

## Assessment of Left Ventricular Function Using Pulsed Tissue Doppler Imaging in Healthy Dogs and Dogs with Spontaneous Mitral Regurgitation

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(Received 1 June 2005/Accepted 10 August 2005)

**ABSTRACT.** Pulsed tissue Doppler imaging (pulsed TDI) has been demonstrated to be useful for the estimation of left ventricular (LV) systolic and diastolic functions in various human cardiac diseases. The objectives of this study were to investigate the relationship between pulsed TDI and LV function by using cardiac catheterization in healthy dogs and to evaluate the clinical usefulness of pulsed TDI in dogs with spontaneous mitral regurgitation (MR). The peak early diastolic velocity ( $E'$ ), peak atrial systolic velocity ( $A'$ ), and peak systolic velocity ( $S'$ ) were detectable in the velocity profiles of the mitral annulus in all the dogs. In the healthy dogs,  $S'$  and  $E'$  were correlated with LV peak  $+dP/dt$  and  $-dP/dt$ , respectively.  $E'$  was lower in dogs with MR than in dogs without cardiac diseases.  $E/E'$  in the MR dogs with decompensated heart failure was significantly increased in comparison with those with compensated heart failure. The sensitivity and specificity of the  $E/E'$  cutoff value of 13.0 for identifying decompensated heart failure were 80% and 83%, respectively. In addition,  $E/E'$  was significantly correlated with the ratio of left atrial to aortic diameter. These findings suggest that canine pulsed TDI can be applied clinically for estimation of cardiac function and detection of cardiac decompensation and left atrial volume overload in dogs with MR.

**KEY WORDS:** canine, cardiac function, echocardiography, mitral regurgitation, pulsed tissue Doppler.

*J. Vet. Med. Sci.* 67(12): 1207–1215, 2005

Doppler echocardiography is a predominant noninvasive modality that provides a large variety of useful information on cardiac conditions in human and small animal patients. Pulsed tissue Doppler imaging (pulsed TDI) derived from Doppler echocardiography can quantify the velocity of myocardial wall and/or valve annulus motions [30, 31, 40]. In humans, pulsed TDI of the mitral annulus and myocardial wall has been demonstrated to reflect the systolic and diastolic left ventricular (LV) function in normal subjects [30, 45] and patients with dilated cardiomyopathy (DCM) [22, 46], hypertrophic cardiomyopathy (HCM) [36, 39, 46], restrictive cardiomyopathy (RCM) [14, 16, 35], constrictive pericarditis [14, 16, 35], ischemic heart diseases [4, 31, 43, 46], heart failure [1, 24], mitral regurgitation (MR) [2, 3, 17], atrial fibrillation [29], arterial hypertension [13, 46], and cardiac amyloidosis [20].

Analysis of pulsed TDI revealed that the peak early diastolic velocity ( $E'$ ), peak atrial systolic velocity ( $A'$ ), and peak systolic velocity ( $S'$ ) are typically derived from the velocity profiles of myocardial or valve annulus motions (Fig. 1) [30]. Several studies have revealed that  $E'$  and  $A'$  are correlated with LV diastolic function [1, 13, 16, 20, 24, 26, 31, 36, 39, 40, 45], and  $S'$  is correlated with LV systolic function [17, 20, 22, 29, 30, 43, 46].  $E'$  was almost independent of preload and showed no pseudonormal pattern in contrast to the peak early diastolic velocity of LV inflow ( $E$ ) [5, 24]. In addition, a ratio of  $E$  to  $E'$  ( $E/E'$ ) showed good cor-

relation with pulmonary capillary wedge pressure (PCWP) and LV diastolic pressure (LVDP) in humans with sinus tachycardia, DCM, and HCM [23–25, 32].

Few reports on TDI have been described in small animal medicine [7–11, 15, 33, 34, 38]. It was demonstrated that an  $E/E'$  value greater than 9.1 indicated a mean left atrial pressure (MLAP) greater than 20 mmHg in dogs with experimentally induced acute MR [34], and TDI was available to clinically differentiate normal cats from cats with spontaneous cardiomyopathy [15]. To our knowledge, however, no

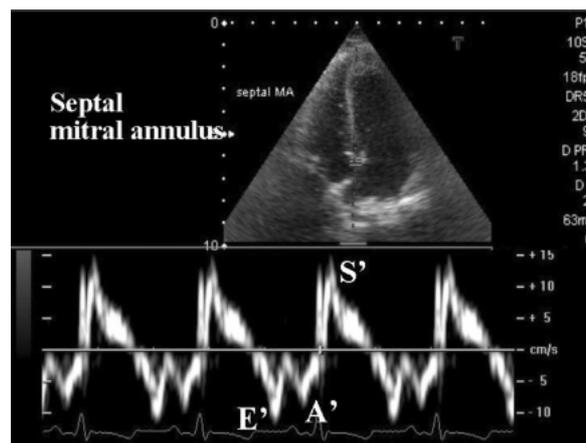


Fig. 1. The velocity profiles ( $E'$ ,  $A'$ , and  $S'$ ) obtained from pulsed tissue Doppler imaging of septal mitral annulus in dogs.  $E'$ : the peak early diastolic velocity.  $A'$ : the peak atrial systolic velocity.  $S'$ : the peak systolic velocity.

