Coronary Flow Reserve Impairment in Apical vs Asymmetrical Septal Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Mechanisms underlying a reduction in coronary flow reserve (CFR) in hypertrophic cardiomyopathy (HCM), especially apical HCM (ApHCM), are elusive. This study set out to evaluate mechanisms underlying a reduction in CFR in 2 HCM subtypes.

Hypothesis: Mechanisms for CFR reduction in HCM are different between the 2 subtypes of HCM.

Methods: Thirty-one patients with asymmetrical septal hypertrophy (ASH), 43 with ApHCM, and 27 healthy volunteers were recruited. Mean diastolic coronary flow velocity (CFmv) was monitored before and after adenosine infusion by transthoracic echocardiography in the mid-to-distal left anterior descending coronary artery. Coronary flow reserve was defined as the ratio between CFmv before and after adenosine infusion. Left ventricular mass index and stress myocardial perfusion were assessed by cardiac magnetic resonance imaging.

Results: Although basal CFmv was higher in ASH patients than in healthy controls ($P < 0.05$), it was similar in ApHCM patients and controls ($P = 0.85$). Poststress CFmv was significantly lower in both HCM subtypes than in controls ($P < 0.05$). Consequently, CFR was higher in controls than in ASH or ApHCM patients ($P < 0.05$). When HCM patients were stratified into 2 groups based on the presence of CFR impairment, no difference was observed between these 2 groups in terms of left ventricular mass index by cardiac magnetic resonance imaging. Multivariate logistic regression analysis identified basal CFmv as the only independent variable associated with CFR reduction in HCM ($r^2 = 0.49$, $P < 0.001$).

Conclusions: Whereas the inability to augment coronary flow to its maximal level during stress was found to underlie CFR impairment in both HCM subtypes, the recruitment of vasodilatory capacity at baseline was more prominent in ASH than in ApHCM patients.

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by a hypertrophied and nondilated left ventricle (LV) in the absence of another obvious cause explaining increased LV mass.¹ Patients with HCM not infrequently present with objective evidence of myocardial ischemia and/or chest pain, despite angiographically

normal coronary arteries.^{2–4} A reduced coronary flow reserve (CFR) has been proposed to underlie this phenomenon in HCM with asymmetric septal hypertrophy (ASH) and apical hypertrophy (ApHCM).^{5–7} Nevertheless, our understanding of the mechanisms responsible for CFR reduction in patients with HCM, especially in patients with ApHCM, is hitherto insufficient.

Thanks to recent advances in imaging technology, CFR can now be accurately assessed by transthoracic Doppler echocardiography.^{8–11} Because of its noninvasiveness, CFR can be easily assessed in unsedated patients, and can be performed in close proximity in time to other tests. Accordingly, impairment of coronary vasodilator capacity in different subsets of HCM patients can be investigated without difficulty. In addition, this technique has enabled the recruitment of and direct comparisons with healthy subjects without ethical concern.

In this study, we used transthoracic Doppler echocardiography to search for the mechanisms involved in CFR

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impairment in HCM patients. To calculate left ventricular mass index (LVMI) and to assess stress myocardial perfusion status more accurately, cardiac magnetic resonance imaging (CMR) was employed in a subset of HCM patients.

Methods

The overall study population consisted of 101 subjects; 31 patients with ASH (age, 55 ± 12 y; 22 males), 43 with ApHCM (age, 57 ± 11 years; 36 males), and 27 healthy volunteers (age, 54 ± 12 years; 7 males). Diagnosis of ASH was based on the conventional echocardiographic criteria (ie, an interventricular septal thickness > 15 mm and a septum-to-posterior wall thickness ratio of > 1.3). Diagnostic criteria for ApHCM included echocardiographic demonstration of pure LV apical hypertrophy, without increased LV wall extended to septum.¹² The presence of epicardial coronary artery disease was systematically excluded in all HCM patients by invasive coronary angiography (51 HCM patients) or computed tomographic coronary angiography (23 HCM patients). Patients in normal sinus rhythm were exclusively recruited, and patients with valvular disease, a history of myocardial infarction, or LV outflow tract dynamic obstruction were excluded. No HCM patients complained of chest pain at study enrollment, although 21 HCM patients (28.4%) had a previous history of chest pain. In all HCM patients, medications were withheld for ≥ 24 hours before the index echocardiographic examination. For comparison purposes, age-matched healthy volunteers were also invited and served as the control group. They underwent echocardiography as a part of general medical checkup. Control subjects had no cardiac symptoms, no relevant medical history, normal electrocardiographic (ECG) and echocardiographic findings (left ventricular ejection fraction [LVEF] = $61.1 \pm 5.7\%$, LV end-diastolic volume [LVEDV] = 111.2 ± 30.2 mL, and LV end-systolic volume [LVESD] = 26.6 ± 7.7 mL), and no history of smoking. Coronary stenosis was systematically excluded in all control subjects based on computed tomographic coronary angiography. All HCM patients and controls were requested not to take a beverage containing methylxanthines like coffee, tea, and so on.

