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● *Original Contribution*

NOVEL ESTIMATION OF LEFT VENTRICULAR FILLING PRESSURE USING 3-D SPECKLE-TRACKING ECHOCARDIOGRAPHY: ASSESSMENT IN A DECOMPENSATED SYSTOLIC HEART FAILURE MODEL

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Abstract—*E*/*e*′ allows for the non-invasive estimation of left ventricular (LV) filling pressure; however, Doppler malalignment can make the estimation unreliable, especially in dilated systolic failing hearts. The ratio of peak early diastolic filling rate to peak early diastolic global strain rate (FRe/SRe), which is a parameter derived from 3-D speckle-tracking echocardiography to estimate filling pressure, may be better applied in dilated systolic failing hearts because it can be obtained without the Doppler method. We investigated whether FRe/SRe could provide a better estimation of filling pressure than *E*/*e*′ in 23 dogs with decompensated systolic heart failure induced by microembolization. FRe/SRe had better correlation coefficients with LV end-diastolic pressure (0.75−0.90) than did *E*/*e*′ (0.40). The diagnostic accuracy of FRe/SRe in distinguishing elevated filling pressure was significantly higher than that of *E*/*e*′. This study indicates that FRe/SRe may provide a better estimation of LV filling pressure than *E*/*e*′ in dilated systolic failing hearts. (E-mail: toshi@sahs.med.osaka-u.ac.jp) © 2021 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key Words: **Filling pressure, Heart failure, Myocardial strain, Speckle-tracking echocardiography, Three-dimensional.**

INTRODUCTION

Assessments of left ventricular (LV) filling pressure are indispensable in diagnosing heart failure and determining appropriate therapeutic strategies. Doppler echocardiography has enabled us to estimate filling pressure non-invasively, and the ratio of the early diastolic transmitral flow velocity (*E*) to the early diastolic mitral annular velocity (*e*′) derived from pulsed and tissue Doppler is widely used for this purpose (Nagueh et al. 2016; Andersen et al. 2017). However, *E*/*e*′ may not be reliable in estimating filling pressure in some diseases or conditions (Diwan et al. 2005; Geske et al. 2007; Bhella et al. 2011), especially in dilated and decompensated systolic failing hearts (Mullens et al. 2009; Matsushita et al. 2015). Although some reasons for this unreliability have been considered, malalignment of the Doppler beam seems to be one of the causes. When the left ventricle is dilated, deviation of the Doppler beam from the direction of transmitral flow or mitral annular motion tends to be significant, making accurate alignment more difficult to achieve (*i.e.,* Doppler angle dependence) (Appleton et al. 1997; Dokainish et al. 2008; Kimura et al. 2012). Therefore, assessment of the filling pressure with a parameter that is unaffected by ultrasound beam angle is highly desirable in dilated systolic failing hearts.

Because 3-D speckle-tracking echocardiography allows for the evaluation of not only LV volume (Nesser et al. 2009) but also LV myocardial strain (Seo et al. 2009, 2011), the time derivatives of LV volume (*i.e., dV*/*dt*) and strain (*i.e.,* strain rate) can be simultaneously measured without using the Doppler method. The peak early diastolic filling rate (FRe) in the *dV*/*dt* curve correlates with mitral *E* (Rokey et al. 1985), and the peak early diastolic global strain rate (SRe) reflects LV global relaxation more accurately than *e*′ (Tatsumi et al. 2014). As such, the ratio of FRe to SRe

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(FRe/SRe) may be able to be used as a parameter to estimate filling pressure.

We previously determined that FRe/SRe could estimate filling pressure in dogs with non-dilated hearts that have preserved systolic function (Sakurai et al. 2017). Although this experiment included two models of volume overload and myocardial ischemia, a significant correlation between FRe/SRe and filling pressure could not be identified in the myocardial ischemia model because of the small number of data sets. Therefore, it is still unclear whether FRe/SRe can estimate filling pressure in systolic failing hearts, which is often seen in the clinical setting. We hypothesized that a 3-D non-Doppler parameter, FRe/SRe, could provide a better estimation of filling pressure than E/e', even in dilated systolic failing hearts. To address this hypothesis, we investigated the diagnostic accuracies of both parameters in a canine model of decompensated systolic heart failure induced by coronary microembolization.

METHODS

Animal preparation

The study protocol was approved by the Osaka University Research Ethics Committee for Animal Care. All animal studies were performed in accordance with the institutional guidelines for the care and use of laboratory animals. Twenty-three open-chest female beagles or mongrel dogs (age: 12−24 mo, weight: 9.8 ± 0.8 kg) were used in this study. As a pre-anesthetic medication, xylazine (0.5 mg/kg) was administered intramuscularly. The dogs were anesthetized with intravenous pentobarbital (25.9 mg/kg) injection and subsequently intubated and ventilated using a respirator. Oxygen saturation was monitored with a pulse oximeter, and the electrocardiogram was monitored continuously. Pentobarbital (6 mg/kg/h) and midazolam (0.18 mg/kg/h) were administered continuously to maintain anesthesia. Buprenorphine (4 μg/kg) was intramuscularly injected as an analgesic. After vecuronium (1 mg) was administered for muscle relaxation, the chest was opened through a left parasternal thoracotomy, and the heart was suspended in a pericardial cradle. LV pressure was measured with a 5-Fr micromanometer (Millar Instruments, Houston, TX, USA) inserted into the left ventricle from the left atrial appendage in all dogs except one, in which a fluid-filled catheter was used. A 5-Fr angiographic catheter was inserted into the aortic cusp from the right common carotid artery to inject microspheres for embolization.

Echocardiography

Echocardiography was performed with an Aplio Artida SSH-880 CV ultrasound system (Canon Medical Systems, Otawara, Japan). Data sets for the 3-D image were acquired from apical positions with a PST-25 PX transducer. The volume rate was 34.9 vol/s. The transmitting and receiving frequencies were 2.0 and 4.0 MHz, respectively. The scan angle range was set at 70° × 60°. The 3-D full-volume images were reconstructed from six consecutive cardiac cycles.

Conventional 2-D Doppler data were acquired with a PST-50 BT transducer. The transmitting and receiving frequency was 4.2 MHz. Transmitral flow velocity and mitral annular velocity were recorded according to American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations (Nagueh et al. 2016). We carefully aligned the Doppler beam along the direction of transmitral flow and mitral annular motion. The 3-D and conventional Doppler data were captured through a water bag over the heart while the respirator was temporarily stopped. A microphone (TA-701 S, Nihon Kohden, Tokyo, Japan) for phonocardiography was placed directly on the base of the aorta to determine the timing of aortic valve closure (AVC) (Masuda et al. 2008).

Experimental protocol

3-D and conventional Doppler data were acquired at baseline. Hemodynamic data were recorded at the time of 3-D data acquisition. Polystyrene microsphere suspensions (density = 1.05 g/mL, mean microsphere diameter = 85 μm, Microgenics Corp., Fremont, CA, USA) were used to create a coronary microembolization-induced systolic heart failure model (Maruo et al. 2007). The microsphere suspensions were diluted 1:5 or 1:3 in saline before usage. After confirming that the tip of the angiographic catheter was placed at the ostium of the left coronary artery using an injection of 10% Optison microbubbles (Amersham Health, Princeton, NJ, USA), the microsphere solution (0.02−0.04 g) was repeatedly injected *via* the catheter at an interval of 30 s until the LV contractions were decreased and the LV filling pressure was increased compared with those at baseline. Because arrhythmias tend to occur at the first microsphere injection; lidocaine (2 mg/kg) was administered in advance. Echocardiographic and hemodynamic data during heart failure were acquired when the hemodynamics stabilized after the cessation of microsphere injections. Subsequently, microsphere injections were repeated to create several grades of heart failure conditions. Consequently, one to three different levels of heart failure conditions were obtained in each dog.

