Elevation of the ratio of transmitral E velocity to early diastolic mitral annular velocity continues even after recovery from acute stage in patients with diastolic heart failure

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\textbf{KEYWORDS}
Diastolic heart failure; Hypertension; Tissue Doppler imaging; Pulsed Doppler left ventricular inflow; Plasma BNP level

\textbf{Summary}
\textbf{Background:} Clinical features of diastolic heart failure (DHF) have not been well characterized, leading to an inaccuracy in the diagnosis of DHF. Recently, the ratio of transmitral E velocity to early diastolic mitral annular velocity (E/E') has been shown to be useful to assess LV filling pressure.

\textbf{Purpose:} We tested the hypothesis that persistent elevation of E/E' ratio is one of the characteristics of patients with DHF.

\textbf{Methods:} Candidates of this study were 89 patients who presented to the emergency department because of acute pulmonary congestion. Those with an ejection fraction of >45% on admission comprised the DHF group (n = 18). A control group consisted of consecutive 30 hypertensive patients with an ejection fraction of >45%. Doppler echocardiographic data were obtained with plasma BNP measure in the chronic stage >6 months after the emergent admission.

\textbf{Results:} The E/E' ratio was higher in the DHF group than in the control group (16.7 ± 2.8 vs. 9.4 ± 3.3, p < 0.01). BNP level was also elevated in the DHF group.

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Conclusion: A persistent elevation of E/E' ratio may be an indicator of patients with or at risk of DHF among subjects with preserved systolic function independent of LV hypertrophy.

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Introduction

The clinical syndrome of congestive heart failure occurs over a broad range of underlying left ventricular (LV) systolic function [1—4]. Heart failure with normal or minimally impaired systolic function is attributed to diastolic dysfunction and is termed diastolic heart failure (DHF). Its principal underlying cardiovascular disease is hypertensive heart disease, and there is a growing interest in this type of heart failure. Although non-invasive evaluation of diastolic function by Doppler echocardiographic technique has been widely used in everyday clinical settings [5—7], assessment with the conventional Doppler echocardiographic indices has many limitations in subjects with preserved systolic function [8,9]. The ratio of the early transmitral filling velocity (E) to early diastolic mitral annular velocity (E') has been proposed as an index to assess LV filling pressure [10—13]. LV filling pressure is principally determined by LV diastolic function; however, it may change with the administration of diuretics and/or vasodilators even without the alteration of LV diastolic function. Thus, the feasibility of its use in the diagnosis of DHF remains to be clarified. The aim of this study is to elucidate our hypothesis that persistent elevation of the E/E' ratio is one of the characteristics of patients with DHF.

Methods

Selection of patients

To enroll patients with a history of definitive overt DHF (DHF group) and to minimize the effects of inaccurate diagnosis of DHF, the institution’s medical records identified patients who presented to the emergency department of our hospital due to definitive pulmonary edema with preserved systolic function between January 2003 and April 2006. During this period, 89 patients presented with an acute onset of dyspnea, respiratory distress, and pulmonary rale due to pulmonary congestion as confirmed by chest radiography in the absence of acute coronary syndrome. Of these patients, those who met the following entry criteria were identified: (1) echocardiographic confirmation of ejection fraction (EF) >45% on admission; and (2) relief of the symptoms by treatment with diuretics and/or vasodilators after the emergent admission. Patients with congenital heart disease, severe valvular disease, atrial fibrillation, or old myocardial infarction or those who were not followed up in our outpatient clinics were excluded. Among the patients who met these criteria, a DHF group in this study comprised 18 patients, who agreed with the participation in this study. All of these patients were stable when they participated in this study and had hypertension as an underlying disease. There was no significant change in their electrocardiogram and no increase in plasma levels of troponin T or in the MB isoenzyme of creatine phosphokinase at and after the emergent admission. As a control group, 30 consecutive hypertensive patients referred for echocardiography laboratory who met all of the following criteria were included: (1) no symptoms of heart failure up to the study enrollment; (2) EF > 45%. All participants gave informed consent for this study.

Study protocol

Patients of the DHF and control groups were referred for echocardiographic examination to record both transmitral flow velocity curve and tissue Doppler imaging of the mitral annulus in the chronic stage more than 6 months after the admission. With patients in the left lateral decubitus position, conventional transthoracic two-dimensional and Doppler echocardiography were performed with a commercially available echocardiographic machine (SONOS 5500, Philips) with a broadband (1—3 MHz) phased array transducer as previously described [14]. EF was calculated by a modification of the method of Quinones et al. [15]. The pulsed Doppler transmitral flow velocity curve was recorded to measure a ratio of peak mitral E wave velocity to peak mitral A wave velocity (E/A ratio) and the deceleration time of the mitral E wave velocity (DT) [14]. TEI index was also measured [16]. The apical four-chamber view was used to obtain tissue Doppler imaging of the mitral annulus. A sample volume was positioned at the septal side of the mitral annulus to record the spectral signal of the early diastolic mitral
Figure 1  Chest radiography (left panel), transmitral Doppler velocity signals (upper right panel), and tissue Doppler imaging (lower right panel) in a patient with diastolic heart failure in the chronic stage. The E/E′ ratio showed high score despite good recovery course from heart failure with medical treatment. EF = 51%, E/A = 1.1, E/E′ = 19.5 E′, early diastolic mitral annular velocity; A′, late diastolic mitral annular velocity.

annular velocity (E′) (Fig. 1). Plasma BNP level was measured at the same time as previously described [14]. Medications were not withheld before this study for ethical reasons.

