

Clinical Investigation

Presence and Implication of Temporal Nonuniformity of Early Diastolic Left Ventricular Wall Expansion in Patients With Heart Failure

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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 nonuniformity 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)—as well as 31 normal control subjects. 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 nonuniformity. Intra-LV pressure difference (IVPD) was estimated with the use of color M-mode Doppler data as a parameter of LV diastolic suction. Although normal control subjects had symmetric LV expansion in early diastole, $T_{E-e'}$ and $Delay_{C-L}$ were significantly prolonged in HF regardless of EF ($P < .01$ vs control for all). Multivariate analysis revealed that $Delay_{C-L}$ was the independent determinant of IVPD among the parameters of LV geometry and contraction ($\beta = -0.21$; $P < .05$).

Conclusion: An abnormal temporal nonuniformity of early-diastolic expansion is present in HF regardless of EF, which was associated with reduced LV suction. (*J Cardiac Fail* 2016;■■:■■–■■)

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

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 owing to the progressive IVPD from left atrium to the LV apex.⁴ Therefore, 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 (EFs).⁸ This result suggests that, in patients with HF, regardless of LV EF, there is diastolic temporal nonuniformity with a delay of longitudinal relative to cir-

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cumferential expansion in early diastole. Moreover, this temporal nonuniformity would effect an effective pressure fall in LV cavity in early diastole, ie, LV suction, in patients with HF. Accordingly, the aim of the present study was to determine the temporal nonuniformity in early diastole in patients with HF and preserved EF (HFpEF) and with reduced EF (HFrEF) and to test the influence of the temporal nonuniformity on LV suction.

Methods

Study Population

The study protocol was approved by the Institutional Review Boards of University of Mississippi Medical Center (#2013-0254). From November 2013 to April 2014, we prospectively and consecutively enrolled patients who underwent clinically indicated transthoracic echocardiography and had a documented history of congestive HF based on the Framingham criteria.⁹ Exclusion criteria were nonsinus 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 study inclusion, 115 patients with insufficient 2-dimensional echocardiographic images for speckle-tracking analysis were also excluded. The remaining 143 HF patients were included in the final analysis to test the presence of temporal nonuniformity in HF. Thirty-one subjects who had neither history of cardiovascular risk factors nor any abnormal echocardiographic findings served as normal control subjects. In 148 subjects who had color M-mode Doppler (CMMD) images for the analysis of IVPD, we tested the influence of the temporal nonuniformity of LV expansion on LV suction.

Two-Dimensional and Doppler Echocardiography

Echocardiography was performed with the use of 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 40–140) 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 the 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 with the use of pulsed-wave tissue Doppler imaging, and averages of the septal and lateral velocities were used for the subsequent analysis. The ratio of E to e' (E/e') was calculated. The times from the peak of QRS wave to the

onset of the E wave, to e' onset, and their difference ($T_{E-e'}$)⁷ were measured as a parameter of the delay of LV longitudinal wall expansion (Fig. 1). 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 with the use of Qlab Advanced Quantification Software version 9.0 (Phillips Medical Systems) as previously described.^{12,13} Briefly, the longitudinal parameter was obtained from the apical 4-chamber, 2-chamber, and long-axis views and the circumferential parameter from the midventricular short-axis view. The global strain/SR curve was extracted with the use of the 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 times from peak of QRS wave to longitudinal SR_E and to circumferential SR_E were measured and their difference (Delay_{C-L}) calculated as an amount of temporal nonuniformity of early diastolic wall expansion (Fig. 1). The timings of the all events were normalized to AVC and expressed as the percentage of the duration of systole¹⁴ 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 automated software, the IVPD was measured as a parameter of the strength of LV diastolic suction.⁵ The CMMD data were used to integrate the 1-dimensional Euler equation as previously described.^{5,8} The pressure difference at each point, along with the scan line, was measured relative to the 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 with 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 2-dimensional echocardiographic images, and 1 blinded observer repeated the analysis on a separate day. The mean and SD of the absolute difference between 2 measurements by an observer and between observers were, respectively, 6 ± 6 ms and 9 ± 8 ms for the onset of E-wave, 6 ± 4 ms and 7 ± 7 ms for the onset of e', 3 ± 2 ms and 13 ± 6 ms for longitudinal SR_E, and 4 ± 5 ms and 12 ± 5 ms for circumferential SR_E. As a result, intra-

