In Hypertrophic Cardiomyopathy Reduction of Relative Resting Myocardial Blood Flow Is Related to Late Enhancement, T2-Signal and LV Wall Thickness

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Abstract

**Objectives**: To quantify resting myocardial blood flow (MBF) in the left ventricular (LV) wall of HCM patients and to determine the relationship to important parameters of disease: LV wall thickness, late gadolinium enhancement (LGE), T2-signal abnormalities (dark and bright signal), LV outflow tract obstruction and age.

**Materials and Methods**: Seventy patients with proven HCM underwent cardiac MRI. Absolute and relative resting MBF were calculated from cardiac perfusion MRI by using the Fermi function model. The relationship between relative MBF and LV wall thickness, T2-signal abnormalities (T2 dark and T2 bright signal), LGE, age and LV outflow gradient as determined by echocardiography was determined using simple and multiple linear regression analysis. Categories of reduced and elevated perfusion in relation to non- or mildly affected reference segments were defined, and T2-signal characteristics and extent as well as pattern of LGE were examined. Statistical testing included linear and logistic regression analysis, unpaired t-test, odds ratios, and Fisher’s exact test.

**Results**: 804 segments in 70 patients were included in the analysis. In a simple linear regression model LV wall thickness (p<0.001), extent of LGE (p<0.001), presence of edema, defined as focal T2 bright signal (p<0.001), T2 dark signal (p<0.001) and age (p=0.032) correlated inversely with relative resting MBF. The LV outflow gradient did not show any effect on resting perfusion (p=0.901). Multiple linear regression analysis revealed that LGE (p<0.001), edema (p<0.026) and T2 dark signal (p=0.019) were independent predictors of relative resting MBF. Segments with reduced resting perfusion demonstrated different LGE patterns compared to segments with elevated resting perfusion.

**Conclusion**: In HCM resting MBF is significantly reduced depending on LV wall thickness, extent of LGE, focal T2 signal abnormalities and age. Furthermore, different patterns of perfusion in HCM patients have been defined, which may represent different stages of disease.

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic disorder with a prevalence of 0.2%. It is characterized by left ventricular (LV) hypertrophy in the absence of any other cardiac or systemic disease. HCM is heterogeneous in terms of various gene mutations, histopathology, presentation, clinical course and prognosis [1,2,3,4]. Therefore, it is important to define subgroups that are at risk for adverse cardiac events, to allow personalized risk-adjusted treatment. Several risk factors have been identified, including non-sustained ventricular tachycardia, family history of HCM and sudden cardiac death, syncope, low blood pressure in response to exercise, LV hypertrophy ≥30 mm [5,6], LV outflow tract obstruction [7] and extensive myocardial delayed enhancement (LGE) on magnetic resonance imaging (MRI) [8,9].

Myocardial perfusion abnormalities are common in HCM patients and seem important for pathophysiology and prognosis [10]. They may be related to abnormal intramyocardial coronary
arteries [11], inadequate capillary density in relation to increased myocardial mass or impairment of LV relaxation and may lead to myocardial ischemia and scarring. Nuclear medicine studies show that focal perfusion defects both at rest and during exercise are associated with arrhythmia, cardiac arrest and syncope in HCM patients [12,13,14,15]. A higher degree of microvascular dysfunction has been shown to be an independent predictor for worse prognosis and death in HCM patients [16].

Local differences in myocardial blood flow (MBF) at rest and their relationship to tissue characteristics as evaluated by LGE and T2-weighted imaging have not yet been examined in detail. This is especially important as signal characteristics of a single sequence are not specific for certain pathologies in HCM: For example LGE in HCM patients may not only represent fibrosis, but also myocardial disarray, inflammation, and necrosis [17]. High signal intensity on T2-weighted images indicates edema and can be due to inflammation or ischemia [18], whereas dark signal on T2-weighted images indicates chronic fibrosis [19]. Combining LGE and T2-weighted MRI with perfusion imaging may be helpful to further characterize the complex histopathology and stage of lesions in HCM patients.

