New Parameter Derived from Three-dimensional Speckle-tracking Echocardiography for the Estimation of Left Ventricular Filling Pressure in Nondilated Hearts

Daisuke Sakurai, MSc, Toshihiko Asanuma, MD, PhD, Kasumi Masuda, PhD, Hikaru Koriyama, MSc, Satoshi Nakatani, MD, PhD

From the Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine, Suita, Osaka, Japan.

Dr. Nakatani has received a research grant from Toshiba Medical Systems.

Corresponding author:

Toshihiko Asanuma, MD, PhD

Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine, 1-7 Yamadaoka, Suita, Osaka, 565-0871, Japan.

E-mail: toshi@sahs.med.osaka-u.ac.jp

Abstract

Background: E/e' is clinically useful for noninvasive assessment of left ventricular (LV) filling pressure. However, its use in some conditions is controversial, and angle dependence of the Doppler measurement and preload dependence of mitral e' in nondilated hearts represent major problems. The ratio of early filling rate derived from the time derivative of LV volume to early diastolic strain rate (FRe/SRe), similar to E/e', by three-dimensional (3D) speckle-tracking echocardiography has the potential to address such limitations. This study investigated whether FRe/SRe could estimate acute changes in LV filling pressure using the models of volume overload and myocardial ischemia in the nondilated heart.

Methods: In 25 dogs, hemodynamic conditions were varied by acute volume overload and coronary occlusion. FRe and SRe were obtained from the same beat and automatically analyzed by the 3D speckle-tracking method, and global SRe was measured from longitudinal (L-SRe), circumferential (C-SRe), and area strain rate (A-SRe). E/e' was measured by two-dimensional echocardiography. LV pressure was derived from a micro-manometer catheter and recorded simultaneously with the acquisition of the 3D images.

Results: Mitral e' and L-SRe varied by changes in preload, whereas C-SRe and A-SRe did not. The time constant of LV relaxation was more strongly correlated with C-SRe and A-SRe than mitral e' and L-SRe. FRe/C-SRe and FRe/A-SRe had relatively high correlations with LV pre-atrial contraction (pre-A) pressure and end-diastolic pressure, but E/e' and FRe/L-SRe did not. Receiver operating characteristics curve analysis showed that FRe/C-SRe and FRe/A-SRe had larger areas under the curve for the estimation of

increased LV filling pressure.

Conclusion: The novel parameter, FRe/SRe, has the potential as a surrogate marker of LV filling pressure. Especially in nondilated hearts, FRe/C-SRe and FRe/A-SRe, may be useful to more accurately predict LV filling pressure than E/e', although their applicability in dilated hearts requires further investigation.

Keywords: E/e'; filling pressure; speckle-tracking echocardiography; three-dimensional

Abbreviations

3D = Three-dimensional

A-SRe = Area early diastolic strain rate

AUC = Area under the curve

C-SRe = Circumferential early diastolic strain rate

dV/dt = Time derivative of the left ventricular volume curve

FRe = Early filling rate

HFpEF = Heart failure with preserved ejection fraction

ICC = Intra-class correlation coefficient

L-SRe = Longitudinal early diastolic strain rate

LAD = Left anterior descending artery

LV = Left ventricular

Mitral A = Mitral inflow late diastolic velocity

Mitral E = Mitral inflow early diastolic velocity

Mitral e' = Mitral annular early diastolic velocity

ROC = Receiver operating characteristic

SRe = Early diastolic strain rate

Tau = Time constant of left ventricular relaxation

Introduction

Noninvasive evaluation of left ventricular (LV) filling pressure is important for the diagnosis and treatment of heart failure. The ratio of the mitral inflow early diastolic velocity to the mitral annular early diastolic velocity (E/e') is used as a noninvasive parameter for estimating LV filling pressure.[1, 2] When LV diastolic dysfunction progresses and filling pressure increases, mitral E increases, and mitral e' is almost always reduced without depending on preload; hence, E/e' increases. However, several limitations can hamper the clinical utility of E/e'. For example, inappropriate measurement of E/e' is not rare in cases who are difficult to adjust the Doppler beam alignment. Extrapolation of global diastolic function by regional measurements of mitral e' seems to be another problem. Moreover, E/e' may not reflect filling pressure in normal subjects and patients with heart failure with preserved ejection fraction (HFpEF) because mitral e' is dependent on preload in such nondilated hearts.[3, 4]