Transthoracic echocardiographic examinations were performed with a commercially available echocardiographic system (Vivid 7; GE Medical Systems, Milwaukee, WI). Routine standard echocardiographic examinations included measurements of LV end-diastolic wall thicknesses, LV end-diastolic and end-systolic volumes, and LVEF using the modified biplane Simpson's method, pulsed-wave Doppler examination of the mitral inflow, and pulsed-wave tissue Doppler imaging at the medial mitral annulus. From the mitral inflow Doppler signals, early transmitral inflow velocity (E), late transmitral inflow velocity (A), and deceleration time of E were obtained with the sample volume placed between the tips of mitral leaflets. Left ventricular outflow tract pressure gradient was measured by continuous-wave Doppler. Standard M-mode and 2D images were obtained during end-expiratory breath-hold for better image acquisition and stored in cine loop format from 3 consecutive beats.

Coronary flow velocity was measured at the mid-to-distal left anterior descending (LAD) coronary artery using

Figure 1. Measurement of coronary flow velocity. Mean diastolic coronary flow velocity was calculated by dividing time velocity integral of diastolic coronary flow velocity by the diastolic interval of coronary flow velocity. Abbreviations: CFmv, mean diastolic coronary flow velocity; CFtvi, time velocity integral of diastolic coronary flow velocity; Dint, diastolic interval of coronary flow velocity.

a 3.5-MHz transducer in the morning over 8-hour fasting state. For optimal coronary Doppler flow imaging, the Nyquist limit was set between 12 and 25 cm/second using a Doppler sample volume of 2–3 mm. Color gain was adjusted to provide optimal imaging. After the anterior interventricular sulcus was imaged by modifying the angle of ultrasound beam, coronary blood flow of mid-to-distal LAD was searched for under the guidance of Doppler flow mapping. After acquisition of the baseline coronary flow velocity curve, adenosine was continuously infused over 3 minutes at a dose of 0.14 mg/kg/minute to enable spectral Doppler signals to be recorded during hyperemic conditions. Coronary flow was continuously monitored after initiating adenosine infusion, and mid-to-distal LAD coronary flow was measured repeatedly using the peak velocity curve obtained under peak hyperemic conditions. Blood pressure and heart rate were measured before and after adenosine infusion. Left ventricular end-systolic pressure (LVESP) was calculated with the equation previously suggested.¹³ For monitoring of cardiac rhythm, 12-lead electrocardiography was used throughout examinations. Time velocity integral of diastolic coronary flow (CFtvi), diastolic interval (Dint), and mean diastolic coronary flow velocity (CFmv) were measured using coronary flow velocity recordings (Figure 1). Coronary flow reserve was defined as the ratio of CFmv after to before adenosine infusion. Measurements were made by investigators unaware of subject information or status (hyperemic vs baseline). All parameters were averaged over 3 consecutive cycles for statistical analysis.

Cardiac magnetic imaging was performed in a subgroup of 51 HCM patients on a 1.5-T scanner system (Sonata Magnetom; Siemens, Erlangen, Germany) at the same day to echocardiography. Cine CMR was performed using a steady-state, free precession imaging sequence after scout and localizer image acquisition. The slice thickness was set at 6 mm (gap = 4 mm) and LV short-axis images were acquired from the apex to the base to include the entire LV volume. Repeated breath-holds were required in order

to create adequate images. Temporal resolution was 25–30 frames per R-R interval. Left ventricular mass was measured with commercially available software (QMASS MR; Medis, Leiden, Netherlands) by a single experienced observer who was blinded to echocardiographic data. Briefly, after selecting an end-diastolic still frame, endocardial and epicardial borders were manually traced in every LV slice. Short-axis images were cross-referenced to long-axis images to differentiate between atrial and ventricular locations at the LV base. Papillary muscles and LV trabeculation were excluded from endocardium and included in the LV cavity volume. Finally, LV mass was indexed to body surface area.

