# Prognostic Role of Myocardial Blood Flow Impairment in Idiopathic Left Ventricular Dysfunction

Danilo Neglia, MD; Claudio Michelassi, BSc; Maria Giovanna Trivieri, MD; Gianmario Sambuceti, MD; Assuero Giorgetti, MD; Lorenza Pratali, MD; Michela Gallopin, MD; Piero Salvadori, PhD; Oreste Sorace, BSc; Clara Carpeggiani, MD; Rosa Poddighe, MD; Antonio L'Abbate, MD; Oberdan Parodi, MD

***Background***—Depressed myocardial blood flow (MBF) has been reported in dilated cardiomyopathy. The aim of this study was to investigate whether MBF impairment is an independent predictor of prognosis in patients with idiopathic left ventricular (LV) dysfunction.

***Methods and Results***—Sixty-seven patients (52 male, mean age 52±12 years) with different degrees of idiopathic LV systolic dysfunction (average LV ejection fraction, 0.34±0.10; range, 0.07 to 0.49) were prospectively enrolled. Thirty-four subjects (51%) had no history of heart failure symptoms at enrollment (NYHA class I). All patients underwent clinical and functional evaluation and a PET study to measure absolute MBF at rest and after intravenous dipyridamole. During a mean follow-up of 45±37 months, 24 patients had major cardiac events, including cardiac death in 8 and development or progression of heart failure in 16 patients. Multivariate regression analysis (Cox proportional hazards model) revealed heart rate ($\chi^2$ 11.06, $P<0.001$), LV end-diastolic dimension ($\chi^2$ 11.73, $P<0.001$), and dipyridamole MBF ($\chi^2$ 11.04, $P<0.001$) as independent predictors of subsequent cardiac events. Dipyridamole MBF $\leq 1.36$ mL · min$^{-1}$ · g$^{-1}$ was associated with an increase in the relative risk of death, development, or progression of heart failure of 3.5 times over other more common clinical and functional variables.

***Conclusions***—The present study demonstrates that severely depressed MBF is a predictor of poor prognosis in patients with idiopathic LV dysfunction independently of the degree of LV functional impairment and of the presence of overt heart failure. **(*Circulation*. 2002;105:186-193.)**

**Key Words:** cardiomyopathy ■ microcirculation ■ prognosis



Myocardial blood flow (MBF) abnormalities despite angiographically normal coronary arteries have been observed in patients with idiopathic left ventricular (LV) dysfunction attributable to dilated cardiomyopathy. In particular, a reduction in resting MBF[1,2] and in coronary vasodilation in response to metabolic[3] or pharmacological stimuli[4–9] has been reported. Perfusion abnormalities were initially attributed to extravascular mechanisms and thought to occur in the late stages of the disease.[1–3,5,8]

Actually, MBF impairment may be found also in patients with less severe idiopathic LV dysfunction and without overt heart failure.[10] In these patients, impaired myocardial perfusion, likely secondary to coronary microcirculatory dysfunction, might have an independent role in the progression of the disease. This hypothesis has not yet been tested, because available large prognostic studies did not include an evaluation of MBF at enrollment.

This is a prospective follow-up study in a consecutive population of patients with idiopathic LV systolic dysfunction in which an absolute measurement of MBF at rest and during pharmacologic vasodilation was obtained by positron emission tomography (PET). The aim of the study was to assess whether MBF impairment might predict mortality and development or progression of heart failure in this population independently of other clinical and functional indexes.

## Methods

### Population

Ninety-eight consecutive patients with idiopathic LV systolic dysfunction were admitted at the Institute of Clinical Physiology, National Research Council, from January 1989 to January 1999. Coronary artery disease was excluded by means of either coronary angiography or negative exercise and stress echocardiography. All patients with vasospastic angina, congenital, valvular, or hypertensive heart disease, hypertrophic cardiomyopathy, myocarditis, pericarditis, diabetes, and thyroid disease were also excluded. Among this population, 67 patients were prospectively enrolled into the study according to the following criteria: (1) incidentally discovered LV systolic dysfunction in the absence of any previous history of heart failure symptoms (NYHA class I) or recent history of mild-to-

Received May 11, 2001; revision received October 18, 2001; accepted November 2, 2001.

From the C.N.R. Institute of Clinical Physiology, Pisa, Italy; Ospedale Civile Tabarracci, Viareggio, Italy (R.P.); and C.N.R. Institute of Clinical Physiology, Milan, Italy (O.P.).

Correspondence to Danilo Neglia, CNR Institute of Clinical Physiology, Via G Moruzzi, 1, 56126 Pisa, Italy. E-mail dneglia@ifc.pi.cnr.it



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moderate symptoms of heart failure (NYHA class II and III) stable under oral treatment; (2) LV ejection fraction <50% at equilibrium radionuclide angiography or at two-dimensional (2D) echocardiography; (3) presence of sinus rhythm; (4) exclusion of alcohol abuse or other systemic diseases, such as neoplasty, liver, or renal disease; and (5) written informed consent.

