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Early diastolic mitral annular velocity at the interventricular septal annulus correctly reflects left ventricular longitudinal myocardial relaxation.

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ABSTRACT:

Aims: Early diastolic mitral annular velocity (e') obtained by tissue Doppler imaging (TDI) is widely used to evaluate left ventricular (LV) diastolic function based on the assumption that it reflects myocardial relaxation in the long-axis direction. In this study, we aimed to determine whether or not e' truly reflects early diastolic longitudinal myocardial relaxation, and which is the most useful for evaluating LV diastolic function among e' measured at the interventricular-septal annulus (IS- e'), that measured at the lateral annulus (LW- e') or their mean value (M- e').

Methods and results: IS- e' , LW- e' and M- e' were measured using color TDI in 15 patients with hypertrophic cardiomyopathy, 13 patients with hypertension and 19 control subjects. Using two-dimensional speckle tracking imaging, early diastolic myocardial strain rates (SR_E) were measured for the IS (IS- SR_E), LW (LW- SR_E) and entire LV myocardium (G- SR_E). IS- e' was excellently correlated with IS- SR_E ($r=0.90$, $p<0.001$); the correlation was better than that between LW- e' and LW- SR_E ($r=0.75$, $p<0.001$). IS- e' and M- e' were well correlated with G- SR_E ($r=0.88$, $p<0.001$ and $r=0.86$, $p<0.001$, respectively) and with LV early diastolic flow propagation velocity ($r=0.77$, $p<0.001$ and $r=0.78$, $p<0.001$, respectively). The correlations of LW- e' to G- SR_E ($r=0.80$, $p<0.001$) and flow propagation velocity ($r=0.75$, $p<0.001$) did not reach this level.

Conclusion: IS- e' well reflected LV longitudinal myocardial relaxation and LV diastolic function, and was found to be more useful in evaluating LV diastolic function than LW- e' .

Key words: Tissue Doppler imaging, Early diastolic mitral annular velocity, Two-dimensional speckle tracking imaging, Left ventricular longitudinal myocardial relaxation.

INTRODUCTION

Early diastolic mitral annular velocity (e') derived from tissue Doppler imaging (TDI) is widely used to evaluate left ventricular (LV) diastolic function based on the assumption that it reflects the myocardial relaxation in the long-axis direction.¹⁻⁴ It can be performed easily with excellent reproducibility,¹⁻⁶ and many investigators have reported the usefulness of the ratio of early diastolic transmitral flow velocity to e' (E/e') in estimating LV filling pressure.^{1,5,7,8} In this way the value of e' measurement has been established through many clinical and physiological studies, but it remains still unclear whether or not the mitral annular velocity truly reflects the LV longitudinal myocardial relaxation. In addition, the measurement of e' have been performed at the interventricular septal annulus (IS- e')^{2,5,7} and/or lateral annulus (LW- e')^{1,9} in the apical 4-chamber view; their mean value (M- e')^{8,10} has also been used. However, it is not clear which of IS- e' , LW- e' or M- e' is the best to evaluate LV diastolic function.

Two-dimensional speckle tracking imaging (2DSTI) is a recently developed echocardiographic technique that automatically tracks myocardial motion throughout the entire cardiac cycle on the basis of pattern-matching techniques and provides myocardial strain and strain rate.¹¹⁻¹³ This technique can provide an accurate evaluation of myocardial longitudinal contraction and relaxation without any angle dependency and the effect of apical translation, both of which are critical limitations of TDI. In this study, we aimed to determine whether the mitral annular velocity truly reflects the LV longitudinal myocardial relaxation and which e' measurement, IS- e' , LW- e' or M- e' , is the most useful for evaluating LV diastolic function.

