Relevance of Coronary Microvascular Flow Impairment to Long-Term Remodeling and Systolic Dysfunction in Hypertrophic Cardiomyopathy

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OBJECTIVES   This study sought to evaluate whether the entity of microvascular dysfunction, assessed by positron emission tomography (PET), predicts the long-term development of left ventricular (LV) remodeling and systolic dysfunction in hypertrophic cardiomyopathy (HCM).

BACKGROUND   A subgroup of patients with HCM developed LV dilation and systolic impairment. A causal role of coronary microvascular dysfunction has been suggested as the underlying pathophysiological mechanism.

METHODS   Fifty-one patients (New York Heart Association functional class I to II) were followed up for 8.1 ± 2.1 years after measurement of resting and dipyridamole (Dip) myocardial blood flow (MBF). Left ventricular systolic dysfunction was defined as an ejection fraction (LVEF) <50%.

RESULTS   The Dip-MBF was blunted in HCM patients compared with a group of healthy control patients (1.50 ± 0.69 ml/min/g vs. 2.71 ± 0.94 ml/min/g; p < 0.001). At final evaluation, 11 patients (22%) had an LVEF <50%; in most (n = 7), systolic dysfunction was associated with a significant increase in LV cavity dimensions (>5 mm) during follow-up. These 11 patients showed lower Dip-MBF than the 40 with preserved LV function (1.04 ± 0.38 ml/min/g vs. 1.63 ± 0.71 ml/min/g, respectively; p = 0.001); Dip-MBF was particularly blunted in five patients with clinical progression to severe heart failure symptoms or death (Dip-MBF 0.89 ± 0.15 ml/min/g). At multivariate analysis, the two independent predictors of systolic dysfunction were Dip-MBF in the lowest tertile (<1.1 ml/min/g; relative hazard, 7.5; p = 0.038) and an end-diastolic LV dimension in the highest tertile (>45 mm; relative hazard, 12.3; p = 0.031).

CONCLUSIONS   Severe microvascular dysfunction is a potent long-term predictor of adverse LV remodeling and systolic dysfunction in HCM. Our findings indicate microvascular dysfunction as a potential target for prevention of disease progression and heart failure in HCM.   (J Am Coll Cardiol 2006;47:1043–8) © 2006 by the American College of Cardiology Foundation

Since its early descriptions, hypertrophic cardiomyopathy (HCM) has been characterized by a small, markedly hypertrophied, hypercontractile left ventricle (LV) (1). In a significant minority of patients, however, progressive LV dilation and impairment of systolic function may become prominent clinical features, and lead to the so-called end-stage phase (1–7). Although other causes may concur, this process is thought to represent the consequence of recurrent, diffuse myocardial ischemia attributable to coronary microvascular dysfunction (8–11).

Using positron emission tomography (PET), we have recently shown that severe blunting of the coronary vasodilator response to dipyridamole (Dip), reflecting microvascular dysfunction, is a potent predictor of outcome in a cohort of HCM patients, mostly related to heart failure and its complications (12). That work, however, did not address the relationship between microvascular dysfunction and long-term changes in LV morphology and function, so that such an association remains unproven. Therefore, in the same HCM patient cohort, we aimed to assess whether the severity of coronary microvascular dysfunction was predictive of adverse long-term LV remodeling, systolic dysfunction, and progression to the end-stage phase.

PATIENTS AND METHODS

Patients. The study cohort comprises 51 patients from a large regional HCM population, closely followed up at two community-based institutions in Tuscany. The baseline features and clinical outcome of the study group have been previously reported (12). The diagnosis of HCM was based on the echocardiographic evidence of myocardial hypertrophy (wall thickness >15 mm), in the absence of any other

Abbreviations and Acronyms

Dip = dipyridamole
HCM = hypertrophic cardiomyopathy
LV = left ventricle/ventricular
MBF = myocardial blood flow
NYHA = New York Heart Association
PET = positron emission tomography

cardiac or systemic cause of LV hypertrophy (1). Exclusion criteria were a history of hypertension or coronary artery disease and severe congestive heart failure (New York Heart Association [NYHA] functional class III to IV). All patients had Maron type II or III morphology (1). The mean age was 44 ± 13 years, 36 (71%) patients were male, and 21 (41%) were in NYHA functional class II. Fourteen patients (27%) complained of typical angina and were enrolled after documentation of angiographically normal coronary arteries.