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studies have thus far demonstrated the validation of correlation between pulsed TDI and cardiac function in dogs. In addition, LV function has not yet been evaluated using pulsed TDI in clinical cases of canine spontaneous MR.

The objectives of this study were to validate the correlation between pulsed TDI and LV systolic and diastolic functions derived from cardiac catheterization in healthy dogs and to evaluate the clinical usefulness of pulsed TDI for estimation of LV function in dogs with naturally occurring MR.

## MATERIALS AND METHODS

*Validation of correlation of LV function between pulsed TDI and catheterization (Study 1):* Five female Beagle dogs (body weight between 10.0 and 13.0 kg) were used in this study. The dogs were confirmed to be healthy by physical examination, complete blood count (CBC), serum biochemistry, electrocardiogram (ECG), thoracic radiography, and echocardiography. All the dogs were cared for in accordance with the principles outlined in the Guidebook for the Care and Use of Laboratory Animals approved by the College of Bioresource Sciences, Nihon University.

Each dog was premedicated with midazolam hydrochloride (0.2 mg/kg, IV), butorphanol tartrate (0.2 mg/kg, IV), and meloxicam (0.2 mg/kg, SC) and was intubated after the induction of anesthesia with propofol (5 mg/kg, IV). General anesthesia was maintained by inhalation of isoflurane (1.5%) and oxygen (2 L/min) under mechanical ventilation (respiratory rate, 10 breaths/min; respiratory pressure, 10–15 cmH<sub>2</sub>O; end-expiratory carbon dioxide concentration, 40 mmHg) along with the intravenous administration of pancuronium bromide (0.04–0.05 mg/kg).

Each dog was placed in dorsal recumbency, and the neck was clipped and prepared aseptically. After a midline incision of the neck, a 6-Fr micromanometer-tipped catheter (PC-460, Millar Instruments Inc, Houston, U.S.A.) was directly inserted into the isolated right carotid artery and was advanced into the LV chamber under fluoroscopic guidance.

After the position of the dog was changed to left lateral recumbency, hemodynamic and echocardiographic measurements were simultaneously recorded in a blinded manner with the dog under a transient respiratory arrest. The peak values of the positive first derivative of LV pressure (LV peak +dP/dt) and negative first derivative of LV pressure (LV peak -dP/dt) were calculated from the LV pressure profiles recorded by the catheter. Five consecutive LV peak +dP/dt and -dP/dt values were selected and averaged.

A diagnostic ultrasound system, Nemio (SSA-550A, Toshiba Medical Systems, Tokyo, Japan), was used for the echocardiographic measurements. LV inflow was recorded using the pulsed Doppler method. The sample volume was set at 2-mm wide and was placed at the level of the tips of mitral valve leaflets in the left apical four-chamber view. E, the peak atrial contraction velocity (A), and their ratio (E/A) were determined. For pulsed TDI, the acoustic power of the system was set at 10%–20%, the Doppler filter frequency

was set at the lowest values possible (50 Hz), and the Doppler gain was minimized to allow for a clear tissue signal with minimal background noise. The Nyquist limit was adjusted to a velocity range between -20 and 20 cm/sec. A 2-mm sample volume was placed at the septal mitral annulus using the same view as that used while obtaining LV inflow. E', A', the E'/A' ratio, S', and the E/E' ratio were determined. Five consecutive waves obtained at the time of recording the LV pressure profiles were used to calculate the mean values of the parameters of pulsed TDI.

These measurements were repeated with changes in cardiac contractility and lusitropy induced by continuous drip infusion of dobutamine (5 to 10 µg/kg/min) or intravenous propranolol (0.1–0.2 mg/kg).

*Pulsed TDI in clinical cases with MR (Study 2):* One hundred five dogs that were referred to the Animal Medical Center of Nihon University between October 2003 and September 2004 were used for this study. Of the 105 dogs, 66 dogs were diagnosed as free of cardiac disease based on the results of physical examination, CBC, serum biochemistry, ECG, thoracic radiography, and echocardiography and were classified as Group 0. In the remaining 39 dogs, MR attributable to chronic mitral valve disease was identified by the same examinations. The dogs with MR were divided into 4 categories—Group I (n=12), Group II (n=12), Group III (n=9), and Group IV (n=6) based on the modified New York Heart Association functional classification for heart failure (NYHA class) [21]. In addition, Groups I and II were categorized as compensated congestive heart failure (CHF) [CHF (-), n=24], and Groups III and IV were categorized as decompensated CHF [CHF (+), n=15]. A diagnostic ultrasound system, Nemio (SSA-550A, Toshiba Medical Systems, Tokyo, Japan), was used for echocardiography.

Echocardiographic measurements were obtained without sedation and anesthesia. Fractional shortening (FS), the ratio of left atrial to aortic diameter (LA/Ao), LV inflow (E, A, E/A), and pulsed TDI (E', A', E'/A', S', and E/E') for septal mitral annulus were recorded.