SUBJECTS AND METHODS

1. Subjects

The study subjects consisted of 15 patients with hypertrophic cardiomyopathy (HCM) (11 men and 4 women, 54.3 ± 14.5 years), 13 age-matched patients with hypertension (HT) (7 men and 6 women, 52.2 ± 12.5 years) and 19 age-matched normal control subjects (11 men and 8 women, 52.6 ± 9.2 years) in whom good quality of echocardiographic images could be obtained. HCM was defined as LV hypertrophy not explained by any cardiac or systemic abnormalities and with an interventricular septal thickness/posterior wall thickness ratio in end-diastole of more than 1.3 by two-dimensional echocardiography. HT was defined as a repeatedly elevated blood pressure (greater than 140 mmHg at systole or 90 mmHg at diastole) or having anti-hypertensive medications with a history of hypertension. We excluded patients with obvious systolic dysfunction whose echocardiographic LV ejection fraction was less than 55%, apparent pulmonary hypertension or cardiac rhythm disturbances such as atrial fibrillation or artificial pacing. Patients with congestive heart failure, diabetes mellitus, coronary heart disease with apparent LV asynergy, congenital anomaly, valvular heart disease, or other systemic diseases that cause LV hypertrophy were also excluded. Furthermore, we excluded subjects in whom an ultrasound beam could not be inserted correctly from the apex in the apical four-chamber view.

Medications for patients with HT were beta-blocker in 1 patient, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockade in 5, calcium antagonist in 1, alpha blocker in 2, diuretics in 4, anti-arrhythmic drug in 1 and nitrate in 1; those for HCM patients were beta-blocker in 10 patients, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockade in 5, calcium antagonist in 3, diuretics in 2, anti-arrhythmic drug in 2 and nitrate in 1. The control group consisted of healthy volunteers without any clinical or echocardiographic evidence of cardiovascular disease.

This study was approved both by the Research Ethics Committee of Hokkaido University Hospital and by the Ethics Committee of Faculty of Health Sciences in Hokkaido University.

2. Basic echocardiographic measurements

Echocardiography was performed using a Vivid 7 ultrasonographic machine (GE Healthcare UK Ltd Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA, England) with an M4S transducer. The LV end-diastolic dimension and left-atrial end-systolic dimension were measured from a parasternal long-axis B-mode image. The thicknesses of the interventricular septum and LV posterior wall were measured in the parasternal short-axis image at the level of the chordate tendineae at end-diastole. The LV ejection fraction was calculated by Simpson's biplane method of discs according to the American Society of Echocardiography¹⁴. Pulsed-Doppler echocardiography was performed to measure peak early and late diastolic transmitral flow velocities (E and A, respectively, cm/s), and the early diastolic wave deceleration time (DT, ms) of the transmitral flow and to calculate the ratio of early to late transmitral flow velocities (E/A). LV isovolumic relaxation time (IRT, ms) was measured using an apical continuous-wave Doppler recording, which clearly depicted both LV inflow and outflow. LV early diastolic flow propagation velocity (FPV, cm/s) was measured using apical color M-mode Doppler imaging of the LV inflow along with the previously reported method^{15, 16}.

3. Measurement of mitral annular velocity by tissue Doppler imaging (Figure 1)

An apical 4-chamber image of the color tissue Doppler technique was acquired at a frame rate of 69.8 to 147.7 frames per second. Tissue Doppler digital data were stored and analyzed offline using an EchoPAC PC (GE Healthcare UK Ltd Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA, England). We measured the peak early diastolic and late diastolic velocity (e' and a' , respectively, cm/s) at the mitral annuli of the interventricular septum (IS) and lateral wall (LW) sides, and calculated the ratio of early to late diastolic annular velocities (e'/a'). The mean value of the two-site measurements ($M-e'$, $M-a'$ and $M-e'/a'$) was also calculated for each study subject.

4. Measurement of strain rate by two-dimensional speckle tracking imaging (Figure 2)

Two-dimensional harmonic images (transmit/receive 1.9/4.0 MHz) in a 4-chamber view were scanned with frame rates of 49-69/s. Digital data were stored and analyzed off-line using an EchoPAC PC. The

LV endocardial surface of the end-systolic frame was traced manually, and the speckle tracking width was modified so as to cover the whole LV wall thickness to obtain a so-called 'global' strain rate curve. From that curve, the peak early diastolic and late-diastolic longitudinal strain rates ($G\text{-SR}_E$ and $G\text{-SR}_A$, respectively, S^{-1}) were measured. Then, the basal interventricular septal ROI was extended toward the apex, and the strain rate curve of the whole interventricular septum was obtained to measure the peak early diastolic and late diastolic interventricular septal strain rates ($IS\text{-SR}_E$ and $IS\text{-SR}_A$, respectively, S^{-1}). In a similar manner, a strain rate curve for the whole lateral wall was obtained, and the 2 peak strain rates were measured ($LW\text{-SR}_E$ and $LW\text{-SR}_A$, S^{-1}). In addition, the ratio of the early to late diastolic peak was calculated each for the global, interventricular and lateral strain rates ($G\text{-SR}_E/SR_A$, $IS\text{-SR}_E/SR_A$ and $LW\text{-SR}_E/SR_A$). Success or failure of the tracking was determined chiefly based on visual inspection of the tracking motion image, referring to the results of the automatic judgment function of the software, and manual readjustments were made if needed. Subjects for whom tracking was not completely successful were excluded from the study. All strain-rates were expressed as absolute values.

