

ORIGINAL ARTICLE

# Coronary Microvascular Dysfunction and Prognosis in Hypertrophic Cardiomyopathy

Franco Cecchi, M.D., Iacopo Olivetto, M.D., Roberto Gistri, M.D.,  
Roberto Lorenzoni, M.D., Giampaolo Chiriatti, M.D., and Paolo G. Camici, M.D.

## ABSTRACT

### BACKGROUND

Microvascular dysfunction, reflected by an inadequate increase in myocardial blood flow in response to dipyridamole infusion, is a recognized feature of hypertrophic cardiomyopathy. Its long-term effect on the prognosis is unknown. We prospectively evaluated a cohort of patients with hypertrophic cardiomyopathy after they had undergone quantitative assessment of myocardial blood flow by positron-emission tomography (PET).

### METHODS

Fifty-one patients (New York Heart Association class I or II) were followed for a mean ( $\pm$ SD) of  $8.1\pm 2.1$  years after PET. Twelve subjects with atypical chest pain served as controls. Measurement of flow was performed at base line and after the infusion of the coronary vasodilator dipyridamole, with the use of nitrogen-13-labeled ammonia. Patients were then divided into three equal groups with increasing values of myocardial blood flow.

### RESULTS

The response of myocardial blood flow to dipyridamole was severely blunted in the patients, as compared with the controls ( $1.50\pm 0.69$  vs.  $2.71\pm 0.94$  ml per minute per gram of tissue,  $P<0.001$ ). Sixteen patients (31 percent) had an unfavorable outcome (death from cardiovascular causes, progression to New York Heart Association class III or IV, or sustained ventricular arrhythmias requiring the implantation of a cardioverter-defibrillator) 2.2 to 9.1 years after PET. Reduced blood flow in response to dipyridamole was strongly associated with an unfavorable outcome. Multivariate analysis showed that among patients in the lowest of the three flow groups the age-adjusted relative hazard of death from cardiovascular causes was 9.6 ( $P=0.02$ ) and the relative hazard of an unfavorable outcome (a combined end point) was 20.1 ( $P=0.003$ ), as compared with patients in the two other flow groups. Specifically, all four patients who died from heart failure and three of five who died suddenly were in this subgroup.

### CONCLUSIONS

In patients with hypertrophic cardiomyopathy, the degree of microvascular dysfunction is a strong, independent predictor of clinical deterioration and death. Severe microvascular dysfunction is often present in patients with mild or no symptoms and may precede clinical deterioration by years.

From the Regional Referral Center for Myocardial Diseases, Azienda Ospedaliera Careggi, Florence (F.C., I.O., R.G.); the Cardiology Unit, Ospedale di Lucca, Lucca (R.L.); the Cardiology Unit, Ospedale di Pescia, Pescia (G.C.); the Consiglio Nazionale delle Ricerche Institute of Clinical Physiology, Pisa (P.G.C.) — all in Italy; and the Medical Research Centre, Hammersmith Hospital, Imperial College, London (P.G.C.). Address reprint requests to Dr. Cecchi at Via Jacopo Nardi 30, 50132 Florence, Italy, or at franco.cecchi@asf.toscana.it.

N Engl J Med 2003;349:1027-35.

Copyright © 2003 Massachusetts Medical Society.

**H**YPERTROPHIC CARDIOMYOPATHY IS a genetically determined disease with diverse clinical manifestations and pathophysiological substrates.<sup>1-14</sup> Although several factors have been associated with an unfavorable outcome, the identification of patients at risk for sudden death or progression to heart failure remains a formidable challenge.<sup>8-11,14,15</sup>

An inadequate increase in myocardial blood flow after intravenous administration of the vasodilator dipyridamole indicates microvascular dysfunction in the absence of coronary stenoses and is detected on positron-emission tomography (PET) in the majority of patients with hypertrophic cardiomyopathy.<sup>16-19</sup> Microvascular dysfunction, in turn, represents a predisposing factor for myocardial ischemia, which is also a common feature of hypertrophic cardiomyopathy.<sup>3,7,20-27</sup> The effect of microvascular dysfunction on the prognosis, however, has not been investigated. The issue is of relevance, since both microvascular dysfunction and myocardial ischemia may be amenable to treatment.<sup>28,29</sup> Thus, we prospectively evaluated the relation between myocardial blood flow as assessed by PET and the long-term outcome in a cohort of patients with hypertrophic cardiomyopathy.

## METHODS

### STUDY POPULATION

#### *Patients*

The study cohort was part of a regional population of patients closely followed by a small number of physicians with expertise and a long-standing interest in hypertrophic cardiomyopathy at hospitals in Florence and Pescia, Italy. The diagnosis of hypertrophic cardiomyopathy was based on echocardiographic evidence of myocardial hypertrophy (as defined by a left ventricular wall thickness of at least 15 mm) in the absence of any other cardiac or systemic cause of left ventricular hypertrophy.<sup>1</sup> All patients older than 18 years of age who were seen at these two community-based hospitals from January 1989 to May 1990 were asked to undergo PET. The only exclusion criterion was severe congestive heart failure, as defined by a New York Heart Association (NYHA) functional class of III or IV.

