Myocardial Blood Flow and Fibrosis in Hypertrophic Cardiomyopathy

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ABSTRACT

Background: We investigated the relationship between myocardial blood flow (MBF), fibrosis, risk factors for sudden death, and clinical manifestations in hypertrophic cardiomyopathy (HCM).

Methods and Results: Sixty-two patients with HCM (45 men, overall mean age 47 ± 16 years), 15 acromegalic patients with left ventricular hypertrophy (9 man, overall mean age 47 ± 12years), and 20 healthy subjects underwent cardiac magnetic resonance. Resting MBF was measured as the ratio between coronary sinus flow measured by phase-contrast technique and left ventricular mass. Myocardial fibrosis was evaluated by late gadolinium enhancement (LGE) technique. In HCM patients, MBF was significantly lower than in control subjects and acromegalic patients. Patients with LGE had lower MBF than those without it (0.46 ± 0.2 vs 0.66 ± 0.29 $mL \cdot min^{-1} \cdot g^{-1}$; $P < .005$). Patients with ventricular tachycardia at Holter monitoring had lower MBF (0.4 ± 0.14 vs 0.6 ± 0.29 $mL \cdot min^{-1} \cdot g^{-1}$; $P < .04$). Among patients with preserved systolic function, those in New York Heart Association (NYHA) functional class ≥II had lower MBF than those in NYHA functional class I (0.46 ± 0.2 vs 0.69 ± 0.3 $mL \cdot min^{-1} \cdot g^{-1}$; $P < .003$). MBF was the only independent predictor of worse clinical status (NYHA ≥II; $P = .01$).

Conclusions: In HCM patients low resting MBF is associated with the presence of fibrosis. MBF is a predictor of worse clinical status. (*J Cardiac Fail 2011;17:384–391*)

Key Words: Hypertrophic cardiomyopathy, myocardial fibrosis, late gadolinium enhancement, cardiac magnetic resonance, myocardial blood flow.

Hypertrophic cardiomyopathy (HCM) is an inherited disease with phenotypic variability and is an important cause of sudden death.[1] Sudden cardiac death in HCM is probably the consequence of electrically unstable myocardial substrate with reentrant ventricular tachyarrhythmias.[2] Postmortem studies have evidenced the association between sudden cardiac death and the presence of myocardial disarray and scarring.[3] Recently, the noninvasive detection of myocardial fibrosis with magnetic resonance (MR) technique of late gadolinium enhancement (LGE) provided new information in the arrhythmic risk stratification in patients with HCM.[4,5]

Myocardial ischemia in the absence of coronary artery disease is another important physiopathologic factor in HCM.[6] It is considered to be a prognostic marker in HCM and may be involved as trigger of lethal ventricular tachyarrhythmias, directly and/or indirectly, as a possible cause of fibrosis.[7] Moreover, myocardial ischemia could be a cause of chest pain and dyspnea during effort.[8] In the absence of significant stenosis in epicardial coronary vessels, in HCM myocardial ischemia may be secondary to small vessel disease, fibrosis or to a disproportion between the vascular bed and the increased myocardial mass.[1] Then, myocardial blood flow (MBF) may be lower in HCM than in healthy subjects even in resting condition.

The purposes of the present study were: 1) to evaluate the association between MBF and the extent of fibrosis in patients with HCM by cardiac magnetic resonance (CMR); 2) to assess the relationship between MBF and fibrosis with "clinically established" risk factors for sudden death; and 3) to demonstrate the role of a reduced MBF and the

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presence of LGE in HCM for the occurrence of symptoms. CMR with velocity-encoded phase-contrast technique (PC-CMR) is a validated method to quantify blood flow.[9] Coronary sinus blood flow constitutes 96% of the total venous drainage of coronary blood flow. Therefore, quantification of coronary sinus flow by PC-CMR is an alternative way to assess myocardial blood flow (MBF) without exposing patients to ionizing radiation. Earlier studies demonstrated excellent agreement between positron-emission tomography and PC-CMR for the quantification of MBF.[10,11]

Methods

Patient Population

A total of 64 consecutive patients with HCM (45 men, overall mean age 47 ± 16 years) were enrolled in the study from January 2007 to June 2009. The diagnosis of HCM was based on previously reported criteria.[1]

As a model of non-HCM left ventricular hypertrophy, we included patients with cardiac acromegaly: From an initial population of 35 consecutive patients with untreated active acromegaly who underwent MRI, we selected 15 patients (9 man, overall age 47 ± 12 years old) having left ventricular mass index higher than the referral range. Twenty healthy normal subjects (14 men, overall mean age 48 ± 10 years) were enrolled as a control group.

To exclude the presence of coronary artery disease, we included HCM and acromegaly patients with a negative coronary angiography, a negative exercise test, or a low (<10%) 10-year risk for coronary events.[12] The study was approved by the internal Ethical Committee of our institute.

