Left ventricular (LV) diastolic dysfunction carries a substantial risk for the subsequent development of heart failure and reduced survival, even when it is asymptomatic. Thus, the early identification of LV diastolic dysfunction in patients without overt symptoms may provide an opportunity to manage the underlying cause and prevent progression to diastolic heart failure. Quantitative and precise elucidation of LV diastolic function requires cardiac catheterization of the left ventricle, but it is invasive and potentially complex. In contrast, elevated plasma brain natriuretic peptide (BNP) level and tissue Doppler imaging indexes provide powerful incremental assessment of LV diastolic function. Accordingly, the aim of this study was to clarify whether these methodologies could identify LV diastolic dysfunction without heart failure in 280 patients with preserved LV ejection fractions (≥50%) who underwent echocardiography and cardiac catheterization for the evaluation of coronary artery disease. Patients were classified into 2 groups, those with diastolic dysfunction (τ ≥48 ms; n = 91) and those with normal diastolic function (τ <48 ms; n = 189). Plasma BNP ≥22.4 pg/ml, an unexpectedly low value, had sensitivity of 74.7% and specificity of 60.8% for identifying isolated LV diastolic dysfunction; the combined use of BNP ≥22.4 pg/ml and mitral annular velocity during early diastole <7.4 cm/s had relatively low sensitivity of 44.0% but high specificity of 86.8%. In conclusion, using plasma BNP level and with the combination of BNP level and mitral annular velocity during early diastole, invasively proved isolated LV diastolic dysfunction without heart failure could be identified in patients with coronary artery disease. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:87–91)
LV pressure waves were obtained with a catheter-tipped micromanometer (SPC-454D; Millar Instruments, Inc., Houston, Texas) and recorded on a polygraph system (RMC-3000; Nihon Kohden, Inc., Tokyo, Japan) and on a digital data recorder (NR-2000; Keyence, Osaka, Japan), as we have reported elsewhere. From the recorded pressure waves, a time constant, \( \tau \), of decrease in LV pressure was computed by applying a monoexponential fitting with zero asymptote to LV pressure decay. LV end-diastolic pressure was also determined. LV end-systolic and end-diastolic volumes were obtained from biplane left ventriculography using the method proposed by Chapman et al. These volumes in each patient were corrected by each body surface area and were expressed as LV end-systolic and end-diastolic volume indexes.

Patients were divided into 2 groups on the basis of their LV early diastolic function, that is, whether they had time constant \( \tau \) values of LV relaxation \( \geq 48 \) or \( < 48 \) ms. This threshold value of 48 ms to distinguish LV early diastolic dysfunction was derived from the report by the European Study Group on Diastolic Heart Failure.

Venous blood samples (6 ml) for the assay of plasma BNP concentration were collected from the right femoral veins of all patients at cardiac catheterization. Blood samples were centrifuged and then stored at \(-70^\circ\text{C}\). Plasma BNP concentrations were measured with an immunoradiometric assay specific for human BNP (Shionoria; Shionogi Company, Ltd., Osaka, Japan). With this method, the minimal detectable quantity of human BNP is 2 pg/ml.

Table 1

Comparisons of clinical characteristics and hemodynamic data between patients with normal left ventricular diastolic function and those with isolated diastolic dysfunction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Diastolic Function (( \tau &lt; 48 ) ms)</th>
<th>Isolated Diastolic Dysfunction (( \tau \geq 48 ) ms)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>131/58</td>
<td>74/17</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.3 ± 8.5</td>
<td>67.4 ± 8.2</td>
<td>0.30</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.1 ± 3.3</td>
<td>24.8 ± 3.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.0 ± 9.7</td>
<td>63.1 ± 9.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>95.3 ± 11.0</td>
<td>94.4 ± 11.4</td>
<td>0.53</td>
</tr>
<tr>
<td>( \tau ) (ms)</td>
<td>39.6 ± 5.2</td>
<td>54.0 ± 6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>68.8 ± 8.5</td>
<td>64.8 ± 8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic volume index (ml/m²)</td>
<td>76.8 ± 15.7</td>
<td>86.0 ± 17.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic volume index (ml/m²)</td>
<td>24.2 ± 9.4</td>
<td>30.5 ± 11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>12.3 ± 4.2</td>
<td>17.1 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41.9%</td>
<td>42.2%</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29.8%</td>
<td>28.9%</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Data are expressed as frequency, mean ± SD, or percentage.

Figure 1. Comparisons of plasma BNP level (A) and Ea (B) between patients with isolated LV diastolic dysfunction and those with normal LV diastolic function. BNP level was significantly higher and Ea significantly lower in patients with isolated LV diastolic dysfunction than in those with normal diastolic function. (A) Box defines the interquartile range, with the median indicated by the crossbar. The error bars indicate the 5th and 95th percentiles of distribution. (B) Mean and standard deviation are shown.
Results

Table 1 lists the baseline characteristics of the patients. No significant difference was found in age, heart rate, body mass index, or mean blood pressure between patients with isolated LV diastolic dysfunction and those with normal LV diastolic function. LV ejection fractions were significantly higher in patients with normal LV diastolic function than in those with isolated LV diastolic dysfunction. LV end-diastolic pressure were significantly greater in patients with isolated LV diastolic dysfunction than in the group with normal LV diastolic function. Slight LV remodeling was observed in patients with isolated LV diastolic dysfunction, even if they had preserved LV systolic function.