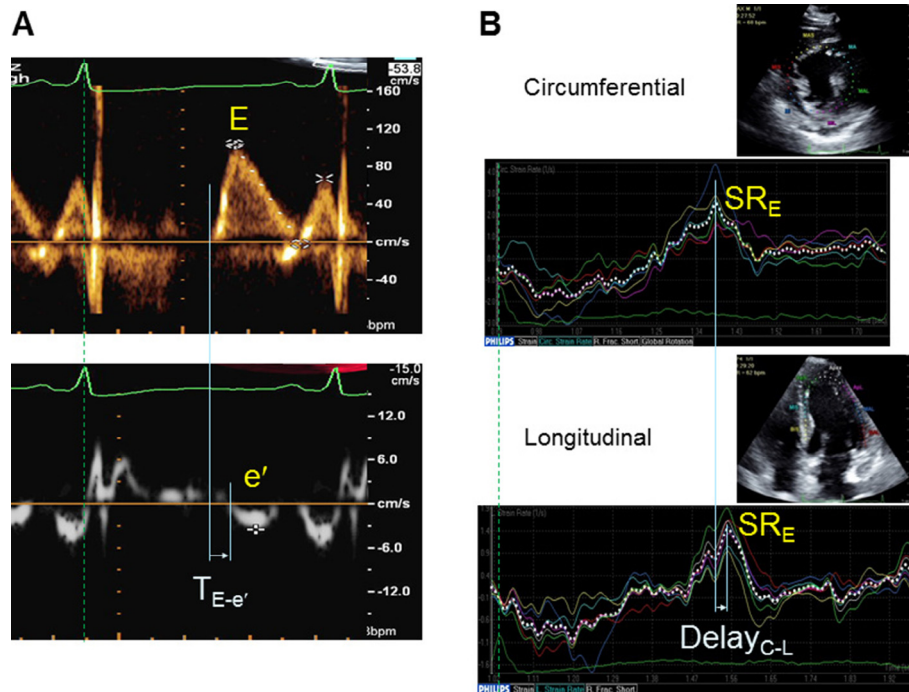


Fig. 1. Mitral Doppler (A) inflow and mitral annular velocities and (B) speckle tracking–derived strain rate curves. (A) Time delay of e' onset from E-wave onset ($T_{E-e'}$) was measured as time from QRS wave to e' onset minus that to E onset. (B) Colored lines indicate segmental strain rates, and white 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; $Delay_{C-L}$, delay of longitudinal SR_E relative to circumferential SR_E .

and interobserver variabilities were, respectively, 10 ± 5 ms and 12 ± 5 ms for $T_{E-e'}$ and 5 ± 5 ms and 12 ± 11 ms for $Delay_{C-L}$.

Statistical Analysis

All statistical analyses were performed with the use of JMP software by (SAS Institute). Continuous variables were expressed as mean \pm SD and compared among the groups by means 1-way analysis of variance (ANOVA), and post hoc analysis was then performed with the use of Tukey-Kramer test. Proportions were compared by means of chi-square analysis. Linear regression analysis was used for the detection of correlation between 2 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 means of a multiple regression analysis with incorporating the previously reported influencing factors of the IVPD. For all tests, a P value of $<.05$ was considered to be 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 (≥ 0.50) and 93 patients had a reduced

LVEF (<0.50). The HF patients were older and had a higher systolic blood pressure than the normal control subjects. Female sex was more frequent in HFpEF than in HFrEF. The patients with HFrEF had a higher heart rate than the control subjects. 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, whereas nonischemic dilated cardiomyopathy was most frequent in patients with HFrEF. The use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers and beta-blockers was less frequent in HFpEF than in HFrEF. In contrast, calcium antagonists were given more frequently in the patients with HFpEF than 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 with the control subjects. LV end-diastolic and end-systolic volumes were larger and EF was lower in the HFrEF patients than in the control subjects, whereas they were similar between HFpEF and control subjects. Left atrial size (diameter and volumes) was greater in HFpEF and HFrEF than in control subjects. 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 earlier reports.¹⁸ Speckle-