Therefore, the purpose of this study was to quantify resting LV MBF by MRI and to determine its relationship to important parameters of disease such as LV wall thickness, LGE, T2-signal changes, LV outflow tract obstruction and age.

Methods

Ethics Statement

This prospective, Health Insurance Portability and Accountability Act (HIPAA)-compliant study was approved by the Johns Hopkins Medicine institutional review board (Baltimore, MD, USA). Written informed consent was obtained from all participants.

Study Population

Seventy patients with HCM were recruited mostly during their initial visit at our tertiary referral center and underwent cardiac MRI between November 2007 and May 2011. Patients with MRI contra-indications such as cardiac pacemaker and implantable cardioverter defibrillator (ICD) were excluded. Diagnosis of HCM was based on the presence of LV hypertrophy (end-diastolic LV wall thickness ≥15 mm) not originating from other causes [20]. The LV outflow gradient at rest was measured by Doppler echocardiography. Echocardiography and MRI were conducted at the same visit usually on the same day.

MRI Protocol

All cardiovascular MRI examinations were performed on a 1.5 T MRI system (Avanto; Siemens Health Care, Erlangen, Germany) using a 6-channel array surface coil and a spine coil. Cine MRI was acquired in the short-axis view using a retrospective, electrocardiographically gated, balanced steady-state free precession (SSFP) sequence: Repetition time (TR)/ echo time (TE) 2.9/ 1.2 ms, flip angle 76°, matrix 256×154, slice thickness 8 mm, reconstructed cardiac phases 30. In order to assess myocardial T2-signal abnormalities a spectral attenuated inversion recovery (SPAIR) T2-weighted dark blood turbo spin echo sequence was applied in the short-axis view: 1400/ 76 ms TR/TE, echo train length 13, matrix 256×186, slice thickness 8 mm. For perfusion imaging a bolus of gadopentetate dimeglumine (Bayer Schering Pharma, Berlin, Germany) was injected at a dose of 0.04 mmol/kg bodyweight, which was followed by a 20 ml saline flush; both were injected at a rate of 5 ml/s. Images were obtained using a saturation preparation SSFP sequence: TR/ TE 2.4/ 1.0 ms, inversion delay 180 ms, flip angle 40°, parallel acquisition acceleration factor 2 (generalized autocalibrating partially parallel acquisitions, GRAPPA), matrix 192×134, slice thickness 8 mm [21,22]. Two short-axis slices at the basal and mid-ventricular or at the mid-ventricular and apical level for apical forms of HCM were acquired during one heartbeat, resulting in a temporal resolution of one R-R interval. Short-axis segmented inversion-recovery gradient-echo turbo fast low angle shot (FLASH) images were obtained ten minutes after injection of an additional 0.16 mmol/kg gadopentetate dimeglumine dose (total dose = 0.2 mmol/kg) using the following parameters: TR/ TE 2.9/ 3.3 ms, flip angle 25°, TI as determined from T1 scout matrix 256×156, slice thickness 8 mm.

Imaging planes and positions of cine, T2-weighted and LGE MRI were matched to the slice location of the cardiac perfusion sequence to allow direct comparison of all parameters within the same myocardial region. Cine and LGE sequences covered the entire left ventricle, but only the matching slices were used for comparison with myocardial perfusion.

MRI Analysis

Quantitative analysis of cine and perfusion MRI were performed by one reader (XX 2 years of cardiac MRI experience), who was blinded to clinical history and echocardiographic findings. In order to determine local differences of myocardial perfusion, LV wall thickness, LGE and T2-signal, the LV myocardium was divided into 6 segments per slice in each of the acquired short-axis slice according to the recommendation of the American Heart Association [23]. Each segment was further subdivided into an endocardial and an epicardial subsegment (Fig. 1).