Three-dimensional (3D) speckle-tracking echocardiography is a promising method for the quantitative assessment of whole LV deformation without the through-plane problem.[5] This technique allows the simultaneous evaluation of LV volume and global myocardial strain. The rate of LV volume change (dV/dt), which is equivalent to the flow rate, is calculated by numerical differentiation of LV volume as a function of time. Flow rate denotes the product of blood velocity and cross-sectional area. Assuming that mitral annular area is constant during diastole, the early filling rate (FRe) derived from dV/dt could reflect mitral E.[6] On the other hand, global early diastolic strain rate (SRe) has recently been demonstrated to be better correlated with the time constant of LV relaxation (tau) than mitral e'.[7] Hence, the ratio of FRe to SRe

(FRe/SRe) may be used as an alternative to E/e'. This parameter can be analyzed from one 3D acquisition and need not take into account the Doppler alignment, because the Doppler method is not used.

Global SRe can be measured from three different directions: radial, longitudinal, and circumferential strain rate. Recently, the area tracking based-deformation parameter (area strain rate), which combines circumferential and longitudinal components, can be also measured by 3D speckle-tracking analysis.[8] However, it remains unclear which deformation parameter is most suitable for SRe measurement; one that minimizes preload dependence and reflects LV relaxation. Therefore, the goal of this study was to investigate (1) whether FRe/SRe could estimate acute changes in filling pressure and (2) which SRe was best for this assessment using the models of volume overload and myocardial ischemia in the nondilated heart.

Methods

Animal preparation

Our experimental study was approved by the animal experimentation committee and performed in accordance with the guidelines for the care and use of laboratory animals at our institution. Thirty open-chest dogs weighing from 8.5 kg to 14.6 kg were used in this study. Dogs were anesthetized with intramuscular xylazine (0.5 mg/kg) followed by intravenous pentobarbital sodium (25.9 mg/kg), and then were intubated and ventilated using a respirator. Oxygen saturation was monitored by a pulse oximeter and was maintained within normal ranges. Anesthesia was induced with pentobarbital sodium (6 mg/kg/h) and

midazolam (0.18 mg/kg/h) throughout the experiment. Buprenorphine (4 μg/kg) was administered intramuscularly for analgesia. The electrocardiogram was monitored continuously. A 6-Fr micro-manometer catheter (Millar Instruments, Houston, TX) was inserted via the right femoral artery into the LV to measure LV pressure. The chest was opened via a left parasternal thoracotomy, and the heart was exposed. In the model of volume overload, the pericardium was not opened, so as to prevent rapid distension of the LV. In the models of myocardial ischemia and changes in inotropic states, the pericardium was opened, and the heart was suspended in a pericardial cradle. In the model of myocardial ischemia, the proximal portion of the left anterior descending artery (LAD) was dissected free from surrounding tissues, and a vascular occluder was placed around the artery.

Echocardiography

Echocardiography was performed with an Aplio Artida SSH-880CV ultrasound system (Toshiba Medical Systems, Otawara, Japan). 3D full-volume datasets were acquired from apical positions with a PST-25PX transducer, which was placed on a water bath as a standoff. The frequency was 2 MHz on transmit and 4 MHz on receive. The scan range angle was set from 70°×70° to 80°×90°. The acquisition was done during six consecutive heartbeats using electrocardiogram triggering, resulting in a volume rate of 31.2 to 38.8 volumes/s.

Doppler images were recorded with a PST-50BT transducer. The transmitting and receiving frequency was 4.2 MHz. Mitral inflow velocity and mitral annular velocity at the septal and lateral sites were measured. Doppler recordings were obtained while keeping the ultrasound beam as parallel as possible to

the direction of blood flow or cardiac longitudinal motion.

3D and Doppler images were acquired while the respirator was stopped to minimize the effect of heart motion caused by breathing.

Experimental protocol

Protocol 1: The relationships between FRe/SRe and LV filling pressure during acute changes in the model of volume overload were investigated in 14 dogs. Esmolol was infused at 300 μg/kg/min from the beginning of this protocol because of two reasons; one is that volume overload alone causes reactive tachycardia and the other is the difficulty in increasing LV filling pressure in healthy dogs. LV filling pressure was escalated by two stepwise infusion of dextran solution (100 mL over 5 min each time). Echocardiographic data were obtained at baseline, and after 100 mL and 200 mL of dextran infusion.

The relationships between FRe/SRe and LV filling pressure in the model of myocardial ischemia were investigated in eight dogs. Echocardiographic data were obtained before and 1 min after LAD occlusion.