5. Statistical analysis

Statistical analysis was performed using standard statistical software (Stat View version 5.0, SAS Institute, Cary, NC, USA). All numerical data were represented as means \pm standard deviation. Differences among the three groups were tested by one-way analysis of variance at first, and, when a significant difference was detected, each difference between the individual two groups was tested using a post-hoc test. The relationship between two parameters was examined using linear correlation and regression analysis. The significance of the difference between two correlation coefficients was calculated using Fisher's r-to-z transformation. For all statistical tests, a P value less than 0.05 was used to indicate significance.

RESULTS

1. Clinical background and echocardiographic parameters (Table)

There were no significant differences among the control, HT and HCM groups in age, sex, heart rate, body surface area, LV end-diastolic dimension, LV ejection fraction, E, A and E/A. Systolic blood pressure and diastolic blood pressure were significantly greater in the HT group compared to the control or HCM group. Interventricular septal thickness, LV posterior wall thickness and IRT were significantly greater, and FPV was significantly reduced in both the HT and HCM groups compared to the control group. The left atrial dimension and DT were greater in the HCM group compared with the control group. The left atrial dimension and interventricular septal thickness were significantly greater, and FPV and LV posterior wall thickness were significantly lower in the HCM group than in the HT group. IS-e', LW-e', M-e', IS-SR_E, LW-SR_E and G-SR_E were significantly reduced both in the HT group and in the HCM group compared to the control group. IS-SR_E and G-SR_E were significantly reduced in the HCM group compared to the HT group.

2. Relationship between mitral annular velocities and strain rates of the corresponding wall (Figure 3)

IS-e' was significantly and well correlated with IS-SR_E ($r=0.90$, $p<0.001$). LW-e' was significantly, but less strongly, correlated with LW-SR_E ($r=0.75$, $p<0.001$). The correlation coefficient between IS-e' and IS-SR_E was significantly higher than that between LW-e' and LW-SR_E ($p<0.05$). Significant and good correlation was also observed both between IS-e'/a' and IS-SR_E/SR_A ($r=0.88$, $p<0.001$) and between LW-e'/a' and LW-SR_E/SR_A ($r=0.84$, $p<0.001$).

3. Relationship between mitral annular velocities and LV global strain rate (Figure 4)

IS-e' and M-e' were significantly and well correlated with G-SR_E ($r=0.88$, $p<0.001$ and $r=0.86$, $p<0.001$, respectively). IS-e'/a' and M-e'/a' were also well correlated with G-SR_E/SR_A ($r=0.89$,

$p < 0.001$, and $r = 0.90$, $p < 0.001$). The correlations between LW- e' and G-SR_E ($r = 0.80$, $p < 0.001$) and between LW- e'/a' and G-SR_E/SR_A ($r = 0.82$, $p < 0.001$) were also good but a little weaker.

4. Relationship between mitral annular velocities and LV global function (Figure 5)

Both IS- e' and M- e' were well correlated with FPV ($r = 0.77$, $p < 0.001$ and $r = 0.78$, $p < 0.001$, respectively), and significantly correlated with transmitral E ($r = 0.48$, $p < 0.001$ and $r = 0.47$, $p < 0.001$, respectively), DT ($r = 0.49$, $p < 0.001$ and $r = 0.45$, $p < 0.01$, respectively) and IRT ($r = 0.55$, $p < 0.001$, and $r = 0.54$, $p < 0.001$, respectively). IS- e'/a' and M- e'/a' were significantly and well correlated with the transmitral E/A ratio ($r = 0.74$, $p < 0.001$ and $r = 0.79$, $p < 0.001$, respectively). LW- e' was significantly correlated with E ($r = 0.44$, $p = 0.020$), DT ($r = 0.39$, $p < 0.05$), IRT ($r = 0.50$, $p < 0.001$) and FPV ($r = 0.75$, $p < 0.001$), and LW- e'/a' was also significantly correlated with E/A ($r = 0.75$, $p < 0.001$). However, those correlation coefficients were tended to be slightly weaker.