Of 222 eligible patients, 51 (23 percent) agreed to participate and constituted the study group (Table 1). Their mean ( $\pm$ SD) age was  $44\pm 13$  years. Of these 51 patients, 14 (27 percent) reported typical

angina and were enrolled after the documentation of angiographically normal coronary arteries. The 171 eligible patients who did not participate were also followed up and did not differ significantly with respect to base-line characteristics and long-term survival free of cardiovascular events ( $P=0.21$ ).

#### *Control Subjects*

The control group comprised 12 subjects who had a syndrome of atypical chest pain (4 were men); their mean age was  $51\pm 8$  years ( $P=0.1$  for the comparison with the patients). All had normal findings on physical examination, electrocardiography, echocardiography, treadmill exercise testing, and coronary and left ventricular angiography.

#### MEASUREMENT OF MYOCARDIAL BLOOD FLOW

All PET scans were performed at the Institute of Clinical Physiology in Pisa, Italy, between June 1990 and May 1993. To eliminate any effects of drug treatment on the assessment of microvascular function, all studies were performed after an appropriate period of pharmacologic washout.<sup>16</sup>

Regional myocardial blood flow was measured with the use of PET with nitrogen-13-labeled ammonia under basal conditions and during near-maximal hyperemia induced by dipyridamole (0.56 mg per kilogram of body weight administered intravenously over a period of four minutes), as described previously.<sup>16,28</sup> Briefly, patients were positioned on the couch of a three-slice PET tomograph (ECAT3, CTI), and a five-minute rectilinear transmission scan was recorded to facilitate positioning of the left ventricle within the field of view of the camera. Then, a 20-minute transmission scan was obtained to correct the subsequent emission scans for tissue attenuation.

For each measurement of myocardial blood flow, a bolus of nitrogen-13-labeled ammonia (0.25 mCi per kilogram) was injected intravenously over a period of 15 to 20 seconds and dynamic acquisition was started simultaneously.<sup>16</sup> Myocardial blood flow was remeasured 50 minutes after the basal scan had been obtained, according to the same acquisition protocol, four minutes after the end of the dipyridamole infusion.

Absolute regional myocardial blood flow was calculated in milliliters per minute per gram of tissue as described previously.<sup>16</sup> The average flow value for the entire left ventricle was obtained by drawing a region of interest that encompassed the

**Table 1. Base-Line Characteristics of the Patients at the Time of Positron-Emission Tomography (PET), According to the Level of Myocardial Blood Flow (MBF) after Dipyridamole Infusion.\***

Characteristic	All Patients (N=51)	Lowest MBF (0.59–1.11 ml/min/g) (N=18)	Middle MBF (1.13–1.57 ml/min/g) (N=16)	Highest MBF (1.62–3.77 ml/min/g) (N=17)	P Value
Age — yr	44±13	48±12	39±14	43±13	0.10
Duration of follow-up after PET — yr	8.1±2.1	7.5±2.0	7.9±2.1	8.8±2.1	0.18
Male sex — no. (%)	36 (71)	17 (94)	12 (75)	7 (41)	0.002
Family history — no. (%)					
Hypertrophic cardiomyopathy	17 (33)	7 (39)	6 (37)	4 (24)	0.57
Sudden death from cardiac causes	8 (16)	3 (17)	2 (12)	3 (18)	0.83
NYHA functional class — no. (%)					0.25
I	30 (59)	10 (56)	12 (75)	8 (47)	
II	21 (41)	8 (44)	4 (25)	9 (53)	
Angina — no. (%)	14 (27)	5 (28)	2 (12)	7 (41)	0.18
Syncope — no. (%)	9 (18)	4 (22)	1 (6)	4 (24)	0.35
Paroxysmal or chronic atrial fibrillation — no. (%)	6 (12)	5 (28)	1 (6)	0	0.03
Unsustained ventricular tachycardia on Holter ECG — no. (%)	10 (20)	3 (17)	5 (31)	2 (12)	0.34
Echocardiographic findings					
Left atrial dimension — mm	39±7	41±9	36±5	39±7	0.10
LV end-diastolic dimension — mm	44±5	47±5	43±5	42±5	0.04
LV end-systolic dimension — mm	27±6	31±5	26±4	24±5	0.001
LV fractional shortening — %	38±10	33±10	41±8	42±9	0.01
Maximal LV thickness — mm	22±5	22±5	22±6	22±5	0.95
Basal LV obstruction (≥30 mm Hg) — no. (%)	8 (16)	1 (6)	2 (12)	5 (29)	0.13
Medical treatment — no. (%)	38 (74)	18 (100)	7 (44)	13 (76)	0.01
Class III antiarrhythmic agents	6 (12)	4 (22)	1 (6)	1 (6)	0.23
Beta-blockers	20 (39)	10 (56)	4 (25)	6 (35)	0.17
Verapamil or diltiazem	21 (41)	8 (44)	5 (31)	8 (47)	0.61
ACE inhibitors, diuretics, or both	3 (6)	3 (17)	0	0	0.05
LV myotomy–myectomy — no. (%)	1 (2)	1 (6)	0	0	
LV percutaneous septal ablation — no. (%)	2 (4)	0	1 (6)	1 (6)	1.0
Basal MBF — ml/min/g	0.84±0.32	0.64±0.17	0.80±0.21	1.08±0.36	<0.001
Interventricular septum	1.02±0.41	0.79±0.28	0.96±0.24	1.33±0.48	<0.001
LV free wall	0.78±0.33	0.63±0.21	0.75±0.29	0.95±0.39	0.01
MBF after dipyridamole infusion — ml/min/g	1.50±0.69	0.89±0.16	1.36±0.13	2.28±0.61	<0.001†
Interventricular septum	1.69±0.77	1.06±0.27	1.55±0.26	2.49±0.76	<0.001†
LV free wall	1.47±0.69	0.92±0.25	1.34±0.27	2.18±0.69	<0.001†
Coronary vasodilator reserve‡	1.84±0.67	1.47±0.42	1.79±0.43	2.28±0.83	0.001
Difference between septal and free-wall MBF — ml/min/g					
At base line	0.25±0.20	0.15±0.11	0.21±0.12	0.38±0.26	0.001
After dipyridamole	0.38±0.42	0.22±0.17	0.30±0.24	0.61±0.60	0.01