Patients with atrial fibrillation were excluded because of the difficulty in obtaining a correct estimation of LV ejection fraction and because of the possible independent effects of the arrhythmia on MBF. The study was approved by the local ethics committee, and patients signed informed consent before entering the study.

## Study Protocol

The study consisted of clinical and functional evaluation at entry, MBF measurement at entry, and follow-up.

## Clinical and Functional Evaluation

Clinical history, NYHA class, physical examination, resting ECG, blood chemistry data, 2D echocardiography, equilibrium radionuclide angiography (53 patients), and 24-hour Holter monitoring were obtained at enrollment. Left heart catheterization and coronary angiography by Judkins technique were performed in the 53 patients who accepted the procedure.

## MBF Measurements

All patients were studied in the absence of any medical therapy after an overnight fasting period; caffeine, theophylline, and theophylline derivatives were withdrawn 24 hours before imaging. Patients were positioned on the bed of a 2-ring positron tomograph (ECAT III, CTI Inc), which provides 3 simultaneous cross-sectional planes. The protocol of the PET study using $^{13}$N-ammonia to measure MBF at rest and after intravenous dipyridamole (0.56 mg/kg body weight) has been described elsewhere.[10] Mean LV MBF ($mL \cdot min^{-1} \cdot g^{-1}$) was computed in the best cross-sectional plane by one experienced cardiologist unaware of the clinical findings according to a method that was previously validated[11] and already applied in patients with dilated cardiomyopathy.[10] Homogeneity of MBF distribution was evaluated by the coefficient of variation (calculated as the percent ratio of the standard deviation to the mean) of MBF values obtained in the same cross-sectional plane in 6 myocardial regions of interest (2 in the septal, 2 in the anterior, and 2 in the posterolateral wall). MBF reserve was defined as the ratio between hyperemic mean MBF and baseline mean MBF.

## Follow-Up

Patients entered a clinical follow-up with regular visits at 6- to 12-month intervals. Patients who did not attend the scheduled program were reached by telephone. A standard questionnaire was used during the follow-up visit or the telephone interview. The follow-up started from the date of the PET study and ended with a cardiac event or on the date of the most recent follow-up visit (or interview). Two cardiac events were considered. The first considered was cardiac death, ascertained by medical records or death certificate and defined as death attributable to refractory congestive heart failure or sudden death (cardiac arrest or death from circulatory failure occurring within the first hour after the onset of symptoms in patients not in NYHA class IV). The second event considered was development or progression of heart failure, ascertained by review of medical records and defined as at least one of the following: worsening of functional class to NYHA class III and IV, new hospitalization for heart failure, or heart transplantation. When more than one of these events occurred, the patient was censored at the time of the earliest event. Patients who died of noncardiac causes were censored on the day before their death.

In 52 of 67 patients, a functional follow-up was also performed by means of 2D echocardiography and radionuclide angiography. In particular, LV function was reassessed near the time of the last follow-up visit or near the time of a cardiac event. No patient was lost at follow-up.

## Statistical Analysis

Data are expressed as mean±SD. Groups were compared for categorical data or frequency of events using the $\chi^2$ test (Yates correction or Fisher's exact test, as appropriate in smaller sample size) and for continuous variables using ANOVA followed by the Scheffe F-test. The LV functional data obtained at enrollment and at follow-up were compared by the Student's *t* test for paired samples. All tests were 2-sided, and $P<0.05$ was considered statistically significant. Linear regression analysis by the least-square method was used to correlate different variables.

Univariate and multivariate survival analyses were performed using the Cox proportional-hazards model and a dedicated statistical software (BMDP)[12] to establish the combined risk of cardiac death or disease progression for the variables assessed. Continuous variables were entered into the model with their individual values; an automatic stepwise selection procedure, using the maximum partial likelihood ratio $\chi^2$ statistic ($\chi^2$ test) to enter (≤0.05 level) or remove (>0.05 level) a covariate into the model, was used. To assess the incremental proportional risk associated with PET-derived indexes over usual clinical parameters, the continuous variables were also dichotomized according to the median value in the whole population, and an interactive stepwise selection procedure was chosen, entering PET variables after all of the other variables. Five-year event-free survival curves were generated using the Kaplan-Meier method to account for censored survival times in patients with different patterns of the main prognostic variables and were compared using the log-rank test (Mantel-Cox).

# Results

## Baseline Characteristics of the Study Population

At enrollment, 34 patients (51%) had no previous history of heart failure symptoms (NYHA class I). They had come to medical attention because of incidentally discovered LV systolic dysfunction in the presence of chest pain, palpitation, documented ventricular arrhythmias, or conduction disturbances. Most of these patients were already under medical treatment. The remaining patients had a history (29±43 months) of heart failure symptoms and evidence of a more severe LV dysfunction; PET data, including mean LV MBF values and homogeneity of MBF distribution, were not different in the two subgroups (Table 1).