Table 1. Clinical Characteristics of the Study Subjects

Characteristic	Control (n = 31)	Heart Failure		P Value*
		EF ≥ 0.50 (n = 50)	EF < 0.50 (n = 93)	
Age, y	39 \pm 14	59 \pm 16 [†]	53 \pm 13 [†]	<.001
Female, n (%)	18 (58)	35 (70)	27 (29)	<.001
Body surface area, m ²	1.84 \pm 0.26	1.99 \pm 0.31	2.03 \pm 0.25 [†]	.002
Systolic blood pressure, mm Hg	117 \pm 18	142 \pm 24 [†]	132 \pm 26 [†]	<.001
Diastolic blood pressure, mm Hg	68 \pm 9	76 \pm 20	82 \pm 19 [†]	.001
Heart rate, beats/min	72 \pm 15	78 \pm 15	80 \pm 14 [†]	.023
QRS duration, ms	83 \pm 10	94 \pm 20	104 \pm 22 ^{†*}	<.001
NYHA functional class, n (%)				.054
I	NA	0 (0)	0 (0)	
II	NA	31 (62)	42 (45)	
III or IV	NA	19 (38)	51 (55)	
Cardiac disease, n (%)				<.001
Ischemic heart disease	NA	11 (22)	26 (28)	
Nonischemic 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)	.002
Diabetes Mellitus	NA	22 (44)	38 (41)	.717
Dyslipidemia	NA	10 (20)	11 (12)	.196
Medication, n (%)				
ACE-I or ARB	NA	23 (46)	67 (72)	.002
Beta blockers	NA	32 (64)	78 (84)	.008
Calcium antagonists	NA	15 (30)	14 (15)	.037
Diuretics	NA	33 (66)	52 (56)	.239
Aspirin	NA	27 (54)	47 (51)	.739
Statin	NA	21 (42)	50 (50)	.179

EF, left ventricular ejection fraction; NYHA, New York Heart Association; NA, not applicable for control subjects; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

*P values are for the analysis of variance for continuous variables and for chi-square tests for categorical variables.

[†]P < .05 vs normal group.

[‡]P < .05 vs heart failure with EF ≥ 0.50 by Tukey-Kramer post hoc test.

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 means of speckle-tracking, except circumferential SR_{sys}, were reduced in HFpEF compared with control subjects 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 compared with control subjects.

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 was unchanged among the groups, resulting in a significant prolongation of Delay_{C-L} in HF regardless of EF (Table 3; Fig. 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 < .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 \pm 23 ms and 34 \pm 26 ms; Delay_{C-L}: 26 \pm 25 ms and 31 \pm 29 ms; respectively; P < .01 vs control for all). The group-averaged global SR curves showed temporal nonuniformity 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 symmetric wall expansion in normal control subjects (Fig. 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 EF, 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 whereas it

Table 2. Echocardiographic Measurements

Measurement	Control	Heart Failure		P Value*
		EF ≥0.50	EF <0.50	
2-Dimensional findings				
LV mass index, g/m ²	75 ± 21	138 ± 46 [†]	154 ± 58 [†]	<.001
LV end-diastolic volume, mL	86 ± 30	102 ± 35	172 ± 55 ^{†‡}	<.001
LV end-systolic volume, mL	30 ± 13	39 ± 18	120 ± 48 ^{†‡}	<.001
LV EF	0.65 ± 0.06	0.62 ± 0.07	0.32 ± 0.09 ^{†‡}	<.001
Left atrial diameter, mm	30 ± 5	40 ± 7 [†]	42 ± 6 [†]	<.001
Indexed left atrial volume, mL/mm ²	18 ± 7	32 ± 13 [†]	38 ± 13 [†]	<.001
Doppler findings				
E-wave velocity, cm/s	83 ± 17	93 ± 24	93 ± 26	.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 ^{†‡}	<.001
E-wave deceleration time, ms	199 ± 38	200 ± 47	166 ± 60 ^{†‡}	<.001
s', cm/s	9.3 ± 2.2	6.4 ± 1.3 [†]	5.0 ± 1.3 ^{†‡}	<.001
e', cm/s	12.0 ± 2.3	6.1 ± 1.5 [†]	6.0 ± 1.5 [†]	<.001
E/e'	7.1 ± 1.6	15.8 ± 4.5 [†]	16.2 ± 5.1 [†]	<.001
Speckle-tracking findings				
Longitudinal global strain, %	-21.4 ± 3.1	-16.3 ± 3.8 [†]	-8.7 ± 3.2 ^{†‡}	<.001
Longitudinal SR _{Sys} , s ⁻¹	-1.19 ± 0.19	-0.94 ± 0.20 [†]	-0.56 ± 0.18 ^{†‡}	<.001
Longitudinal SR _E , s ⁻¹	1.54 ± 0.42	0.95 ± 0.26 [†]	0.64 ± 0.24 ^{†‡}	<.001
Circumferential global strain, %	-29.9 ± 6.9	-26.0 ± 7.9 [†]	-12.0 ± 4.6 ^{†‡}	<.001
Circumferential SR _{Sys} , s ⁻¹	-1.71 ± 0.43	-1.57 ± 0.49	-0.78 ± 0.30 ^{†‡}	<.001
Circumferential SR _E , s ⁻¹	2.20 ± 0.64	1.62 ± 0.53 [†]	0.97 ± 0.42 ^{†‡}	<.001
CMMD findings				
IVPD, mm Hg	3.20 ± 1.06	2.59 ± 0.82 [†]	2.31 ± 0.86 [†]	<.001
	(n = 27)	(n = 34)	(n = 72)	