The following markers of increased risk of sudden death in patients with HCM were evaluated: family history of sudden death, extreme left ventricular (LV) wall thickness (≥30 mm), unexplained (nonvasovagal) syncope, and nonsustained ventricular tachycardia (VT) on ambulatory electrocardiogram Holter recordings (>4 ventricular beats). By clinical interrogation, each patient was classified in an NYHA functional class, assessed by a physician blinded to CMR data, on the basis of the presence and the severity of dyspnea before the CMR examination. The history of other symptoms (chest pain, palpitation) was also recorded. A 12-lead resting ECG was recorded on the day of the MRI examination. The presence of LV outflow tract obstruction was evaluated by echocardiography and defined as an LV outflow gradient of ≥30 mm Hg.

Magnetic Resonance Acquisition Protocol

MRI study was performed with a dedicated 1.5 Tesla (Signa Hdx; General Electrics Healthcare, Milwaukee, Wisconsin) with an 8-channel cardiac phased-array coil.

Short-axis cine images from the mitral plane valve to the left ventricular apex were acquired using a steady-state free precessing (FIESTA) pulse sequence with the following parameters: 30 phases, slice thickness 8 mm, no gap, 8 views per segment, NEX 1, field of view 40 cm, phase field of view 1, matrix 224 × 224, reconstruction matrix 256 × 256, flip angle 45°, TR/TE 3.5/1.5, and bandwidth 125 KHz.

Coronary sinus flow was obtained by acquiring images orthogonal to the coronary sinus, using imaging planes as close as possible to the right atrium, to include as many posterior cardiac veins as possible. A free breathing velocity-encoded phase-contrast gradient-echo cine sequence with cardiac and respiratory gating was used. The following parameters were applied: TR/TE 12/5 ms, flip angle 20°, field of view 30, phase field of view 1, matrix 192 × 160, reconstruction matrix 256 × 256, slice thickness 5 mm, number of excitations 5. Flow sensitivity was set to 50 cm/s of encoded velocity and raised if aliasing artifact occurred. By the respiratory gating, the image data were phase reordered to minimize respiratory artifact. The use of free breathing velocity-encoded phase-contrast technique was previously validated by the comparison with flow probe measurement in coronary sinus and in coronary artery.[13]

LGE technique was used to evaluate the extent of myocardial necrosis. LGE images were acquired in short-axis views from mitral plane valve to the left ventricular apex by a 2D segmented inversion-recovery–prepared gradient echo pulse sequence.

Images were acquired 10 minutes after administration of Gd-DTPA (Magnevist; Schering) with a dosage of 0.2 mmol/kg in short-axis views. The following parameters were used: field of view 40 mm, slice thickness 8 mm, no gap between each slice, repetition time 4.6 ms, echo time 1.3, flip angle 20°, matrix 224 × 192, reconstruction matrix 256 × 256, number of excitation 1, R-R interval 2. The appropriate inversion time was set to null normal myocardium (range 250–350 ms).

At the end of the examination, a phantom was placed in the MRI scanner and a velocity-encoded fast contrast gradient-echo cine sequence was acquired with the same acquisition plane and parameters used for the patient.[14]

Image Postprocessing

Analysis of MRI images was performed using a commercially available research software package (Mass Analysis, Leyden, The Netherlands). Left ventricular (LV) mass was measured by the analysis of the cine short-axis images. The endocardial and epicardial contours of LV myocardium were traced in the end-diastolic and the end-systolic phases. End-diastolic volume index (EDVi), end-systolic volume index (ESVi), and mass index were measured as previously described.[15,16]

The LV and right ventricular (RV) volumetric data were plotted against the time (in ms) in a volumetric filling time curve. LV diastolic parameters were calculated from the volumes/time curve as previously described.[17] Briefly, a dV/dT curve was generated as the first-derivative transformation of the volumetric filling time curve. The early (E) and late (A) peak filling rate (PFR) were measured in dV/dT curve as, respectively, the early and the late diastolic peaks of dV/dT curve. The PFRE/PFRA ratio was defined as the ratio between the early and the late peak filling rates.

Mitral regurgitant volume was measured as the difference between LV and RV stroke volumes. Coronary sinus flow was measured as previously described.[18] Briefly, the coronary sinus contour was traced first on the magnitude images at each cine frame. Then the traced region of interest was applied on the corresponding phase image (Fig. 1). The effect of through-plane motion caused by cardiac contraction in the oblique coronary plane was relatively small. However, phase-offset errors were minimized for each cardiac phase by subtracting the signal from the phase images acquired in the phantom at the end of the MRI examination. Cross-sectional area of the coronary sinus was measured in the magnitude images throughout the cardiac cycle. Mean flow velocity of coronary sinus was obtained in the respective phase image. Blood flow was calculated as the product of area and mean flow velocity in each cardiac phase. Coronary sinus was multiplied

