of the PV and PA diameters were performed on 2-D and time–motion mode (MM) echocardiographs. As described previously,\textsuperscript{11} the diameters of both vessels were measured on a line perpendicular to the long axis of the PV and bisecting the PA (Figure 1). To obtain PV:PA, mean values were calculated for at least 3 PV and PA diameter measurements obtained from the 2-D and MM echocardiographs. Both blood vessel diameters were measured with the inner edge-to-inner edge method at the end of the T wave. The diameter of the AO was measured in the right parasternal short-axis view with the inner edge-to-inner edge method immediately after aortic valve closure, as described previously, to calculate PV:AO and PA:AO for normalizing PV and PA diameter, which are weight-dependent variables.\textsuperscript{10,19} As with the echocardiograms, PV:PA was obtained on the basis of sagittal images after multiplanar reconstruction of CT scans. The diameter of the PV was measured perpendicular to the long
axis of the vessel on an image showing the PV longitudinally before entering the left atrium through the right ostium, and the maximum diameter of the PA was measured on an image showing the PA transversely, dorsal to the right PV (Figure 2). Most measurements of PV and PA diameters on CT scans were made on slices on which the cranial and caudal vena cavae were shown together. The PV diameter was measured before the vessel entered the left atrium, after fusion of the right middle and cranial lobar PVs. Subjectively, the trunk formed after the confluence of these 2 blood vessels was increased in width but was of similar or slightly increased height in the sagittal plane. Subsequently, the widest short-axis diameter of the AO was measured on the transverse plane. Measurements of PV, PA, and AO diameters were performed 3 times to evaluate intraobserver variability. To investigate interobserver variability, 2 additional observers (JC and LB) performed the same measurements as described.

**Statistical analysis**

All statistical analyses were performed by a veterinarian (JL) with statistical software (SPSS Statistics 25; IBM Corp). Statistical significance was set at values of \( P < .05 \). All variables were assessed with the Shapiro-Wilk test to determine whether they were normally distributed. To display graphically the variability in CT measurements among observers, measurements obtained by each observer for each CT scan protocol were averaged and displayed as box-and-whisker plots. Using mean values for all 3 observers, the difference in PV:PA values between CT protocols was determined with the Friedman test because some variables did not follow a normal distribution. The Wilcoxon signed-rank test was used for post hoc pairwise comparisons with a Bonferroni-corrected alpha cutoff of 0.008 (0.05/6) for the 6 pairwise comparisons. The strength of the relationship between PV:PA values obtained with each CT protocol and echocardiography was investigated by calculating the Pearson or Spearman correlation, according to the variable distribution. Comparisons between each CT- and echocardiography-based value were performed with a \( t \) test or Mann-Whitney test for normally and non-normally distributed variables, respectively. In addition, intra- and interobserver variability associated with vascular measurements was assessed.
To determine intra- and interobserver variability of PV:PA, PV:AO, and PA:AO, intra- and interobserver coefficients of variation were calculated. If the coefficient of variation was less than 10%, agreement was considered good.

**Results**

Pulmonary arterial pressure could not be measured because TR and PR were not observed in any of the dogs in our study. PH was considered absent on the basis of physical examination, thoracic radiographic, and echocardiographic findings.

On precontrast CT scans of all 10 dogs, the boundary between the PV and PA was unclear (Figure 2). Therefore, measurements were performed on the basis of difference in the shapes and courses of the 2 vessels on successive sagittal images. Variability in PV:PA values among the 3 observers for each CT protocol were assessed graphically (Figure 3). To investigate the effect of the CT protocol on measured values, protocols were compared on the basis of mean measured values from all 3 observers (Table 1). There was a significant difference among PV:PA values obtained with the 4 protocols, and post hoc pairwise comparisons showed that the expiratory protocol had significantly greater PV:PA values than the inspiratory protocol for both the pre- and postcontrast scans. This difference was a result of increased PV and decreased PA diameters, as recognized by changes in PV:AO and PA:AO. There was no significant difference between pre- and postcontrast PV:PA values obtained with the inspiratory (P = .333) or expiratory (P = .959) protocols.

