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Evaluation of left ventricular function with cardiac magnetic resonance imaging and echocardiography after administration of dobutamine and esmolol in healthy beagle dogs

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ABSTRACT. Unlike echocardiography, cardiac magnetic resonance imaging (cardiac MRI) results in a near-exact assessment of cardiac structures and function. However, most veterinary studies have focused on dogs with normal cardiac function. We hypothesized that there would be significant differences in cardiac measurements between cardiac MRI and echocardiography when left ventricular (LV) function was abnormal. This study was undertaken to compare measurements of LV function produced by cardiac MRI and echocardiography in dogs whose LV function was altered by pharmacological agents. This study was conducted with six healthy beagle dogs. We increased left ventricular contractility by administration of dobutamine; we decreased cardiac contractility with esmolol. Stroke volume measurements were made by using both cardiac MRI and echocardiography under seven different conditions with general anesthesia: control, three doses of esmolol (100, 200, and 500 µg/kg/min), and three doses of dobutamine (10, 20, and 50 µg/kg/min). Experiments involving each condition were conducted at least 1 week apart. When LV contractility was normal, ejection fraction (EF) and stroke volume (SV), as measured by echocardiography and cardiac MRI, were not significantly different. However, when contractility was changed by pharmacological agents, EF and SV were overestimated by echocardiography, compared to MRI. Evaluation of cardiac function in patients treated with pharmacological agents should be conducted carefully because EF and SV measured by echocardiography can be overestimated, compared with EF and SV obtained by cardiac MRI.

KEY WORDS: dobutamine, echocardiography, esmolol, left ventricular function, magnetic resonance imaging

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Cardiac MRI provides a large field of view, unlimited scanning planes, high tissue contrast, and three-dimensional (3D) images. These characteristics make this technique useful for the diagnosis and staging of the severity of cardiac diseases, including cardiomyopathy, congenital heart diseases, valvular diseases, and pulmonary hypertension [9]. The established clinical role of cardiac MRI in human medicine is to perform morphological and functional assessment of complex diseases of the heart and great vessels; cardiac MRI is considered the gold standard in human medicine for measuring left ventricular (LV) volume and function [2]. In contrast, echocardiography utilizes geometric modeling with 3D cardiac volumes calculated from two-dimensional (2D) measurements. The limitations of echocardiography result from the assumption that the heart is ellipsoid-shaped and that volume calculations are derived from 2D measurements; some probe angles result in foreshortened views of the LV, and different views cannot be obtained during a single cardiac cycle [4]. In a study of human patients, end diastolic volume (EDV) and end systolic volume (ESV), as measured by echocardiography, were smaller than those measured by cardiac MRI [13].

In beagle dogs, a recent study showed no significant differences in EDV, ESV, stroke volume (SV), or ejection fraction (EF), as measured by contrast echocardiography, compared to measurements made by cardiac MRI [6]. Further, when compared to echocardiography, LV function was more accurately assessed by cardiac MRI in clinically normal domestic cats [8]. However, these studies were performed on healthy animals; the two modalities have not been compared in a study of altered LV function.

We hypothesized that when LV function was altered, EF, EDV, ESV, and SV measured by echocardiography would significantly differ from values measured by cardiac MRI. This study was undertaken to compare measurements of LV function evaluated by

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cardiac MRI and echocardiography in healthy dogs whose LV function was altered by pharmacological agents.

MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee of the Laboratory Animal Research Center, Chungbuk National University (CBNUA-1005-16-01).

Dog

Six beagle dogs (three males, three females; 1–3 years of age; weight: 8.7 ± 1.5 kg), were used in this study. Dogs were determined to be healthy based on physical examination, serum biochemical analysis (7020 clinical analyzer, HITACHI Co., Tokyo, Japan), complete blood count (ProCyte hematology analyzer, IDEXX Laboratories, Westbrook, ME, USA), electrolyte assessment (9180 electrolyte analyzer, HITACHI Co.), radiography (Toshiba Rotanode™, Toshiba Co., Tokyo, Japan), echocardiography (ProSound Alpha 7, Hitachi Aloka Medical Ltd., Tokyo, Japan), and urinalysis (IDEXX Vetlab UA, IDEXX Laboratories).

Study design

Cardiac MRI and echocardiography were performed under seven different conditions. For the control condition, 0.9% normal saline was continuously infused through the right cephalic vein at a rate two-fold greater than maintenance for placebo. Furthermore, two kinds of pharmacological agents were used intravenously: 1) the cardio-selective beta-1 receptor blocker esmolol (Brevibloc™, Jaeil Co., Seoul, Korea), to decrease contractility; 2) the sympathomimetic amine dobutamine (Toburex™, Iyeon Inc., Seoul, Korea), to increase contractility. Two pharmacological agents were administered at three different rates: low (100 µg/kg/min), middle (200 µg/kg/min), and high (500 µg/kg/min) in esmolol; and low (10 µg/kg/min), middle (20 µg/kg/min), and high (50 µg/kg/min) in dobutamine. These two pharmacological agents were diluted by using 0.9% normal saline, and the rate of infusion was identical to the control condition. In each dog, experiments involving the seven conditions were performed in random order. At least 7 days elapsed between each application of different drug or different concentrations to prevent drug interaction. The first echocardiography scan after drug administration was performed from the moment when heart rate (HR) and blood pressure (BP) reached a constant state and required approximately 10 to 15 min per dog. Cardiac MRI was scanned immediately after examination of echocardiography, such that the dogs could be maintained in the same condition. All MRI and echocardiography procedures were performed under general anesthesia.

Anesthesia

Anesthesia was induced with propofol (Provide injection™ 1%, Claris Injectables Ltd., Ahmedabad, India), administered intravenously at a dose of 6 mg/kg, and then maintained, after endotracheal intubation, with 2% isoflurane (Terrell™, Piramal Critical Care, Inc., Bethlehem, PA, USA). The respiratory rate was set at 8 to 11 breaths/min by using a ventilator, and tidal volume was adjusted to maintain end-tidal $PaCO_2$ between 30 and 35 mmHg. Heart rate (HR) was continuously measured by electrocardiography (ECG), and indirect systolic and diastolic and mean blood pressure (BP) were measured every 10 min at right pelvic limb. These anesthetic indices were monitored by a veterinary exclusive monitoring device (Cardell 9500 HD, MIDMARK, Dayton, OH, USA). All dogs completely recovered from anesthesia.

