Hypertrophic cardiomyopathy (HCM) is a heterogeneous condition with highly variable phenotypic expression and is the leading cause of sudden cardiac death in young athletes worldwide. The clinical profile of athletes with HCM capable of competing in sporting activities at an extraordinarily high level has not been characterized. Traditional methods for differentiating physiological left ventricular hypertrophy (athlete’s heart) from HCM have relied on parameters derived from sedentary HCM patients and healthy athletes. Anecdotal evidence suggests that such algorithms may not be directly applicable to athletes with HCM.

This study sought to characterize the clinical profile of young athletes with HCM diagnosed during preparticipation cardiovascular evaluation or in the context of family screening. The results were compared with young sedentary HCM patients to determine differences in disease phenotype between individuals with HCM who exercise regularly and those who are sedentary. The results from a small subset of athletes with HCM revealing mild (13–16 mm) concentric left ventricular hypertrophy (LVH) were also compared with a group of healthy athletes with physiological LVH to ascertain the reliability of current discriminating structural and functional left ventricular (LV) parameters used to differentiate between the 2 entities.

Methods

Setting

This study was collaboration between 2 specialist cardiomyopathy centers in the United Kingdom and France. These institutions receive direct referrals from preparticipation cardiovascular evaluation of young professional athletes, including those suspected with HCM.
St George’s Hospital (London, United Kingdom) and the French Institute of Health and Medical Research (Rennes, France) are dedicated Sports Cardiology centers and work closely with the charitable organization Cardiac Risk in the Young and the French National Sports Ministry, respectively, both of whom conduct National screening programs for elite athletes. Since 2010, both institutions have received referrals from Qatar Orthopedic and Sports Medicine Hospital (Doha, Qatar), which has a highly active cardiovascular screening program that serves the entire Persian Gulf region. All elite athletes receive a 12-lead ECG and 2-dimensional echocardiography as part of these screening programs.9

Athletes With HCM
Between 2000 and 2014, 106 consecutive, young (aged 14–35 years), asymptomatic athletes were diagnosed with HCM. The preliminary cardiac investigations resulting in the diagnosis were conducted during a period when these athletes were still actively engaged in competitive sports and before any decision regarding disqualified or cessation of exercise. Of the 106 athletes, 78 (76%) were detected during sports participation screening, and the remainder were identified through familial screening. All athletes with HCM competed at regional, national, or international level and 86 (81.1%) had performed at national or international level during their career. Athletes with HCM competed in a range of sports, including soccer (n=41, 38.7%), rugby (n=11, 10.4%), basketball (n=11, 10.4%), tennis (n=17, 6.6%), cycling (n=4, 3.8%), handball (n=4, 3.8%), distance running (n=4, 3.8%), swimming (n=3, 2.8%), and a mix of other sports (n≥2/sport; n=21, 19.8%). All individuals had baseline blood pressures of <140/90 mm Hg. The diagnosis of HCM was based on LVH >16 mm in any myocardial segment, as assessed on echocardiography and cardiac MRI (CMRI), in the absence of another cardiac disorder or systemic condition capable of producing the same magnitude of LVH.10,11 In cases of mild LVH, HCM was diagnosed in the context of a combination of electrocardiographic anomalies and left ventricular outflow tract obstruction; (4) late gadolinium enhancement relative; (2) nonconcentric patterns of LVH; (3) dynamic left ven-
tion capable of producing the same magnitude of LVH.10,11 In cases

Healthy Athletes With Mild LVH
A second comparison was made between 15 of the 106 athletes with HCM who expressed mild concentric LVH (13–16 mm) and 55 healthy athletes with mild physiological LVH (13–16 mm). The latter were selected from a database of 3210 elite athletes evaluated between 2000 and 2012 with ECG and transthoracic echocardiography, as previously reported. These athletes competed in a range of sports, including soccer (n=12, 21.8%), rugby (n=8, 14.5%), rowing (n=6, 10.9%), boxing (n=5, 9.1%), cycling (n=4, 7.3%), swimming (n=3, 5.5%), and a mix of other sports (n≤2/sport; n=17, 31%). All healthy athletes underwent cardiopulmonary exercise testing, 24-hour Holter monitoring, and CMRI as part of additional work-up to exclude HCM. Figure 1 summarizes the 2 comparison arms. For the purposes of this study, electrocardiographic and echocardiographic analysis was performed on the presenting ECG and echocardiogram.

Electrocardiography
Electrocardiography was performed using standard 12-lead positions using a GE Marquette Hellige (Milwaukee, USA) or Philips Pagewriter Trim III (Bothel, Washington) as described elsewhere.9 Electrocardiograms were analyzed and deemed normal or abnormal in accordance with current European recommendations.13 T-wave inversion of ≥−0.1 mV in ≥2 leads was considered significant (excluding AVR, V1+lead III in isolation). Biphasic T-wave inversion was counted as abnormal if the negative deflection of the T-wave exceeded ≥−0.1 mV. Deep T-wave inversion was defined as a T-wave deflection ≥−0.2 mV.