At 2D echocardiography, LV end-diastolic dimension was <55 mm in 10 patients (15%), 55 to 65 mm in 41 patients (61%), and >65 mm in 16 patients (24%). In 53 patients, left heart catheterization was performed and ruled out coronary artery disease; LV end-diastolic pressure was elevated (>10 mm Hg) in 20 patients (38%). LV endomyocardial biopsy, performed in 16 patients, showed moderate-to-severe myocyte hypertrophy or interstitial and subendocardial fibrosis in 12 patients. Mononuclear cell infiltrates were detected in 8 cases, but none had a diagnosis of active myocarditis.[13]

At PET evaluation, in the whole population, resting MBF was 0.69±0.23 $mL \cdot min^{-1} \cdot g^{-1}$, dipyridamole MBF was 1.53±0.79 $mL \cdot min^{-1} \cdot g^{-1}$, and MBF reserve was 2.22±0.89, all values being significantly lower ($P<0.001$) than those obtained in a control population of 15 healthy subjects (6 male patients, 49±7 years of age) previously studied in the same laboratory (resting MBF, 1.04±0.22 $mL \cdot min^{-1} \cdot g^{-1}$; dipyridamole MBF, 3.67±0.86 $mL \cdot min^{-1} \cdot g^{-1}$; and MBF reserve, 3.63±0.97) and already published in part.[10] In patients, resting MBF was negatively correlated with LV end-diastolic dimension ($r=-0.26$, $P<0.05$) and LV end-diastolic pressure ($r=-0.44$, $P<0.001$). There was also a negative correlation

**TABLE 1. Baseline Clinical, Functional, and PET Data in the Whole Population of Patients and in Patients With or Without Heart Failure Symptoms at Enrollment**

| Parameters | All Patients (n=67) | NYHA I (n=34) | NYHA II and III (n=33) | *P*, NYHA I vs II and III |
|---|---|---|---|---|
| Clinical data | | | | |
| Age, y | 52±12 | 48±11 | 57±11 | <0.001 |
| Men, % | 78 | 85 | 70 | 0.22 |
| Mean BP, mm Hg | 95±9 | 94±9 | 97±9 | 0.20 |
| HR, beats/min | 69±16 | 67±17 | 72±14 | 0.16 |
| S3, % | 21 | 9 | 33 | <0.05 |
| Medications | | | | |
| ACE inhibitors, % | 78 | 76 | 79 | 0.95 |
| Digoxin, % | 46 | 24 | 70 | <0.001 |
| Diuretics, % | 51 | 29 | 73 | <0.005 |
| Amiodarone, % | 15 | 24 | 6 | 0.10 |
| Nitrates, % | 12 | 18 | 6 | 0.28 |
| β-blockers, % | 10 | 6 | 15 | 0.40 |
| ECG, Holter data | | | | |
| CVA, % | 43 | 50 | 36 | 0.38 |
| IVCD, % | 61 | 53 | 70 | 0.24 |
| LV function data | | | | |
| LVEDD, mm | 62±8 | 59±7 | 64±8 | <0.01 |
| LVEF, % | 34±10 | 39±8 | 30±9 | <0.001 |
| LVEDP, mm Hg | 11.8±7.9 | 9.6±7.3 | 14.0±8.1 | <0.05 |
| PET MBF data | | | | |
| MBF bas, mL/min per g | 0.69±0.23 | 0.67±0.20 | 0.71±0.25 | 0.42 |
| MBF dip, mL/min per g | 1.53±0.79 | 1.60±0.87 | 1.45±0.70 | 0.46 |
| MBF reserve | 2.22±0.89 | 2.34±0.90 | 2.11±0.87 | 0.28 |
| VC bas, % | 16±9 | 15±9 | 16±9 | 0.58 |
| VC dip, % | 20±11 | 19±9 | 21±12 | 0.52 |

BP indicates blood pressure; HR, heart rate; S3, third heart sound; CVA, complex ventricular arrhythmias; IVCD, intraventricular conduction delay (QRS≥120 msec); LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVEDP, LV end-diastolic pressure (n=27 NYHA I patients and n=26 NYHA II and III patients); bas, baseline; dip, dipyridamole; and VC, variation coefficient.

between dipyridamole MBF and LV end-diastolic dimension ($r=-0.27$, $P<0.05$) or LV end-diastolic pressure ($r=-0.29$, $P<0.05$) and a positive correlation between dipyridamole MBF and LV ejection fraction ($r=0.26$, $P<0.05$).

