Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disease, characterized by a hypertrophied non-dilated left ventricle, with diverse clinical, morphologic and functional spectrum. Although left ventricular (LV) diastolic dysfunction with impaired filling is a characteristic feature in HCM, there are some patients who might exhibit latent systolic dysfunction or who can progress to overt LV systolic dysfunction with LV remodeling. Therefore, combined assessment of both LV diastolic and systolic function is much more desirable in HCM. In this respect, the myocardial performance index (Tei index), an easily obtainable Doppler-derived index that reflects both systolic and diastolic function, has potential of clinical importance in the non-invasive assessment of global cardiac function in patients with HCM. Although the myocardial performance index has been reported to be useful in assessing various cardiac disease status including dilated cardiomyopathy, cardiac amyloidosis and congestive heart failure, its clinical significance in HCM has not been fully investigated.

The plasma level of brain natriuretic peptide (BNP) is reported to be markedly elevated in patients with HCM, especially in those with a gradient. However, the mechanism of BNP elevation in HCM remains to be established, particularly in relation to LV function.

The purpose of the present study is to elucidate: (i) the usefulness of measurement of Tei index; and (ii) the relationship between plasma BNP level and Tei index in patients with HCM.
Echocardiographic Studies

Transthoracic echocardiography was performed using commercially available ultrasound machines: Toshiba SSA-260A (Tokyo, Japan) and Sequoia 512 (Mountain View, California, USA). Images were taken with patients in the left lateral decubitus position. Conventional M-mode and 2-D echocardiographic measurements were done according to the guidelines of the American Society of Echocardiography. The magnitude and distribution of LV hypertrophy were assessed prospectively in the parasternal short axis plane by dividing the ventricle into 4 equal segments: anterior septum, posterior septum, lateral wall, and posterior wall. Wall thickness was measured at the level of the mitral valve, papillary muscles, in each of the 4 segments, and at the apical level in the anterior and posterior segments as previously reported. The greatest thickness in any of the 10 segments was regarded as the maximal wall thickness. In order to evaluate the extent of LV hypertrophy semiquantitatively, a point score (Wigle score) was calculated according to Devereux et al, LV mass in grams was also calculated as \( 1.04 \times [(LVDd + PWT + IVST)^3 - LVDd^3] \times 0.8 + 0.6 \), where LVDd is the LV end-diastolic diameter, PWT is the posterior wall thickness and IVST is the interventricular septal thickness. With the guidance of color Doppler imaging, intraventricular pressure gradient was obtained with continuous-wave Doppler.

The mitral inflow velocity was recorded from the apical 4-chamber view with the pulsed-wave Doppler sample volume positioned between the tips of the mitral leaflets during diastole. Early filling wave (E) and atrial filling wave (A) velocities of mitral inflow were obtained. The LV outflow velocity pattern was recorded from the apical long-axis view with the pulsed wave Doppler sample volume positioned just below the aortic valve. Doppler tracings were recorded at a paper speed of 50 or 100 mm/s.

Calculation of Tei Index

Tei index, defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ejection time (ET), was obtained from Doppler recordings of LV inflow and outflow (Fig 1). Tei index is derived as \( \frac{a - b}{b} \), where a is the interval between cessation and onset of mitral inflow, and b is the ET of LV outflow. In measuring a and b, it was confirmed that the preceding RR intervals were the same in duration in each patient. ICT and IRT were also calculated by the method described by Tei et al.

Measurement of Plasma BNP Level

A blood sample was taken from the antecubital vein at the time or within 1 month of echocardiography without changing medication. Plasma BNP level was measured in each patient as reported elsewhere with a specific immunoassay assay using a commercially available kit (Shionoria kit, Shionogi, Tokyo, Japan).

Statistical Analysis

Data are expressed as the mean value ± SD. Comparisons between groups for continuous variables were made using unpaired t-tests. Correlations between echocardiographic parameters and plasma BNP level were analyzed using linear regression analysis. A probability value of <0.05 was considered significant.

