Young patients with hypertrophic cardiomyopathy, but not subjects at risk, show decreased myocardial perfusion reserve quantified with CMR

Tom Gyllenhammar1, Eva Fernlund2, Robert Jablonowski1, Jonas Jögi1, Henrik Engblom1, Petru Liuba2, Håkan Arheden1, and Marcus Carlsson1*

1Department of Clinical Physiology, Lund University, Lund University Hospital, Lund 221 85, Sweden; and 2Department of Pediatric Cardiology, Lund University, Lund University Hospital, Lund, Sweden

Received 17 December 2013; accepted after revision 25 June 2014; online publish-ahead-of-print 19 August 2014

Aims
To determine if myocardial perfusion (MP) during hyperaemia is decreased in young patients with hypertrophic cardiomyopathy (HCM). Also, to determine if an MP decrease is associated with diastolic dysfunction, and to investigate if young subjects at risk of HCM show differences in MP compared with controls.

Methods and results
This study included 10 HCM patients (age 22.3 ± 6.4 years), 14 subjects at risk for HCM 'HCM risk' (age 18.9 ± 3.8 years), and 12 controls (age 22.8 ± 4.5 years). HCM patients were examined at rest and during hyperaemia (adenosine 140 μg/kg/min) with cardiovascular magnetic resonance (CMR) and echocardiography. MP was calculated as the ratio of coronary sinus flow and left ventricular mass (LVM) from CMR. Myocardial fibrosis was assessed using late gadolinium enhancement. Diastolic function was quantified with both echocardiography and CMR. At rest, MP (mL/min/g) was similar in the control, HCM risk, and HCM patients (0.8 ± 0.1, 1.0 ± 0.1, and 0.9 ± 0.1, respectively, P = ns). During adenosine, MP was lower in HCM patients (2.5 ± 0.4, P < 0.05) compared with both HCM risk (5.0 ± 0.5) and controls (3.9 ± 0.3). Subjects at HCM risk showed no significant difference in MP during adenosine compared with controls. One HCM patient showed mild diastolic dysfunction. Neither controls nor HCM risk individuals showed any sign of myocardial fibrosis, whereas 7/10 HCM patients had fibrosis (5 ± 1% of the total LVM).

Conclusion
Young individuals with HCM, but not those at risk, show decreased MP during hyperaemia compared with controls even in the absence of diastolic dysfunction or LV outflow obstruction. These results may suggest that microvascular disease contributes to the decreased MP in the investigated population.

Keywords
Hypertrophic cardiomyopathy • Cardiovascular magnetic resonance imaging • Coronary sinus flow • Global myocardial perfusion • Flow imaging

Introduction
Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiovascular diseases with a wide spectrum of adverse clinical outcomes. Young patients have higher mortality rates than older patients, with a peak in mortality between 9 and 12 years of age. Older patients suffering from HCM often express perfusion deficits both at rest and during hyperaemia, but, to our knowledge, there are no such data available in the paediatric population. Myocardial perfusion (MP) studies in young cohorts with HCM are important, since myocardial ischaemia is associated with cardiac arrest and syncope. Myocardial fibrosis is also prognostic of the worse clinical outcome in HCM patients and is associated with decreased MP in adult cohorts. There are no data on the combination of myocardial fibrosis and MP defects in patients with early onset of HCM.

* Corresponding author. Tel: +46 461 739 89; Fax: +46 461 151 769; E-mail: marcus.carlsson@med.lu.se

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: journals.permissions@oup.com.
Left ventricular (LV) end-diastolic filling pressure (EDP) and small vessel disease have been suggested as causes of decreased MP in adult HCM patients. However, the pathophysiology behind MP in HCM patients is not fully understood.

Although echocardiography remains the gold standard in the diagnosis of HCM by showing LV hypertrophy, early detection particularly in individuals with HCM heredity or known HCM risk genotypes remains very challenging. This is particularly true in young patients given their further somatic growth and difficulties in applying strict criteria for LV hypertrophy as in adults. Thus, further diagnostic techniques are needed to improve diagnosis of young individuals with incipient HCM.

To the best of our knowledge, there are no published studies on MP in young patients with HCM or on subjects at risk of HCM in the same age range. Furthermore, it is not known if MP is decreased even in the absence of diastolic dysfunction, extensive fibrosis, and LV outflow tract (LVOT) obstruction.

