Characterization of Left Ventricular Diastolic Function by Tissue Doppler Imaging and Clinical Status in Children With Hypertrophic Cardiomyopathy

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Background—Conventional transmitral Doppler indices are unreliable in assessing clinical status in patients with hypertrophic cardiomyopathy (HCM) because they are affected by loading conditions. This study sought to determine whether tissue Doppler velocities are predictive of adverse clinical outcomes including death, cardiac arrest, ventricular tachycardia (VT), significant cardiac symptoms, and exercise capacity in children with HCM.

Methods and Results—We studied 80 consecutive children (median age 12 years, median follow-up 26 months) evaluated at 1 hospital from January 1999 to August 2003 compared with 80 age- and gender-matched controls. Patients underwent echocardiography, ambulatory Holter monitoring, and upright exercise testing. Children with HCM had significantly decreased early diastolic tissue Doppler velocities at the lateral mitral (13.2 versus 19.3 cm/s), tricuspid (13.3 versus 16.3 cm/s), and septal (9.4 versus 13.5 cm/s) annuli compared with controls (P<0.001 for each comparison). By forward stepwise regression analysis, early transmitral left ventricular filling velocity (E)/septal Ea ratio predicted death, cardiac arrest, or VT (r=0.610, R²=0.37, P<0.001). Peak oxygen consumption (VO₂) was most predictive of children who developed symptoms (r=0.427, R²=0.182, P<0.001). Peak VO₂ correlated inversely with E/Ea septal ratio (r=−0.740, P<0.01).

Conclusions—Transmitral E/septal Ea ratio predicts children with HCM who are at risk of adverse clinical outcomes including death, cardiac arrest, VT, and significant cardiac symptoms. Peak VO₂ correlated with peak exercise capacity in HCM patients. (Circulation. 2004;109:1756-1762.)

Key Words: cardiology • echocardiography • pediatrics

Hypertrophic cardiomyopathy (HCM), characterized by abnormal diastolic relaxation, represents the leading cause of sudden cardiac death (SCD) in children and young adults.1–3 In the adult population with HCM, specific risk factors for SCD include younger age at diagnosis, family history of HCM, massive left ventricular (LV) hypertrophy, prior ventricular tachycardia (VT) or cardiac arrest, and underlying mutations within specific genes.4–6 Children with HCM are a unique population compared with adults, and it is important to independently determine prognostic risk factors for adverse clinical outcomes in this group, such as death, arrhythmia, cardiac symptoms, and decreased exercise capacity. There are limited reports of echocardiographic predictors of adverse outcomes in infants and young children.7,8 Despite evidence that diastolic relaxation abnormalities in HCM may influence outcome in adults, there have been no reports investigating whether diastolic indices that use tissue Doppler (TD) imaging can predict adverse clinical outcomes in children with HCM.9

Conventional echocardiographic Doppler indices that evaluate diastolic ventricular function are unreliable in predicting clinical status, including cardiac symptoms and exercise capacity, among adults with HCM, primarily because of their dependence on loading conditions.10,11 Recently, newer echocardiographic modalities such as TD have demonstrated clinical relevance among patients with a variety of myocardial disorders.12 In the adult population, TD has been shown to predict gene mutations underlying HCM, estimate left atrial (LA) filling pressure, and correlate response to specific therapies in HCM patients.9,13–16 TD velocities are an attractive index of diastolic ventricular function because they are relatively load independent and may provide insight into whether diastolic function is an important factor in clinical symptoms and exercise capacity in children with HCM.13,17
The purpose of the present study was to determine whether TD can predict the risk of VT, cardiac arrest or death, and development of cardiac symptoms in addition to exercise capacity in children with HCM.

Methods

We prospectively studied consecutive pediatric patients with HCM at Texas Children’s Hospital between January 1999 and August 2003. Exclusion criteria included patients with congenital heart lesions, systemic hypertension, metabolic disorders, or genetic syndromes and patients who underwent previous surgical myectomy. Eighty-six children with HCM were diagnosed with or followed up with HCM during the study period. Six patients were excluded because of poor echocardiographic windows or incomplete acquisition of study data. Excluded patients were of similar age and gender and had similar 2D echocardiographic parameters as study patients. Age- and gender-matched control subjects were also studied. Study approval was obtained from the Internal Review Board of Baylor College of Medicine.