Echocardiography
Two-dimensional echocardiography was performed using either a GE Vivid 1 (Tirat, Israel), Philips Sonos 7500, Philips iE33, or Philips CX50 (Bothel, Washington). Standard views were obtained and cavity and wall thickness measurements performed using established guidelines.14 LV wall thickness was measured in the parasternal long axis at end-diastole and the parasternal short axis at end-diastole at the levels of the mitral valve, papillary muscles, and apex, with the maximal LV wall thickness defined as the greatest measurement obtained. The relative wall thickness was derived by dividing the sum of the end diastolic LV septal and posterior wall thicknesses by the left ventricular end diastolic dimension (LVEDD). Pulsed Doppler recordings were performed at the distal margins of the mitral valve leaflets for early (E) and late (A) diastolic velocities. Tissue Doppler imaging of septal and lateral mitral annular movement was recorded from the apical 4-chamber views to obtain systolic (S′) and diastolic early (E′) and late (A′) peak velocities.15 The ratio of the E′ velocity to the E′ septal and lateral annular velocities were averaged to provide an index of diastolic function.16 Left ventricular ejection fraction was calculated from LV volumes using Simpson’s rule.14

Further Investigations
Further investigations in all individuals with HCM included a maximal exercise tolerance test, 24-hour Holter monitor, and CMRI. Additionally, athletes with HCM were subject to an upright cardiopulmonary exercise test using a COSMED E100w cycle ergometer (Rome, Italy).18

Ethical and Institutional Review Board Approval
Ethical approval was granted by the National Research Ethics Service, Essex 2 Research Ethics Committee in the United Kingdom, the French Ministry of health and youth in France, and Shafallah Medical Genetic Center in Qatar. The study was approved by an institutional review committee, and all participants gave informed consent.

Investigations in Athletes and Sedentary HCM Patients
All individuals with HCM (both athletes and sedentary patients) and healthy athletes with physiological LVH were evaluated as follows.

Figure 1. Comparison arms of the study. HCM indicates hypertrophic cardiomyopathy; and LVH, left ventricular hypertrophy.
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Table 1. Demographics of Athletes With HCM and Sedentary HCM Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Athletes With HCM, n=106</th>
<th>Sedentary HCM Patients, n=101</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation, y</td>
<td>24.3±6.9</td>
<td>25.8±6.0</td>
<td>0.101</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>94.3</td>
<td>90.1</td>
<td>0.253</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
<td>0.763</td>
</tr>
<tr>
<td>White</td>
<td>59.4</td>
<td>64.4</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>33.3</td>
<td>28.7</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>7.5</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.95±0.18</td>
<td>2.00±0.27</td>
<td>0.299</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.7±11.9</td>
<td>121.27±14.8</td>
<td>0.443</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72.7±10.7</td>
<td>74.1±10.7</td>
<td>0.537</td>
</tr>
<tr>
<td>Family history of HCM or SCD, %</td>
<td>26.4</td>
<td>47.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Murmur on examination, %</td>
<td>16.5</td>
<td>33.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>

HCM indicates hypertrophic cardiomyopathy; and SCD, sudden cardiac death.

Statistical Analysis

Data were expressed as mean±standard deviation or percentages as appropriate and analyzed using IBM SPSS software, version 20 (Armonk, NY). Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Group differences were tested using Student’s t test or Mann–Whitney U test for normally and non-normally distributed variables, respectively. The chi-squared test or Fisher exact test was used as appropriate to test group differences of proportions. To identify the most parsimonious predictors of athletic status in HCM patients, stepwise logistic regression (forward likelihood ratio) was used. Variables included in the model consisted of those identified as significant predictors of athletic status in univariate analysis and those considered clinically important. Receiver operating characteristic curve analysis was used to test the sensitivity and specificity of those variables that showed significant differences between athletes with morphologically mild concentric HCM and healthy athletes with physiological LVH. Optimal cut-off values, defined as the best compromise between sensitivity and specificity, were calculated by Youden’s Index. Significance was defined as a 2-tailed P value of <0.05 throughout.

Results

Comparison of Athletes With HCM to Sedentary HCM Patients

Demographics

There were no significant differences between athletes with HCM and sedentary HCM patients with respect to age, sex, ethnicity, body surface area, and blood pressure profile (Table 1). A higher proportion of sedentary patients had a family history of HCM, a family history of sudden cardiac death, or a cardiac murmur.