Using dedicated cardiac software (MASS 7.2, Medis, Leiden, The Netherlands) LV mass index, LV end-diastolic and end-systolic volume index and ejection fraction were determined from short-axis cine MRI. The end-diastolic LV wall thickness was measured in each segment, matching the cardiac perfusion segments.

T2-signal changes and LGE were scored visually in corresponding slices and segments by consensus of two experienced readers (YY 9 years of cardiac MRI experience and XX). Edema, defined as focally increased T2-signal when compared to remote T2-signal, was scored as absent = 0 or present = 1 for each myocardial segment. Similarly, T2 dark signal (chronic fibrosis), defined as focally reduced T2-signal when compared to remote T2-signal, was recorded as absent = 0 or present = 1. The extent of LGE within each segment was scored visually from 0 to 4 based on the percentage area with hyperenhancement: 0 = no LGE, 1 = 1–25%, 2 = 26–50%, 3 = 51–75% and 4 = 76–100% LGE (Fig. 2).

For absolute quantification of MBF, perfusion maps were generated on a pixel-by-pixel basis using the Fermi function model and dedicated perfusion software as previously described [24,25,26,27]. Perfusion images were motion corrected and denoised [28]. The arterial input function was obtained by placing a region of interest (ROI) in the LV cavity. On both slices of the short-axis perfusion MRI an ROI was drawn, outlining the LV walls. Myocardial segments were defined as described above and ROIs were copied to perfusion maps (Fig. 1). For each segment and each epicardial and endocardial half mean MBF was calculated and corrected for heart rate and blood pressure by dividing the absolute MBF by the rate-pressure product and multiplying the quotient by 10,000 [29,30].
To further assess regional differences in MBF, relative perfusion values were calculated. In each patient, we first defined reference segments as non- or mildly affected segments with myocardial thickness <20 mm and LGE score 0–1 in the segment as well as the respective epi- and endocardial subsegments. These thresholds were chosen because some patients did not have segments without LGE and myocardial wall thickness <15 mm. The mean MBF of reference segments in one patient was calculated and relative perfusion for all segments in one patient was then calculated in relation to this mean value. In addition, mean relative MBF of all reference segments of all 70 patients (per definition 100%) and the standard deviation (SD) were determined and three categories of relative perfusion were defined: reduced perfusion <mean -1 SD (86.75%), elevated perfusion ≥mean+1 SD (113.25%) and perfusion within one SD of reference segments (86.75–113.25%), referred to as reference (Fig. 3).

Statistical Analysis

Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Values are expressed as mean and 95% confidence interval [CI]. P <0.05 was considered to indicate significance.

In order to characterize the association of LGE with T2 signal changes and LV wall thickness a logistic regression with repeated
measures was performed. The presence of LGE (score 1–4) vs. no LGE (score 0) was defined as response variable; LV wall thickness, edema and T2 dark signal as independent factors. In a linear regression model with repeated measures the relationship of relative resting MBF with LV wall thickness, LGE score, edema score, T2 dark score, LV outflow gradient at rest (determined by Doppler echocardiography) and age was determined. All statistically significant parameters (p < 0.05) were then evaluated together in a multiple linear regression model. Although the distribution of relative resting MBF was slightly skewed to the left, we regarded the data as approximately normally distributed owing to the rather large sample size.

As relative resting MBF was heterogeneous even in segments with LGE (range 33.5–147.2%), a subgroup analysis including all segments with LGE (score 1–4) was performed. Within this subgroup segments with reduced or elevated perfusion in combination with LGE (n = 78 and n = 24 segments, respectively) were evaluated for the presence of LV wall thickness ≥ 20 mm, focally elevated and decreased T2-signal and the pattern of LGE. The frequency of those parameters in reduced and elevated perfusion segments of this subgroup was compared to the frequency of parameters in reference segments of the subgroup using Fisher’s exact test; odds ratios and relative risks were calculated. The respective extent of LGE in elevated and reduced perfusion segments in this subgroup was compared using an unpaired t-test. It should be noticed that the subgroup analysis was performed descriptively on a per segment basis, and only descriptive p-values are given.