*Statistical analysis:* Data are expressed as the mean value ± standard deviation. Simple linear regression analysis was used to validate the correlation between the LV pressure parameters and pulsed TDI parameters in study 1. Kruskal Wallis test and the post-hoc test (Scheffé test) were used to compare the pulsed TDI parameters among the groups in study 1 and study 2. Sensitivity and specificity of E/E' for CHF (+) were calculated. In addition, single linear regression analysis was used to investigate the influences of aging, heart rate, and body weight on the pulsed TDI in Group 0 (without cardiac diseases). Statistical significance was defined as  $p < 0.05$ .

## RESULTS

*Study 1:* Pulsed TDI could be measured under various contractile and lusitropic conditions in all dogs. In healthy dogs, E' was  $7.1 \pm 1.5$  cm/sec, A' was  $4.2 \pm 2.9$  cm/sec, S' was  $4.8 \pm 0.8$  cm/sec, E'/A' was  $2.3 \pm 1.8$ , and E/E' was 8.4

Table 1. The values of echocardiographic and hemodynamic parameters in healthy dogs (n = 5)

	Baseline	Dobutamine 5γ	Dobutamine 10γ	Propranolol 0.1 mg/kg	Propranolol 0.2 mg/kg
LV peak +dP/dt (mmHg/sec)	897.2 ± 152.0	1436.4 ± 192.4 <sup>a)</sup>	1634.5 ± 116.1 <sup>a)</sup>	1100.0 ± 89.0 <sup>b,c)</sup>	1000.0 ± 87.0 <sup>b,c)</sup>
LV peak -dP/dt (mmHg/sec)	-765.4 ± 116.2	-1181.4 ± 129.5 <sup>a)</sup>	-1337.7 ± 195.7 <sup>a)</sup>	-1042.5 ± 115.4 <sup>c)</sup>	-984.7 ± 68.7 <sup>c)</sup>
E (cm/sec)	59.2 ± 11.8	76.2 ± 11.0	90.9 ± 13.7 <sup>a)</sup>	66.7 ± 9.9 <sup>c)</sup>	57.1 ± 11.7 <sup>c)</sup>
A (cm/sec)	27.3 ± 14.8	41.2 ± 20.1	59.4 ± 9.1	33.7 ± 12.1	32.0 ± 7.2
E/A	3.2 ± 2.7	2.3 ± 1.3	1.7 ± 0.6	2.1 ± 1.4	1.9 ± 0.9
S' (cm/sec)	4.8 ± 0.8	11.2 ± 1.9 <sup>a)</sup>	14.0 ± 1.2 <sup>a)</sup>	5.4 ± 1.6 <sup>b,c)</sup>	5.7 ± 2.7 <sup>b,c)</sup>
E' (cm/sec)	7.1 ± 1.5	8.4 ± 1.3	10.7 ± 1.7	6.8 ± 2.3 <sup>c)</sup>	6.7 ± 1.8 <sup>c)</sup>
A' (cm/sec)	4.2 ± 2.9	4.7 ± 2.0	6.8 ± 1.3	4.2 ± 1.2	4.9 ± 1.1
E'/A'	2.3 ± 1.8	2.2 ± 1.2	1.6 ± 0.5	1.8 ± 1.0	1.5 ± 0.7
E/E'	8.4 ± 1.1	9.3 ± 2.4	8.7 ± 2.2	9.3 ± 2.0	8.7 ± 2.1

All values were expressed as mean ± SD. E: the peak early diastolic velocity of LV inflow; A: the peak atrial systolic velocity of LV inflow, E/A: a ratio of E to A, E': the peak early diastolic velocity of mitral annulus; A': the peak atrial systolic velocity of mitral annulus, S': the peak systolic velocity of mitral annulus, E'/A': a ratio of E' to A', E/E': a ratio E to E'.

a) Significant difference with Baseline (p<0.05). b) Significant difference with Dobutamine 5γ (p<0.05). c) Significant difference with Dobutamine 10γ (p<0.05).

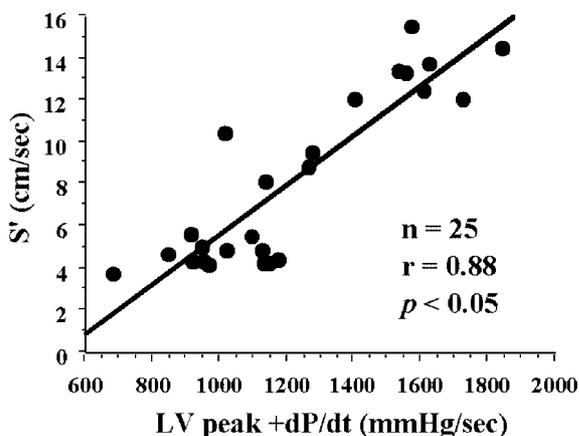


Fig. 2-1. Relationship between S' and LV peak +dP/dt in healthy dogs. A significant positive correlation was observed between S' and LV peak +dP/dt. S': the peak systolic velocity of mitral annulus.

