Background: Although impaired left ventricular (LV) diastolic function is a prominent feature of hypertrophic cardiomyopathy (HCM), diastolic function and its relation to exercise capacity in apical HCM (ApHCM) has not been explored previously. This study was sought to determine the relationship between diastolic mitral annular velocities combined with conventional Doppler indexes and exercise capacity in patients with ApHCM.

Patients: Twenty-nine patients with ApHCM (24 men; mean age ± SD, 57 ± 10 years) underwent supine bicycle exercise with simultaneous respiratory gas analysis and two-dimensional and Doppler echocardiographic study.

Results: The mitral inflow velocities (early filling [E], late filling, and deceleration time) were traced and measured. Early diastolic mitral annular velocity (E’) was measured at the septal corner of mitral annulus by Doppler tissue imaging (DTI) from the apical four-chamber view. Pro-brain natriuretic peptide (proBNP) was measured at the time of echocardiography using a quantitative electrochemiluminescence immunoassay. E/E’ ratio correlated inversely with maximal oxygen uptake (V˙O₂max) [r = −0.47, p = 0.0106]. There was a significant positive correlation between E’ and V˙O₂max (r = 0.41, p = 0.024). However, no correlation was found between conventional two-dimensional, Doppler indices, and proBNP and V˙O₂max). Of all the echocardiographic and clinical parameters assessed, E/E’ ratio had the best correlation with exercise capacity (r = 0.47) and was the strongest independent predictor of V˙O₂max by multivariate analysis (p = 0.0106).

Conclusions: DTI-derived indexes (E’, E/E’ ratio), an estimate of myocardial relaxation and LV filling pressures, correlate with exercise capacity in patients with ApHCM, suggesting that abnormal diastolic function may be a factor limiting exercise capacity.

Key words: apical hypertrophic cardiomyopathy; Doppler tissue imaging; exercise capacity; mitral annular velocity

Abbreviations:
- A = late filling
- ApHCM = apical hypertrophic cardiomyopathy
- DT = deceleration time
- DTI = Doppler tissue imaging
- E = early filling
- E’ = early diastolic mitral annular velocity
- EF = ejection fraction
- HCM = hypertrophic cardiomyopathy
- LA = left atrial
- LV = left ventricle
- proBNP = pro-brain natriuretic peptide
- V˙O₂max = maximal oxygen uptake

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease in which a hypertrophied, nondilated left ventricle (LV) is the morphologic hallmark.1–3 Distribution of hypertrophy is often diffuse but may also be mild and localized.4,5 Apical HCM (ApHCM) is a unique form of HCM in which the hypertrophy of the myocardium predominantly involves the apex of the LV. Although ApHCM has been reported to have a benign prognosis in terms of cardiovascular mortality, one third of ApHCM patients may experience unfavorable clinical events and potentially life-threatening complications, such as myocardial infarction, atrial fibrillation, and stroke.6 It is well known that many of the clinical and pathophysiologic features of HCM result from a complex disturbance of diastolic function.7–12 However, diastolic function and its relation to exercise capacity in patients with ApHCM have not been explored previously.
Doppler echocardiographic evaluation of transmirtal LV filling velocities is widely used to assess LV diastolic function. However, most studies\textsuperscript{13,14} have failed to show significant correlations between Doppler-derived transmitral flow velocities and exercise capacity, or mean left atrial (LA) pressure in patients with HCM. Conventional echocardiographic Doppler indexes are unreliable for assessing LV diastolic function in such patients, probably because of their dependence on loading conditions.\textsuperscript{15-18} Early diastolic mitral annular velocity (E') measured by Doppler tissue imaging (DTI) has been reported to be a preload independent index of myocardial relaxation,\textsuperscript{19,20} and LV filling pressures can be estimated by combining mitral inflow (early filling [E]) and E'.\textsuperscript{20,21} We hypothesized that DTI-derived indices, which are better estimates of myocardial relaxation and filling pressures, rather than conventional Doppler parameters, will correlate with exercise capacity in patients with ApHCM. Therefore, the purpose of this study was to determine the relationship between diastolic annular velocities combined with conventional Doppler indexes and exercise capacity in patients with ApHCM.

