Peripheral microvascular function is altered in young individuals at risk for hypertrophic cardiomyopathy and correlates with myocardial diastolic function.

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Familial hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease, being characterized by gradual thickening of cardiac muscle and increased risk for major cardiac events, including ventricular arrhythmias and sudden cardiac death (9, 23). HCM is inherited in an autosomal dominant fashion, with a 50% risk for transmission of the disease-causing mutation to each child of the affected family (23, 24). The risk for HCM-related cardiac events, including sudden cardiac death, appears to be highest in childhood, with a peak incidence of up to 10% during the first decades of life (3, 26, 29, 42). ECGs are often normal through the early phases of hypertrophy (18, 25). The diagnosis of HCM, currently based on echocardiographic demonstration of regional or diffuse thickening of the myocardium, is more difficult in younger patients due to the progressive nature of the disease (33, 36). Furthermore, distinguishing physiological from pathological hypertrophy is often very challenging in children and young adults who also participate in endurance physical activities. In many individuals with HCM, major cardiac events are the main reason for cardiac assessment leading to diagnosis (48). Imbalance between myocardial perfusion demand and supply exacerbated during stress may represent one of the main culprits of HCM-related cardiac events (41). Although hypertrophy is thought to contribute to increased flow demand, especially in the endocardial territory (43), there seems to be a poor correlation between the risk for clinical complications and degree of hypertrophy (6, 45), particularly in the young (45). Several studies in adult patients with HCM have demonstrated functional and morphological abnormalities in the coronary circulation (2, 28). Coronary vasomotor dysfunction in the microcirculation is an independent predictor of HCM mortality in adults (2) and also one of the key contributors to the development of cardiac remodeling and myocardial dysfunction in HCM. A few previous investigations conducted on adults with HCM suggested that the vascular dysfunction in HCM encompasses both coronary and peripheral vessels (1, 2, 14, 41). Peripheral vascular dysfunction also has prognostic value in patients with coronary risk factors (32, 38). In the present study, we investigated peripheral vascular and myocardial diastolic function in a young cohort of familial HCM. We compared their results with those of healthy controls, including to those of a small group of endurance-trained young athletes with known physiological left ventricular (LV) hypertrophy (LVH). We hypothesized that peripheral vascular and myocardial diastolic function would be altered in individuals at risk for HCM compared with control individuals and athletes and that any changes in peripheral vascular function might also correlate with changes in myocardial diastolic function.

Materials and Methods

Young individuals with familial HCM (mean age: 14 ± 1 yr, n = 36; HCM group) were recruited from outpatient clinics of pediatric cardiology and clinical physiology at Skane University Hospital (Lund, Sweden) between 2010 and 2014. Familial HCM was defined as LVH associated with known HCM-causing mutation or heredity for early diagnosis; myocardial hypertrophy; diastology; endothelium; athletes’ heart

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Table 1. Demographic characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>HCM-Risk Group</th>
<th>HCM-Risk G+ Group</th>
<th>HCM Group</th>
<th>Athlete Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>85</td>
<td>30</td>
<td>11</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Age, yr</td>
<td>14.1 ± 0.1</td>
<td>10.0 ± 1.1</td>
<td>7.3 ± 1.4</td>
<td>13.7 ± 1.4</td>
<td>18.2 ± 0.5</td>
</tr>
<tr>
<td>HCM heredity</td>
<td>0</td>
<td>30</td>
<td>11</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Boys/girls</td>
<td>39/46</td>
<td>16/14</td>
<td>4/7</td>
<td>23/13</td>
<td>12/0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>49.6 ± 0.3</td>
<td>37.3 ± 3.7</td>
<td>29.1 ± 5.2</td>
<td>50.1 ± 4.8</td>
<td>68.9 ± 1.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>151.6 ± 0.3</td>
<td>134.5 ± 5.6</td>
<td>127.2 ± 10.3</td>
<td>145.7 ± 6.5</td>
<td>172.8 ± 1.1</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.4 ± 0.05</td>
<td>1.2 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>19.9 ± 0.4</td>
<td>18.8 ± 0.5</td>
<td>17 ± 0.5</td>
<td>20.5 ± 0.8</td>
<td>22.5 ± 1</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>107/67 ± 1.3/0.8</td>
<td>103/63 ± 2.7/2</td>
<td>99/65 ± 3.3/3.1</td>
<td>105/66 ± 2.6/1.7</td>
<td>109/72 ± 3.3/2.1</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE. The “risk G+” group includes individuals with hypertrophic cardiomyopathy (HCM)-causing mutation and no identifiable left ventricular hypertrophy (LVH) on echo. The HCM-risk group includes both the risk G+ group and first-degree relatives of HCM patients without HCM-causing mutation and no LV hypertrophy on echo.