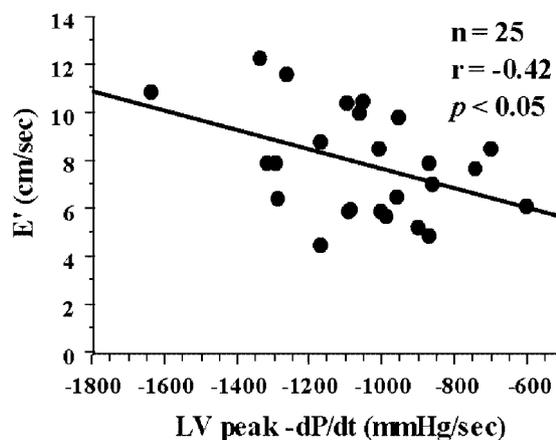


Fig. 2-2. Relationship between E' and LV peak -dP/dt in healthy dogs. A significant negative correlation was found between E' and LV peak -dP/dt. E': the peak early diastolic velocity of mitral annulus.

± 1.1 prior to the changes in contractile and lusitropic status (Table 1).

A significant positive correlation was observed between S' and LV peak +dP/dt (Fig. 2-1) and significant negative correlations were observed between E' and LV peak -dP/dt (Fig. 2-2) and between E and LV peak -dP/dt. In contrast, no correlations were observed between A' and LV peak -dP/dt, between E'/A' and LV peak -dP/dt, between E/E' and LV peak +dP/dt, and between E/E' and LV peak -dP/dt.

**Study 2:** Pulsed TDI could be measured in the 66 dogs without cardiac diseases and the 39 dogs with spontaneous MR. In Group 0, heart rate was 115 ± 25 beats/min (range, 60–180 beats/min), age was 5.0 ± 3.8 years (range, 0–13 years), and body weight was 12.1 ± 11.4 kg (range, 1.6–42.5 kg) (Table 2). The heart rate significantly increased in Group IV (152 ± 25 beats/min; range, 124–184) in comparison with that in Group 0. The age of the dogs was significantly greater in Groups I (10.0 ± 2.5 years; range, 5–13

years), II (10.3 ± 2.9 years; range, 6–16 years), III (12.7 ± 2.6 years; range, 10–16 years), and IV (10.0 ± 3.4 years; range, 7–14 years) than that in Group 0. No significant differences were observed in body weight and gender distribution among the NYHA classes.

In Group 0, FS was 39.1% ± 6.4%, LA/Ao was 1.25 ± 0.14, E was 69.4 ± 12.0 cm/sec, A was 59.2 ± 12.3 cm/sec, E/A was 1.4 ± 0.3, S' was 9.1 ± 3.1 cm/sec, E' was 9.2 ± 2.4 cm/sec, A' was 7.7 ± 2.3 cm/sec, E'/A' was 1.2 ± 0.4, and E/E' was 7.9 ± 1.8.

Significant differences in the values of E, A, LA/Ao, E', E'/A', and E/E' were observed among the NYHA classes. E/A and A' were insignificant among the NYHA classes. FS and S' were insignificant among the NYHA classes. However, FS was more likely to increase in proportion with the NYHA class in contrast to S' (Table 2). S' showed an insignificant correlation with FS. E and A showed a signif-

Table 2. Characteristics and the values of echocardiographic measurements in dogs without cardiac diseases (n=66) and with MR (n=39)

	Group 0	Group I	Group II	Group III	Group IV
Number	66	12	12	9	6
Gender (female/male)	36/30	6/6	7/5	5/4	2/4
HR (bpm)	115 ± 25 (60–180)	116 ± 23 (84–160)	121 ± 22 (80–160)	106 ± 21 (82–132)	152 ± 25 <sup>a,d)</sup> (124–184)
BW (kg)	12.1 ± 11.4 (1.6–42.5)	7.9 ± 4.2 (2.5–15.0)	8.0 ± 3.6 (2.8–15.0)	7.7 ± 4.1 (2.0–13.2)	3.6 ± 1.0 (2.7–5.5)
Age (years)	5.0 ± 3.8 (0–13)	10.0 ± 2.5 <sup>a)</sup> (5–13)	10.3 ± 2.9 <sup>a)</sup> (6–16)	12.7 ± 2.6 <sup>a)</sup> (10–16)	10.0 ± 3.4 <sup>a)</sup> (7–14)
FS (%)	39.1 ± 6.4	39.7 ± 6.6	38.2 ± 8.2	43.5 ± 6.8	48.7 ± 11.3
LA/Ao ratio	1.25 ± 0.14	1.32 ± 0.21	1.30 ± 0.21	1.71 ± 0.47	2.02 ± 0.53 <sup>a-d)</sup>
E (cm/sec)	69.4 ± 12.0	57.2 ± 14.2	65.4 ± 15.0	87.2 ± 28.6 <sup>b)</sup>	113.2 ± 28.3 <sup>a-c)</sup>
A (cm/sec)	59.2 ± 12.3	58.0 ± 9.8	59.2 ± 14.6	80.1 ± 20.2 <sup>a)</sup>	102.6 ± 33.4 <sup>a-c)</sup>
E/A	1.4 ± 0.3	1.0 ± 0.3	1.1 ± 0.2	1.1 ± 0.2	1.3 ± 0.7
S' (cm/sec)	9.1 ± 3.1	8.1 ± 1.6	7.9 ± 2.3	9.0 ± 2.6	8.9 ± 2.7
E' (cm/sec)	9.2 ± 2.4	6.0 ± 1.8 <sup>a)</sup>	6.7 ± 1.5 <sup>a)</sup>	6.7 ± 2.2	6.7 ± 1.0
A' (cm/sec)	7.7 ± 2.3	8.4 ± 2.1	9.5 ± 2.7	10.1 ± 1.3	9.5 ± 1.9
E'/A'	1.2 ± 0.4	0.7 ± 0.3 <sup>a)</sup>	0.7 ± 0.2 <sup>a)</sup>	0.7 ± 0.3 <sup>a)</sup>	0.7 ± 0.2 <sup>a)</sup>
E/E'	7.9 ± 1.8	10.0 ± 2.2	10.0 ± 2.4	13.3 ± 2.6 <sup>a-c)</sup>	17.1 ± 4.8 <sup>a-c)</sup>