\* Plus–minus values are means ±SD. NYHA denotes New York Heart Association, ECG electrocardiography, LV left ventricular, and ACE angiotensin-converting enzyme. P values were calculated with the use of the chi-square test across the three groups.

† The significant difference was part of the study design.

‡ The coronary vasodilator reserve was calculated as the mean MBF after dipyridamole infusion divided by the basal MBF.

entire left ventricle on a transaxial PET slice. Coronary vasodilator reserve was calculated as the ratio of myocardial blood flow after dipyridamole infusion to basal myocardial blood flow.

The study protocol was approved by the research ethics committee at each institution, and written informed consent was obtained from each patient and control subject. The scans were obtained and analyzed in a blinded manner by physicians with expertise in nuclear cardiology. The results of the scans were eventually made available to the patients' physicians, although no decision regarding treatment was based on these results.

#### FOLLOW-UP STRATEGY

Patients were prospectively followed for an average of  $8.1 \pm 2.1$  years (range, 2.2 to 11.1) after PET to assess the long-term prognostic value of studies of myocardial blood flow. There was no prespecified cutoff value for myocardial blood flow. The follow-up protocol and chosen end points were the same ones that are used for the entire cohort of patients with hypertrophic cardiomyopathy who are followed at our institutions, as previously described.<sup>11-14,30</sup> Patients were followed at yearly intervals or more often if required, with clinical and echocardiographic examinations, 12-lead electrocardiography, and 24- to 48-hour ambulatory electrocardiography.<sup>12</sup> In the case of an acute cardiac event, the patient was admitted to one of the two institutions. Patients who had not been seen for one year were contacted by telephone by a research nurse. Causes of death were determined by autopsy whenever possible or by interviewing the patients' relatives and physicians.

At the time of the PET study and during follow-up, standard medical treatment was used to control symptoms, left ventricular outflow obstruction, supraventricular arrhythmias, or recurrent nonsustained ventricular tachycardia.<sup>12</sup> Implantable cardioverter-defibrillators have been used at our facilities since 1992 for the prevention of sudden death in patients with hypertrophic cardiomyopathy.<sup>15</sup>

#### ECHOCARDIOGRAPHIC STUDIES

All patients underwent base-line echocardiography at the time of PET. Standard M-mode measurements were obtained in the parasternal long- and short-axis views.<sup>31</sup> The peak instantaneous left ventricular outflow tract gradient was estimated under basal conditions with the use of continuous-wave Doppler echocardiography.<sup>32</sup>

#### ASSESSMENT OF OUTCOME

Two end points were assessed. One was death from cardiovascular causes, defined as death due to hypertrophic cardiomyopathy-related heart failure (occurring in the context of cardiac decompensation and a progressive course of disease, particularly one complicated by pulmonary edema or progression to end-stage disease), sudden and unexpected death (including cardiac arrest with resuscitation after cardiac arrest), and ischemic stroke.<sup>13</sup> The second end point, defined as an unfavorable outcome, was a combined end point that included death from cardiovascular causes, progression to severe functional limitation (NYHA class III or IV), and sustained, life-threatening ventricular arrhythmias requiring the implantation of a cardioverter-defibrillator. Events were adjudicated by the two senior cardiologists who were directly responsible for the care of all study patients.