Hemodynamic data analysis

LV systolic pressure, LV end-diastolic pressure (LVEDP) and LV mean diastolic pressure ($LVDP_{mean}$) as filling pressure; maximum and minimum time derivatives of LV pressure (dP/dt_{max} and dP/dt_{min}); and the time constant of LV pressure decay during isovolumic relaxation period (τ) were averaged over three cardiac cycles. End-diastole was defined at the peak of the R-wave on the electrocardiogram, and end-systole was defined by AVC. Accordingly, LVEDP was measured at the peak of the R-wave. $LVDP_{mean}$ was calculated by averaging from the approximate time of mitral valve opening, which is a point 5 mm Hg above LVEDP in LV pressure decay, to end-diastole (Yamamoto et al. 1996). Elevated filling pressure was defined as an LVEDP >16 mm Hg or $LVDP_{mean}$ >12 mm Hg. τ was calculated assuming a non-zero asymptote in the data from the point of the minimum time derivative of the LV pressure to the point at which pressure decreased to the level of the LVEDP (Takeuchi et al. 1985). LVEDP, $LVDP_{mean}$, and τ were measured by an observer blinded to the echocardiographic data.

Echocardiographic data analysis

Conventional Doppler data were averaged from three cardiac cycles. The value of e' was averaged from the septal and lateral annuli. The data in which the peak of mitral E or e' was fused with the atrial component were excluded from the analysis. The presence and severity of mitral regurgitation and aortic regurgitation were visually assessed.

As illustrated in Figure 1, 3-D speckle-tracking analysis was performed by offline software (Ultra Extend, Canon Medical Systems, Otawara, Japan) (Kawagishi 2008; Takeguchi et al. 2010). The reference mark (*i.e.,* zero strain) was set at end-diastole. The endocardial borders in the four-chamber and two-chamber views, which were cut out from the 3-D images, were manually traced at end-diastole. Epicardial borders were determined by setting an even width of the myocardium. Subsequently, 3-D endocardial and epicardial borders were automatically reconstructed and adjusted on short-axis images. After completion of these processes, the LV volume curve and the LV global strain rate curve, averaged over all 16 segments, were displayed simultaneously. With the use of customized software, the values of FRe and SRe were semi-automatically measured from these curves (Sakurai et al. 2017). The SRe value was derived from radial, circumferential, longitudinal and area strain rates, and the FRe/SRe ratio was calculated. Radial strain was measured from the endocardial and epicardial borders, whereas the circumferential, longitudinal and area strains were measured from the endocardial border only. Area strain is calculated as the percentage change in a segmental endocardial surface area. In this analysis, the atrial component (*i.e.,* late diastolic wave) of the filling rate or strain rate was not always shown because the data from the last frame in the diastolic phase were excluded from the analysis. To avoid the possibility of fusion with the atrial component, the data in which the peak of FRe or SRe was detected after onset of the P wave in the electrocardiogram were excluded. LV end-diastolic volume, LV end-systolic volume and LV ejection fraction were calculated from the 3-D volume curve data.

Mitral E and FRe are expected to accurately reflect an increase in transmitral flow (Nagueh et al. 1997). In dilated systolic failing hearts, however, the mitral E velocity derived from the Doppler method may underestimate the maximum velocity of transmitral flow because of angle dependence. Therefore, the relationships of E and FRe with LV end-diastolic volume were evaluated. Because e' and SRe were expected to reflect LV relaxation, the relationships of e' and SRe with τ were assessed (Nagueh et al. 1997).

Inter-observer and intra-observer reliability

Ten 3-D images captured from different dogs were randomly selected from all data to determine the inter-observer and intra-observer reliability of FRe, SRe and FRe/SRe. To determine inter-observer reliability, the analysis was repeated by a second observer who was blinded to the values obtained by the first observer. To determine intra-observer reliability, the analysis was repeated more than 2 mo later by the same observer.

Statistical analysis

Data are expressed as the mean ± standard deviation. Normality of the echocardiographic and hemodynamic data was assessed with the Kolmogorov−Smirnov test, and comparisons between baseline and heart failure were performed with the unpaired t-test or Mann−Whitney U-test. The correlation between echocardiographic parameters and hemodynamics was assessed by regression analysis. Receiver operating characteristic (ROC) curves were created to determine the diagnostic accuracy of E/e' and FRe/SRe in distinguishing elevated filling pressure. Areas under the curves (AUCs) were compared using the method of DeLong et al. (1988). The inter-observer and intra-observer reliability of the single measures FRe, SRe and FRe/SRe was determined with intra-class correlation coefficients (ICCs). Additionally, p values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics Version 20.0 (IBM Corp., Armonk, NY, USA), MedCalc Version 19.1.3 (MedCalc Software, Ostend, Belgium), JMP Pro Version 13.1.0 (SAS Institute, Cary, NC, USA) and Origin 2017 (OriginLab, Northampton, MA, USA).

RESULTS

Of the 23 dogs used in this study, 4 died after the first series of microsphere injections. Data during heart failure induced by microembolization were acquired