**Results**

**Study Population**

In 70 HCM patients (mean age 51.7 years, CI [47.7, 55.8]) 804/840 segments were included in the analysis. Patient characteristics are given in Table 1. 36 segments had to be excluded completely due to motion artifacts. In addition 24 segments had severe motion artifacts in T2-weighted MRI and were excluded from T2 analysis only.

![Figure 3. Frequency and range of relative resting MBF.](https://doi.org/10.1371/journal.pone.0041974.g003)

**Table 1. Characteristics of HCM patients.**

| Characteristic                  | Value               |
|--------------------------------|---------------------|
| Age, y                         | 51.7 [47.7, 55.8]   |
| Male gender, %                 | 80                  |
| Heart rate, bpm                | 64.4 [62.2, 66.7]   |
| Blood pressure, mmHg           | 132 [128, 136]      |
| LV outflow gradient at rest, mmHg | 27.2 [19.8, 34.5] |
| LV EDV index, ml/m²            | 62.7 [59.0, 66.5]   |
| LV ESV index, ml/m²            | 12.3 [11.2, 13.4]   |
| LV ejection fraction, %        | 80.1 [78.6, 81.6]   |
| LV mass index, g/m²            | 98.5 [91.3, 105.7]  |
| Patients with LGE (score 1–4), n (%) | 54 (77%)             |
| Segments with LGE (score 1–4), n (%) | 258 (32%)            |
| Patients with LV wall thickness ≥20 mm, n (%) | 36 (51%)            |
| Segments with LV wall thickness ≥20 mm, n (%) | 102 (13%)            |
| Patients with T2 bright signal (edema), n (%) | 25 (36%)            |
| Segments with T2 bright signal (edema), n (%) | 120 (15%)            |
| Patients with T2 dark signal, n (%) | 18 (26%)             |
| Segments with T2 dark signal, n (%) | 40 (5%)             |
| Normalized MBF at rest, ml/min⁻¹·g⁻¹·(mmHg·bpm/10⁴)⁻¹ | 1.54 [1.43, 1.65] |

Results for n = 70 patients with diagnosis of HCM and a total of 804 segments (12 segments per patient) are given as mean [95% confidence interval (CI)]. EDV, end-diastolic volume; ESV, end-systolic volume; LV, left-ventricular; normalized MBF, myocardial blood flow corrected for the rate-pressure product; LGE, late gadolinium enhancement.

All morphological phenotypes of HCM were included: 45 septal, 9 mid-wall, 7 apical and 9 diffuse types. LGE was detected in 258 segments (32%) within 54 patients. In a logistic regression model the odds for the presence of LGE were 1.25 (CI [1.18; 1.31], p < 0.001) for each millimeter increase in end-diastolic LV wall thickness.
wall thickness. The odds for the presence of LGE were 16.31 (CI [7.96; 33.43], p<0.001) in segments with focal T2 bright signal and 14.02 (CI [5.40; 36.42], p<0.001) in segments with focal T2 dark signal (Table 2).

Resting Myocardial Perfusion

Absolute resting MBF was not significantly different between segments with varying severities of myocardial wall thickening or LGE. Also there were no significant differences between absolute epicardial and endocardial resting MBF.

In a simple linear regression model for repeated measurements LV wall thickness [p<0.001], LGE score [p<0.001], edema [p<0.001], T2 dark signal [p<0.001] and age [p=0.032] but not LV outflow gradient [p=0.901] showed a significant effect when correlated with relative resting perfusion (Table 3). For example, an increase of LV wall thickness of 1 mm was associated with an average reduction of relative myocardial perfusion of 0.3%. An increase of ten years in age was related to an average reduction of relative myocardial perfusion of 0.1%. Multiple linear regression analysis involving LV wall thickness, LGE score, edema score, T2 dark score and age as parameters revealed that LGE (p<0.001), edema (p = 0.026) and T2 dark signal (p = 0.019) were independent predictors for a reduction of relative resting perfusion. For example, an average relative MBF in a segment with LGE score 4 was 19.5% lower than in a segment without LGE (score 0). In segments with edema (score 1) the average relative MBF was 4.0% lower compared to segments without edema (score 0). In segments with T2 dark signal (score 1) the average relative MBF was 6.5% lower than in segments without T2 dark signal (score 0).

