Title	Presence and Implication of Temporal Nonuniformity of Early Diastolic Left Ventricular Wall Expansion in Patients With Heart Failure
Author(s)	Iwano, Hiroyuki; Kamimura, Daisuke; Fox, Ervin R.; Hall, Michael E.; Vlachos, Pavlos; Little, William C.
Citation	Journal of Cardiac Failure, 22(12), 945-953 https://doi.org/10.1016/j.cardfail.2016.04.007
Issue Date	2016-12
Doc URL	http://hdl.handle.net/2115/67745
Rights	© 2016. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/
Rights(URL)	http://creativecommons.org/licenses/by-nc-nd/4.0/
Type	article (author version)
File Information	JCardFail22_945.pdf

[Instructions for use](#)

Presence and implication of temporal non-uniformity of early diastolic left ventricular wall expansion in patients with heart failure

Hiroyuki Iwano, MD, PhD^{1,2}, Daisuke Kamimura, MD, PhD², Ervin R. Fox, MD², Michael E. Hall, MD², Pavlos Vlachos, PhD³, William C. Little, MD^{2*}

¹Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

²Division of Cardiology, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA

³School of Mechanical Engineering, Purdue University, 585 Purdue Mall West Lafayette, IN 47907-2088, USA

*Passed away July 9, 2015.

Short title: Temporal non-uniformity of LV wall expansion

Address for Correspondence:

Hiroyuki Iwano, MD, PhD

Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine

1-33-802, Kita 20, Nishi 5, Kita-ku, Sapporo 001-0020, Japan

Tel: +81 11 706 6973

Fax: +81 11 706 7874

E-mail address: h-iwano@med.hokudai.ac.jp

Abstract

Background

Early-diastolic left ventricular (LV) longitudinal expansion is delayed with diastolic dysfunction. We hypothesized that, in patients with heart failure (HF) regardless of LV ejection fraction (EF), there is diastolic temporal non-uniformity with a delay of longitudinal relative to circumferential expansion.

Methods and Results

Echocardiography was performed in 143 HF patients: 50 with preserved EF (HFpEF) and 93 with reduced EF (HFrEF) and 31 normal controls. The delay of early-diastolic mitral annular velocity from the mitral Doppler E ($T_{E-e'}$) was measured as a parameter of the longitudinal-expansion delay. The delay of the longitudinal early-diastolic global strain rate (SR_E) relative to circumferential SR_E ($Delay_{C-L}$) was calculated as a parameter of temporal non-uniformity. Intra LV pressure difference (IVPD) was estimated by using color M-mode Doppler data as a parameter of LV diastolic suction. Although normal controls had symmetrical LV expansion in early diastole, $T_{E-e'}$ and $Delay_{C-L}$ were significantly prolonged in HF regardless of EF ($P < 0.01$ vs controls for all). Multivariate analysis revealed that $Delay_{C-L}$ was the independent determinant of IVPD among the parameters of LV geometry and contraction ($\beta = -0.21$, $P < 0.05$).

Conclusion

An abnormal temporal non-uniformity of early-diastolic expansion is present in HF regardless of EF, which was associated with reduced LV suction.

Key Words: Heart failure, Left ventricular diastolic function, Echocardiography

Introduction

To function as an effective pump, the left ventricle (LV) needs to fill without an elevation of left atrial pressure.¹ During ejection, the mitral annulus is pulled toward the apex which compresses elastic elements in the wall of the LV, allowing the annulus to recoil away from the apex in early diastole.² This longitudinal annular motion and circumferential recoil contribute to the pressure fall in the LV cavity and subsequent rapid filling.³ Normally, the LV pressure falls below the left atrial pressure in early diastole, which generates intra ventricular pressure difference (IVPD) and the LV fills due to the progressive IVPD from left atrium to the LV apex.⁴ Therefore, the IVPD is regarded as a measure of the strength of LV suction⁵ and plays a role in the development of heart failure (HF).

It has been reported that the early diastolic mitral annular Doppler velocity (e'), determined by the rate of longitudinal expansion of the LV wall is progressively reduced and delayed with diastolic dysfunction.^{6, 7} However, the influence of LV systolic function on the delay of e' has not been elucidated. In addition, we have recently reported that circumferential wall expansion in early diastole was not delayed with diastolic dysfunction in patients with various LV ejection fractions (EF).⁸ This result suggests that, in patients with HF regardless of LV EF, there is diastolic temporal non-uniformity with a delay of longitudinal relative to circumferential expansion in early diastole. Moreover, this temporal non-uniformity would affect an effective pressure fall in LV cavity in early diastole, i.e. LV suction, in patients with HF. Accordingly, the aim of this study was to determine the temporal non-uniformity in early diastole in patients with HF and preserved EF (HFpEF) and those with reduced EF (HFrEF) and to test the influence of the temporal non-uniformity on LV suction.