Protocol 2: The relationships of tau with mitral e' and SRe in the model of changes in inotropic states were investigated in eight dogs. Inotropic states were altered by stepwise infusion of esmolol from 100 μg/kg/min to 300 μg/kg/min. Echocardiographic data were obtained before and 5 min after esmolol infusion at 300 μg/kg/min.

LV pressure was recorded simultaneously with the acquisition of the 3D image. LV systolic pressure, LV pre-A pressure, LV end-diastolic pressure, and tau were averaged over five consecutive cardiac cycles. LV pre-A pressure reflects mean left atrial pressure as a surrogate parameter of LV filling pressure[9] and was

defined as the LV pressure at the onset of the P wave on an electrocardiogram. LV end-diastolic pressure was defined as the LV pressure at the peak of the R wave.[10] Tau was calculated assuming non-zero asymptote in the data from the point of the minimum time derivatives of the LV pressure to the point at which pressure decreased to the level of the LV end-diastolic pressure.[11]

Data analysis

3D speckle-tracking analysis was performed by offline software (Ultra Extend; Toshiba, Otawara, Japan) (**Figure 1**). From 3D full-volume datasets, the apical four-chamber and two-chamber views, and three short-axis views were displayed. The endocardial borders of the four-chamber and two-chamber images were manually traced at end-diastole. The epicardial borders were determined by setting an even width of myocardium. 3D endocardial and epicardial surfaces were automatically reconstructed, and traced borders were finely adjusted on short-axis images. After these tracing processes, the LV volume and regional strain rate curves were measured. FRe (obtained from the derivative of the LV volume curve) and SRe (obtained from the global strain rate curve averaged over all 16 segments) were used to calculate FRe/SRe. Global SRe was measured from longitudinal strain rate (L-SRe), circumferential strain rate (C-SRe), and area strain rate curves (A-SRe).

From Doppler recordings, mitral E and e' were measured, and mitral e' was averaged at septal and lateral sites. Doppler parameters were obtained from three consecutive cardiac cycles. When mitral E and mitral inflow late diastolic velocity (mitral A) were fused, the datasets were excluded in the final analysis.

Interobserver and intraobserver variability

Seven image clips were randomly selected from the model of volume overload. To determine the interobserver variability for FRe and SRe, the analysis was repeated by a second observer who was blind to values obtained by the first observer. To determine the intraobserver variability, the analysis was repeated 3 months later by the same observer.

Statistical analysis

Data are expressed as mean ± SD. Hemodynamic and echocardiographic measurements were compared at baseline and at two stages of dextran infusion by one-way analysis of variance followed by a Tukey-Kramer post hoc test. The data before and after LAD occlusion and esmolol infusion were compared by the paired t-test. Regression analysis was applied to examine the relationship between echocardiographic and hemodynamic parameters. The slopes of the regression lines in the models of volume overload and myocardial ischemia were compared by the analysis of covariance. Increased LV filling pressure was defined as LV pre-A pressure ≥ 12 mmHg and LV end-diastolic pressure ≥ 16 mmHg.[12] Receiver operating characteristic (ROC) curve analysis was performed to determine the ability of FRe/SRe to estimate the increased filling pressure, and the areas under the ROC curve (AUCs) were calculated. These AUCs were compared with the line of no information (AUC = 0.50). The interobserver and intraobserver variability for FRe and SRe was determined by intra-class correlation coefficients (ICCs). Values of $P < .05$ were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc for Windows, version 15.2.2 (MedCalc Software, Ostend, Belgium).

Results

In Protocol 1, four dogs with fusion of mitral E and A during volume overload or myocardial ischemia and one dog with insufficient image quality for speckle-tracking analysis were excluded. Because three datasets which had fusion of mitral E and A only at 200 mL infusion of dextran in the remaining dogs were also excluded, 42 datasets from a total of 17 dogs (11 dogs with volume overload and six dogs with myocardial ischemia) were included in the final analysis. In Protocol 2, FRe/SRe could be analyzed in 16 datasets from a total of eight dogs.

Protocol 1

Hemodynamic and echocardiographic measurements

Hemodynamic and echocardiographic data are shown in **Table 1**. Stepwise infusion of dextran induced a significant gradual increase of LV pre-A pressure and LV end-diastolic pressure. E/e' did not change during dextran infusion. FRe/SRe in all directions tended to increase during 100 mL infusion of dextran. FRe/C-SRe and FRe/A-SRe significantly increased during 200 mL infusion of dextran compared with baseline, but FRe/L-SRe did not.