#### STATISTICAL ANALYSIS

Data are expressed as means  $\pm$ SD. An unpaired Student's *t*-test or one-way analysis of variance was used for the comparison of normally distributed data. Fisher's exact test was used to compare noncontinuous variables expressed as proportions. Relative hazards and 95 percent confidence intervals were calculated with the use of univariate and multivariate Cox proportional-hazards regression models.

For multivariate analyses of survival, patients were divided into three equal groups with increasing values of myocardial blood flow after dipyridamole infusion (cutoff values for these groups were 0.59 to 1.11, 1.13 to 1.57, and 1.62 to 3.77 ml per minute per gram). The relation of this ordinal variable to the outcome was assessed in an age-adjusted manner. Multivariate analyses were performed with the use of a stepwise forward regression model, with an entry probability for each variable set at 0.05.

Survival curves were constructed according to the Kaplan-Meier method. In the analysis of death from cardiovascular causes, other causes of death were censored. A receiver-operating-characteristic curve was used to identify the optimal threshold value for myocardial blood flow after dipyridamole infusion.

All reported *P* values are two-sided; a *P* value of less than 0.05 was considered to indicate statistical significance. No interim analyses were performed during follow-up.

RESULTS

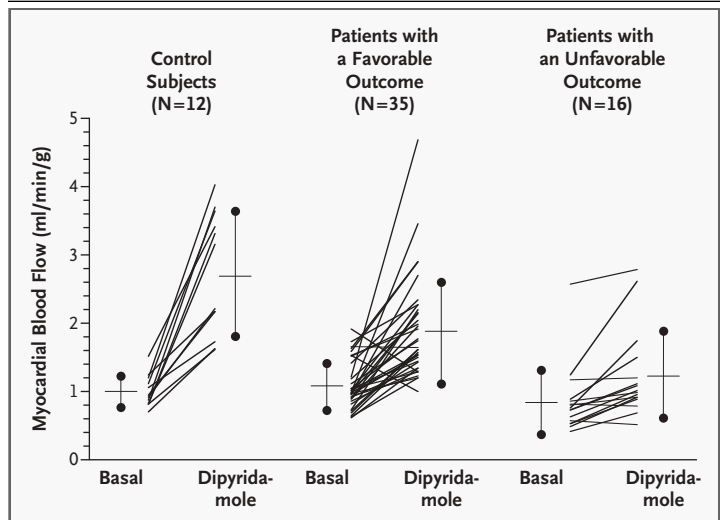
MYOCARDIAL BLOOD FLOW

Under basal conditions, myocardial blood flow did not differ significantly between patients and control subjects ( $0.84 \pm 0.31$  and  $1.00 \pm 0.23$  ml per minute per gram, respectively;  $P=0.10$ ). By contrast, the response of myocardial blood flow to dipyridamole infusion was severely blunted in patients with hypertrophic cardiomyopathy, as compared with the control subjects ( $1.50 \pm 0.69$  and  $2.71 \pm 0.94$  ml per minute per gram, respectively;  $P<0.001$ ) (Fig. 1); among the patients, the extent of impairment was similar in the interventricular septum and the left ventricular free wall (Table 1). The coronary vasodilator reserve was also smaller in the patients ( $1.8 \pm 0.7$ , as compared with  $2.7 \pm 0.9$  in the controls;  $P<0.001$ ). There was no significant difference in myocardial blood flow after dipyridamole infusion between patients with angina and those without angina or between those with left ventricular outflow obstruction (peak outflow gradient, 30 mm Hg or greater) and those without obstruction. No relation was found between the maximal left ventricular thickness and myocardial blood flow after dipyridamole infusion ( $R^2=0.03$ ,  $P=0.23$ ).

Patients in the lowest of the three categories of myocardial blood flow after dipyridamole infusion ( $0.59$  to  $1.11$  ml per minute per gram) were significantly more likely to be male, to have atrial fibrillation, and to have received medical treatment, and on average, they had larger end-systolic and end-diastolic dimensions and less fractional shortening than the patients in the other two categories of blood flow, but the three groups had otherwise similar base-line characteristics (Table 1). Specifically, the proportion of patients who were receiving pharmacologic agents with potential anti-ischemic properties — that is, beta-blockers and calcium-channel blockers — was similar in each category of flow after dipyridamole infusion, both at the time of PET and during follow-up (overall  $P$  value  $>0.1$  for all comparisons) (Table 1).

CLINICAL COURSE AND OUTCOME

No patient was lost to follow-up, and the condition of 35 patients (69 percent) remained stable, in NYHA class I or II with a benign clinical course. By contrast, 16 patients (31 percent) had an unfavorable outcome: 9 died from cardiovascular causes (sudden death in 5 and heart failure or stroke in 4), recurrent sustained ventricular tachycardia developed in 1 and required the implantation of a car-



**Figure 1. Myocardial Blood Flow under Resting (Basal) Conditions and after Dipyridamole Infusion in the 12 Control Subjects, the 35 Patients with a Favorable Clinical Outcome, and the 16 Patients with an Unfavorable Outcome.** Values are the average of the entire left ventricle. Vertical bars indicate mean ( $\pm$ SD) values for each group.