Methods

Study Population

The study protocol was approved by the institutional review boards of University of Mississippi Medical Center (#2013-0254). Between November 2013 and April 2014, we prospectively and consecutively enrolled patients who underwent clinically indicated transthoracic echocardiography and had a documented history of congestive heart failure based on the Framingham criteria.⁹ Exclusion criteria were non-sinus rhythm, left bundle branch block, fusion of early and late diastolic mitral inflow, significant left-sided valvular disease, prosthetic valve, and LV assist device. From the 258 patients who were eligible for the study inclusion, 115 patients with insufficient two-dimensional echocardiographic images for speckle-tracking analysis were also excluded. Accordingly, the remaining 143 HF patients were included in the final analysis to test the presence of temporal non-uniformity in HF. Thirty-one subjects who had neither history of cardiovascular risk factors nor any echocardiographic abnormal findings served as normal controls. In 148 subjects who had color M-mode Doppler (CMMD) images for the analysis of IVPD out of the 174 subjects, we tested the influence of the temporal non-uniformity of LV expansion on LV suction.

Two-dimensional and Doppler Echocardiography

Echocardiography was performed by using an iE33 ultrasound system with a multiple frequency transducer (Phillips Medical Systems, Andover, Massachusetts). Digital 2-dimensional cine loops were obtained in the apical 4-chamber, 2-chamber, and long-axis views and midventricular short-axis view at a frame rate of 73 ± 17 (range 40 to 140) s^{-1} .

LV and left atrial volumes were measured according to the recommendations

of the American Society of Echocardiography.¹⁰ LV mass was calculated according to Devereux formula.¹¹ The Doppler LV outflow was recorded in the apical long-axis view, and the time from peak of QRS wave to aortic valve closure (AVC) was measured. Transmitral Doppler flow was recorded in the apical 4-chamber view, and peak early diastolic velocity (E), peak atrial velocity (A), and E/A ratio were measured. Septal and lateral peak systolic annular velocities (s') as well as early diastolic peak of mitral annular velocities (e') were measured from the apical 4-chamber view by using pulsed-wave tissue Doppler imaging and average of the septal and lateral velocities were used for the subsequent analysis. The ratio of E to e' (E/e') was calculated. The time from the peak of QRS wave to the onset of the E wave, that to e' onset, and their difference ($T_{E-e'}$)⁷ were measured as a parameter of the delay of LV longitudinal wall expansion (**Figure 1**). Color M-mode Doppler (CMMD) images were recorded with a cursor parallel to LV inflow in the apical 4-chamber view.

Speckle-tracking analysis

Myocardial strain and strain rate (SR) were analyzed offline using QLAB Advanced Quantification Software version 9.0 (Phillips Medical Systems) as previously reported.^{12, 13} Briefly, the longitudinal parameter was obtained from the apical 4-chamber, 2-chamber, and long-axis views and the circumferential parameter was from mid-ventricular short-axis view. The global strain/SR curve was extracted with the use of entire LV wall in the image and peak global strain, peak systolic global SR (SR_{Sys}), and peak early diastolic global SR (SR_E) were measured. The time from peak of QRS wave to longitudinal SR_E and that to circumferential SR_E were measured and their difference ($Delay_{C-L}$) was calculated as an amount of temporal non-uniformity of early diastolic wall expansion (**Figure 1**). The timings of the all events were normalized to AVC and expressed as the percentage of the duration of systole

(%systole)¹⁴ as well as the absolute values. All parameters were measured from 2 consecutive cardiac cycles and averaged. Longitudinal indices from the apical 4-chamber, 2-chamber, and long-axis views were also averaged and used for the final analysis.

Analysis of the intraventricular pressure difference

In 132 out of 148 subjects (89%) who had an adequate CMMD image for the analysis by an automated software, the IVPD was measured as a parameter of the strength of LV diastolic suction.⁵ The CMMD data was used to integrate the one-dimensional Euler equation as previously described.^{5, 8} The pressure difference at each point along with the scan line was measured relative to left atrium just above the mitral valve at the mitral annulus just before mitral valve opening by calculating the line integral between them. From the temporal profile of the IVPD, the peak IVPD from the left atrium to LV apex was calculated. This method has been validated by comparison to direct measurements with micromanometers^{15, 16} and tested clinically in patients with diastolic dysfunction, dilated cardiomyopathy, and systolic HF.^{5, 15, 17}