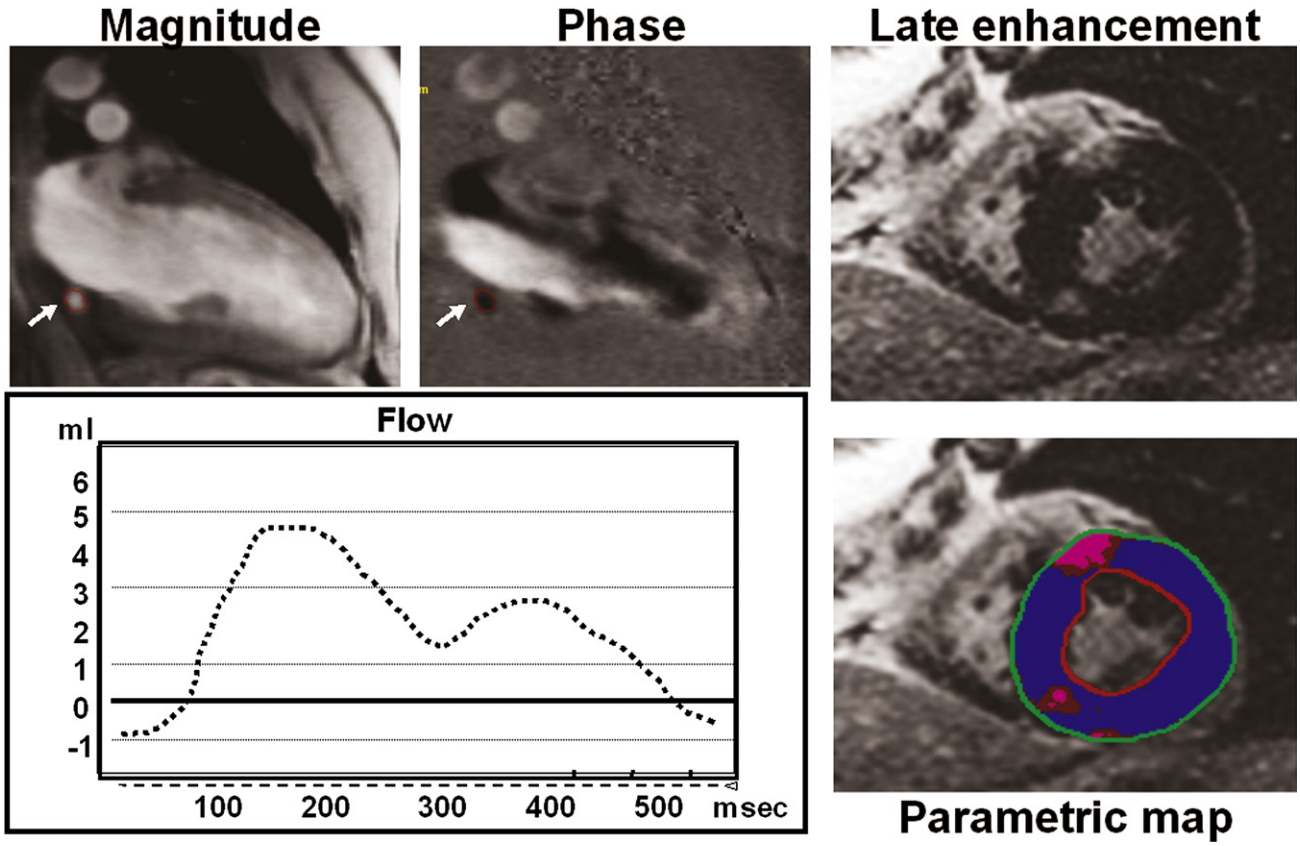

Fig. 1. Coronary sinus flow measurement. Cross-sectional coronary sinus area was traced in all of the magnitude images (top left), and identical area is automatically traced in phase images (top middle). Blood flow was calculated as the product of cross-sectional area and mean flow velocity in each cardiac phase (bottom left). In the same patient, areas of late gadolinium enhancement were detected, as evidenced in a short-axis image (top right) and in its parametric map (bottom right).

for the heart rate, obtaining the coronary sinus flow/minutes. The MBF was calculated as coronary sinus flow/minutes divided by LV mass and expressed as $mL \cdot min^{-1} \cdot g^{-1}$.

The extent of LGE was measured as previously described.[19] A region of interest (ROI) was selected in the background of the image. Mean signal intensity and standard deviation (SD) of this ROI were measured. The LV myocardium was delimited by endocardial and epicardial contours traced manually. Enhanced myocardium was defined as myocardium with a signal intensity of ≥6 SDs above the mean of the ROI. The extent of LGE was expressed as percentage of the LV mass. LGE was defined as undetected when the measured extent was <0.1% of LV mass.

Statistical Analyses

All data were analysed using JMP software (version 4.0). Data are presented as continuous variables and proportions (percentages). Continuous variables are expressed as mean ± 1 SD. Categoric variables were compared by Pearson chi-square test or Fisher exact test when appropriate. One-way analysis of variance or Bonferroni post hoc test, when appropriate, was used to compare quantitative variables across groups. A P value of <.05 was considered to be statistically significant. A multiple regression analysis, including MBF as dependent and the presence of LGE, the extent of LGE, the maximal end-diastolic wall thickness, history of atrial fibrillation, and age as independent variables, was performed with a stepwise selection procedure to assess the predictors of MBF in the HCM population. Logistic regression analysis with a stepwise selection procedure ($P < .05$ for entry; $P > .10$ for removal) was used to evaluate the influence of covariates on NYHA functional class >I. A Bland-Altman plot was used to evaluate the interobserver reproducibility of the MBF measurement (Fig. 2) performed by 2 blinded observers.