HCM in first-degree relatives. LVH was defined as an echocardiography-based Z-score for intraventricular septum (IVS) and/or LV posterior wall (PW) thickness > 2.5 SD for individuals < 18 yr of age or > 13 mm for individuals > 18 yr of age (29). Subjects with a known HCM-causing mutation or heredity for familial HCM but with normal myocardial appearance on echo (Z-score for IVS and PW < 2.5 SD) were categorized as the HCM-risk group (mean age: 10 ± 1 yr, n = 30). This group was detected following clinical and genetic cascade screening. HCM-risk and HCM individuals were recruited from 28 unrelated families affected of familial HCM. Healthy volunteers (mean age: 14 ± 1 years, n = 85; control group) and young athletes (mean age: 18 ± 2 yr, n = 12; athlete group) with physiological LVH (Z-score for IVS and/or PW on echo > 2 SD) due to endurance physical exercise (>10 h/wk) were also studied. Neither control subjects nor athletes had any history or heredity for cardiac disease.

Exclusion criteria were familial HCM with outflow obstruction and LVH due to other causes, including congenital heart disease (aortic stenosis or coarctation of the aorta), Noonan syndrome, neuromuscular and metabolic disorders, smoking, and hypertension.

All participants and their guardians (for those under 18 yr of age) were given verbal and written information, and written consent was obtained. This study was approved by the Ethics Committee for Human Research of Lund University.

A complete medical history and physical examination, along with resting 12-lead ECG and echocardiographic and microvascular assessment, were obtained for all participants. A research nurse collected all demographic data. Information regarding the presence of the disease-causing mutation and family history of HCM was obtained from medical records. Genetic screening was performed as part of the standard care in all HCM cases and in 11 of the HCM-risk cases. This included DNA sequencing and examination of the coding exons of the 11 most common HCM-associated genes: myosin heavy chain 7 (MYH7), myosin-binding protein-C3 (MYBPC3), myosin light chain (MYL2), MYL3, troponin T type 2 (TNNT2), troponin I (TPM1), cardiac muscle α-actin (ACTC), troponin I type 3 (TN13), cysteine- and glycine-rich protein 3 (CSRP3), titin cap (TCAP), and the promoter area of phospholamban (PLN) (13) in the proband or as presymptomatic screening of the identified disease-causing mutation in first-degree family members. Genetic analyses were performed by Statens Serum Institut (Copenhagen, Denmark).

Electrocardiography and heart rate variability assessment. Conventional 12-lead resting ECG (Schiller AT-102) was performed in all participants and analyzed using standard ECG criteria (5, 30, 44). A single-lead ECG was recorded for 5 min with a handheld heart rate variability (HRV) device (DailCare BioMedical, Chungli, Taiwan). Each QRS complex was detected, and normal-to-normal (NN) intervals were identified. Recordings were automatically analyzed by HRV analysis software (DailyCare Biomedical). The ratio of low-frequency (LF) to high-frequency (HF) peaks (LF/HF) and mean SD of RR intervals (SDNN) were used as indexes of cardiac autonomic function (12, 45a).