A saturation prepared (prepulse delay = 100 msec) single-shot spoiled gradient-echo sequence was used for perfusion imaging. The acquisition parameters were as follows: repetition time/echo time, 2.8/1.4 msec; flip angle, 12°; field of view, 225 × 300 mm; acceleration factor, 2; turbo factor, 62; matrix, 128 × 88; and slice thickness, 7 mm. A dynamic series of 3 short-axis sections with a spatial resolution of 1.7 × 3.4 × 7 mm were acquired continuously for 40 consecutive cardiac cycles. For stress perfusion imaging, adenosine (140 µg/min/kg) was given over 3 minutes. Scanning was started during the last minute of vasodilator stress using an intravenous bolus of 0.07 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at an injection rate of 4 mL/second, followed by a flush of 20 mL of saline at the same rate. During adenosine infusion, ECG activity was continuously monitored, and blood pressure and heart rate measurements were obtained at 1-minute intervals. Patients were instructed to hold their breath as long as possible during imaging and to continue breathing shallowly when it was no longer possible. Rest perfusion imaging was performed using the same geometry used for the short-axis cine views and a bolus of the same contrast agent given during stress imaging after a 15-minute rest to allow for myocardial washout.

Data are expressed as mean ± standard deviation or as median with interquartile ranges (IQR) for continuous variables and as frequencies and percentages for categorical variables. After evaluating the distributions of continuous variables for normality using the Shapiro-Wilk test, the unpaired *t* test or the Mann-Whitney *U* test was used for comparison of continuous variables. The Fisher exact test was employed to compare categorical variables, and Pearson correlation coefficients were calculated to quantify correlations between continuous variables. To identify parameters independently associated with an abnormal CFR in HCM, multivariate linear regression analysis and multiple logistic regression analysis using the forward stepwise selection process were undertaken. All statistical analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, IL), and a *P* value of <0.05 was considered statistically significant.

Results

Clinical, ECG, and conventional echocardiographic variables are summarized in Table 1.

Coronary Flow Velocity Measurements

The mean CFR of controls was 3.03 ± 0.39 , and there was no control subject who had a CFR value of <2 (Table 2). Baseline heart rates were similar for HCM patients and controls. However, CFmv before adenosine infusion tended to be higher in all HCM patients (combined ASH and ApHCM groups) than in controls (*P* = 0.06). When HCM patients were classified into 2 subgroups based on hypertrophic type, an elevation in CFmv at baseline was only observed in ASH patients (for ASH, *P* < 0.05 vs controls; for ApHCM, *P* = 0.85 vs controls). On the other hand, CFmv after adenosine infusion was significantly higher in controls than ASH or ApHCM patients (*P* < 0.05), but without significant differences between the 2 HCM subtypes (*P* = 0.37). As a result, CFR was significantly impaired in HCM, regardless of HCM subtype. Coronary flow reserve was highest in the controls (3.03 ± 0.39), followed by ApHCM patients (2.39 ± 0.79), and ASH patients (1.93 ± 0.46).

Comparison of Clinical and Echocardiographic Characteristics of HCM Patients Classified by Normal or Abnormal Coronary Flow Reserve Value

To determine which parameters are associated with a decrease in CFR, all 74 HCM patients were allocated to 2 groups based on a CFR value. According to previous reports,^{14–16} a CFR value of <2 were defined as abnormal. Using this cutoff value, 34 patients had an abnormal CFR (1.66 ± 0.27) and 40 had a normal CFR (2.67 ± 0.62). An abnormal CFR was observed more frequently in patients with a lower LVESV (*P* = 0.02), a higher A wave (*P* = 0.005), a higher E/E' ratio (*P* = 0.048), a higher baseline CFmv (*P* < 0.001), and a higher rate-pressure product before (*P* = 0.016) and after (*P* = 0.014) adenosine infusion. Left ventricular mass index by CMR was not associated with a decrease in CFR (*P* > 0.99) (Table 3). Prevalence of stress myocardial perfusion abnormality on CMR was similar between patients with normal CFR and those with abnormal CFR (57.1% vs 41.7%, *P* = 0.27). However, patients with an abnormal stress myocardial perfusion on CMR tended to have a lower CFR than those without (1.97 ± 0.57 vs 2.38 ± 0.92 , *P* = 0.056) (Figure 2). There was no significant difference in poststress CFmv in these 2 groups (*P* = 0.41) (Table 2). Although statistically significant, relationships between CFR and the above-mentioned parameters were rather weak, with the exception of basal CFmv, as shown in Table 4. Multiple linear regression analysis using the above-mentioned continuous variables and age revealed that only basal CFmv demonstrated an independent association with CFR ($r^2 = 0.33$, *P* < 0.001) (Table 4). Multivariate forward stepwise logistic regression analysis, adjusted for previously known confounders such as age, gender, and hypertrophic type together with variables found to be statistically significant by univariate analysis, also showed that a higher baseline CFmv was the only independent variable associated with a CFR decrease in HCM patients ($r^2 = 0.49$, *P* < 0.001 for the final model). For all HCM population, CFmv at baseline displayed an inverse correlation with CFR ($r = -0.57$, *P* < 0.001) (Figure 3). The negative correlation observed between CFmv at baseline and CFR tended to be

