Clinical Significance of Abnormal Relaxation Pattern of the Transmitial Flow Velocity Waveform in Older Patients With Preserved Left Ventricular Ejection Fraction

Shohei Kikuchi, MD; Kazuaki Wakami, MD; Toshihiko Goto, MD; Hidekatsu Fukuta, MD; Hiroo Sonoda, MD; Tomomitsu Tani, MD; Nobuyuki Ohte, MD

Background: The pathophysiology of abnormal relaxation pattern in the transmitial flow (TMF) velocity waveform has not been fully elucidated.

Methods and Results: A total of 173 patients who underwent comprehensive Doppler echocardiography and diagnostic cardiac catheterization for coronary artery disease were enrolled in the study. Peak early and late diastolic TMF velocities (E and A, respectively) were measured. Minimum left ventricular (LV) pressure; LV pre-A wave pressure ( surrogate of mean left atrial [LA] pressure); time constant (r) of LV pressure decay; and LV ejection fraction (LVEF) were calculated. Patients with E/A ratio <1.0 and LVEF ≥50% were enrolled. Patients with r ≥48 ms and those with r <48 ms were compared. The 2 groups had no significant differences in E or E/A. Minimum LV pressure (6.9±2.2 mmHg vs. 3.6±2.9 mmHg, P<0.0001) and LV pre-A wave pressure (9.5±2.4 mmHg vs. 6.1±3.0 mmHg, P<0.0001) were significantly higher in patients with r ≥48 ms compared to those with r <48 ms, but the difference between the LV pre-A and minimum LV pressures was similar between the groups (2.6±1.4 mmHg vs. 2.5±1.5 mmHg, P=0.89).

Conclusions: Proportional elevations in minimum LV and pre-A pressures, due to deteriorated LV relaxation, resulted in no changes in the pressure gradient between the LA and LV in early diastole, E, or E/A. (Circ J 2013; 77: 2551–2557)

Key Words: Coronary artery disease; Left ventricular relaxation; Preserved ejection fraction; Transmitial flow velocity waveform

Heart failure with preserved left ventricular (LV) ejection fraction (HFpEF) accounts for nearly half of all HF cases. Patients with HF with reduced EF and those with HFpEF have a similar risk of adverse events and mortality. Although many etiologies of HFpEF have been reported, LV diastolic dysfunction is a major cause of HFpEF; furthermore, LV diastolic dysfunction was associated with the development of HF in a previous study. Recently, delayed LV relaxation became the focus of several studies as a major cause of the symptoms in HFpEF. In clinical practice, Doppler echocardiography is the most effective diagnostic modality for non-invasively assessing the diastolic properties of the LV. Due to its simplicity, the transmitial flow (TMF) velocity waveform is commonly used as a surrogate measure of LV diastolic function. Many patients with HFpEF have an abnormal relaxation pattern in the TMF velocity waveform, when the HF is compensated. Older, healthy people, however, have a similarly abnormal relaxation pattern, despite a relatively preserved LV relaxation compared to patients with cardiac disease. Although some groups have suggested that the mechanism underlying these findings may be dependent on the alterations in left atrial (LA) and LV pressures, as seen in dogs, to our knowledge, no supporting data have been reported in a clinical setting. Accordingly, we investigated this classical, but not adequately clarified, issue in patients who underwent LV pressure measurements with a catheter-tipped micromanometer during cardiac catheterization.

Methods

Subjects
The initial cohort included 416 consecutive patients who underwent comprehensive Doppler echocardiography, including tissue Doppler imaging and diagnostic cardiac catheterization, for the evaluation of coronary artery disease (CAD). All patients had symptoms of exercise-induced angina and/or clinical signs of CAD, including positive exercise electrocardiographic changes, abnormal myocardial perfusion scintigraphic findings, and...
coronary artery stenosis on contrast enhanced computed tomography. Patients were excluded if they had renal insufficiency (serum creatinine ≥1.5 mg/dl), electronic pacemaker, hemodynamically significant valvular disease, post-prosthetic valve replacement conditions, atrial fibrillation/flutter, idiopathic dilated or hypertrophic cardiomyopathy, or acute coronary syndrome. Finally 173 patients who had LVEF ≥50%, measured on left ventriculography, and a ratio of peak early diastolic (E) to peak late diastolic (A) TMF velocity (E/A) <1.0, measured on Doppler ventriculography, and a ratio of peak early diastolic (E) to peak late diastolic (A) TMF velocity (E/A) <1.0, measured on Doppler echocardiography were enrolled. Patients were then grouped, based on the time constant (τ) of isovolumic pressure decline, which we used in LV pressure just before atrial contraction; the latter measure- is derived from a monoexponential fit to the LV pressure decay, with a zero asymptote.