## Follow-Up

The mean duration of the follow-up was 45±37 months (range, 6 to 120 months). Major cardiac events occurred in 24 patients (36%). Eight patients died of cardiac causes (sudden death in 7 and refractory heart failure in 1 patient), and 16 patients showed development or progression of heart failure, characterized by worsening of NYHA functional class in all (to NYHA class III and IV), hospitalization because of new episodes of congestive heart failure in 10, and heart transplantation in 2. Death attributable to noncardiac causes (neoplasty and acute cerebral ischemia) occurred in 2 patients. Cardiac events occurred in 10 of 34 patients (29%) in NYHA class I at enrollment, resulting in death in 3 patients and development of heart failure in 7 patients, and in 14 of 33 patients (42%) in NYHA class II and III at enrollment, resulting in death in 5 patients and progression of heart failure in 9 patients. Compared with event-free survivors, patients who experienced major cardiac events at follow-up had a higher resting heart rate, higher frequency of third heart sound and intraventricular conduction delay, larger LV end-diastolic dimension, lower LV ejection fraction, and lower dipyridamole MBF and MBF reserve at enrollment (Table 2).

A functional follow-up was completed in 52 patients, and 15 showed an increase of LV end-diastolic dimension of ≥5 mm and/or a decrease of LV ejection fraction of ≥5%. At enrollment, these 15 patients differed from the remaining subjects because of a more depressed dipyridamole MBF and MBF reserve (Figure 1). Progression of LV dysfunction at follow-up was more frequent in patients showing major cardiac events than in event-free survivors (11 of 19 or 58% vs 4 of 33 or 12%, $P<0.01$). On average, LV end-diastolic dimension additionally increased from 64±9 to 68±10 mm ($P<0.01$) in the former group and was unchanged, from 60±6 to 59±6 mm (not significant), in the latter group. LV ejection fraction additionally decreased from 30±11% to

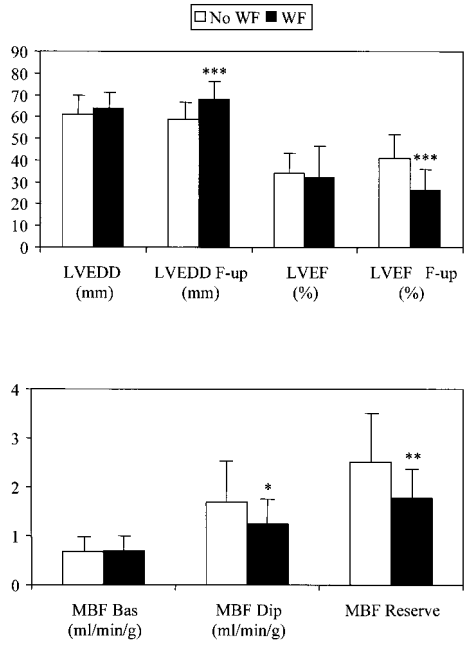


**Figure 1.** Top, Mean values of LV end-diastolic dimension (LVEDD) and ejection fraction (LVEF) at enrollment and at functional follow-up (F-up) are compared between patients with (WF) or without (No WF) worsening of LV function at follow-up. Bottom, Mean values of MBF at rest (MBF Bas) and during dipyridamole (MBF Dip) and of MBF reserve are compared between the two groups. *$P<0.05$; **$P<0.01$; ***$P<0.001$.

26±9% ($P=0.07$) in the former group, whereas it increased from 37±8% to 43±8% ($P<0.001$) in the latter group (Table 2).

## Determinants of Event-Free Survival

Variables included in the Cox model and results of the univariate and multivariate survival analysis are reported in Tables 3 and 4. When continuous variables were entered with individual values (Table 3), the multivariate regression analysis revealed resting heart rate, LV end-diastolic dimension, and dipyridamole MBF as the only independent and additional predictors of subsequent cardiac events. During the procedure, LV ejection fraction and end-diastolic dimension showed a significant colinearity so that only the latter was included. When continuous variables were dichotomized and included in the model according to the median cutoff value (Table 4), NYHA class, resting heart rate, and LV end-diastolic dimension were significant independent predictors of cardiac events. The PET variables had an independent prognostic value, showing an incremental relative risk of 3.47 for dipyridamole MBF $\leq 1.36$ mL $\cdot$ min$^{-1}$ $\cdot$ g$^{-1}$ and of 3.31 for resting MBF $\leq 0.65$ mL $\cdot$ min$^{-1}$ $\cdot$ g$^{-1}$ over the other more common clinical and functional variables. In multivariate survival analysis, no significant colinearity could be demonstrated between LV end-diastolic dimension and flow measurements despite the inverse relationships shown for these variables at enrollment. This finding confirmed that the relative risk values for increased end-diastolic dimension and reduced flow were indeed independent of one another.