Study End Points

The primary end point of the study was defined as patients who died, experienced a cardiac arrest, or had documented VT, either sustained or nonsustained. Sustained VT was defined as lasting longer than 30 seconds. The secondary end point was defined as patients who developed significant cardiac symptoms, including chest pain on exertion, syncope, dyspnea, or exercise intolerance.

Patient Analysis

Demographic data that included age at diagnosis, gender, presence of a positive family history, and medical therapy were collected. Patients were questioned about whether they had experienced any of the defined symptoms. New York Heart Association (NYHA) classification was recorded for each patient at the start and end of the study. Twenty-four-hour Holter monitors were reviewed to determine incidence of significant arrhythmia, defined as VT. ECGs were reviewed and abnormalities documented; QRS and QTc duration were measured. Dysynchronous ventricular activation was defined on the ECG by the presence of intraventricular conduction delay or left bundle-branch block. Exercise capacity was determined with a ramp protocol (Bruce or modified Bruce protocol). Maximum oxygen consumption (VO₂) was defined as the mean of the highest values obtained during the last 15 seconds of the protocol. Holter monitors, ECG, and treadmill tests were performed within 1 month of echocardiograms.

Echocardiographic Analysis

A single blinded observer performed the echocardiographic analysis (C.J.M.). Patients were defined as having asymmetric (predominantly septal hypertrophy), concentric (involving the entire LV), or posterior (isolated to the posterior LV wall) LV hypertrophy. 2D measurements included LV end-diastolic and end-systolic dimensions, posterior wall thickness, interventricular septal thickness, and LV ejection fraction. In the parasternal short-axis view, the LV was divided into 4 quadrants (anterior septum, posterior septum, lateral, and posterior wall segments). The greatest LV wall thickness was measured in each of these quadrants in diastole and systole at the level of the mitral valve papillary muscles. Maximal LV wall thickness was defined as the greatest thickness in any of these segments. The peak LV outflow tract gradient was determined from the modified Bernoulli equation. Pulsed Doppler was used to record mitral and tricuspid inflow patterns at the leaflet tips in the apical 4-chamber view. TD imaging was obtained from an apical 4-chamber view to obtain longitudinal annular velocities at the lateral mitral wall, septum, and lateral tricuspid wall adjacent to the AV valve hinge points. Filters and gains were adjusted to allow a clear tissue signal and minimize background noise. LA volumes and LV mass were determined by the truncated ellipsoid method and M-mode, respectively, for each patient and were indexed to body surface area. Mitral inflow Doppler was measured in standard fashion to determine peak E- and A-wave velocities, deceleration time of the transmitral E wave, and isovolumic contraction and relaxation times. Pulmonary venous inflow Doppler patterns were analyzed to determine the peak velocities of the systolic, diastolic, and atrial reversal waves. The Tei index, defined as the sum of isovolumic contraction and relaxation times divided by LV ejection time, was calculated as reported previously. Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) TD velocities were measured at the lateral mitral, septal, and lateral tricuspid walls and subsequently averaged over 3 cardiac cycles in accordance with previous reports (Figure 1). Transmural E/Ea ratios (lateral and septal) were calculated for each patient.

Statistical Analysis

Statistical analysis was performed with SPSS Sigma Stat statistical software (SPSS for Windows version 3.0, SPSS Inc). Data are expressed as mean±SD or median (25th to 75th percentile) based on whether they have a normal distribution or not. Forward stepwise regression was performed to determine predictors of the primary and secondary end points. A probability value <0.05 was required for retention within the final stepwise regression model. Statistical significance was taken as P<0.05.

Results

Patient Characteristics

Eighty patients with HCM (age range 1 to 18 years) were compared with 80 age- and gender-matched controls. The median age at diagnosis was 12 years (range 1 to 18 years), and median duration of patient follow-up was 26 months (range 2 to 51 months). The pattern of LV hypertrophy was asymmetric in 54 patients, concentric in 25, and isolated posterior wall hypertrophy in 1 patient. One additional patient had significant LV hypertrophy, which initially normalized and then recurred. Nineteen patients had LV outflow tract obstruction with a peak gradient >20 mm Hg (mean gradient 16 mm Hg, range 10 to 64 mm Hg). Eighteen patients had a positive family history of HCM (23%) ranging from 1 affected family member to 1 family with 20 affected members. In this affected family, 13 members died, 8 of whom died of SCD. Seventy-four patients were treated with β-blockers and 6 with calcium channel blockers.