LAD occlusion induced a significant decrease in LV systolic pressure and a significant increase in LV pre-A pressure and LV end-diastolic pressure. E/e' did not change during LAD occlusion. FRe/C-SRe and FRe/A-SRe significantly increased during LAD occlusion. FRe/L-SRe tended to increase, but the increase

was not statistically significant.

Correlations of echocardiographic parameters with LV filling pressure in the model of volume overload

A range of pre-A pressure from 2 mmHg to 22 mmHg was achieved by dextran infusion. According to Doppler measurements, mitral E and e' gradually increased along with the stepwise infusion of dextran (**Figure 2**). Positive correlations with pre-A pressure were found for mitral E and e', resulting in no correlation between pre-A pressure and E/e'. Positive correlations with LV end-diastolic pressure were also found for mitral E and e', but not for E/e' (**Table 2**).

According to 3D speckle-tracking analysis, FRe gradually increased, whereas C-SRe did not change along with stepwise infusion of dextran (**Figure 3**). A-SRe did not change either, but L-SRe increased. Moderate positive correlations with pre-A pressure were found for FRe and L-SRe, but not for C-SRe and A-SRe. Therefore, FRe/C-SRe and FRe/A-SRe had relatively high correlations with pre-A pressure, and FRe/L-SRe had a modest correlation with pre-A pressure. The correlations between 3D echocardiographic parameters and LV end-diastolic pressure were similar to those seen between 3D echocardiographic parameters and pre-A pressure. (**Table 2**).

Estimation of increased LV filling pressure

In the composite of the model of volume overload and myocardial ischemia, FRe was moderately correlated with mitral E ($r = 0.52$, $P < .05$). An inverse correlation with pre-A pressure was found for E/e' ($r = -0.39$, $P = .01$), which is primarily expected to be positively correlated with filling pressure. On the other

hand, relative high positive correlations with pre-A pressure were found for FRe/C-SRe ($r = 0.73$, $P < .001$) and FRe/A-SRe ($r = 0.72$, $P < .001$). Pre-A pressure was not correlated with FRe/L-SRe (**Figure 4)**. Positive correlations with LV end-diastolic pressure were also found for FRe/C-SRe ($r = 0.66$, $P < .001$) and FRe/A-SRe ($r = 0.65$, $P < .001$).

In the single model of myocardial ischemia, FRe/C-SRe and FRe/A-SRe tended to show positive correlations with pre-A pressure although these relationships did not reach the level of statistical significance (FRe/C-SRe: $r = 0.53$, $P = .08$; FRe/A-SRe: $r = 0.52$, $P = .08$) (**Figure 4**). The slopes of the regression lines were different between volume overload and myocardial ischemia models (FRe/C-SRe: 0.44 mL/mmHg vs. 0.12 mL/mmHg, $P < .01$; FRe/A-SRe: 0.71 mL/mmHg vs. 0.24 mL/mmHg, $P < .05$).

In the ROC curve analysis of FRe/SRe for detecting increased pre-A pressure, the AUCs for FRe/C-SRe (0.90 [95% confidence interval 0.77-0.97]) and FRe/A-SRe (0.85 [0.70-0.94]) were significantly larger than the line of no information. The AUC for FRe/L-SRe (0.51 [0.35-0.67]) was not statistically significant. (**Figure 5**). With regard to LV end-diastolic pressure, the AUCs for FRe/C-SRe (0.84 [0.70-0.94]) and FRe/A-SRe (0.85 [0.71-0.94]) were also significantly larger than the line of no information. The AUC for FRe/L-SRe (0.56 [0.39-0.71]) was not statistically significant.

Protocol 2

Correlations of tau with mitral e' and SRe in the model of changes in inotropic states

Esmolol infusion induced significant prolongation of tau from 47 ± 6 ms to 55 ± 9 ms ($P < .05$). Mitral e' and L-SRe tended to decrease during esmolol infusion compared with before infusion, but were not

statistically significant (Mitral e', 4.0 ± 1.3 cm/s vs. 3.0 ± 0.9 cm/s, P = .07; L-SRe, 0.8 ± 0.2 /s vs. 0.7 ± 0.3 /s, P = .27). C-SRe and A-SRe significantly decreased during esmolol infusion (C-SRe, 2.5 ± 0.9 /s vs. 2.1 ± 0.9 /s, P < .05; A-SRe, 3.0 ± 1.1 /s vs. 2.6 ± 1.0 /s, P < .05). Consequently, tau was moderately correlated with mitral e' and L-SRe, and was strongly correlated with C-SRe and A-SRe (**Figure 6**).