At the Kaplan-Meier analysis, the 5-year survival rate and event-free survival rate were 85.8% and 59.5%, respectively,

**TABLE 2. Clinical, Functional, and PET Data in Patients Categorized According to Cardiac Events at Follow-Up**

| Parameters | Event-Free Survivors (n=43) | Cardiac Events (n=24) | *P* |
|---|---|---|---|
| Clinical data | | | |
| Age, y | 53±12 | 50±12 | 0.39 |
| Men, % | 74 | 83 | 0.59 |
| NYHA>I, % | 44 | 58 | 0.39 |
| Mean BP, mm Hg | 95±9 | 95±9 | 0.88 |
| HR, beats/min | 64±13 | 78±17 | <0.001 |
| S3, % | 12 | 38 | <0.05 |
| Medications | | | |
| ACE inhibitors, % | 81 | 71 | 0.49 |
| Digoxin, % | 44 | 50 | 0.84 |
| Diuretics, % | 44 | 63 | 0.24 |
| Nitrates, % | 9 | 17 | 0.62 |
| Amiodarone, % | 16 | 13 | 0.95 |
| $\beta$-blockers, % | 7 | 17 | 0.41 |
| ECG, Holter data | | | |
| CVA, % | 40 | 50 | 0.57 |
| IVCD, % | 51 | 79 | <0.05 |
| LV function data | | | |
| LVEDD, mm | 60±6 | 64±9 | <0.05 |
| LVEDD at F-up, mm* | 59±6 | 68±10 | <0.001 |
| LVEF, % | 37±8 | 30±11 | <0.05 |
| LVEF at F-up, %* | 43±8 | 26±9 | <0.001 |
| LVEDP, mm Hg† | 10.6±7.9 | 13.7±7.9 | 0.17 |
| PET MBF data | | | |
| MBF bas, mL/min per g | 0.71±0.21 | 0.65±0.25 | 0.36 |
| MBF dip, mL/min per g | 1.67±0.72 | 1.27±0.85 | <0.05 |
| MBF reserve | 2.40±0.85 | 1.92±0.88 | <0.05 |
| VC bas, % | 16±9 | 15±8 | 0.42 |
| VC dip, % | 20±12 | 20±7 | 0.84 |

F-up indicates follow-up. Other abbreviations as in Table 1.
*n=33 event-free survivors and n=19 cardiac-event patients.
†n=33 event-free survivors and n=20 cardiac-event patients.

in the whole population (Figure 2). The 5-year event-free survival rate was significantly lower in patients with dipyridamole MBF $\leq 1.36$ mL $\cdot$ min$^{-1}$ $\cdot$ g$^{-1}$ (35.8%) than in patients with higher dipyridamole MBF values (79%), whereas it was still lower, but not significantly, in patients with resting MBF $\leq 0.65$ (49.1%) than in patients with higher resting MBF values (68.9%) (Figure 3). Cardiac events were most frequent in patients with a combination of dipyridamole MBF $\leq 1.36$ mL $\cdot$ min$^{-1}$ $\cdot$ g$^{-1}$ and the presence of heart failure symptoms or larger LV end-diastolic dimension at enrollment (Figure 4).

## Discussion

This is the first study that shows a relevant prognostic value of MBF impairment in patients with idiopathic LV systolic dysfunction. In the whole population, severely depressed dipyridamole and resting MBF were associated, respectively, with a 3.5 and 3.3 relative risk of death or development or progression of heart failure. Although other known prognos-

**TABLE 3. Univariate and Multivariate Relation Between Baseline Clinical, Functional, and PET Variables and Cardiac Events**

| | Univariate Analysis | | Multivariate Analysis (Automatic and Interactive Stepwise Selection) | | | |
|---|---|---|---|---|---|---|
| Variables | $\chi^2$ | *P* | $\chi^2$ | *P* | Relative Risk | Confidence Limits |
| Clinical | | | | | | |
| Age, y | 0.01 | 0.91 | | | | |
| Sex | 0.98 | 0.32 | | | | |
| NYHA | 5.22 | <0.05 | | | | |
| Mean BP, mm Hg | 0.00 | 0.97 | | | | |
| HR, beats/min | 10.33 | <0.01 | 11.06 | <0.001 | 1.04 | 1.02–1.07 |
| S3 | 4.83 | <0.05 | | | | |
| ECG, Holter | | | | | | |
| CVA | 0.00 | 0.99 | | | | |
| IVCD | 4.02 | <0.05 | | | | |
| LV function | | | | | | |
| LVEDD, mm | 10.70 | <0.01 | 11.73 | <0.001 | 1.09 | 1.04–1.15 |
| LVEF, % | 11.64 | <0.001 | | | | |
| LVEDP, mm Hg* | 6.22 | <0.05 | | | | |
| PET MBF | | | | | | |
| MBF bas, mL/min per g | 3.31 | 0.07 | | | | |
| MBF dip, mL/min per g | 10.34 | <0.01 | 11.04 | <0.001 | 3.21 | 1.51–6.82 |
| MBF reserve | 7.80 | <0.01 | | | | |
| VC bas, % | 0.16 | 0.69 | | | | |
| VC dip, % | 0.21 | 0.64 | | | | |

Continuous variables are entered with individual values.
Abbreviations as in Table 1.
*Analysis performed in 53 patients.



tic indexes, such as NYHA functional class, resting heart rate, and LV end-diastolic dimension, were significant independent predictors of outcome in this population, multivariate regression analysis revealed PET-derived MBF as an additional independent predictor of subsequent cardiac events.