Cardiovascular magnetic resonance (CMR) has the ability to non-invasively quantify MP without ionizing radiation using quantification of coronary sinus flow (CSF) and LV mass with high accuracy and precision. Therefore, the objectives of this study was to: (i) determine if MP is decreased already at a young age in patients with HCM using CMR, (ii) measure if a MP decrease is associated with diastolic dysfunction, and (iii) investigate if young subjects at risk of HCM show differences in MP compared with controls.

**Methods**

**Study population**

The study was approved by the regional ethics committee, Lund, Sweden. Written informed consent was obtained from the subjects and their parents for those under the age of 18.

The study participants, aged 12–30 years, were recruited from the outpatient clinic of the Departments of Pediatric and Adult Cardiology. Participants were defined as either HCM or HCM risk using the following criteria: (i) HCM, if the patient had an interventricular septum and/or posterior wall (PW) thickness exceeding 13 mm (young adults, >18 years of age) or >3 SD on Z-score (paediatric patients) on echocardiography with confirmed increased wall thickness and/or fibrosis on CMR, (ii) HCM risk, if HCM was present among first-degree relatives, but without signs of LV hypertrophy or fibrosis on CMR.

Further inclusion/exclusion criteria are listed in Appendix.

**CMR imaging**

CMR was performed using a 1.5T MR scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands) with a 32-channel coil. CSF was measured at rest and after 5 min of adenosine infusion (140 μg/kg/min) using phase-encoded velocity mapping as previously described. Imaging of LV function, first-pass perfusion, and late gadolinium enhancement (LGE) was also performed. CMR sequence parameters are listed in Appendix.

**CMR image analysis**

All image analysis was done using the software Segment version 1.9 R2675 (http://segment.heiberg.se). Manual delineation of the coronary sinus was performed throughout the cardiac cycle (Figure 1). CMR analysis is further described in Appendix. The LV vascular resistance (R) was calculated as the ratio between mean arterial pressure (MAP) and the CSF. Resistance was normalized against LVM (R × LVM), which gives the vascular resistance per gram myocardium (mmHg/(mL/min/g)).

**Echocardiography**

Transthoracic echocardiography with Tissue Doppler was performed at rest by an experienced echocardiographist using a Philips iE33 (Philips Healthcare). Analysis of diastolic function and LVOT obstruction were performed (see Appendix for details).

**Statistical analysis**

All statistical analyses were performed using GraphPad Prism v5.01 (CA, USA). Results are presented as mean ± SEM unless otherwise stated. Because of the small cohort size, the Mann–Whitney non-parametric test was used to compare groups. Pearson’s correlation was used when comparing e’ measured with CMR vs. echocardiography, and Spearman’s rank-order test was used to test correlation between

---

**Figure 1:** Example of a delineation of the coronary sinus (dashed line) on a modulus image to the left with the corresponding phase image to the right in a patient with HCM. LA, left atrium; LV, left ventricle.
We investigated 10 HCM patients (2 women, 22.3 ± 6.4 SD years, range 12–30 years), and 12 controls (3 women, 22.8 ± 6.6 SD years, range 16–30 years). The participants’ characteristics are presented in Table 1. CMR was performed in all subjects. Haemodynamic response during adenosine is presented in Table 2.

In the HCM group, all patients underwent genetic testing. Seven of 10 patients were positive for known mutations associated with HCM, whereas no known HCM mutation could be identified in the remaining patients.

In the HCM risk group, gene testing found four subjects with MYBPC3 and in one subject TNNT2, and another MYH7. The remaining subjects had no identified gene in the proband with HCM to test for or declined genetical testing.

### Location of hypertrophy

All patients had basal and/or mid-ventricular LV hypertrophy of the septal wall (n = 4) or the anteroseptal wall (n = 6).

### Myocardial perfusion

Representative CSF curves for one subject from each group as well as mean curves for all subjects divided per group are shown in Figure 2. The curves were similar at rest with a peak flow during diastole. During adenosine, HCM patients show a marked decrease in flow during systole. MP at rest were similar in both HCM patients (P = 0.55) and subjects at HCM risk (P = 0.2) compared with controls (Table 3 and Figure 3). During hyperaemia, the MP was significantly lower in HCM patients compared with both controls (P = 0.03) and subjects at HCM risk (P = 0.0006). MP was similar in controls and subjects at HCM risk during hyperaemia (P = 0.11).