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.

**P* values are for the analysis of variance.

[†]*P* < .05 vs normal group.

[‡]*P* < .05 vs heart failure with EF ≥0.50 by Tukey-Kramer post hoc test.

Table 3. Results of the Time Measurements

Measurement	Control	Heart Failure		<i>P</i> Value*
		EF ≥0.50	EF <0.50	
Time from QRS wave				
E-wave onset				
ms	398 ± 45	414 ± 58	396 ± 52	.14
%Systole	120 ± 6	122 ± 9	123 ± 8	.20
e' onset				
ms	392 ± 46	448 ± 58 [†]	430 ± 56 [†]	<.001
%Systole	117 ± 5	132 ± 10 [†]	134 ± 10 [†]	<.001
Longitudinal SR _E				
ms	452 ± 45	486 ± 63 [†]	461 ± 55 [‡]	.011
%Systole	136 ± 8	144 ± 12 [†]	143 ± 10 [†]	.002
Circumferential SR _E				
ms	454 ± 50	454 ± 66	435 ± 50	.08
%Systole	137 ± 7	133 ± 9	135 ± 10	.18
T _{E-e'}				
ms	-6 ± 19	34 ± 24 [†]	34 ± 25 [†]	.002
%Systole	-2 ± 6	10 ± 7 [†]	10 ± 8 [†]	<.001
Delay _{C-L}				
ms	-4 ± 15	33 ± 25 [†]	26 ± 27 [†]	<.001
%Systole	-1 ± 5	10 ± 8 [†]	8 ± 8 [†]	<.001

%Systole, percentage of the duration of systole; 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 as in Table 2.

**P* values are for the analysis of variance.

[†]*P* < .05 vs normal group.

[‡]*P* < .05 vs heart failure with EF ≥0.50 by Tukey-Kramer post hoc test.

expands symmetrically in normal control subjects. This temporal nonuniformity of early diastolic expansion was due to a delay of longitudinal relative to circumferential expansion. Furthermore, the longitudinal delay was observed regardless of EF; ie, it occurred both in HFpEF and HFrEF. We also found that the temporal nonuniformity 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 (60% ischemic etiology, 30% idiopathic cardiomyopathy) with diastolic dysfunction.⁷ However, the influence of LV systolic function on T_{E-e'} was not determined. Moreover, those findings had not been tested in clinically diagnosed HF patients. In the present study, we demonstrated the delay of LV wall expansion (ie, prolonged T_{E-e'}) in both HFpEF and HFrEF, suggesting that the delay of the longitudinal expansion exists in HF regardless of LV EF.