The relationship between echocardiographic variables and plasma BNP level were analyzed in the total HCM population and also in patients with non-obstructive HCM.
Table 1 Clinical Profiles of Patients With HCM and Controls

<table>
<thead>
<tr>
<th></th>
<th>HCM (n=45)</th>
<th>Controls (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±15</td>
<td>59±14</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>26 (58)</td>
<td>11 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>HF symptom</td>
<td>26 (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>128±17</td>
<td>126±16</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60±8</td>
<td>67±8</td>
<td>0.004</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ß-blocker</td>
<td>13 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>7 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>8 (18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as the mean value±SD, or number of subjects (percent). HCM, hypertrophic cardiomyopathy; NS, not significant (p>0.05); HF, heart failure; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Table 2 Echocardiographic Findings in Patients With HCM and Controls

<table>
<thead>
<tr>
<th></th>
<th>HCM (n=45)</th>
<th>Controls (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-mode echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>45±6</td>
<td>45±5</td>
<td>NS</td>
</tr>
<tr>
<td>LVDS (mm)</td>
<td>27±5</td>
<td>28±4</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>41±9</td>
<td>38±4</td>
<td>NS</td>
</tr>
<tr>
<td>IVST (mm)</td>
<td>16±4</td>
<td>9±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>11±2</td>
<td>9±1</td>
<td>0.0001</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>41±6</td>
<td>34±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>232±68</td>
<td>129±26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Doppler echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVOI gradient (mmHg)</td>
<td>18±23</td>
<td>9±4</td>
<td>0.09</td>
</tr>
<tr>
<td>E velocity (cm/s)</td>
<td>67±20</td>
<td>71±19</td>
<td>NS</td>
</tr>
<tr>
<td>A velocity (cm/s)</td>
<td>70±21</td>
<td>77±22</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0±0.5</td>
<td>1.0±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>230±79</td>
<td>233±88</td>
<td>NS</td>
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<tr>
<td>ICT (ms)</td>
<td>44±30</td>
<td>29±15</td>
<td>0.04</td>
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<tr>
<td>IRT (ms)</td>
<td>119±26</td>
<td>79±19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ET (ms)</td>
<td>299±26</td>
<td>302±22</td>
<td>NS</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.55±0.12</td>
<td>0.36±0.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are expressed as the mean value±SD. HCM, hypertrophic cardiomyopathy; LVDD, left ventricular (LV) end-diastolic diameter; NS, not significant (p>0.05); LVDS, LV end-systolic diameter; FS, fractional shortening; IVST, interventricular septal thickness; PWT, posterior wall thickness; LAD, left atrial diameter; LVOI, LV out-flow tract; E, early filling wave of mitral inflow; A, atrial filling wave of mitral inflow; E/A ratio, the ratio of E and A wave velocities; DT, deceleration time of E wave; ICT, isovolumic contraction time; IRT, isovolumic relaxation time; ET, ejection time.

Results

Patient Characteristics

Patient characteristics are shown in Table 1. Nineteen patients were asymptomatic. Twenty-six patients had dyspnea; 24 patients were in New York Heart Association functional class II and 2 patients were in class III. Maximal LV wall thickness was 21±4 mm (range: 15–34 mm). The morphologic pattern of LV hypertrophy was asymmetrical in 30 patients, concentric in 4 patients, and localized to the apex in 11 patients. Ten patients had intraventricular gradient (obstructive HCM: peak pressure gradient of more than 30 mmHg), and 35 patients had no gradient (non-obstructive HCM). Beta-blockers, calcium antagonists, and anti-arrhythmics were given in 8, 2, and 4 of the 10 patients with obstructive HCM, and in 5, 11, and 4 of the 35 patients with non-obstructive HCM, respectively.