Electrocardiographic Changes

The electrocardiographic differences between athletes with HCM and sedentary HCM patients are illustrated in Table 2. T-wave inversion was common in all individuals with HCM, but was more frequent in the athletic cohort compared with sedentary patients (96.2% versus 84.2%, P=0.003). The majority of T-wave inversion in both groups was deep and affected the lateral leads. There were no significant differences between the groups with respect to other abnormal ECG patterns.13 Two athletes with HCM had an entirely normal ECG. The diagnosis of HCM in these individuals was triggered by an abnormal echocardiogram and a positive family history for the condition.

Structural Changes

The echocardiographic and CMRI characteristics of athletes with HCM and sedentary HCM patients are presented in Table 3. Athletes with HCM exhibited a lower mean maximal left ventricular wall thickness compared with sedentary patients (15.8±3.4 versus 19.7±6.5 mm, P<0.001) and a larger LVEDD (47.8±6.0 versus 44.3±7.7 mm, P<0.001). Correspondingly, the relative wall thickness was smaller in athletes with HCM compared with sedentary patients (0.57±0.21 versus 0.71±0.34, P<0.001). In total, 15 (14.2%) athletes with HCM revealed an LVEDD of ≥54 mm. Important differences were observed in the pattern of LVH between athletes with HCM and sedentary patients. Asymmetrical septal hypertrophy was the predominant pattern in both groups, but athletes with HCM were more likely to exhibit apical LVH (35.8% versus 11.9%, P<0.001; Figure 2). Of note, only 15 (14.2%) athletes with HCM exhibited concentric LVH.

The LV end-diastolic volumes measured on CMRI were greater in athletes with HCM compared with sedentary HCM patients. There were, however, no differences in LV mass between the 2 groups. A similar proportion of athletes with HCM and sedentary patients revealed LGE.

Table 2. Electrocardiographic Characteristics of Athletes With HCM and Sedentary HCM Patients

<table>
<thead>
<tr>
<th>Electrocardiographic Parameter</th>
<th>Athletes With HCM, n=106</th>
<th>Sedentary HCM Patients, n=101</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>59.9±9.9</td>
<td>67.1±14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sinus rhythm, %</td>
<td>100</td>
<td>98.0</td>
<td>0.145</td>
</tr>
<tr>
<td>1st degree heart block, %</td>
<td>11.5</td>
<td>8.6</td>
<td>0.496</td>
</tr>
<tr>
<td>Left-axis deviation, %</td>
<td>7.5</td>
<td>11.9</td>
<td>0.291</td>
</tr>
<tr>
<td>Right-axis deviation, %</td>
<td>1.9</td>
<td>5.9</td>
<td>0.130</td>
</tr>
<tr>
<td>Left bundle branch block, %</td>
<td>0.0</td>
<td>5.0</td>
<td>0.020</td>
</tr>
<tr>
<td>Right bundle branch block, %</td>
<td>1.9</td>
<td>4.0</td>
<td>0.374</td>
</tr>
<tr>
<td>Right ventricular hypertrophy*, %</td>
<td>11.5</td>
<td>18.9</td>
<td>0.145</td>
</tr>
<tr>
<td>Left ventricular hypertrophy*</td>
<td>61.3</td>
<td>51.5</td>
<td>0.154</td>
</tr>
<tr>
<td>Left atrial enlargement, %</td>
<td>39.6</td>
<td>37.6</td>
<td>0.768</td>
</tr>
<tr>
<td>Right atrial enlargement, %</td>
<td>17.9</td>
<td>17.8</td>
<td>0.985</td>
</tr>
<tr>
<td>Pathological Q-waves, %</td>
<td>23.6</td>
<td>19.8</td>
<td>0.510</td>
</tr>
<tr>
<td>TWI, %</td>
<td>96.2</td>
<td>84.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Confined to V1–V4</td>
<td>0.9</td>
<td>4.0</td>
<td>0.158</td>
</tr>
<tr>
<td>Extending to inferior leads</td>
<td>9.4</td>
<td>6.9</td>
<td>0.512</td>
</tr>
<tr>
<td>Extending to lateral leads</td>
<td>85.8</td>
<td>73.3</td>
<td>0.024</td>
</tr>
<tr>
<td>Deep TWI, %</td>
<td>85.7</td>
<td>73.3</td>
<td>0.027</td>
</tr>
<tr>
<td>ST-segment elevation, %</td>
<td>63.8</td>
<td>49.5</td>
<td>0.038</td>
</tr>
<tr>
<td>ST-segment depression, %</td>
<td>57.1</td>
<td>42.6</td>
<td>0.049</td>
</tr>
<tr>
<td>QRS fragmentation, %</td>
<td>22.3</td>
<td>39.6</td>
<td>0.008</td>
</tr>
</tbody>
</table>

HCM indicates hypertrophic cardiomyopathy; and TWI, T-wave inversion.