DISCUSSION

In the present study, IS- e' was excellently correlated with IS-SR_E, and LW- e' was fairly well correlated with LW-SR_E, indicating that e' well reflects LV longitudinal myocardial relaxation. The use of e' as a parameter of LV diastolic function seems to be based on the assumption that it reflects LV longitudinal myocardial relaxation, but this assumption has not been confirmed. Recently, Opdahl et al. reported that good correlation was observed between early diastolic mitral annular velocity measured using TDI and myocardial relaxation assessed by sonomicrometry in mongrel dogs.¹⁷ However, no sufficient evidence for human has been provided in previous studies. The present study validated the assumption in human and provided better understanding of the property of e' as an index for LV diastolic function.

In the recommendation for the evaluation of LV diastolic function issued by the American Society of Echocardiography, e' plays an important role for the management of patients with heart failure.¹⁸

However, there has been no established consensus on the measurement site, that is, whether we should measure e' at the interventricular septal annulus, lateral side annulus or both. In the present study, the correlation between IS- e' and IS-SR_E was significantly better than that between LW- e' and LW-SR_E. In addition, IS- e' and M- e' were excellently correlated with G-SR_E, and these correlations were slightly better than that between LW- e' and G-SR_E. These results suggest that IS- e' is more useful in assessing LV diastolic function than LW- e' .

There have been several reports comparing IS- e' and LW- e' . Peverill et al. reported that LW- e' was greater than IS- e' and the correlation between the two parameters was inadequate.¹⁹ Park et al. also indicated a discrepancy between the two measurements and concluded that IS- e' tended to overestimate the LV diastolic dysfunction.²⁰ However, they did not show any clear evidence to indicate the superiority of LW- e' over IS- e' . In the present study, the correlation between IS- e' and IS-SR_E was significantly better than that between LW- e' and LW-SR_E. On the other hand, the correlation between LW- e'/a' and LW-SR_E/SR_A was clearly better than that between LW- e' and LW-SR_E. These results indicate that the inadequate correlation between e' and SR_E in the lateral wall is attributable to the angle dependency of TDI. Thus, the IS- e' can more accurately reflect the LV longitudinal myocardial relaxation. In this study, M- e' reflected LV diastolic function with a similar accuracy as IS- e' . It is estimated that M- e' may be useful in the evaluation of patients with regional myocardial dysfunction such as myocardial ischemia and regional LV hypertrophy, and in those with right ventricular disease and/or increased right ventricular pressure, which may affect the IS- e' value.

In this study, we employed SR_E measured by using 2DSTI as the standard of longitudinal myocardial relaxation. The accuracy of this method has been reported by several investigators based on comparisons with sonomicrometry and with tagging MRI.^{13,21-23} The e' measured using TDI is widely

used as an index for global diastolic function rather than the regional one, based on the hypothesis that mitral annular motion reflects longitudinal shortening and lengthening of the myocardium from the base to the apex. Thus, we measured so-called 'semi-global' SR_E with ROIs in the whole interventricular septum and the whole lateral wall for the comparisons with IS-e' and LW-e', respectively.

Recently, there have been several reports showing the superiority of E/SR_E over E/e' in the estimation of the LV filling pressure. Dokainish et al. reported that, in patients with an LV ejection fraction $\geq 50\%$ and an E/e' value from 8 to 15, E/SR_E by 2DSTI was a better predictor of LV filling pressure than E/e' by TDI.²⁴ In addition, Ng et al. reported that E/E_{2D} (E_{2D} : left ventricular myocardial velocity derived from 2DSTI) was more useful in identifying elevated LV end diastolic pressure than E/e' .²⁵ Although these results should be sufficiently appreciated, e' measured using TDI has inevitable merits in clinical practice because it can be very easily measured with good reproducibility and there is a great amount of accumulated clinical evidence supporting its use. In addition, 2DSTI requires high-end ultrasound devices, and its analysis requires good image quality of the whole left ventricle. Furthermore, because the 2DSTI's data analysis algorithm varies according to the ultrasound manufacturer, the criterion value remains unclear. At the present time, 2DSTI is not being administered in all routine examinations.