Fourteen patients reached the primary end point during the study period. Eight patients had sustained VT and underwent placement of an implanted cardiac defibrillator. There were 3
Demographics

HCM patients compared with controls. There were no significant differences in mitral inflow Doppler velocities fractions and Tei indices than controls. There were no differences in mitral inflow Doppler velocities between groups. There was a significant reduction in all early diastolic TD velocities and septal late diastolic velocity in HCM patients compared with controls.

2D echocardiographic and TD variables comparing HCM patients with controls are presented in Table 1. As expected, HCM patients had smaller LVs, thicker interventricular septal thickness and LV posterior walls, and increased LV ejection fractions and Tei indices than controls. There were no significant differences in mitral inflow Doppler velocities between groups. There was a significant reduction in all early diastolic TD velocities and septal late diastolic velocity in HCM patients compared with controls.

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### TABLE 1. Echocardiographic and TD Characteristics of 80 Children With HCM

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCM Patients (n=80)</th>
<th>Control Subjects (n=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>12.0 (1–18)</td>
<td>11.7 (1–18)</td>
<td>...</td>
</tr>
<tr>
<td>Male gender</td>
<td>52</td>
<td>52</td>
<td>...</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>105/75</td>
<td>103/56</td>
<td>0.31</td>
</tr>
<tr>
<td>Cycle length, ms</td>
<td>793±177</td>
<td>758±172</td>
<td>0.22</td>
</tr>
<tr>
<td>Mitral inflow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral E velocity, cm/s</td>
<td>88±20.1</td>
<td>93±16</td>
<td>0.08</td>
</tr>
<tr>
<td>Mitral A velocity, cm/s</td>
<td>58 (54–65)</td>
<td>62 (54–77)</td>
<td>0.09</td>
</tr>
<tr>
<td>E deceleration time, ms</td>
<td>143±43</td>
<td>119±20</td>
<td>0.002</td>
</tr>
<tr>
<td>IVCT, ms</td>
<td>76±17</td>
<td>77±15</td>
<td>0.74</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>72±15</td>
<td>67±14</td>
<td>0.07</td>
</tr>
<tr>
<td>Transmural E/Ea (septal)</td>
<td>9.2 (7.5–11.9)</td>
<td>6.9 (5.6–8.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>E/Ea (lateral)</td>
<td>7.0 (5.3–9.2)</td>
<td>4.8 (4.0–5.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tei index (LV)</td>
<td>0.49 (0.40–0.57)</td>
<td>0.34 (0.30–0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tei index (RV)</td>
<td>0.46 (0.39–0.57)</td>
<td>0.32 (0.26–0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>65 (58–72)</td>
<td>57 (52–65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TD velocities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral mitral Ea, cm/s</td>
<td>13.2 (9.3–16.3)</td>
<td>19.3 (15.3–22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral mitral Aa</td>
<td>6.7 (4.9–7.9)</td>
<td>6.2 (5.4–7.7)</td>
<td>0.61</td>
</tr>
<tr>
<td>Lateral mitral Sa</td>
<td>8.5±2.7</td>
<td>10.6±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral septal Ea, cm/s</td>
<td>9.4 (6.4–11.9)</td>
<td>13.5 (11.3–15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral septal Aa</td>
<td>6.0 (5.0–7.0)</td>
<td>6.2 (5.2–7.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>Mitral septal Sa</td>
<td>7.3±1.8</td>
<td>8.2±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral tricuspid Ea, cm/s</td>
<td>13.3±4.1</td>
<td>16.3±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral tricuspid Aa</td>
<td>11.0 (7.8–12)</td>
<td>9.6 (8.1–12.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Lateral tricuspid Sa</td>
<td>12.2 (10.4–14.2)</td>
<td>13.4 (12.2–15.1)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

IVCT indicates isovolumetric contraction time; IVRT, isovolumetric relaxation time; RV, right ventricle; and LVEF, LV ejection fraction.

Data are expressed as median±SD or mean (25th to 75th percentile).