Subgroup Analysis of Segments with LGE (score 1–4) in Categories of Reduced and Elevated Perfusion

LGE (score 1–4) was present in 49.4% (78/158) of segments with reduced perfusion (<mean -1 SD) and in 22.2% (24/108) of segments with elevated perfusion (≥mean +1 SD). In reduced perfusion segments LGE was more frequently accompanied by T2 bright signal (edema), T2 dark signal (chronic fibrosis) and increased LV wall thickness ≥20 mm compared to reference segments. In elevated perfusion segments LGE was only more frequently accompanied by increased LV wall thickness compared to reference segments (Table 4). The extent of LGE was higher in reduced perfusion segments (mean LGE score, 2.11, CI [1.88; 2.33]) than in elevated perfusion segments in this subgroup (LGE score 1.54, CI [1.26; 1.82], p = 0.014). The pattern of LGE in reduced perfusion segments (Fig. 4a-c) was mainly characterized by high signal intensities and was well circumscribed (54/78 segments). In contrast, regions of elevated perfusion were associated with a diffuse and patchy LGE of low to intermediate signal intensity (23/24 segments), but not frequently with foci of T2 dark signal (3/23, Fig. 4d-e).}

Discussion

In this study focal differences of relative resting MBF in HCM patients were observed using MRI. Relative perfusion correlated inversely with LV wall thickness [p<0.001], extent of LGE (p<0.001), edema (p=0.001), T2 dark signal changes (p<0.001) and age (p=0.032). The LV outflow gradient did not affect resting myocardial perfusion, which is consistent with previous studies [16].

Myocardial perfusion is an important parameter in HCM, because perfusion abnormalities may lead to ischemia and myocardial scarring and thus, increase the risk for adverse cardiac outcomes.

### Table 2. Results of simple logistic regression with LGE as the outcome.

| Parameter        | Comparison | Odds Ratio | 95% CI       | p-value |
|------------------|------------|------------|--------------|---------|
| Myocardial thickness | global     | 1.25       | 1.18; 1.31   | <0.001  |
| Edema            | 1 vs. 0    | 16.31      | 8.00; 33.43  | <0.001  |
| T2 dark signal   | 1 vs. 0    | 14.02      | 5.40; 36.42  | <0.001  |

### Table 3. Results of simple and multiple regression analysis with relative MBF as the outcome.

| Parameter        | Comparison | Simple linear regression | Multiple linear regression |
|------------------|------------|--------------------------|----------------------------|
|                  |            | Regression coefficient (β) | 95% CI | p-value | Regression coefficient (β) | 95% CI | p-value |
| LV wall thickness| global     | -0.3                     | -0.5; -0.1 | <0.001 | -0.1                     | -0.1; 0.3 | 0.431 |
| LGE              | global     | <0.001                   |         |         | <0.001                   |         |         |
|                  | 1 vs. 0    | -2.9                     | -5.6; -0.2 | 0.037 | -1.8                     | -4.8; 1.1 | 0.220 |
|                  | 2 vs. 0    | -5.9                     | -10.1; -1.7 | 0.006 | -3.9                     | -8.7; 0.9 | 0.108 |
|                  | 3 vs. 0    | -12.9                    | -17.7; -8.0 | <0.001 | -8.9                     | -14.6; -3.2 | 0.002 |
|                  | 4 vs. 0    | -23.2                    | -31.2; -15.1 | <0.001 | -19.5                    | -28.4; -10.6 | <0.001 |
| Edema            | 1 vs. 0    | -8.3                     | -5.2; -11.3 | <0.001 | -4.0                     | -5.0; -7.5 | 0.026 |
| T2 dark signal   | 1 vs. 0    | -12.3                    | -7.2; -17.4 | <0.001 | -6.5                     | -1.2; -11.8 | 0.019 |
| Age              | global     | -0.07                    | -0.14; -0.01 | 0.032 | -0.05                    | -0.11; 0.01 | 0.108 |
| LV outflow tract gradient | global | 0 | -0.03; 0.04 | 0.901 | - | - | - |