### First-pass perfusion

There were no visible perfusion deficits in controls or subjects at HCM risk neither at rest nor during adenosine stress. In a subset of HCM patients (n = 3), only two short-axis slices (mid-ventricular and apical) were acquired due to high heart rate. Therefore, a total of 126 segments were available for analysis in HCM patients. There were no perfusion deficits at rest. Six of nine patients with a total of 30/126 segments (24%) showed a perfusion defect during adenosine stress. In 12 of the 30 segments, the deficit was subendocardial and in the rest (n = 18), a transmural deficit was observed. A mild–moderate perfusion deficit was seen in 11/12 of the subendocardial segments and 7/18 of the transmural segments, and the remaining segments (n = 12) had severe perfusion deficits. Regional perfusion deficits were most prominent in areas with LV hypertrophy.

---

### Table 1

**Patients’ characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HCM risk</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>12</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.8 ± 4.5</td>
<td>18.9 ± 3.8</td>
<td>22.3 ± 6.4</td>
</tr>
<tr>
<td>Females</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.05</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
| End-diastolic volume/BSA (mL/m²) | 110 ± 5   | 89 ± 3
| End-systolic volume/BSA (mL/m²) | 49 ± 3   | 38 ± 2
| Ejection fraction (%) | 55 ± 2  | 57 ± 1   | 59 ± 3 |
| LVM/BSA (g/m²)       | 56 ± 3   | 46 ± 2   | 75 ± 12† |
| Left atrial size (mL) | 82 ± 11  | 64 ± 4   | 90 ± 6† |
| Maximum interventricular septum thickness (mm) | 8.9 ± 0.5 | 8.5 ± 0.3 | 19.0 ± 2.4† |
| Maximum PW thickness (mm) | 7.2 ± 0.4 | 6.6 ± 0.2 | 9.6 ± 1.0† |

BSA, body surface area.

†n = 10 and ‡n = 9 due to incomplete coverage of the left atrium.

*P < 0.05 compared with controls.

**Table 2**

**Haemodynamic response**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Risk</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>59 ± 4</td>
<td>67 ± 2*</td>
<td>74 ± 4*</td>
</tr>
<tr>
<td>SP (mmHg)</td>
<td>117 ± 3</td>
<td>112 ± 3</td>
<td>116 ± 3</td>
</tr>
<tr>
<td>DP (mmHg)</td>
<td>66 ± 2</td>
<td>64 ± 2</td>
<td>64 ± 3</td>
</tr>
<tr>
<td>Adenosine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>95 ± 4</td>
<td>98 ± 4</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>SP (mmHg)</td>
<td>114 ± 3</td>
<td>109 ± 3</td>
<td>114 ± 4</td>
</tr>
<tr>
<td>DP pressure (mmHg)</td>
<td>68 ± 2</td>
<td>62 ± 2</td>
<td>69 ± 4</td>
</tr>
</tbody>
</table>

SP, systolic pressure; DP, diastolic pressure.

*P < 0.05 compared with controls.

---

**Results**

We investigated 10 HCM patients (2 women, 22.3 ± 6.4 SD years, range 12–30 years), 14 subjects at HCM risk (7 women, 18.9 ± 3.8 SD years, range 13–27 years), and 12 controls (3 women, 22.8 ± 4.5 SD years, range 16–30 years). The participants’ characteristics are summarized in Table 1. CMR was performed in all subjects. Haemodynamic response during adenosine is presented in Table 2.

In the HCM group, all patients underwent genetic testing. Seven of 10 patients were positive for known mutations associated with HCM, whereas no known HCM mutation could be identified in the remaining patients.

In the HCM risk group, gene testing found four subjects with MYBPC3 and in one subject TNNT2, and another MYH7. The fibrosis and MP. Comparisons with a P < 0.05 were considered statistically significant.
Three of six patients with a visible regional perfusion deficit also had a MP below the range in the control group (<2.1 mL/min/g). Three patients had no visible regional perfusion deficit during adenosine stress; however, one of them had an MP (1.9 mL/min/g) below the range of the controls.