Echocardiographic Findings in HCM and Controls

Table 2 shows the comparison of echocardiographic findings between patients with HCM and controls. The value of Tei index was higher in patients with HCM than that in controls (0.55±0.12 vs 0.36±0.08, p<0.0001). IRT and ICT were prolonged in patients with HCM compared with control subjects. Except LV outflow gradient, other Doppler variables were not statistically different between the groups. The average value of E wave velocity was a little smaller than that of A wave velocity in controls, reflecting aging-related diastolic abnormalities (9 of the control subjects were older than 60 years old).

Plasma BNP Level and Echocardiographic Findings in Obstructive vs Non-Obstructive HCM

The average value of plasma BNP level in patients with HCM was 193±193 pg/ml, which is much higher than the normal range previously reported in healthy subjects.27 When compared according to the presence or absence of gradient in HCM, the value of plasma BNP level was higher in patients with a gradient than those without a gradient (322±291 vs 156±140 pg/ml, p=0.02). The intraventricular pressure gradient was 59±18 mmHg in obstructive HCM, and 10±6 mmHg in non-obstructive HCM. Although patients with obstructive HCM showed somewhat longer ET than those with non-obstructive HCM (31±3±2 vs
295±23 ms, p=0.08), IRT and ICT were almost the same between the 2 groups (IRT: 122±39 vs 118±22 ms, NS; ICT: 43±28 vs 44±31 ms, NS). The value of Tei index (0.53±0.9 vs 0.56±0.12), and other clinical and echocardiographic data were not significantly different irrespective of the presence of a gradient.

**Correlation Between the Tei Index and Plasma BNP Level**

Correlation between the Tei index and plasma BNP level is shown in Fig 3. Weak, but significant correlation was observed in overall HCM patients (r=0.34, p=0.02), and it became more significant when 10 patients with obstructive HCM were excluded (r=0.61, p=0.0001). There was no significant correlation between Tei index and plasma BNP level in obstructive HCM (r=0.16, p=0.65).

**Multivariate Analysis**

The plasma BNP level also correlated with some echocardiographic variables in non-obstructive HCM (Table 3). Plasma BNP levels were significantly related to systolic time intervals (ET and ICT) and the ratio of E and A wave velocities (E/A ratio), and also related to the extent and severity of LV hypertrophy (Wigle score, LV mass, maximal wall thickness, and interventricular septal thickness).

As plasma BNP level relates to the extent and severity of LV hypertrophy, we conducted bivariate analyses using Wigle score, LV mass, maximal wall thickness, or interventricular septal thickness as a confounding variable, in which plasma BNP level showed significant correlation to Tei index independently of these variables. As age-dependence of plasma BNP concentration has been reported, we performed bivariate analysis as the age as a confounding factor, and the correlation was still significant.

Multiple stepwise regression analysis using echocardiographic variables statistically significant in the univariate analyses identified E/A ratio (r=0.49, F=13.1) and Tei index (r=0.37, F=7.6) as independent predictors of higher plasma BNP level (r=0.75, p<0.0001) (Table 3).

**Discussion**

**Myocardial Performance Index in HCM**

We demonstrated in the present study that Tei index, a myocardial performance index combining systolic and diastolic time intervals of cardiac cycle, was abnormal in patients with HCM. Although the myocardial performance index has been reported to be useful in various cardiac diseases, there are only a few investigations on its clinical significance in HCM. To the best of our knowledge, this is the first report showing that Tei index is elevated in adult patients with HCM compared with control subjects. Tei index is easily and reproducibly obtainable by Doppler echocardiography, and it is reported to be less dependent on preload or heart rate. Good correlations between Tei index and invasive indices of both systolic and diastolic cardiac function have been reported.

In the current study, IRT was prolonged in HCM patients compared with control subjects, which suggests that the elevation of Tei index in HCM is partly explained by diastolic dysfunction, a characteristic feature of HCM. However, in patients who showed much higher value of Tei index, ‘latent’ systolic dysfunction (that is, with resting LV ejection fraction preserved within normal range) might have contributed to its elevation. Depressed myocardial contractility is suggested in an animal model of HCM. Previous studies have also shown that patients with HCM often exhibit latent systolic dysfunction, even if the resting ejection fraction is preserved within normal range might have contributed to its elevation. Depressed myocardial contractility is suggested in an animal model of HCM.