Interobserver and intraobserver variability

For the interobserver and intraobserver variability in FRe, ICCs were 0.98 [95% confidence interval 0.88-1.00] and 0.97 [0.85-1.00], respectively. ICCs in L-SRe were 0.90 [0.56-0.98] and 0.96 [0.81-0.99], respectively. ICCs in C-SRe were 0.88 [0.42-0.98] and 0.97 [0.86-1.00], respectively. ICCs in A-SRe were 0.90 [0.54-0.98] and 0.98 [0.92-1.00], respectively.

Discussion

In the present study, we examined the utility of a novel parameter FRe/SRe derived from 3D speckle-tracking echocardiography for estimating LV filling pressure during its acute changes in the nondilated heart models. In these models, conventional E/e' was not a reliable estimate of filling pressure. However, FRe/SRe, especially with the circumferential and area strain rate, seemed to be a more reliable and robust parameter for the estimation of increased filling pressure.

E/e' and a novel parameter FRe/SRe

Doppler echocardiographic measurements have played an important role in the noninvasive evaluation of LV diastolic function. E/e' is widely used in the clinical settings because it works well in majority of

heart failure patients and is part of the screening criteria for increased filling pressure in published guidelines.[9] However, Doppler limitations, such as angle dependence and extrapolation of global diastolic function by regional measurements, can sometimes prevent accurate assessment of filling pressure by E/e'. Therefore, we developed a parameter alternative to E/e', which derived from global myocardial deformation without the use of Doppler echocardiography.

Instead of mitral E, we used FRe, which is a parameter of dynamic LV volume change. Rokey et al. have demonstrated the similarity between the dV/dt curve determined by angiographic measurement and Doppler-derived mitral inflow velocity.[6] Because the measurement of LV volume by 3D speckle-tracking echocardiography has reasonable accuracy and reproducibility,[13] we considered FRe could be an alternative to mitral E.

Instead of mitral e', we used SRe which is a parameter of global LV myocardial deformation change. Tatsumi et al. evaluated the utility of A-SRe (designated as E-ACR in their study) for the estimation of LV relaxation and filling pressure using 3D speckle-tracking echocardiography.[7] In their study, A-SRe was better correlated with LV relaxation than mitral e', and the ratio of mitral E to A-SRe was a better predictor of increased filling pressure than E/e'. Other studies also have shown that the assessment of SRe was useful for patients with HFpEF,[14] those with idiopathic dilated cardiomyopathy,[15] and those with decompensated heart failure.[16] Based on these observations, we hypothesized that FRe/SRe derived from 3D speckle-tracking echocardiography could estimate filling pressure without the need for Doppler echocardiography. Because FRe and SRe are simultaneously derived from one 3D image acquisition,

automatic calculation of FRe/SRe is available in this program, which can make the assessment of filling pressure easier and more reproducible.

Limitations of E/e'

Several studies have shown that the filling pressure is high when E/e' is > 10 (mitral e' at the lateral site)[1] or 15 (mitral e' at the septal site)[2]. However, the assessment of E/e' has been reported to be less reliable in selected populations, including subjects with mitral stenosis,[17] mitral regurgitation,[18] symptomatic hypertrophic cardiomyopathy.[19] and constrictive pericarditis.[20] Most recently, Mullen et al. found a poor correlation between E/e' and filling pressure in decompensated advanced systolic heart failure with large LV volume, impaired cardiac output, and the presence of cardiac resynchronization therapy.[21] In the dilated failing heart, it is often difficult to align the Doppler beam direction and correct measurement of E/e' may not be easy.

Preload dependence of mitral e', which is well-known in the normal heart,[3, 22-24] seems to be another reason why E/e' fails to estimate filling pressure. Jacques et al. showed that mitral e' was dependent on preload, particularly in the setting of normal LV function and low filling pressure.[3] They observed that E/e' was significantly and negatively correlated with filling pressure because the rate of change in mitral e' was larger than that in mitral E, which is consistent with our results. In contrast, in the failing heart, E/e' can estimate filling pressure because mitral E increases with preload augmentation but mitral e' does not increase.[22-24] Therefore, the preload dependence of mitral e' has been considered a minor problem in the clinical settings. However, Bhella et al. recently evaluated individual linear regression slopes for mitral e'

versus filling pressure in patients with HFpEF and demonstrated preload dependency of mitral e' in the majority of patients.[4] Their results suggest that preload dependence of mitral e' cannot be ignored even in the clinical settings.