There are some limitations to be acknowledged in the present study. First, we employed color TDI instead of pulsed TDI, which is more widely used in the clinical settings. To evaluate the correspondence between TDI and 2DSTI, we thought it better to perform these two measurements offline from the same image over using pulsed TDI, which requires some additional procedures during examination. Because the correspondence in the mitral annular velocity between color TDI and pulsed TDI was reported to be excellent,²⁶ the results of this study may be readily applicable to measurements using pulsed TDI. Secondly, e' and SR_E were studied only in the interventricular

septum and lateral wall in the 4-chamber view. Analyses using more imaging planes might provide a better measuring site of e' or a better averaged value. However, we consider that the analysis of the 4-chamber view is sufficient from a practical view; this plane is very commonly used, and multiplane analysis may limit the ease of this measurement, which is the greatest merit of TDI. Thirdly, the population of this study was too small to perform subgroup analysis. Further study may be needed to evaluate differences among diseases.

CONCLUSION

In conclusion, early mitral annular velocity (e'), derived using TDI, especially measured at the septal side annulus, well reflects the LV longitudinal myocardial relaxation. The e' measured at the septal annulus should be used for the clinical evaluation of LV diastolic function rather than the value at the lateral annulus.

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Table: Clinical characteristics and echocardiographic features

	Control (n=19)	HT (n=13)	HCM (n=15)
Age (year)	52.6±9.2	52.2±12.5	54.3±14.5
Male (%)	11(58%)	7(54%)	11(73%)
Body surface area (cm ²)	1.69±0.16	1.62±0.23	1.69±0.20
Heart rate (bpm)	62.3±8.7	63.7±8.6	59.6±8.8
Systolic blood pressure (mmHg)	118±11	132±18 **	115±14 ^{††}
Diastolic blood pressure (mmHg)	73±8	82±13 *	67±11 ^{†††}
LV end-diastolic dimension (mm)	48.1±2.9	46.2±2.7	46.6±5.8
LA end-systolic dimension (mm)	34.4±4.2	37.6±4.4	43.7±7.0 *** ^{††}
Interventricular septal thickness (mm)	9.2±1.4	13.3±1.3 **	20.4±5.5 *** ^{†††}
LV posterior wall thickness (mm)	8.6±1.3	11.4±0.5 ***	10.2±1.1 *** ^{††}
LV ejection fraction (%)	67.3±4.8	66.5±4.2	70.6±8.5
E (cm/s)	77.9±17.2	68.5±14.8	69.3±20.0
A (cm/s)	65.2±12.3	71.6±13.7	73.0±23.2
E/A	1.26±0.45	0.99±0.28	1.09±0.66
DT (ms)	193±34	224±34	261±82***
IRT (ms)	77.6±9.4	92.3±11.4 **	90.0±20.6 *
FPV (cm/s)	55.5±8.7	45.5±8.6 **	37.5±12.6 *** [†]
IS-e' (cm/s)	7.05±1.67	4.39±1.67***	3.48±2.32***
LW-e' (cm/s)	9.06±1.84	5.88±1.62***	5.21±3.18***
M-e' (cm/s)	8.06±1.62	5.13±1.55***	4.34±2.69***
IS-SR _E (S ⁻¹)	1.37±0.31	1.00±0.28**	0.62±0.41*** ^{††}
LW-SR _E (S ⁻¹)	1.71±0.36	1.12±0.38***	0.89±0.47***
Global-SR _E (S ⁻¹)	1.52±0.35	1.03±0.32***	0.70±0.39*** [†]

HT = hypertension; HCM = hypertrophic cardiomyopathy; LV = left ventricle; LA = left atrium; E =

peak early diastolic transmitral flow velocity; A = peak late diastolic transmitral flow velocity; E/A = ratio of E to A; DT = early diastolic wave deceleration time of the transmitral flow; FPV = LV early diastolic flow propagation velocity; IRT = LV isovolumic relaxation time; e' = peak early diastolic mitral annular velocity; IS = interventricular septum; LW = lateral wall; M-e' = the mean value of IS-e' and LW-e'; SR_E = peak early diastolic strain rate.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus Control; † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$ versus HT-LVH

FIGURE LEGENDS

Figure 1. Measurement of mitral annular velocity using color tissue Doppler imaging. In the apical 4-chamber view (left panel), the peak early diastolic and peak late diastolic mitral annular velocities (e' and a' , respectively) were measured at the interventricular septal (IS) and lateral wall (LW) side annulus (right panel).