Control patients. The control group included 12 patients with an atypical chest pain syndrome (4 men) ages 51 ± 8 years (p = 0.1 vs. patients). All had a normal physical examination, electrocardiogram, echocardiogram, treadmill exercise test result, and coronary and LV angiograms.

Measurement of myocardial blood flow. All PET scans were performed at the Institute of Clinical Physiology, in Pisa, between June 1990 and May 1993 (9,12). Regional myocardial blood flow (MBF) was measured using PET with nitrogen-13-labeled ammonia under basal conditions and during near maximal hyperemia induced by Dip (0.56 mg/kg, administered intravenously over 4 min) as previously reported (9). For each MBF measurement, a dynamic acquisition was started simultaneously with an intravenous bolus of nitrogen-13–labeled ammonia (0.25 mCi/kg of body weight). The Dip-MBF was measured 50 min after the basal scan and 4 min after the end of Dip infusion, following the same protocol. Absolute regional MBF (in ml/min/g) was calculated as previously reported (9). The study protocol was approved by the research ethics committees of each institution, and written consent was obtained from each patient.

Clinical and echocardiographic follow-up. Patients were followed up for an average of 8.1 ± 2.1 years after the PET scan with clinical and echocardiographic examinations. For each patient, we compared echocardiographic measurements at the time of PET with the last available echocardiogram at the end of follow-up.

Table 1. Clinical and Echocardiographic Features of the 51 Study Patients Based on Dip-MBF Values

	Overall Study Group (n = 51)		Lowest Tertile of Dip-MBF <1.11 ml/mg/min (n = 18)		Middle Tertile of Dip-MBF 1.11–1.60 ml/mg/min (n = 16)		Highest Tertile of Dip-MBF >1.60 ml/mg/min (n = 17)	
	At the Time of PET Scan	At Final Evaluation	At the Time of PET Scan	At Final Evaluation	At the Time of PET Scan	At Final Evaluation	At the Time of PET Scan	At Final Evaluation
Age (yrs)	44 ± 13	52 ± 13	48 ± 12	56 ± 12	39 ± 14	47 ± 13	43 ± 13	51 ± 13
NYHA functional class III to IV	0	9 (18%)	0	6 (33%)‡	0	1 (6%)	0	2 (12%)
With LV outflow obstruction (≥30 mm Hg)	8 (16%)	4 (8%)	1 (6%)	1 (6%)	2 (12%)	1 (6%)	5 (29%)	2 (12%)
Follow-up (yrs)	—	8.1 ± 2.1	—	7.7 ± 2.3	—	7.9 ± 2.1	—	8.5 ± 2.1
Left atrial dimension (mm)	39 ± 7	45 ± 9*	41 ± 9	47 ± 11*	36 ± 5	43 ± 6*	39 ± 7	44 ± 7*
Maximum LV thickness (mm)	22 ± 5	21 ± 5*	22 ± 5	20 ± 5	22 ± 6	20 ± 3	22 ± 5	22 ± 6
LV end-diastolic diameter (mm)	44 ± 5	47 ± 6*	46 ± 5§	50 ± 8‡*	43 ± 5	45 ± 5*	41 ± 4	45 ± 4*
LV end-systolic diameter (mm)	27 ± 6	30 ± 8*	31 ± 5‡	36 ± 9‡*	26 ± 4	28 ± 5*	24 ± 5	27 ± 5
LV end-diastolic volume (ml)	87 ± 23	105 ± 37*	100 ± 25§	125 ± 43‡*	86 ± 21	94 ± 23*	75 ± 16	93 ± 17*
Change in LV end-diastolic volume (ml)	—	+18 ± 25	—	+25 ± 35	—	+8 ± 15	—	+18 ± 17
LV end-systolic volume (ml)	28 ± 15	40 ± 15*	39 ± 16‡	59 ± 35‡*	23 ± 9	31 ± 14*	21 ± 10	27 ± 12
Change in LV end-systolic volume (ml)	—	+12 ± 21	—	+20 ± 29	—	+8 ± 10	—	+6 ± 12
LVEF (%)	69 ± 12	59 ± 14*	61 ± 14‡	49 ± 16‡*	73 ± 7	64 ± 10*	73 ± 9	63 ± 10*
Change in LVEF (% of basal value)	—	−15 ± 13	—	−19 ± 15	—	−12 ± 12	—	−13 ± 12
With LV ejection fraction <50%	3 (6%)	11 (22%)	3 (17%)	9 (50%)‡	0	1 (6%)	0	1 (6%)
With LVEF <50% and progression to NYHA functional class III to IV	0	5 (10%)	0	5 (28%)‡	0	0	0	0