**Table 2. Outcome among the 51 Patients Overall and According to Myocardial Blood Flow (MBF) after Dipyridamole Infusion.\***

Outcome	All Patients (N=51)	Lowest MBF	Middle MBF	Highest MBF
		(0.59–1.11 ml/min/g) (N=18)	(1.13–1.57 ml/min/g) (N=16)	(1.62–3.77 ml/min/g) (N=17)
		<i>no. of patients (%)</i>		
Unfavorable outcome*	16 (31)	12 (67)	1 (6)	3 (18)
Progression to NYHA class III or IV†	6 (12)	4 (22)	1 (6)	1 (6)
Implantation of cardioverter-defibrillator for primary prevention	1 (2)	1 (6)	0	0
Death from cardiovascular causes	9 (18)	7 (39)	0	2 (12)
Sudden death (or resuscitation after cardiac arrest)	5	3	0	2
Heart failure or stroke-related	4	4	0	0
Death from noncardiac causes	2 (4)	0	1 (6)	1 (6)

\* An unfavorable outcome was defined as progression to NYHA class III or IV, life-threatening ventricular arrhythmias requiring the implantation of a cardioverter-defibrillator, or death from cardiovascular causes.

† NYHA denotes New York Heart Association.

dioverter–defibrillator, and 6 had progression to NYHA functional class III or IV (including 1 patient in whom typical restrictive end-stage features of hypertrophic cardiomyopathy developed) (Table 2). These end points occurred 2.2 to 9.1 years after PET (average, 5.5±2.3).

**RELEVANCE OF MYOCARDIAL BLOOD FLOW TO CLINICAL OUTCOME**

As compared with patients who had a benign clinical course, those with an unfavorable outcome had

a more severely blunted response of myocardial blood flow to dipyridamole infusion (Fig. 1). An age-adjusted univariate survival analysis showed that myocardial blood flow values under basal conditions and after dipyridamole infusion were inversely related to the risk of death from any cause, death from cardiovascular causes, and an unfavorable outcome (Table 3); myocardial blood flow after dipyridamole infusion showed the strongest association with each end point.

Multivariate analysis showed that the myocar-

**Table 3. Results of Univariate Cox Regression Analyses of the Relation between Myocardial Blood Flow (MBF) Values and Clinical Outcome, Adjusted for Age.\***

Variable	Death from Any Cause		Death from Cardiovascular Causes		Unfavorable Outcome†	
	Relative Hazard (95% CI)	P Value	Relative Hazard (95% CI)	P Value	Relative Hazard (95% CI)	P Value
Mean basal MBF (per unit increase)	0.02 (0.0005–0.90)	0.04	0.01 (0.0001–0.43)	0.02	0.005 (0.0001–0.23)	0.006
Mean MBF after dipyridamole infusion (per unit increase)	0.14 (0.03–0.86)	0.03	0.02 (0.0001–0.48)	0.02	0.02 (0.002–0.23)	0.002
Coronary vasodilator reserve (per unit increase)	0.66 (0.26–1.69)	0.33	0.47 (0.12–1.62)	0.17	0.38 (0.14–1.01)	0.05
Difference between septal and free-wall MBF (per unit increase)						
At base line	0.15 (0.002–5.15)	0.38	0.003 (<0.0001–1.68)	0.09	0.001 (<0.0001–0.20)	0.01
After dipyridamole infusion	0.43 (0.08–2.33)	0.32	0.64 (0.0007–5.42)	0.24	0.17 (0.01–2.06)	0.16

\* All models were adjusted for age as a stratification factor. Patients were divided into three equal groups on the basis of age. The age cutoffs for the three groups were 19 to 36, 37 to 50, and 51 to 74 years. CI denotes confidence interval.

† An unfavorable outcome was defined as progression to New York Heart Association class III or IV, life-threatening ventricular arrhythmias requiring the implantation of a cardioverter–defibrillator, or death from cardiovascular causes.

**Table 4. Results of the Multivariate Cox Regression Analyses Assessing the Relation between Base-Line Clinical Variables and Outcome, Adjusted for Age.\***

Variable	Death from Any Cause		Death from Cardiovascular Causes		Unfavorable Outcome†	
	Relative Hazard (95% CI)	P Value	Relative Hazard (95% CI)	P Value	Relative Hazard (95% CI)	P Value
Level of mean MBF after dipyridamole infusion (lowest to highest)	0.36 (0.15–0.89)	0.03	0.14 (0.03–0.78)	0.02	0.081 (0.023–0.41)	0.002
LV obstruction ≥30 mm Hg	—	0.15	—	0.25	13.80 (1.49–128.10)	0.02
Maximal LV thickness ≥30 mm	—	0.13	—	0.10	15.67 (0.92–266.09)	0.06
NYHA class (II vs. I)	—	0.28	—	0.57	4.63 (0.90–23.91)	0.07
Atrial fibrillation	—	0.83	—	0.89	—	0.84

\* All models were adjusted for age as a stratification factor. Patients were divided into three equal groups on the basis of age. The age cutoffs for the three groups were 19 to 36, 37 to 50, and 51 to 74 years. CI denotes confidence interval, MBF myocardial blood flow, LV left ventricular, and NYHA New York Heart Association. Dashes denote variables that were removed from the final model, and the corresponding P values denote the level of significance that led to their exclusion.