Reproducibility analysis

The reproducibility of the time measurement was assessed in 15 of the study subjects. Two independent observers analyzed the same Doppler and two-dimensional echocardiographic images and one blinded observer repeated the analysis on a separate day. The mean and SD of the absolute difference between two measurements within an observer and between observers were 6 ± 6 msec and 9 ± 8 msec for the onset of E wave, 6 ± 4 msec and 7 ± 7 msec for the onset of e', 3 ± 2 msec and 13 ± 6 msec for longitudinal SR_E, and 4 ± 5 msec and 12 ± 5 msec for circumferential SR_E, respectively. As a result, intra- and inter-observer variabilities were 10 ± 5 msec and 12 ± 5 msec for

$T_{E-e'}$ and 5 ± 5 msec and 12 ± 11 msec for Delay_{C-L} , respectively.

Statistical Analysis

All statistical analyses were performed using JMP software by SAS Institute Inc. Continuous variables were expressed as mean $\pm$ SD and compared among the groups by using one-way analysis of variance (ANOVA), and post hoc analysis was then performed by using Turkey-Kramer's test. Proportions were compared using chi-square analysis. Linear regression analysis was used for the detection of correlation between two continuous variables. Analysis of covariance was used for the adjustment of age, systolic blood pressure, and heart rate for the comparison of time measurements among different groups. The influence of Delay_{C-L} on IVPD was tested by using a multiple regression analysis with incorporating the previously reported influencing factors of the IVPD. For all tests, a P value of <0.05 was considered significant.

Results

Patient characteristics

The clinical characteristics of the study subjects are presented in **Table 1**. Among the 143 HF patients, 50 patients had a preserved LVEF (HFpEF, EF $\geq$ 0.50) and 93 patients had a reduced LVEF (HFrEF, EF $<$ 0.50). The HF patients were older and had a higher systolic blood pressure than normal controls. Female gender was more frequent in HFpEF than in HFrEF. The patients with HFpEF had a higher heart rate than controls. All patients had some HF symptoms which tended to progress with a decrease in EF. The majority of the patients with HFpEF had a hypertensive heart disease while non-ischemic dilated cardiomyopathy was most frequent in patients with HFrEF. The use of angiotensin converting enzyme inhibitor or angiotensin II receptor blockers and beta blockers were less frequent in HFpEF than in HFrEF. In contrast, calcium antagonists were given more frequently in the patients with HFpEF than in those with HFrEF.

Comparison of cardiac function

The echocardiographic parameters of systolic and diastolic function are summarized in **Table 2**. LV mass index was similarly increased in HFpEF and HFrEF compared to the controls. LV end-diastolic and end-systolic volumes were larger and EF was lower in the groups of HFrEF than in controls whereas they were comparable between HFpEF and controls. Left atrial size (diameter and volumes) was greater in HFpEF and HFrEF than in the controls. E/A was highest and E wave deceleration time was shortest in HFrEF. Although e' was similarly decreased in HF regardless of EF, s' was progressively decreased in HF as EF decreased, which was consistent with previous reports.¹⁸ Speckle-tracking analyses for the longitudinal indices were possible in 2

apical images in 66 out of 174 patients (38%) and in 3 apical images in the remaining 108 patients (62%). All systolic and diastolic functional measures assessed by speckle-tracking except for circumferential SR_{sys} were reduced in HFpEF than in controls and further decreased in HFrEF. Circumferential SR_{sys} was preserved in HFpEF and reduced only in HFrEF. IVPD was significantly reduced in HFpEF and HFrEF than in controls.

Timings of LV wall expansion

The onset of e' was delayed in HF groups whereas that of E wave did not change, resulting in a prolongation of $T_{E-e'}$ in HF patients regardless of EF (**Table 3**). Similarly, longitudinal SR_E was delayed in HF groups and the timing of circumferential SR_E unchanged among the groups, resulting in a significant prolongation of $Delay_{C-L}$ in HF regardless of EF (**Table 3 and Figure 2**). These prolongations of $T_{E-e'}$ and $Delay_{C-L}$ were observed after the adjustment of age, systolic blood pressure, and heart rate, respectively ($P < 0.001$ for all). When the HF patients were divided by the median value of longitudinal global strain of -10.8% , both HF patients with reduced global strain and preserved global strain had similarly prolonged $T_{E-e'}$ as well as $Delay_{C-L}$ ($T_{E-e'}$: 35 ± 23 ms and 34 ± 26 ms; $Delay_{C-L}$: 26 ± 25 ms and 31 ± 29 ms, respectively, $P < 0.01$ vs controls for all). The group-averaged global SR curves showed temporal non-uniformity of wall expansion in early diastole with a delay of longitudinal SR relative to circumferential SR both in HFpEF and HFrEF as well as a symmetrical wall expansion in normal controls (**Figure 3**).