*By Sokolow–Lyon criteria.
Sheikh et al  Athletes With Hypertrophic Cardiomyopathy

**Functional Changes**
Athletes with HCM showed superior LV diastolic indices compared with sedentary HCM patients, as assessed by Tissue Doppler imaging in both the septal and lateral mitral annulus (Table 3). The average E/E' ratio was smaller in athletes with HCM compared with sedentary HCM patients (7.9±2.4 versus 10.7±3.9, *P*<0.001). The majority of athletes with HCM exhibited diastolic indices within traditionally accepted normal limits;19,20 92.5% had an average E/E' <12,21 59.4% had a septal-E' ≥0.09 m/s, and 86.8% had a lateral-E' ≥0.09 m/s.

Athletes with HCM demonstrated a lower prevalence of systolic anterior motion of the mitral valve leaflets (SAM), left ventricular outflow tract pressure gradients of ≥30 mm Hg under basal conditions, and moderate or severe mitral regurgitation compared with sedentary patients.

**Exercise Testing and Holter Monitoring**
Athletes with HCM obtained mean peak oxygen consumption (pVO_{2}) of 110%±24% of that predicted for age and sex and a quarter (25.5%) achieved a pVO_{2} of ≥120% of predicted. Fourteen (13.2%) athletes with HCM displayed abnormalities on exercise testing. Nine athletes with HCM (8.5%) demonstrated a blunted blood pressure response to exercise (systolic rise of <25 mm Hg) compared with 23 sedentary HCM patients (22.8%, *P*=0.004). Exercise-induced arrhythmias were observed in 6 (5.6%) athletes with HCM, specifically nonsustained ventricular tachycardia (n=1); supraventricular tachycardia (n=2); atrial fibrillation (n=1); and frequent ventricular ectopics (n=2).

During ambulatory 24-hour Holter monitoring, 13 athletes with HCM (12.3%) revealed arrhythmias, specifically nonsustained ventricular tachycardia (n=9); supraventricular...

### Table 3. Structural Characteristics of Athletes With HCM and Sedentary HCM Patients on Echocardiography and Cardiac MRI

<table>
<thead>
<tr>
<th>Structural Characteristic</th>
<th>Athletes With HCM, n=106</th>
<th>Sedentary HCM Patients, n=101</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial dimension, mm</td>
<td>38.1±6.5</td>
<td>38.7±6.6</td>
<td>0.347</td>
</tr>
<tr>
<td>Left ventricular end diastolic dimension, mm</td>
<td>47.8±6.0</td>
<td>44.3±7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal left ventricular wall thickness, mm</td>
<td>15.8±3.4</td>
<td>19.7±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.57±0.21</td>
<td>0.71±0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>41.1±9.3</td>
<td>40.5±10.0</td>
<td>0.391</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>67.7±6.6</td>
<td>58.6±12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic anterior motion of the mitral valve leaflets at rest, %</td>
<td>8.1</td>
<td>23.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Resting left ventricular outflow tract gradient ≥30 mm Hg, %</td>
<td>2.0</td>
<td>12.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Mitral inflow E-wave, m/s</td>
<td>0.79±0.19</td>
<td>0.75±0.17</td>
<td>0.173</td>
</tr>
<tr>
<td>Mitral inflow A-wave, m/s</td>
<td>0.49±0.17</td>
<td>0.52±0.16</td>
<td>0.061</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.73±0.53</td>
<td>1.55±0.51</td>
<td>0.018</td>
</tr>
<tr>
<td>Mitral valve deceleration time</td>
<td>193.9±49.0</td>
<td>193.6±55.7</td>
<td>0.974</td>
</tr>
<tr>
<td>Lateral S', m/s</td>
<td>0.10±0.02</td>
<td>0.08±0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral E', m/s</td>
<td>0.13±0.04</td>
<td>0.10±0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lateral E/E'</td>
<td>6.7±2.4</td>
<td>8.9±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal E', m/s</td>
<td>0.09±0.03</td>
<td>0.07±0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal E/E'</td>
<td>9.3±3.2</td>
<td>12.6±5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average E/E'</td>
<td>7.9±2.4</td>
<td>10.7±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral regurgitation &gt;mild, %</td>
<td>2.9</td>
<td>30.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular hypertrophy pattern, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal</td>
<td>45.3</td>
<td>50.5</td>
<td></td>
</tr>
<tr>
<td>Apical</td>
<td>35.8</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Concentric</td>
<td>14.2</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>4.7</td>
<td>35.6</td>
<td></td>
</tr>
<tr>
<td>Cardiac MRI, %</td>
<td>66.0</td>
<td>66.3</td>
<td></td>
</tr>
<tr>
<td>Left ventricular end diastolic volume index, mL/m²</td>
<td>83.6±16.8</td>
<td>73.4±19.5</td>
<td>0.021</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>70.8±7.9</td>
<td>72.5±8.9</td>
<td>0.221</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>102.6±31.1</td>
<td>104.4±42.3</td>
<td>0.931</td>
</tr>
<tr>
<td>Late gadolinium enhancement, %</td>
<td>33.0</td>
<td>40.6</td>
<td>0.258</td>
</tr>
</tbody>
</table>

HCM indicates hypertrophic cardiomyopathy; and LVEF, left ventricular ejection fraction.