**Fibrosis**

Seven of the 10 patients with HCM had fibrosis on LGE-MRI [5 ± 1% scar of the LVM, range (1–12%)]). The intramural diffuse/patchy fibrosis was predominantly located in hypertrophic areas of the septal and anteroseptal wall. Interestingly, in one patient there was extensive fibrosis in a non-hypertrophied lateral wall.

There was no correlation between degree of fibrosis and MP during adenosine stress ($r = -0.33$, $P = 0.36$). No subjects at risk or controls showed fibrosis on LGE.

**Diastolic function**

The early peak filling rate (PFR$_E$/end-diastolic volume (EDV) was similar in controls (4.0 ± 0.3) compared with subjects at HCM risk (3.9 ± 0.3, $P = 0.57$). Subjects at HCM risk had similar PFR$_E$/EDV compared with HCM patients ($P = 0.65$). There was a moderate correlation between $e'$ measured with echocardiography and CMR ($r = 0.55$, $P = 0.0011$), and the bias was 0.3 ± 2.9 cm/s. At rest, $e'$ measured with CMR was similar in controls (12 ± 1 cm/s) compared with subjects at HCM risk (12 ± 1 cm/s, $P = 0.79$) but lower in HCM patients (8 ± 1 cm/s, $P = 0.029$). HCM patients had significantly lower $e'$ at rest compared with subjects at HCM risk ($P = 0.005$). During adenosine stress, $e'$ measured with CMR was similar in controls (17 ± 1 cm/s) compared with subjects at HCM risk (16 ± 1 cm/s, $P = 0.32$) and HCM patients (14 ± 2 cm/s, $P = 0.13$). Subjects at HCM risk had similar $e'$ during adenosine compared with HCM patients ($P = 0.46$).

One HCM patient was found to have $E/e' > 15$ measured with echocardiography ($E/e' = 16.6$), which was the cut-off to indicate increased LV end-diastolic filling pressure.\textsuperscript{19,20}

**LV vascular resistance**

The LV vascular resistance was significantly higher in HCM patients during adenosine compared with both controls ($P = 0.016$) and

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
 & Controls & Risk & HCM \\
\hline
At rest & & & \\
\hline
$N$ & 11 & 14 & 10 \\
MP (mL/min/g) & 0.8 ± 0.1 & 1.0 ± 0.1 & 0.9 ± 0.1 \\
\hline
Adenosine & & & \\
\hline
$N$ & 12 & 13 & 9 \\
MP (mL/min/g) & 3.9 ± 0.3 & 5.0 ± 0.5 & 2.5 ± 0.4$^{*}$ \& \\
\hline
\end{tabular}
\caption{Myocardial perfusion}
\end{table}
subjects at HCM risk ($P = 0.001$; Table 4 and Figure 4). At rest, the LV vascular resistance was significantly lower in subjects at HCM risk compared with controls ($P = 0.035$). HCM patients had similar LV vascular resistance at rest compared with controls ($P = 0.42$).

**Discussion**

This study has shown that: (i) young patients with HCM have significantly lower MP during adenosine compared with controls, (ii) this decrease is found in HCM patients without diastolic dysfunction or LVOT obstruction, and (iii) MP in young subjects at HCM risk is similar to controls.

**Comparison with earlier studies**

This study shows, for the first time, that MP is decreased in young patients with HCM, which is in line with findings from previous studies on older populations.$^{5,18,21,22}$ Our results lend support to the concept that disturbed perfusion is an early primary pathological change in young HCM patients, as suggested by findings on microscopy of vascular changes in autopsy studies.$^{23-25}$ These results are important since it is known that decreased MP in HCM patients is associated with the worse clinical outcome, and that the highest mortality rates are seen in young individuals.$^{1,21}$ Earlier CMR studies on adult HCM patients have demonstrated the worse clinical outcome in adult HCM patients with myocardial fibrosis, which has been shown to correlate with decreased MP.$^7$ It has been suggested that fibrosis in HCM patients develops in response to ischaemia.$^1$ We found the presence of fibrosis in the HCM patients but with no correlation to perfusion, although this may be due to the small patient cohort.