Echocardiography

For the Teichholz method of measurement, examination was performed with the dog in right lateral recumbency. For the modified Simpson method of measurement, examination was performed with the dog in left lateral recumbency. Three experienced sonographers (J.H.R., L.H.B., and J.J.H.) independently obtained scans in each experimental condition. Also three sonographers were blinded to the group. Videos from three cardiac cycles were recorded. In three cycles of images, each sonographer selected one cardiac cycle and images with the largest and smallest ventricular lumen were selected, via visual assessment, as the end-diastolic and end-systolic images, respectively. The measured echocardiographic indices (LVIDd and LVIDs of the Teichholz method; 2D measurement of LV dimension by manual tracing of the Simpson method) were the mean values of the three sonographers' measurements. The three times of echocardiography scan required an average of approximately 20 min.

In the Teichholz method at the right parasternal short-axis view, left ventricular systolic and diastolic internal diameters were measured, and EDV and ESV were calculated by using the following formula: LV volume=$(7 \times LVID^3) / (2.4 + LVID)$, where LVID is the left ventricular diameter [1].

In left apical 4 chamber view, the modified Simpson method, which traces the LV endocardial border, was used to measure LV volume. Computerized calculations treated the ventricle as a stack of discs, and the volumes for all discs were added to determine the total LV volume.

Cardiac MRI

MRI scans were performed by using a 1.5-Tesla MRI (Vantage Elan™, Toshiba Co.) with a 1-channel upper torso coil. Dogs were positioned in dorsal recumbency, and MRI-compatible ECG leads were applied to the left chest wall near the heart for ECG gating. During scanning for short-axis bright blood cine acquisitions, breath holding was applied to avoid motion artifacts. Short-axis bright blood cine acquisitions for cardiac motion used steady-state free precession sequence and were obtained with the following settings: matrix, 128 × 144; thickness, 8 mm; slice gap, 0 mm; time to repetition [TR], 4.6 msec; echo time [TE], 2.3

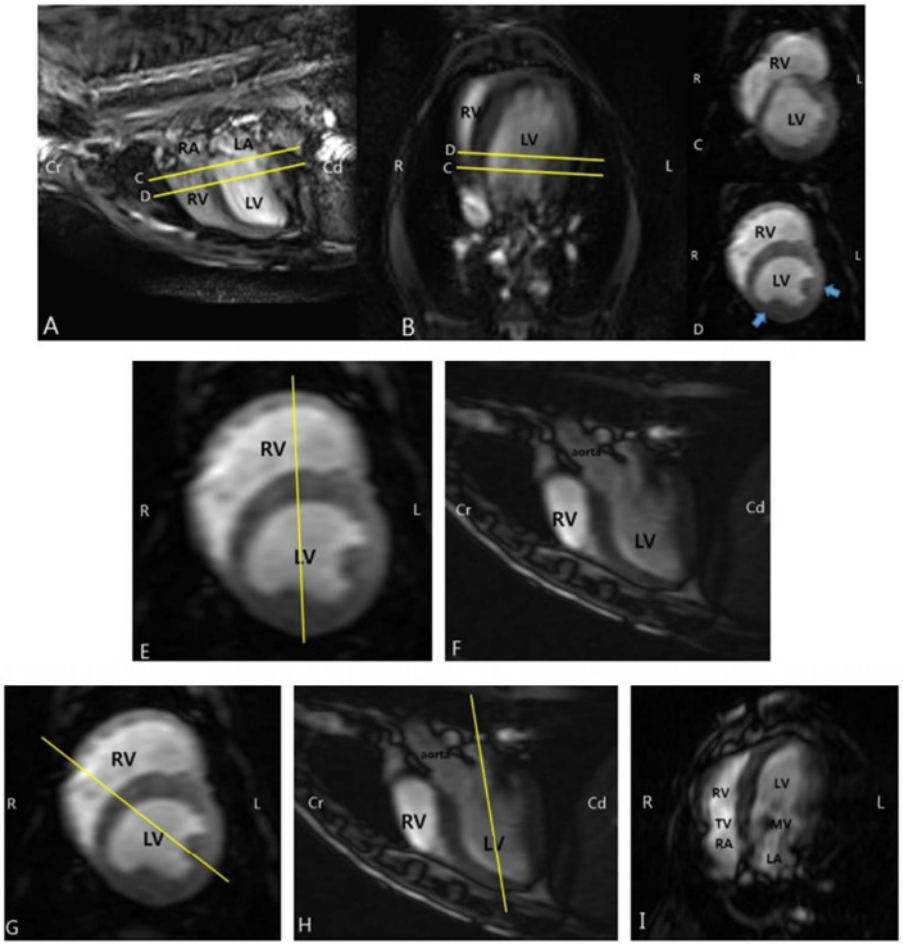

Fig. 1. Image planning to acquire a short-axis view, long-axis 3-chamber view (LVOT), and long-axis 4-chamber view in cardiac MRI. The left ventricle is shown on scout images of sagittal (A) and transverse (B) view. The yellow lines serve as a guide to obtain short-axis view (C, D). Check image of the short-axis view, including papillary muscles (D, arrows). In this short-axis view of papillary muscle level (E), left ventricular outflow tract (LVOT) view (F) is set along the yellow line. The imaging plane of long-axis 4-chamber view (I) is made along the yellow line in the short-axis view of papillary muscle level (G) or set perpendicular to the mitral valve in LVOT view (H).

msec; and flip angle, 45°. The number of slices to cover the whole LV was seven in each of the dogs.

To obtain the short-axis view, images containing LV were obtained in the sagittal and dorsal scout images (Fig. 1). In these LV scout images, the imaging plane was set under the mitral valve. The transverse view identified the papillary muscles. From this short-axis view, the left ventricle outflow tract (LVOT) and the four-chamber view were obtained (Fig. 1). When obtaining the four-chamber views, the image plane was rotated slightly to avoid the aorta (Fig. 1). This method of cardiac MRI scan was established by our previous study. [7] From the LVOT or four-chamber views, from the apex to the mitral valve level, short-axis images of LV were obtained (Fig. 2) to calculate cardiac output.

LV function assessment for cardiac MRI (bright blood cine imaging), including scanning for reference position, required 30 to 40 min; total scan time from echocardiography to cardiac MRI, including the time consumed for induction and general anesthesia and drug administration, required 60 to 70 min.