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tachycardia (n=2); and atrial fibrillation (n=2). A further 10 athletes with HCM (9.4%) demonstrated nonspecific findings, namely couplets and triplets (n=7), frequent (>2000/ per 24 hours) ventricular ectopic beats (n=2), and a junctional rhythm (n=1).

**Multivariable Analysis**
Stepwise logistic regression revealed the following variables to be the strongest predictors of athletic status (Table 4): (1) apical or concentric patterns of LVH as opposed to a mixed pattern; (2) lower maximum LV wall thickness; (3) absence of >mild mitral regurgitation; (4) ST-segment elevation on the ECG; (5) absence of QRS fragmentation on the ECG. The final model had a Nagelkerke $R^2$ of 0.524.

**Comparison of Athletes With Morphologically Mild HCM to Healthy Athletes With Physiological LVH**
The majority of athletes with HCM exhibited either a left ventricular wall thickness ≥15 (n=48; 45.3%) and non-concentric patterns of LVH (n=91; 85.8%), which would be considered diagnostic of HCM based on current algorithms.2–5

Fifty-eight athletes with HCM revealed morphologically mild LVH (13–16 mm). Of these, only a small minority exhibited concentric LVH (n=15; 14.2%) consistent with the conventional gray zone.2–3 These athletes had a higher prevalence of T-wave inversion compared with athletes with physiological LVH (100% versus 5.5%, $P<0.001$). Deep T-wave inversion in the lateral leads (93.3%), pathological Q-waves (26.7%), and ST-segment depression (46.7%) were observed exclusively in athletes with HCM.

Athletes with mild concentric HCM revealed smaller LV cavities (49.3±4.4 mm versus 54.9±4.7 mm, $P<0.001$) and a higher $E/E'$ ratio (7.1±2.0 versus 5.5±1.1, $P<0.001$) compared with athletes with physiological LVH. A small proportion (13.3%) of athletes with mild concentric HCM revealed an LVEDD of ≥54 mm, 66.7% had a septal $E'$ of ≥0.09 m/s and 93.3% had a lateral $E'$ of ≥0.09 m/s. All 15 athletes showed an average $E/E'$ of <12 and 87% had a normal left atrial dimension. Receiver operating characteristic curve analysis demonstrated that most structural and functional parameters had poor ability to differentiate between morphologically mild concentric HCM and physiological LVH in athletes (Table 5). Only an LVEDD ≤51 mm and septal $E'$ ≤0.11 m/s showed good discriminating ability (area under the curve >0.8).

**Role of Other Investigations**
None of the 15 athletes with mild concentric HCM revealed abnormalities on exercise testing. One athlete (6.7%) with mild concentric HCM demonstrated arrhythmias on 24-hour Holter monitoring, namely nonsustained ventricular tachycardia. None of the healthy athletes with physiological LVH demonstrated abnormalities on exercise testing or Holter monitoring.

Athletes with mild concentric HCM obtained a similar percentage predicted pVO$_2$ compared with athletes with physiological LVH (113%±22% versus 122%±14%, $P=0.057$). Five (33.3%) athletes with mild concentric HCM obtained a pVO$_2$ of >120% of that predicted compared with 31 (56.9%) athletes with physiological LVH. Four athletes with mild concentric HCM (26.7%) revealed LGE on CMRI compared with none of the athletes with physiological LVH.

**Discussion**
Hypertrophic cardiomyopathy is generally characterized by reduced functional capacity,18,22 and most patients are unable to engage in competitive sport involving high-intensity exercise.23 However, several reports in the literature have described affected individuals capable of extraordinary feats of athletic achievement.6–8 Our knowledge of the ability of these individuals to perform at such a high level, and whether their phenotype differs from ordinary (sedentary) patients, is limited. Furthermore, the superadded effect of cardiac loading conditions associated with exercise itself on the HCM phenotype is also unknown. The differentiation of physiological LVH from morphologically mild HCM is challenging, and an erroneous diagnosis has potentially serious consequences. When faced with such a dilemma, the differentiation places considerable reliance on other structural and functional LV parameters, assuming that they are similar to those in sedentary HCM patients. The present study provided a unique opportunity for examining the HCM phenotype in affected young asymptomatic athletes.