Statistical analysis

Values are expressed as mean ± S.D. All statistical analyses were performed using a commercially available statistical software (STATVIEW version 5.0, SAS Institute Inc., Cary, NC, USA). Differences between the two groups were assessed using the unpaired t test. Categorical variables were compared by use of χ² tests. Results were considered significant at a probability value of less than 0.05.

Results

Blood pressure was 148–220 (mean 167) mmHg, heart rate was 92–145 (mean 111) bpm, and EF was 46–69 (mean 56.4) % in the DHF group at admission. Seven of eighteen patients showed severe pulmonary edema and others showed moderate pulmonary congestion. Patients’ characteristics of the DHF and control groups at the time of the study enrollment are summarized in Table 1. There was no significant difference in age, gender, blood pressure, heart rate, or percentage of high-grade mitral regurgitation between the groups. The frequency of the usage of 2 or more of diuretics, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and beta-blocker was not different between the groups. There was no significant difference in wall thickness of the interventricular septum and LV posterior wall, peak E wave velocity, E/A ratio, DT, and TEI index between the groups, either. LV end-diastolic and end-systolic dimensions and left atrial dimension were significantly larger in the DHF group than in the control group. Despite a similar distribution in LV hypertrophy, the E/E′ ratio was higher in the DHF group than in the control group (16.7 ± 2.8 vs. 9.4 ± 3.3, p < 0.01) (Fig. 2). Although plasma BNP levels were also significantly higher in the DHF group than in the control group (209 ± 120 vs. 31 ± 5 pg/mL, p < 0.01) (Fig. 2), there was no correlation between the E/E′ ratio and plasma BNP level in the DHF group (Fig. 3). Eleven of the eighteen DHF patients represented BNP < 100 pg/ml, but 10 of the 11 patients showed E/E′ > 8, which is a minimum cut-off value for detecting patients with elevated LV filling pressure [17].

Discussion

Abnormal LV diastolic function has been recognized as a possible cause of congestive heart failure in patients with normal EF [18]. DHF occurs in a high
Elevation of the ratio of transmitral $E$ velocity to early diastolic mitral annular T

Table 1

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<tr>
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<th>Control</th>
<th>DHF</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59.8 ± 15.0</td>
<td>64.8 ± 15.9</td>
</tr>
<tr>
<td>Women (%)</td>
<td>53</td>
<td>61</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>138 ± 19</td>
<td>133 ± 18</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70 ± 14</td>
<td>73 ± 11</td>
</tr>
<tr>
<td>Mitral regurgitation (&gt; grade II) (%)</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Medication: 2 or more drugs of diuretics, ACE-I, ARB, beta-blocker (%)</td>
<td>53</td>
<td>78</td>
</tr>
<tr>
<td>Left ventricular end-diastolic dimension (mm)</td>
<td>49.0 ± 4.7</td>
<td>54.1 ± 5.4*</td>
</tr>
<tr>
<td>Left ventricular end-systolic dimension (mm)</td>
<td>30.2 ± 3.2</td>
<td>37.2 ± 6.5*</td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
<td>38.2 ± 5.2</td>
<td>41.9 ± 4.8*</td>
</tr>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td>9.6 ± 1.5</td>
<td>9.2 ± 1.5</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness (mm)</td>
<td>9.6 ± 1.5</td>
<td>9.4 ± 1.4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>68.1 ± 4.3</td>
<td>58.8 ± 9.4*</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.92 ± 0.38</td>
<td>0.80 ± 0.22</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>67.7 ± 17.0</td>
<td>66.2 ± 19.3</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>206 ± 40</td>
<td>219 ± 41</td>
</tr>
<tr>
<td>TEI index</td>
<td>0.40 ± 0.10</td>
<td>0.43 ± 0.17</td>
</tr>
<tr>
<td>$E'$ (cm/s)</td>
<td>6.4 ± 1.7</td>
<td>5.1 ± 1.4*</td>
</tr>
<tr>
<td>$A'$ (cm/s)</td>
<td>8.5 ± 1.8</td>
<td>7.9 ± 1.5</td>
</tr>
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ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. *p < 0.05 vs. the control group.

proportion of patients with heart failure and causes significant mortality and morbidity [1,2,19,20]. Its prevalence has increased without an improvement in the prognosis as the population becomes older [21]. However, diagnostic criteria for DHF have not been established. The current consensus is that the assessment of LV diastolic function with the analysis of the transmitral flow velocity curves has many limitations [8,9,22], particularly in patients with preserved EF [23,24]. In fact, diagnostic criteria for diastolic dysfunction proposed in several previous studies are not consistent [25–28]. Thus, objective information regarding clinical characteristics of DHF is required to provide a reliable diagnosis.