All values were expressed as mean ± SD. HR: heart rate, BW: body weight, bpm: beats per minute, LA/Ao ratio: a ratio of left atrial and aortic diameter, FS: fractional shortening, E: the peak early diastolic velocity of LV inflow; A, the peak atrial systolic velocity of LV inflow, E/A: a ratio of E to A, E': the peak early diastolic velocity of mitral annulus, A': the peak atrial systolic velocity of mitral annulus, S': the peak systolic velocity of mitral annulus, E'/A': a ratio of E' to A', E/E': a ratio of E to E', Group 0: dogs without cardiac diseases, Group I, II, III and IV: dogs with MR classified by the NYHA classes.

a) Significant difference with Group 0 ( $p < 0.05$ ). b) Significant difference with Group I ( $p < 0.05$ ). c) Significant difference with Group II ( $p < 0.05$ ). d) Significant difference with Group III ( $p < 0.05$ ).

icant difference among the groups. E' was significantly reduced in Group I ( $6.0 \pm 1.8$  cm/sec), and II ( $6.7 \pm 1.5$  cm/sec) and more likely to be reduced in Group III ( $6.7 \pm 2.2$  cm/sec), and IV ( $6.7 \pm 1.0$  cm/sec) in comparison with that in Group 0 ( $9.2 \pm 2.4$  cm/sec) (The values are mean ± SD as indicated by the "x" marks in Fig. 3–1). E'/A' significantly decreased in Group I ( $0.7 \pm 0.3$ ), II ( $0.7 \pm 0.2$ ), III ( $0.7 \pm 0.3$ ), and IV ( $0.7 \pm 0.2$ ) in comparison with that in Group 0 ( $1.2 \pm 0.4$ ) (The values are mean ± SD as indicated by the "x" marks in Fig. 3–2). A significant difference was observed in the E/E' value among the groups (The values are mean ± SD as indicated by the "x" marks in Fig. 3–3).

The LA/Ao and E values significantly were increased in CHF (+) (LA/Ao,  $1.84 \pm 0.50$ ; E,  $100.2 \pm 29.7$  cm/sec) in comparison with those in CHF (–) (LA/Ao,  $1.31 \pm 0.21$ ; E,  $61.5 \pm 14.7$  cm/sec) and Group 0 (LA/Ao,  $1.25 \pm 0.14$ ; E,  $69.4 \pm 12.0$  cm/sec). However, a significant difference was not observed between CHF (–) and Group 0. E/E' was significantly increased in CHF (+) ( $14.8 \pm 4.0$ ) in comparison with those in CHF (–) ( $10.0 \pm 2.7$ ) and Group 0 ( $7.9 \pm 1.8$ ). E/E' was also significantly increased in CHF (–) in comparison with that in Group 0. The sensitivity and specificity of the E/E' cutoff value of 13.0 for identifying CHF (+) were 80% and 83%, respectively (The values are mean ± SD as indicated by the "x" marks in Fig. 4–1, Table 3). A significant correlation was detected between E/E' and LA/Ao ( $r = 0.57$ , Fig. 4–2).

The S', E', A', E'/A', and E/E' values were not signifi-

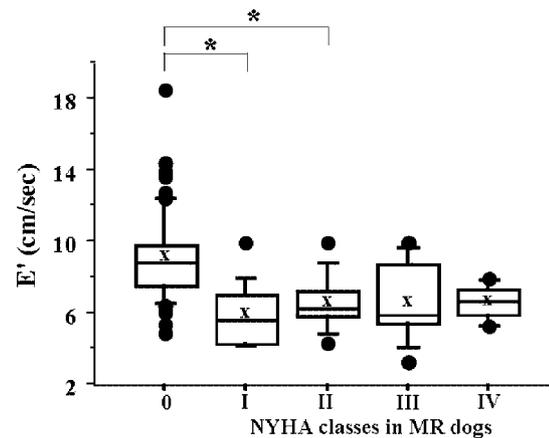


Fig. 3–1. E' among the NYHA classes in MR dogs. E' significantly decreased in Groups I, and II in comparison with that in Group 0. Dogs without cardiac diseases were included in Group 0. The boxes represent the 25th to 75th percentiles (i.e., the middle 50 percent of the data). The whiskers represent the 10th to 90th percentiles. "x" marks represent the mean ± SD. E': the peak early diastolic velocity of mitral annulus. \*: Significant difference.

cantly correlated with heart rate in Group 0. However, E'/A' had a weak and significant inverse correlation with aging (Table 4). E', A', and S' values had a significant correlation with body weight (Fig. 5).

