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Blunted Myocardial Oxygenation Response During Vasodilator Stress in Patients With Hypertrophic Cardiomyopathy

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Objectives This study sought to assess myocardial perfusion and tissue oxygenation during vasodilator stress in patients with overt hypertrophic cardiomyopathy (HCM), as well as in HCM mutation carriers without left ventricular (LV) hypertrophy, and to compare findings to those in athletes with comparable hypertrophy and normal controls.

Background Myocardial perfusion under vasodilator stress is impaired in patients with HCM. Whether this is associated with impaired myocardial oxygenation and tissue ischemia is unknown. Furthermore, it is not known whether perfusion and oxygenation are impaired in HCM mutation carriers without left ventricular hypertrophy (LVH).

Methods A total of 27 patients with overt HCM, 10 HCM mutation carriers without LVH, 11 athletes, and 20 healthy controls underwent cardiovascular magnetic resonance (CMR) scanning at 3-T. Myocardial function, perfusion (perfusion reserve index [MPRI]), and oxygenation (blood-oxygen level dependent signal intensity [SI] change) under adenosine stress were assessed.

Results MPRI was significantly reduced in HCM (1.3 ± 0.1) compared to controls (1.8 ± 0.1, $p < 0.001$) and athletes (2.0 ± 0.1, $p < 0.001$), but remained normal in HCM mutation carriers without LVH (1.7 ± 0.1; $p = 0.61$ vs. controls, $p = 0.02$ vs. overt HCM). Oxygenation response was attenuated in overt HCM (SI change $6.9 \pm 1.4\%$) compared to controls ($18.9 \pm 1.4\%$, $p < 0.0001$) and athletes ($18.7 \pm 2.0\%$, $p < 0.001$). Interestingly, HCM mutation carriers without LVH also showed an impaired oxygenation response to adenosine ($10.4 \pm 2.0\%$; $p = 0.001$ vs. controls, $p = 0.16$ vs. overt HCM, $p = 0.003$ vs. athletes).

Conclusions In overt HCM, both perfusion and oxygenation are impaired during vasodilator stress. However, in HCM mutation carriers without LVH, only oxygenation is impaired. In athletes, stress perfusion and oxygenation are normal. CMR assessment of myocardial oxygenation has the potential to become a novel risk factor in HCM.
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Hypertrophic cardiomyopathy (HCM) is a genetic disease with a broad spectrum of clinical manifestations and pathophysiological substrates (1). Using a variety of imaging modalities, myocardial perfusion under vasodilator stress has been shown to be impaired in patients with HCM (2–4). In the absence of coronary stenoses, this finding is indicative of microvascular dysfunction, but it remains unclear whether the hypoperfusion seen in HCM during stress leads to myocardial tissue deoxygenation and ischemia (5). Furthermore, it is unknown whether HCM mutation carriers without hypertrophy show impaired perfusion and associated deoxygenation during stress.

Blood-oxygen level-dependent (BOLD) cardiovascular magnetic resonance (CMR) or oxygenation-sensitive CMR provides the unprecedented capability to noninvasively assess myocardial tissue oxygenation during vasodilator stress

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Abbreviations and Acronyms

BOLD = blood-oxygen level-dependent

CMR = cardiovascular magnetic resonance

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

LGE = late gadolinium enhancement

LVH = left ventricular hypertrophy

MPRI = myocardial perfusion reserve index

PET = positron emission tomography

SI = signal intensity

(6–11). BOLD CMR capitalizes on the paramagnetic properties of deoxygenated hemoglobin, which acts as an intrinsic contrast mechanism leading to signal loss in oxygenation-sensitive MR sequences (6,8,10). The change in signal intensity (SI) during vasodilator stress directly reflects myocardial oxygenation status. Oxygenation measurements using BOLD CMR have been shown to be proportional to changes in coronary sinus oxygen saturation (8). As recently shown in patients with coronary artery disease, oxygenation-sensitive CMR can not only identify deoxygenated myocardial segments subtended by stenosed vessels, but also segments with microvascular dysfunction and intermediate SI changes to adenosine stress when compared to normal volunteers (6,7,10). Importantly, myocardial perfusion can be dissociated from oxygenation (i.e., hypoperfusion is not necessarily commensurate with tissue hypoxia). The oxygen demand of the heart muscle may vary in different states, as it may be reduced in hibernating myocardium in line with the down-regulated contractility (12) or may be increased in HCM due to the increased energy cost of contraction (13,14). Thus, compared to perfusion, regional myocardial oxygenation may be a superior parameter reflecting more directly the imbalance between oxygen demand and supply that characterizes ischemia.