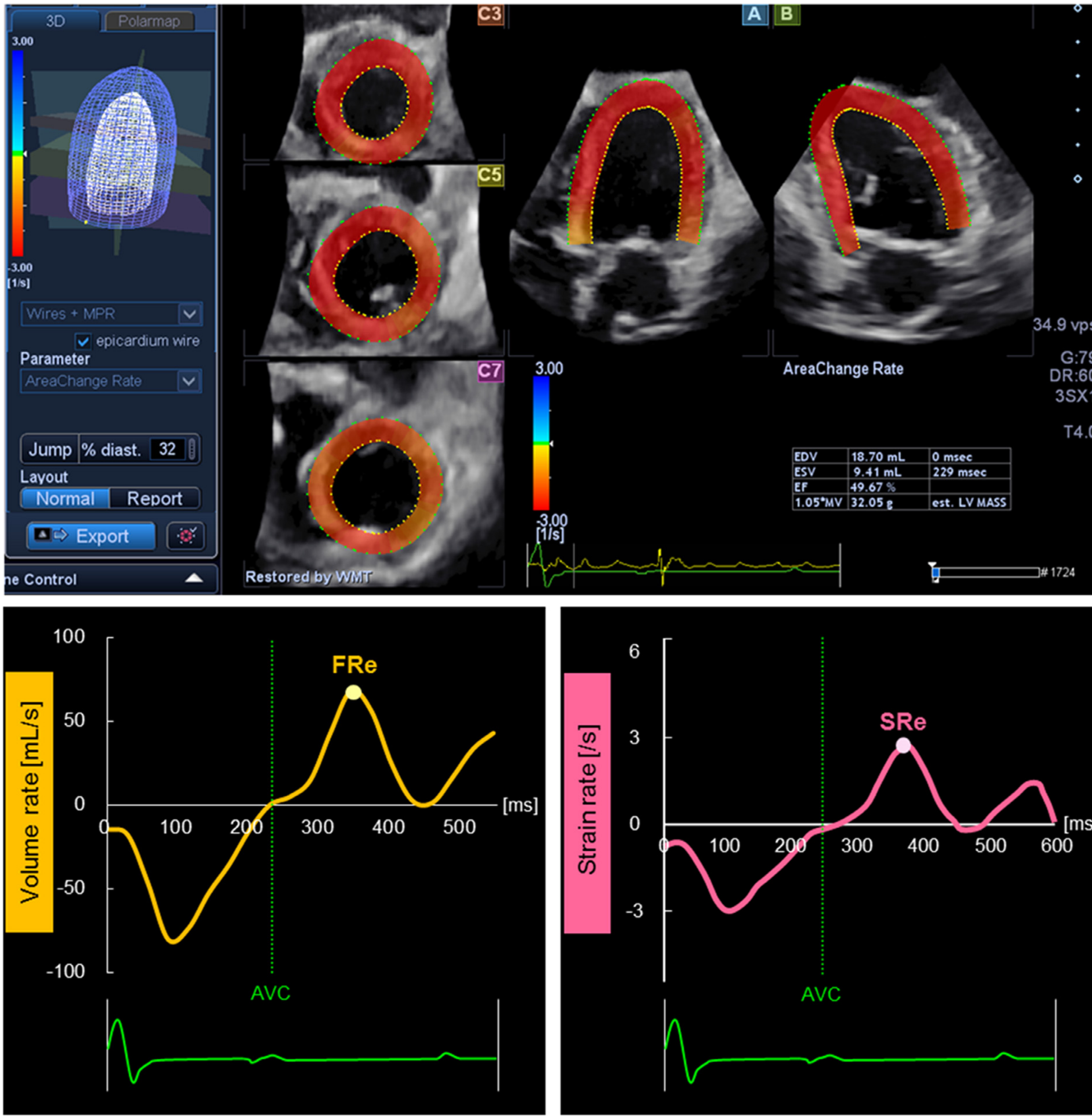

Fig. 1. Three-dimensional speckle-tracking echocardiography and analysis of the ratio of peak early diastolic filling rate to peak early diastolic global strain rate (FRe/SRe). (Top) Multiplanar reconstruction images derived from 3-D full-volume data sets are color-coded by area strain rate. (Bottom) The left ventricular (LV) volume rate curve (*i.e., dV/dt*) and the LV global strain rate curve averaged over all 16 segments are simultaneously obtained by 3-D speckle-tracking analysis. By use of customized software, the values of FRe and SRe can be semi-automatically calculated without arbitrary measurements. AVC = aortic valve closure.

from the remaining 19 dogs. Because data during heart failure were obtained in one to three different conditions per dog, 30 data points during heart failure and 23 data points at baseline were used for further analyses.

For the dog in which a fluid-filled catheter was used (2 data points), only LV systolic pressure and LVEDP were measured as hemodynamic data. In the analyses of E/e' and FRe/SRe, because of the fusion of each parameter with the atrial component or inability to determine the peak value, 6 data points for mitral E, 2 data points for e', 2 data points for FRe, 6 data points for SRe (radial), 4 data points for SRe (circumferential), 3 data points for SRe (longitudinal) and 2 data points for SRe (area) were excluded. The late diastolic transmitral flow velocity (*i.e.*, mitral A) could not be detected in 3 data points, which had excessive increases in LVEDP.

Mild and more-than-moderate mitral regurgitation was observed in 8 and 2 data points, respectively, but these were not excluded. Significant aortic regurgitation was not detected in this model.

Hemodynamic and echocardiographic measurements

During heart failure, LV end-diastolic volume was significantly increased (15 ± 4 to 24 ± 9 mL, range: 6.8−38.9 mL), and LV ejection fraction was significantly decreased (52 ± 5 to 31 ± 10%, range: 67%−17%) (Table 1). τ was significantly prolonged, and LVEDP and $LVDP_{mean}$ were significantly increased (6 ± 2 to 17 ± 10 mm Hg and 5 ± 1 to 14 ± 9 mm Hg, respectively). E/e' and all FRe/SRe ratios were also significantly increased.

Estimation of LV filling pressure using E/e′ *and FRe/SRe*

The changes in E/e' and FRe/SRe derived from area strain rate before and during heart failure in a representative dog are illustrated in Figure 2. In this dog, LVEDP and $LVDP_{mean}$ increased from 5 to 21 mm Hg and from 4 to 16 mm Hg, respectively. With respect to the measurements of mitral E and FRe, both parameters increased during heart failure; however, the rate of increase in mitral E was smaller than the rate of increase in FRe. Regarding the measurements of e' and SRe, SRe decreased during heart failure, whereas e' slightly increased. As a result, FRe/SRe, but not E/e', increased during heart failure.

In all data, there was no significant correlation between E/A and LVEDP (Fig. 3). However, there was a significant but moderate correlation between E/e' and LVEDP. Additionally, all FRe/SRe ratios had better correlations with LVEDP than E/e'. This trend was also observed when analyzing the correlations of E/e' and FRe/SRe with $LVDP_{mean}$. The correlation coefficients were 0.02 for E/A, 0.49 for E/e', 0.79 for FRe/SRe (radial), 0.82 for FRe/SRe (circumferential), 0.88 for FRe/SRe (longitudinal) and 0.88 for FRe/SRe (area).

In the ROC curve analysis to distinguish elevated filling pressure, the AUCs of all FRe/SRe ratios were significantly larger than those of E/e' (Fig. 4). In particular, FRe/SRe (area) and FRe/SRe (circumferential) tended to provide better diagnostic accuracy than the other FRe/SRe ratios, although there was no significant difference between the AUCs of various FRe/SRe ratios.

Table 1. Hemodynamic and echocardiographic data

	Baseline	Heart failure	p
Hemodynamic data			
Heart rate, bpm	118 ± 13	120 ± 14	0.561
LV systolic pressure, mm Hg	103 ± 20	89 ± 24	0.031
LVEDP, mm Hg	6 ± 2	17 ± 10	<0.001
$LVDP_{mean}$, mm Hg	5 ± 1	14 ± 9	<0.001
dP/dt_{max}, mm Hg/s	2497 ± 609	1386 ± 536	<0.001
dP/dt_{min}, mm Hg/s	−1926 ± 512	−1148 ± 480	<0.001
τ, ms	42 ± 7	64 ± 25	<0.001
Echocardiographic data			
LV end-diastolic volume, mL	15 ± 4	24 ± 9	<0.001
LV end-systolic volume, mL	7 ± 2	17 ± 8	<0.001
LV ejection fraction, %	52 ± 5	31 ± 10	<0.001
Mitral E, cm/s	51 ± 10	49 ± 8	0.315
E/A	1.4 ± 0.3	1.6 ± 0.5	0.149
Mitral e’, cm/s	5.5 ± 1.3	4.0 ± 1.2	<0.001
E/e’	9.5 ± 1.9	14.1 ± 6.5	<0.001
FRe, mL/s	64.0 ± 18.0	70.9 ± 21.1	0.215
SRe (radial), /s	1.8 ± 0.6	1.4 ± 0.6	0.020
SRe (circumferential), /s	2.4 ± 0.5	1.6 ± 0.5	<0.001
SRe (longitudinal), /s	1.0 ± 0.3	0.7 ± 0.2	<0.001
SRe (area), /s	3.1 ± 0.6	2.1 ± 0.6	<0.001
FRe/SRe (radial), mL	36.4 ± 9.4	59.3 ± 32.9	<0.001
FRe/SRe (circumferential), mL	27.1 ± 6.8	49.7 ± 21.3	<0.001
FRe/SRe (longitudinal), mL	67.9 ± 20.5	120.0 ± 60.9	<0.001
FRe/SRe (area), mL	21.0 ± 5.1	36.8 ± 14.8	<0.001

dP/dt_{max} = maximum time derivative of left ventricular pressure; dP/dt_{min} = minimum time derivative of left ventricular pressure; FRe = peak early diastolic filling rate; LV = left ventricular; $LVDP_{mean}$ = left ventricular mean diastolic pressure; LVEDP = left ventricular end-diastolic pressure; mitral E = early diastolic transmitral flow velocity; mitral e' = early diastolic mitral annular velocity; SRe = peak early diastolic global strain rate; τ = time constant of left ventricular pressure decay during isovolumic relaxation period.