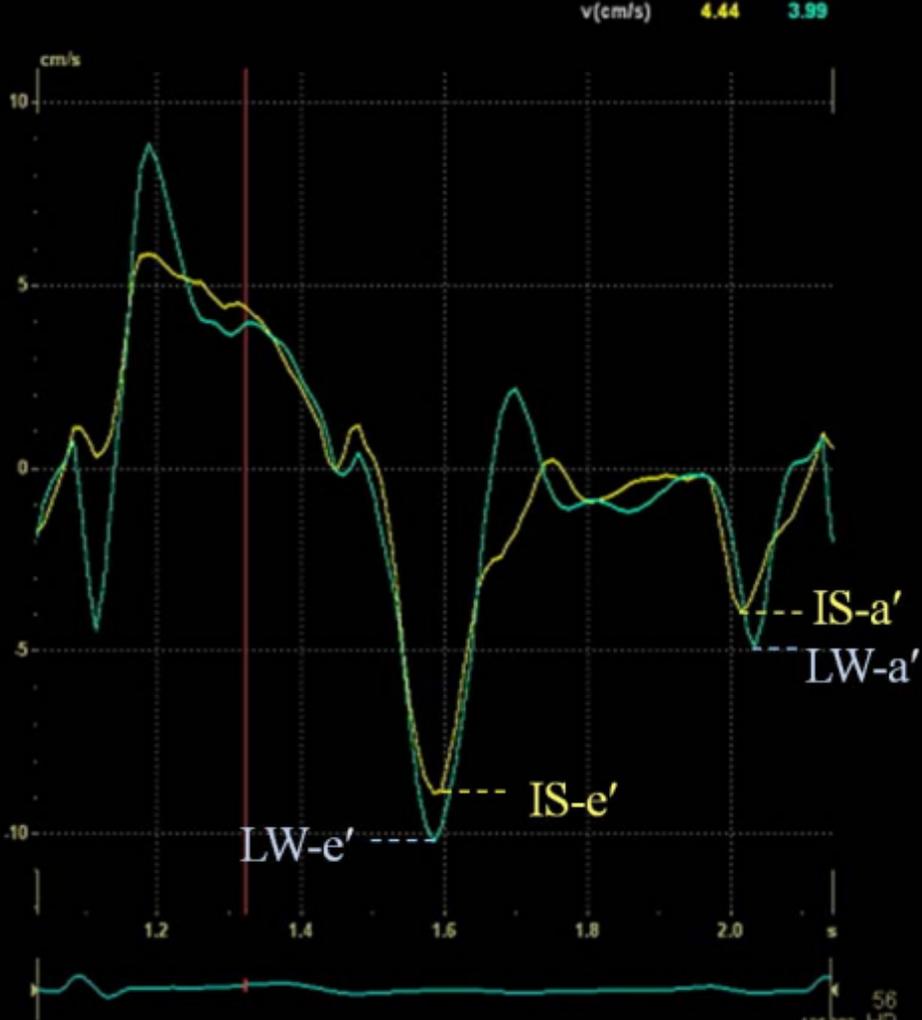
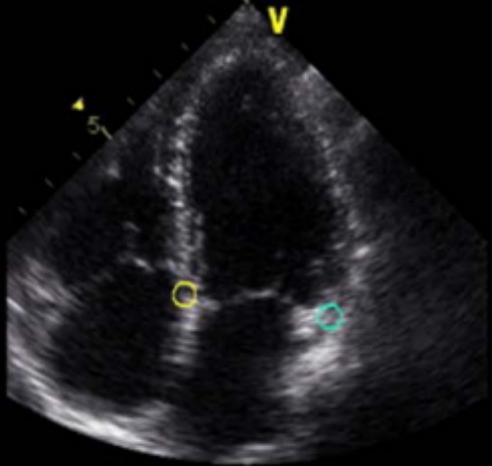
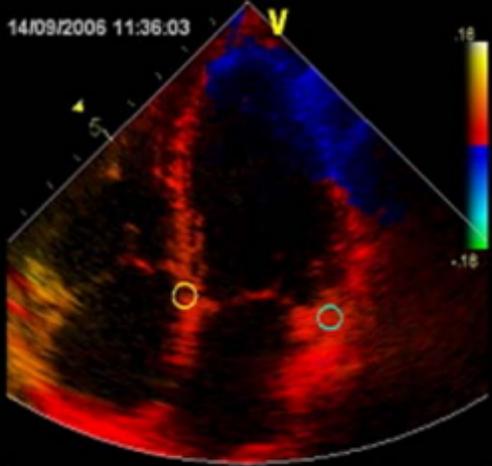
Figure 2. Measurement of myocardial strain rates using two-dimensional speckle tracking imaging. Left ventricular global strain rates (upper panels): An ROI for speckle tracking analysis was set on the entire LV myocardium in the apical 4-chamber view (left panel). The peak early diastolic and late diastolic myocardial global strain rates ($G-SR_E$ and $G-SR_A$, respectively) were measured (right panel). The interventricular septal (IS) strain rates (lower panels): An ROI was set on the IS from the base to the apex (left panel), and the peak early diastolic and late diastolic IS strain rates ($IS-SR_E$ and $IS-SR_A$, respectively) were measured (right panels).