*p < 0.05 versus same group at the time of PET scan. ‡p < 0.05 versus patients in other tertiles. §p < 0.05 versus patients in the highest tertile.
Dip = dipyridamole; EF = ejection fraction; LV = left ventricular; MBF = myocardial blood flow; NYHA = New York Heart Association; PET = positron emission tomography.
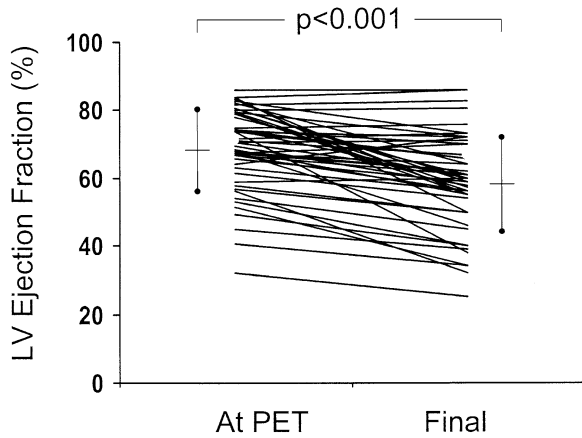
Figure 1. Comparison of left ventricular (LV) ejection fraction at the time of positron emission tomography (PET) and at final evaluation in the 51 study patients. **Vertical bars** indicate mean ± SD for each group.

Standard measurements of left atrial, LV end-diastolic, and end-systolic diameter were obtained in the parasternal long-axis view (13). In all patients, maximum LV wall thickness values were in the basal or mid anterior septum and were measured in the same region of the LV wall both at the time of PET and at final evaluation. Obstruction of the LV outflow was considered present when a peak outflow gradient of ≥30 mm Hg was present under basal conditions (1). The LV ejection fraction (LVEF) was measured in the standard four-chamber view by the area-length method (13). The LV systolic dysfunction was defined as an LVEF <50%.

Statistical analysis. For the purpose of this study, patients were grouped into tertiles of Dip-MBF, and the relationship of this ordinal variable with the development of systolic dysfunction was assessed. Data were expressed as mean values ± SD. For the comparison of normally distributed data, the Student *t* test was used for single comparisons; one-way analysis of variance was used for comparisons among tertiles of Dip-MBF, followed by the Bonferroni post-hoc test. Chi-square or Fisher exact tests, as appropriate, were used to compare non-continuous variables expressed as proportions. Relative hazard and 95% confidence intervals (CIs) were calculated using a stepwise forward Cox proportional hazard regression model, with an entry probability for each variable set at 0.05. All p values are two-sided and considered significant when <0.05.