Estimation of filling pressure by FRe/SRe

In our results, L-SRe increased along with the increase in filling pressure as with the response of mitral e', but C-SRe did not change. Consequently, FRe/C-SRe was a better parameter for the estimation of filling pressure than FRe/L-SRe. FRe/C-SRe seems to work well during acute changes of filling pressure in volume overload and myocardial ischemia. However, Hasegawa et al. reported that in a heart failure model induced by rapid pacing during 4 weeks, the peak lengthening rate of the LV anteroposterior dimension and septolateral dimension was positively related to filling pressure although mitral e' was not.[23]

This discrepancy may be explained by the alteration of the LV geometry and myocardial fiber orientation. Inner (and outer) oblique fibers in a nondilated heart are relatively directed to the longitudinal axis, but those in a dilated failing heart are altered to a more circumferential orientation.[25] The LV in our model was not dilated and the myocardial fibers of the longitudinal direction were preserved because of the acute experiment, resulting in preload dependency in the longitudinal direction. In contrast, the myocardial fibers seem to have a more circumferential orientation in the model of Hasegawa et al. because the LV is usually dilated in the rapid pacing model.[26] This alteration might have caused preload dependency in the circumferential direction.

C-SRe was strongly correlated with tau but L-SRe was only moderately correlated, which seems to be

another reason why FRe/C-SRe was better than FRe/L-SRe. The reason of the better correlation of C-SRe with tau is unclear. However, it has been demonstrated that in the simulated 3D ultrasound datasets of normal LV, the mean absolute error of estimated circumferential strain values is smaller than that of longitudinal strain values when the noise level is low.[27] In the speckle-tracking analysis, an end point of the tracing line on the myocardium always returns to a start point in the global circumferential strain, but not in the global longitudinal strain, suggesting robustness of circumferential strain measurement. The superiority of C-SRe may be related to methodological issues of 3D speckle-tracking analysis.

A-SRe, which combines the factors of both longitudinal and circumferential deformations, can assess changes in endocardial surface area and quantify LV function.[8] FRe/A-SRe as well as FRe/C-SRe could be used as a predictive parameter of filling pressure because A-SRe was also strongly correlated with tau and tended to be less preload-dependent.

The regression line in the myocardial ischemia data was different from that in the volume overload data. This result suggests that FRe/C-SRe and FRe/A-SRe may be more sensitive to the increase of filling pressure in the LV with dysfunction than without dysfunction. This difference should be confirmed by further studies.

Study limitations

Although the results in the present study show that FRe/C-SRe and FRe/A-SRe can estimate filling pressure during its acute changes in the nondilated heart models of volume overload and myocardial ischemia, it is still unknown whether these parameters work well in a chronic dilated failing heart that has

increased chamber stiffness. Moreover, in the model of myocardial ischemia, the expected increase of pre-A pressure was not achieved because the area perfused by the LAD was small in dogs and the duration of occlusion was short. Further studies in the models of severer LV dysfunction are needed for the use in the clinical setting.

Late filling rate and late diastolic strain rate could not be shown in some of the data because the data of the last frame in the diastolic phase were excluded from the analysis in our system. However, FRe and SRe could be analyzed in 25 of 26 dogs, except for datasets with fusion of mitral E and A. We think that the high feasibility and reproducibility in our data were due to relatively good image quality in the open-chest models. The low temporal resolution of 3D speckle-tracking echocardiography would be the potential limitation for underestimation of FRe and SRe. Therefore, the feasibility and reproducibility in the clinical settings should be tested in the next step.

Clinical implications

Because 3D echocardiography allows more accurate measurement of ejection fraction than 2D,[28, 29] it is becoming routine in the clinical echo laboratories. FRe/SRe may be still conceptual at the present time, but this parameter can be simultaneously obtained with measurement of ejection fraction, which would enable quick and easy examination of LV systolic and diastolic function. Moreover, simultaneous acquisition of FRe and SRe could circumvent problems with beat-to-beat variations. If 3D images can be acquired with one beat, it would provide greater utility when studying patients with atrial fibrillation. For such advantages, we think that FRe/SRe is a potential method in the 3D echo era.