One interesting observation is that subjects at HCM risk showed significantly decreased left ventricular vascular resistance at rest compared with controls. This decrease of resistance was a result of an increase in MP and a decrease in MAP. The lowest values of resistance at rest were seen in the individuals with the highest MP at rest. Karamitso et al.$^{26}$ recently showed that patients with HCM-associated genes but no hypertrophy had decreased oxygenation yet normal perfusion during hyperaemia compared with controls. Our results suggest that some subjects with risk of HCM could be compensating for possible altered cardiac energetics$^{27}$ by increased MP.

In line with the findings of Petersen et al.$^{28}$, the regional perfusion deficits are most often found in hypertrophic areas of the LV extending from the endo- to the epicardium. In the present study, the subendocardial perfusion deficits were predominantly mild-to-moderate, and the transmural deficits were more severe. Of note, one patient with global hypoperfusion did not show regional perfusion deficits. This indicates that decreased global MP calculated from CSF measurements may be an additional marker for disease in these patients.

To the extent of our knowledge, no previous study has showed averaged CSF curves from a HCM patient cohort. These curve profiles show that the decreased MP is accompanied by changed flow patterns. It seems like the normal biphasic hyperaemic flow with flow peaks in systole and diastole in healthy controls is replaced by a more steady CS flow in HCM patients (Figure 2).

**Pathophysiological considerations**

MP is the result of two factors: driving pressure and vascular resistance. Coronary vascular resistance is affected by the vascular tone and the cyclic compression of the cardiac muscle. This causes a perfusion of the myocardium mainly during the diastolic phase of the cardiac cycle. The driving pressure is the difference between the pressure in the coronary arteries and the pressure at the orifice of the coronary sinus, which drains the LV wall.$^{29,30}$

---

**Table 4  Resistance**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Risk</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>11</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Resistance $\times LVM^a$</td>
<td>113 ± 10</td>
<td>84 ± 9$^*$</td>
<td>107 ± 15</td>
</tr>
<tr>
<td>Adenosine</td>
<td>23 ± 2</td>
<td>17 ± 12</td>
<td>45 ± 11$^*$ $^+$</td>
</tr>
</tbody>
</table>

One HCM risk subject had no blood pressure recorded at rest and adenosine, and one patient with HCM had no blood pressure recorded during adenosine due to technical problems.

$^a$Resistance $\times LVM$ [mmHg/(mL/min/g)] ± SEM.

$^*$P < 0.05 compared with controls.

$^+$P < 0.05 compared with subjects at HCM risk.

---

**Figure 3**: MP at rest and during administration of adenosine for each individual in all three groups. The error bars show the mean ± SEM. MP was significantly lower during adenosine in HCM patients compared with controls and subjects at HCM risk.
This study has shown an increase of LV vascular resistance and a decrease of MP in patients with HCM during adenosine stress compared with controls. The normal physiological response to adenosine is vasodilation with a subsequent decrease of the resistance in the arterioles causing increased MP. The HCM patients showed a decreased LV vascular resistance compared with controls during hyperaemia.

The autoregulatory function of the vascular resistance in the myocardium is attributed to the arterioles. Small vessel disease is characterized by endothelial dysfunction together with fibrosis and narrowing of the vessel. Small vessel disease has been found in postmortem studies of HCM patients, and decreased myocardial capillary density has been shown in vivo in adult patients with HCM. Microvascular changes in the myocardium have been documented histologically in autopsy studies, but this important feature is not assessable with current CMR technologies. Our results show that mean coronary vascular resistance in controls and subjects at HCM risk was variable at rest but within a narrow range during administration of adenosine. We interpret that this is due to the normal regulation of vascular tone at rest. In our results, HCM patients showed increased mean coronary vascular resistance during administration of adenosine compared with the other groups. Increased resistance in HCM patients has previously been showed by Camici et al. who found regional increased vascular resistance in non-hypertrophied myocardium during dipyramidole hyperaemia using positron emission tomography (PET). Tadamura et al. demonstrated similar findings in paediatric HCM patients using PET. Our results indicate that calculation of mean coronary vascular resistance using CMR may be useful when evaluating microvascular function in future studies.

