Introduction

With respect to the recent clinical issue of isolated left ventricular (LV) diastolic dysfunction, many studies have reported that 30% to 40% of patients with congestive heart failure (CHF) have preserved LV systolic function [1-3]. When pulmonary congestion, that is, an increase in left atrial pressure, is observed in such patients, the transmitral flow (TMF) velocity shows a pseudonormalized or restrictive pattern in many of the patients [4,5]. However, in clinical practice, the peak early diastolic TMF velocity (E) is lower than the peak atrial systolic TMF velocity (A) (E/A<1) in most patients with LV diastolic dysfunction, suggesting relaxation abnormalities. Therefore, it is difficult to predict whether isolated diastolic dysfunction will cause CHF in the future in individual patients with E/A<1. Douglas [6] indicated that the left atrial size reflects the history of LV diastolic dysfunction, and that the level of left atrial enlargement is associated with the serum HbA1c concentration in patients with diabetes. The development of ultrasonic strain imaging has facilitated the evaluation of regional myocardial systolic and diastolic function and is not influenced by whole heart motion or tethering [7]. In the present study, we divided patients, in whom LV pump function was maintained with TMF showing a relaxation abnor-
mality pattern (E/A<1), into 2 groups either with or without a history of CHF in a selected common disease cohort and compared the clinical and echocardiographic parameters between the 2 groups.

**Methods**

**Patient population**

Study patients were recruited from the outpatient cardiovascular clinic of our hospital and those routinely receiving medication for hypertension, diabetes, hypercholesterolemia, and/or coronary artery disease without signs of significant stenosis or obstruction of the coronary arteries or LV asynergy. We identified 72 consecutive patients who had been referred for a comprehensive transthoracic echocardiographic examination between January 2006 and April 2007. On routine echocardiograms, they had an early diastolic to atrial systolic TMF velocity ratio (E/A) <1 on pulsed wave Doppler echocardiography and preserved LV systolic function, defined as an ejection fraction ≥50% by the modified Simpson’s method for 2-dimensional echocardiography.

Patients were excluded if they had any of the following: 2+ or greater mitral regurgitation, aortic regurgitation, any degree of valvular stenosis, overt coronary artery disease, hypertrophic cardiomyopathy, atrial fibrillation or other major arrhythmias, left bundle branch block, chronic kidney disease (serum creatinine ≥1.0 mg/dl), pericardial disease, right ventricular failure, chronic obstructive pulmonary disease, or inadequate acoustic windows.

The patients were divided into 2 groups based on the presence or absence of previous evidence of new-onset CHF: 7 patients with CHF (CHF group) and 65 patients with no CHF (control group). The 7 patients met the criteria for diagnosis of CHF established in the Framingham study [8]. Briefly, major criteria included paroxysmal nocturnal dyspnea or orthopnea, neck vein distention, rales, cardiomegaly, acute pulmonary edema, the presence of a third heart sound, increased venous pressure (>16 cm H2O) and hepatojugular reflux. Minor criteria included dependent edema, night cough, exertional dyspnea, hepatomegaly, pleural effusion, and tachycardia (≥120 beats/min). For inclusion, 2 major or 1 major plus 2 minor criteria were required.

All patients gave written informed consent, and the study was approved by the ethics committee of the institution involved.

**Echocardiography**

On the M-mode echocardiogram, the LV end-diastolic dimension (LVDd) and maximal left atrial dimension (LAD) were measured. The LV mass was determined using the following equation [9]: 
\[
LV \text{ mass} = 1.04 \times \left( \left[ LVDd + PWth + VSth \right]^3 - LVDd^3 \right) - 13.6,
\]
where PWth is end-diastolic thickness of the LV posterior wall, and VSth is end-diastolic thickness of the ventricular septum. The LV mass index was determined by dividing each measurement by the body surface area. LV end-diastolic and end-systolic volumes were calculated from the apical 2- and 4-chamber views using a modified Simpson’s method. LV ejection fraction was calculated as: 
\[
(EDV - ESV)/EDV \times 100,
\]
where EDV is the end-diastolic volume, and ESV is the end-systolic volume.

The peak early diastolic velocity (E), the peak atrial systolic velocity (A), and the E/A ratio were assessed from the TMF velocity pattern. The mitral annular motion velocity was recorded in the LV posterior wall site in the apical LV long-axis view using the pulsed Doppler method. The peak systolic motion velocity (Sw), peak early diastolic motion velocity (Ew), peak atrial systolic motion velocity (Aw), and E/Ew were determined [10]. The acoustic power and filter frequencies of the ultrasound system were set to the lowest values possible, and the sample volumes (width of approximately 8 mm) were set at the mitral annulus of the LV posterior wall.