Previous studies have also shown that patients with HCM often exhibit latent systolic dysfunction, even if the resting ejection fraction is preserved within normal range might have contributed to its elevation. Depressed myocardial contractility is suggested in an animal model of HCM. In addition, interstitial fibrosis or regional myocyte loss can occur in the hypertrophied segments in some patients with HCM, which might precede the progression to LV systolic dysfunction with LV remodeling, so-called end-stage heart failure. In these respects, measurement of Tei index of the left ventricle, with combined assessment of both diastolic and systolic function, would be useful in assessing the disease severity of HCM patients.
Plasma BNP Level in HCM

Plasma BNP level was elevated in patients with HCM in the present study, especially in those with a gradient. This result is compatible with previous reports. BNP is a neurohormonal factor secreted mainly from the ventricles in response to volume expansion and pressure overload. Its expression in the ventricles is induced by ventricular wall stretch and myocardial ischemia. Measurement of plasma BNP level has been shown to be useful in various cardiac diseases, such as dilated cardiomyopathy and congestive heart failure. In patients with dilated cardiomyopathy, or congestive heart failure, plasma BNP level is reported to be associated with several indices of cardiac function, such as LV end-diastolic pressure or ejection fraction, and it has prognostic implication in these patients.

Although plasma BNP level is elevated in patients with HCM, especially in obstructive form, the mechanism of its elevation in non-obstructive HCM has not been fully understood. Maron et al reported that plasma BNP level was independently related to the presence and magnitude of heart failure symptoms in patients with HCM, although they also suggested LV wall thickness and age as confounding variables. Ogino et al reported that plasma BNP concentration in HCM might reflect intraventricular pressure gradient and LV diastolic dysfunction, although they also observed high plasma BNP levels in some of the patients with non-obstructive HCM. Therefore, obstruction seems to be one of the determinants of plasma BNP level in HCM, but the mechanism of BNP elevation in non-obstructive HCM is yet to be resolved. In order to elucidate this mechanism, we investigated the relationship between echocardiographic variables and plasma BNP level after excluding obstructive form.

Relationship Between the Tei Index and Plasma BNP Level in Non-Obstructive HCM

We demonstrated in the current study that Tei index was related to plasma BNP level in patients with non-obstructive HCM. The positive correlation between Tei index and plasma BNP level might partly be explained by the latent systolic dysfunction in HCM, reflecting the process of early remodeling, because plasma BNP level significantly correlated with ET and ICT in patients with HCM. Maron et al reported that HCM patients with LV systolic dysfunction had BNP values, which were 3-fold those of symptomatic patients with preserved systolic function. Mizuno et al reported that both LV end-diastolic pressure and cavity size contributed to elevated plasma BNP level in HCM and dilated cardiomyopathy, suggesting the importance of systolic dysfunction and diastolic dysfunction in the secretion of BNP. Silent myocardial ischemia might also have affected the correlation between Tei index and plasma BNP level, because silent ischemia is reported to have associations with both elevated plasma BNP level and LV systolic dysfunction. Thus, not only LV diastolic, but also systolic function can be determinants of plasma BNP level in non-obstructive HCM.

Our results suggest that LV function itself has a critical role in determining plasma BNP level in non-obstructive HCM, because Tei index was independently related to plasma BNP level after adjusting for age or the extent and magnitude of LV hypertrophy. Previous studies in HCM with preserved systolic function failed to show a significant relationship between plasma BNP level and conventional echocardiographic indices of LV systolic or diastolic function, such as LV fractional shortening. This might partly be because of the difficulty of non-invasive assessment of cardiac function in HCM, a disease with diverse morphologic and hemodynamic presentation. Measurement of Tei index, which is independent of LV morphology in its concept, not only enables the non-invasive and combined assessment of LV systolic and diastolic function, but also might serve as a sensitive marker of subclinical functional impairment. These advantages of Tei index might explain the positive result in the current study, an association between cardiac function and plasma BNP level. Our result is also compatible with the report by Ono et al, where the Tei index significantly correlated with plasma BNP level in various heart diseases, although they included only 3 patients with HCM.