Conclusions

The novel 3D speckle-tracking parameter, FRe/SRe, seems to have the potential as a surrogate marker of LV filling pressure. Especially in nondilated hearts, FRe/C-SRe and FRe/A-SRe may be useful for the estimation of acute changes in LV filling pressure, although their applicability in dilated hearts requires further investigation.

Acknowledgements

We thank Mr. Yasuhiko Abe (Toshiba Medical Systems) for technical advice and development of 3D speckle-tracking echocardiography and customized software.

References

1. 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.

2. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-1794.

3. Jacques DC, Pinsky MR, Severyn D, Gorcsan J III. Influence of alterations in loading on mitral annular velocity by tissue Doppler echocardiography and its associated ability to predict filling pressures. Chest 2004;126:1910-1918.

4. Bhella PS, Pacini EL, Prasad A, Hastings JL, Adams-Huet B, Thomas JD, et al. 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.

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

6. 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.

7. Tatsumi K, Tanaka H, Matsumoto K, Sawa T, Miyoshi T, Imanishi J, et al. 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.

8. Seo Y, Ishizu T, Enomoto Y, Sugimori H, Aonuma K. Endocardial surface area tracking for assessment of regional LV wall deformation with 3D speckle tracking imaging. J Am Coll Cardiol Img 2011;4:358-365.

9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. 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.

10. Nishimura RA, Schwartz RS, Holmes DR Jr, Tajik AJ. Failure of calcium channel blockers to improve ventricular relaxation in humans. J Am Coll Cardiol 1993;21:182-188.

11. Takeuchi M, Fujitani K, Kurogane K, Bai HT, Toda C, Yamasaki T, et al. 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.

12. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. European Heart Journal 2007;28:2539-2550.

13. Corsi C, Lang RM, Veronesi F, Weinert L, Caiani EG, MacEneaney P, et al. Volumetric quantification of global and regional left ventricular function from real-time three-dimensional echocardiographic images. Circulation 2005;112:1161-1170.

14. Kasner M, Gaub R, Sinning D, Westermann D, Steendijk P, Hoffmann W, et al. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis. Eur J Echocardiogr 2010;11:743-751.

15. Meluzin J, Spinarova L, Hude P, Krejci J, Podrouzkova H, Pesl M, et al. Estimation of left ventricular filling pressures by speckle tracking echocardiography in patients with idiopathic dilated cardiomyopathy. Eur J Echocardiogr 2011;12:11-18.

16. Kimura K, Takenaka K, Ebihara A, Okano T, Uno K, Fukuda N, et al. Speckle tracking global strain rate E/E' predicts LV filling pressure more accurately than traditional tissue Doppler E/E'. Echocardiography 2012;29:404-410.

17. 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.

18. Bruch C, Stypmann J, Gradaus R, Breithardt G, Wichter T. Usefulness of tissue Doppler imaging for estimation of filling pressures in patients with primary or secondary pure mitral regurgitation. Am J Cardiol 2004;93:324-328.

19. 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.

20. Ha JW, Oh JK, Ling LH, Nishimura RA, Seward JB, Tajik AJ. Annulus paradoxus: transmitral flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. Circulation 2001;104:976-978.

21. 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.

22. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. J Am Coll Cardiol 2001;37:278-285.

23. Hasegawa H, Little WC, Ohno M, Brucks S, Morimoto A, Cheng HJ, et al. Diastolic mitral annular velocity during the development of heart failure. J Am Coll Cardiol 2003;41:1590-1597.

24. Masutani S, Little WC, Hasegawa H, Cheng HJ, Cheng CP. Restrictive left ventricular filling pattern does not result from increased left atrial pressure alone. Circulation 2008;117:1550-1554.

25. Buckberg G, Athanasuleas C, Conte J. Surgical ventricular restoration for the treatment of heart failure. Nat Rec Cardiol 2012;9:703-716.

26. Cheng CP, Suzuki M, Ohte N, Ohno M, Wang ZM, Little WC. Altered ventricular and myocyte response to angiotensin II in pacing-induced heart failure. Circ Res 1996;78:880-892.

27. Elen A, Choi HF, Loeckx D, Gao H, Claus P, Suetens P, et al. Three-dimensional cardiac strain estimation using spatio-temporal elastic registration of ultrasound images: a feasibility study. IEEE Trans Med Imaging 2008;27:1580-1591.

28. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. J Am Coll Cardiol 2004;44:878-886.

29. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol 2012;59:1799-1808.