Correlations of mitral E *and FRe with LV end-diastolic volume*

The correlation between mitral E and FRe was significant but less than moderate (r = 0.39), and the rate of increase in mitral E was lower than that in FRe (Fig. 5). FRe exhibited a significant correlation with LV end-diastolic volume in the baseline group and the heart failure group. Mitral E exhibited a tendency to increase with LV end-diastolic volume in the baseline group; however, such a tendency was not observed in the heart failure group.

Correlations of e′ *and SRe with* τ

Although e' and all SRe values had significant correlations with τ, the correlation of e' with τ was weaker than that of SRe (Fig. 6). SRe (area) and SRe (circumferential) tended to exhibit better correlations than the other parameters.

Inter-observer and intra-observer reliability

Inter-observer and intra-observer reliability of FRe, SRe and FRe/SRe are summarized in Table 2. The intra-class correlation coefficient of FRe/SRe (area) was more than 0.8, even at the lower limit of the 95% confidence interval.

Correction of weight in FRe/SRe

Because FRe/SRe is not dimensionless like E/e' but has units of volume, this parameter may be affected by body volume or weight. Thus, we also evaluated the

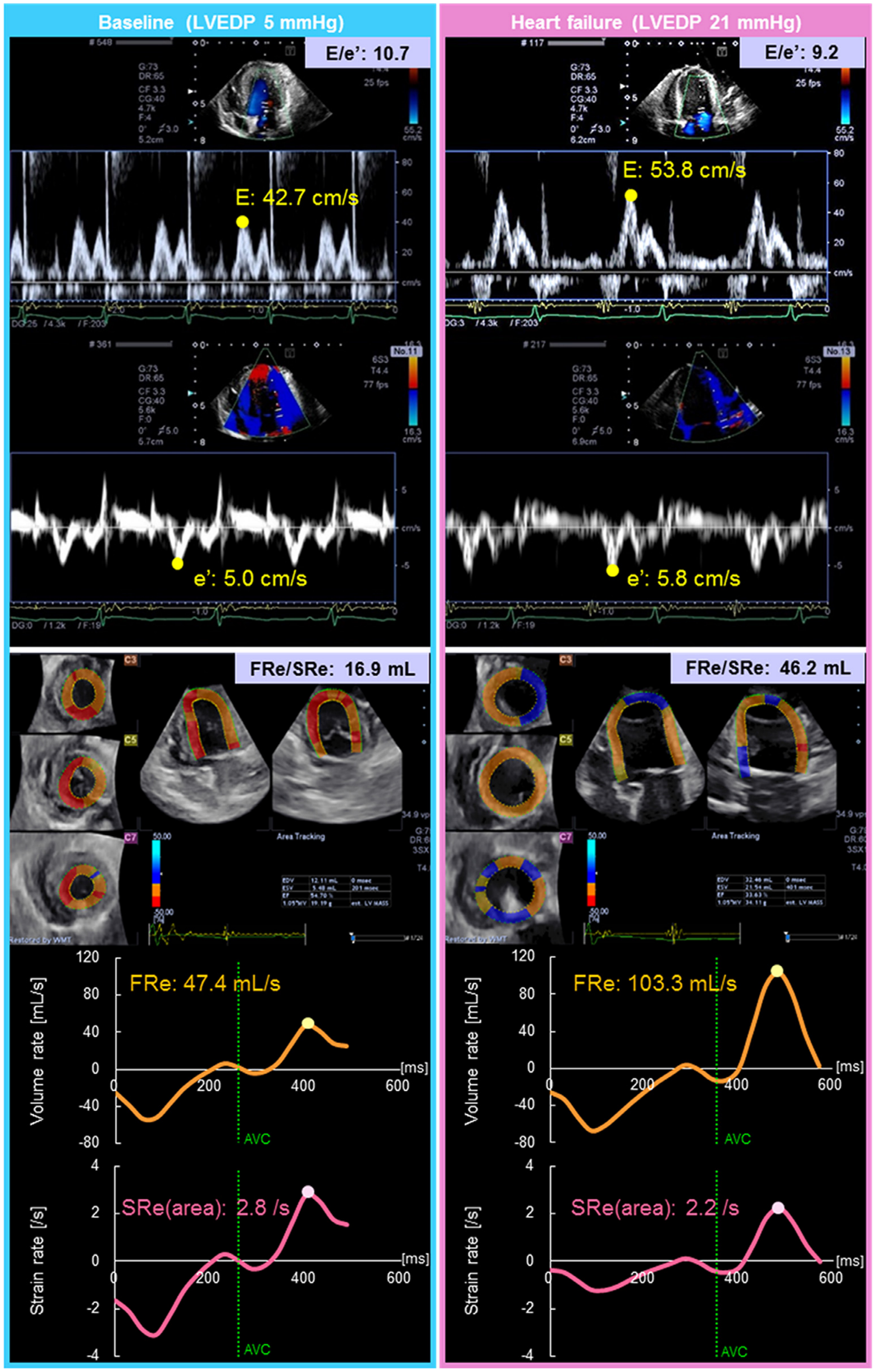

Fig. 2. Changes in E/e' and the peak early diastolic filling rate to peak early diastolic global strain rate (FRe/SRe) ratio derived from area strain rate in a representative dog. Left ventricular (LV) ejection fraction decreased from 54% to 35%, and the LV end-diastolic volume increased from 12 to 32 mL during heart failure. LV end-diastolic pressure (LVEDP) and mean diastolic pressure increased from 5 to 21 mm Hg and from 4 to 16 mm Hg, respectively. Regarding the measurements of mitral E and FRe, both parameters increased during heart failure; however, the rate of increase in mitral E was smaller than that in FRe. Regarding the measurements of e' and SRe, SRe decreased during heart failure, whereas e' slightly increased. Consequently, FRe/SRe, but not E/e', increased during heart failure. The grade of mitral regulation was mild.