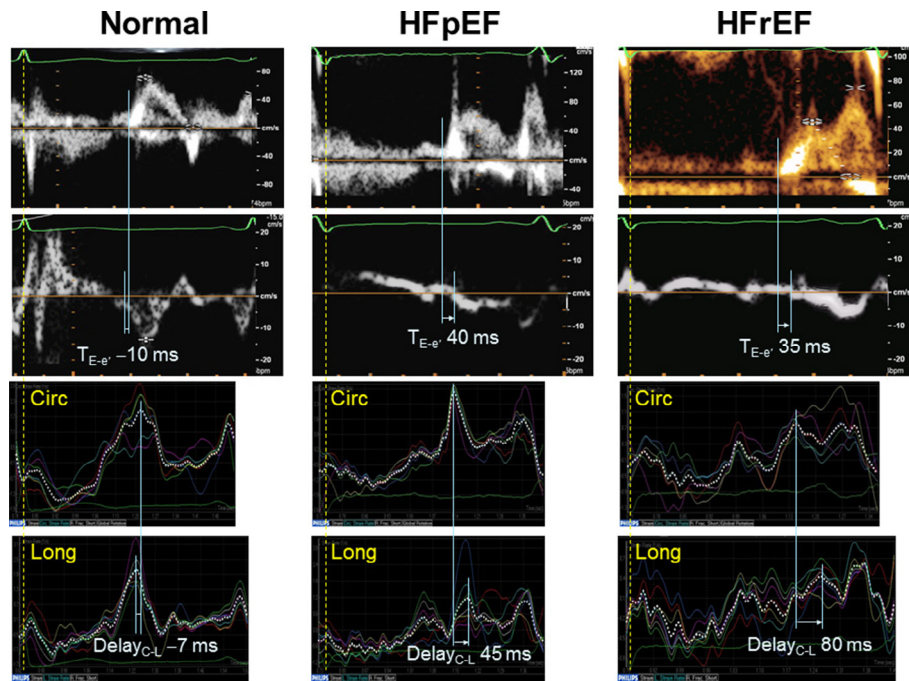


Fig. 2. Mitral Doppler inflow, mitral annular velocity, and strain rate curves obtained from a normal subject, a patient with heart failure with preserved ejection fraction (HFpEF), and a patient with heart failure with reduced ejection fraction (HFrEF). In the normal subject, a simultaneous occurrence 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 patients with HFpEF and HFrEF. Circ, circumferential; Long, longitudinal; other abbreviations are the same as Fig. 1.

Temporal Nonuniformity 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 nonuniformity with a delay of longitudinal relative to circumferential expansion could exist in patients with HF. Indeed, the present study demonstrated a clear temporal nonuniformity of LV wall expansion during early diastole in HF patients (Fig. 3). These delay of longitudinal expansion could be a consequence of reduced longitudinal diastolic recoil resulting from reduced longitudinal shortening.²⁴ Because 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 the 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 nonuniformity. Ashikaga et al reported that there is a transmural dispersion of LV myofiber relaxation with a delay of

endocardial layer relative to the 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 the longitudinally oriented inner layer could be significantly delayed relative to that of the circumferentially-oriented midwall, resulting in significant temporal nonuniformity of wall expansion. Although we cannot confirm this speculation, because studies have not tested this phenomenon in HF patients, the transmural heterogeneity would explain one of the reasons for the temporal nonuniformity.

Clinical Implications

As discussed above, the temporal nonuniformity could be a result of the delayed longitudinal expansion which is a consequence of reduced longitudinal recoil. Therefore, the amount of temporal nonuniformity 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, asymmetric 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, ie, 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 nonuniformity was an independent determinant of IVPD, a measure of the strength of LV diastolic suction, which could suggest this nonuniformity