RESULTS

MBF and baseline echocardiographic features. Resting MBF was not significantly different in patients and control patients (0.84 ± 0.31 ml/min/g vs. 1.00 ± 0.23 ml/min/g, respectively; p = 0.10). By contrast, Dip-MBF was severely blunted in HCM patients (1.50 ± 0.69 ml/min/g vs. 2.71 ± 0.94 ml/min/g in the control patients; p < 0.001). Table 1 shows patients' features with respect to tertiles of Dip-MBF. At the time of PET, all patients were in NYHA functional class I or II. On average, patients in the lower

tertile of Dip-MBF (0.59 to 1.11 ml/min/g) had larger LV cavity dimensions and a lower EF compared with patients in the other two tertiles (Table 1).

LV remodeling and prevalence of systolic dysfunction. Average follow-up was 8.1 ± 2.1 years. Compared with baseline, final evaluation showed an overall increase in LV end-diastolic diameter (+8 ± 10%) and a decrease in LVEF (−15 ± 13%) (Table 1, Fig. 1). At initial evaluation, three patients (6%) had an LVEF <50%; eight additional patients developed systolic dysfunction during follow-up. Thus, the total number of patients with LVEF <50% at final evalu-
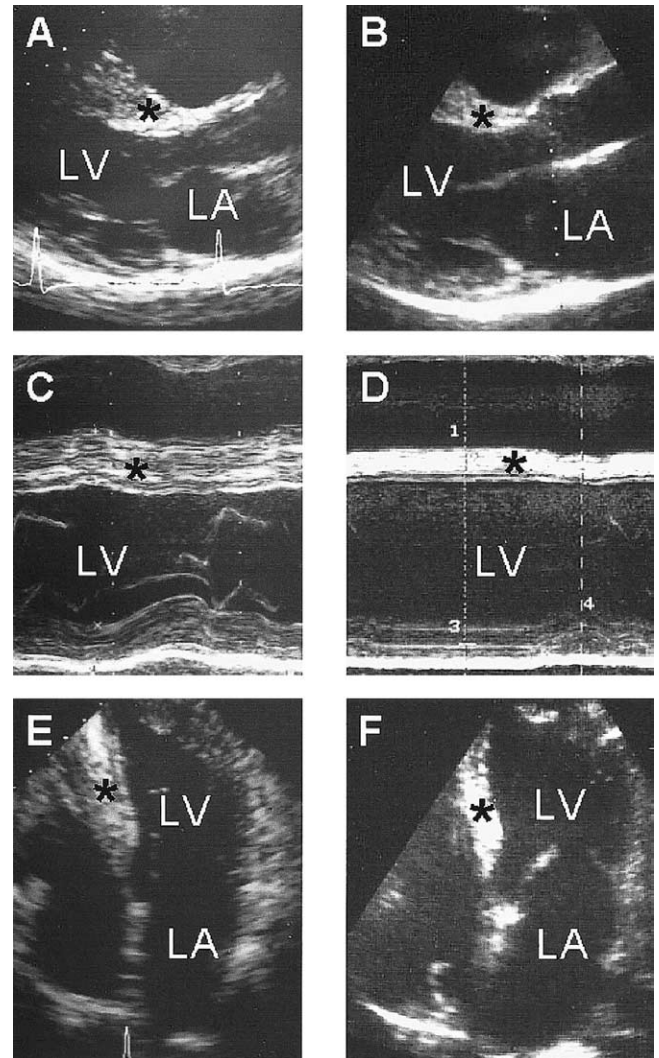
Figure 2. Stop frames of echocardiograms obtained at the time of the positron emission tomography (PET) scan (age 33 years, **panels A, C, and E**) and at final evaluation (age 42 years, **panels B, D, and F**) in a hypertrophic cardiomyopathy (HCM) patient with missense mutations of the myosin beta-heavy chain and of the myosin binding protein C genes (Arg723Cys and Glu165Asp, respectively). Individual measurements are provided in Table 2 (Patient #1). Comparison of the two echocardiograms shows progression of LV cavity enlargement and systolic impairment, with regression of septal hypertrophy. This patient had no functional limitation at the time of PET; over nine years of follow-up he progressively developed congestive symptoms, and at final evaluation he was severely limited, with dyspnea on minimal effort. **(A to D)** Parasternal long-axis view. **(E and F)** Apical four-chamber view. *Interventricular septum. LA = left atrium, LV = left ventricle.