In describing patient characteristics, hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with anti-hypertensive drugs. Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or treatment with blood glucose-lowering medicine. Hypercholesterolemia was defined as low-density lipoprotein cholesterol >140 mg/dl or treatment with cholesterol-lowering medicine. All patients provided written informed consent for participation in the study. The study protocol was approved by the Ethics Guidelines Committee of Nagoya City University Graduate School of Medical Sciences.

Echocardiography
We performed comprehensive transthoracic Doppler echocardiography with an Aplio80™ or Artida™ (Toshiba Medical Systems, Tokyo, Japan) on the day before cardiac catheterization. TMF velocity waveform was obtained at the level of the mitral valve annulus using the prolate-ellipsoid method and then indexed to body surface area of each patient.

Keyence, Osaka, Japan), as reported elsewhere. From the recorded pressure waves, τ was derived from a monoexponential fit to the LV pressure decay, with a zero asymptote. The minimum LV pressure was defined as the nadir of pressure during early diastole, and the LV pre-A wave pressure was defined as the pressure just before atrial contraction; the latter measurement was taken as an estimation of the mean LA pressure. Subsequent to the LV pressure measurements, left ventriculography and coronary angiography were performed. LVEF was derived from European guidelines for diagnosing HF in patients with normal LVEF. In describing patient characteristics, hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with anti-hypertensive drugs. Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or treatment with blood glucose-lowering medicine. Hypercholesterolemia was defined as low-density lipoprotein cholesterol >140 mg/dl or treatment with cholesterol-lowering medicine. All patients provided written informed consent for participation in the study. The study protocol was approved by the Ethics Guidelines Committee of Nagoya City University Graduate School of Medical Sciences.

Cardiac Catheterization
LV pressure waves were obtained with a catheter-tipped micromanometer (SPC–454D; Millar Instruments, Houston, TX, USA) and recorded on a polygraph system (RMC-3000; Nihon Kohden, Tokyo, Japan) and on a digital data recorder (NR–2000; Keyence, Osaka, Japan), as reported elsewhere. From the recorded pressure waves, τ was derived from a monoexponential fit to the LV pressure decay, with a zero asymptote. The minimum LV pressure was defined as the nadir of pressure during early diastole, and the LV pre-A wave pressure was defined as the pressure just before atrial contraction; the latter measurement was taken as an estimation of the mean LA pressure. Subsequent to the LV pressure measurements, left ventriculography and coronary angiography were performed. LVEF was derived from European guidelines for diagnosing HF in patients with normal LVEF. In describing patient characteristics, hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with anti-hypertensive drugs. Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or treatment with blood glucose-lowering medicine. Hypercholesterolemia was defined as low-density lipoprotein cholesterol >140 mg/dl or treatment with cholesterol-lowering medicine. All patients provided written informed consent for participation in the study. The study protocol was approved by the Ethics Guidelines Committee of Nagoya City University Graduate School of Medical Sciences.

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Table. Subject Clinical Characteristics and Medication

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Impaired left ventricular relaxation</th>
<th>Preserved left ventricular relaxation</th>
<th>P-value</th>
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<tbody>
<tr>
<td>n</td>
<td>68</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.9±7.2</td>
<td>69.2±8.0</td>
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</tr>
<tr>
<td>Male</td>
<td>78</td>
<td>70</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>62.0±8.3</td>
<td>64.0±7.3</td>
<td>0.10</td>
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<tr>
<td>Mean blood pressure (mmHg)</td>
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<td>99±16</td>
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</tr>
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<td>8</td>
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<tr>
<td>Non-coronary artery disease</td>
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<tr>
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<td>38</td>
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<tr>
<td>β-blockers</td>
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<td>Calcium channel blockers</td>
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<tr>
<td>Oral hypoglycemic drugs</td>
<td>16</td>
<td>25</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Data given as mean±SD or %. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers.
Abnormal Relaxation Pattern of TMF