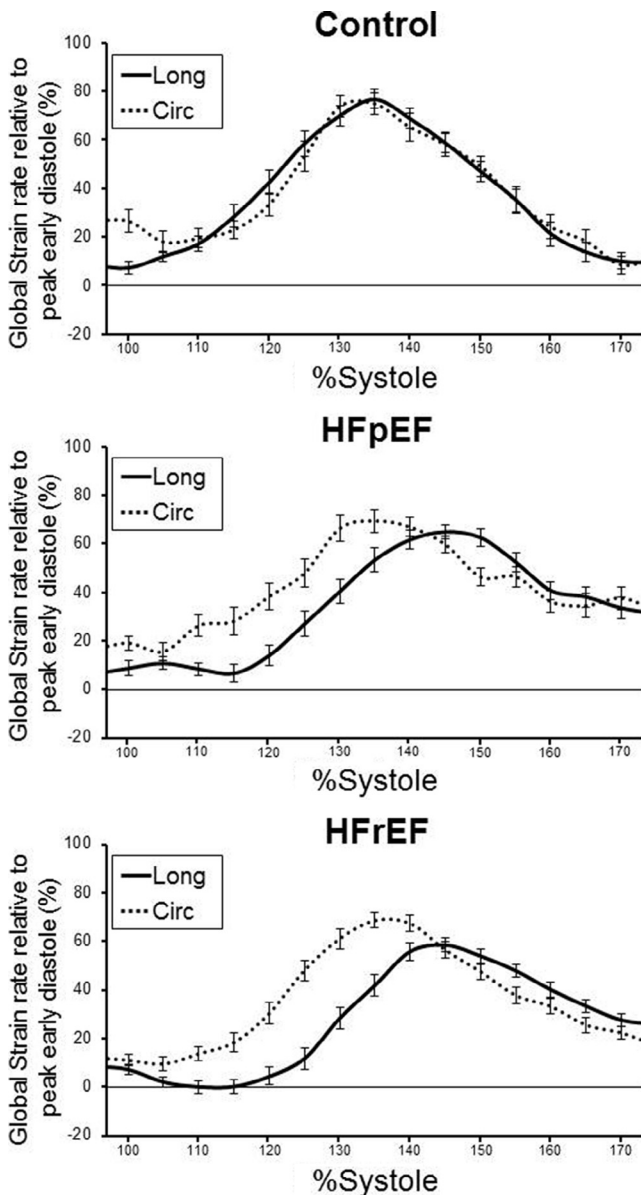


Fig. 3. Group-averaged global strain rate curves with their standard errors are presented. Because the absolute values of strain rate are varied among the patients, the global strain rate was expressed as a percentage relative to the patient's early diastolic peak of global strain rate. This relative global strain rate was averaged at every 5% of the percentage of the duration of systole (%systole) in normal control, HFpEF, and HFrEF subjects. Abbreviations as in Fig. 2. Note that similar delay of longitudinal strain rate relative to circumferential strain rate are observed in both HFpEF and HFrEF subjects whereas they occur simultaneously in normal control subjects.

Table 4. Determinants of the Intra-Left Ventricular Pressure Difference

Variable	Univariate		Multivariate		VIF
	R	P Value	β	P Value	
Age	-0.28	.001	-0.17	NS	1.15
LV mass index	-0.03	NS	0.12	NS	1.32
LV EF	0.26	.002	-0.06	NS	5.00
Global longitudinal strain	-0.31	<.001	-0.23	NS	5.40
Global circumferential strain	-0.29	<.001	-0.01	NS	4.12
Delay _{C-L}	-0.28	.001	-0.21	.023	1.20

VIF, variance inflation factor. Other abbreviations as in Tables 2 and 3.

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 HF, this study did 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. Therefore, we can not clearly determine that temporal nonuniformity of the wall expansion is characteristic of all HF patients. Second, in this study, the normal control subjects were younger and had lower systolic blood pressure and heart rate than the HF patients. We tested the influence of age, systolic blood pressure, and heart rate on the Delay_{C-L} by adjusting for these factors, resulting in the consistent prolongation of Delay_{C-L} in HF patients, so these factors were considered to have small influences on Delay_{C-L}. Third, we analyzed longitudinal strain and SR from 3 apical views, whereas we analyzed circumferential strain and SR from the midventricular short-axis view, in the manner of previous studies that assessed global strain/SR with the use of the 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 midventricular to basal level—but the results can not be applied to the apical level. Therefore, further study to assess circumferential deformation in whole LV is needed to confirm our observations. Fourth, we could not obtain a reliable marker of regional dyssynchrony in early diastole, which has been reported to be common in patients with HF³³ and those with hypertension,³⁴ 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} ($R = 0.24$; $P < .01$), which might suggest the dyssynchrony may be related to the temporal nonuniformity. Fifth, because we used the biplane method of disks, which generally has a limitation of underestimation, to measure the LV volumes, 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 Fig. 3, which contain not only the peak timing but also the data of temporal changes of global SR during early diastole, support the relative accuracy of this method.

Conclusion

An abnormal temporal nonuniformity 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

None.

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