Strain imaging data were collected from the transthoracic approach using an ultrasound system (Power Vision 6000, Toshiba Medical Systems, Japan) equipped with a 2.5-MHz transducer, and were acquired at a frame rate of 68 frames/s and a sector angle of 30 degrees. The apical 4-chamber views were used to evaluate the ventricular septal and LV lateral walls (Figure 1). The measurements were taken in the longitudinal direction from the inner half of both the LV walls, and mean values for the peak systolic, early diastolic, and atrial systolic strain rates (s-SR, e-SR, and a-SR, respectively) were used for the comparison between the 2 groups. Semiautomated tissue tracking kept the regions of interest overriding the subendocardium throughout the cardiac cycle. Three consecutive heart cycles were recorded during brief breath holding. Image analysis was performed offline on a personal computer workstation using custom analysis software (ApliQ, Toshiba Medical Systems, Japan).
Statistical analysis

Values are expressed as the mean ± SD. Differences in the mean values between the 2 groups were compared using the Mann-Whitney U test. A p value less than 0.05 was considered statistically significant.

Results

Of the 72 patients, the presence of previous CHF was confirmed in 7 patients (9.7%). The CHF group tended to be older and have more hypertension and/or diabetes, although the differences were not significant compared to the control group (Table 1). There were no significant differences in the incidence of gender or coronary heart disease. The LV mass index was significantly greater, and the maximal left atrial dimension was markedly greater in the CHF group than in the control group (Table 2). The s-SR and e-SR were significantly lower in the CHF group than in the control group. The CHF group tended to have a lower LVEF, Sw, and Ew compared to the control group. There was no significant difference in E/Ew between the 2 groups.

Discussion

The recent widespread use of pulsed Doppler echocardiography has facilitated TMF and pulmonary venous flow (PVF) velocity recording in clinical practice, and the important role of the left atrium in the pulmonary vein-left atrium-LV relationship has been recognized [11]. According to previous studies [1-3], LV

Table 1. Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 65)</th>
<th>CHF group (n = 7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 10</td>
<td>76 ± 15</td>
<td>ns</td>
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<tr>
<td>Men/Women</td>
<td>34 / 31</td>
<td>4 / 3</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 3 (18 – 29)</td>
<td>23 ± 3 (20 – 27)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12</td>
<td>4</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>26</td>
<td>4</td>
<td>ns</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8</td>
<td>2</td>
<td>ns</td>
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CHF, congestive heart failure; ns, not significant.
systolic function is normal in 30% to 40% of patients with CHF. Therefore, it is important to evaluate Doppler parameters of LV diastolic function to determine the pathogenesis of pulmonary congestion in patients with left heart failure [12,13].

CHF in the presence of isolated LV diastolic dysfunction results from a single hemodynamic mechanism. However, the underlying pathophysiology may vary [14]. Risk factors for diastolic heart failure include advanced age [2,15], female gender [2,16], hypertension [17,18], obesity and/or diabetes [13,15], and vascular stiffness [19,20]. However, in the absence of these risk factors, the incidence of isolated diastolic heart failure is low even in elderly persons [21]. Furthermore, a small LV chamber, concentric LV hypertrophy, and relaxation abnormalities may be involved in the pathogenesis of diastolic heart failure [22]. To maintain normal cardiac output under these conditions, a high LV filling pressure is required, resulting in pulmonary congestion [23].

Some studies have reported that the LV ejection fraction is preserved in patients with isolated diastolic heart failure [1-3]. However, recent studies using tissue velocity and ultrasonic strain imaging have demonstrated that systolic LV myocardial contractile force is impaired despite a normal ejection fraction [24-26]. In the present study, the LV mass index was significantly greater, and the LV ejection fraction, systolic and early diastolic wall motion velocities tended to be lower in the CHF group than in the control group, although there were no significant differences. This is consistent with the results of previous studies. In addition, systolic and early diastolic strain rates of the LV walls were significantly lower, and maximal left atrial dimension was markedly increased in the CHF group.

To evaluate the prognosis of various myocardial diseases, many Doppler parameters, such as a restrictive pattern for the TMF, [12, 13] blunted systolic wave of the PVF [27], an increase in difference in duration of PVF and TMF velocity during atrial contraction [28], and decreases in early diastolic [29] and atrial systolic [30] mitral annular motion velocities using tissue velocity imaging, all measured at specific points or during a short period, have been used. However, it is very difficult to predict the onset of CHF using these parameters in patients with no increase in left atrial pressure (E/Ew<10) [10,31] and an E/A ≤ 1, under the conditions such as our common disease cohort.