Figure 3. Correlations between diastolic mitral annular velocity and myocardial strain rate of the corresponding wall. e' = peak early diastolic mitral annular velocity; e'/a' = the ratio of the e' to the peak late diastolic mitral annular velocity; SR_E = peak early diastolic strain rate; SR_E/SR_A = the ratio of SR_E to the peak late diastolic strain rate; HCM = patients with hypertrophic cardiomyopathy; HT = patients with hypertension; IS = interventricular septum; LW = left ventricular lateral wall; N = control subjects.

Figure 4. Correlations between the early diastolic myocardial ‘global’ strain rate ($G-SR_E$) and early diastolic mitral annular velocities in the interventricular septum (IS), lateral wall (LW) and their mean (M). e' = peak early diastolic mitral annular velocity; HCM = patients with hypertrophic cardiomyopathy; HT = patients with hypertension; N = control subjects.

Figure 5. Correlations between left ventricular early diastolic flow propagation velocity (FPV) and early diastolic mitral annular velocities in the interventricular septum (IS), lateral wall (LW) and their mean (M). e' = peak early diastolic mitral annular velocity; HCM = patients with hypertrophic cardiomyopathy; HT = patients with hypertension; N = control subjects.

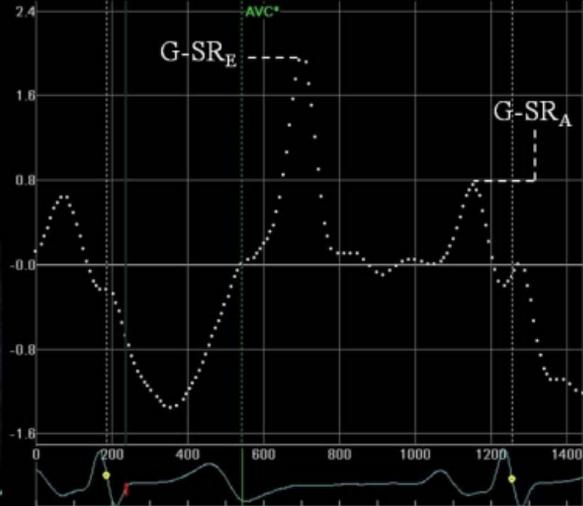
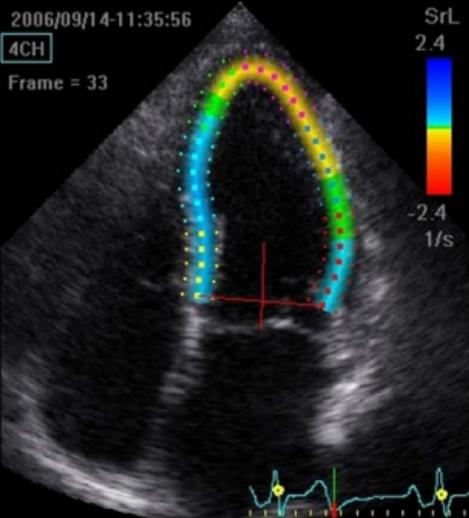
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