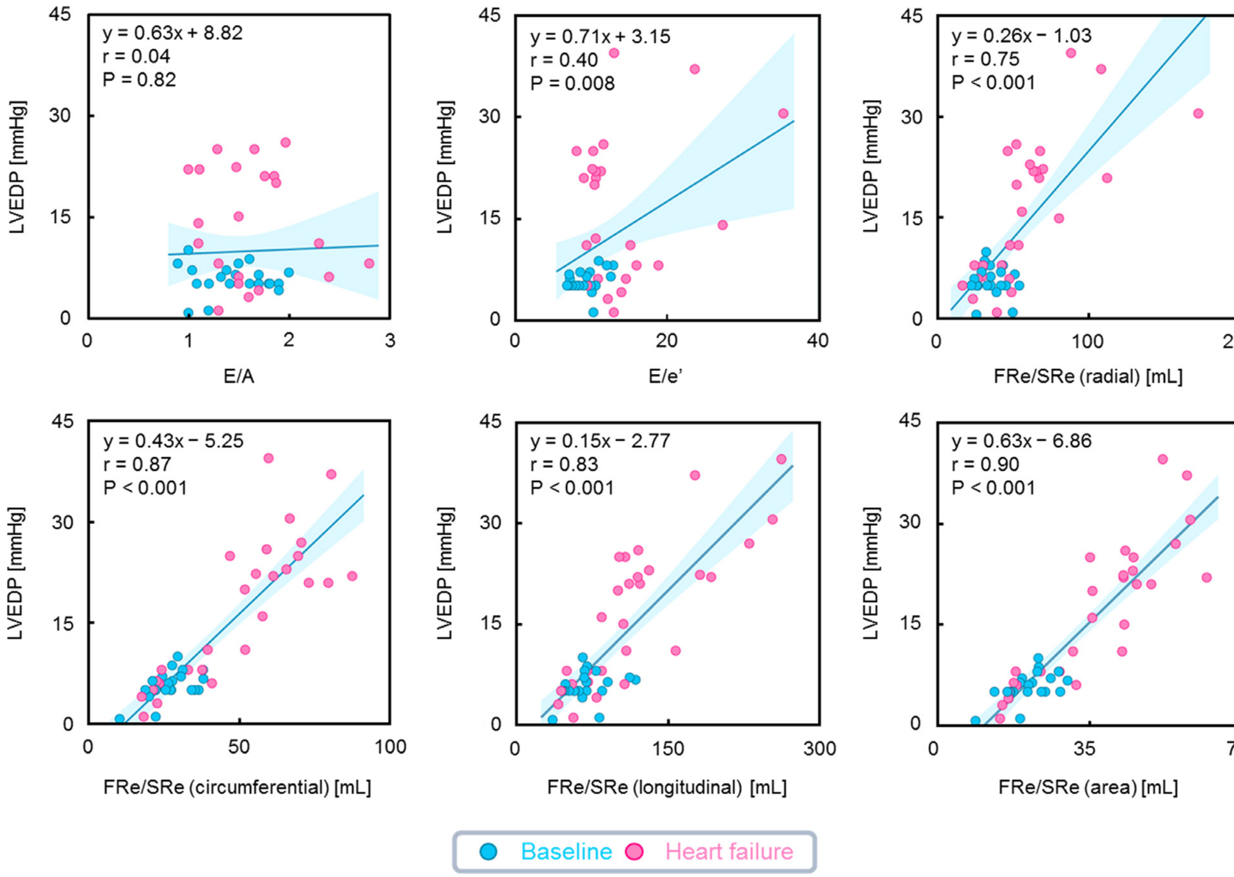

Fig. 3. Correlation between each echocardiographic parameter and left ventricular end-diastolic pressure (LVEDP) with a regression line and 95% confidence interval. The *blue and pink circles* represent the data at baseline and during heart failure, respectively. E/e', but not E/A, was significantly correlated with LVEDP. Moreover, all values of FRe/SRe (peak early diastolic filling rate/peak early diastolic global strain rate) ratios had better correlations with LVEDP than with E/e'.

correlations of weight-corrected FRe/SRe with LV filling pressure (Table 3) and its AUC in the ROC curve analysis for distinguishing elevated LV filling pressure (Table 4). The results of weight-corrected FRe/SRe did not seem to differ from those of uncorrected FRe/SRe.

DISCUSSION

In the present study, we investigated the diagnostic accuracy of E/e' and the novel parameter FRe/SRe in estimating LV filling pressure in dogs with decompensated systolic heart failure. In this model, LV ejection fraction decreased from 52% to 31%, and LV end-diastolic volume increased by approximately 1.6 times. FRe, but not mitral E, reflected a change in LV end-diastolic volume, and SRe correlated with τ better than did e'. Additionally, there was a strong correlation between FRe/SRe and filling pressure, whereas there was a moderate correlation between E/e' and filling pressure. Collectively, these data indicate that FRe/SRe can provide a more accurate estimation of filling pressure than E/e'.

Estimation of LV filling pressure in decompensated systolic heart failure

Although E/e' is widely used as a non-invasive parameter to estimate filling pressure, limited diagnostic accuracy has been reported in some diseases or conditions. For instance, E/e' has not been reliable in decompensated patients with advanced systolic heart failure (Mullens et al. 2009; Matsushita et al. 2015). Mullens et al. (2009) indicated that E/e' was not a reliable parameter in these patients, especially in those with larger LV volumes and more impaired cardiac indices. While a definite reason behind such an observation remains elusive, we believe that the Doppler angle dependence could be a causative factor. It is well known that the direction of transmitral flow deviates from that of the Doppler beam in dilated systolic failing hearts because the flow shifts from the apical to the lateral direction (Appleton et al. 1997; Otsuji et al. 1998). The direction of mitral annular motion is also difficult to align with the Doppler beam in dilated hearts (Kimura et al. 2012).

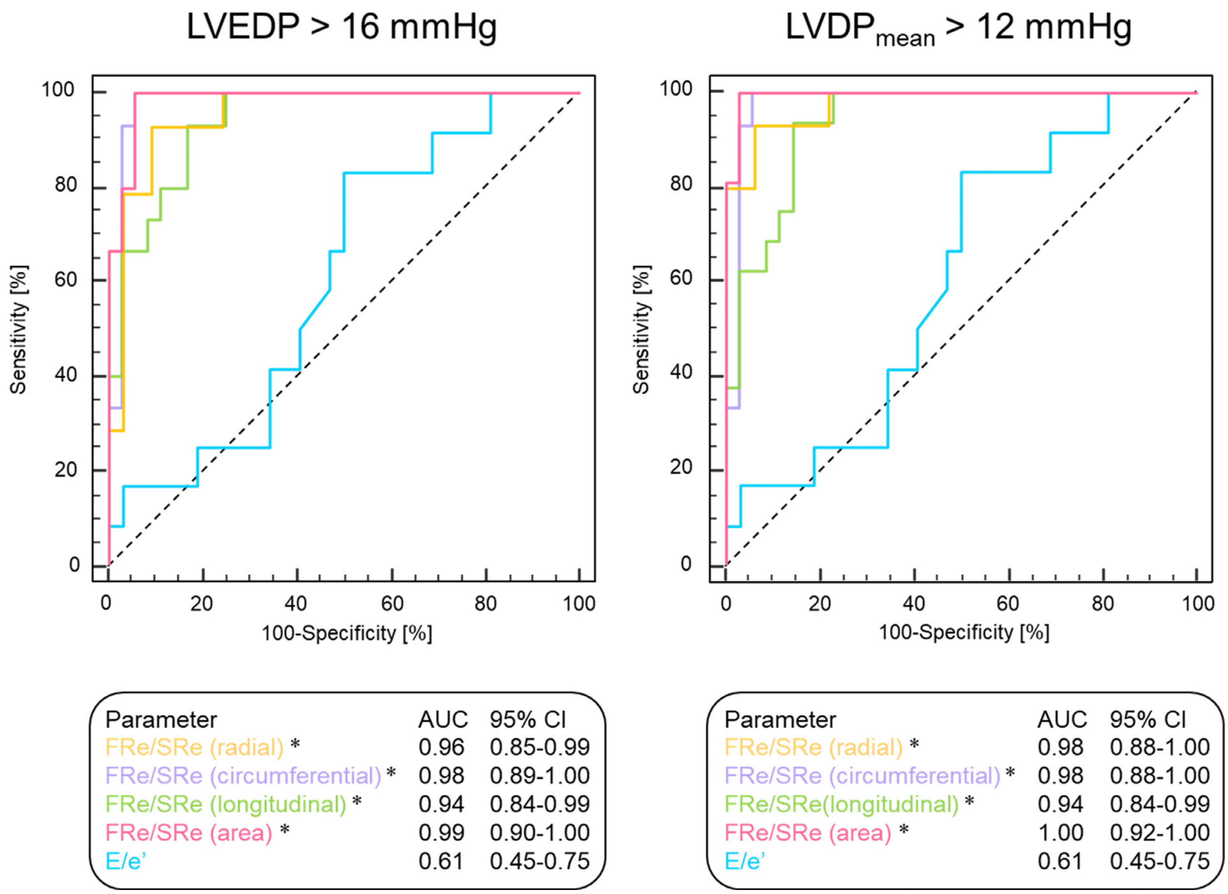

Fig. 4. Receiver operating characteristic (ROC) curve analysis of E/e' and the peak early diastolic filling rate to peak early diastolic global strain rate (FRe/SRe) ratio (for distinguishing elevated left ventricular filling pressure, which is defined as a left ventricular end-diastolic pressure (LVEDP) >16 mm Hg (left) and mean diastolic pressure ($LVDP_{mean}$) >12 mm Hg (right). The areas under the curve (AUCs) for all FRe/SRe ratios were significantly larger than those for E/e'. In particular, FRe/SRe (area) and FRe/SRe (circumferential) tended to have better diagnostic accuracy than the other FRe/SRe ratios. $*p < 0.001$ versus E/e' in the comparison of AUCs.