Materials and Methods

Study Patients

We prospectively studied consecutive ApHCM patients at Yonsei University Cardiovascular Hospital between January 2003 and January 2004. Exclusion criteria included patients with atrial fibrillation and inability to exercise due to orthopedic problems. Twenty-nine consecutive patients (24 men and 5 women; mean age ± SD, 57 ± 10 years [range, 34 to 81 years]) with ApHCM were studied prospectively. One patient was excluded due to atrial fibrillation, and another patient was excluded due to inability to exercise > 25 W. Six patients were in class 2 of symptom status at the time of evaluation. Two patients had evidence of previous clinical heart failure. Eleven patients were receiving calcium-channel blockers and ß-blockers (Table 1). Angiotensin receptor blockers were administered in five patients, and one patient was receiving an angiotensin-converting enzyme inhibitor. However, all medications were withheld before the exercise stress test. Study approval was obtained from the Internal Review Board of Yonsei University College of Medicine.

Diagnostic Criteria

The diagnostic criteria for ApHCM included demonstration of LV hypertrophy, confined predominantly to the LV apex with an apical wall thickness ≥ 15 mm and a ratio of maximal apical to posterior wall thickness ≥ 1.3 based on two-dimensional echocardiography. An echocardiographic contrast agent (perfluorocarbon exposed dextrose albumin) was administered IV in all patients to confirm the diagnosis.

Echocardiography

All patients underwent a comprehensive evaluation with pulsed-wave Doppler echocardiography of mitral inflow and DTI. Two-dimensional and Doppler echocardiography was performed with a commercially available echocardiography unit equipped with an imaging transducer having pulsed-wave and DTI capability. The ejection fraction (EF) was calculated by two-dimensional echocardiography with a modification of the method of Quinones et al.\textsuperscript{22} LA volume was measured by the prolate ellipsoid method.\textsuperscript{23,24} From the apical window, the pulsed Doppler sample volume was placed at the mitral valve tips, and 5 to 10 cardiac cycles were recorded. From the mitral inflow velocities, the following variables were measured: peak velocity of E and late filling (A), and deceleration time (DT) of the E-wave velocity. For DTI, the filter setting was lowered, and the Nyquist limit was adjusted to a range of 15 to 20 cm/s. Gain was minimized to allow for a clear tissue signal with minimal background noise. E' was measured from the apical four-chamber view with a 2- to 5-mm sample volume placed at the septal corner of the mitral annulus. Measurements were recorded with simultaneous electrocardiography at a sweep speed of 50 to 100 mm/s. The mean of three to six measurements was used for analysis. The E/E' ratio was calculated. This ratio has been reported to correlate with LV filling pressure.\textsuperscript{14,21}

Measurement of N-terminal Pro-Brain Natriuretic Peptide

Blood samples for pro-brain natriuretic peptide (proBNP) analysis were drawn at the time of echocardiography and kept at 4°C and analyzed within 4 h of sampling. Before analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed in triplicate by electrochemiluminescence immunoassay method for proBNP (Elecsys proBNP; Roche Diagnostics; Basel, Switzerland).

Metabolic Exercise Testing

All patients underwent symptom-limited exercise testing on a supine bicycle ergometer with simultaneous respiratory gas analysis and BP recording. Exercise testing was performed immediately after the echocardiographic examination. Exercise began