Results

The clinical characteristics of the HCM patients are summarized in Table 1. Coronary angiography was performed in 35 patients. Ischemic provocative test was performed in 12 patients. In 17 patients, aged < 30 years, with an estimated risk of coronary artery disease lower than 10%, no ischemic provocative test were performed. Two patients were excluded because of the presence of coronary artery disease, found by angiography. The final population included 62 patients with HCM. In the acromegalic patients, mean serum growth hormone and insulin-like growth factor concentrations were 7.1 ± 9.9 μg/L and 736 ± 222 μg/L, respectively. As evidenced in Table 1, LV mass index was significantly higher in HCM than in control subjects but not significant different between HCM and acromegaly

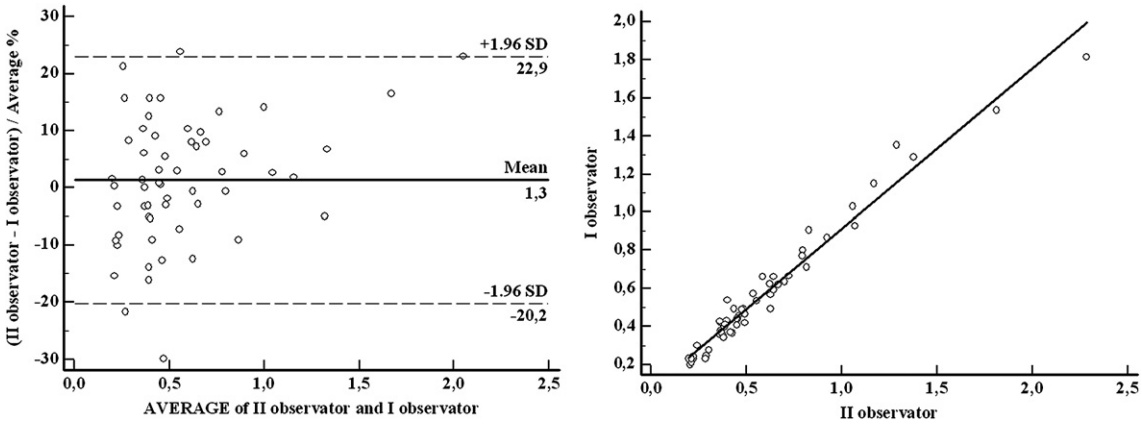

Fig. 2. Bland-Altman plot for the interobserver reproducibility of the measurement of myocardial blood flow (left) and the scatter diagram (right panel) showed good agreement between the observers.

patients. Acromegaly patients had higher LV mass index than control subjects (92 ± 30 vs 74 ± 25 g/m^2; $P < .05$).

Resting MBF was significantly lower in patients with HCM than in control subjects (0.56 ± 0.28 vs 0.92 ± 0.5 mL·min^{-1}·g^{-1}; $P < .04$; Fig. 3). MBF was also significantly lower in patients with HCM than in acromegaly patient.

LGE was detected in 39 patients with HCM (63%) and in none of the acromegalic patients and control subjects. HCM patients with and without detectable LGE were similar for age (45 ± 14 vs 48 ± 18 years, respectively; $P = .45$) and gender (71% vs 73% male, respectively). MBF was lower in HCM patients with positive LGE than in those with

Table 1. Clinical Variables of the Hypertrophic Cardiomyopathy (HCM) Population

Variable	Control	*P* Value*	HCM	*P* Value†	Acromegaly
n	20		62		15
Age (y)	48 ± 10	.79	47 ± 16	.99	47 ± 12
Male (n)	14 (70%)	.94	45 (72%)	.52	9 (60%)
Family history of HCM, n (%)	—		6 (10%)		—
Risk factors for SCD, n (%)					
Family history of SCD	—		3 (5%)		—
Maximal wall thickness ≥30 mm	—		1 (2%)		—
Outflow pulse gradient >30 mm Hg	—		15 (24%)		—
Unexplained syncope	—		4 (6%)		—
VT at 24-hour Holter monitoring	—		10 (16%)		—
Clinical manifestation, n (%)					
Angina	—		15 (24%)		—
Palpitation	—		15 (24%)		—
Dyspnea	—				—
NYHA ≥II			41 (66%)		
NYHA ≥II			38 (61%)		
NYHA III			3 (5%)		
History of atrial fibrillation	—		9 (44%)		—
CMR findings					
Maximal end-diastolic thickness (mm)	8 ± 3	<.0001	20 ± 5	<.0001	13 ± 8
LV mass (g)	129 ± 30	<.0001	197 ± 54	.06	167 ± 60
LV mass index (g/m^2)	74 ± 25	.01	104 ± 28	.18	93 ± 30
LV end-diastolic volume index (mL/m^2)	86 ± 11	.5	80 ± 16	.24	85 ± 9
LVEF (%)	64 ± 5	.06	69 ± 8	.18	66 ± 7
LVEF <50%, n (%)	0		4 (6%)		0
Extent of LGE (% of LV mass)	0		9.4 ± 13.5		0
MBF (mL·min^{-1}·g^{-1})	0.92 ± 0.5	.04	0.56 ± 0.28	<.0001	1.36 ± 0.5
Therapy, n (%)			26 (42%)		
Beta-Blockers	—		21 (34%)		—
Calcium antagonist	—		4 (6%)		—
ACE inhibitors	—		7 (11%)		—
Diuretic	—		5 (8%)		—
Antiarrhythmic	—		1 (1.6%)		—