Echocardiography. Transthoracic ECG-triggered echo was performed using an iE33 system (Philips), Integrated M-mode and two-dimensional echo experiments were performed to determine LV wall thickness, chamber dimensions, and cardiac function in accordance with recommendations of the American Society of Echocardiography (15, 20, 21, 37). All echo measurements were performed offline on digital pictures stored in an integrated multimodality image management database (Xcelera, Philips).

Table 2. Electrocardiographic characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Conventional ECG Parameters</th>
<th>Control Group</th>
<th>HCM-Risk Group</th>
<th>HCM-Risk G+ Group</th>
<th>HCM Group</th>
<th>Athlete Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>85</td>
<td>30</td>
<td>11</td>
<td>36</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Normal ECG</td>
<td>66</td>
<td>22</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>19</td>
<td>8</td>
<td>3</td>
<td>20</td>
<td>4</td>
<td></td>
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<tr>
<td>Sinus bradycardia</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular block I</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>P wave pathology</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Left-axis deviation</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>LBBB/RBBB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Minor intraventricular conduction delay</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Pathologic RVS/SV1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deep S in V2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
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<tr>
<td>Elevated QRS amplitudes</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td></td>
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<tr>
<td>Prolonged ventricular activation time</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>S-T or T wave pathology</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Q-wave V5-V6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Corrected QT time borderline/prolongation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are numbers of subjects n. LBBB, LV bundle branch block; RBBB, right ventricular bundle branch block.
LVH was defined as LV wall thickness in end-diastole exceeding +2 SD (in athletes) or +2.5 SD (in HCM) from the mean corrected for age, sex, and body surface area. The thickness of the IVS and PW was expressed as the Z-score in relation to normal distributions adjusted for age and body surface area (15, 21, 33). For statistical analyses, the same algorithm was applied to those older than 18 yr of age to derive a comparable Z-score for use in this group, with their normal upper limit for IVS or PW ultimately being set at 13 mm (30). Body surface area was calculated using the Dubois formula.

LV diastolic myocardial function was assessed via pulsed Doppler of the mitral inflow by measuring the early filling (E) peak velocity (8, 11, 31, 37). Tissue Doppler imaging was performed to measure early diastolic velocity (e'). The E-to-e' ratio (E/e' ratio) was used as an index of LV diastolic filling pressure (11, 31). LV mass was calculated from M-mode measurements (7, 10) and corrected for body surface area. All echo measurements were carried out by a single investigator (E. Fernlund). The intraobserver variability was <10% for all echo variables.

Assessment of cutaneous microvascular vasomotor function via laser Doppler. Cutaneous blood flow responses to endothelium-dependent and -independent agonists were assessed using a laser Doppler multifiber probe (Perimed, Stockholm, Sweden) during transdermal iontophoresis of ACh and sodium nitroprusside (SNP), respectively, on the volar side of the forearm (16, 34, 39). The nondominant upper extremity was chosen in all patients. Anodal iontophoresis was used for ACh, whereas SNP was delivered via cathodaliontophoresis. The current was set at 100 μA for 20 s for both drugs, based on previous work (34, 35, 39, 40, 46). Five consecutive doses were applied for both drugs to generate dose-response curves. Baseline perfusion and changes in response to ACh and SNP were expressed as areas under the curve.

Statistical analysis. Data are expressed as means ± SEM unless otherwise specified. Differences between the groups were calculated using ANOVA. When significant, Bonferroni post hoc testing was used. P values of <0.05 were considered statistically significant. Log transformation was used for those variables with skewed (non-Gaussian) distributions. All analyses were performed using Statview 4.0 for Windows statistical software (SAS Institute).

RESULTS

In total, 163 children, adolescents, and young adults (mean age: 14 yr) were enrolled in the present study. Demographic characteristics of the study population are shown in Table 1.