Table 1—Clinical and Echocardiographic Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57 ± 10</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>24/5</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.77 ± 0.16</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypertension</td>
<td>13</td>
</tr>
<tr>
<td>Cardiac medications</td>
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<tr>
<td>Calcium-channel blockers</td>
<td>11</td>
</tr>
<tr>
<td>ß-Blockers</td>
<td>11</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 11</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>129 ± 19</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>51 ± 4</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>32 ± 3</td>
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<tr>
<td>EF, %</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>LA volume index, mL/m²</td>
<td>33 ± 12</td>
</tr>
<tr>
<td>Exercise duration, s</td>
<td>593 ± 175</td>
</tr>
<tr>
<td>N-terminal proBNP, pg/mL</td>
<td>413 ± 478</td>
</tr>
<tr>
<td>V0,max, mL/min/kg</td>
<td>21 ± 6</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No.
with 25 W after a 1-min unload phase, followed by a ramp protocol with increments of 25 W every 3 min. Oxygen uptake, carbon dioxide production, and minute ventilation were measured using a breath-by-breath gas analysis (Medical Graphics; St. Paul, MN). A 12-lead ECG was continuously registered to exclude significant myocardial ischemia. BP was recorded every 3 min by a cuff sphygmomanometer. Maximal oxygen uptake (V\textsubscript{O\textsubscript{2}}\textsuperscript{max}) was defined as the mean of the highest values obtained over the last 10 s of exercise. The physician who performed and analyzed the cardiopulmonary exercise test was unaware of the results of echocardiography and proBNP testing.

**Results**

**Echocardiography**

LV end-diastolic and end-systolic dimensions and EF were 51 ± 4 mm, 32 ± 3 mm, and 69 ± 5%, respectively. None of the patients had LV systolic dysfunction (EF < 50%). Ventricular septum and posterior wall thickness were 12 ± 2 mm and 11 ± 2 mm, respectively. Apical anterior wall and posterior wall thickness were 16.5 ± 2.8 and 16.0 ± 2.4 mm, respectively. Basal anterior wall and posterior wall thickness were 9.8 ± 1.0 mm and 10.2 ± 1.1 mm, respectively. Mean LA volume index was 33 ± 12 mL/m\textsuperscript{2}. The LA volume index was above normal, > 23 mL/m\textsuperscript{2}, in all but five patients. E, A, E/A ratio, and DT were 0.58 ± 0.13 m/s, 0.51 ± 0.14 m/s, 1.2 ± 0.4, and 199 ± 34 ms, respectively. E' was < 0.08 m/s in all patients (mean, 0.05 ± 0.01 m/s). E/E' ratio was > 10 in 17 of 29 patients (59%) and > 15 in 6 of 29 patients (21%) [mean, 12 ± 5].

**Metabolic Exercise Testing**

Exercise duration ranged from 329 to 974 s (mean, 593 ± 175 s). Mean V\textsubscript{O\textsubscript{2}}\textsuperscript{max} was 21 mL/kg/min (range, 7 to 32 mL/kg/min). Leg fatigue was the most common cause for stopping the exercise (20 of 29 patients). Seven patients stopped exercise due to dyspnea as a primary reason. Exercise duration was significantly shorter in women compared with that of men (628 ± 33 s vs 427 ± 71 s, p = 0.0011).

**Plasma Levels of proBNP**

proBNP ranged from 18 to 2,364 pg/mL (mean, 414 ± 478 pg/mL). proBNP was above normal (> 315 pg/mL, approximately the upper normal value of proBNP in the published literature) in 12 of 29 patients (41%).

**Determinants of Exercise Capacity**

There were no significant differences in mitral inflow velocity variables (E, A, E/A ratio, DT) and proBNP between patients with lower V\textsubscript{O\textsubscript{2}}\textsuperscript{max} (< 18 mL/kg/min, n = 8) and higher V\textsubscript{O\textsubscript{2}}\textsuperscript{max} (> 18 mL/kg/min, n = 21). However, E' was significantly lower and E/E' ratio was significantly higher in patients with lower V\textsubscript{O\textsubscript{2}}\textsuperscript{max} (Table 2). There was no significantly correlation between age, gender, LV end-diastolic and end-systolic dimensions, EF, LA volume index, and V\textsubscript{O\textsubscript{2}}\textsuperscript{max}. None of the conventional Doppler indexes (E, A, E/A ratio, DT) correlated with V\textsubscript{O\textsubscript{2}}\textsuperscript{max} (Fig 1). E/E' ratio was inversely correlated with V\textsubscript{O\textsubscript{2}}\textsuperscript{max} (r = - 0.47, p = 0.0106) [Fig 2]. proBNP and log-transformed proBNP did not correlate with V\textsubscript{O\textsubscript{2}}\textsuperscript{max} (r = - 0.2, p = 0.33; and r = - 0.08, p = 0.68, respectively). Of all the echocardiographic and clinical parameters assessed, E/E' ratio had the best correlation with exercise capacity (r = - 0.47) and was the strongest independent predictor of V\textsubscript{O\textsubscript{2}}\textsuperscript{max} by multivariate analysis (p = 0.0106).