SCD, sudden cardiac death; VT, ventricular tachycardia; NYHA, New York Heart Association functional class; CMR, cardiac magnetic resonance; LV, left ventricular; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; MBF, myocardial blood flow; ACE, angiotensin-converting enzyme.

*Control vs HCM.

†HCM vs acromegalic patients.

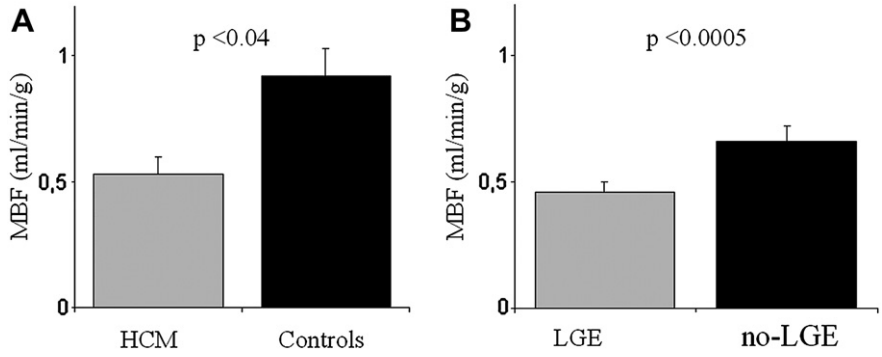

Fig. 3. (A) Myocardial blood flow (MBF) was significantly lower in hypertrophic cardiomyopathy (HCM) than in control subjects. (B) Patients with HCM and myocardial fibrosis (late gadolinium enhancement, LGE) had significantly lower MBF than patients without fibrosis (no-LGE).

negative LGE (0.46 ± 0.2 vs 0.66 ± 0.29 mL·min^{-1}·g^{-1}; P = .005; Fig. 3B). Patients in the HCM group without LGE had lower MBF than control subjects (P = .04). For multiple regression analysis, the independent predictors of MBF were the presence of LGE (P = .03, coefficient −0.025) and the LV mass index (P = .012; coefficient −0.004).

Risk Factors and MBF

MBF was not significantly different in patients with than in those without family history of sudden cardiac death (0.41 ± 0.07 vs 0.57 ± 0.3 mL·g-1·min-1; P = .31). Patients with unexplained syncope had significantly higher MBF (0.91 ± 0.1 vs 0.55 ± 0.3 mL·min^{-1}·g^{-1}; P < .02). MBF was lower in patients with ≥1 risk factor than in patients without any risk factors (0.48 ± 0.27 vs 0.63 ± 0.27 mL·min^{-1}·g^{-1}; P < .05).

At 24 hours ECG Holter monitoring, VT was recorderd in 10 patients (16%). As presented in Table 2, patients with VT had significantly lower MBF than patients without. However, patients with nonsustained VT had significantly higher extent of LGE, higher maximal end-diastolic thickness, and total risk score.

Clinical Manifestations and MBF

The incidence of symptoms in the total population of HCM is presented in Table 1. Of the HCM population, 38 patients were in NYHA functional class II, 3 in class III, and none in class IV. However, average MBF was 0.44 ± 0.22 mL·min^{-1}·g^{-1} for patients in class II and 0.43 ± 0.2 mL·min^{-1}·g^{-1} in class III.

Compared with asymptomatic patients, MBF was not different in patients with angina (0.61 ± 0.32 vs 0.57 ± 0.26 mL·min^{-1}·g^{-1}; P = .8), palpitations (0.61 ± 0.32 vs 0.61 ± 0.3 mL·min^{-1}·g^{-1}; P = .99), and history of atrial fibrillation (0.61 ± 0.32 vs 0.57 ± 0.2 mL·min^{-1}·g^{-1}; P = .7). In Table 3, the clinical and CMR parameters of HCM patients with preserved LV

Table 2. Occurrence of Ventricular Tachycardia (VT)* in Population With Hypertrophic Cardiomyopathy (HCM)

Variable	Nonsustained VT	Absence of Nonsustained VT	*P* Value
n	10	52	
Male	7 (70%)	37 (74%)	
Age (y)	53 ± 12	46 ± 16	.09
Risk factors for SCD			
Family history of SCD	0	3 (5%)	
Unexplained syncope	3 (5%)	0	.5
Maximal end-diastolic wall thickness (mm)	23 ± 3	19 ± 5	.05
Outflow pulse gradient (mm Hg)	16 ± 25	15 ± 26	.9
Total risk score (no. of risk factors per SCD)	1.6 ± 0.9	0.4 ± 0.6	<.01
CMR			
Extent of LGE (% of LV mass)	29.3 ± 4.5	7.3 ± 1.9	<.0001
MBF (mL·min^{-1}·g^{-1})	0.4 ± 0.14	0.6 ± 0.29	<.04
LV mass index (g/m^2)	109 ± 24	104 ± 29	.9
LVEF (%)	66 ± 11	70 ± 8	.34
PFRE (mL/s)	319 ± 169	398 ± 280	.5
PFRA (mL/s)	211 ± 101	229 ± 95	.7
PFRE/PFRA	3.4 ± 4.1	1.9 ± 1.2	.2