In the multivariate analysis, plasma BNP level was positively related to both Tei index and the mitral E/A ratio. A positive correlation between plasma BNP level and E/A ratio in the present study can be partly explained by elevated LV filling pressure in some patients with higher E/A ratio (pseudonormal or restrictive pattern). Previous reports also suggested the association between higher plasma BNP level and elevated LV end-diastolic pressure in HCM. Our result that plasma BNP level did not correlate with IRT, but with E/A ratio, might suggest that higher plasma BNP level is related to more advanced stage of LV diastolic dysfunction (pseudonormal or restrictive pattern). Lubien et al found that patients with restrictive filling pattern had significantly higher BNP level than patients with impaired relaxation, when they consecutively evaluated those with normal systolic function. Ono et al also reported that plasma BNP level was significantly correlated with mitral E/A ratio, but not with IRT. However, Zhang et al reported that Tei index is useful in the differentiation of normal from pseudonormal/restrictive mitral inflow pattern, suggesting that measurement of Tei index has a complementary role in addition to the measurement of mitral E/A ratio. Thus, assessment of both Tei index and E/A ratio might enable a better prediction of plasma BNP level.

Plasma BNP Level and Tei Index in Obstructive HCM

Plasma BNP level was higher in patients with obstructive HCM than those with non-obstructive HCM in the current study. Our result is compatible with previous observations, in which increased LV systolic wall stress as a result of LV outflow pressure gradient was considered to be the principal stimulus of BNP secretion in obstructive HCM. Hasegawa et al and Nishigaki et al showed that markedly elevated plasma BNP level with an increase in the production of BNP in the myocardial myocytes is a specific feature of obstructive HCM, and that its elevation could not be explained by hemodynamic and echocardiographic findings. We cannot extract a definitive conclusion about the mechanism of BNP elevation in obstructive HCM from the present study, because of a relatively small number of patients with gradients.

In the current study, the relationship between plasma BNP level and Tei index was observed in non-obstructive HCM, but not in obstructive HCM. One of the reasons would be that plasma BNP level is strongly influenced by obstruction in HCM. Another possible explanation is that severe LV outflow tract obstruction might increase ET in obstructive HCM, as indicated by Wigle et al, and therefore can reduce the value of Tei index.
in the presence of marked afterload elevation was reported in patients with aortic stenosis. It has not been clarified, however, to what extent this reduction can occur in HCM with LV outflow gradient. In contrast, a report showed improvement of Tei index after percutaneous transluminal septal myocardial ablation for obstructive HCM. Clinical significance and limitation of Tei index in obstructive HCM need further investigation.

**Study Limitations**

First, invasive measurements of LV systolic and diastolic function were not obtained, and we did not evaluate other newly developed echocardiographic factors, such as mitral annular velocities assessed using tissue Doppler imaging. However, there are several reports showing significant associations between Tei index and invasive parameters of cardiac function. Second, in the current study, we compared the value of Tei index between HCM patients and control subjects, and we did not include those with secondary LV hypertrophy, such as hypertensive heart disease. Therefore, it is not certain whether the elevated value of Tei index is a result of LV hypertrophy or primary myocardial change itself. Further investigation would be required to clarify this issue. Third, echocardiographic studies and measurements of plasma BNP level were performed without withholding medications.

**Conclusion**

Myocardial performance index was abnormal in patients with HCM, reflecting both LV systolic and diastolic abnormalities in this disorder. Tei index correlated with plasma BNP level in patients with non-obstructive HCM, independently from age or the extent and severity of LV hypertrophy. Our results might suggest that plasma BNP level is related to both LV systolic and diastolic function in non-obstructive HCM.

**References**