Table 1. Comparison of Clinical and Conventional Echocardiographic Parameters

	ASH, n = 31	ApHCM, n = 43	P Value
Clinical variables			
Age (y)	54.5 ± 12.5	57.1 ± 10.9	0.17 ^a
Median (IQR)	53.0 (47.0–66.0)	57.0 (52.0–64.5)	
Male (%)	22 (71.0)	36 (83.7)	0.25
Chest pain history (%)	9 (29.0)	12 (27.9)	>0.99
Family history of SCD (%)	4 (12.9)	1 (2.3)	0.15
Family history of HCM (%)	5 (16.1)	0 (0)	0.01
Previous history of syncope (%)	7 (22.6)	3 (7.0)	0.08
DM (%)	1 (3.2)	3 (7.0)	0.64
Hypertension (%)	11 (35.5)	23 (53.5)	0.16
Smoking (%)	1 (3.2)	5 (11.6)	0.39
NYHA class			0.35 ^b
I	13	24	
II	17	16	
III	1	3	
IV	0	0	
Electrocardiography			
Strain pattern and/or T-wave inversion (%)	16 (51.6)	41 (95.3)	0.01
Any ST-T abnormality (%)	18 (58.1)	41 (95.3)	0.01
LV hypertrophy (%)	18 (58.1)	33 (76.7)	0.09
Conventional echocardiographic variables			
IVSd, mm	17.1 ± 4.1	10.6 ± 1.8	<0.001 ^a
Median (IQR)	16.6 (14.3–18.9)	10.6 (9.5–11.5)	
LVPWd, mm	9.5 ± 2.2	9.9 ± 2.0	0.80 ^a
Median (IQR)	9.9 (7.7–10.9)	9.7 (8.7–10.9)	
LVEDV, mL	97.4 ± 19.5	99.8 ± 24.4	0.48 ^a
Median (IQR)	99.2 (82.0–112.3)	98.7 (87.3–117.1)	
LVESV, mL	33.0 ± 9.5	35.4 ± 11.4	0.40 ^a
Median (IQR)	31.5 (24.7–41.8)	36.6 (27.1–41.3)	
LVEF (%) ^a	66.1 ± 6.2	66.1 ± 5.6	0.98
E, m/sec	0.59 ± 0.16	0.60 ± 0.14	0.92
A, m/sec	0.59 ± 0.21	0.55 ± 0.17	0.48
DT, msec	202.1 ± 50.7	189.6 ± 52.7	0.31
S', m/sec	0.06 ± 0.01	0.06 ± 0.01	0.76
E', m/sec	0.04 ± 0.01	0.04 ± 0.01	0.69
A', m/sec	0.06 ± 0.02	0.07 ± 0.02	0.02
E/E' ratio	18.4 ± 8.7	14.0 ± 4.4	0.02

Abbreviations: A, late diastolic mitral inflow velocity; A', late diastolic mitral annular velocity; ACEI, angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin receptor blocker; ASH, hypertrophic cardiomyopathy with asymmetrical septal hypertrophic type; CCB, calcium-channel blocker; DM, diabetes mellitus; DT, deceleration time of E wave; E, early mitral inflow velocity; E', early diastolic mitral annular velocity; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; IVSd, end-diastolic interventricular septal thickness; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, LV end-systolic volume; LVIDs(d), left ventricular end-systolic (end-diastolic) dimension; LVPWd, LV end-diastolic posterior wall thickness; NYHA, New York Heart Association; S', systolic mitral annular velocity; SCD, sudden cardiac death. ^aBy Friedman test. ^bBy linear-by-linear association test.