To minimize effects of such inconsistency of the diagnosis on the current study, the DHF group in this study consisted of patients who met the following criteria: (1) a history of an acute onset of dyspnea, respiratory distress, and pulmonary rale due to pulmonary congestion, as confirmed by chest radiography; and (2) echocardiographic confirmation of preserved EF on admission. Our previous study [14]

Figure 2. The $E/E'$ ratio and plasma BNP levels in the control and DHF Group. The $E/E'$ ratio was higher in the DHF group than in the control group (left panel). Plasma BNP level was higher in the DHF group than in the control group (right panel).
showed that LV chamber dimension, LV mass index, and the parameters derived from the transmitral flow velocity curves in the DHF group were not different from those in the control group consisting of hypertensive patients who had been asymptomatic. That report additionally showed that plasma BNP level remained elevated in the DHF group even after symptoms of heart failure were controlled to NYHA class I. The current study expanded our previous study by demonstrating that E/E′ ratio was significantly elevated in DHF patients compared to asymptomatic hypertensive patients.

In the past decade, an alternative Doppler method, namely tissue Doppler imaging, has been proposed, and the E/E′ ratio has been shown to be useful in the assessment of the LV filling pressure [10—12]. Nagueh et al. [11] showed that E/E′ correlated well with pulmonary capillary wedge pressure (PCWP). Ommen et al. [17] compared E/E′ with the directly measured LV filling pressure and reported that E/E′ > 15 indicates a raised LV filling pressure. LV filling pressure is principally determined by LV diastolic function. However, it can be changed by pharmacological intervention without the alteration of LV diastolic function, and thus, there has been an argument against the measure of LV diastolic function with E/E′ ratio. We showed that the E/E′ ratio is still elevated in patients with DHF even after the hemodynamic deterioration has been improved with medications. Recent studies have addressed the prognostic implication of the E/E′ ratio in patients with various cardiac diseases [29—33]. Okura et al. [34] showed that the E/E′ ratio is the strongest independent echocardiographic prognostic predictor in patients with non-valvular atrial fibrillation. The relationship between serial changes in the E/E′ ratio and prognosis in DHF patients needs further investigation.

The E/E′ ratio did not correlate with plasma BNP level in this study. Troughton et al. reported that significant relationships were noted for BNP with the E/E′ ratio [35], but their study subjects were patients with reduced EF. As Fig. 3 shows, most DHF patients with BNP < 100 pg/ml represented E/E′ > 8, which is a minimum cut-off value for detecting patients with elevated LV filling pressure [17]. Although we previously reported that the elevation of BNP is one characteristic for DHF patients [14], this study suggests that the elevation of E/E′ ratio might be more specific to DHF patients compared to BNP, and further clinical studies are awaited to clarify which one is more sensitive to DHF. High E/E′ ratio 6 months after a congestive heart failure event might indicate the remaining high left atrial pressure is secondary to LV diastolic dysfunction. E′ may be more appropriate to assess LV diastolic function considering its relation with the time constant of LV relaxation [36], and this study also showed lower E′ in the DHF group than in the control group in spite of the lack of the difference in E (Table 1). Therefore, the increase in E/E′ ratio in the DHF group is at least partly attributed to the progressive impairment of LV relaxation [36]. However, another component of diastolic function, LV stiffness which plays a crucial role in the transition from the compensatory hypertrophic stage to DHF stage in hypertensive heart disease [37], cannot be assessed with E′, and thus, we may have to assess both E′ and E/E′.

There are some limitations of this study. First, the number of the study subjects is not large. This is because of the current inaccuracy of the diagnosis of DHF. To enroll only the definitive DHF patients in this study, the DHF group consisted of those who had a definitive history of acute pulmonary congestion on admission without reduced EF and were still followed up by our outpatient clinics. However, the small number of the subjects might be responsible for the different results from the previous reports in some data such as LV end-diastolic dimension or EF, and could not allow us to clarify the characteristics of DHF enough in this study. Second, it is unclear whether the current findings can be extrapolated to patients with mild symptoms due to diastolic dysfunction and without a history of acute pulmonary congestion. However, the current results suggest that a future prospective study with a large number of subjects to analyze the utility of E/E′ as a diagnostic or predictive tool for DHF is promising.

Conclusion

We found the E/E′ ratio was still high even at the chronic stage of DHF after the hemodynamics and symptoms were stabilized with pharmacological
interventions. In particular, $E/E'$ was still elevated even after medications decreased BNP below 100 pg/ml. Considering a significant correlation of $E/E'$ with LV filling pressure and a close relation between LV filling pressure and LV stiffening [36], the remaining elevation of $E/E'$ after enough medications may indicate increased LV stiffness. The result of this study suggests that the elevation of the $E/E'$ ratio is an index of patients with or at risk of DHF among subjects with preserved LV systolic function.

References