**Discussion**

The principal findings of this study are as follows: (1) conventional transmitral inflow Doppler, two-dimensional echocardiographic measures, and proBNP are limited in predicting exercise capacity in patients with ApHCM; (2) however, DTI-derived indexes (E', E/E' ratio), an estimate of myocardial relaxation and LV filling pressures, correlate with exercise capacity in patients with ApHCM, suggesting that abnormal diastolic function may be a factor limiting exercise capacity.

<table>
<thead>
<tr>
<th>Variables</th>
<th>V\textsubscript{O\textsubscript{2}}\textsuperscript{max} &lt; 18 mL/min/kg (n = 8)</th>
<th>V\textsubscript{O\textsubscript{2}}\textsuperscript{max} &gt; 18 mL/min/kg (n = 21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E, m/s</td>
<td>0.59 ± 0.15</td>
<td>0.58 ± 0.13</td>
<td>0.90</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.54 ± 0.17</td>
<td>0.49 ± 0.13</td>
<td>0.47</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>0.77</td>
</tr>
<tr>
<td>DT, ms</td>
<td>199 ± 40</td>
<td>199 ± 32</td>
<td>0.99</td>
</tr>
<tr>
<td>E', cm/s</td>
<td>4.0 ± 1.1</td>
<td>5.5 ± 1.2</td>
<td>0.0088</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>16 ± 7</td>
<td>10 ± 3</td>
<td>0.048</td>
</tr>
<tr>
<td>proBNP, pg/mL</td>
<td>670 ± 761</td>
<td>316 ± 284</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.

**Table 2—Comparison of Brain Natriuretic Protein and Echocardiographic Variables Between Lower vs Higher V\textsubscript{O\textsubscript{2}}\textsuperscript{max}**
Diastolic Function in ApHCM

Although extensive investigations have been made regarding diastolic function in patients with HCM, few studies evaluated diastolic function in patients with ApHCM. The demonstration of diastolic dysfunction can be done by showing abnormal relaxation of the myocardium and/or increased LV filling pressures. Myocardial relaxation is best assessed by the time constant of LV isovolumic pressure fall ($\tau$), which is derived from invasively measured high-fidelity LV pressure. E' recorded by DTI has been correlated with $\tau$ and is thought to reflect myocardial relaxation.\(^{19}\) Additionally, mitral annulus velocity was shown to be relatively preload independent, especially in patients with impaired relaxation.\(^{25-27}\) When myocardial relaxation is normal, E' is usually $\geq 0.1$ m/s. In this study, E' was $< 0.1$ m/s in all patients, which suggests impaired myocardial relaxation in patients with ApHCM. Impaired LV relaxation in patients with HCM, including ApHCM, has been previously proposed as a mechanism for progressive LA enlargement and subsequent atrial fibrillation. LA volume, a faithful mirror of elevated LV and LA filling pressures in the absence of mitral valve disease, was above normal in 83% of the study patients, suggesting the presence of chronic diastolic dysfunction. However, elevated filling pressure at rest was observed in approximately 20% of patients based on the findings of elevated E/E' ratio. As LV filling pressure increase, mitral E velocity becomes progressively higher, whereas E' velocity remains reduced. Therefore, the assessment of mitral annular velocity by DTI may be useful in the evaluation of diastolic dysfunction and has overcome some of the inherent difficulties in assessing diastolic function utilizing transmitral inflow velocities alone. Naguh et al\(^{20}\) showed that when the mitral E velocity was corrected for the influence of myocardial relaxation (ie, the E/E' ratio), it was found to correlate well with the mean pulmonary capillary wedge pressure. In their study,\(^{20}\) an E/E' ratio (lateral annulus) ratio of $> 10$ detected a mean pulmonary capillary wedge pressure $> 15$ mm Hg with a sensitivity of 97% and specificity of 78%. Ommen et al\(^{21}\) assessed the association between E' (septal annulus) and LV filling pressures in 100 consecutive patients referred for cardiac catheterization and found that E/E' ratio $> 15$ identified increased LV filling pressure. Thus, in clinical practice, E/E' ratio $< 8$ suggests normal LV filling pressures. In contrast, E/E' ratio $> 15$ indicates elevated filling pressures. Brain natriuretic peptide, a neurohormone secreted from the cardiac ventricles in response to stretching of the chamber,\(^{28-30}\) has been shown as a good predictor of high LV end-diastolic pressure in patients with systolic dysfunction.\(^{31}\) In this study, approximately 40% of the patients had an elevated plasma level of proBNP, further supporting the presence of elevated filling pressures at rest in some of the ApHCM patients.