Cardiac magnetic resonance imaging analysis

Evaluation of the magnetic resonance images was performed by using semi-automated software (Osirix v.8.5., Bernex, Geneva, Switzerland). Using short-axis planes, regions of interest were semi-automatically drawn along the endocardial border of all images for the measurement of LV volume by one author (L.H.B.). The range of the LV was defined from the apex to the imaging plane with more than 25% of the annulus visible (Fig. 2) [3]. Whole LV was included in seven slices of short-axis imaging in all six dogs. EDV and ESV were defined as the smallest and largest LV volumes from each cardiac cycle, respectively. EDV and ESV were calculated by multiplying the cross-sectional area by 8 mm (the slice thickness), and adding all volumes derived from the seven slices. SV and EF were calculated by using the following equations:

$$SV\ (ml) = EDV - ESV$$

$$EF\ (\%) = (EDV - ESV) / EDV \times 100$$

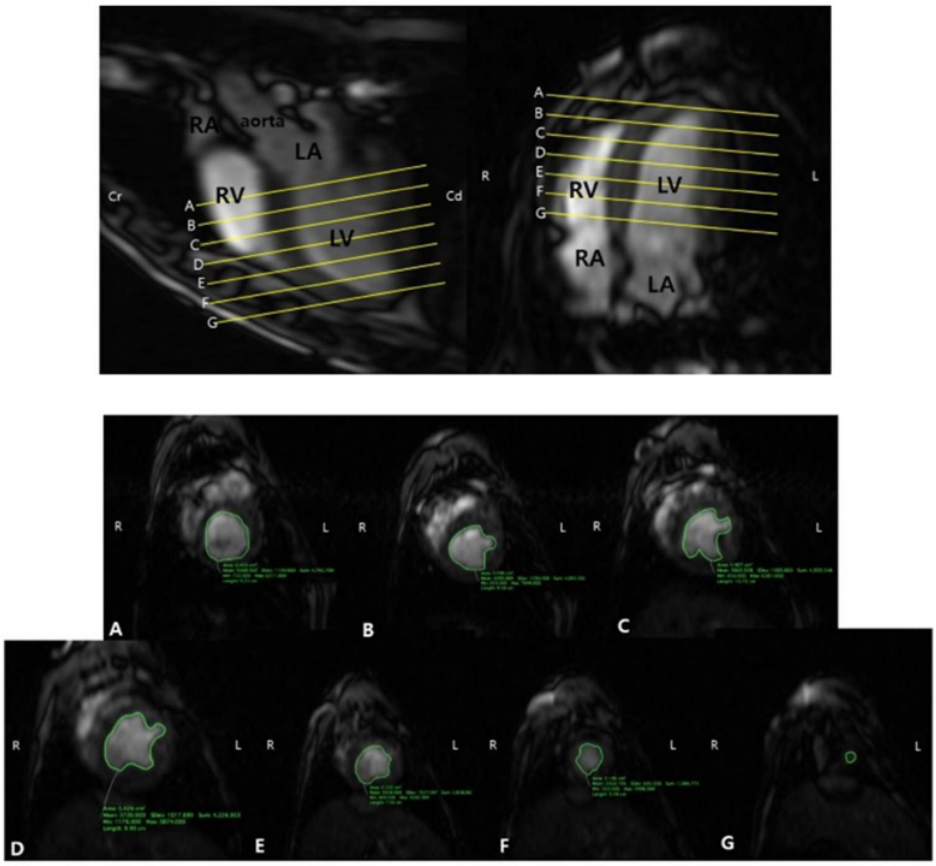

Fig. 2. Image planning to acquire short-axis view of whole left ventricle for measurement of cardiac output in cardiac MRI. In the long-axis 3-chamber view (LVOT) or 4-chamber view, short-axis images of left ventricle (A to G) are obtained along the yellow lines from mitral valve level to apex level, perpendicularly to interventricular septum. Using semi-automating software, the left ventricular endocardial area (A to G, green line) was traced and each area of the two-dimensional plane was added on both end systolic and end diastolic cycles. End diastolic volume (EDV) and end systolic volume (ESD) were calculated by multiplication of slice thickness (8 mm). The cardiac output was induced by using differences between EDV and ESV.

Statistical analysis

Statistical analysis was performed by using commercially available software (SPSS 11.0 for Windows, SPSS Inc., Chicago, IL, USA; Prism 6.0, Graph-pad Software, San Diego, CA, USA). In seven conditions, the number of subject in each group was six dogs. Since the number is small, a non-parametric statistical test was conducted. Under seven conditions, the SV and the EF measured by MRI were compared with those measured by echocardiography through the Teichholz method and Simpson method as respectively, by using the Wilcoxon signed rank test and the Bland-Altman analysis. P value of 0.017 was considered to indicate statistical significance (accounting for Bonferroni correction) to identify the difference between two modalities for each cardiac state. Wilcoxon signed rank test was used to compare drug-induced changes in cardiac function at each modality. A post hoc Bonferroni test was performed for each of conditions was compared with a corrected P value (P=0.05 / number of *post-hoc* comparisons, 0.002). Intra-class correlation coefficients (ICC) were calculated to determine the inter-observer reliability (0.8–1, good; 0.6–0.79, fair; 0.59 <, poor) for both the Teichholz and Simpson methods, for all three sonographers.

RESULTS

No significant reductions in heart rate or mean blood pressure after anesthesia were observed during cardiac MR scans following echocardiography examination. Therefore, the mean values of mean blood pressure and heart rate measured in each condition are shown in Table 1. Heart rate did not significantly differ between drug dosages, except at the dobutamine high dose (Table 1).

EDV tended to be consistent in all conditions, when measured by MRI. Although ESV increased and SV decreased as the dose of esmolol increased, ESV decreased and SV increased as the dose of dobutamine increased (Tables 2 and 3).

In echocardiography, EDV, ESV, and SV in each condition showed a similar relationship in cardiac MRI, depending on the method used to calculate volume, either Teichholz or Simpson (Tables 2 and 3). However, EDV was lowest at the high dose of dobutamine.

The results for the SV in each of the measurement methods are shown in Table 3. The SV measured by the Teichholz method

Table 1. Mean blood pressure and heart rate during cardiac MRI and echocardiography scans

Median (Range)	Drug concentration						
	E(H)	E(M)	E(L)	N	D(L)	D(M)	D(H)
Mean Blood Pressure (mmHg)	85.6 (70.5–100.8)	88.3 (76.6–100.0)	95.8 (83.8–107.8)	114.2 (103.9–124.4)	125.5 (115.2–135.7)	136.2 (115.6–156.6)	118.5 (110.9–126.1)
Heart rate (beats/min)	87 (69.4–104.5)	89.8 (72.3–107.4)	90.8 (73.9–107.7)	105.8 (79.7–131.9)	93.3 (71.0–115.6)	102.2 (82.6–121.6)	165.0 (139.9–190.1)

E(H), esmolol high dose (500 µg/kg/min); E(M), esmolol middle dose (200 µg/kg/min); E(L), esmolol low dose (100 µg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 µg/kg/min); D(M), dobutamine middle dose (20 µg/kg/min); D(H), dobutamine high dose (50 µg/kg/min).