Determinants of the IVPD

Because LV geometry and contractility as well as aging have been reported to correlate with IVPD,^{19, 20} LV mass index, LV ejection fraction, global longitudinal

strain, global circumferential strain, and age were incorporated into a multivariate model together with Delay_{C-L} to determine the contributing factors of IVPD. In univariate analyses, all of the variables except for LV mass index significantly correlated with IVPD (**Table 4**). Multivariate analysis revealed that Delay_{C-L} was the independent determinant of IVPD (**Table 4**).

Discussion

In this study, we showed that, in early diastole, the LV expands asymmetrically in subjects with HF while it expands symmetrically in normal controls. This temporal non-uniformity of early diastolic expansion was due to a delay of longitudinal relative to circumferential expansion. Furthermore, the longitudinal delay was observed regardless of EF; i.e. it occurred both in HFpEF and HFrEF. We also found that the temporal non-uniformity of wall expansion was associated with reduced LV suction.

Delay of the early diastolic LV wall expansion

The early diastolic longitudinal LV expansion (indicated by e' and longitudinal SR_E) is reduced and delayed with diastolic dysfunction.²¹ This delay has been observed as a delay of e' onset relative to E wave onset ($T_{E-e'}$).^{7, 22, 23} Rivas-Gotz et al. reported a strong correlation between $T_{E-e'}$ and LV relaxation pressure decay in an animal experiment and a significant prolongation of $T_{E-e'}$ in sick patients (ischemic etiology 60%, idiopathic cardiomyopathy 30%) with diastolic dysfunction.⁷ However, the influence of LV systolic function on $T_{E-e'}$ was not determined. Moreover, these findings have not been tested in clinically-diagnosed HF patients. In the present study, we demonstrated the delay of LV wall expansion (i.e. prolonged $T_{E-e'}$) in both HFpEF and HFrEF, suggesting that the delay of the longitudinal expansion exists in HF regardless of LV EF.

Temporal non-uniformity of early diastolic LV wall expansion in heart failure

We recently reported that in addition to the delay of longitudinal wall expansion in subjects with diastolic dysfunction, there is no apparent delay of circumferential wall expansion in this group.⁸ This finding suggests that a temporal non-uniformity with a

delay of longitudinal relative to circumferential expansion could exist in patients with HF. Indeed, the present study demonstrated a clear temporal non-uniformity of LV wall expansion during early diastole in HF patients (**Figure 3**). These delay of longitudinal expansion could be a consequence of reduced longitudinal diastolic recoil resulting from reduced longitudinal shortening.²⁴ Since hypertension, diabetes mellitus, and coronary artery disease are frequent in HFpEF,²⁵ these patients tend to have interstitial fibrosis and myocardial ischemia. In this situation, the vulnerability of longitudinally-oriented inner myocardial layer to deleterious effects of the interstitial fibrosis²⁶ and hypoperfusion²⁷ can play a role in the decreased longitudinal systolic function and subsequent delay of longitudinal expansion. In cases of HFrEF, the increased ratio of end-systolic meridional to circumferential wall stress in the spherical LV²⁸ may be the reason for the delay of longitudinal expansion.

Another consideration is that transmural heterogeneity of myofiber lengthening in early diastole affects temporal non-uniformity. Ashikaga *et al.* reported that there is a transmural dispersion of LV myofiber relaxation with a delay of endocardial layer relative to epicardial layer despite lack of dispersion in electrical repolarization in normal canines.²⁹ If this dispersion is enhanced in the failing heart, the myocardial lengthening of longitudinally-oriented inner layer could be significantly delayed relative to that of circumferentially-oriented midwall, resulting in significant temporal non-uniformity of the wall expansion. Although we cannot confirm this speculation because studies have not tested this phenomenon in heart failure patients, the transmural heterogeneity would explain one of the reasons for the temporal non-uniformity.

Clinical implications

As discussed earlier, the temporal non-uniformity could be a result of the delayed

longitudinal expansion which is a consequence of reduced longitudinal recoil. Therefore, the amount of temporal non-uniformity may reflect the amount of reduced longitudinal diastolic function and be an additional marker of LV diastolic function. On the other hand, from a hemodynamic view, asymmetrical wall expansion may affect the effective pressure fall of the LV cavity in early diastole. To decrease the chamber pressure in early diastole, the LV needs to deform so that the cavity enlarges rapidly. In normal conditions, the LV expands symmetrically, i.e. longitudinal lengthening and circumferential expansion occur almost simultaneously; this would produce an effective pressure drop in the LV cavity and contribute to a progressive IVPD from the left atrium to LV apex.^{2, 6} In the failing heart, however, delayed longitudinal lengthening relative to circumferential expansion would diminish the rapid deformation of the cavity, resulting in a reduced pressure fall and subsequent IVPD. In the present study, we found that the amount of temporal non-uniformity was an independent determinant of IVPD, a measure of the strength of LV diastolic suction, which could suggest this non-uniformity plays a role in the reduced LV diastolic function and subsequent development of HF. We consider that the present findings provide additional information for understanding LV diastolic function.