Mean ± SD PV:PA values obtained by the 3 observers with 2-D and MM echocardiography were 1.065 ± 0.050 and 1.078 ± 0.269, respectively. Mean PV:PA values obtained by the 3 observers using each protocol were compared (Table 2). There were significant linear relationships between precontrast inspiratory CT PV:PA values and echocardiographic values, and between postcontrast inspiratory CT values and echocardiographic values. No linear relationships were observed between precontrast expiratory PV:PA values and echocardiographic values or between postcontrast expiratory CT values and echocardiographic values. In addition, PV:PA values measured with pre- and postcontrast expiratory CT protocols were significantly greater than those measured with echocardiography. The PV:PA values obtained with pre- or postcontrast inspiratory CT protocols did not differ significantly from those measured with echocardiography.

For CT and echocardiographic measurements, the mean interobserver coefficient of variation

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**Figure 3**—Box plots of the pulmonary vein (PV)-to-pulmonary artery (PA) ratio measured by each of 3 observers on images obtained with 4 thoracic CT protocols. Mean values obtained by each observer are included above each box. For each plot, the box represents the interquartile (25th to 75th percentile) range, the horizontal line in each box represents the median, and the whiskers represent the range.

**Table 1**—Mean ± SD for the pulmonary vein (PV)-to-pulmonary artery (PA) ratio, PV-to-aorta (AO) ratio, and PA-to-AO ratio measured by 3 observers on images of 10 healthy dogs obtained with 4 CT protocols.

<table>
<thead>
<tr>
<th>Thoracic CT protocol</th>
<th>Precontrast inspiratory</th>
<th>Precontrast expiratory</th>
<th>Postcontrast inspiratory</th>
<th>Postcontrast expiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV:PA</td>
<td>1.058 ± 0.072 a</td>
<td>1.259 ± 0.094 b</td>
<td>1.040 ± 0.053 a</td>
<td>1.239 ± 0.066 b</td>
</tr>
<tr>
<td>PV:AO</td>
<td>0.474 ± 0.057 a</td>
<td>0.539 ± 0.070 b</td>
<td>0.497 ± 0.069</td>
<td>0.536 ± 0.062</td>
</tr>
<tr>
<td>PA:AO</td>
<td>0.449 ± 0.035</td>
<td>0.428 ± 0.030</td>
<td>0.477 ± 0.056</td>
<td>0.432 ± 0.036</td>
</tr>
</tbody>
</table>

Within a row, values with different letters are significantly different (P < .005).
for PV:PA, PV:AQ, and PA:AQ ranged from 2.2% to 11.0%. Meanwhile, the mean intraobserver coefficient of variation ranged from 0.6% to 5.2%, showing good inter- and intraobserver agreement, except for PA:AQ values obtained with the precontrast inspiratory CT protocol, for which the interobserver coefficient of variation was 11.0%.

**Discussion**

In our study, PV:PA values obtained during the inspiratory phase of thoracic CT were comparable to values obtained by means of echocardiography. However, PV:PA values measured during the expiratory phase of CT were significantly greater than values obtained with echocardiography and values obtained during the inspiratory phase of thoracic CT.

According to previous studies\(^{20-22}\) of PV anatomy in dogs, the PVs anastomose before entering the left atrium to form cone-shaped trunks that connect to 3 ostia (cranial left ostium, caudodorsal ostium, and right ostium). The right ostium of the PV is formed by the fusion of the right middle and cranial lobar PVs and is separated from the other 2 ostia by the PA, which runs dorsally.\(^{20-22}\) In our study, all measurements of the PV on CT scans and echocardiographs were performed at the anastomosis of the blood vessels that continued to the right ostia. However, the sectional plane obtained by CT scanning, in which the vessel diameter is measured parallel to the long axis of the dog in the gantry, is different from the axis of the heart as imaged by echocardiography. Moreover, because the measurement is not performed in a perfectly circular structure, differences in measurements may be caused by angle differences.