PFRE, peak of filling rate E; PFRA, peak of filling rate A; other abbreviations as in Table 1.
*Patients with or without an episode of VT on 24-hour Holter monitoring.

function (ejection fraction ≥50%) are reported. This selection of patients was done to assess the role of reduced MBF and the presence of fibrosis in the absence of LV dysfunction as a potential cause of dyspnea. In this selected group of HCM patients, those in NYHA functional class ≥II had lower MBF than patients in class I.

Moreover, the patients in NYHA functional class ≥II showed a larger extent of LGE, higher maximal end-diastolic wall thickness, greater left atrium, and higher mitral regurgitant volume than the patients in NYHA functional class I. Furthermore, the patients in NYHA functional class ≥II had significantly lower PFRA.

In the logistic regression model, including MBF, extent of LGE, age, maximal LV wall thickness, and left atrial diameter, MBF was the only independent predictor of NYHA functional class >I (coefficient 5.8, standard error 2.37; $P = .01$).

Discussion

The main results of this study could be synthesized as follows: 1) Resting MBF was significantly lower in HCM than in control subjects and patients with acromegalic LV hypertrophy; 2) patients with HCM presenting fibrosis as detected by LGE showed lower MBF than those without; 3) an association between nonsustained VT and MBF was found in this population; and 4) MBF was the only independent predictor of worse functional class (NYHA functional class ≥II).

Resting MBF in HCM

Kawada et al. evaluated MBF by PC-CMR in 29 patients with HCM in resting condition and during hyperemia induced by dypiridamole.[18] They demonstrated a reduced hyperemic response to vasodilator in HCM patients than in control subjects, with a nonsignificant difference in resting MBF. The results of the present study showed that basal MBF was significantly lower in HCM than in healthy control subjects. This could be explained because of the larger size of the population in our study than in the earlier one. Moreover, the selection of patients was different: We enrolled patients with previous history of atrial fibrillation and/or impaired ejection fraction which were excluded in the earlier study. Patients with HCM complicated by episode of paroxystic atrial fibrillation or by decreased EF could be in advanced stage of disease and have lower MBF than those without. The finding of a decreased MBF is concordant with the physiopathologic mechanism of ischemia in HCM. In fact, a mismatch between disproportionate LV hypertrophy, lack of capillary growth, and abnormally narrowed intramural coronary arteries was previously demonstrated in HCM and could be used to partially explain the reduced supply of blood flow at rest.[20,21] Myocardial fibrosis could participate in the decruitment of capillary vessels, and be involved in decreasing resting MBF. Alternatively, replacement fibrosis could be secondary to brief episodes of repeated ischemia.

Table 3. Functional Status in Patients With Ejection Fraction ≥50%

Variable	NYHA >I	NYHA I	*P* Value
n	24	34	
Age (y)	51 ± 16	40 ± 14	.03
Family history of HCM	3 (17%)	2 (9%)	.44
History of atrial fibrillation	3 (14%)	5 (15%)	.67
Mitral regurgitant volume (mL)	9 ± 10	7 ± 8	.4
Maximal end-diastolic wall thickness (mm)	22 ± 5	19 ± 5	.02
Outflow pulse gradient (mm Hg)	18 ± 3	14 ± 3	.5
CMR			
Extent of LGE (% of LV mass)	10.4 ± 7	7 ± 6	.05
MBF ($mL \cdot min^{-1} \cdot g^{-1}$)	0.44 ± 0.2	0.69 ± 0.3	.003
LV mass index (g/m^2)	107 ± 30	10 ± 26	.43
EDVi (mL/m^2)	82 ± 17	79 ± 14	.41
ESVi (mL/m^2)	25 ± 7	25 ± 11	.8
Left atrial minimum diameter (mm)	53 ± 22	41 ± 21	.04
PFRE (mL/s)	312 ± 212	481 ± 367	.04
PFRE/PFRA	2.7 ± 3	1.9 ± 1.4	.2

EDVi, end-diastolic volume index; ESVi, end-systolic volume index; other abbreviations as in Tables 1 and 2.

In the present study, the presence of detectable LGE and the LV mass index were independent predictors of MBF in HCM. The mismatch between the coronary flow supply and the increased LV mass may result in a reduction of global MBF. The disproportion between increased mass and flow was an intrinsic feature of HCM, as demonstrated by the comparison with acromegalic LV hypertrophy . We chose LV hypertrophy in acromegaly because it is a model of organized myocardial hypertrophy, without disarray and, as we previously demonstrated, with the absence of detectable LGE.[22]

In age- and gender-matched patients with acromegaly and LV hypertrophy, a significantly lower maximal wall thickness than in HCM was found, although the LV mass index was not different. Despite similar LV mass index, significantly higher MBF than in HCM was measured. Thus, in acromegaly the increased LV mass index was balanced by a proportionate increase in coronary flow, resulting in a preserved MBF.