Predictors of Primary End Point

Echocardiographic variables including TD velocities are shown in Table 2 for patients who met the primary end point. Univariate correlation coefficients for variables entered into the stepwise regression analysis are presented in Table 4. The only significant variable predictive of the primary end point by stepwise regression analysis was the septal E/Ea ratio \( r=0.61, R^2=0.37, P<0.001 \). Interestingly, although the lateral transmural E/Ea ratio was also increased in patients who met the primary end point, this did not reach statistical significance \( P=0.31 \).
TABLE 3. Echocardiographic and TD Parameters in Symptomatic Children With HCM

| Variable                        | Symptoms (n=21) | No Symptoms (n=59) | P  
|---------------------------------|-----------------|--------------------|---- 
| Left heart dimensions           |                 |                    |    
| LVEDD, mm                       | 40±8            | 36±10.5            | 0.09  
| LVEDD Z score                   | −1.4±1.8        | −1.9±2.0           | 0.39  
| IVS thickness, mm               | 17.0 (13.3–23.9) | 13.0 (10.0–17.8)  | 0.01  
| IVS Z score                     | 4.2 (2.9–6.2)   | 3.2 (1.8–4.6)      | 0.06  
| PW thickness, mm                | 12.7 (8.6–15.7)  | 9.5 (7.8–15)       | 0.21  
| PW Z score                      | 3.1±2.3         | 2.0±1.8            | 0.56  
| Maximal LV thickness, mm        | 17.5 (14.0–25.1) | 12.5 (9.8–17.5)   | 0.01  
| LA volume, mL                   | 22.3±10.1       | 16.2±13.0          | 0.11  
| LA volume*                      | 13.5 (10.0–20.0) | 12.0 (9.3–14.2)   | 0.19  
| LV mass, g                      | 193±130         | 132±93             | 0.12  
| LV mass*                        | 121±52          | 95±39              | 0.12  
| Mitral inflow                   |                 |                    |    
| E-wave velocity, cm/s           | 89±22           | 90±20              | 0.83  
| A-wave velocity, cm/s           | 57 (42–68)      | 57 (48–64)         | 0.89  
| Transmirtal E/Ea (septal)       | 11.9 (10.1–14.2) | 8.1 (7.4–10.9)    | <0.001 
| A/Ea (lateral)                  | 7.8 (5.3–11.8)  | 6.6 (5.4–8.3)      | 0.13  
| A-PA A reverse, ms              | 27.1±6.3        | 36.1±6.1           | 0.002 
| Ventricular function            |                 |                    |    
| Tei index (LV)                  | 0.50±0.15       | 0.47±0.10          | 0.44  
| Tei index (RV)                  | 0.55 (0.49–0.58) | 0.53 (0.43–0.56) | 0.24  
| LVEF, %                         | 65 (58–69)      | 65 (58–77)         | 0.42  
| TD velocities                   |                 |                    |    
| Lateral mitral Ea, cm/s         | 10.8±4.3        | 13.5±4.3           | 0.02  
| Lateral mitral Aa,              | 6.6±2.4         | 7.8±2.8            | 0.06  
| Lateral mitral Sa,              | 6.7 (5.8–11.4)  | 8.4 (6.9–9.8)      | 0.31  
| Mitral septal Ea, cm/s          | 7.4±3.1         | 10.0±3.2           | 0.002 
| Mitral septal Sa,               | 5.8 (4.4–7.2)   | 6.1 (5.2–7.0)      | 0.58  
| Mitral septal Sa,               | 6.9±1.8         | 7.5±1.8            | 0.18  
| Lateral tricuspid Ea, cm/s      | 11.4±5.1        | 14.0±3.4           | 0.01  
| Lateral tricuspid Aa            | 10.3±3.1        | 10.8±3.2           | 0.57  
| Lateral tricuspid Sa            | 11.3±2.9        | 12.5±2.9           | 0.11  

A-PA A reverse indicates mitral A-wave minus pulmonary reverse A-wave duration (ms); all other abbreviations are as in Table 2.

Data are expressed as median±SD or mean (25th to 75th percentile).

Predictors of Secondary End Point

Echocardiographic and TD parameters of patients who developed the secondary end point are outlined in Table 3. By univariate analysis, septal E/Ea and maximum VO2 predicted development of significant cardiac symptoms (Table 4). There was strong inverse correlation between maximum VO2 and septal E/Ea (γ=54−2x, r=−0.74, P<0.01). Given the strong correlation between septal E/Ea and maximum VO2, when both were entered into the forward stepwise regression model, only maximum VO2 was predictive of patients experiencing symptoms (r=0.427, R2=0.182, P<0.001). Interestingly, by univariate analysis, lateral transmirtal E/Ea ratio did not correlate with patients who experienced symptoms. ECG data demonstrated prolonged QRS and QTc duration among symptomatic patients. In addition, a significant number of symptomatic patients had ECG evidence of dysynchronous ventricular activation compared with asymptomatic children (Table 5).