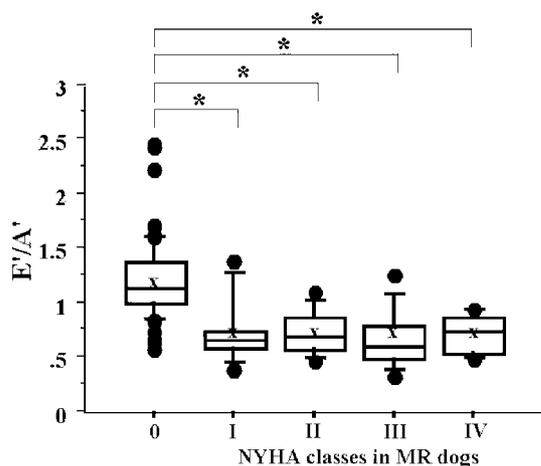


Fig. 3-2.  $E'/A'$  among the NYHA classes in MR dogs.  $E'/A'$  significantly decreased in Groups I, II, III, and IV in comparison with that in Group 0. Dogs without cardiac diseases were included in Group 0. The boxes represent the 25th to 75th percentiles (i.e., the middle 50 percent of the data). The whiskers represent the 10th to 90th percentiles. "x" marks represent the mean  $\pm$  SD.  $E'/A'$ : a ratio of  $E'$  to  $A'$ . \*: Significant difference.

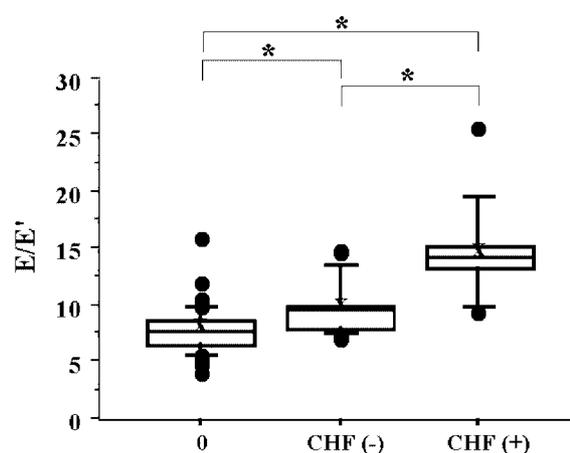


Fig. 4-1. The values of  $E/E'$  of dogs without cardiac diseases (Group 0), CHF (-), and CHF(+) dogs.  $E/E'$  was significantly increased in CHF (+) in comparison with that in CHF (-). The boxes represent the 25th to 75th percentiles (i.e., the middle 50 percent of the data). The whiskers represent the 10th to 90th percentiles. "x" marks represent the mean  $\pm$  SD. CHF (+): decompensated heart failure, CHF (-): compensated heart failure. \* Significant difference.

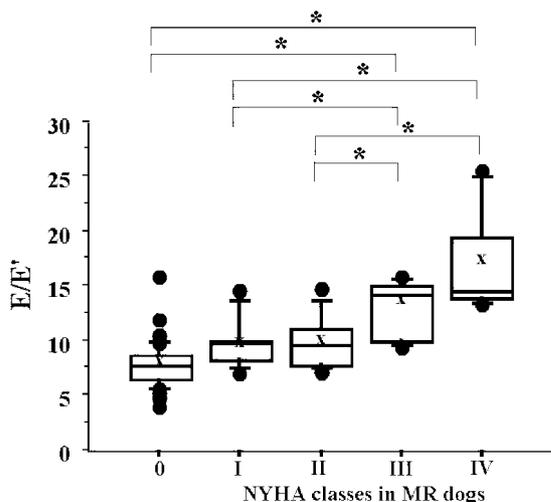


Fig. 3-3.  $E/E'$  among the NYHA classes in MR dogs. A significant difference was observed in the  $E/E'$  values among the groups. Dogs without cardiac diseases were included in Group 0. The boxes represent the 25th to 75th percentiles (i.e., the middle 50 percent of the data). The whiskers represent the 10th to 90th percentiles. "x" marks represent the mean  $\pm$  SD.  $E/E'$ : ratio of E to  $E'$ . \*: Significant difference.

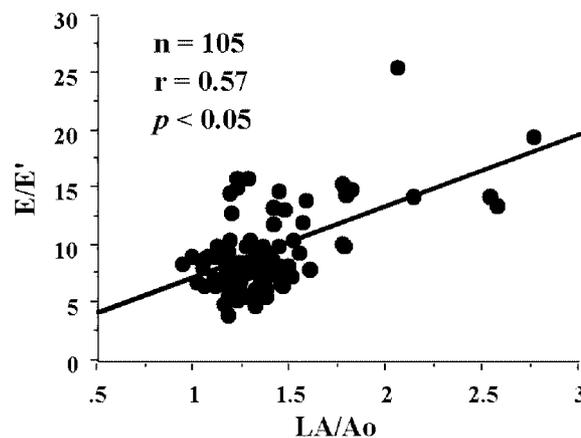


Fig. 4-2. Relationship between  $E/E'$  and  $LA/Ao$  in dogs. A significant correlation was detectable between  $E/E'$  and  $LA/Ao$ .  $E/E'$ : ratio of  $E'$  (peak early diastolic velocity of mitral annulus) to E (peak early diastolic velocity of LV inflow).  $LA/Ao$ : a ratio of left atrial to aortic diameter.