Table 2. Volumes measured by cardiac MRI and echocardiography using the Teichholz and Simpson methods at each condition

Volume (ml) Median (Range)		Drug concentration						
		E(H)	E(M)	E(L)	N	D(L)	D(M)	D(H)
EDV	MR	27.8 (26.3–29.3)	25.9 (24.4–27.6)	25.1 (23.4–26.8)	26.9 (25.3–28.5)	28.0 (24.2–31.8)	28.4 (23.1–33.7)	27.4 (21.6–33.2)
	Echo(Tei)	21.8 (17.0–26.5)	20.7 (16.2–25.1)	19 (12.9–25.1)	19.5 (13.5–25.5)	22.1 (18.7–25.4)	22.5 (16.7–28.3)	13.8 (10.0–17.6)
	Echo(Sim)	13.5 (12.1–14.9)	13.6 (12.1–15.1)	13.5 (12.3–14.7)	13.5 (11.6–15.4)	14.5 (12.8–16.1)	14.8 (13.2–16.4)	10.5 (8.7–12.2)
ESV	MR	23.1 (17.3–28.8)	20.5 (15.0–26.1)	18.4 (13.1–23.7)	14.9 (8.7–21.1)	12.6 (8.8–16.4)	10.47 (7.3–14.2)	8.1 (5.2–11.0)
	Echo(Tei)	16.1 (12.2–19.9)	13.6 (10.0–17.2)	10.7 (7.1–14.3)	9.95 (6.3–13.6)	4.7 (3.2–6.1)	3.9 (2.0–5.7)	0.8 (0–2.26)
	Echo(Sim)	9.8 (8.9–10.7)	8.5 (8.0–8.9)	7.1 (6.6–7.6)	6.1 (5.2–6.9)	4.2 (3.5–4.9)	2.9 (1.9–3.8)	0.8 (0–1.7)

EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; E(H), esmolol high dose (500 µg/kg/min); E(M), esmolol middle dose (200 µg/kg/min); E(L), esmolol low dose (100 µg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 µg/kg/min); D (M), dobutamine middle dose (20 µg/kg/min); D(H), dobutamine high dose (50 µg/kg/min); MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

Table 3. Stroke volumes measured by cardiac MRI and echocardiography using the Teichholz and Simpson methods at each condition

Drug concentration	Stroke Volume (ml) Median (Range)			*P* value		
	MR	Echo(Tei)	Echo(Sim)		MR vs. Echo(Tei)	MR vs. Echo(Sim)
E(H)	2.8 (1.6–4.1)	5.6 (4.3–7.1)	3.5 (2.6–4.4)	0.002	0.002*	0.180
E(M)	5.4 (3.8–7.0)	7.1 (5.9–8.2)	5.3 (3.8–6.8)	0.014	0.017*	0.085
E(L)	6.7 (5.1–8.3)	8.2 (5.8–10.6)	6.7 (5.5–7.9)	0.176	0.180	0.090
N	8.8 (5.4–12.1)	9.5 (7.2–11.8)	7.5 (6.2–8.8)	0.122	0.571	0.258
D(L)	12.8 (10.5–15.0)	17.4 (12.9–21.8)	10.4 (9.1–11.6)	0.001	0.011*	0.009*
D(M)	15.2 (12.3–18.1)	18.6 (13–24.2)	11.9 (10.6–13.2)	0.001	0.093	0.008*
D(H)	17.1 (14.6–19.7)	12.9 (10.6–15.3)	13.6 (12.4–14.8)	0.001	0.004*	0.004*
P value	0.001	0.001	0.001			

*$P<0.017$. E(H), esmolol high dose (500 µg/kg/min); E(M), esmolol middle dose (200 µg/kg/min); E(L), esmolol low dose (100 µg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 µg/kg/min); D(M), dobutamine middle dose (20 µg/kg/min); D(H), dobutamine high dose (50 µg/kg/min); MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

showed a statistically significant difference in high and middle doses of esmolol, and in high, middle, and low doses of dobutamine, when compared with cardiac MRI. The SV measured by Simpson method was significantly different from SV measured by cardiac MRI only at high, middle, and low doses of dobutamine.

The EF was calculated from the LV volumes (EDV, ESV) measured by the Teichholz and Simpson methods through echocardiography and cardiac MRI (Table 4). The SV and EF significantly differed between echocardiography and cardiac MRI, except for the normal and esmolol conditions, between the Simpson method of echocardiography and cardiac MRI.

A significant difference was observed in the change of SV and EF induced by the drug at seven conditions in each modality (cardiac MRI, Teichholz method, and Simpson method). In post hoc analysis, the significance between adjacent conditions was additionally indicated in Fig. 3. There was a significant difference between most adjacent conditions.

Table 4. Ejection fraction measured by cardiac MRI and Echocardiography with Teichholz and Simpson methods at each condition

Drug concentration	Ejection Fraction (%) Median (Range)			*P* value		
	MR	Echo(Tei)	Echo(Sim)		MR vs. Echo(Tei)	MR vs.Echo(Sim)
E(H)	11.4 (6.1–16.7)	26.9 (20.9–32.9)	28.6 (25.0–32.2)	0.001	0.011*	0.001*
E(M)	21.2 (15.8–26.6)	34.9 (31.2–38.7)	37.6 (32.6–42.5)	0.001	0.003*	0.003*
E(L)	27.3 (20.3–34.4)	44.1 (41.1–47.0)	47.3 (43.6–51.1)	0.001	0.003*	0.001*
N	43.0 (28.2–57.8)	48.9 (45.0–52.8)	53.7 (50.3–57.0)	0.035	0.308	0.117
D(L)	54.2 (42.4–65.9)	78.0 (68.6–87.4)	70.2 (66.9–73.5)	0.001	0.011*	0.009*
D(M)	61.6 (51.0–72.2)	82.8 (73.6–91.9)	82.6 (78.7–86.6)	0.001	0.004*	0.001*
D(H)	70.7 (62.7–78.7)	96.8 (92.7–100.0)	92.4 (87.6–97.2)	0.001	0.001*	0.002*
P value	0.001	0.001	0.001			

*P<0.017. E(H), esmolol high dose (500 μg/kg/min); E(M), esmolol middle dose (200 μg/kg/min); E(L), esmolol low dose (100 μg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 μg/kg/min); D(M), dobutamine middle dose (20 μg/kg/min); D(H), dobutamine high dose (50 μg/kg/min); MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