Table 2. Coronary Flow Velocity Measurements

	Controls (n = 27)	HCM Patients			P Value by ANOVA (Control vs ASH vs ApHCM)
		All (n = 74)	ASH (n = 31)	ApHCM (n = 43)	
Before adenosine infusion					
HR, bpm	66 ± 10	62 ± 10	64 ± 10	61 ± 10	0.12
CFTvi, cm	16.3 ± 4.2	19.5 ± 6.7 ^a	19.9 ± 6.7 ^b	19.2 ± 6.8	0.11 ^c
Median (IQR)	15 (14–18)	18.8 (14.2–24.2)	22.2 (14.0–24.7)	17.7 (14.2–23.7)	
CFmv, m/sec	0.030 ± 0.010	0.034 ± 0.012	0.035 ± 0.011 ^a	0.033 ± 0.013	0.12 ^c
Median (IQR)	0.030 (0.025–0.035)	0.032 (0.025–0.039)	0.036 (0.024–0.042)	0.031 (0.025–0.036)	
After adenosine infusion					
HR, bpm	93 ± 13	74 ± 11 ^a	76 ± 13 ^a	72 ± 10 ^a	<0.001
CFTvi, cm	33.0 ± 6.8	34.1 ± 13.0	31.2 ± 12.1	36.2 ± 13.3	0.21 ^c
Median (IQR)	32 (28–39)	30.6 (23.9–43.0)	28.1 (23.0–36.0)	17.7 (14.2–23.7)	
CFmv, m/sec	0.092 ± 0.019	0.069 ± 0.019 ^a	0.066 ± 0.019 ^a	0.072 ± 0.019 ^a	<0.001 ^c
Median (IQR)	0.09 (0.0749–0.1049)	0.067 (0.056–0.084)	0.066 (0.055–0.080)	0.068 (0.056–0.085)	
CFR	3.03 ± 0.39	2.20 ± 0.70 ^a	1.93 ± 0.46 ^a	2.39 ± 0.79 ^{a,d}	<0.001
Abbreviations: ANOVA, analysis of variance; ApHCM, apical hypertrophic cardiomyopathy; ASH, hypertrophic cardiomyopathy with asymmetrical septal hypertrophic type; CFTvi, time velocity integral of the diastolic coronary flow; CFmv, mean diastolic coronary flow velocity; CFR, coronary flow reserve; HCM, hypertrophic cardiomyopathy; HR, heart rate; IQR, interquartile range. ^a P < 0.05 vs controls. ^b P = 0.05 vs controls. ^c By Friedman test. ^d P < 0.05 vs ash group.					

higher in ApHCM patients ($r = -0.63$, $P < 0.001$) than in ASH patients ($r = -0.44$, $P < 0.001$), but without statistical significance ($P = 0.26$). Of note, for all HCM cohort, CFmv at baseline displayed a positive correlation with the baseline rate-pressure product ($r = 0.34$, $P = 0.003$), whereas it was not correlated with age, LVMI, LVESV, LVEDV, LVEF, or E/E' ratio (all $P > 0.05$). Cardiac magnetic resonance imaging–determined LVMI were not found to be associated with CFR ($r = -0.049$, $P = 0.73$) or basal CFmv ($r = 0.11$, $P = 0.46$).

Measurement Variabilities

Image clips from 20 randomly selected HCM patients were reviewed by the same observer for CFmv measurements at >2 weeks apart and independently by a second observer. The CFmv measurements made by these 2 independent observers were found to be correlated with an r value of 0.92 (standard error of estimate = 0.0045). In terms of intraobserver variability, the correlation between the 2 was $r = 0.96$ (standard error of estimate = 0.0031) without a trend for overestimation or underestimation. Bland-Altman analysis also showed good intraobserver and interobserver agreements (limits of agreement = 0.0046 ± 0.0017 and 0.0030 ± 0.0016 , respectively).

Discussion

Coronary flow reserve is determined by the ability of 2 components of myocardial perfusion, namely the epicardial coronary artery stenosis resistance and the microvascular resistance, to achieve maximal coronary blood flow.

In the absence of epicardial coronary artery stenosis, microvascular resistance is the main determinant of CFR (as was found in HCM patients in the present study). Under this condition, 3 components are responsible for CFR alterations: (1) coronary perfusion pressure, (2) the level of coronary flow before stress, and (3) the position of the pressure-flow relationship during maximal vasodilation (Figure 4).^{17,18} The fact that no differences in blood pressure and LVESV in the 2 groups of Table 2 were found, in association with no chest pain and no epicardial coronary stenosis, reduces the possibility that coronary perfusion pressure might exert a significant impact on CFR differences. The second component (ie, the level of coronary flow before vasodilation) varies with myocardial metabolic demand or myocardial oxygen demand in the basal state.^{18–20} As shown by Figure 4, an increase in resting coronary flow can reduce measured CFR even without a change in flow during maximum vasodilation. A variety of different conditions augment resting coronary flow, that is, recent ischemia, LV hypertrophy, or LV preload.^{18–22} Because our HCM patients did not have any subjective complaint of chest pain at study enrollment, we do not believe that recent myocardial ischemia is likely to elevate basal CFmv. It is generally believed that in the presence of pressure-induced LV hypertrophy resting total coronary flow is elevated such that flow per unit mass of myocardium remains almost normal.^{17,21,22} However, LV hypertrophy itself presumably had a minimal role in the CFmv elevation observed at baseline in our HCM patients, given the lack of a statistical difference in CMR-determined LVMI between the 2 groups in Table 3