Most of the previous prognostic studies in idiopathic LV dysfunction included patients with dilated cardiomyopathy characterized by severe LV impairment and overt heart failure. Mortality and transplantation were used as end points, and different indexes, mainly of the severity of LV dysfunction or related to the activation of the neuroendocrine system, have been tested.[14–18] Less attention has been devoted to patients with less severe LV dysfunction and to indexes linked to putative mechanisms of disease progression. Several studies suggested that one such mechanism could be chronic hypoperfusion of the myocardium attributable to coronary microcirculatory abnormalities.[2–10]

In the present study, half of the patients were asymptomatic and had a less severe LV dysfunction at enrollment than those presenting with heart failure symptoms. In the whole population, some of the clinical variables associated with disease severity were independent predictors of successive cardiac events. However, most surprisingly, the extent of MBF impairment, which expresses more the severity of coronary microcirculatory abnormalities than of ventricular functional abnormalities, was a powerful and additional predictor of prognosis independent of more common indicators.

## Pathophysiological Role of Depressed MBF in Idiopathic LV Dysfunction

Recent studies have suggested that in patients with dilated cardiomyopathy, an abnormal coronary microcirculatory flow may cause impairment of myocardial perfusion and regional metabolic changes compatible with myocardial ischemia.[19,20] The present study demonstrates that the severity of MBF limitation predicts death and progressive heart failure in patients with idiopathic LV dysfunction and is associated with LV enlargement and deterioration of LV systolic function over time. These results support the hypothesis that chronic myocardial hypoperfusion or repetitive myocardial ischemia attributable to abnormal coronary microcirculatory flow could have a pathophysiological role in the evolution of idiopathic LV dysfunction toward overt dilated cardiomyopathy.

At variance with present results, recent PET studies in small populations of patients with dilated cardiomyopathy showed that mean resting MBF was either normal[19] or not correlated with prognosis.[21] These discrepancies do not seem to be attributable to different methods in MBF measurements, because a depression of resting MBF was demonstrated in several other studies performed in patients with dilated

**TABLE 4. Univariate and Multivariate Relation Between Baseline Clinical, Functional, and PET Variables and Cardiac Events**

| | | Univariate Analysis | | Multivariate Analysis (Interactive Stepwise Selection) | | | |
|---|---|---|---|---|---|---|---|
| Variables | Median Cutoff Value or Category | $\chi^2$ | *P* | $\chi^2$ | *P* | Relative Risk | Confidence Limits |
| Clinical | | | | | | | |
| Age, y | >52 | 0.11 | 0.74 | | | | |
| Sex | Male vs female | 0.98 | 0.32 | | | | |
| NYHA | II and III vs I | 4.46 | <0.05 | 9.69 | <0.01 | 4.59 | 1.68–12.50 |
| Mean BP, mm Hg | >95 | 0.22 | 0.64 | | | | |
| HR, beats/min | >67 | 5.58 | <0.05 | 10.92 | <0.01 | 4.50 | 1.75–11.58 |
| S3 | Present vs absent | 4.88 | <0.05 | | | | |
| ECG, Holter | | | | | | | |
| CVA | Present vs absent | 0.00 | 0.99 | | | | |
| IVCD | Present vs absent | 4.02 | <0.05 | | | | |
| LV function | | | | | | | |
| LVEDD, mm | >60 | 7.34 | <0.01 | 5.57 | <0.05 | 2.88 | 1.18–7.07 |
| LVEF, % | ≤35 | 1.63 | 0.20 | | | | |
| LVEDP, mm Hg* | >10 | 2.35 | 0.13 | | | | |
| PET MBF | | | | | | | |
| MBF bas, mL/min per g | ≤0.65 | 3.41 | 0.06 | 5.53 | <0.05 | 3.31 | 1.19–9.20 |
| MBF dip, mL/min per g | ≤1.36 | 11.29 | <0.001 | 6.79 | <0.01 | 3.47 | 1.31–9.18 |
| MBF reserve | ≤2.00 | 6.92 | <0.01 | | | | |
| VC bas, % | >13.8 | 0.02 | 0.89 | | | | |
| VC dip, % | >18.0 | 0.47 | 0.49 | | | | |

Continuous variables are dichotomized.
Abbreviations as in Table 1.
*Analysis performed in 53 patients.



cardiomyopathy with different methodological approaches. Discrepancies most probably could be explained by different sample sizes.