Figure 1 shows a comparison of BNP level and Ea between the groups. Plasma BNP level was significantly higher in patients with isolated LV diastolic dysfunction than in those with normal diastolic function (median 39.2 pg/ml, interquartile range 21.2 to 75.5, vs median 16.9 pg/ml, interquartile range 6.9 to 32.8; p < 0.001). Ea was significantly less (7.1 ± 2.1 vs 8.6 ± 2.6 cm/s, p < 0.001) in patients with isolated LV diastolic dysfunction than in those with normal diastolic function. Logarithmically transformed plasma BNP level was weakly but significantly correlated with the time constant τ of LV relaxation (r = 0.35, p < 0.001), and Ea was also weakly but significantly correlated with τ (r = −0.23, p < 0.001) in this patient cohort.

Receiver-operating characteristic analysis indicated that plasma BNP level and Ea had significant potential for identifying isolated LV diastolic dysfunction. The areas under the curves for BNP level and Ea to detect isolated LV diastolic dysfunction most precisely using each parameter. A BNP level ≥22.4 pg/ml and an Ea of 7.4 cm/s were determined as the cut-off values for identifying isolated LV diastolic dysfunction most specifically using each parameter. A BNP level ≥22.4 pg/ml was most sensitive, and the combination of BNP ≥22.4 pg/ml and Ea < 7.4 cm/s was most specific for identifying isolated LV diastolic dysfunction (Table 2).

Discussion

In the present study, we tried noninvasively to identify isolated LV diastolic dysfunction that was already proved invasively and to demonstrate the potential of plasma BNP measurement for the sensitive detection of this condition and the combination of plasma BNP and tissue Doppler imaging parameter Ea to improve the specificity for this detection.

Plasma BNP level can be clinically applied to evaluate LV diastolic dysfunction in patients with a wide range of systolic function. In patients with hypertension, Mottram et al reported that patients with LV diastolic dysfunction assessed using transmitral flow patterns by Doppler echocardiography had elevated plasma BNP levels compared to patients with normal LV diastolic function. Wei et al also reported a similar finding in patients with hypertension and proposed that a BNP value >40 pg/mL measured using the Triage BNP (Biosite Diagnostics, Inc., San Diego, California) could identify LV diastolic dysfunction. In patients with preserved LV systolic function, Lubien et al demonstrated that plasma BNP level increased with the progression of LV diastolic dysfunction evaluated with transmitral flow patterns; however, this method was less sensitive for...
the identification of LV diastolic dysfunction compared to the established invasive method. They indicated that a BNP level of 62 pg/ml (Triage BNP) was useful for distinguishing LV diastolic dysfunction from normal LV diastolic function.

Yamamoto et al.5 reported that plasma BNP level was positively and significantly correlated with the LV relaxation time constant τ. We previously reported that plasma BNP level was significantly higher in patients with τ ≥ 48 ms than in those with τ < 48 ms, even if their LV ejection fractions were < 50%.11 In that study, the threshold BNP value for detecting LV diastolic dysfunction was ≥ 104 pg/ml, measured with the Shionoria. These findings suggested that elevation of plasma BNP level signals LV diastolic dysfunction.

Because LV diastolic function had already been evaluated invasively and precisely, the results of our present study provide solid information about the threshold BNP level needed to distinguish isolated LV diastolic dysfunction without apparent heart failure. We propose a BNP value of ≥ 22.4 pg/ml for this purpose. This value may seem unexpectedly low, but it is close to the upper range of BNP values (18.4 pg/ml) measured using the Shionoria and observed in a Japanese population without cardiac disease or hypertension.19 BNP values may be different among the methods used for measurement. A close linear relation has been reported between BNP values measured with the Shionoria and with the Triage BNP, which is widely used in the United States.20 A BNP value of 22.4 pg/ml measured with the Shionoria may correspond to that of 32.4 pg/ml with the Triage BNP.

Slight LV remodeling with elevated LV end-diastolic pressure was observed in patients with isolated LV diastolic dysfunction, even if their systolic function range was normal. This finding suggests that small but significant LV enlargement is related to increased excretion of BNP from the left ventricle in patients with coronary artery disease. The effects of LV hypertrophy on BNP level were not directly evaluated, but their effect on LV function was basically included in the elongation of the time constant τ.

A transmitial flow pattern obtained by conventional Doppler echocardiography may not be adequate for the precise diagnosis of LV diastolic dysfunction, especially in patients with preserved LV systolic function.2,4,6 Most patients with diastolic heart failure show abnormal relaxation patterns in their transmitial flow.21,22 Most older healthy individuals also show a similar abnormal relaxation pattern.23 The Ea value may differentiate a pathologically abnormal relaxation pattern from a physiologically abnormal relaxation pattern using this method in older patients.24 Tissue Doppler imaging parameters such as Ea should be more sensitive for identifying and grading LV diastolic dysfunction than the transmitial flow pattern. The combined use of plasma BNP level and Ea may bring more specific evaluation of isolated LV diastolic dysfunction. We demonstrated that a combination of plasma BNP ≥ 22.4 pg/ml and Ea < 7.4 cm/s provided higher specificity for identifying isolated LV diastolic dysfunction.

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