**Differences in Athletes With HCM and Sedentary HCM Patients**
Compared with sedentary HCM patients, athletes with HCM revealed milder LVH and the apical variant of the condition in more than a third of the cohort, both of which were independent predictors of athletic status (Figure 3). The apical variant of HCM could also be classified into the mild LVH category because the hypertrophy is localized to a small segment of the left ventricle and may not affect the dynamics of the chamber as much as more generalized hypertrophy.

Similar to studies comparing healthy athletes with sedentary controls, athletes with HCM showed larger LV cavity dimensions compared with sedentary HCM patients. Indeed, only a small proportion of sedentary HCM patients (3%) showed dimensions exceeding 54 mm compared with 14.2% of the athletes with HCM. It is generally recognized that a dilated left ventricle is usually observed in the end stages of HCM in ≈5% of patients and is associated with poor contraction and functional capacity.24 In the case of athletes with HCM, the enlarged LV cavity is likely to represent physiological adaptation to increased cardiac workload associated with exercise.25
with exercise. The preservation of radial contraction, longitudinal systolic function, and high pVO₂ favors a physiological process.

Most athletes with HCM showed normal indices of diastolic function according to conventional cut-off values on Tissue Doppler imaging. Only 2% of athletes with HCM revealed left ventricular outflow tract obstruction at rest. Thus, the combination of a larger LV volume, normal LV diastolic function, and absence of dynamic left ventricular outflow tract obstruction likely facilitate the augmentation of stroke

### Table 4. Univariable and Multivariable Predictors of Athletic Status in Patients With HCM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate P Value</th>
<th>Multivariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>0.97 (0.93–1.01)</td>
<td>0.103</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>0.55 (0.19–1.56)</td>
<td>0.259</td>
</tr>
<tr>
<td>Family history of hypertrophic cardiomyopathy/sudden cardiac death</td>
<td>0.40 (0.22–0.71)</td>
<td>0.002</td>
</tr>
<tr>
<td>Murmur on examination</td>
<td>0.39 (0.20–0.77)</td>
<td>0.006</td>
</tr>
<tr>
<td>Heart rate, per 10 bpm</td>
<td>0.61 (0.47–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-wave elevation</td>
<td>4.8 (1.55–14.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>ST elevation</td>
<td>1.80 (1.03–3.14)</td>
<td>0.039</td>
</tr>
<tr>
<td>ST depression</td>
<td>1.73 (1.0–3.0)</td>
<td>0.052</td>
</tr>
<tr>
<td>QRS fragmentation</td>
<td>0.44 (0.24–0.81)</td>
<td>0.009</td>
</tr>
<tr>
<td>LV end diastolic diameter, mm</td>
<td>1.08 (1.03–1.12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximum LV wall thickness, mm</td>
<td>0.88 (0.83–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic anterior motion of anterior mitral valve leaflets (at rest)</td>
<td>0.28 (0.12–0.66)</td>
<td>0.004</td>
</tr>
<tr>
<td>LV outflow tract gradient &gt;30 mm Hg (at rest)</td>
<td>0.15 (0.03–0.69)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mitral E/A</td>
<td>1.97 (1.11–3.49)</td>
<td>0.020</td>
</tr>
<tr>
<td>Average E/E</td>
<td>0.74 (0.66–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral regurgitation (&gt;mild)</td>
<td>0.07 (0.02–0.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV hypertrophy pattern</td>
<td>&lt;0.001</td>
<td>&lt;0.001 (1)</td>
</tr>
<tr>
<td>Apical versus mixed</td>
<td>22.8 (7.3–71.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal versus mixed</td>
<td>6.78 (2.46–18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concentric versus mixed</td>
<td>54 (9.4–309.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia on 24 h Holter</td>
<td>0.32 (0.13–0.75)</td>
<td>0.009</td>
</tr>
<tr>
<td>Documented atrial fibrillation</td>
<td>0.09 (0.02–0.38)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In the multivariable P value column, the numbers in parentheses indicate the order of significance of the independent variables selected in the final forward likelihood ratio model. HCM indicates hypertrophic cardiomyopathy; and LV, left ventricular.