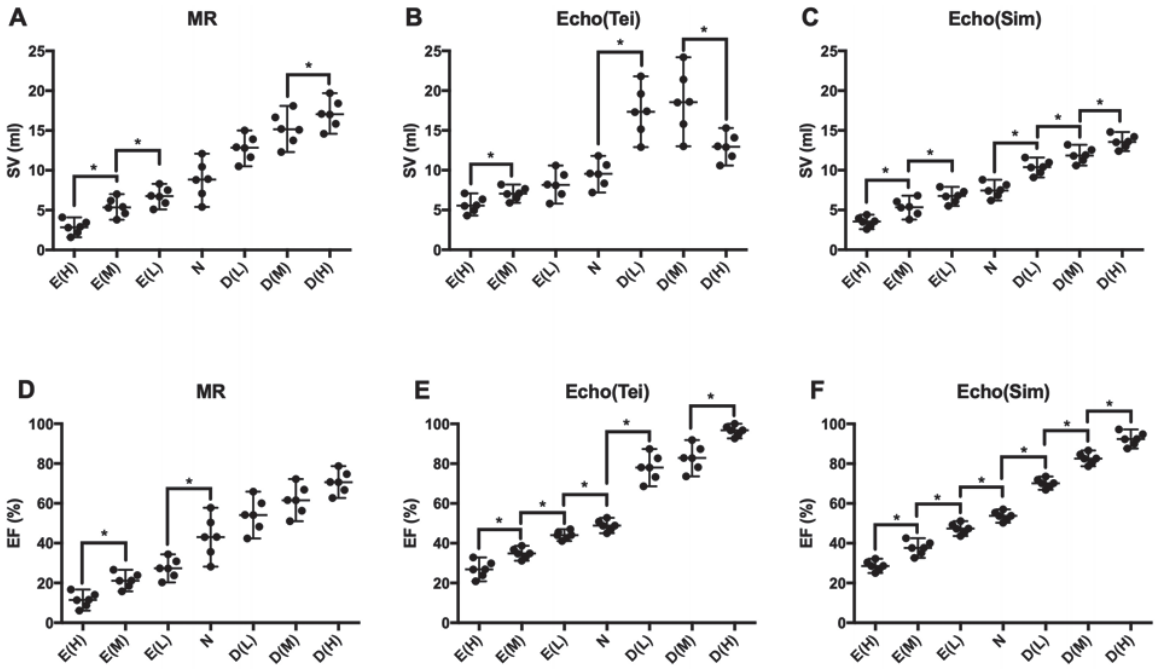

Fig. 3. Graphical presentation about stroke volume at cardiac MRI (A). Teichholz (B) and Simpson (C) method, and about ejection fraction at cardiac MRI (D), Teichholz (E) and Simpson (F) method with median and range. *P<0.002. SV, stroke volume; EF, ejection fraction; MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

A Bland-Altman analysis was performed to evaluate the agreement between the EF and the SV measured in two modalities (Table 5). The Bland-Altman plots about the SV and EV were also presented at Figs. 4–6 as respectively.

Inter-observer reliability among the three sonographers was the Teichholz method (mean ICC 0.957, confidence interval (CI): 0.91–0.988) and the Simpson method (mean ICC 0.916, confidence interval (CI): 0.89–0.952). The ICC for both methods was relatively high (ICC>0.9).

DISCUSSION

In the present study, there were no significant differences between the SV and EF measured by cardiac MRI and echocardiography in the normal condition. This result is consistent with the previously reported study in veterinary medicine [6]. The extent to which cardiac function decreases by anesthesia remains unclear. However, our results suggested that cardiac MRI and echocardiography do not show cardiac effects due to anesthesia. This is also evident because heart rate and mean blood pressure were maintained when echocardiography was performed first and cardiac MRI was performed during the experiment.

However, in each condition, the administration of both esmolol and dobutamine caused a significant difference in EF when

Table 5. Comparison of Left ventricular functional indices measured by cardiac MRI and Echocardiography with Teichholz and Simpson methods

			Bland-Altman	
			Difference (Bias)	± 1.96 SD
Stoke Volume (ml)	MR–Echo(Tei)	E(H)	−2.792	0.149
		E(M)	−1.675	0.319
		E(L)	−1.467	0.5715
		N	−0.725	0.743
		D(L)	−4.567	1.558
		D(M)	−3.4	1.909
		D(H)	4.167	0.163
		Whole	−1.494	2.794
	MR–Echo(Sim)	E(H)	−0.675	0.249
		E(M)	0.067	0.108
		E(L)	0.000	0.283
		N	1.308	1.453
		D(L)	2.433	0.708
		D(M)	3.3	1.131
		D(H)	3.525	0.955
		Whole	1.423	1.769
Ejection Fraction (%)	MR–Echo(Tei)	E(H)	−15.47	0.502
		E(M)	−13.73	1.167
		E(L)	−16.72	2.900
		N	−5.867	7.708
		D(L)	−23.86	1.663
		D(M)	−21.21	1.030
		D(H)	−25.88	3.082
		Whole	−17.53	7.132
	MR–Echo(Sim)	E(H)	−17.17	1.205
		E(M)	−16.41	0.332
		E(L)	−20.00	2.333
		N	−10.68	8.096
		D(L)	−16.03	5.975
		D(M)	−21.03	4.702
		D(H)	−21.70	2.263
		Whole	−17.57	5.400

E(H), esmolol high dose (500 μg/kg/min); E(M), esmolol middle dose (200 μg/kg/min); E(L), esmolol low dose (100 μg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 μg/kg/min); D(M), dobutamine middle dose (20 μg/kg/min); D(H), dobutamine high dose (50 μg/kg/min); MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method; SD, standard deviation.

MRI measurements were compared to those from echocardiography (P<0.017). EF measured by echocardiography was greater than that measured by MRI. This suggests that when LV function increases or decreases, EF measured by echocardiography may be overestimated and cannot be interchangeable with cardiac function indices obtained from the two modalities. To calculate LV volume by MRI, the endocardial border is traced. This is considered the golden standard for SV measurement and cardiac function evaluation in human medicine [11]. In echocardiography, the formula for calculating the volume assumes that the LV has an ellipsoidal shape. This assumption results in an overestimation of LV volume, compared to the volume measured by MRI.

In contrast, in the SV measured after esmolol administration, the Teichholz method showed significant differences from the SV measured by cardiac MRI. However, in the Simpson method, no significant differences were observed. This is consistent with several previous studies [12], which showed that the Simpson method measured SV more accurately than the Teichholz method.