Study limitations

First, because we selected HF patients based on their history of worsening of HF, this study does not include the HF patients who have symptoms only during exertion which is a frequent symptom among HF patients. In addition, we did not analyze patients without HF who have evidence of diastolic dysfunction. Thus, we cannot clearly determine that temporal non-uniformity of the wall expansion is characteristic of all HF patients. Second, in this study, the normal controls were younger and had lower systolic blood pressure and heart rate than the HF patients. We thus tested the

influence of age, systolic blood pressure, and heart rate on the Delay_{C-L} by adjusting these factors, resulting in the consistent prolongation of Delay_{C-L} in heart failure patients. Therefore, these factors were considered to have small influences on Delay_{C-L}. Third, we analyzed longitudinal strain and SR from 3 apical views whereas did circumferential ones from mid-ventricular short-axis view in the manner of previous studies which assessed global strain/SR using speckle-tracking method.^{30, 31} Based on the basal to apical propagation of circumferential wall expansion in the LV wall,³² our results suggest the preceding circumferential expansion relative to longitudinal global expansion in two-thirds of the LV: from mid-ventricular to basal level, but the results cannot be applied to the apical level. Therefore, further study which assesses circumferential deformation in whole LV is needed to confirm our observations. Fourth, we could not obtain reliable marker of regional dyssynchrony in early diastole which has been reported to be common in patients with HF³³ and those with hypertension³⁴ because multiple peaks of early-diastolic SR in some segments made the measurement difficult. In this study, QRS duration correlated weakly with Delay_{C-L} (R=0.24, P<0.01), which might suggest the dyssynchrony may be related to the temporal non-uniformity. Fifth, because we used the biplane method of disks to measure the LV volumes which generally has a limitation of underestimation, the stroke volume estimated from end-diastolic and end-systolic volumes were relatively low. Finally, the frame rate of the speckle-tracking was somewhat low for temporal analysis of the early diastole. However, the group-averaged SR curves shown in **Figure 3** which contain not only the peak timing but also the data of temporal changes of global SR during early diastole supports the relative accuracy of this method.

Conclusions

An abnormal temporal non-uniformity of early diastolic expansion is present in HF

regardless of EF, with a delay of longitudinal relative to circumferential expansion. This delay was associated with reduced longitudinal LV wall expansion and could influence the reduced LV suction.

Disclosures

The authors have no conflict of interest to be disclosed.

Reference

1. Little WC. Diastolic dysfunction beyond distensibility: Adverse effects of ventricular dilatation. *Circulation*. 2005;112:2888-90
2. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. *Circulation*. 2009;120:802-9
3. Bell SP, Nyland L, Tischler MD, McNabb M, Granzier H, LeWinter MM. Alterations in the determinants of diastolic suction during pacing tachycardia. *Circulation research*. 2000;87:235-40
4. Cheng CP, Freeman GL, Santamore WP, Constantinescu MS, Little WC. Effect of loading conditions, contractile state, and heart rate on early diastolic left ventricular filling in conscious dogs. *Circulation research*. 1990;66:814-23
5. Stewart KC, Kumar R, Charonko JJ, Ohara T, Vlachos PP, Little WC. Evaluation of lv diastolic function from color m-mode echocardiography. *JACC Cardiovasc Imaging*. 2011;4:37-46
6. 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;41:1590-7
7. Rivas-Gotz C, Khoury DS, Manolios M, Rao L, Kopelen HA, Nagueh SF. Time interval between onset of mitral inflow and onset of early diastolic velocity by tissue doppler: A novel index of left ventricular relaxation: Experimental studies and clinical application. *J Am Coll Cardiol*. 2003;42:1463-70
8. Iwano H, Pu M, Upadhyaya B, Meyers B, Vlachos P, Little WC. Delay of left ventricular longitudinal expansion with diastolic dysfunction: Impact on load dependence of e' and longitudinal strain rate. *Physiological reports*. 2014;2:e12082
9. McKee PA, Lemmon WB, Hampton JW. Streptokinase and urokinase activation

of human, chimpanzee and baboon plasminogen. *Thrombosis et diathesis haemorrhagica*. 1971;26:512-22