Figure legends

Figure 1. Measurement of FRe/SRe by 3D speckle-tracking analysis.

The multi-planar reconstruction images from 3D full-volume datasets show A) apical four-chamber view B) two-chamber view, C) apical short-axis view, D) mid LV short-axis view, E) basal short-axis view. LV volume curve profile (F: dotted line) and 16 segmental strain rate profiles (F: each color line) are calculated simultaneously by 3D speckle-tracking analysis. With customized software, dV/dt (upper right) and global strain rate (lower right) curves are measured. FRe and global SRe are automatically detected, and FRe/SRe is calculated.

Figure 2. Representative mitral inflow velocity (top) and mitral annular velocity at the lateral site (bottom) during dextran infusion.

LV pre-A pressure is 7 mmHg at baseline, 10 mmHg during 100 mL infusion of dextran, and 16 mmHg during 200 mL infusion of dextran. Mitral E and e' gradually increase in response to stepwise infusion of dextran.

Figure 3. Representative dV/dt (top) and global circumferential strain rate (bottom) during dextran infusion.

The data are from the same dog as in Figure 2. FRe gradually increases, but C-SRe does not change in response to stepwise infusion of dextran.

Figure 4. Relationship of pre-A pressure with E/e' and FRe/SRe.

The red line and circles correspond to the model of volume overload, and the blue line and circles

correspond to the model of myocardial ischemia. The black line shows the relationship of all data.

FRe/C-SRe and FRe/A-SRe have relative high positive correlations with pre-A pressure, but E/e' and

FRe/L-SRe do not.

Figure 5. ROC curve analysis of FRe/SRe for the estimation of pre-A pressure ≥ 12 mmHg.

The AUCs for FRe/C-SRe and FRe/A-SRe are significantly larger than line of no information (AUC = 0.5:

dashed line), whereas the AUC for FRe/L-SRe is not statistically significant.

Figure 6. Relationship of tau with mitral e' and SRe.

Tau is more strongly correlated with C-SRe and A-SRe than mitral e' and L-SRe in the model of changes in

inotropic state.

Table 1. Hemodynamic and echocardiographic data

	Baseline	100 mL infusion of dextran	200 mL infusion of dextran	Baseline	LAD occlusion
Hemodynamic data					
Heart rate (beats/min)	99 ± 13	99 ± 15	102 ± 8	123 ± 12	129 ± 17
LV systolic pressure (mmHg)	111 ± 19	127 ± 21	137 ± 25	104 ± 8	97 ± 11*
LV pre-A pressure (mmHg)	7 ± 2	11 ± 4*	16 ± 4*†	3 ± 1	6 ± 1*
LV end-diastolic pressure (mmHg)	8 ± 3	15 ± 4*	21 ± 4*†	6 ± 2	8 ± 2*
Echocardiographic data					
E/e’	9.6 ± 3.0	9.9 ± 3.9	9.7 ± 3.0	12.0 ± 2.8	12.3 ± 2.7
FRe/L-SRe (mL)	68.7 ± 11.9	73.7 ± 17.1	73.3 ± 13.6	75.0 ± 13.4	101.4 ± 22.2
FRe/C-SRe (mL)	33.1 ± 8.3	40.5 ± 6.6	47.4 ± 8.2*	29.3 ± 4.6	39.9 ± 9.8*
FRe/A-SRe (mL)	24.2 ± 4.8	28.3 ± 4.5	32.2 ± 5.5*	22.1 ± 2.5	28.9 ± 3.1*

Data are expressed as mean ± SD

*$p < 0.05$ versus baseline, †$p < 0.05$ versus 100 mL infusion of dextran

Table 2. Correlations of echocardiographic parameters with LV pre-A pressure and end-diastolic pressure in the model of volume overload

	Correlation coefficients (r)	
	LV pre-A pressure	LV end-diastolic pressure
Doppler		
Mitral E (cm/s)	0.48*	0.55*
Mitral e' (cm/s)	0.65*	0.52*
E/e'	−0.27	−0.10
3D speckle-tracking echocardiography		
FRe (mL/s)	0.76*	0.68*
L-SRe (/s)	0.56*	0.54*
C-SRe (/s)	0.18	0.17
A-SRe (/s)	0.35	0.33
FRe/L-SRe (mL)	0.40*	0.32
FRe/C-SRe (mL)	0.80*	0.70*
FRe/A-SRe (mL)	0.78*	0.69*

* Correlation is significant at the 0.05 level.