However, when using dobutamine, the same result was observed with the EF; this suggests that echocardiography is not sufficiently accurate to measure SV when cardiac function is altered. In addition, when using dobutamine, the EDV, ESV, and SV measured by the Simpson method were lower than those measured by cardiac MRI and Teichholz method. Three sonographers performed a scan without interacting with each other; the values from the Teichholz method were higher than those measured by cardiac MRI. The mean ICC of the Teichholz method was 0.957, whereas the mean ICC of the Simpson method was 0.916. Inter-observer reliability among the three sonographers was greater in the Teichholz method; however, both methods showed satisfactory inter-observer reliability (>0.9). Both methods reliably assessed LV functional measurements, as determined by the three sonographers. Thus, an excessive increase in cardiac motion by dobutamine administration may make it difficult to scan the

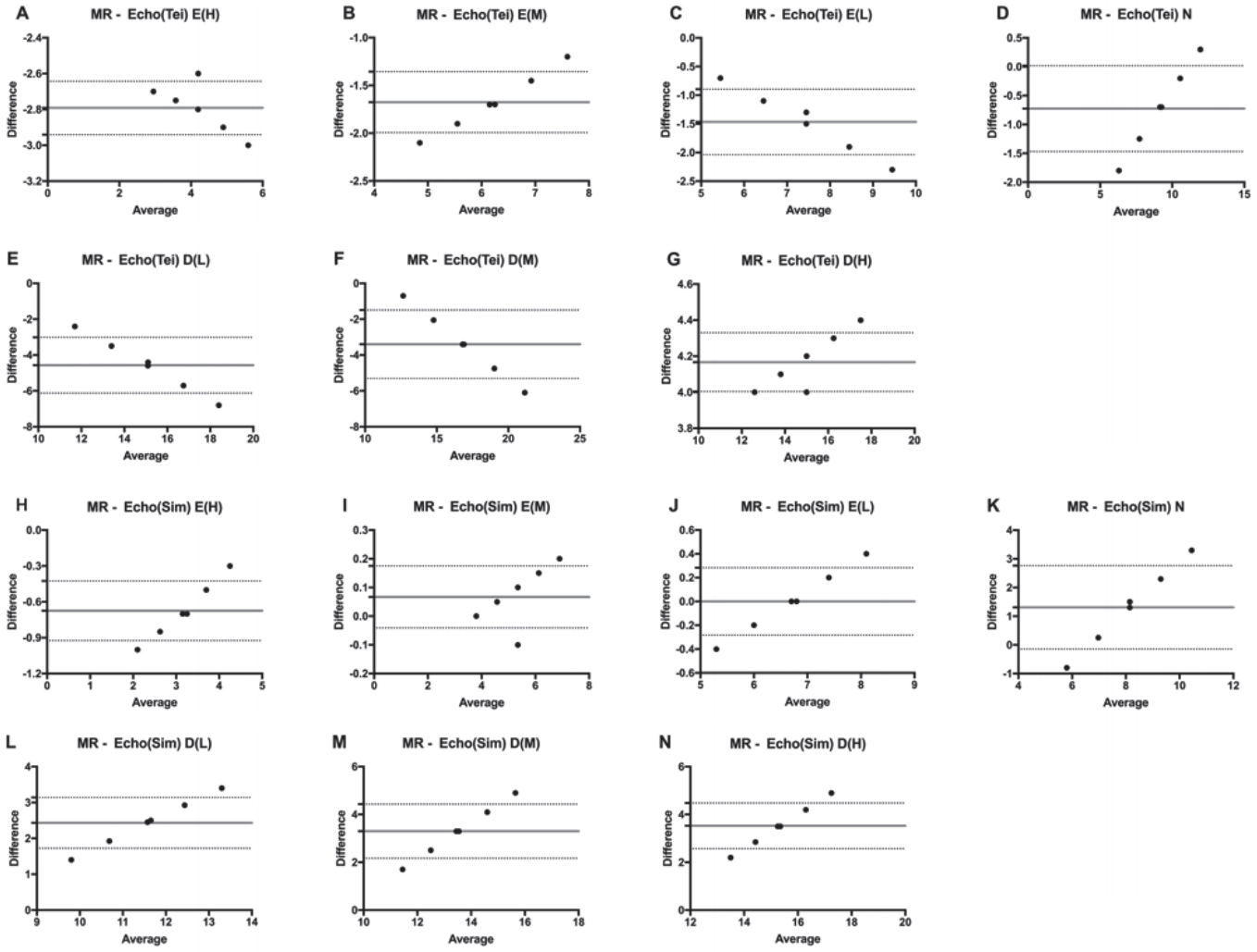

Fig. 4. Graphical presentation about comparison of stroke volume between cardiac MRI and echocardiography with Teichholz (A to G) and Simpson (H to N) method in Bland-Altman plots. Continuous lines depict the mean of differences; dashed lines denote limits of agreement (mean ± 1.96 times of standard deviation). E(H), esmolol high dose (500 μg/kg/min); E(M), esmolol middle dose (200 μg/kg/min); E(L), esmolol low dose (100 μg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 μg/kg/min); D(M), dobutamine middle dose (20 μg/kg/min); D(H), dobutamine high dose (50 μg/kg/min); MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

correct left apical view [5]. Therefore, scanning of long axis also might be foreshortened in this study [4].

After the administration of esmolol, SV decreased in a dose-dependent fashion, while EDV remained unchanged, and ESV increased. After the administration of dobutamine, SV increased in a dose-dependent fashion. However, at a high dose of dobutamine, EDV and ESV measured by echocardiography, using both measurement methods, were smaller than EDV and ESV measured at lower doses (Tables 2 and 3). Dobutamine has a mild chronotropic effect; at high doses, it can cause tachycardia [10]. In the present study, a high dose of dobutamine increased the mean heart rate to 165 beats/min, with a compensatory drop in mean BP. In patients with tachycardia, there is insufficient time for the LV to dilate, resulting in decreased diastolic filling.

A comparison of the difference in cardiac function indices obtained from the two modalities can be confirmed in the Bland-Altman analysis (Table 5, Figs. 4–6) as well. The value of variation (range of the mean of difference ± 2 standard deviations) between two modalities are too large to be clinically accepted. Therefore, the difference and the disagreement of the cardiac indices from two modalities which obtained in cardiac MRI and echocardiography in ventricular function altered were confirmed simultaneously. The measurement of EV from echocardiography is overestimated as in the paired comparison, and the SV measured by echocardiography and cardiac MRI may not be interchangeable.