The vascular resistance of the myocardium during diastole is also affected by the LV wall pressure. The LV wall pressure may be elevated if a patient has increased LV end-diastolic filling pressure (EDP) due to severe diastolic dysfunction and diastolic dysfunction is seen in advanced stages of HCM. We hypothesized that diastolic dysfunction may be a contributing factor to decreased MP in young HCM patients. The results, however, showed only one patient with diastolic dysfunction and the MP during adenosine in this patient (2.8 mL/min/g) was within the range seen in our control group. Therefore, decreased MP in the HCM patients was seen even without signs of increased filling pressures.

LVOT obstruction creates a pressure gradient between the LV and the aorta with a reduced aorta pressure relative to the myocardial wall pressure, hence affecting the MP. LVOT obstruction is a common finding in HCM patients. Since no patients with LVOT obstruction were included in this study, global perfusion deficiency during adenosine as assessed with CMR was not caused by LVOT obstruction in the investigated study population. Previously, Bravo et al. described that LVOT obstruction was not an independent predictor of MP using PET.

The absence of diastolic dysfunction and LVOT obstruction in the investigated subjects does not weaken the hypothesis that the impaired perfusion during hyperaemia noted in this study in young patients with HCM is caused by small vessel disease. If small vessel disease is an early pathological alteration in HCM, it could explain some of the other findings and symptoms of the disease such as fibrosis, cardiac failure, sudden cardiac death, and diastolic dysfunction which all are associated with chronic myocardial ischaemia. Future studies are needed to address whether global MP quantified with CMR could predict the adverse clinical outcome even in young patients with HCM.

### Diagnostic implications

Since HCM may be present in a heart without clinical evidence of myocardial hypertrophy, screening is a diagnostic challenge. Notably, none of the subjects at HCM risk demonstrated a decreased MP during administration of adenosine compared with controls. In the investigated subjects, an MP during administration of adenosine <2 mL/min/g was seen only in HCM patients. Our findings indicate that investigation of MP using CMR may be useful to detect HCM in earlier phase of the disease using MP during adenosine-induced stress. Future prospective studies are needed to investigate if MP is useful as a prognostic tool in HCM patients.

### Limitations

Coronary artery disease (CAD) may also cause lowered MP. However, CAD is rarely seen among young individuals and coronary arteries may even have an increased lumen size in HCM patients. LVOT gradients and E′ using echocardiography were only measured at rest and not during administration of adenosine. CMR e′ at rest showed a fair agreement with the e′ measured by echocardiography at rest.

---

**Figure 4:** LV vascular resistance at rest and during administration of adenosine for each individual in all three groups. The error bars show the mean ± SEM. There was a wide variation in LV vascular resistance at rest in all groups. During adenosine, the vascular resistance is within a narrow range in controls and subjects at HCM risk, but was increased with a wide range in HCM patients.
Due to the relatively small cohort size, further studies are needed to characterize the relationship between MP and diastolic dysfunction in this patient group. LVOT obstruction was an exclusion criterion in this study; therefore, the results in patients with LVOT obstruction may be different. The cross-sectional nature of this study represents another limitation. A prospective 3-year follow-up study of these patients is planned.

Conclusion
This study shows that young patients suffering from HCM exhibit a decreased MP and increased LV vascular resistance during adenosine vasodilation. Though drawing definitive conclusion is not possible due to the relatively small cohort size, the perfusion deficit was present even in the absence of diastolic dysfunction or LVOT obstruction in the investigated HCM patients. Our findings imply that perfusion is likely to be primarily decreased due to small vessel disease.

Conflict of interest: None declared.

Appendix
Inclusion/exclusion criteria
Included patients with HCM and subjects with risk of HCM were recruited from 15 unrelated families with familial HCM to minimize the influence of ‘common genetics’ and all had been offered genetic testing. The study groups were negative for other cardiac diseases apart from familial HCM. All controls had a negative history and heredity for cardiac disease, and all had normal 12-lead ECGs.

Exclusion criteria were: LVOT obstruction, LV hypertrophy due to other causes, including congenital heart disease, Noonan syndrome, malformation syndromes, neuromuscular, and metabolic disorders including diabetes and hypertension, and contraindications for CMR such as implanted CMR-non-compatible devices. All participants were non-smokers.