10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-63
11. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol*. 1986;57:450-8
12. Dedobbeleer C, Hadeji A, Naeije R, Unger P. Left ventricular adaptation to acute hypoxia: A speckle-tracking echocardiography study. *J Am Soc Echocardiogr*. 2013;26:736-45
13. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr*. 2011;24:277-313
14. Cheng-Baron J, Chow K, Khoo NS, Esch BT, Scott JM, Haykowsky MJ, et al. Measurements of changes in left ventricular volume, strain, and twist during isovolumic relaxation using MRI. *Am J Physiol Heart Circ Physiol*. 2010;298:H1908-18
15. Yotti R, Bermejo J, Antoranz JC, Desco MM, Cortina C, Rojo-Alvarez JL, et al. A noninvasive method for assessing impaired diastolic suction in patients with dilated cardiomyopathy. *Circulation*. 2005;112:2921-9

16. Greenberg NL, Vandervoort PM, Firstenberg MS, Garcia MJ, Thomas JD. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. *Am J Physiol Heart Circ Physiol*. 2001;280:H2507-15
17. Rovner A, Greenberg NL, Thomas JD, Garcia MJ. Relationship of diastolic intraventricular pressure gradients and aerobic capacity in patients with diastolic heart failure. *Am J Physiol Heart Circ Physiol*. 2005;289:H2081-8
18. Brucks S, Little WC, Chao T, Kitzman DW, Wesley-Farrington D, Gandhi S, et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. *Am J Cardiol*. 2005;95:603-6
19. Firstenberg MS, Greenberg NL, Garcia MJ, Thomas JD. Relationship between ventricular contractility and early diastolic intraventricular pressure gradients: A diastolic link to systolic function. *J Am Soc Echocardiogr*. 2008;21:501-6
20. Popovic ZB, Prasad A, Garcia MJ, Arbab-Zadeh A, Borowski A, Dijk E, et al. Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: Impact of age and fitness. *Am J Physiol Heart Circ Physiol*. 2006;290:H1454-9
21. 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;37:278-85
22. Garcia MJ, Rodriguez L, Ares M, Griffin BP, Thomas JD, Klein AL. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: Assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. *J Am Coll Cardiol*. 1996;27:108-14
23. Min PK, Ha JW, Jung JH, Choi EY, Choi D, Rim SJ, et al. Incremental value of measuring the time difference between onset of mitral inflow and onset of early diastolic mitral annulus velocity for the evaluation of left ventricular diastolic

pressures in patients with normal systolic function and an indeterminate E/e'.
Am J Cardiol. 2007;100:326-30

24. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. *Circulation.* 2002;105:1195-201
25. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med.* 2006;355:251-9
26. Martinez DA, Guhl DJ, Stanley WC, Vailas AC. Extracellular matrix maturation in the left ventricle of normal and diabetic swine. *Diabetes research and clinical practice.* 2003;59:1-9
27. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation.* 1977;56:786-94
28. Douglas PS, Morrow R, Ioli A, Reichek N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol.* 1989;13:311-5
29. Ashikaga H, Coppola BA, Hopenfeld B, Leifer ES, McVeigh ER, Omens JH. Transmural dispersion of myofiber mechanics: Implications for electrical heterogeneity in vivo. *J Am Coll Cardiol.* 2007;49:909-16
30. Cho GY, Marwick TH, Kim HS, Kim MK, Hong KS, Oh DJ. Global 2-dimensional strain as a new prognosticator in patients with heart failure. *J Am Coll Cardiol.* 2009;54:618-24
31. Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. *J Am Coll Cardiol.* 2010;56:1812-22

32. Sengupta PP, Khandheria BK, Korinek J, Wang J, Jahangir A, Seward JB, et al. Apex-to-base dispersion in regional timing of left ventricular shortening and lengthening. *J Am Coll Cardiol*. 2006;47:163-72
33. Yu CM, Zhang Q, Yip GW, Lee PW, Kum LC, Lam YY, et al. Diastolic and systolic asynchrony in patients with diastolic heart failure: A common but ignored condition. *J Am Coll Cardiol*. 2007;49:97-105
34. Kwon BJ, Lee SH, Park CS, Kim DB, Park HJ, Jang SW, et al. Left ventricular diastolic dyssynchrony in patients with treatment-naïve hypertension and the effects of antihypertensive therapy. *J Hypertens*. 2015;33:354-65

Figure legends

Figure 1 Mitral Doppler inflow and mitral annular velocities (**A**) and speckle-tracking derived strain rate curves (**B**). **A**: Time delay of e' onset from E wave onset ($T_{E-e'}$) was measured as time from QRS wave to e' onset minus that to E onset. **B**: Colored lines indicate segmental strain rates and white dashed curve indicates global strain rate. The time delay of longitudinal SR_E from circumferential SR_E ($Delay_{C-L}$) was calculated as time from QRS to longitudinal SR_E minus that to circumferential SR_E . E, early diastolic mitral Doppler inflow; e' , early diastolic mitral annular velocity; SR_E , early diastolic peak of global strain rate.