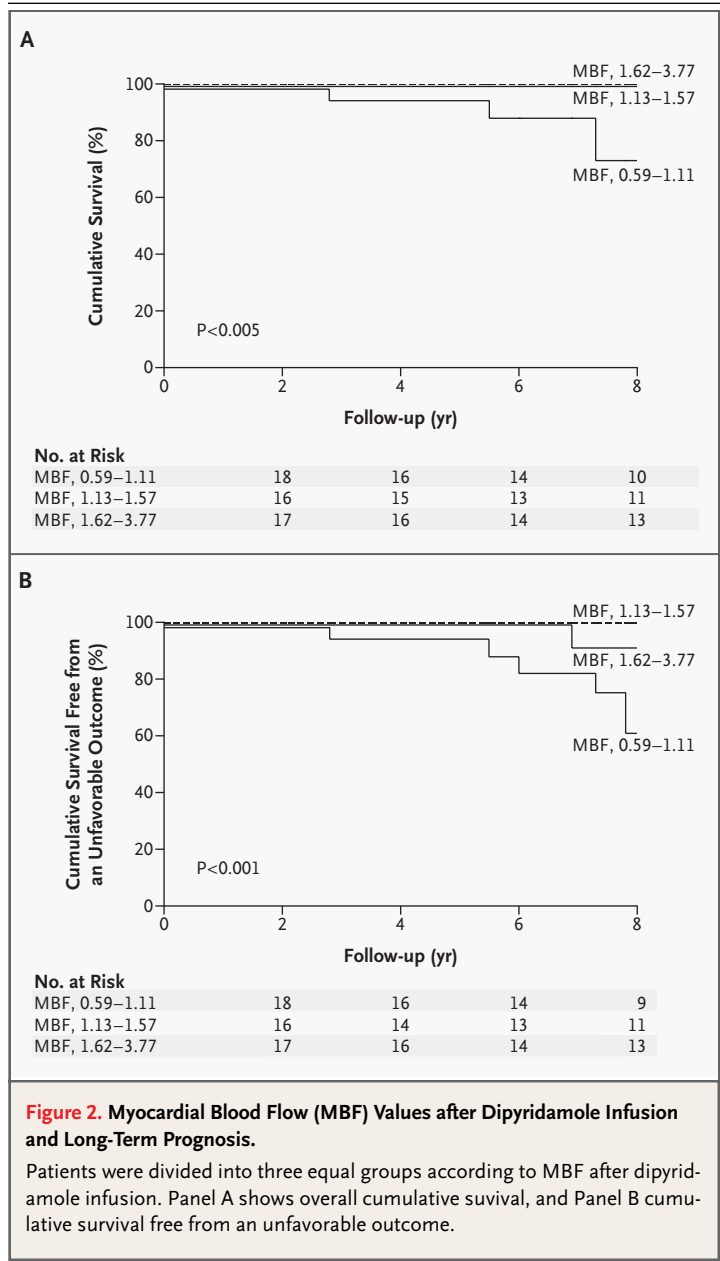
† An unfavorable outcome was defined as progression to NYHA class III or IV, life-threatening ventricular arrhythmias requiring the implantation of a cardioverter–defibrillator, or death from cardiovascular causes.

dial blood flow after dipyridamole infusion was the only independent predictor of death and the most potent predictor of an unfavorable outcome (Table 4). Specifically, patients in the group with the lowest myocardial blood flow after dipyridamole infusion had a markedly increased likelihood of both death from cardiovascular causes and an unfavorable outcome (Fig. 2). The relative risk associated with the lowest myocardial blood flow, as compared with the two higher categories, on age-adjusted multivariate analysis was 9.6 with respect to death from cardiovascular causes (95 percent confidence interval, 1.1 to 88.4;  $P=0.02$ ) and 20.1 with respect to an unfavorable outcome (95 percent confidence interval, 2.4 to 167.8;  $P=0.003$ ). All four patients who subsequently died from heart failure or stroke and three of five who died suddenly were in the lowest category (Table 2). Analysis of the receiver-operating-characteristic curve identified a myocardial blood flow value of 1.1 ml per minute per gram or less after dipyridamole infusion as the best threshold for the identification of patients at risk for an unfavorable outcome.