Regarding decompensated systolic heart failure, Nagueh et al. (2011) rebutted Mullens et al.'s argument. They pointed out the failure of Doppler measurements in Mullens et al.'s data, such as poor alignment of the Doppler beam or incorrectly defined spectral envelope, and concluded that E/e' provided reliable assessment even in these patients. Thus, the results of Nagueh et al. suggest that E/e' may be useful even in patients with decompensated systolic heart failure as long as careful attention is given to the Doppler measurements. However, obtaining ideal measurements in these patients is rather challenging in the clinical setting.

FRe/SRe derived from 3-D speckle-tracking echocardiography

To circumvent this problem, we developed a new parameter, FRe/SRe, derived from 3-D speckle-tracking echocardiography, to estimate filling pressure. FRe/SRe is not affected by the ultrasound beam angle, as it is obtained without the use of Doppler. The values of FRe and SRe can be easily, semi-automatically and simultaneously calculated from LV volume and strain data without distress by a broad spectral envelope in the Doppler method. These advantages suggest that FRe/SRe could be a better alternative than E/e' for estimating filling pressure in patients with decompensated systolic heart failure. On the other hand, measurement of FRe/SRe using 3-D echocardiography has some disadvantages. The inferior spatial and temporal resolution of the 3-D images compared with those of 2-D images is an unavoidable limitation. Especially in dilated systolic failing hearts, spatial and temporal resolution inevitably decrease, which may make accurate estimations difficult.

The usefulness of FRe/SRe has been reported in non-dilated hearts that have preserved systolic function (Sakurai et al. 2017); however, the importance of this parameter remains elusive in dilated systolic failing hearts. Therefore, we investigated the feasibility and

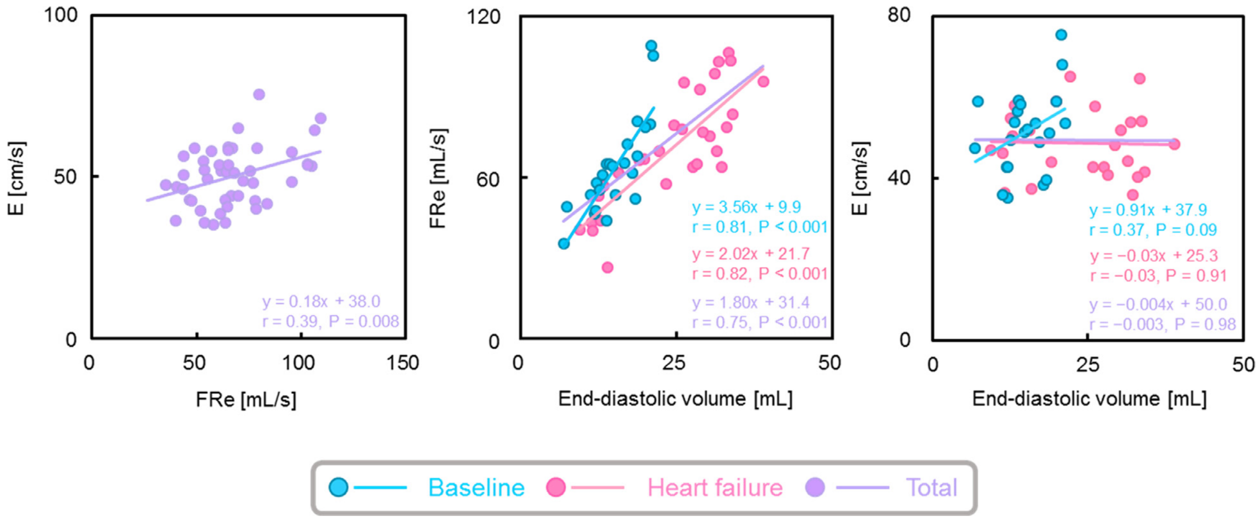

Fig. 5. Correlations of mitral *E* and peak early diastolic filling rate (FRe) with left ventricular (LV) end-diastolic volume. The *blue and pink circles* represent the data at baseline and during heart failure, respectively. The *purple circles* represent total data. The correlation between mitral *E* and FRe was significant but less than moderate, and the rate of increase in mitral *E* was small compared with that in FRe. FRe had a significant correlation with LV end-diastolic volume in the baseline group and the heart failure group. Mitral *E* exhibited a tendency to increase with LV end-diastolic volume in the baseline group; however, such a tendency was not observed in the heart failure group.