Figure 1. Comparable morphology of representative transmitral flow (TMF) velocity waveforms between a patient with impaired left ventricular (LV) relaxation and a patient with preserved LV relaxation. (A) Waveform from a 67-year-old man with prior anterior myocardial infarction and impaired LV relaxation. Doppler echocardiographic and LV pressure data: E, 72 cm/s; A, 90 cm/s; e’, 5.0 cm/s; minimum LV pressure, 10 mmHg; LV pre-A pressure, 15 mmHg. (B) Waveform from a 73-year-old woman with atypical chest pain. Doppler echocardiographic and LV pressure data: E, 68 cm/s; A, 85 cm/s; e’, 9.0 cm/s; minimum LV pressure, 2 mmHg; LV pre-A pressure, 7 mmHg. A, peak late diastolic TMF velocity; E, peak early diastolic TMF velocity; e’, annular velocity during early diastole.

Figure 2. Comparisons of Doppler echocardiographic parameters between patients with impaired (τ ≥ 48 ms) or preserved (τ < 48 ms) left ventricular (LV) relaxation. (A) E, peak early diastolic transmitral flow (TMF) velocity. No significant difference was observed. (B) E/A, in which A indicates peak late diastolic TMF velocity. No significant difference was found. (C) e’ (annular velocity during early diastole) was significantly slower in patients with impaired relaxation than in those with preserved relaxation. (D) E/e’ was significantly greater in patients with impaired relaxation than in those with preserved relaxation.
obtained from biplane left ventriculography with the method proposed by Chapman et al.24

Statistical Analysis

Data are given as mean±SD or frequency (%). Comparisons between the 2 groups were performed with unpaired Student t-test. Differences in prevalence between the 2 groups were compared with the chi-squared test. Relationships between the 2 parameters were evaluated on univariate linear regression analysis. SPSS version 17.0 (SPSS, Chicago, IL, USA) was used for all statistical analysis. P<0.05 was considered statistically significant.

Results

Patient characteristics are listed in Table. No significant differences were found in age, gender, heart rate, mean blood pressure, comorbidities, or medication. A greater number of patients with impaired LV relaxation were taking diuretics and β-blockers compared to patients with preserved LV relaxation. Patients with impaired LV relaxation, compared to those with preserved LV relaxation, had a significantly longer LV relaxation time constant (53.8±4.5 ms vs. 40.8±5.0 ms, P=0.0001), significantly higher LV end-diastolic pressure (17.1±5.2 mmHg vs. 12.4±4.4 mmHg, P=0.0001), and significantly lower LVEF (63.6±9.0 vs. 68.7±8.2%, P=0.0002). Figure 1 shows representative TMF velocity waveforms recorded in a male patient with prior myocardial infarction and in a female patient with atypical chest pain. Although the TMF velocity waveforms were similar, the hemodynamic data were apparently different (Figure 1). The conventional and tissue Doppler echocardiographic indices were compared between the 2 groups (Figure 2). There were no significant differences between groups in E (60.9±14.2 cm/s vs. 60.3±14.2 cm/s, P=0.78), A (81.3±14.5 cm/s vs. 82.9±15.5 cm/s, P=0.49), E/A (0.8±0.1 vs. 0.7±0.1, P=0.35), or the deceleration time of the E wave (210.7±52.4 ms vs. 218.6±42.4 ms, P=0.28). In contrast, e’ was significantly slower in patients with impaired LV relaxation than in those with preserved LV relaxation (6.4±1.5 cm/s vs. 7.1±1.7 cm/s, P=0.009) and E/e’ was significantly higher in the former group than in the latter (9.8±2.7 vs. 8.8±2.3, P=0.006). The values of e’ and E/e’, however, considerably overlapped between the groups (Figure 2C,D). Another parameter reflecting LV diastolic dys-