Genetics. In the HCM group, a disease-causing mutation was found in 26 of 36 HCM cases (72%). MYBPC3 mutations were the most common, being identified in 15 cases. MYH7 mutations were found in seven cases, TNNT2 mutation in two cases, TNNI3 in one case, and TCAP mutation in one case, whereas in the remaining cases of HCM, genetic testing did not reveal any known HCM-causing mutation. In one case with a severe form of HCM (7 yr of age), disease-causing mutations were detected in both MYBPC3 and MYH7. One of the young adults with severe HCM had also double mutations affecting MYBPC3.

In the HCM-risk group, disease-causing mutations were found in 11 patients, as follows: MYBPC3 mutations in 5 cases, MYH7 mutation in 2 cases, TNNT2 mutation in 2 cases, and double mutations detected in both MYBPC3 and MYH7 in 2 cases. No known HCM-causing mutation could be identified in the remaining cases.

Resting 12-lead electrocardiography. Electrocardiographic characteristics of the study population are shown in Table 2. ECG abnormalities were detected in 56% of the HCM cases (20 of 36 cases), consisting of left-axis deviation (13 of 36

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Fig. 1. Heart rate variability (HRV) indexes in the study groups. The “risk G+” group includes individuals with a hypertrophic cardiomyopathy (HCM)-causing mutation and no identifiable left ventricular (LV) hypertrophy on echo. The “HCM-risk” group includes both the risk G+ group and first-degree relatives of HCM patients without a HCM-causing mutation and no LV hypertrophy on echo. Data are shown as medians and interquartile ranges. A: mean SD of RR intervals (SDNN) was similar in all groups. NS, not significant. B: SD1/SD2 was similar in all groups. C: the ratio of low-frequency to high-frequency bands (LF/HF) was higher in the athlete group than in the other groups. *P < 0.01.
cases), ST-T changes and T wave pathology (12 of 36 cases), elevated QRS amplitude (10 of 36 cases), QT prolongation (4 of 36 cases), and deep S in V2 (3 of 36 cases). Some HCM cases had more than one ECG abnormality. In the HCM-risk cases, more minor ECG changes occurred in 27% (8 of 30 cases), specifically sinus bradycardia (3 of 30 cases), pathological R-to-S ratio (2 of 30 cases), ST-T changes or T-wave pathology (3 of 30 cases), and deep S in V2 (1 of 30 cases). Among control subjects and athletes, there were minor ECG changes in 25% and 30%, respectively. The ECG “abnormalities” in these two groups included sinus bradycardia, atrioventricular block I, minor intraventricular conduction delay, delayed juvenile T wave progression, and T wave anamoly.

HRV analysis showed no significant differences in SDNN or LF/HF among control, HCM-risk, and HCM groups (P > 0.1). In athletes, LF/HF was higher than in control subjects (P < 0.01), whereas SDNN was comparable to that in the other groups (Fig. 1).

Echocardiography. Echocardiographic characteristics of the study population are shown in Table 3.

The degree of LVH and LV mass were comparable (P > 0.2) in HCM (means ± SD for PW at diastole: 8.7 ± 3.3 mm, IVS at diastole: 14.6 ± 7.2 mm, and LV mass: 112 ± 53 g/m²) and athlete groups (means ± SD for PW at diastole: 9.4 ± 1.4 mm, IVS at diastole: 10.7 ± 1.4 mm, and LV mass: 100 ± 18 g/m²), whereas control and HCM-risk groups had similar LV thicknesses and LV masses (P > 0.7). The lack of significance in LV IVS between HCM and athlete groups, despite the relatively large difference in the groups' mean values, was probably due to the fact that no differences in the mitral E:A ratio by conventional Doppler were noted between the groups (P > 0.2), nor was any LV outflow obstruction noted.