Our results agree with a previous study [13], which showed that an increase in HR significantly influences LV internal dimension. In particularly, there was a decrease in EDV that remained constant in all conditions. However, no significant decrease in cardiac MRI was observed, compared to echocardiography. This phenomenon shows that directly measuring LV volume in cardiac MRI by measuring the internal area of the LV is more accurate than the method of estimating LV volume in

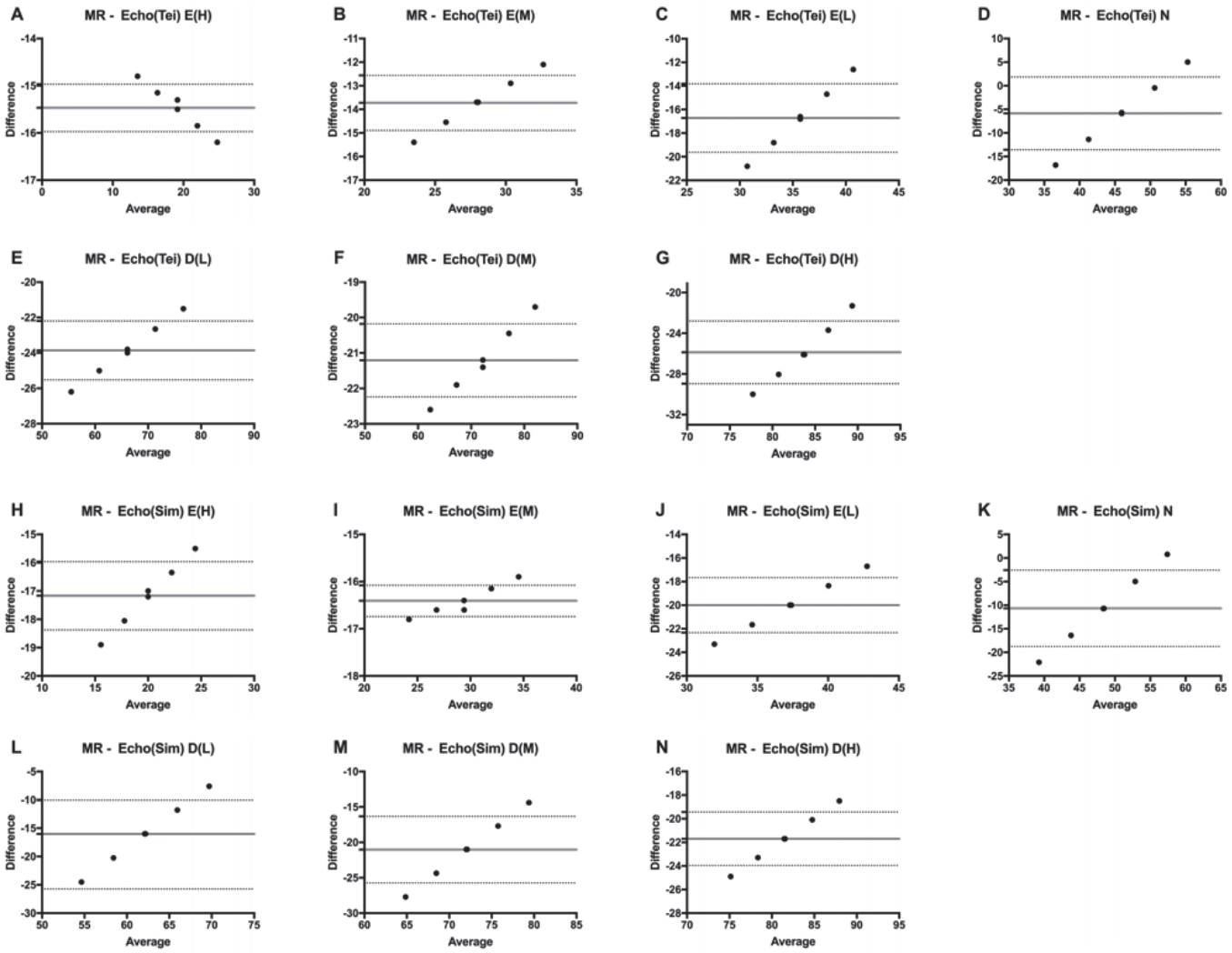

Fig. 5. Graphical presentation about comparison of ejection fraction between cardiac MRI and echocardiography with Teichholz (A to G) and Simpson (H to N) method in Bland-Altman plots. Continuous lines depict the mean of differences; dashed lines denote limits of agreement (mean ± 1.96 times of standard deviation). E(H), esmolol high dose (500 µg/kg/min); E(M), esmolol middle dose (200 µg/kg/min); E(L), esmolol low dose (100 µg/kg/min); N, normal (no administration of drugs); D(L), dobutamine low dose (10 µg/kg/min); D(M), dobutamine middle dose (20 µg/kg/min); D(H), dobutamine high dose (50 µg/kg/min); MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

echocardiography through geometric assumptions, although cardiac function has changed extensively.

Cardiac MRI is considered the gold standard modality to assess LV function [2]. However, there are some disadvantages when applied to veterinary medicine. First, it is essential to anesthetize the patient for a cardiac MRI examination. Anesthesia is a risk for patients with cardiac disease. Furthermore, anesthesia may alter functional variables. In previous reports [3], fractional shortening in anesthetized dogs was smaller than in dogs that were not anesthetized.

Second, in our study, the average duration of the MRI examination, including patient positioning, acquisition of localized images, and cardiac examination, was 35 ± 5 min longer than that of echocardiography. This is the amount of time required to perform partial examination to evaluate only LV function; the time for general cardiac MRI imaging to acquire additional information can require 1 hr or more.

However, when compared to cardiac CT, in which image quality suffers when the heart rate is greater than 80 beats/min, high-quality images can be obtained by cardiac MRI with heart rates as high as 160 beats/min. Cardiac CT scans using ECG-gating in multidetector CT with rapid rotation speed have recently been introduced in veterinary medicine [5], but it is generally advisable to lower heart rate to 80 beats/min or less for cardiac CT scans. The use of iodine contrast agent and radiation exposure are disadvantages of cardiac CT imaging. Therefore, cardiac MRI considered as a gold standard for cardiac function evaluation is probably to be applied in the future, and can be considered for applications in disease, based on the results of this study.