function, LA volume index, was significantly greater in patients with impaired LV relaxation than in those with preserved LV relaxation (33.1±10.3 ml/m² vs. 27.4±10.1 ml/m², P=0.0008; Figure 3). Figure 4 shows that r was positively correlated with minimum LV pressure (r=0.65, P<0.0001) and with the LV pre-A wave pressure (r=0.65, P<0.0001). Both the minimum LV pressure (6.9±2.2 mmHg vs. 3.6±2.9 mmHg, P<0.0001) and the LV pre-A wave pressure (9.5±2.4 mmHg vs. 6.1±3.0 mmHg, P<0.0001) were significantly higher in patients with impaired than in those with preserved LV relaxation (Figure 5). Nevertheless, the difference between the LV pre-A and minimum LV pressures was not significantly different between the groups (2.6±1.4 mmHg vs. 2.5±1.5 mmHg, P=0.89; Figure 6).

Discussion

This study focused on patients with preserved LVEF, but who had an abnormal relaxation pattern in the TMF velocity waveform. We found that E and E/A were not significantly different between patients with impaired LV relaxation and those with preserved LV relaxation. Nevertheless, both the minimum LV pressure and LV pre-A pressure were significantly different between the groups. This could be explained by an increase in both pressures in parallel in patients with impaired LV relaxation.

Since the early 1980s, the TMF velocity waveform has been used in the evaluation of LV diastolic function.25 Because the TMF velocity waveform is determined by the pressure gradient across the mitral valve, E and A reflect the peak pressure gradients between the LA and LV chambers in early and late diastole, respectively.26,27 LV relaxation and mean LA pressure are mainly related to the pressure gradient in early diastole.25 In contrast, LV stiffness and LA contractile function mainly determine the pressure gradient during late diastole.27 Therefore, the TMF velocity waveform represents the overall diastolic behavior of the LV and LA. This waveform exhibits changes when LV diastolic function is aggravated.16,26,27 An abnormality of the LV relaxation is the earliest manifestation of LV diastolic dysfunction.8,9,16,26 An abnormal relaxation pattern in the TMF velocity waveform is observed in patients with hypertension, CAD, or cardiomyopathies, and also many older people without overt cardiac disease.13,14 Generally, older people without overt cardiac disease are expected to have slow LV relaxation compared to young healthy people, but the extent of deterioration in older healthy people may not be as critical as that observed in patients with cardiac disease.29 Thus, among subjects who have an abnormal relaxation pattern in the TMF velocity waveform, there may be no significant difference in E or E/A between patients with relatively impaired and those with relatively preserved LV relaxation. Accordingly, in the present study, the aim was to clarify the mechanism that produces similar TMF velocity waveforms in patients with apparently different LV relaxation performance.

The following observations have been reported in conscious, normal dogs and pacing-induced HF dogs.16 In normal dogs, a low minimum LV pressure was observed with fast LV relaxation and resulted in a larger pressure gradient between the LA and LV chambers in early diastole compared with dogs in early stage HF. In dogs with such a stage of HF, the minimum LV pressure increased in proportion to the deterioration of LV relaxation, but a significant increase in LV stiffness that would cause a considerable elevation of LA pressure was not occurring at this stage. Thus, a decrease in the pressure gradient between the LA and LV chambers in early diastole and a reduction in E were observed.16 Although an increase in LV stiffness can cause apparent in-

![Figure 3](image-url). Comparison of maximum left atrial volume index between patients with impaired (τ ≥48 ms) or preserved (τ <48 ms) left ventricular relaxation. The maximum left atrial volume index was significantly larger in patients with impaired relaxation than in those with preserved relaxation.
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pressure; this results in an unchanged pressure gradient between the LA and LV chambers in early diastole, similar to the gradient observed in patients with relatively preserved LV relaxation.

In the present study, we found that both minimum LV pressure and LV pre-A pressure, a surrogate of mean LA pressure, significantly increased in proportion to the deterioration of LV relaxation; as a result, E and the pressure gradient between the LA and LV chambers in early diastole were maintained at the same levels despite the worsening of LV relaxation performance.