Figure 2 Mitral Doppler inflow, mitral annular velocity, and strain rate curves obtained from a normal subject, patient with HFpEF, and that with HFrEF. In the normal subject, a simultaneous occurrence is observed in the early diastolic mitral inflow and mitral annular velocity as well as in the circumferential SR_E and longitudinal SR_E . In contrast, a prolongation of $T_{E-e'}$ as well as $Delay_{C-L}$ was observed in the patient with HFpEF and that with HFrEF. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Circ, circumferential; Long, longitudinal. Other abbreviations are the same as Figure 1.

Figure 3 Group-averaged global strain rate curves with their standard errors are presented. Because the absolute values of strain rate are varied among the patients, the global strain rate was expressed as a percentage relative to the patient's early diastolic peak of global strain rate. This relative global strain rate was averaged at every 5% of the %systole in normal controls, HFpEF, and HFrEF. Abbreviations are the same as Figures 1 and 2. Note that similar delay of longitudinal strain rate relative to

circumferential strain rate are observed in both HFpEF and HFrEF whereas they occurs simultaneously in normal controls.

Table 1 Clinical characteristics of the study subjects

	Control (n=31)	Heart failure		P value
		EF≥0.50 (n=50)	EF<0.50 (n=93)	
Age, years	39±14	59±16 [†]	53±13 [†]	<0.001
Female, n (%)	18 (58)	35 (70)	27 (29)	<0.001
Body surface area, m ²	1.84±0.26	1.99±0.31	2.03±0.25 [†]	0.002
Systolic blood pressure, mmHg	117±18	142±24 [†]	132±26 [†]	<0.001
Diastolic blood pressure, mmHg	68±9	76±20	82±19 [†]	0.001
Heart rate, bpm	72±15	78±15	80±14 [†]	0.023
QRS duration, ms	83±10	94±20	104±22 ^{†‡}	<0.001
NYHA functional class				0.054
I	NA	0 (0)	0 (0)	
II	NA	31 (62)	42 (45)	
III or IV	NA	19 (38)	51 (55)	
Cardiac disease, n (%)				<0.001
Ischemic heart disease	NA	11 (22)	26 (28)	
Non-ischemic dilated cardiomyopathy	NA	1 (2)	38 (41)	
Hypertensive heart disease	NA	33 (66)	16 (17)	
Undefined	NA	3 (6)	12 (13)	
Others	NA	2 (4)	1 (1)	
Comorbidity, n (%)				
Hypertension	NA	48 (96)	72 (77)	0.002
Diabetes Mellitus	NA	22 (44)	38 (41)	0.717
Dyslipidemia	NA	10 (20)	11 (12)	0.196
Medication, n (%)				
ACE-I or ARB	NA	23 (46)	67 (72)	0.002
Beta blockers	NA	32 (64)	78 (84)	0.008
Calcium antagonists	NA	15 (30)	14 (15)	0.037
Diuretics	NA	33 (66)	52 (56)	0.239
Aspirin	NA	27 (54)	47 (51)	0.739
Statin	NA	21 (42)	50 (50)	0.179

P values are for the analysis of variance (ANOVA) for continuous variables and for chi-square tests

for categorical variables. [†]P<0.05 vs normal group, [‡]P<0.05 vs heart failure with EF≥0.50 by

Tukey-Kramer's post-hoc test. EF, left ventricular ejection fraction; NYHA, New York Heart

Association; NA, not applicable for controls; ACE-I, angiotensin converting enzyme inhibitor; ARB,

angiotensin II receptor blocker.