DISCUSSION

Pulsed TDI is used for the measurement of the velocity of LV wall and valve annulus motions, whereas the traditional pulsed Doppler is used for the determination of various laminar blood flow velocities. As observed in our study, the measurement of the velocity of LV wall and valve annulus

motions was possible using pulsed TDI in healthy dogs and dogs with spontaneous chronic MR. The use of pulsed TDI is therefore feasible in canine cardiac diseases, similar to its use in humans.

In study 1,  $S'$  derived from pulsed TDI of septal mitral annulus was associated with LV systolic function in healthy dogs. In a previous study, it was demonstrated that  $S'$  of mitral annulus was significantly decreased in human patients with myocardial infarction when compared with that in normal subjects, and  $S'$  and ejection fraction (EF) or LV peak

Table 3. The values of E/E' in CHF (-) (n=24) and CHF (+) (n=15) dogs

	Group 0	CHF (-)	CHF (+)
Number	66	24	15
LA/Ao ratio	1.25 ± 0.14	1.31 ± 0.21	1.84 ± 0.50 <sup>a,b)</sup>
E (cm/sec)	69.4 ± 12.0	61.5 ± 14.7	100.2 ± 29.7 <sup>a,b)</sup>
E/E'	7.9 ± 1.8	10.0 ± 2.7 <sup>a)</sup>	14.8 ± 4.0 <sup>a,b)</sup>

All values were expressed as mean ± SD. LA/Ao ratio: a ratio of left atrial and aortic diameter, E: the peak diastolic velocity of LV inflow, E/E': the ratio of E to E', CHF (-): compensated heart failure, CHF (+): compensated heart failure, Group 0: dogs without cardiac diseases.

a) Significant difference with Group 0 ( $p < 0.05$ ). b) Significant difference with CHF (-) ( $p < 0.05$ ).

Table 4. Relationship between pulsed TDI and heart rate, body weight or aging in dogs without cardiac diseases (n=66)

	HR (bpm)	BW (kg)	Age (years)
S' (cm/sec)	r=0.02 p=ns	r=0.71 p<0.05	r=0.22 p=ns
E' (cm/sec)	r=-0.05 p=ns	r=0.47 p<0.05	r=-0.01 p=ns
A' (cm/sec)	r=0.06 p=ns	r=0.45 p<0.05	r=0.31 p<0.05
E'/A'	r=-0.09 p=ns	r=-0.03 p=ns	r=-0.34 p<0.05
E/E'	r=0.15 p=ns	r=-0.33 p<0.05	r=-0.04 p=ns

All values were expressed as mean ± SD. HR: heart rate, BW: body weight, bpm: beats per minute, E': the peak early diastolic velocity of mitral annulus, A': the peak atrial systolic velocity of mitral annulus, S': the peak systolic velocity of mitral annulus, E'/A': the ratio of E' to A', E/E': a ratio of E to E', ns: no significant.

+dP/dt were significantly correlated [43]. In addition, LV systolic dysfunction in human patients with primary amyloidosis was shown to be detectable based on S' of mitral annulus, even when EF was in the normal range [20]. In our study, S' of mitral annulus was correlated with LV peak +dP/dt in the healthy dogs. Subsequently, in study 2, we investigated S' of mitral annulus in canine clinical cases with MR. The results of study 2 indicated that S' did not significantly differ among the NYHA classes. This result may suggest that significant systolic dysfunction was not identified in dogs with MR. However, lower S' values at rest and after exercise have been demonstrated to indicate reduced cardiac contractile reserve in human patients with MR. In contrast, EF at rest was not found to be associated with cardiac contractile in human patients with MR [17]. Because EF is clearly dependent on preload and afterload, and these load have a major influence on the utility of EF in MR. In addition, S' was reported to function as an independent predictor of postoperative EF reduction in human asymptomatic patients with severe MR [2] and as a better factor for identifying human patients with MR who are at risk for adverse outcomes [41]. On the other hand, it was reported

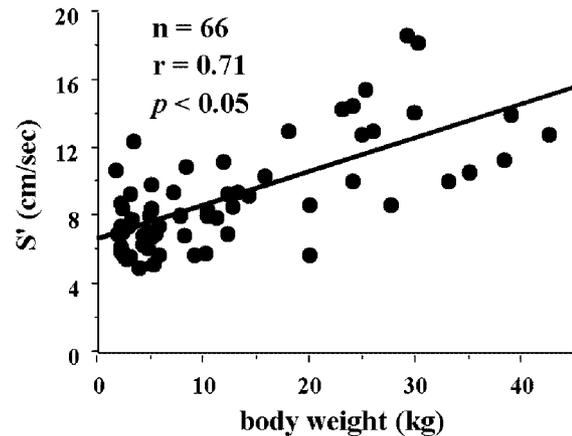


Fig. 5. Relationship between S' and body weight in dogs without cardiac diseases. A significant positive correlation was observed between S' and body weight. S': the peak systolic velocity of mitral annulus.

that S' in human patients significantly increased in primary MR (mitral valve prolapse or flail leaflet) in comparison with that in asymptomatic patients without MR [6]. In our study, no difference was observed in the S' values of dogs with MR among the NYHA classes. Also, FS, an ejection phase index, was more likely to increase in proportion to the severity of clinical signs of left-sided heart failure. These findings suggest that LV systolic function in canine patients with MR is relatively preserved even in NYHA class IV.