Tissue Doppler echocardiography. Mitral valve septal tissue Doppler velocity (e') was decreased in the HCM group (P < 0.001) and also in the HCM-risk group (P < 0.05) compared with control and athlete groups (Fig. 2A). The e' ratio was increased in both HCM and HCM-risk groups compared with the control group (9.7 ± 0.1 and 8.4 ± 0.1 vs. 7.1 ± 0.1, P < 0.001).
respectively, \( P < 0.05 \); Fig. 2B). The \( E/e' \) ratio was significantly increased in the HCM group compared with the athlete group (\( P < 0.0001 \)). In the HCM group, there was no difference in \( E/e' \) ratio between mutation-positive and mutation-negative patients (\( P > 0.1 \)). No significant difference was noted in the \( E/e' \) ratio between control and athlete groups (7.1 ± 0.1 and 6.6 ± 0.2, respectively, \( P = 0.3 \); Fig. 2B).

All athletes had an \( E/e' \) ratio of less than eight. A cutoff \( E/e' \) ratio of greater than eight had a specificity of 100% with respect to distinguishing patients with HCM from athletes. Using the same cutoff, in the HCM group, sensitivity was 58% and specificity 79% to differentiate HCM from healthy control individuals. In the whole study cohort, the microvascular response to ACh correlated with the \( E/e' \) ratio (\( r = 0.5, P = 0.001 \); Fig. 5). An example of an ACh-induced response in the forearm is shown in Fig. 6.

**DISCUSSION**

As recently reinforced by the European Society of Cardiology (9), the diagnosis of HCM relies on echocardiographic detection of myocardial hypertrophy in the presence of heredity for familial HCM (25–30% of the HCM cases) or demonstration of HCM sarcomere protein gene mutations (up to 60% of HCM cases). Structural cardiac changes, such as myocyte disarray, fibrosis, and coronary microvascular dysfunction, have been demonstrated in adult HCM (2, 9, 19, 28, 32). However, the precise timeline of these structural changes, including whether they also occur in early stages of HCM, remains unclear. In addition, while it is believed that structural changes might underlie the onset of major adverse events, such adverse events as sudden death also often occur at young ages, even though the degree of structural change (e.g., hypertrophy) is less pronounced (45). In our cohort of children, adolescents, and young adults, changes in LV filling function and peripheral microvascular vasomotor function were observed both in HCM patients and in individuals at risk for HCM. The perturbed vasomotor dysfunction was characterized by augmented cutaneous vasomotor responses to the endothelial agonist ACh. In
addition, there was a relationship between the microvascular response to ACh and myocardial diastolic function, as assessed by tissue Doppler. Of note, no differences in these indexes were found between healthy individuals and athletes, although the LVH in the athlete group was comparable to that in the HCM group. Tissue Doppler imaging is of limited diagnostic value in the older population due to age-related abnormalities in LV filling function, but, at younger ages, it appears to be a valuable tool to differentiate HCM from the “athlete’s heart.” Although echocardiographic demonstration of LVH in the absence of abnormal loading conditions is currently viewed as the gold standard for the diagnosis of HCM (33), in young individuals, particularly in those enrolled in endurance sporting activities, the differential diagnosis between compensatory (physiological) myocardial hypertrophy and HCM remains a difficult clinical task. Accurate assessment is thus crucial, especially given the relatively high risk for major cardiac events in true HCM. The importance of a “correct diagnosis at [an] early stage” is further underscored by the fact that young HCM patients who have only mild or moderate LVH are nonetheless at a similarly increased risk for developing severe complications as HCM patients with more severe forms of hypertrophy (6, 45, 48).

Standard 12-lead ECG, although useful for detecting indirect signs of LVH and overload in patients with overt HCM, has poor specificity in the early phase of the disease and low predictability of major cardiac events (18, 25). It is also unable to distinguish HCM from the physiological hypertrophy often observed in young endurance athletes (4, 18, 25, 44). The ECG-related findings in the present study further corroborate these previous results.