CMR protocol and sequence parameters
CSF: images were taken as close as possible to the orifice in the right atrium to include as many LV cardiac veins as possible. The middle cardiac vein was included since we aimed to investigate the total flow of the left ventricle. The same imaging plane used to measure the coronary sinus was used to perform measurements of the mitral valve movement. CSF was quantified using a breath-hold turbo field echo (TFE) phase-contrast CMR with retrospective ECG triggering, repetition time (TR) 5 ms, echo time (TE) 2.6 ms, α 15°, segmentation factor 4, acquired temporal resolution of 34.4 ms reconstructed to typically 20 phases through the cardiac cycle, sensitivity encoding (SENSE) factor 2, and a VENC of 200 cm/s.

Cine imaging was performed in the short-axis view covering the LV with a steady-state free precession sequence (SSFP) in breath-hold with TR 2.9 ms, TE 1.5 ms, α 60°, segmentation factor 17, acquired temporal resolution of 50 ms reconstructed to 30 time phases over the cardiac cycle, acquired spatial resolution 2 × 2 × 8 mm reconstructed to 1.3 × 1.3 × 8 mm, 0 mm gap, and SENSE factor 2.

Regional perfusion imaging was performed with a balanced turbo fast field echo sequence in breath-hold with TR 2.7, TE 1.4, α 50°, acquired spatial resolution 2 × 2 × 10 mm reconstructed to 1.4 × 1.4 × 10 mm, and SENSE factor 3. Images were acquired during the first pass of a bolus of 0.05 mmol/kg gadolinium-based contrast agent Dotarem (Guerbet, Roissy, France). Perfusion images were acquired in three short-axis slices at basal, mid-ventricular, and apical levels. Images were acquired during adenosine (140 μg/kg/min) hyperaemia and at rest 10 min after cessation of adenosine.

LGE imaging was performed with a 3D-inversion recovery gradient-echo (IR GRE) sequence acquired during mid-diastole during end-expiratory breath-hold. Short-axis slices covering the entire left ventricle from base to apex and three long-axis projections were collected 10–20 min after an intravenous administration of additional 0.1 mmol/kg of Dotarem after the resting perfusion. Five slices per acquisition were reconstructed with slice gap 0 mm, slice thickness 8 mm, and in-plane resolution 1.5 × 1.5. Typical image parameters were: TE 1.3 ms, effective TR every heartbeat, flip angle 15°, and inversion time of 220–280 ms.

CMR image analysis
LVM was obtained from manual delineation of the endocardium and epicardium of the left ventricle in the short-axis SSFP cine images at both end-systole and end-diastole. LVM was calculated as the myocardial volume multiplied with a factor of 1.05 g/mL (myocardial density). MP (mL/min/g) was quantified as CSF (mL/min)/LVM (g).

Flow data were linearly interpolated to a constant number of time phases for averaged CSF curves. Diastolic function was quantified with CMR using two methods: (i) early peak filling rate (PFR E) normalized against end-diastolic volume (PFR E/EDV) from short-axis images, and (ii) peak velocity of the mitral valve movement during the early rapid filling phase in long-axis images (e').

The assessment of regional perfusion was done by visual analysis in six basal, six mid-ventricular, and four apical segments. Each segment was graded regarding transmural extent of the deficit in each segment (≤50% or >50%). The severity of the perfusion deficit was graded as mild/moderate or severe based on the visually estimated degree of hypo-enhancement by the observer.

Fibrosis was quantified in LGE images using a semi-automatic method with manual corrections.

Echocardiography
Diastolic function was expressed as E/e', where E is the peak mitral flow velocity of the diastolic early rapid filling of the left ventricle and e' is the longitudinal velocity of the mitral valve annulus during the same period. E/e' correlates with the LV end-diastolic filling pressure and diastolic filling pressure is considered elevated if E/e' >15 in adults. LVOT obstruction was quantified using Doppler measurement of the velocity between the left ventricle and aorta to calculate the pressure gradient. The cut-off level for LVOT obstruction was set to 30 mmHg as previously proposed.
References


10. Ackerman MJ, Priori SG, Willem S, Berul C, Brugada R, Calzins H et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 2011; 8:1308–39.