DISCUSSION

Our principal finding is that the severity of coronary microvascular dysfunction, assessed by PET, is an independent predictor of long-term clinical deterioration and death from cardiovascular causes in patients with hypertrophic cardiomyopathy. Microvascular dysfunction is a common feature of hypertrophic cardiomyopathy<sup>16-19,27-29</sup> and reflects the interplay of a variety of mechanisms, including reduced arteriolar density, fibrosis, myocyte disarray, and elevated left ventricular end-diastolic pressure.<sup>3-5,24,25</sup> Moreover, structural abnormalities of small vessels have been described in patients with hypertrophic cardiomyopathy and are thought to represent a primary abnormality.<sup>3</sup> The failure of myocardial blood flow to increase adequately on demand in patients with hypertrophic cardiomyopathy is clinically relevant in that it predisposes them to myocardial ischemia, which in turn, has been implicated in the pathogenesis of syncope, an abnormal blood-pressure response to exercise, left ventricular systolic dysfunction, and sudden death.<sup>1,7,20-22</sup>

In agreement with prior investigations,<sup>16-19,27,33</sup> our study showed that most patients with hypertrophic cardiomyopathy had various degrees of impairment in myocardial blood flow in response to dipyridamole infusion. During an average follow-



**Figure 2. Myocardial Blood Flow (MBF) Values after Dipyridamole Infusion and Long-Term Prognosis.**

Patients were divided into three equal groups according to MBF after dipyridamole infusion. Panel A shows overall cumulative survival, and Panel B cumulative survival free from an unfavorable outcome.

up of more than eight years, 31 percent of the patients died or had a severe deterioration in their condition: both end points were significantly associated with a low value for myocardial blood flow after dipyridamole infusion. Age-adjusted multivariate analysis showed that the myocardial blood flow after dipyridamole infusion was the most powerful independent predictor of the outcome in our cohort. Patients in the group with the lowest myocardial blood flow appeared to be at particularly high

risk, with an independent increase in the risk of death from cardiovascular causes that was almost 10 times as high as that in the other two groups. It was noteworthy that all four deaths from heart failure and three of the five sudden deaths were in this subgroup. Such an adverse outcome could hardly have been predicted on the basis of the base-line clinical characteristics of our patients, since none had severe symptoms at the time of PET and only a few would have been considered at high risk on the basis of the established indicators of outcome.<sup>1,2,8-11,14</sup> Nevertheless, substantial microvascular dysfunction could already be demonstrated several years before clinical progression in most of the patients who subsequently had a deterioration in their condition or died. It is worth emphasizing that no event occurred during the first two years of follow-up and that the average time to an end point exceeded five years.

Myocardial ischemia is difficult to evaluate in patients with hypertrophic cardiomyopathy, and its effect on the prognosis has often been surmised.<sup>1,24-26</sup> Our demonstration of blunted myocardial blood flow after dipyridamole infusion is not itself a proof of myocardial ischemia, unlike the documentation of lactate production in the coronary sinus or of typical electrocardiographic changes.<sup>21,24</sup> Nevertheless, dipyridamole infusion elicits electrocardiographic signs of myocardial ischemia in patients with hypertrophic cardiomyopathy, which can be used to identify patients at increased risk for cardiac events.<sup>21</sup> This finding suggests that the failure of myocardial blood flow to increase predisposes patients with hypertrophic cardiomyopathy to myocardial ischemia in the presence of triggers that abruptly increase oxygen consumption<sup>22,29</sup> and may explain the ominous effects of atrial fibrillation with rapid ventricular response,<sup>30,31</sup> as well as the frequent occurrence of an abnormal response of blood pressure to exercise in these patients.<sup>22</sup>

Although drug treatment may have some ben-

eficial effect on microvascular dysfunction<sup>28</sup> and silent ischemia<sup>29</sup> in patients with hypertrophic cardiomyopathy, we believe our results are largely independent of therapy. The proportion of patients who received pharmacologic agents with potential anti-ischemic properties — that is, beta-blockers and calcium-channel blockers — did not differ significantly among the three groups with different levels of myocardial blood flow after dipyridamole infusion. Furthermore, none of these pharmacologic agents are known to alter the progression or outcome of hypertrophic cardiomyopathy.

The small size of our cohort is one reason to exercise caution in extrapolating these results to the broad spectrum of hypertrophic cardiomyopathy. PET is a highly sophisticated technique with limited availability, and its use in cardiology is virtually confined to research purposes. Therefore, sample size has been a constant limitation of PET studies. Nevertheless, we were able to obtain meaningful data through the use of a very extended follow-up and to provide a rationale for the clinical use of PET in large populations of patients with hypertrophic cardiomyopathy.

Finally, our findings may have implications for patients with cardiomyopathy from other causes. Indeed, a smaller degree of microvascular dysfunction has been documented in patients with left ventricular hypertrophy due to pressure overload.<sup>33,34</sup> Furthermore, an impaired response of myocardial blood flow to dipyridamole has been shown to be associated with a poor prognosis in patients with idiopathic dilated cardiomyopathy.<sup>35</sup> Thus, our findings support the hypothesis that microvascular dysfunction may represent a common pathway leading to disease progression in different cardiomyopathies,<sup>36</sup> including conditions as prevalent as aortic stenosis and hypertensive heart disease.