Table 2. Individual Features of 11 Patients With Systolic Dysfunction at Final Evaluation

Patient	Gender	Basal MBF (ml/mg/min)	Dip-MBF (ml/mg/min)	Tertile of Dip-MBF	Age (yrs) At PET	Final	Atrial Fibrillation At PET	Final	NYHA Functional Class At PET	Final	Outcome
1	M	0.71	1.06	Lowest	33	42	0	Paroxysmal	I	III/IV	Evaluation for Tx
2	M	0.85	0.91	Lowest	36	42	0	Paroxysmal	II	IV	Awaiting Tx
3	M	0.65	0.74	Lowest	50	59	Chronic	Chronic	II	III	HF death
4	M	0.50	0.68	Lowest	66	72	Paroxysmal	Chronic	II	III	HF death
5	M	0.87	0.89	Lowest	69	77	Paroxysmal	Paroxysmal	I	III	Embolic stroke
6	M	1.09	0.82	Lowest	53	61	0	0	II	II	Alive
7	M	0.46	1.05	Lowest	51	59	0	Chronic	I	II	Alive
8	M	0.60	0.76	Lowest	56	64	Chronic	Chronic	II	II	Alive
9	M	0.68	1.07	Lowest	42	51	0	0	II	II	ICD
10	F	0.64	1.47	Middle	56	65	0	0	I	II	Alive
11	F	0.61	1.99	Highest	47	58	0	0	I	I	Alive
Overall		0.70 ± 0.18	1.04 ± 0.38		51 ± 11	59 ± 11			1.5 ± 0.5	2.4 ± 0.8	

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ation was 11 (22%); in this group, the average decrease in LVEF from baseline was −27 ± 11% (Table 2). In most (n = 7), development of systolic dysfunction was associated with a >5 mm increase in LV end-diastolic diameter (average, 9 mm); however, four patients showed little variation (<5 mm; average, 3 mm) (Table 2).

At final evaluation, 5 of the 11 patients with LVEF <50% progressed to NYHA functional class III to IV, including two patients who eventually died of heart failure and two who have been evaluated for cardiac transplantation (Fig. 2, Table 2). Among these five patients, the final LV end-diastolic dimension ranged from 44 to 68 mm, and the LVEF from 25% to 46%. Of note, only two patients already had an LVEF <50% at the time of PET (Table 2).

Relevance of MBF impairment to LV remodeling. Average Dip-MBF was significantly lower in the 11 patients in whom LV systolic dysfunction developed, compared with the 40 with preserved LV function (1.04 ± 0.38 ml/min/g vs. 1.63 ± 0.71 ml/min/g, respectively; p = 0.001). The MBF impairment was particularly severe among the five patients whose condition progressed to NYHA functional class III to IV or who died (Dip-MBF, 0.89 ± 0.15 ml/min/g). Prospectively, patients in the lowest tertile of Dip-MBF (≤1.11 ml/min/g) showed a greater increase in LV dimensions and decrease in LVEF during follow-up as compared with each other tertile, even though there was considerable individual variability in each group (Table 1, Fig. 3). Specifically, 9 of the 11 patients with systolic dysfunction belonged to the lowest Dip-MBF tertile, compared with only 2 of the 40 patients with preserved LV function (Table 2). After exclusion of the three patients with LVEF <50% at initial evaluation, the positive and negative predictive values of Dip-MBF ≤1.11 ml/min/g to foretell the development of systolic dysfunction were 40% and 94%, respectively.

In a multivariate Cox regression model including age, gender, NYHA functional class, initial LV dimensions, maximum LV thickness, and magnitude of LV outflow gradient, the only two independent long-term predictors of

LV systolic dysfunction were a Dip-MBF in the lowest tertile (relative hazard, 7.5; 95% CI: 1.1 to 50.4; p = 0.038) and an end-diastolic LV dimension in the highest tertile (>45 mm; relative hazard, 12.3; 95% CI: 1.2 to 121.5; p = 0.031).