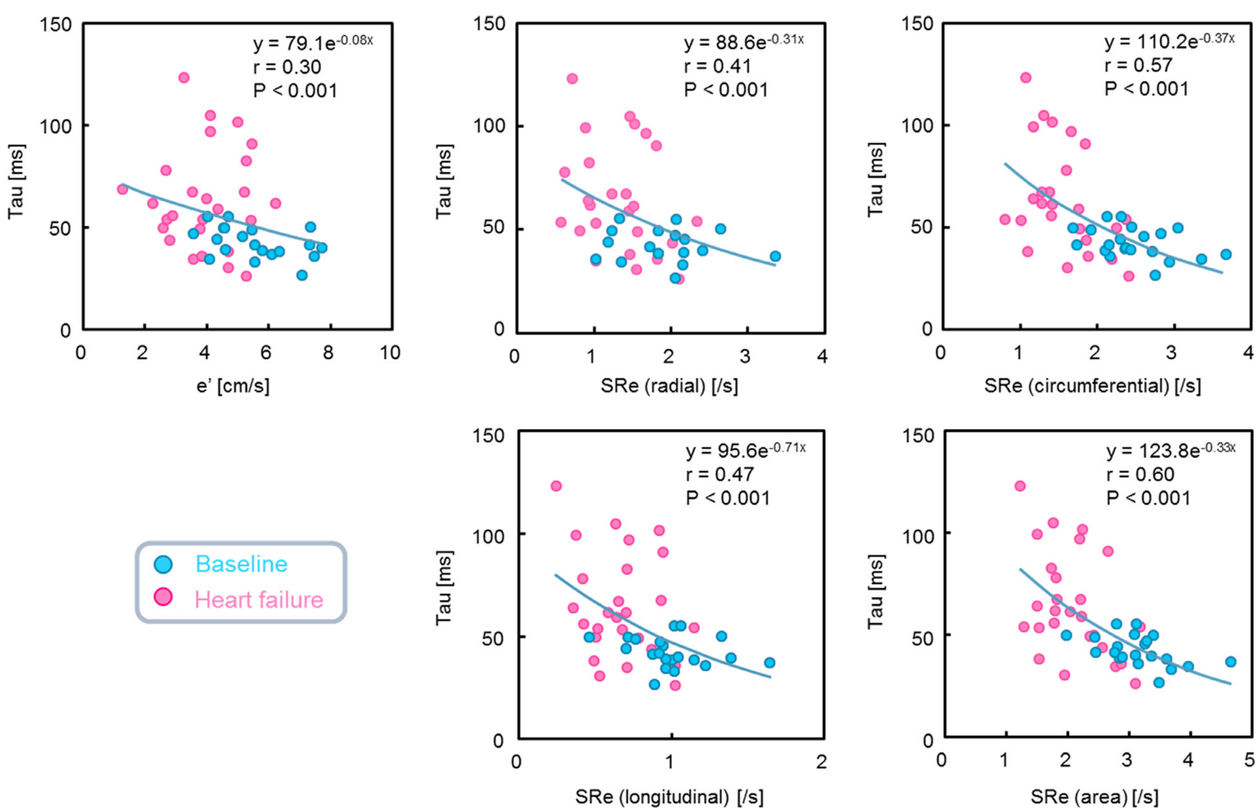

Fig. 6. Correlations of e' and peak early diastolic global strain rate (SRe) with τ. The *blue and pink circles* represent the data at baseline and during heart failure, respectively. Although e' and all SRe values had significant correlations with τ, SRe (area) and SRe (circumferential) tended to have better correlations than the other parameters.

Table 2. Inter-observer and intra-observer reliability

	Intraclass correlation coefficient (95% confidence interval)	
	Inter-observer	Intra-observer
FRe	0.97 (0.87–0.99)	0.97 (0.91–0.99)
SRe (radial)	0.70 (0.22–0.92)	0.92 (0.74–0.98)
SRe (circumferential)	0.90 (0.67–0.98)	0.85 (0.52–0.96)
SRe (longitudinal)	0.90 (0.49–0.98)	0.97 (0.88–0.99)
SRe (area)	0.95 (0.82–0.99)	0.91 (0.69–0.98)
FRe/SRe (radial)	0.90 (0.66–0.98)	0.96 (0.85–0.99)
FRe/SRe (circumferential)	0.95 (0.82–0.99)	0.94 (0.78–0.98)
FRe/SRe (longitudinal)	0.95 (0.55–0.99)	0.98 (0.94–1.00)
FRe/SRe (area)	0.97 (0.87–0.99)	0.96 (0.86–0.99)

FRe = peak early diastolic filling rate; SRe = peak early diastolic global strain rate.

Table 3. Correlations of weight-corrected FRe/SRe with LDEDP and $LVDP_{mean}$

Weight-corrected	Correlation coefficient (r)	
	LDEDP	$LVDP_{mean}$
FRe/SRe (radial)	0.72	0.77
FRe/SRe (circumferential)	0.89	0.85
FRe/SRe (longitudinal)	0.84	0.90
FRe/SRe (area)	0.93	0.92

FRe = peak early diastolic filling rate; SRe = peak early diastolic global strain rate; $LVDP_{mean}$ = left ventricular mean diastolic pressure; LVEDP = left ventricular end-diastolic pressure.

Table 4. Receiver operating characteristic curve analysis of weight-corrected FRe/SRe for distinguishing elevated left ventricular filling pressure

Weight-corrected	Area under the curve (95% confidence interval)	
	LVEDP > 16 mm Hg	$LVDP_{mean}$ > 12 mm Hg
FRe/SRe (radial)	0.96 (0.86–1.00)	0.98 (0.89–1.00)
FRe/SRe (circumferential)	1.00 (0.93–1.00)	1.00 (0.93–1.00)
FRe/SRe (longitudinal)	0.96 (0.87–1.00)	0.96 (0.86–1.00)
FRe/SRe (area)	0.99 (0.92–1.00)	1.00 (0.93–1.00)

FRe = peak early diastolic filling rate; SRe = peak early diastolic global strain rate; $LVDP_{mean}$ = left ventricular mean diastolic pressure; LVEDP = left ventricular end-diastolic pressure.

diagnostic accuracy of FRe/SRe in dogs with decompensated systolic heart failure. Our results indicate the reasonable feasibility and robust diagnostic accuracy of FRe/SRe compared with E/e' in estimating filling pressure.

Possible reasons for better diagnostic accuracy of FRe/SRe

Rokey et al. (1985) reported the similarity between the dV/dt curve determined by angiographic measurement and the Doppler-derived mitral inflow velocity. The mechanism underlying alterations in mitral E and FRe during the development of heart failure is also fully understood (Ohno et al. 1994). Both parameters should theoretically change in parallel, but the rate of increase in mitral E was lower than that of FRe, as illustrated in Figure 5. One reason for this might be that mitral E is underestimated when end-diastolic volume increases. The poor correlation between mitral E and end-diastolic volume also indicates the difficulty in measuring peak E velocity in dilated hearts. Although we carefully aligned the Doppler beam with transmitral flow on color flow mapping, the maximum flow velocity might not have been measured in the dilated systolic failing hearts. Even when the Doppler beam is completely adjusted on the 2-D images, the actual main flow can be out-of-plane in the 2-D images in dilated hearts. Time-resolved, three-directional velocity data derived from magnetic resonance imaging (MRI) have suggested that the direction of transmitral flow during early diastolic filling is three-dimensionally deviated in patients with dilated cardiomyopathy (Eriksson et al. 2016). Stroke volume calculated from transmitral flow can also be underestimated compared with that derived from MRI (Thavendiranathan et al. 2012). In contrast, FRe, which can be obtained without Doppler, is able to accurately reflect an increase in transmitral flow because of its better correlation with end-diastolic volume, even under limited spatial and temporal resolution.

In the relationships of e' and SRe with τ, SRe had a better correlation with τ than e'. This tendency is consistent with previous results, which were assessed in dogs with non-dilated hearts and in patients (Tatsumi et al. 2014; Sakurai et al. 2017), suggesting the superiority of SRe measured from all LV segments without being affected by tethering or through-plane motion. As with FRe, the angle independence of SRe is another advantage because e' cannot reflect the true motion of mitral annuli in dilated systolic failing hearts (Dokainish et al. 2008; Kimura et al. 2012).

Which strain rate should be analyzed?

In the present study, SRe was derived from radial, circumferential, longitudinal and area strain rates. FRe/SRe (area) and FRe/SRe (circumferential) tended to provide better estimations of LVEDP than the other FRe/SRe ratios. When comparing area and circumferential strain rates, the use of the area strain rate should be recommended because of its higher intra-class correlation coefficient. Area strain has been reported to offer a more accurate and robust measurement of regional myocardial deformation than 1-D myocardial strain (Seo et al. 2011; Hioki et al. 2020).

Study limitations

Our study has limitations that are highlighted below. Although filling pressure and τ were measured in an unbiased (blinded) manner, the observer who analyzed echocardiographic data could infer elevated filling pressure from the visual impression of LV end-diastolic volume and ejection fraction and thus could be biased. The relatively low spatial and temporal resolution of 3-D full-volume images would be another potential limitation in accurately estimating FRe and SRe in human dilated left ventricles (Yodwut et al. 2012). Moreover, satisfactory 3-D images may be hard to obtain in patients with decompensated heart failure because of difficulties in maintaining the left lateral position and with breathholding. FRe is influenced not only by transmitral flow but also by aortic regurgitant flow, so FRe/SRe may not be accurate in patients with significant aortic regurgitation.

Thus, further studies are required to assess the feasibility and diagnostic accuracy of this parameter in estimating filling pressure in the clinical setting. The acquisition of good-quality images in patients with heart failure would be required for high feasibility. Given that FRe/SRe has units of volume, normalization to body volume or weight will likely be needed in clinical applications.