Supported by a grant from the Italian Ministry for Scientific and Technologic Research (COFIN 2002).

We are indebted to Dr. Perry M. Elliot for his critical review of the manuscript and helpful suggestions and to Ms. Daniela Vargiu, R.N., for valuable assistance.

#### REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;287:1308-20.
2. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997;336:775-85.
3. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;8:545-57.
4. Tanaka M, Fujiwara H, Onodera T, Wu DJ, Hamashima Y, Kawai C. Quantitative analysis of myocardial fibrosis in normals, hypertensive hearts, and hypertrophic cardiomyopathy. *Br Heart J* 1986;55:575-81.
5. Schwartzkopff B, Mundhenke M, Strauer BE. Alterations of the architecture of subendocardial arterioles in patients with hypertrophic cardiomyopathy and impaired coronary vasodilator reserve: a possible cause for myocardial ischemia. *J Am Coll Cardiol* 1998;31:1089-96.
6. McKenna WJ, Stewart JT, Nihoyannopoulos P, McGinty F, Davies MJ. Hypertrophic cardiomyopathy without hypertrophy: two families with myocardial disarray in the absence of increased myocardial mass. *Br Heart J* 1990;63:287-90.

7. 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.
8. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;36:2212-8.
9. Spirito P, Bellone P, Harris KM, Bernabò 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.
10. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;357:420-4.
11. Olivetto I, Gistri R, Petrone P, Pedemonte E, Vargiu D, Cecchi F. Maximum left ventricular thickness and risk of sudden death in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;41:315-21.
12. Cecchi F, Olivetto I, Monterege A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. *J Am Coll Cardiol* 1995;26:1529-36.
13. Maron BJ, Olivetto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* 2000;102:858-64.
14. Maron MS, Olivetto 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.
15. Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:365-73.
16. Camici PG, Chiriacchi 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.
17. Camici PG, Cecchi F, Gistri R, et al. Dipyridamole-induced subendocardial underperfusion in hypertrophic cardiomyopathy assessed by positron emission tomography. *Coronary Artery Dis* 1991;2:837-41.
18. Choudhury L, Elliott P, Rimoldi O, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. *Basic Res Cardiol* 1999;94:49-59.
19. 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.
20. Dilsizian V, Bonow RO, Epstein SE, Fananapazir L. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993;22:796-804.
21. Lazzeroni E, Picano E, Morozzi L, et al. Dipyridamole-induced ischemia as a prognostic marker of future adverse cardiac events in adult patients with hypertrophic cardiomyopathy. *Circulation* 1997;96:4268-72.
22. Yoshida N, Ikeda H, Wada T, et al. Exercise-induced abnormal blood pressure responses are related to subendocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1998;32:1938-42.
23. O'Gara PT, Bonow RO, Maron BJ, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. *Circulation* 1987;76:1214-23.
24. Cannon RO III, Dilsizian V, O'Gara PT, et al. Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. *Circulation* 1991;83:1660-7.
25. Cannon RO III, Rosing DR, Maron BJ, et al. Myocardial ischaemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. *Circulation* 1985;71:234-43.
26. Elliott PM, Kaski JC, Prasad K, et al. Chest pain during daily life in patients with hypertrophic cardiomyopathy: an ambulatory electrocardiographic study. *Eur Heart J* 1996;17:1056-64.
27. Krams R, Kofflard MJ, Duncker DJ, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation. *Circulation* 1998;97:230-3.
28. 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.
29. Udelson JE, Bonow RO, O'Gara PT, et al. Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. *Circulation* 1989;79:1052-60.
30. Olivetto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;104:2517-24.
31. Stafford WJ, Trohman RG, Bilsker M, Zaman L, Castellanos A, Myerburg RJ. Cardiac arrest in an adolescent with atrial fibrillation and hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;7:701-4.
32. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of the distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide angle, two dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981;48:418-28.
33. Choudhury L, Rosen S, Patel D, Nihoyanopoulos P, Camici PG. Coronary vasodilator reserve in primary and secondary left ventricular hypertrophy: a study with positron emission tomography. *Eur Heart J* 1997;18:108-16.
34. Rajappan K, Rimoldi OE, Dutka DP, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. *Circulation* 2002;105:470-6.
35. Neglia D, Michelassi C, Trivieri MG, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. *Circulation* 2002;105:186-93.
36. Gnechchi-Ruscione T, Taylor J, Mercuri E, et al. Cardiomyopathy in Duchenne, Becker and sarcoglycanopathies: a role for coronary dysfunction? *Muscle Nerve* 1999;22:1549-56.

Copyright © 2003 Massachusetts Medical Society.