DISCUSSION

MBF impairment and LV systolic dysfunction in HCM. The main finding of the present study was that severe impairment of the coronary vasodilator response to Dip is strongly associated with long-term adverse LV remodeling and systolic dysfunction in HCM patients. Over an average follow-up >8 years, patients with a Dip-MBF in the lowest tertile showed a 7.5-fold higher risk of developing systolic dysfunction (defined as an LVEF <50%) compared with the other two tertiles. The only other independent predictor of systolic dysfunction was a baseline end-diastolic LV dimension in the highest tertile (>45 mm), possibly suggesting an early propensity toward cavity dilation.

We previously described the association of an impaired Dip-MBF with increased LV dimensions and reduced fractional shortening in HCM patients studied cross-sectionally (14). Indeed, the baseline data of the present study are consistent with a certain degree of LV remodeling before study enrolment among patients in the lowest tertile of Dip-MBF. However, we now show that even in the presence of a normal LV cavity size and function, the degree of microvascular dysfunction is a potent predictor of remodeling and systolic impairment. Indeed, with a negative predictive value as high as 94%, a Dip-MBF in the lowest tertile seemed to be a necessary prerequisite for long-term impairment of systolic dysfunction in HCM patients, whereas a relatively preserved vasodilator capacity showed a powerful protective effect. Thus, PET studies of microvascular function potentially represent a valuable tool for the identification of HCM patients at risk of severe disease progression, even in individuals with no or mild symptoms and normal LV function (12). This is particularly relevant in

Table 2. Continued

Left Atrium (mm)		Maximum LV Thickness (mm)		LV EDD/ESD (mm)		LV EDV/ESV (ml)		LV Ejection Fraction (%)		SAM-Related LVOT Gradient (mm Hg)	
At PET	Final	At PET	Final	At PET	Final	At PET	Final	At PET	Final	At PET	Final
39	42	17	12	51/36	68/55	124/54	239/147	56	32	0	0
49	55	33	30	50/31	58/42	118/38	167/79	68	46	23	0
61	70	24	22	49/38	51/39	113/62	124/66	45	39	0	0
42	51	18	16	52/39	55/39	130/66	147/66	50	40	0	0
49	49	24	24	40/34	44/32	70/47	82/61	32	25	45	25
36	44	17	15	41/33	44/35	74/44	88/51	41	34	0	0
40	47	22	17	48/35	53/40	108/51	135/70	53	40	0	0
62	73	20	20	53/39	58/46	135/66	167/97	51	34	0	0
32	40	26	18	47/27	65/50	102/27	216/118	74	38	0	0
33	45	21	17	45/28	50/37	92/30	118/58	68	46	0	0
37	40	20	18	40/29	45/28	70/32	85/32	54	45	0	0
44 ± 10	50 ± 12	22 ± 5	19 ± 5	47 ± 5/33 ± 4	53 ± 9/41 ± 7	103 ± 24/47 ± 14	140 ± 55/76 ± 34	54 ± 12	38 ± 7	2/11	1/11

EDD = end-diastolic dimension; ESD = end-systolic dimension; FU = follow-up; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVOT = LV outflow tract; MBF = myocardial blood flow; NYHA = New York Heart Association; SAM = systolic anterior motion of the mitral valve; Tx = cardiac transplantation; other abbreviations as in Table 1.