Table 2 Echocardiographic measurements

	Control	Heart failure		
		EF≥0.50	EF<0.50	
Two-dimensional findings				
LV mass index, g/m ²	75±21	138±46 [†]	154±58 [†]	<0.001
LV end-diastolic volume, mL	86±30	102±35	172±55 ^{†‡}	<0.001
LV end-systolic volume, mL	30±13	39±18	120±48 ^{†‡}	<0.001
LV ejection fraction	0.65±0.06	0.62±0.07	0.32±0.09 ^{†‡}	<0.001
Left atrial diameter, mm	30±5	40±7 [†]	42±6 [†]	<0.001
Indexed left atrial volume, mL/mm ²	18±7	32±13 [†]	38±13 [†]	<0.001
Doppler findings				
E wave velocity, cm/s	83±17	93±24	93±26	0.123
A wave velocity, cm/s	65±16	90±31 [†]	59±24 [‡]	<0.001
E/A	1.33±0.41	1.16±0.52	1.90±1.03 ^{†‡}	<0.001
E wave deceleration time, ms	199±38	200±47	166±60 ^{†‡}	<0.001
s', cm/s	9.3±2.2	6.4±1.3 [†]	5.0±1.3 ^{†‡}	<0.001
e', cm/s	12.0±2.3	6.1±1.5 [†]	6.0±1.5 [†]	<0.001
E/e'	7.1±1.6	15.8±4.5 [†]	16.2±5.1 [†]	<0.001
Speckle-tracking findings				
Longitudinal global strain, %	−21.4±3.1	−16.3±3.8 [†]	−8.7±3.2 ^{†‡}	<0.001
Longitudinal SR _{sys} , /s	−1.19±0.19	−0.94±0.20 [†]	−0.56±0.18 ^{†‡}	<0.001
Longitudinal SR _E , /s	1.54±0.42	0.95±0.26 [†]	0.64±0.24 ^{†‡}	<0.001
Circumferential global strain, %	−29.9±6.9	−26.0±7.9 [†]	−12.0±4.6 ^{†‡}	<0.001
Circumferential SR _{sys} , /s	−1.71±0.43	−1.57±0.49	−0.78±0.30 ^{†‡}	<0.001
Circumferential SR _E , /s	2.20±0.64	1.62±0.53 [†]	0.97±0.42 ^{†‡}	<0.001
CMMD findings				
IVPD, mmHg	3.20±1.06	2.59±0.82 [†]	2.31±0.86 [†]	<0.001
	(N=27)	(N=34)	(N=72)	

P values are for the analysis of variance (ANOVA). [†]*P*<0.05 vs normal group, [‡]*P*<0.05 vs heart failure with EF $\geq$ 0.50 by Tukey-Kramer's post-hoc test. EF, left ventricular ejection fraction; LV, left ventricular; E, early diastolic peak of mitral inflow; A, atrial peak of mitral inflow; s', peak systolic mitral annular velocity; e', early diastolic mitral annular velocity; SR_{sys}, peak systolic global strain rate; SR_E, early diastolic peak of global strain rate; CMMD, color M-mode Doppler imaging; IVPD, intra left ventricular pressure difference.

Table 3 Results of the time-measurements

	Control	Heart failure		P value
		EF≥0.50	EF<0.50	
Time from QRS wave				
E wave onset				
ms	398±45	414±58	396±52	0.14
%Systole	120±6	122±9	123±8	0.20
e' onset				
ms	392±46	448±58 [†]	430±56 [†]	<0.001
%Systole	117±5	132±10 [†]	134±10 [†]	<0.001
Longitudinal SR _E				
ms	452±45	486±63 [†]	461±55 [‡]	0.011
%Systole	136±8	144±12 [†]	143±10 [†]	0.002
Circumferential SR _E				
ms	454±50	454±66	435±50	0.08
%Systole	137±7	133±9	135±10	0.18
T _{E-e'}				
ms	-6±19	34±24 [†]	34±25 [†]	0.002
%Systole	-2±6	10±7 [†]	10±8 [†]	<0.001
Delay _{C-L}				
ms	-4±15	33±25 [†]	26±27 [†]	<0.001
%Systole	-1±5	10±8 [†]	8±8 [†]	<0.001

P values are for the analysis of variance (ANOVA). [†]*P*<0.05 vs normal group, [‡]*P*<0.05 vs heart

failure with EF $\geq$ 0.50 by Tukey-Kramer's post-hoc test. T_{E-e'}, delay of e' onset from E wave onset;

Delay_{C-L}, delay of longitudinal SR_E from circumferential SR_E. Other abbreviations are the same as

Table 2.

Table 4 Determinants of the intra left ventricular pressure difference

Variables	Univariate		Multivariate		VIF
	R	P value	β	P value	
Age	−0.28	0.001	−0.17	NS	1.15
LV mass index	−0.03	NS	0.12	NS	1.32
LV ejection fraction	0.26	0.002	−0.06	NS	5.00
Global longitudinal strain	−0.31	<0.001	−0.23	NS	5.40
Global circumferential strain	−0.29	<0.001	−0.01	NS	4.12
Delay _{C-L}	−0.28	0.001	−0.21	0.023	1.20

VIF, variance inflation factor. Other abbreviations were the same as Tables 2 and 3.

Fig.1

A

B

Circumferential

Longitudinal

Fig.2

Normal

HFpEF

HFrEF

Fig.3