Table 3. Comparison of Clinical and Echocardiographic Characteristics in HCM Patients With or Without Normal CFR

	CFR < 2, n = 34	CFR ≥ 2, n = 40	P Value
Clinical variables			
Age, y	57.3 ± 11.9	55.0 ± 11.3	0.27*
Median (IQR)	59 (52–66)	55 (5–65)	
Male (%)	24 (70.6)	34 (85.0)	0.16
Chest pain history (%)	11 (32.4)	10 (25.0)	0.61
Family history of sudden cardiac death (%)	2 (5.9)	3 (7.5)	>0.99
Family history of HCM (%)	3 (8.8)	2 (5.0)	0.66
Previous history of syncope (%)	5 (14.7)	5 (12.5)	>0.99
DM (%)	2 (5.9)	2 (5.0)	>0.99
Hypertension (%)	14 (41.2)	20 (50.0)	>0.99
Smoking (%)	2 (5.9)	4 (10.0)	0.68
Medications (%)			
ACEI/ARB	12 (35.3)	13 (32.5)	0.81
β-Blocker	7 (20.6)	10 (25.0)	0.78
Dihydropyridine CCB	5 (14.7)	5 (12.5)	>0.99
Nondihydropyridine CCB	14 (41.2)	13 (32.5)	0.48
Diuretics	6 (17.6)	6 (15.0)	0.76
HCM type (%)			0.08
Asymmetrical septal hypertrophy	18 (58.1)	13 (41.9)	
Apical hypertrophy	16 (37.2)	27 (62.8)	
NYHA class			0.92
I	18	19	
II	13	20	
III	3	1	
IV	0	0	
Conventional echocardiographic variables			
IVSd (mm)	14.2 ± 5.1	12.7 ± 3.6	0.19 ^a
Median (IQR)	12.5 (10.8–17.3)	11.5 (9.9–15.3)	
LVPWd (mm)	9.9 ± 2.4	9.5 ± 1.8	0.39 ^a
Median (IQR)	9.8 (8.7–11.4)	9.7 (8.2–10.7)	
LVEDV (mL)	94.9 ± 20.4	102.1 ± 23.7	0.12 ^a
Median (IQR)	92.0 (82.3–112.4)	103.5 (86.3–117.1)	
LVESV (mL)	31.4 ± 9.6	36.9 ± 10.9	0.02 ^a
Median (IQR)	31.5 (24.6–39.0)	37.9 (28.4–42.6)	
LVEF (%)*	67.0 ± 6.0	65.3 ± 5.6	0.21
E, m/sec	0.60 ± 0.16	0.59 ± 0.15	0.72