the face of preliminary evidence that certain pharmacologic agents, such as verapamil and angiotensin-converting enzyme inhibitors, may positively influence the coronary microcirculation (15,16).
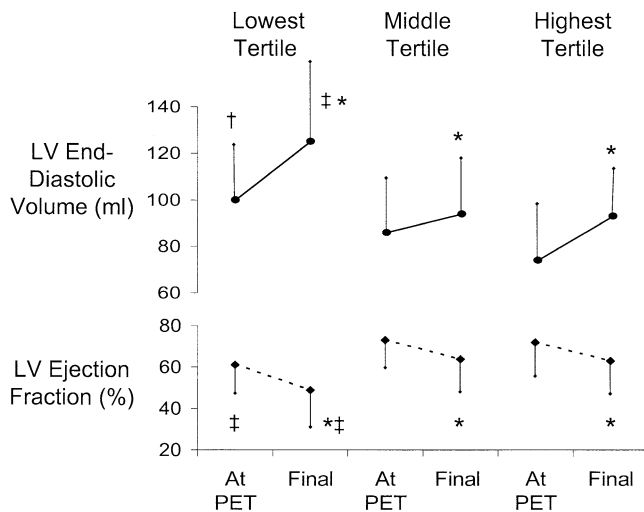
Of note, some patients in the lowest tertile of Dip-MBF already had evidence of relative LV dilation and somewhat reduced systolic function at study entry, which may have emphasized the differences observed during follow-up compared with the other tertiles. For those patients, we could not quantify the morphologic change occurring before enrolment, nor its possible relevance to coronary microvascular function (e.g., because of elevated filling pressures) (8). Nevertheless, when initial LV end diastolic dimensions and LVEF were taken into account in a multivariate model,

Figure 3. Comparison of left ventricular (LV) end-diastolic volume and ejection fraction at the time of positron emission tomography (PET) and at final evaluation according to tertiles of dipyridamole myocardial blood flow. **Vertical bars** indicate mean ± SD for each group. *p < 0.05 versus same group at the time of PET scan; †p < 0.05 versus patients in the highest tertile; ‡p < 0.05 versus patients in other tertiles.

Dip-MBF remained a powerful independent predictor of systolic dysfunction in our cohort.

End-stage phase progression. The most dramatic clinical consequence of LV remodeling in HCM is represented by progression to the so-called "end-stage" phase, which may be difficult to distinguish from a primary dilated cardiomyopathy, is associated with severe clinical signs of heart failure and may require heart transplantation (1–7). In the present study, all patients with such progression had an extremely impaired vasodilator response to Dip, not exceeding and often below the resting MBF values measured in healthy control patients. Thus, although lesser degrees of LV remodeling also occurred in patients with relatively preserved Dip-MBF, severe degrees of systolic dysfunction, LV dilation, and clinical progression to heart failure were confined to patients with extreme impairment of flow.

We acknowledge that the prevalence of end-stage progression in our study cohort overestimates that in the general HCM population. Indeed, the prevalence of systolic dysfunction was found to be ≤5% in most reports (1). In the overall Florence HCM database, which includes more than 500 patients, 13% of the patients progressed to an end-stage phase over an average follow-up of about 10 years (F. Cecchi and I. Olivotto, unpublished observation, 2005) compared with 22% in the present study. Such a discrepancy suggests an undefined selection bias that led to a preferential inclusion of patients with progressive disease, despite the fact that individuals with overt heart failure were excluded by the study protocol.

Pathophysiology of LV remodeling in HCM. The most likely mechanism by which microvascular dysfunction is implicated in LV remodeling is represented by substantial lowering of the ischemic threshold, increased likelihood of recurrent ischemic damage to the myocardium, re-

placement fibrosis, chamber dilation, and loss of contractile function (2,3,5,9–12). A similar process is thought to occur in patients surviving acute myocardial infarction, in whom persistent microvascular dysfunction after successful reperfusion represents a powerful predictor of LV dilation and heart failure (17). Of note, although the absolute change in LVEF and cavity dimensions was greater in the lowest tertile of Dip-MBF, considerable variability existed within each tertile. This is consistent with the fact that the individual ischemic burden may vary considerably based on the relevance of triggers such as exercise, arrhythmias, and outflow obstruction (18–19). In addition, pathophysiological mechanisms such as primary fibrosis (20), apoptosis (21), and inappropriately increased adrenergic stimulation (22) may add to interindividual variability.