Exercise Capacity

Upright exercise testing was performed in 38 patients >8 years of age, 16 (67%) of whom were symptomatic (Table 5). There were significant differences in exercise duration and maximum VO2 between symptomatic and asymptomatic patients. Maximum VO2 correlated inversely with septal E/Ea ratio (r=0.740, P<0.01; Figure 2). By linear regression analysis, there was a significant inverse relationship between NYHA class and VO2max (r=0.669, P<0.001) and between NYHA class and septal E/Ea ratio (r=0.576, P<0.001). Of the symptomatic patients who underwent exercise testing, 81% had a blunted heart rate response compared with 18% of patients who were symptom free; blunted blood pressure response occurred in 50% and 10% of symptomatic and asymptomatic patients, respectively (P<0.01). Correlation

TABLE 4. Univariate Predictors of Primary and Secondary End Points

| Predictors of End Points | F Value | P  
|-------------------------|---------|---- 
| Univariate predictors of primary end point |         |    
| Septal E/Ea             | 20.74   | <0.001 
| Peak VO2                | 7.85    | 0.008  
| Maximal ST              | 0.49    | 0.490  
| Septal Ea               | 4.26    | 0.046  
| Univariate predictors of secondary end points |      |    
| Septal E/Ea             | 6.00    | 0.019  
| Peak VO2                | 7.58    | 0.009  
| Maximal ST              | 3.76    | 0.060  
| Septal Ea               | 3.40    | 0.074  
| Tricuspid Ea            | 0.09    | 0.767  
| Mitral Ea               | 2.60    | 0.117  

TABLE 5. ECG Characteristics and Exercise Capacity in Symptomatic Children With HCM

| Clinical Status          | Symptomatic | Symptom Free | P  
|--------------------------|-------------|--------------|---- 
| ECG                      |             |              |    
| QRS duration, ms         | 100 (95–145)| 95 (87–106)  | 0.01 
| QTc, ms                  | 428 (411–494)| 420 (399–434)| 0.03 
| LV hypertrophy           | 12/21       | 35/59        | NS  
| Dysynchronous activation | 13/21       | 4/59         | <0.01 
| Exercise capacity         |             |              |    
| VO2max mL · kg−1 · min−1 | 24.5±9.4   | 37.3±10.9    | <0.001 
| Maximum exercise time, min | 9.2±1.9  | 12.1±2.8     | 0.003 
| Peak heart rate, bpm      | 151±24     | 176±19       | 0.004 
| Exercise capacity, percent | <10th     | 50±0.07      | 0.05 
| Respiratory exchange ratio | 1.05±0.09 | 1.03±0.07    | 0.57 
| Blunted heart rate response | 13/16     | 4/22         | <0.01 
| Blunted blood pressure response | 8/16      | 2/22         | <0.01 

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coefficients for NYHA class and exercise variables in symptomatic patients are presented in Table 6.

**Discussion**

Risk factors for SCD in adults with HCM include massive LV hypertrophy, VT, syncope, flat blood pressure response to exercise, early age at diagnosis, and positive family history.1-7,19,21,22 The importance of septal thickness as a predictor of SCD remains contentious. Spirito et al5 reported no incidence of SCD in 400 patients with septal thickness <15 mm compared with a 2% annual risk in patients with a septal thickness >30 mm. Maron et al23 reported an increased LV outflow tract gradient correlated with adverse clinical events. Conversely, Elliot et al16 evaluated 630 adults with HCM in whom most deaths occurred in patients with a septal thickness <30 mm. Mortality was influenced by the presence of several other clinical markers.6 Two pediatric reports have studied adverse clinical outcomes in children >1 year of age. In a study of 99 children, Yetman et al22 reported a 2.7% annual risk of death in children >8 years age. Risk factors for death included increased QTc dispersion, VT, and myocardial bridging of the left anterior descending coronary artery. By univariate analysis, Romeo et al24 identified reduced LV ejection fraction, syncopal episodes, increased LV end-diastolic pressure, and severe dyspnea to be associated with a poor prognosis in 37 children <14 years of age. Multivariate analysis revealed ejection fraction and syncopal episodes as independent predictors of survival in this cohort. Suda et al7 investigated LV and septal dimensions as predictors of adverse clinical outcomes in 19 infants with HCM. Irrespective of the underlying cause, nonsurvivors were shown to have earlier or progressive hypertrophy of the LV posterior wall (LV Z score 5.2 versus 1.3 for nonsurvivors versus survivors) and to be more prevalent among children with metabolic disease or Noonan’s syndrome.