In the present study, resting MBF, more than dipyridamole MBF, was correlated with indexes of LV dysfunction at enrollment. This relationship could be interpreted as being attributable either to the effects of reduced MBF on LV function or to the effects of high systolic and diastolic wall stress associated with LV dysfunction on myocardial perfusion. These results can be paralleled with those reported in hibernating myocardium in ischemic heart disease, where ventricular dilatation and dysfunction are associated with reduced resting MBF and residual, although reduced, coronary reserve.[22] Both hypoperfusion and repetitive ischemia may cause progressive LV dilatation and systolic dysfunction, which in turn may affect myocardial perfusion. This mechanism of reciprocal interaction between depressed flow and impaired function could explain why both dipyridamole MBF and LV end-diastolic dimension are independent but additional predictors of disease progression in our population. Although compatible with the present results, the microvascular ischemic hypothesis remains speculative and deserves more extensive investigation to demonstrate, for example, the presence of metabolic fingerprints of myocardial ischemia, as suggested by the study of van den Heuvel[20] and our own recent study.[23]

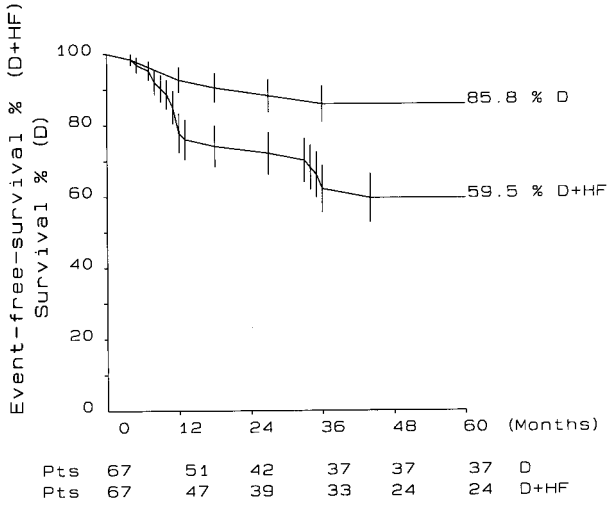


**Figure 2.** Kaplan-Meier survival (D) and event-free survival (D+HF) plots at 5 years for the whole population.

## Limitations of the Study

We observed 8 deaths over a mean follow-up period of 4 years. This finding did not allow us to perform a survival

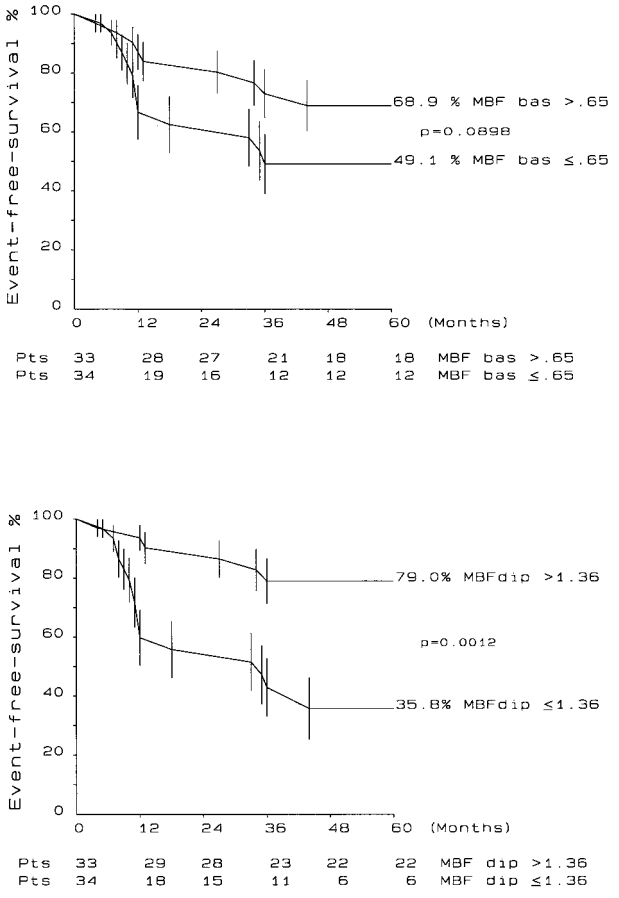


**Figure 3.** Kaplan-Meier event-free survival plots at 5 years are shown for patients subdivided into groups according to resting MBF (top) and dipyridamole MBF (bottom).