Table 3. *Continued*

	CFR < 2, n = 34	CFR ≥ 2, n = 40	P Value
A, m/sec	0.63 ± 0.19	0.51 ± 0.17	0.005
DT, msec	199 ± 55	191 ± 50	0.50
S', m/sec	0.06 ± 0.01	0.06 ± 0.01	0.69
E', m/sec	0.04 ± 0.01	0.04 ± 0.01	0.83
A', m/sec	0.07 ± 0.02	0.07 ± 0.02	0.86
E/E' ratio	17.5 ± 8.1	14.3 ± 5.0	0.048
Hemodynamic variables			
Before adenosine infusion			
HR, bpm	66 ± 9	60 ± 10	0.004
SBP/DBP, mm Hg	127 ± 14 / 76 ± 10	125 ± 16 / 75 ± 10	0.56/0.68
LVESP, mm Hg	98 ± 5	97 ± 6	0.56
Rate-pressure product	8325 ± 1531	7409 ± 1640	0.016
CFmv, m/sec	0.041 ± 0.014	0.027 ± 0.007	<0.001
Median (IQR)	0.038 (0.035–0.045)	0.027 (0.023–0.032)	
After adenosine infusion			
HR, bpm	77 ± 13	71 ± 9	0.02
SBP/DBP, mm Hg	123 ± 16 / 73 ± 12	120 ± 14 / 72 ± 11	0.30/0.72
LVESP, mm Hg	97 ± 6	95 ± 6	0.30
Rate-pressure product	9512 ± 2003	8484 ± 1483	0.014
CFmv, m/sec	0.067 ± 0.021	0.071 ± 0.017	0.41
Median (IQR)	0.064 (0.056–0.082)	0.068 (0.055, 0.087)	
LVMI by CMR, g/m ²	124.1 ± 41.0 (n = 23)	124.1 ± 40.0 (n = 28)	>0.99
Perfusion decrease on CMR during adenosine stress (%)	16 (57.1)	10 (41.7)	0.27
Abbreviations: A, late diastolic mitral inflow velocity; A', late diastolic mitral annular velocity; ACEI, angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin receptor blocker; ASH, hypertrophic cardiomyopathy with asymmetrical septal hypertrophic type; CCB, calcium channel blocker; CFR, coronary flow reserve; CMR, cardiovascular magnetic resonance imaging; DBP, diastolic blood pressure; DM, diabetes mellitus; DT, deceleration time of E wave; E, early mitral inflow velocity; E', early diastolic mitral annular velocity; HCM, hypertrophic cardiomyopathy; HR, heart rate; IQR, interquartile range; IVSd, end-diastolic interventricular septal thickness; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESP, left ventricular end-systolic pressure; LVESV, left ventricular end-systolic volume; LVIDs(d), left ventricular end-systolic (end-diastolic) dimension; LVMI, left ventricular mass index; LVPWd, left ventricular end-diastolic posterior wall thickness; NYHA, New York Heart Association; S', systolic mitral annular velocity; SBP, systolic blood pressure. ^a By Mann-Whitney U test.			

and no correlation between baseline CFmv and LVMI. In addition, LV preload does not seem to be able to effectively account for differences in basal CFmv between these 2 groups, because LVEDV was similar. Although we cannot propose plausible explanation for this unexpected phenomena based on our findings alone, we presume that the relations between basal CFmv and LV hypertrophy or LV preload are altered by intricate interplay between as-yet-unidentified factors in HCM patients. However, we did find that the basal rate-pressure product showed a clear statistical difference between patients with abnormal and normal CFR values. Moreover, it was found that basal CFmv was positively correlated with only basal rate-pressure

product ($r = 0.34$, $P = 0.003$), supporting the critical role of the basal rate-pressure product in the determination of basal CFmv.

Coronary flow reserve can also be reduced if maximal coronary flow response is attenuated in the absence of any change in coronary perfusion pressure, and thus, the pressure-flow relationship during stress becomes less steep (line A to C in Figure 4).³ Chronic reductions in maximal coronary flow during vasodilation, with corresponding decreases in CFR, have been documented in pressure- and/or volume-overload LV hypertrophy.²³ This concept also appears to be true in HCM, which is not associated with a pressure- or a volume-overload state, because poststress

Figure 2. Comparison of CFR according to the presence or absence of stress myocardial perfusion abnormality. Abbreviations: CFR, coronary flow reserve.

CFmv was significantly lower in HCM patients than in normal controls. On the other hand, myocardial ischemia is also known to produce a decrease in CFmv after stress. Because patients with stress-perfusion abnormality tended to have a lower CFR than those without ($P = 0.056$), the contribution made by myocardial ischemia to decreases in poststress CFmv with subsequent CFR reductions appears to play a certain role in both types of HCM patients.

Interestingly, an elevation in basal CFmv was more prominent in ASH patients rather than in ApHCM patients. On the other hand, no recognizable difference was observed between the 2 HCM subtypes in terms of the poststress CFmv decline (Table 2). Hence, although recruitment of vasodilatory capacity in the basal state has a major effect on CFR reduction in ASH patients, both HCM subtypes share another pathophysiological mechanism that causes CFR reduction, that is, an impaired capacity to augment coronary flow delivery during stress.

The present study has some clinical implications. Because basal CFmv is predominantly determined by basal rate-pressure product, the avoidance of a basal CFmv elevation is the key to mitigating CFR decline in both HCM subtypes.

Figure 3. Linear regression analysis of coronary flow reserve vs basal mean diastolic coronary flow velocity by hypertrophic cardiomyopathy subtype. Abbreviations: ApHCM, apical hypertrophic cardiomyopathy; ASH, asymmetrical septal hypertrophy; CFmv, mean diastolic coronary flow velocity; CFR, coronary flow reserve.

Because major difference in basal rate-pressure product was derived from resting heart rate differences, effective control of heart rate is clinically important in the preservation of CFR in the setting of appropriate systemic blood pressure control. In addition, given a lower CFR in patients with stress myocardial perfusion abnormality than those without (though with borderline statistical significance) (Figure 2), development of a treatment strategy to curb the extent of stress myocardial perfusion abnormality may be clinically relevant to prevention of CFR impairment.