Limitations of the present study include the small number of dogs and their homogeneity in terms of breed and weight. Because of these conditions, there might be statistical power limits due to using non-parametric statistic method. In addition, to

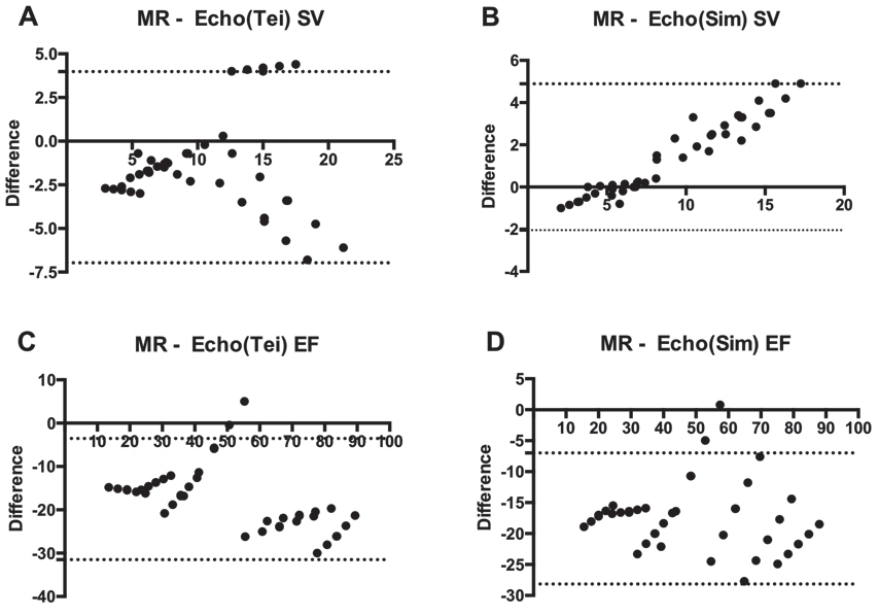

Fig. 6. Graphical presentation about comparison of stroke volume between cardiac MRI and echocardiography with Teichholz (A) and Simpson (B) method, and about comparison of ejection fraction between cardiac MRI and echocardiography with Teichholz (C) and Simpson (D) method in Bland-Altman plots. Continuous lines depict the mean of differences; dashed lines denote limits of agreement (mean ± 1.96 times of standard deviation). MR, cardiac MRI; Echo(Tei), echocardiography using Teichholz method; Echo(Sim), echocardiography using Simpson method.

evaluate responses to drugs under various conditions, different dogs should be used for each condition. Because many dogs were needed in this design, our experiment was performed in the normal manner, by using esmolol from low to high concentrations, and dobutamine from low to high concentrations, in order. Therefore, we cannot exclude the possibility of myocardial damage caused by the drugs. Despite these limitations, it is considered that this experimental design is valid and realistic, since differences in cardiac function indices measured under each condition according to drug administration were observed. The cardiac catheterization is a gold standard for measurement of cardiac output. There is no comparable measurements from gold standard in this study. However the cardiac catheterization is invasive and it is difficult to apply in veterinary medicine. In human medicine, cardiac MRI for assessment of function is considered a gold standard [2], and this study is also based on this assumption. We did not compare between the blood pressure and the cardiac indices. In this study design, the echocardiography was followed by the cardiac MRI exam. Therefore the status of anesthesia remained the same condition. The blood pressure was measured with other vital signs for the purpose of monitoring anesthesia.

When LV function changes, echocardiography may overestimate the EF and SV. Although echocardiography remains an important tool for the diagnosis and evaluation of heart disease with less invasiveness and greater accessibility, this study suggested that the volume of LV might differ from the actual volume when cardiac function is altered.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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REFERENCES

1. Boon, J. A. 2011. Veterinary Echocardiography, 2nd ed., Wiley-Blackwell, Chichester.
2. Constantine, G., Shan, K., Flamm, S. D. and Sivananthan, M. U. 2004. Role of MRI in clinical cardiology. *Lancet* **363**: 2162–2171. [Medline] [CrossRef]
3. Drees, R., Johnson, R. A., Stepien, R. L., Munoz Del Rio, A., Saunders, J. H. and François, C. J. 2015. Quantitative planar and volumetric cardiac measurements using 64 MDCT and 3T MRI vs. standard 2d and M-mode echocardiography: does anesthetic protocol matter? *Vet. Radiol. Ultrasound* **56**: 638–657. [Medline] [CrossRef]
4. Henjes, C. R., Hungerbühler, S., Bojarski, I. B., Nolte, I. and Wefstaedt, P. 2012. Comparison of multi-detector row computed tomography with echocardiography for assessment of left ventricular function in healthy dogs. *Am. J. Vet. Res.* **73**: 393–403. [Medline] [CrossRef]
5. Jacobs, G. and Mahjoob, K. 1988. Influence of alterations in heart rate on echocardiographic measurements in the dog. *Am. J. Vet. Res.* **49**: 548–552. [Medline]
6. Kim, J. H., Lee, M. S., Lee, S. Y., Kim, S. Y., Lee, S. Y., Lee, S. J., Park, Y. W., Yeo, J. H., Song, S. H., Park, N. W., Hong, S. W., Choi, S. I. and

Eom, K. D. 2013. Contrast echocardiography to assess left ventricular volume and function in Beagle dogs: comparison with 3-Tesla dual source parallel cardiac magnetic resonance imaging. *Vet. J.* **198**: 450–456. [Medline] [CrossRef]
7. Lee, Y., Jung, J., Park, J., Jeong, J., Jeon, S., Park, S., Chang, J., Kang, J. H., Lee, C. and Chang, D. 2017. Cardiac magnetic resonance imaging of patent ductus arteriosus in three dogs. *Vet. Radiol. Ultrasound* **58**: 62–75. [Medline] [CrossRef]
8. MacDonald, K. A., Kittleson, M. D., Reed, T., Larson, R., Kass, P. and Wisner, E. R. 2005. Quantification of left ventricular mass using cardiac magnetic resonance imaging compared with echocardiography in domestic cats. *Vet. Radiol. Ultrasound* **46**: 192–199. [Medline] [CrossRef]
9. Pennell, D. J., Baksi, A. J., Carpenter, J. P., Firmin, D. N., Kilner, P. J., Mohiaddin, R. H. and Prasad, S. K. 2013. Review of Journal of Cardiovascular Magnetic Resonance 2012. *J. Cardiovasc. Magn. Reson.* **15**: 76. [Medline] [CrossRef]
10. Plumb, D. C. 2015. Plumb's Veterinary Drug Handbook, 8th ed., Wiley-Blackwell, London.
11. Sugeng, L., Mor-Avi, V., Weinert, L., Niel, J., Ebner, C., Steringer-Mascherbauer, R., Schmidt, F., Galuschky, C., Schummers, G., Lang, R. M. and Nesser, H. J. 2006. Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference. *Circulation* **114**: 654–661. [Medline] [CrossRef]
12. Tidholm, A., Westling, A. B., Höglund, K., Ljungvall, I. and Häggström, J. 2010. Comparisons of 3-, 2-dimensional, and M-mode echocardiographical methods for estimation of left chamber volumes in dogs with and without acquired heart disease. *J. Vet. Intern. Med.* **24**: 1414–1420. [Medline] [CrossRef]
13. Wood, P. W., Choy, J. B., Nanda, N. C. and Becher, H. 2014. Left ventricular ejection fraction and volumes: it depends on the imaging method. *Echocardiography* **31**: 87–100. [Medline] [CrossRef]