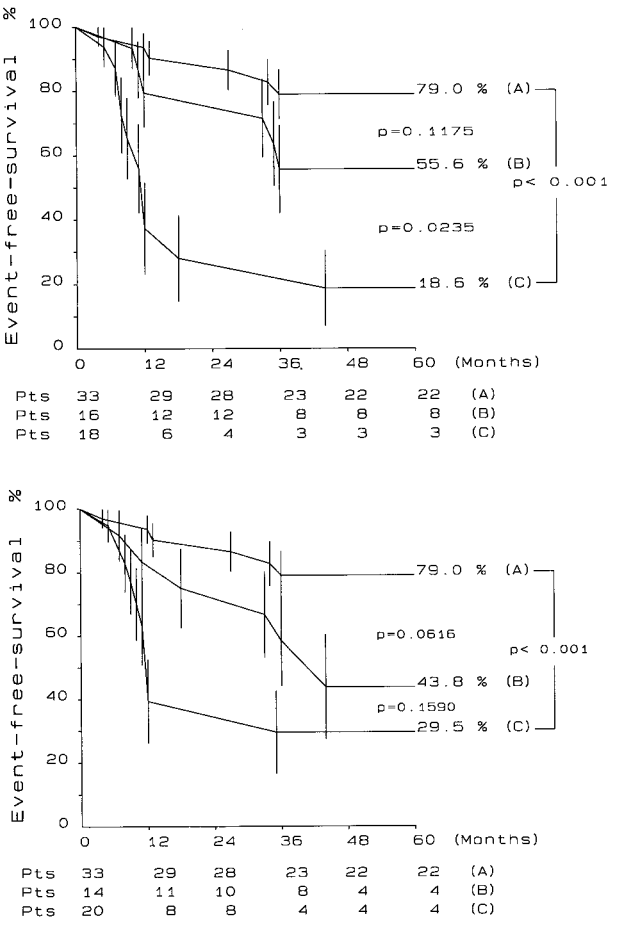


**Figure 4.** Top, Kaplan-Meier plots obtained in patients with dipyridamole MBF >1.36 mL · min$^{-1}$ · g$^{-1}$ irrespective of the NYHA class (A) and in patients with dipyridamole MBF ≤1.36 mL · min$^{-1}$ · g$^{-1}$ subdivided according to the absence (NYHA class I) (B) or presence (NYHA class II and III) (C) of heart failure symptoms at enrollment. Bottom, Kaplan Meier plots obtained in patients with dipyridamole MBF >1.36 mL · min$^{-1}$ · g$^{-1}$ irrespective of the LV end-diastolic dimension (A) and in patients with dipyridamole MBF ≤1.36 mL · min$^{-1}$ · g$^{-1}$ subdivided according to LV end-diastolic dimension ≤60 mm (B) or >60 mm (C) at enrollment.

analysis with mortality as the only end point,[24] preventing a direct comparison with previous studies. The mortality rate is certainly related to the selection criteria, which also included patients with mild LV dysfunction. We selected this kind of population because we were particularly interested in the assessment of early markers of disease progression, which had not been previously explored.

We were unable to investigate some functional or neurohormonal indicators positively related with prognosis in heart failure[14–18]; however, the main purpose of the study was not the direct comparison of PET-derived indexes with the best prognostic markers in heart failure.

The heterogeneity of MBF distribution throughout the left ventricle was evaluated by the coefficient of variation of regional MBF values obtained in a single cross-sectional plane and did not show prognostic relevance. However, a complete measurement of regional MBF in multiple planes covering the entire heart, not allowed by the PET tomograph used, could have provided different results. Moreover, the occurrence of regional ischemia could have been evidenced by the combination of $^{13}$N-ammonia and $^{18}$F-fluorodeoxyglucose administration, but this was beyond the purposes of the present study.

## Conclusions

Heart failure and severe ventricular dilatation and dysfunction were considered for a long time the typical clinical presentations of idiopathic dilated cardiomyopathy.[25] More recently, it has become clear that the natural history of this disease is characterized by an undetermined period of latent ventricular dysfunction, with or without dilatation, during which patients are mostly asymptomatic or complain of palpitations and chest pain rather than dyspnea. Since the widespread use of echocardiography, this presentation seems to be very frequent and is still associated with a severe prognosis, showing a survival rate of 78±8% at 5 years.[26,27] Moreover, the Studies of Left Ventricular Dysfunction prevention trial demonstrated that patients who will develop new or worse heart failure symptoms in the follow-up will have a higher mortality rate.[28] Accordingly, the availability of predictive indexes of heart failure development in patients

presenting with asymptomatic or mildly symptomatic LV dysfunction would be of great value. The present study demonstrates that PET-derived indexes, possibly associated with other simple clinical variables, allow the noninvasive identification of a subgroup of patients with idiopathic LV dysfunction at high risk to develop progressive ventricular deterioration and heart failure. In this subgroup, clinical surveillance and aggressive treatment should be warranted.

## Acknowledgments

This work was supported in part by a grant from the Ministry of Health (Italy). We are indebted to Professor Carlo Contini, who in the early 1980s pushed us to recognize and study patients with early signs of dilated cardiomyopathy. Professor Contini died few years ago, but his teaching made this work possible.

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