In previous studies,\(^{9,10}\) reference intervals of healthy dogs were reported as a mean PV:PA of 1, with excellent intra- and interobserver reproducibility with 2-D and MM echocardiography. The mean PV:PA obtained from the inspiratory CT protocol was close to 1 both before and after contrast administration, which was comparable to the results of previous studies.\(^{9,10}\) However, the PV:PA values obtained from expiratory CT protocols were significantly greater than those obtained from inspiratory CT protocols. This finding indicates there is an effect of the respiratory phase on PV:PA measurements, and the respiratory phase should be considered when measuring PV:PA with thoracic CT. The increased PV:PA value with expiratory CT protocols may be the result of increased PV size and decreased PA size associated with changes in PV:AQ and PA:AQ between protocols. The size of the vessel depends on the blood flow, intravascular hydrostatic pressure, and vascular compliance. PVs are more compliant and generally larger with left ventricular failure or increased pulmonary blood flow.\(^{23}\) PAs enlarge principally because of increases in pulmonary blood flow and PA pressure.\(^{24}\) Cyclic modifications of the heart’s hemodynamics during respiration, including changes in intrathoracic pressure that occur during inspiration and expiration, cause fluctuations in the blood flow in the heart.\(^{25}\) During normal respiration, intrathoracic and intrapericardial pressures decrease with inspiration, which causes an increase in right ventricular filling and stroke volume, with a compensatory decrease in left ventricular filling and stroke volume. With expiration, intrathoracic and intrapericardial pressures increase, resulting in opposite changes.\(^{25-27}\) However, inspiratory CT scans were obtained with positive-pressure breath-holding, and expiratory CT scans were performed without any positive pressure in our study. With positive-pressure ventilation, intrathoracic pressure increases during inspiration, as opposed to what occurs during normal respiration, resulting in decreased venous return, right ventricular cardiac output, and pulmonary blood flow.\(^{28,29}\) In addition, as interstitial pressure increases, compressing the pulmonary capillaries and impeding flow, fluid retention occurs in the interstitium. Intrathoracic pressure decreases during expiration, increasing the capillary flow and venous return.\(^{30}\) Moreover, changes in airway pressure during positive-pressure ventilation cause changes in the transmural pressure of the pulmonary vessels, which is related to vessel diameter.\(^{31}\) When the lungs inflate, the pressure surrounding the extra-alveolar vessels decreases because of the radial traction of the alveolar wall, and the diameter of the blood vessels increases.\(^{32}\) During positive-pressure ventilation, the PA diameter increases as the airway pressure increases.\(^{33}\) We assert that these phenomena combine to cause the significantly different mean PV:PA values with expiratory versus inspiratory CT protocols related to increased PV diameter and decreased PA diameter during expiration.

In our study, imaging with both modalities was performed with the patients under anesthesia so that we could compare PV:PA values measured with thoracic CT and echocardiography. The mean PV:PA ratio measured with echocardiography was close to 1 with both 2-D and MM, as in previous studies performed on awake dogs.\(^{34-41}\) The change in pulmonary vessel diameter is determined by the change in pulmonary blood flow according to the change in pulmonary vascular resistance. Because the anesthetic

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**Table 2**—Correlations between pulmonary vein-to-pulmonary artery ratios obtained with 4 thoracic CT protocols and values obtained with 2-D and time-motion mode (MM) echocardiography.

<table>
<thead>
<tr>
<th>Echocardiographic mode</th>
<th>Thoracic CT protocol</th>
<th>Precontrast inspiratory</th>
<th>Precontrast expiratory</th>
<th>Postcontrast inspiratory</th>
<th>Postcontrast expiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-D</td>
<td></td>
<td>0.727 (.017)</td>
<td>0.010 (.978)</td>
<td>0.654 (.049)</td>
<td>0.179 (.621)</td>
</tr>
<tr>
<td>MM</td>
<td></td>
<td>0.690 (.027)</td>
<td>0.075 (.857)</td>
<td>0.718 (.019)</td>
<td>0.381 (.271)</td>
</tr>
</tbody>
</table>

Data are expressed as correlation coefficient (P value).
agents used in our study are known not to cause significant changes in pulmonary vascular resistance,\textsuperscript{4,33} the PV:PA values would have been similar to those in awake dogs. However, the sensitivity of blood vessels to drugs such as sedatives varies from drug to drug and from vessel to vessel,\textsuperscript{36} and a quantitative analysis of PVs and PAs before and after use of drugs with an effect on vascular resistance in dogs has not been performed. Therefore, although PV:PA measurements could be performed in dogs sedated or anesthetized with specific drugs, dedicated research about the effect of various anesthetic drugs on PVs and PAs is needed.