**Mitral Inflow Patterns and TD**

Among adults with HCM, routine transmitral Doppler inflow velocities have been shown to correlate poorly with symptoms, exercise capacity, mean LA pressure, and LV hypertrophy.8,10,25 Previous adult studies reported HCM patients have lower mitral E-wave velocities, higher A-wave velocities, prolonged E-wave deceleration time, and a mitral E/A ratio <1; however, there is significant overlap, and many patients have either a normal or pseudonormalized pattern.26-28 We have shown that in children with HCM, transmitral E- and A-wave velocities failed to distinguish between patients who reached the clinical end points of this study. The mitral E-wave deceleration time was significantly prolonged in patients with HCM compared with normal controls. Significant variation in mitral inflow velocities with altered loading conditions makes this an unreliable echocardiographic predictor of diastolic dysfunction in children with HCM. The failure of conventional mitral inflow Doppler velocities to predict clinical outcomes in children with HCM led us to evaluate other potentially prognostic echocardiographic variables.

This is the first study to demonstrate that children with HCM have lower early diastolic TD velocities than age- and gender-matched controls. Matsumura et al25 reported similar findings in an adult population with HCM. More importantly, by forward stepwise regression, we were able to identify that the septal E/Ea velocity ratio predicted children at risk of death, VT, and cardiac arrest. This finding has not been reported previously in adult or pediatric populations. The majority of patients in the present study had asymmetric septal hypertrophy, and the finding that the septal E/Ea ratio may predict children who will meet the primary end point may not be surprising. Disorganized myocardial fiber arrangement is likely a major determinant of impaired LV relaxation in HCM patients. A significant increase in the septal E/Ea ratio is most likely secondary to both anatomic and hemodynamic abnormalities in these children. Increasing myocardial cell hypertrophy and fiber disarray may also affect electrical conduction in the ventricular septum, predisposing these patients to an increased propensity for ventricular dysrythmias and SCD. In adult studies, increased LV end-diastolic pressure is consistent with an increased septal E/Ea ratio, and this may play a significant role in the development of symptoms, worsening NYHA class, and decreased exercise performance in these children. Peak VO₂, predicted children at risk of developing significant cardiac symptoms. Although by univariate analysis, several factors predicted development of symptoms, only the peak VO₂ was predictive by stepwise progression.
2D Echocardiographic LV Measures
The present study demonstrated that children who met the primary and secondary end points were more likely to have increased thickness of the LV posterior wall and septum, increased maximal LV wall thickness, and larger LA volumes. However, none of these parameters, including maximal LV thickness, were predictive of death, VT, or cardiac arrest by stepwise forward regression. This would corroborate data from previous studies that proved that patients with the most ventricular and septal hypertrophy were not necessarily those most at risk of SCD or other significant cardiac events.

Exercise Capacity
Matsumura et al. demonstrated that an increased lateral E/Ea ratio was significantly associated with maximum VO2 in adults. The present study demonstrated strong correlation between septal E/Ea ratio and maximum VO2 in pediatric HCM patients. We also showed that NYHA class correlated significantly with maximum VO2, irrespective of presence of LV outflow tract obstruction, hence validating the use of NYHA class among patients in the present study. Hemodynamic mechanisms for impaired exercise tolerance in children with HCM remain poorly defined. Postulated mechanisms in adults include elevated LA pressure, impaired augmentation of stroke volume secondary to abnormal diastolic filling, or impairment in LA and LV systolic performance. From the present study, a significantly shorter Doppler mitral A-wave to pulmonary reverse A-wave duration difference in symptomatic patients would suggest elevated LA pressure to be a similar hemodynamic mechanism in children. Children who were symptomatic also had significantly increased QRS duration and a significant propensity to dyssynchronous ventricular activation by ECG criteria. Similarly, abnormal ventricular depolarization-repolarization with TD has been reported recently in patients with repaired tetralogy of Fallot as a potential risk factor for VT and SCD, with TD has been reported recently in patients with repaired
tolysis-repolarization to dyssynchronous ventricular activation by ECG criteria.

Acknowledgments
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