Results of regression analysis with relative MBF as the outcome. LV wall thickness, age and gradient are continuous variables; LGE (score 0–4), edema (score 0–1) and T2 dark signal (score 0–1) are categorical variables.

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events such as arrhythmias and LV dysfunction. For instance, a reduction of myocardial perfusion reserve at hyperemia or during exercise, indicating microvascular dysfunction, has frequently been described in HCM patients [12,13,15,31]. Cecchi et al. demonstrated its prognostic relevance in HCM: The degree of microvascular dysfunction was associated with worse prognosis and death [16]. Petersen et al. showed by cardiac perfusion MRI reduced MBF values at hyperemia in HCM, which were proportional to the degree of end-diastolic LV wall thickness.

Figure 4. Examples of different perfusion patterns in HCM. 21-year-old patient with non-obstructive HCM (LV outflow gradient 7 mmHg). Large area of intense, well-defined LGE in the anterior septum and the anterior wall (b) with corresponding hypo-perfusion (relative MBF = 33.5%; a). T2-weighted imaging depicts low signal in the central area of the lesion, suggesting macroscopic, chronic fibrosis/scar tissue (red arrow), and adjacent high signal, indicating edema (arrow head, c). Maximum LV wall thickness is 31 mm. Findings of a 46-year-old HCM patient with an LV outflow gradient of 11 mmHg are given in d-f. Resting MBF of the interventricular septum is focally increased to 145% (d). In this area patchy and diffuse LGE with relatively low signal intensity (e) and patchy edema on T2-weighted images (f) are visible (red arrows). Maximum LV wall thickness is 33 mm.

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Table 4. Comparison of frequency of LGE and frequency of LV wall thickening ≥20 mm and T2 signal changes accompanied by LGE in segments of different perfusion categories.

| Parameter                  | Reference segments | Reduced perfusion segments | Elevated perfusion segments |
|----------------------------|--------------------|----------------------------|-----------------------------|
|                            | Frequency          | Relative risk | Odds ratio | p-value | Frequency | Relative risk | Odds ratio | p-value |
| LGE                       | 156/538 (29%)      | 1.70          | 2.39       | <0.001   | 24/108 (22%) | 0.77        | 0.70       | 0.160   |
| LGE + LV wall ≥20 mm      | 38/156 (24%)       | 1.79          | 2.40       | 0.004    | 11/24 (46%) | 1.88        | 2.63       | 0.046   |
| LGE + T2 bright area      | 44/146 (30%)       | 1.91          | 3.16       | <0.001   | 10/23 (44%) | 1.44        | 1.78       | 0.232   |
| LGE + T2 dark area        | 15/146 (10%)       | 2.75          | 3.43       | 0.001    | 3/23 (13%)  | 1.27        | 1.31       | ns      |

Comparison of the frequency of LGE (score 1–4) in segments with reduced and elevated perfusion to segments with perfusion values within one standard deviation of reference segments (reference segments). Similarly the frequencies of LGE accompanied with LV wall thickness ≥20 mm or accompanied with edema (T2 bright) and T2 dark signal were compared. Due to artifacts ten segments in the reference group and one segment in the elevated perfusion group were excluded from the T2 signal analysis. Relative risk, odds ratio and p-values are given for the comparison between reduced and elevated perfusion segments to reference segments.

LV, left-ventricular; LGE, late gadolinium enhancement; ns, not significant.
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