The aim of this study was to assess myocardial perfusion and tissue oxygenation during vasodilator stress in patients with overt HCM, as well as in HCM mutation carriers without left ventricular hypertrophy (LVH), and to compare our findings to those in athletes with comparable hypertrophy and normal controls. We hypothesized that tissue oxygenation during stress would be impaired in HCM and that this would not occur in physiological hypertrophy of athletes. If our hypothesis were proven true, it would suggest a central role of stress-induced ischemia, triggering ventricular tachycardia/ ventricular fibrillation, in the pathophysiology of sudden cardiac death in HCM.

Methods

Study population. The study was approved by our institutional ethics committee and informed written consent was obtained from each participant. Sixty-eight subjects were recruited into the study: 27 HCM patients with LVH, 10 HCM mutation carriers without LVH, 11 athletes, and 20 normal controls. The diagnosis of HCM was determined on the basis of genetic determination of a pathogenic mutation (11 beta-myosin heavy chain, 11 myosin binding protein C). In the absence of an identified mutation (15 subjects), HCM was defined as the presence of asymmetric LVH (wall thickness ≥15 mm or ≥12 mm in documented familial disease) not originating from other causes. All HCM patients had no cardiovascular risk factors and were recruited from the University of Oxford Cardiomyopathy clinic. Athletes and healthy volunteers had no cardiovascular risk factors or symptoms, no family history of cardiomyopathy or sudden death, and had a normal 12-lead echocardiography (ECG). Athletes were recruited from the City of Oxford rowing club tier 1 team. Only those who performed 6 to 10 h minimum training per week and had maximal wall thickness ≥12 mm by CMR were included in the study. Normal controls were recruited using posters and by word of mouth. In the HCM group, subjects were excluded if they had a blood pressure drop on exercise during a standard Bruce exercise tolerance test or if there was a resting LV outflow tract gradient >30 mm Hg on ECG. Subjects with contraindications to CMR scanning (e.g., pacemakers, defibrillators, claustrophobia) or adenosine (asthma, advanced degree heart block) were not enrolled in the study.

CMR Scanning Protocol

CMR was performed on a 3-T system (TIM Trio, Siemens Healthcare, Erlangen, Germany). All participants were instructed to refrain from caffeine in the 24 h preceding the study. Images were acquired with the patient supine, using anterior and posterior phased-array surface coils. For cine CMR, from standard pilot images short-axis cine images covering the entire left ventricle were acquired using a retrospectively ECG-gated balanced steady-state free precession sequence (echo time 1.5 ms, repetition time 3 ms, flip angle 50°). For BOLD-CMR, a set of 2 images was acquired at 3 levels (basal, mid ventricular, and apical) using a T2-prepared ECG-gated balanced steady-state free precession sequence (repetition time/echo time 2.86 ms/1.43 ms, T2 preparation time 40 ms, matrix 168 × 192, field of view 340 × 340 mm, slice thickness 8 mm, flip angle 44°) during peak adenosine stress (140 μg/kg/min) and at rest. Each BOLD image was obtained during a single breath-hold over 6 heartbeats. If necessary, shimming and center frequency adjustments were performed before BOLD imaging, in order to minimize off-resonance artifacts. Immediately following stress BOLD imaging (4 to 5 min after commencing the adenosine infusion), a 0.03 mmol/kg bolus of gadolinium-based contrast (Gadodiamide, Omniscan, GE Healthcare, Oslo, Norway) was injected, followed by 15 ml of saline at a rate of 6 ml/s for first-pass perfusion imaging. During the first-pass of contrast, 3 short-axis images matched in position with the BOLD images were acquired every cardiac cycle using an ECG-gated T1-weighted fast gradient echo sequence (echo time 0.96 ms, repetition time 2 ms, saturation recovery time 95 ms, voxel size 2.1 × 2.6 × 8 mm^3, flip angle 17°, slice thickness 8 mm). The adenosine infusion was then discontinued and, after a break of at least 25 minutes, another bolus of 0.03 mmol/kg bolus of gadolinium contrast was given for resting

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