A recent review has pointed out that the left atrial size reflects the long-term history of LV diastolic dys-

<table>
<thead>
<tr>
<th>Control group (n = 65)</th>
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</tr>
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<tbody>
<tr>
<td><strong>LAD (mm)</strong></td>
<td>35 ± 5 (21 – 46)</td>
<td>41 ± 7 (31 – 50)</td>
</tr>
<tr>
<td><strong>LVDd (mm)</strong></td>
<td>45 ± 6 (40 – 56)</td>
<td>52 ± 7 (45 – 59)</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>74 ± 9 (50 – 86)</td>
<td>67 ± 7 (50 – 80)</td>
</tr>
<tr>
<td><strong>LVMI (g/m²)</strong></td>
<td>102 ± 39 (46 – 182)</td>
<td>168 ± 52 (108 – 240)</td>
</tr>
<tr>
<td><strong>E / A</strong></td>
<td>0.8 ± 0.2 (0.3 – 1.0)</td>
<td>0.8 ± 0.2 (0.5 – 1.0)</td>
</tr>
<tr>
<td><strong>Sw (cm/sec)</strong></td>
<td>11.0 ± 3.8 (5.3 – 23.5)</td>
<td>9.0 ± 3.8 (5.8 – 15.7)</td>
</tr>
<tr>
<td><strong>Ew (cm/sec)</strong></td>
<td>9.8 ± 3.1 (4.4 – 17.4)</td>
<td>8.2 ± 3.9 (3.3 – 14.8)</td>
</tr>
<tr>
<td><strong>Aw (cm/sec)</strong></td>
<td>13.2 ± 3.6 (7.6 – 28.9)</td>
<td>11.7 ± 2.5 (6.9 – 14.5)</td>
</tr>
<tr>
<td><strong>E / Ew</strong></td>
<td>6.5 ± 3.0 (4.0 – 16.6)</td>
<td>6.5 ± 3.8 (4.6 – 12.4)</td>
</tr>
<tr>
<td><strong>s-SR (s⁻¹)</strong></td>
<td>-2.2 ± 0.9 (-0.5 – -3.2)</td>
<td>-1.5 ± 1.2 (-0.5 – -3.6)</td>
</tr>
<tr>
<td><strong>e-SR (s⁻¹)</strong></td>
<td>1.9 ± 0.9 (0.5 – 3.5)</td>
<td>1.2 ± 1.0 (0.6 – 3.0)</td>
</tr>
<tr>
<td><strong>a-SR (s⁻¹)</strong></td>
<td>2.0 ± 0.9 (0.5 – 2.9)</td>
<td>1.6 ± 1.3 (0.6 – 3.9)</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; LAD, maximal left atrial dimension; LVDd, end-diastolic left ventricular diameter; LVEF, left ventricular ejection fraction; BMI, body mass index; LVMI, left ventricular mass index; E/A, peak velocity ratio of early diastolic to atrial systolic wave in the transmitral flow; Sw, peak systolic velocity of the mitral annulus; Ew, peak early diastolic velocity of the mitral annulus; Aw, peak atrial systolic velocity of the mitral annulus; E/Ew, peak early diastolic velocity of the transmitral flow to peak early diastolic velocity of the mitral annulus; s-SR, peak systolic strain rate of the left ventricular wall; e-SR, peak early diastolic strain rate of the left ventricular wall; a-SR, peak atrial systolic strain rate of the left ventricular wall; ns, not significant.
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function [6]. Other studies reported a close relationship between the severity of LV diastolic failure and LV hypertrophy [22, 32] or left atrial size [33]. Furthermore, the left atrial volume [34] in patients with isolated diastolic failure and left atrial dimension [35] in patients with hypertrophic cardiomyopathy are considered to be important parameters for predicting prognosis.

The results of the present study suggest that LV hypertrophy, left atrial dimension, which can be measured using a simple method, and systolic and early diastolic strain rates of the LV walls determined by ultrasonic strain imaging, are useful for predicting the onset of CHF in patients with isolated LV relaxation abnormalities (E/A<1) and preserved LV pump function (EF ≥ 50%).

Limitations

This was a retrospective study of 72 patients with LV relaxation abnormalities in a selected common disease cohort, which excluded hypertrophic cardiomyopathy and/or systemic heart disease. Also, the number of patients included in the present study was not large, making it susceptible to bias. The present study may therefore be insufficiently powered.

References

left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J 2003; 24: 320-8.