Vasomotor abnormalities in the peripheral microcirculation may be present even in young individuals with cardiovascular risk factors for atherosclerosis (40). The microvascular response to ACh as assessed by laser Doppler with iontophoresis was shown to correlate with coronary microvascular function (16) and to predict the risk for later cardiovascular events (2, 14). Impaired coronary microvascular function has been found even in patients with relatively mild LVH (2) and is thought to be a major mechanism in the development of coronary spasm, myocardial dysfunction, and blunted coronary flow reserve, which are important features of HCM (1). With regard to the peripheral circulatory changes noted in our young HCM patients, previous studies (1, 14) have also demonstrated impaired endothelial vasomotor function in adult HCM patients. Brachial artery endotheliopathy, defined as impaired flow-mediated dilation, also correlates with the degree of coronary atherosclerosis, although atherosclerosis is unlikely to be the principal driver of these changes in our young HCM cohort. The abnormal cutaneous microvascular response to ACh in the present study supports the hypothesis of widespread vascular endotheliopathy in familial HCM. ACh is generally regarded as an endothelium-mediated vasodilator, but, particularly in individuals with more advanced coronary dysfunction, it may also elicit vasoconstriction through a direct effect on the smooth muscle cell layer (34, 40). However, the lack of difference in the responses to the endothelium-independent agonist SNP together with the differences in the responses to ACh suggest that it is the endothelium that is affected in the early stage of HCM.

Theoretically, the mechanisms of the abnormal response to ACh in HCM and HCM-risk groups might involve both flow-
related and biochemical changes, with the former particularly in HCM patients with LV outflow tract obstruction due to hypertrophy. However, none of our patients had LV outflow tract obstruction. Since the vascular changes were present even in the absence of hypertrophy, it is less likely that the structural changes in the myocardium contribute to the genesis of peripheral vascular changes. Theoretically, vasoactive mediators from the pulmonary circulation might be released in response to increased LV filling pressure. This hypothesis is in keeping with the correlation between microvascular responses to ACh and the mitral Ele’ ratio, which strongly correlates with LV filling pressure. The enhanced ACh-induced responses in both HCM and HCM-risk groups could also reflect compensatory mechanisms in the early phase of vascular disease, such as upregulation of inducible nitric oxide synthase and cyclooxygenase pathways, with subsequent increased synthesis of vasodilating mediators, including nitric oxide and prostaglandins. Similar findings have also been reported in other young cohorts with cardiovascular risk factors (2, 14). This process presumably becomes outweighed at more advanced stages of HCM. Finally, changes in the autonomic nervous system could also influence microvascular function (12). However, there were no differences in LF/HF or SDNN between control and HCM groups in this study, making the impact of the autonomic nervous system less conceivable.

Study limitations: The size of the HCM cohort was relatively small. In addition, not all HCM probands were positive for known HCM mutations, but they all fulfilled echocardiographic criteria for HCM and had a family history for HCM. The HCM-risk group was also younger than the other groups. Nevertheless, in our cohort, neither Ele’ ratio nor the microvascular response to ACh showed any correlation with age, indicating that age was unlikely responsible for these differences, in line with a previous investigation on young cohorts (17). All individuals in the athlete group were male subjects and older than the other groups. It is uncommon to generate LVH due to physical training at young ages, and this is even more uncommon in female subjects (47). Another potential concern is biased results due to “common family genetics.” However, individuals in HCM and HCM-risk groups were recruited from 28 unrelated families. Intuitively, this would have minimized any such bias.

In conclusion, the present findings suggest that the use of tissue Doppler imaging and peripheral microvascular endothelial function assessment can improve the identification of young individuals at risk for developing HCM. In addition, in individuals participating in endurance athletic activities, tissue Doppler may also help make the distinction between HCM and athletes’ heart. Further studies are needed to validate our findings and to further elucidate the underlying mechanisms.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: E.F. and P.L. conception and design of research; E.F. performed experiments; E.F. and P.L. analyzed data; E.F., P.G.P., M.C., and P.L. interpreted results of experiments; E.F. and P.L. prepared figures; E.F. drafted manuscript; E.F., T.T.S., P.G.P., J.C., M.C., and P.L. edited and revised manuscript; E.F., T.T.S., P.G.P., J.C., M.C., and P.L. approved final version of manuscript.

REFERENCES