We found an association between myocardial fibrosis detected by LGE technique and MBF: Patients with HCM and positive LGE had significantly lower MBF than those with negative LGE. These results suggest a link between fibrosis and MBF, even if it remains unclear whether fibrosis is a consequence of myocardial ischemia or it is a direct cause of reduced MBF at rest.

Resting MBF and Ventricular Arrhythmias

Both myocardial fibrosis and transitory ischemia were considered as potential substrates in triggering malignant ventricular arrhythmias.[23] In agreement with earlier reports, results of the present study confirmed the relation between total risk score, maximal end-diastolic wall thickness, and

extent of LGE with ventricular tachyarrhythmias on 24-hour ECG Holter monitoring.[21,24] Moreover, we found that patients with episodes of nonsustained VT had significantly lower MBF at rest and higher extent of LGE. The occurrence of episodes of nonsustained VT at 24-hour ECG Holter monitoring is generally regarded to be an independent determinant of increased risk of sudden death in this disease.[25,26] Thus, these results highlight the value of LGE as an emerging feature to be evaluated in patients with HCM. LGE could be particularly useful to stratify the risk in subjects with only 1 ''accepted'' risk factor of sudden death.[27]

Recently, 2 large studies evaluated the prognostic role of LGE in HCM, demonstrating that patients with a positive LGE had worse prognosis than those without a detectable LGE.[4,5] However, LGE was described in most of HCM patients (60%−80% of them), and it may be considered to be a sensitive predictor of worse outcome, also taking into account other parameters such as LGE extent, the pattern of distribution of LGE, and MBF to more accurately stratify patients with HCM. Therefore, the impact on the clinical management and the prognostic role of resting MBF in HCM should be evaluated by further long-term follow-up studies.

Resting MBF and NYHA Functional Class

A significant correlation between LGE and impaired functional class (NYHA functional class ≥II) has been already demonstrated.[19] In the present study we also found a reduced MBF in patients with impaired NYHA functional class. The presence of atrial dilatation, maximal wall thickness, and reduced PFRE were also associated with worse functional class. Noteworthily, only MBF was an independent predictor of worse functional class. Therefore, it is hypothesizable that effort dyspnea could be secondary to brief episodes of ischemia, already documented in HCM patients, and that ischemia could more likely occur in patients with a low resting MBF.

Moreover, an earlier study showed that subjects with impaired MBF were more likely to experience LV remodeling with dilatation, wall thinning, and systolic dysfunction.[28]

Study Limitations

The main limitation of the current study was the absence of evaluation of MBF during hyperemia. However, our results suggest that the evaluation of resting MBF could be useful for the clinical stratification in patients with HCM. The prognostic role of impaired resting MBF and coronary reserve must be evaluated by further long-term follow-up studies.

Flow measurement in this study was performed by using a free breathing velocity-encoded phase-contrast pulse, which has been previously validated invasively by comparison with the flow probe measurements of coronary sinus and coronary arteries.[13] Although vessel contours may be blurred with this approach owing to motion artifacts, the potential of using multiple averages (NEX 5) increases signal-to-noise ratio, thus improving image quality. However, flow evaluation during free breathing acquisition may be considered to be more physiologic than the acquisition during long breath-holding. Moreover, as shown in Table 1, most of the HCM patients assumed beta-blockers or calcium antagonist therapy and the heart rate was usually ∼50−60 beats/min. In these patients the acquisition time of the phase-contrast images was longer, lasting usually >25 seconds, and some patients may not be able to keep a complete breath-holding.

Regarding the ability of velocity-encoded phase-contrast imaging MRI to measure flow specifically in small structures, Hofman et al.[29] demonstrated that accurate blood volume flow rates may be determined through small vessels for a number of voxels per vessel diameter value of ∼≥3. In the present study, we found an average coronary end-systolic diameter of 9 ± 2 mm and end-diastolic diameter of 6 ± 1 mm. Coronary sinus cross-section is usually ovoid, and the minor diameter is usually oriented in the superior-inferior direction and the maximal diameter anterior-posterior. In our protocol of acquisition of coronary sinus images, the frequency is usually in the superior-inferior direction and the phase anterior-posterior to avoid the wraparound artifact. Thus, despite a voxel dimensions of 1.6 mm × 1.9 mm, the number of voxels in each direction is usually >3. Moreover, the net flow in coronary sinus is mostly evidenced during the cardiac phase when the coronary sinus has a larger diameter. Then the resulting effect of low spatial resolution may be minimal. The coronary sinus diameters in the present study was slightly higher than those found by van Rossum et al.,[30] but this may be secondary to the difference in age of the population, which was older in our study, or to the improved quality of cine images with the 1.5T scanner.