Finally, although the development of systolic dysfunction was generally associated with progressive LV dilation in our cohort, a minority of patients with progressive loss of systolic function had only a very limited increase in LV cavity size. A potential explanation for this is represented by extensive and diffuse fibrous replacement of the myocardium, leading to loss of contractile function without apparent remodeling of the LV (6). Indeed, systolic dysfunction is not uncommon in the context of a restrictive evolution of HCM, in which LV cavity size is normal or reduced.

CONCLUSIONS

Severe microvascular dysfunction is a potent long-term predictor of LV adverse remodeling and systolic dysfunction in HCM, which can be identified well before irreversible morphologic and functional changes occur. Thus, our findings indicate microvascular dysfunction as a potential target for the prevention of disease progression and heart failure in HCM.

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REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20.
2. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 1998;81:1339–44.
3. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. Am J Cardiol 1987;60:123–9.
4. Maron BJ, Hecht G, Klues HG, et al. Both aborted sudden cardiac death and end-stage phase in hypertrophic cardiomyopathy. Am J Cardiol 1993;72:363–5.
5. Seiler C, Jenni R, Vassalli G, et al. Left ventricular chamber dilatation in hypertrophic cardiomyopathy: related variables and prognosis in patients with medical and surgical therapy. Br Heart J 1995;74:508–16.
6. Hina K, Kusachi S, Iwasaki K, et al. Progression of left ventricular enlargement in patients with hypertrophic cardiomyopathy: incidence and prognostic value. Clin Cardiol 1993;16:403–7.
7. Ko YL, Chen JJ, Tang TK, et al. Malignant familial hypertrophic cardiomyopathy in a family with a 453Arg→Cys mutation in the beta-myosin heavy chain gene: coexistence of sudden death and end-stage heart failure. Hum Genet 1996;97:585–90.
8. Cannon RO, Rosing DR, Maron BJ, et al. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation 1985;71:234–43.
9. Camici PG, Chiriatti G, Lorenzoni R, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. J Am Coll Cardiol 1991;17:879–86.
10. Maron BJ, Wolfson JK, Epstein SE, et al. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986;8:545–57.
11. Basso C, Thiene G, Corrado D, et al. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. Hum Pathol 2000;31:988–98.
12. Cecchi F, Olivotto I, Gistri R, et al. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 2003;349:1027–35.
13. Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/aha guidelines for the clinical application of echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Circulation 1997;95:1686–744.
14. Lorenzoni R, Gistri R, Cecchi F, et al. Coronary vasodilator reserve is impaired in patients with hypertrophic cardiomyopathy and left ventricular dysfunction. Am Heart J 1998;136:972–81.
15. Gistri R, Cecchi F, Choudhury L, et al. Effect of verapamil on absolute myocardial blood flow in hypertrophic cardiomyopathy. Am J Cardiol 1994;74:363–8.
16. Mourad JJ, Hanon O, Deverre JR, et al. Improvement of impaired coronary vasodilator reserve in hypertensive patients by low-dose ACE inhibitor/diuretic therapy: a pilot PET study. J Renin Angiotensin Aldosteron Syst 2003;4:94–5.
17. Bolognese L, Carrabba N, Parodi G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004;109:1121–6.
18. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295–303.
19. Olivotto I, Cecchi F, Casey SA, et al. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001;104:2517–24.
20. Lombardi R, Betocchi S, Losi MA, et al. Myocardial collagen turnover in hypertrophic cardiomyopathy. Circulation 2003;108:1455–60.
21. Ino T, Nishimoto K, Okubo M, et al. Apoptosis as a possible cause of wall thinning in end-stage hypertrophic cardiomyopathy. Am J Cardiol 1997;79:1137–41.
22. Choudhury L, Guzzetti S, Lefroy DC, et al. Myocardial beta adrenoceptors and left ventricular function in hypertrophic cardiomyopathy. Heart 1996;75:50–4.