A moderate-to-strong correlation was found between PV:PA measurements obtained with pre- and postcontrast inspiratory CT protocols and those obtained with echocardiography ($r = 0.6$ to 0.8). There was no significant correlation between measurements obtained with pre- and postcontrast expiratory CT protocols and those obtained with echocardiography, and mean PV:PA values were significantly different between protocols. The absence of a correlation between PV:PA values measured with the expiratory CT protocol and echocardiography may have been a result of inconsistent changes in the diameters of the PV and PA during expiration. The respiratory phase was not considered when measuring PV:PA with echocardiography, whereas with the expiratory CT protocol, respiratory movement was completely restricted to obtain PV:PA measurements. Therefore, there may have been a difference in the mean PV:PA values between the 2 modalities. Other factors associated with these differences may include different angles affecting the sections used to measure vessel diameters. Each cross section obtained at different angles with CT and echocardiography may cause changes in the measured diameter of the PVs and PAs.

Variability within and between observers in the PV and PA measurements on CT scans and echocardiograms was favorable, as demonstrated by the low mean coefficient of variation. Although the boundary between the PV and PA was not clearly demarcated on precontrast CT images in all 10 dogs, it was not difficult to estimate the boundary in successive sagittal reconstructed images, because the 2 vessels had different courses and shapes. Statistical similarity between the PV:PA values obtained with pre- and postcontrast protocols and the repeatability of measurements obtained with pre- and postcontrast protocols implies that contrast is not essential for evaluating the diameter of the PV and PA. It should be noted that distinguishing between the PV and PA on sagittal reconstructed images would be highly dependent on the quality of the reconstruction, which is in part dependent on slice thickness. For clearer distinctions, it is important to keep the slice thickness as thin as possible. In fact, in all CT scans in our study, the slice thickness was 1.0 mm.

One of the limitations of our study was that the presence of PH could not be excluded because direct measurement of pulmonary arterial pressure was not performed through PA catheterization, and TR and PR measurements were not possible in any of the dogs. Moreover, because the number of dogs included in this study was small, the PV:PA values we calculated were insufficient for determining a reference interval. In addition, as most dogs in this study had similar body conformations, the measured values may change when different breeds and conformations are included. In our study, CT was not performed with ECG gating. A previous study\textsuperscript{4} showed that the PV:PA values obtained in systole and diastole in clinically normal dogs were similar. The use of gating for routine clinical measurements is impractical and was not considered in our study. However, PV:AO and PA:AO values differed among cardiac cycle phases in the previous study.\textsuperscript{9} Further research is required to estimate changes in PV:PA values according to the cardiac cycle in dogs with related diseases.

In our study, PV:PA—a new indicator proposed previously in echocardiographic studies—was measured with thoracic CT, yielding values with inspiratory CT protocols similar to those obtained with echocardiography. In diagnosing PH, CT evaluation can help identify abnormalities in both cardiovascular and pulmonary structures; additional information can be obtained if the changes in related blood vessels, such as the PV and PA, are evaluated together. However, the respiratory cycle had a significant effect on the PV:PA value measured with CT, which must be accounted for when evaluating the pulmonary vascular size with this modality. Because the PV:PA values measured with the inspiratory CT protocol were similar to those measured with echocardiography but not with those measured with the expiratory protocol, measurement with the inspiratory CT protocol would be more practical. Further studies comparing the PV:PA values of diseased and healthy control dogs are required to determine the reference range for PV:PA values obtained with CT.

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