Conclusions

CMR may be considered as a valuable imaging tool in HCM, allowing accurate evaluation of cardiac morphology, quantitative measurement of LV mass and wall thickness, detection and quantification of fibrosis, and quantification of MBF in resting and hyperemic conditions. Moreover, CMR is a noninvasive virtually safe technique without administration of ionizing radiation. Thus, CMR may be particularly important for an initial evaluation of patients with a new diagnosis of HCM and for serial evaluation of the progression of this disease.

Disclosures

None.

References

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308−20.
2. Maron BJ. Sudden death in young athletes. N Engl J Med 2003;349: 1064−75.
3. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. Circulation 2001;104:1380−4.
4. Bruder O, Wagner A, Jensen CJ, MD, Ong SP, Kispert E, Nassenstein K, et al. Myocardial Scar visualized by cardiovascular magnetic resonance imaging predicts major events in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:875−87.
5. O'Hanlon R, Grasso A, Roughton M, Moon JC, MD, Clark S, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867−74.
6. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. Hum Pathol 2000;31:988−98.
7. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 2003;349:1027−35.
8. Maron MS, Olivotto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, et al. The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;54:866−75.
9. Van Rossum AC, Visser FC, Hofman MB, Galjee MA, Westerhof N, Valk J. Global left ventricular perfusion: noninvasive measurement with cine MR imaging and phase velocity mapping of coronary venous outflow. Radiology 1992;182:685−91.
10. Schwitter J, DeMarco T, Kneifel S, von Schulthess GK, Jörg MC, Arheden H, et al. Magnetic resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: a comparison with positron emission tomography. Circulation 2000;101:2696−702.
11. Koskenvuo JW, Hartiala JJ, Knuuti J, Sakuma H, Toikka JO, Komu M. Assessing coronary sinus blood flow in patients with coronary artery disease: a comparison of phase-contrast MR imaging with positron emission tomography. AJR 2001;177:1161−8.
12. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1990;121:293−8.
13. Lund GK, Wendland MF, Shimakawa A, Arheden H, Ståhlberg F, Higgins CB, Saeed M. Coronary sinus flow measurement by means of velocity-encoded cine MR imaging: validation by using flow probes in dogs. Radiology 2000;217:487−93.
14. Gatehouse PD, et al. Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. J Cardiovasc Magn Reson 2010;14:12−5.
15. Sechtem U, Pflugfelder PW, Gould RG, Cassidy MM, Higgins CB. Measurement of right and left ventricular volumes in healthy individuals with cine MR imaging. Radiology 1987;163:697−702.
16. Vinnakota KC, Bassingthwaighte JB. Myocardial density and composition: a basis for calculating intracellular metabolite concentrations. Am J Physiol Heart Circ Physiol 2004;286:1742−9.
17. Kawaji K, Codella NCF, Prince MR, Chu CW, Shakoor A, LaBounty TM, et al. Automated segmentation of routine clinical cardiac magnetic resonance imaging for assessment of left ventricular diastolic dysfunction. Circ Cardiovasc Imaging 2009;2: 476−84.
18. Kawada N, Sakuma H, Yamakado T, Takeda K, Isaka N, Nakano T, et al. Hypertrophic cardiomyopathy: MR measurement of coronary blood flow and vasodilator flow reserve in patients and healthy subjects. Radiology 1999;211:129−35.
19. Aquaro GD, Pingitore A, Masci PG, Formisano F, Barison A, Strata E, et al. Usefulness of delayed enhancement by magnetic resonance imaging in hypertrophic. Am J Cardiol 2010;105:392−7.
20. Krams R, Kofflard MJ, Duncker DJ, Von Birgelen C, Carlier S, Kliffen M, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodelling of the coronary microcirculation. Circulation 1998;97:230−3.
21. Krams R, ten Cate FJ, Carlier SG, van der Steen AF, Serruys PW. Diastolic coronary vascular reserve: a new index to detect changes in the coronary microcirculation in hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;43:670−7.
22. Bogazzi F, Lombardi M, Strata E, Aquaro GD, di Bello V, Cosci C, Sardella C, et al. High prevalence of cardiac hypertophy without detectable signs of fibrosis in patients with untreated active acromegaly: an in vivo study using magnetic resonance imaging. Clin Endocrinol 2008;68:261−368.
23. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis 1985;28:1−83.
24. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000;342:1778−85.
25. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212−8.
26. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;45:697−704.
27. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007; 298:405−12.
28. Olivotto I, Cecchi F, Gistri R, Lorenzoni R, Chiriatti G, Girolami F, et al. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. J Am Coll Cardiol 2006;47:1043−8.
29. Hofman MB, Visser FC, van Rossum AC, Vink GQ, Sprenger M, Westerhof N. In vivo validation of magnetic resonance blood volume flow measurements with limited spatial resolution in small vessels. Magn Reson Med 1995;33:778−84.
30. van Rossum AC, Visser FC, Hofman MBM, Galjee MA, Westerhof N, Valk J. Global left ventricular perfusion: noninvasive measurement with cine MR imaging and phase velocity mapping of coronary venous outflow. Radiology 1992;182:685−91.