Study Limitations

We should acknowledge some limitations of this study. Transthoracic Doppler echocardiography does not provide absolute measures of volumetric flow, but rather provides measures of coronary flow velocity, which is viewed as a measure of volumetric flow under the assumption of unchanging vessel diameter in response to vasodilator stress. However, slight increases in epicardial coronary artery diameter have been previously demonstrated after pharmacological stress,²⁴ which would lead to a slight underestimation of flow response to pharmacologic stress, especially in healthy controls. However, this effect would be minimized in HCM patients, in whom endothelial

Table 4. Associations Between Coronary Flow Reserve and Various Parameters in Hypertrophic Cardiomyopathy Patients

	Univariate		Final Model for Multivariate Analysis			
	<i>r</i>	<i>P</i> Value	<i>r</i> ²	<i>P</i> Value	β	95% CI
LVESV	0.22	0.06				
A wave	-0.23	0.045				
E/E' ratio	-0.26	0.02				
Basal CFmv	-0.57	<0.001	0.33	<0.001	-0.57	-42.5 ~ -20.7
Rate-pressure product before adenosine infusion	-0.15	0.02				
Rate-pressure product after adenosine infusion	-0.20	0.095				
Age	-0.06	0.059				

Abbreviations: A, late diastolic mitral inflow velocity; CFmv, mean diastolic coronary flow velocity; CI, confidence interval; E, early mitral inflow velocity; E', early diastolic mitral annular velocity; LVESV, left ventricular end-systolic volume.

Figure 4. The dynamic relationship between coronary flow and coronary perfusion pressure in the left ventricle is depicted. Without a significant increase in myocardial metabolic demand or in myocardial oxygen requirements, coronary flow is well maintained over a wide range of coronary perfusion pressures (line B). In this situation, CFR is represented by line E. Any condition leading to an increase in basal myocardial metabolic demand moves the pressure-flow relationship upward (line D) from line B, which reduces CFR, even without a change in coronary flow during maximum dilation, as demonstrated by line F. The shift to the right of the pressure-flow relationship (from line A to line C) also predisposes a reduction in CFR, even without an upward shift of the basal coronary flow line. In HCM patients, the pressure-flow relationship was shifted upward and to the right, indicating a reduction in CFR. Of note, as described in the text in detail, the shift of the basal coronary flow curve from line B to line D was more obvious in patients with ASH than in patients with apical hypertrophy. Abbreviations: ASH, asymmetrical septal hypertrophy; CFR, coronary flow reserve; HCM, hypertrophic cardiomyopathy.

dysfunction might prevent significant vasodilation in response to adenosine stress. Furthermore, this noninvasive technique has been validated against invasive techniques,²⁵ and it has also been reported that changes in coronary flow velocities induced by coronary vasodilation closely mirror changes in coronary blood flow.^{26,27} Accordingly, we believe that measures of coronary flow velocity, not of coronary flow per se, are a significant limitation to the present study. Secondly, CMR was not performed in all HCM patients. Although a comparison of 51 HCM patients with and 23 without CMR found no significant differences in clinical, echocardiographic, and LV mass determined by CMR, this does not mean that lack of CMR data in 23 HCM patients occurs completely at random. Thirdly, E/E' ratio, commonly used for estimating LV filling pressure, at baseline was different between ASH and ApHCM. However, E/E' ratio failed to show its ability to predict LV filling pressure in HCM patients.²⁸ Thus, we do not believe that the difference in E/E' ratio between the 2 types of HCM exerted a significant influence on our results. Finally, CFR measured in the LAD might not be a representative. However, in adult HCM patients, CFR is abnormal not only in the hypertrophied wall, but also in the nonhypertrophied wall of the LV.² In addition, the CFR value obtained in the coronary artery subtending hypertrophied LV wall is similar to those obtained in the coronary arteries subtending nonhypertrophied wall.²⁹

Conclusion

Mechanisms responsible for CFR impairment in HCM include the following 2 factors: (1) the recruitment of vasodilatory capacity in the basal state, and (2) the inability to augment coronary flow maximally during stress. Although the effect of the latter on CFR reductions is of similar extents in 2 HCM subtypes, the contribution made by the former to CFR reductions is more prominent in ASH than in ApHCM. Given a lower CFR in HCM patients with stress myocardial perfusion abnormality than those without, development of medications that decrease the extent of stress myocardial perfusion abnormality may be a novel strategy to alleviate CFR decrease in both types of HCM.

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