Exercise Capacity and Diastolic Function in ApHCM

Hemodynamic mechanisms for impaired exercise tolerance in patients with ApHCM remain poorly defined. However, postulated mechanisms in HCM include elevated LA pressure, impaired augmentation of stroke volume secondary to abnormal diastolic filling,\(^{32}\) or impairment in LA and LV systolic performance.\(^{33}\) In our study, conventional transmitral inflow Doppler echocardiographic measures did not show significant correlations with exercise capacity in patients with ApHCM. This is consistent with
pervious studies\textsuperscript{11,34} showing that that mitral flow velocity indexes do not reflect a particular symptomatic status and exercise capacity in patients with HCM. Nishimura et al\textsuperscript{15} demonstrated that Doppler-derived mitral flow velocity curves cannot be used to estimate LV filling pressure in patients with HCM; this is because the mitral flow velocity curves are strongly influenced by factors independent of diastolic properties of the LV, such as loading condition.\textsuperscript{15–18} In contrast, Matsumura et al\textsuperscript{34} demonstrated that an increased lateral E/E’ ratio was significantly associated with V\textsubscript{O2max} in patients with HCM. It also shows that this ratio correlates with V\textsubscript{O2max} in patients with HCM with and without LV outflow tract obstruction. As it has been shown that LV filling pressures in patients with HCM correlate with E/E’ ratio, these observations support the hypothesis that dyspnea and exercise intolerance in patients with HCM are related largely to elevated LV filling pressures. Brigouri et al\textsuperscript{35} showed that LA fractional shortening, which is closely related to LV end-diastolic pressure at rest. These results support the role of LV diastolic dysfunction at rest in limiting the exercise capacity of patients with HCM. However, no study has been shown the relationship between DTI-derived indexes and exercise capacity in patients with ApHCM. From the present study, the DTI-derived indexes (E’, E/E’ ratio), an estimate of myocardial relaxation and LV filling pressures, correlate with exercise capacity in patients with ApHCM. However, in our present study, the correlation between E/E’ ratio and V\textsubscript{O2max} was relatively modest, suggesting that other factors such as a reduced stroke volume response, ventilation/perfusion mismatch, and abnormal peripheral oxygen utilization also influence exercise intolerance.\textsuperscript{32,33,36} Further studies are warranted to determine the exact mechanisms of impaired exercise tolerance.

**CONCLUSIONS**

Conventional transmural inflow Doppler, two-dimensional echocardiographic measures, and proBNP are limited in predicting exercise capacity in patients with ApHCM. However, DTI-derived indexes (E’, E/E’ ratio), an estimate of myocardial relaxation and LV filling pressures, correlate with exercise capacity in patients with ApHCM, suggesting that abnormal diastolic function may be a factor limiting exercise capacity.

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