Clinical implications

Our results suggest that FRe/SRe might provide better diagnostic accuracy than E/e' in patients with decompensated systolic heart failure. Although FRe/SRe is still a theoretical parameter, we believe that this parameter can be used regularly in the clinical setting. Semi-automatic analysis of FRe/SRe would provide credible measurements. By use of 3-D speckle-tracking analysis, FRe and SRe can be obtained at the same time as the assessment of LV volume and ejection fraction. Because global strain can also be simultaneously analyzed, this method may enable integrated analyses of systolic and diastolic function at the same time.

CONCLUSIONS

A novel parameter, FRe/SRe, derived from 3-D speckle-tracking echocardiography, exhibited better correlation with LV filling pressure and higher diastolic accuracy than E/e'. This non-Doppler parameter may be useful in estimating elevated filling pressure in dilated and decompensated systolic failing hearts.

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REFERENCES

Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Nagueh SF. Estimating left ventricular filling pressure by echocardiography. J Am Coll Cardiol 2017;69:1937–1948.

Appleton CP, Jensen JL, Hatle LK, Oh JK. Doppler evaluation of left and right ventricular diastolic function: A technical guide for obtaining optimal flow velocity recordings. J Am Soc Echocardiogr 1997;10:271–291.

Bhella PS, Pacini EL, Prasad A, Hastings JL, Adams-Huet B, Thomas JD, Grayburn PA, Levine BD. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. Circ Cardiovasc Imaging 2011;4:482–489.

DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 1988;44:837–845.

Diwan A, McCulloch M, Lawrie GM, Reardon MJ, Nagueh SF. Doppler estimation of left ventricular filling pressures in patients with mitral valve disease. Circulation 2005;111:3281–3289.

Dokainish H, Sengupta R, Pillai M, Bobek J, Lakkis N. Usefulness of new diastolic strain and strain rate indexes for the estimation of left ventricular filling pressure. Am J Cardiol 2008;101:1504–1509.

Eriksson J, Bolger AF, Ebbers T, Carlhäll CJ. Assessment of left ventricular hemodynamic forces in healthy subjects and patients with dilated cardiomyopathy using 4 D flow MRI. Physiol Rep 2016;4:e12685.

Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: Correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation 2007;116:2702–2708.

Hioki A, Asanuma T, Masuda K, Sakurai D, Nakatani S. Detection of abnormal myocardial deformation during acute myocardial ischemia using three-dimensional speckle tracking echocardiography. J Echocardiogr 2020;18:57–66.

Kawagishi T. Speckle tracking for assessment of cardiac motion and dyssynchrony. Echocardiography 2008;25:1167–1171.

Kimura K, Takenaka K, Ebihara A, Okano T, Uno K, Fukuda N, Ando J, Fujita H, Morita H, Yatomi Y, Nagai R. Speckle tracking global strain rate *E/E*' predicts LV filling pressure more accurately than traditional tissue Doppler *E/E*'. Echocardiography 2012;29:404–410.

Maruo T, Nakatani S, Jin Y, Uemura K, Sugimachi M, Ueda-Ishibashi H, Kitakaze M, Ohe T, Sunagawa K, Miyatake K. Evaluation of transmural distribution of viable muscle by myocardial strain profile and dobutamine stress echocardiography. Am J Physiol Heart Circ Physiol 2007;292:H921–H927.

Masuda K, Asanuma T, Taniguchi A, Uranishi A, Ishikura F, Beppu S. Assessment of dyssynchronous wall motion during acute myocardial ischemia using velocity vector imaging. JACC Cardiovasc Imaging 2008;1:210–220.

Matsushita K, Minamishima T, Goda A, Ishiguro H, Kosho H, Sakata K, Satoh T, Yoshino H. Comparison of the reliability of *E/E*' to estimate pulmonary capillary wedge pressure in heart failure patients with preserved ejection fraction versus those with reduced ejection fraction. Int J Cardiovasc Imaging 2015;31:1497–1502.

Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. Circulation 2009;119:62–70.

Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–1533.

Nagueh SF, Bhatt R, Vivo RP, Krim SR, Sarvari SI, Russell K, Edvardsen T, Smiseth OA, Estep JD. Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. Circ Cardiovasc Imaging 2011;4:220–227.

Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, III, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti

P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

Nesser HJ, Mor-Avi V, Gorissen W, Weinert L, Steringer-Mascherbauer R, Niel J, Sugeng L, Lang RM. Quantification of left ventricular volumes using three-dimensional echocardiographic speckle tracking: Comparison with MRI. Eur Heart J 2009;30:1565–1573.

Ohno M, Cheng CP, Little WC. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation 1994;89:2241–2250.

Otsuji Y, Gilon D, Jiang L, He S, Leavitt M, Roy MJ, Birmingham MJ, Levine RA. Restricted diastolic opening of the mitral leaflets in patients with left ventricular dysfunction: Evidence for increased valve tethering. J Am Coll Cardiol 1998;32:398–404.

Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: Comparison with cineangiography. Circulation 1985;71:543–550.

Sakurai D, Asanuma T, Masuda K, Koriyama H, Nakatani S. New parameter derived from three-dimensional speckle-tracking echocardiography for the estimation of left ventricular filling pressure in nondilated hearts. J Am Soc Echocardiogr 2017;30:522–531.

Seo Y, Ishizu T, Enomoto Y, Sugimori H, Yamamoto M, Machino T, Kawamura R, Aonuma K. Validation of 3-dimensional speckle tracking imaging to quantify regional myocardial deformation. Circ Cardiovasc Imaging 2009;2:451–459.

Seo Y, Ishizu T, Enomoto Y, Sugimori H, Aonuma K. Endocardial surface area tracking for assessment of regional LV wall deformation with 3 D speckle tracking imaging. JACC Cardiovasc Imaging 2011;4:358–365.

Takeguchi T, Nishiura M, Abe Y, Ohuchi H, Kawagishi T. Practical considerations for a method of rapid cardiac function analysis based on three-dimensional speckle tracking in a three-dimensional diagnostic ultrasound system. J Med Ultrason 2010;37:41–49.

Takeuchi M, Fujitani K, Kurogane K, Bai HT, Toda C, Yamasaki T, Fukuzaki H. Effects of left ventricular asynchrony on time constant and extrapolated pressure of left ventricular pressure decay in coronary artery disease. J Am Coll Cardiol 1985;6:597–602.

Tatsumi K, Tanaka H, Matsumoto K, Sawa T, Miyoshi T, Imanishi J, Motoji Y, Mochizuki Y, Fukuda Y, Shinke T, Hirata K. Global endocardial area change rate for the assessment of left ventricular relaxation and filling pressure: Using 3-dimensional speckle-tracking study. Int J Cardiovasc Imaging 2014;30:1473–1481.

Thavendiranathan P, Liu S, Datta S, Walls M, Nitinunu A, Van Houten T, Tomson NA, Vidmar L, Georgescu B, Wang Y, Srinivasan S, De Michelis N, Raman SV, Ryan T, Vannan MA. Automated quantification of mitral inflow and aortic outflow stroke volumes by three-dimensional real-time volume color-flow Doppler transthoracic echocardiography: Comparison with pulsed-wave Doppler and cardiac magnetic resonance imaging. J Am Soc Echocardiogr 2012;25:56–65.

Yamamoto K, Nishimura RA, Redfield MM. Assessment of mean left atrial pressure from the left ventricular pressure tracing in patients with cardiomyopathies. Am J Cardiol 1996;78:107–110.

Yodwut C, Weinert L, Klas B, Lang RM, Mor-Avi V. Effects of frame rate on three-dimensional speckle-tracking-based measurements of myocardial deformation. J Am Soc Echocardiogr 2012;25:978–985.