### Table 5. Receiver Operating Characteristic Analysis Evaluating Conventional Structural and Functional Echocardiographic Parameters for Distinguishing Physiological LVH in Healthy Athletes (n=55) From Pathological LVH in Athletes With Mild Concentric HCM (n=15)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area Under the Curve</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD ≤51 mm*</td>
<td>0.819</td>
<td>72.7</td>
<td>81.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD ≤54 mm†</td>
<td>0.819</td>
<td>81.8</td>
<td>61.8</td>
<td></td>
</tr>
<tr>
<td>Average E/E &gt;6.6*</td>
<td>0.653</td>
<td>60.0</td>
<td>79.0</td>
<td>0.171</td>
</tr>
<tr>
<td>Average E/E &gt;12†</td>
<td>0.653</td>
<td>0.0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Relative wall thickness &gt;0.45†</td>
<td>0.760</td>
<td>81.8</td>
<td>65.4</td>
<td>0.013</td>
</tr>
<tr>
<td>Lateral E ≤0.15 m/s*</td>
<td>0.700</td>
<td>90.0</td>
<td>47.4</td>
<td>0.043</td>
</tr>
<tr>
<td>Lateral E ≤0.09 m/s†</td>
<td>0.700</td>
<td>20.0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Left atrium ≤38 mm*</td>
<td>0.602</td>
<td>72.7</td>
<td>45.5</td>
<td>0.263</td>
</tr>
<tr>
<td>Left atrium ≤40 mm†</td>
<td>0.602</td>
<td>90.9</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Septal E ≤0.11 m/s*</td>
<td>0.877</td>
<td>88.9</td>
<td>68.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal E ≤0.09 m/s†</td>
<td>0.877</td>
<td>55.6</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Mitral A wave &gt;0.40*</td>
<td>0.771</td>
<td>100</td>
<td>50.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral A wave &gt;0.46†</td>
<td>0.771</td>
<td>72.7</td>
<td>67.3</td>
<td></td>
</tr>
</tbody>
</table>

HCM indicates hypertrophic cardiomyopathy; LVEDD, left ventricular end diastolic dimension; and LVH, left ventricular hypertrophy.

*Value calculated by Youden’s Index as best compromise between sensitivity and specificity.
†Sensitivity and specificity at traditional cut-off values.
volume, which is the major determinant of peak exercise capacity in HCM in the presence of adequate LV filling.25,26

Myocardial fibrosis is a commonly cited explanation for a noncompliant left ventricle and impaired myocardial relaxation.27 However, a similar proportion of athletes with HCM and sedentary patients demonstrated LGE on CMRI. These results underscore the importance of CMRI as a diagnostic tool in athletes with a high index of suspicion for HCM. At the same time, however, our results suggest that superior methods of detecting generalized fibrosis are necessary to study the pathophysiology of HCM.28 It is also possible that athletes with HCM had a lower ischemic burden because of the absence of severe LVH and mechanical LV obstruction, which enabled more exercise, despite a similar magnitude of scarring.

Differentiation of Athlete’s Heart From Morphologically Mild HCM
Previous studies have reported several parameters, which are now regarded as good discriminators between athlete’s heart and morphologically mild HCM, including LV cavity dimension, indices of LV diastolic function, and left atrial dimension.2,3,11,29 A recent report suggested an LV cavity dimension of ≥54 mm to be a particularly good discriminator, favoring physiological LVH over HCM with both a sensitivity and specificity of 100%.4 However, these studies are limited by the fact that they relied on data from sedentary HCM patients, who do not provide an appropriate comparison group.

Our observations suggest that the vast majority of athletes with HCM exhibit a maximal left ventricular wall thickness of ≥16 mm and nonconcentric patterns of LVH, which would be diagnostic of HCM based on current algorithms for differentiating physiological LVH from morphologically mild HCM. Indeed, only 14% of athletes with HCM seem to fall into the conventional and often challenging gray zone of mild (13–16 mm), concentric LVH. Among athletes in this gray zone, our analysis revealed that an LV cavity ≤51 mm favoring a diagnosis of HCM offers the best compromise between sensitivity and specificity when discriminating physiological from pathologic LVH. A value of ≤54 mm had better sensitivity, but at the expense of higher false-positive results (Table 5). In contrast with a recent report,4 our study failed to identify any cut off value for left atrial diameter that adequately distinguished physiology from pathology. Indices of diastolic function were normal in most athletes with HCM and should not be used in isolation to exclude HCM in an athlete with LVH.

This study reaffirms the value of the ECG in diagnosing HCM in athletes. We concede that our cohort is heavily biased because ECG anomalies, particularly T-wave inversion, were the primary reason for referral after preparticipation screening. The fact remains, however, that 96% of athletes and 84% of patients with HCM exhibited pathological T-wave inversion, the great majority of which involved the lateral leads. Moreover, 57% of athletes with HCM exhibited ST-segment depression and almost a quarter revealed pathological Q-waves. In contrast, none of the athletes with physiological LVH demonstrated deep T-wave inversion in the lateral leads, ST-segment depression, or pathological Q-waves. None of the athletes with HCM exhibited isolated voltage criterion for LVH, reinforcing the message that large QRS complexes in isolation are not necessarily indicative of quiescent HCM.9

Exercise testing and Holter monitoring would have facilitated the diagnosis in only 19% of athletes with HCM. Contrary to a previous publication,18 25% of athletes with HCM achieved a pVO₂ >120% of predicted. In line with a recent publication,30 the value of CMRI is underscored by the
detection of LGE in a third of athletes with HCM, in addition to its ability to delineate the pattern of LVH.