In clinical practice, pulsed Doppler of LV inflow is extensively applied for noninvasive estimation of LV diastolic function in human and small animal patients [18, 19, 27, 28, 37]. However, E and E/A derived from the pulsed Doppler of LV inflow have the potential to show pseudonormalization of LV diastolic function [12, 28, 42, 44]. Some studies on humans [5, 24, 40] reported that E' behaved as a preload-independent index of LV diastolic function and did not show a pseudonormal pattern as seen in E and E/A derived from the pulsed Doppler of LV inflow. In study 1, E' of septal mitral annulus was correlated with LV peak -dP/dt in the healthy dogs. Further, in study 2, we investigated E' of septal mitral annulus in canine clinical cases with spontaneous MR. The result of study 2 indicated that E' was more likely to reduced in dogs with MR in comparison with dogs without cardiac diseases (Group 0). This finding suggested that dogs with MR suffered from diastolic dysfunction. However, a previous study reported that in a canine model of acute MR, E' of lateral mitral annulus increased in comparison with that of an intact annulus before the creation of MR [34]. This discrepancy is believed to be based on the duration of MR. The results of our study possibly suggest that long-term progression of MR causes LV remodeling with LV diastolic dysfunction due to the development of volume overload in clinical cases with chronic MR. This finding may support early clinical application of  $\beta$ -blockers in dogs with MR.

In our study,  $E/E'$  in the MR dogs with decompensated CHF significantly was increased in comparison with that in the MR dogs with compensated CHF, and  $E/E'$  had a significant correlation with LA/Ao, an indicator of LA dilation. These findings indicate that the  $E/E'$  values can be clinically applied to detect LA volume overload in dogs with MR. In previous studies on humans,  $E/E'$  had a strong correlation with PCWP [24] and a moderate to good correlation with LVDP in patients with HCM and sinus rhythm [23, 32]. In small animal medicine, it has been demonstrated that for the lateral mitral annulus,  $E/E'$  greater than 9.1 or less than 6.0 indicates a 95% probability that MLAP was greater than or less than 20 mmHg, respectively [34]. In addition, both  $E/E'$  and  $E$  were linearly correlated with MLAP; however, the  $R^2$  value for  $E/E'$  (0.83) was greater than that for  $E$  (0.73) in a canine model of acute MR [34]. In contrast,  $E/E'$  at a cut-off value of 13 had good sensitivity and specificity for identifying canine decompensated heart failure in our study.  $E/E'$ , therefore, can be clinically applied to detect cardiac decompensation in dogs with MR.

We evaluated the influences of heart rate, aging, and body weight on pulsed TDI in dogs with MR. The results showed that pulsed TDI was independent of heart rate in dogs without cardiac diseases. In our studies,  $E'$  was not significantly correlated with aging in dogs without cardiac diseases, whereas  $E'$  was reported to be inversely correlated with age in healthy humans [45]. This finding may be attributable to the differences in the life spans between humans and dogs. In dogs, cardiac compliance may be less affected by changes during aging due to the shorter life spans. Our study showed that  $S'$  was correlated with body weight, and  $E'$  and  $A'$  tended to increase with increase in weight. This finding may suggest that pulsed TDI is affected by whole heart motion in dogs. More detailed information on the influence of body size may be needed prior to clinical application of pulsed TDI in small animal clinics.

The association between LV systolic and diastolic functions and the parameters of pulsed TDI of only septal mitral annulus was evaluated in this study. This is because based on the results of our preliminary study, canine pulsed TDI showed the highest reproducibility and briefest measurability for the septal mitral annulus when compared with other regions. However, some studies have demonstrated that  $S'$  of not only the mitral annulus but also the other parts of the myocardial wall was correlated with LV peak  $+dP/dt$  in human patients with DCM and atrial fibrillation [22, 29]. In addition, it was also reported that  $E'$  of the posterior wall negatively correlated with the LV relaxation time constant in human patients with various heart diseases [31]. Therefore, it may be important to investigate the association between LV systolic and diastolic functions and the parameters of pulsed TDI of various regions in dogs, excluding the septum of mitral annulus or myocardial walls in dogs.

In conclusion, this study has demonstrated that the use of pulsed TDI is feasible for the estimation of LV systolic and diastolic function in dogs and can detect cardiac decompensation and LA volume overload in canine clinical cases with

MR. Further investigations are necessary to clarify the clinical significance of pulsed TDI in canine patients with other cardiac diseases.

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