In contrast, e′ was significantly slower and E/e′ was significantly greater in patients with impaired LV relaxation than in those with preserved relaxation. The values of e′ and E/e′, however, were apparently overlapping between groups (Figure 2C,D); therefore, patients with impaired LV relaxation could not be identified based on e′ or E/e′. Similarly, LA volume index, which has been acknowledged to reflect LV dia-

Increases in LA pressure and in the pressure gradient between the LA and LV chambers in early diastole, this mechanism takes effect only in the advanced phase of HF, and it produces a much faster E than that observed in early stage HF, causing a phenomenon called “pseudonormalized” or “restrictive” TMF pattern.16,28

In patients with an abnormal relaxation pattern in the TMF velocity waveform, but with relatively preserved (not normal) LV relaxation, when a small increase in the minimum LV pressure occurs and the LA pressure remains at its near original level, the pressure gradient between the LA and LV chambers will be decreased compared with normal subjects; the transmitral E, then, will also be reduced. In patients with an abnormal relaxation pattern and with relatively impaired LV relaxation, the worsened LV relaxation provokes a significant increase in the minimum LV pressure, and a similar level of elevation occurs in the LA pressure; this results in an unchanged pressure gradient between the LA and LV chambers in early diastole, similar to the gradient observed in patients with relatively preserved LV relaxation. In the present study, we found that both minimum LV pressure and LV pre-A pressure, a surrogate of mean LA pressure, significantly increased in proportion to the deterioration of LV relaxation; as a result, E and the pressure gradient between the LA and LV chambers in early diastole were maintained at the same levels despite the worsening of LV relaxation performance.

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Figure 4. Left ventricular (LV) relaxation time constant (τ) is positively correlated with LV pressures. (A) Minimum LV pressure; (B) LV pre-A pressure. Significant positive correlations were observed in both relationships.

Figure 5. Comparisons of left ventricular (LV) pressures between patients with impaired (τ ≥48ms) and those with preserved (τ <48ms) relaxation. (A) minimum LV pressure; (B) LV pre-A pressure. Both pressures were significantly higher in patients with impaired relaxation than in those with preserved relaxation.
Conclusions

In patients with preserved LVEF, parallel elevations of the minimum LV and the LV pre-A pressures resulted in a similarly abnormal TMF velocity pattern in patients with relatively impaired and those with relatively preserved LV relaxation. The present results suggest that it would be difficult to use E or E/A for non-invasively determining the potential for developing HFpEF in patients with impaired LV relaxation pattern in the TMF velocity waveform; furthermore, it may also be difficult to use $e'$, $E/e'$, or LA volume index as a clear surrogate of time constant (r) in patients with preserved LVEF.

References


Study Limitations

We were not able to measure Doppler echocardiographic parameters simultaneously with the invasive data but we did measure on the day before cardiac catheterization. This may be a limitation of this study, but the reliability of comprehensive Doppler echocardiographic parameters obtained in the supine position during cardiac catheterization may be restricted. In addition, if an echo cardiographer tries to obtain non-invasive data simultaneously with the invasive data in the cardiac catheterization laboratory, he or she might access the LV pressure wave tracings whether he or she wanted to or not. Thus, we believe that the present data are still reliable despite the limitation. Another limitation of this study was that most of the present patients had current or suspected CAD, therefore the present results might not apply to healthy, old subjects with an abnormal relaxation pattern in the TMF velocity waveform. In this respect, we previously reported that patients with atrial dysynchropathy but without significant coronary artery stenosis or LV wall motion abnormality had relatively shorter LV relaxation time constant $r$ and relatively faster $e'$, although they had an abnormal relaxation pattern in the TMF velocity waveform. 

In patients with preserved LVEF, parallel elevations of the minimum LV and the LV pre-A pressures resulted in a similarly abnormal TMF velocity pattern in patients with relatively impaired and those with relatively preserved LV relaxation. The present results suggest that it would be difficult to use E or E/A for non-invasively determining the potential for developing HFpEF in patients with impaired LV relaxation pattern in the TMF velocity waveform; furthermore, it may also be difficult to use $e'$, $E/e'$, or LA volume index as a clear surrogate of time constant (r) in patients with preserved LVEF.