Clinical Implications
Our results have significant practical implications for differentiating physiological LVH from morphologically mild HCM. Most athletes with HCM exhibit features which would facilitate the diagnosis of HCM if current diagnostic algorithms are applied. Among the small proportion of athletes with mild concentric LVH of 13 to 16 mm, an increased LV cavity size, normal diastolic function, or superior indices of functional capacity should not be used in isolation to exclude HCM. An exercise test can help facilitate the diagnosis in a fifth of cases, and CMRI is diagnostic in one third of cases after ECG and echocardiography. In athletes with a high index of suspicion for HCM because of the presence of LVH and coexisting polarization anomalies, the assessing physician should use the whole complement of noninvasive cardiac tests to assist the diagnosis. Although not assessed specifically in this study, detraining, familial evaluation, and genetic testing, though challenging, may also have important additional roles.

Limitations
The authors recognize that a small proportion of athletes with HCM may not have been identified during the screening process given the heterogeneity and aged-related penetrance of the condition, resulting in ascertainment bias. However, the use of history, ECG, and echocardiography to screen all athletes coupled with repeat interval screening at later dates should have limited this number to a minimum. In view of the small number of athletes with mild concentric LVH, it was not feasible to confidently identify independent discriminators of pathological versus physiological LVH using logistic regression. The authors recognize the limitations of receiver operating characteristic analysis in isolation and acknowledge the need for large, purposefully built cohorts that aim to identify independent predictors of HCM in athletes with mild concentric LVH.

Conclusions
Athletes with HCM exhibit qualitatively similar physiological cardiac adaptation to normal healthy athletes. An important minority of athletes with HCM (14%) constitute the conventional gray zone of mild (13–16 mm) concentric LVH. In such cases, a large LV cavity or normal indices of diastolic function alone are insufficient to differentiate pathological from physiological LVH. Conventional echocardiographic parameters should be complemented by ECG, exercise stress testing, and CMRI to minimize the risk of false reassurance.

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Disclosures
None.

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14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD,
Complement echocardiography with ECG, exercise stress testing, and cardiac MRI before making a diagnosis.

In athletes falling within the gray zone of LVH, physicians involved in athlete preparticipation screening programs should be aware that measures of diastolic function, are in isolation insufficient to differentiate physiological LVH from HCM. Therefore, when faced with conventional discriminators between athlete’s heart and HCM, particularly a large left ventricular cavity or normal indices of LV function, one should consider the following:

- **Echocardiography**

- **Cardiomyopathies**
  - Compared with sedentary hypertrophic cardiomyopathy (HCM) patients, athletes with HCM exhibit a higher prevalence of diastolic dysfunction and diastolic heart failure.

- **Ongoing research**

- **References**

- **Clinical perspective**
  - Compared with sedentary hypertrophic cardiomyopathy (HCM) patients, athletes with HCM exhibit a higher prevalence of T-wave inversion, milder left ventricular hypertrophy (LVH), larger cavity dimensions, and superior indices of diastolic function. Fourteen percent of athletes with HCM have an left ventricular end diastolic dimension >54 mm and 93% have an E/E’ of <12. Furthermore, over one-third (36%) of athletes with HCM reveal an apical pattern of LVH, and most (86%) have a magnitude and pattern of hypertrophy consistent with a diagnosis of HCM using conventional definitions. Only a small number (14%) fall within the true gray zone of mild (13–16 mm) concentric LVH. In this small but significant subgroup, conventional discriminators between athlete’s heart and HCM, particularly a large left ventricular cavity or normal indices of diastolic function, are in isolation insufficient to differentiate physiological LVH from HCM. Therefore, when faced with an athlete falling within the gray zone of LVH, physicians involved in athlete preparticipation screening programs should complement echocardiography with ECG, exercise stress testing, and cardiac MRI before making a diagnosis.
Clinical Profile of Athletes With Hypertrophic Cardiomyopathy
Nabeel Sheikh, Michael Papadakis, Frédéric Schnell, Vasileios Panoulas, Aneil Malhotra, Mathew Wilson, François Carré and Sanjay Sharma

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/content/8/9/e000010.full.pdf

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In the article by Sheikh et al, “Clinical Profile of Athletes With Hypertrophic Cardiomyopathy,” which appeared in the July 2015 issue of the journal (Circ Cardiovasc Imaging. 2015;8:e003454), a correction was needed.

The authors discovered an error in Figure 3 of the article; the bottom red/pink oval on the right-hand side should read, “An enlarged left ventricular cavity and normal indices of diastolic function do not necessarily exclude HCM in an athlete.” The word “not” was inadvertently omitted.

The authors regret this error.

This correction has been made to the article, which is available at http://circimaging.ahajournals.org/content/8/7/e003454.