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The Extent of Perfusion–F18-Fluorodeoxyglucose Positron Emission Tomography Mismatch Determines Mortality in Medically Treated Patients With Chronic Ischemic Left Ventricular Dysfunction

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OBJECTIVES The purpose of this study was to assess the determinants of mortality in a large group of patients with ischemic cardiomyopathy who are treated medically and the impact of the extent of viable tissue on prognosis.

BACKGROUND Whether the presence of viability drives mortality in patients with ischemic cardiomyopathy who are treated medically and whether the extent of viability is important are issues that are currently unclear.

METHODS Two hundred sixty-one patients with ischemic cardiomyopathy underwent positron emission tomography (PET) for assessment of viability. Prospective follow-up was obtained.

RESULTS Ninety-four patients were revascularized and 167 were not. The cardiac death rate was significantly less in the revascularized patients as compared with medically treated patients (13% vs. 24%, $p < 0.05$). In the revascularized patients, there was a trend toward better survival in patients with viable myocardium as compared with nonviable myocardium (3.5-year survival, 85% and 75% respectively, p = NS). In the medically treated group, age (hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.2 to 3.7), presence of left bundle branch block (HR 3.4, 95% CI 1.6 to 7.2) and extent of perfusion-metabolism mismatch on PET (HR 1.36, 95% CI 1.1 to 1.6) predicted cardiac death during a median follow-up period of 2.1 years. The risk of cardiac death was not significantly increased when the extent of mismatch was ≤20% (HR 0.97, 95% CI 0.46 to 2.05) but was significantly increased when the extent of mismatch was >20% (HR 3.21, 95% CI 1.38 to 7.49).

CONCLUSIONS Medically treated patients with ischemic cardiomyopathy and large areas of viable myocardium on PET are at high risk for cardiac death. (J Am Coll Cardiol 2005;46:1264–9)
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Viability assessment is important for management of patients with ischemic cardiomyopathy. Patients with viable myocardium who undergo revascularization improve in function and have a favorable prognosis (1–4). Pooling of five prognostic F18-fluorodeoxyglucose (FDG) positron emission tomography (PET) studies with 662 patients showed an event rate of 7% in 178 patients with viable myocardium who underwent revascularization (5).

In sharp contrast, patients with viable myocardium who are medically treated seemed to have a high event rate and poor prognosis. In the five pooled FDG PET studies, a 20% event rate was reported in 75 patients with viable myocardium who were treated medically. It has been hypothesized that residual viable myocardium should be considered as an unstable substrate and that medical treatment of these patients results in a high event rate. Whether the viability or other factors drive the high event rate is still unclear. In addition, whether the simple presence of viable myocardium, or rather, the extent of viable tissue is important for long-term prognosis in medically treated patients is also unclear. Accordingly, the aim of the present study was to evaluate which parameters determine the long-term prognosis in patients with ischemic cardiomyopathy who are medically treated, and furthermore, to verify whether small areas of viability might already cause an increase in the risk of death in medically treated patients or that only patients with large areas of viability are at increased risk of death.

METHODS

Study population. A total of 261 patients were clinically referred for assessment of viability by PET; these patients had chronic coronary artery disease (CAD) on angiography with depressed left ventricular (LV) function, as defined by a LV ejection fraction (EF) ≤40%, and underwent evaluation for surgical revascularization. Criteria for revascularization were feasible anatomy, no extensive co-morbidity and informed consent of the patient. Of this population, 167 patients were not revascularized on the basis of poor target vessels (n = 143), extensive co-morbidity (n = 15), or

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
EF = ejection fraction
FDG = F18-fluorodeoxyglucose
LBBB = left bundle branch block
LV = left ventricle/ventricular
MI = myocardial infarction
PET = positron emission tomography

patient refusal for revascularization (n = 9). These patients were prospectively followed-up and represent the study population.

PET. The PET studies were performed with an ECAT EXACT (CTI, Knoxville, Tennessee) scanner, which allows simultaneous acquisition of 47 contiguous transaxial images, with a total axial field of view of 16.2 cm. The resolution of the scanner was 4.8 ± 0108 0.6 mm in the axial direction and 6.1 ± 0108 0.2 mm in the transaxial planes. A transmission scan was obtained for 15 min to allow for attenuation correction with retractable germanium-68 ring sources. For emission studies, the tracers used were N-13 ammonia (NH3) (10 MBq/kg) to assess resting perfusion and FDG (4 MBq/kg) to assess glucose use; FDG was injected 45 min after oral glucose loading (50 g). The emission scans were started 4 min after injection of NH3 and 45 min after FDG injection. Data acquisition lasted 15 min for both tracers. Short-axis and vertical and horizontal long-axis slices (thickness 0.8 cm each) were reconstructed with a Hanning filter (cut-off 1.18 cycle/cm) and corrected for attenuation. Both studies were performed on the same day in all of the patients: first, the N13-ammonia study, followed by the FDG study 2 h later.

For image evaluation, a semi-quantitative analysis was performed, dividing the LV into 16 segments. After normalization to the maximum counts in the myocardium, the relative percentage of NH3- and FDG-uptake was then calculated in regions of interest (8 × 8 mm-sized), drawn in the center of each segment.

Segments with reduced perfusion (tracer uptake <70% of maximum) and relatively preserved FDG uptake (tracer uptake ≥70%) were considered viable (perfusion-FDG mismatch). Segments with reduced perfusion and concordantly reduced FDG uptake (both tracers uptake <70% of maximum, perfusion-FDG match) were considered nonviable (6). The presence of a perfusion-FDG mismatch in ≥1 segment was used to classify patients as having viable tissue. The extent of the viable area was calculated as the percentage of the LV with a mismatch pattern and the extent of the nonviable area was calculated as the percentage of the LV with a match pattern. All studies were analyzed by three experienced observers, and a majority decision was achieved.

Long-term follow-up. Long-term follow-up was obtained from patient interviews at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, close relative, or referring physician. Only cardiac death was taken into account as event. Death was defined as cardiac if strictly related to proven cardiac causes (i.e., fatal reinfarction, refractory heart failure, or ventricular arrhythmias).

Statistical analysis. Continuous variables are presented as median values, and categorical variables are presented as percentages. Survival curves were estimated and plotted on the basis of the Kaplan-Meier estimator. The individual effect of clinical (age, gender, hypertension, dyslipidemia, smoking, diabetes, history of infarction, previous revascularization procedures, left bundle branch block [LBBB] on electrocardiogram [ECG]), angiographic (three-vessel disease, LVEF), and PET data (presence/absence of viability, extent of the viable area, and extent of the nonviable area) on survival was evaluated by Cox proportional-hazards regression analysis. First, univariate hazard ratios (HRs) for each of the observed covariate were computed along with their 95% confidence intervals (CIs). Then, a multivariate Cox proportional hazard model was selected. All variables considered were entered into the model "as is" (i.e., without any transformation or cutting-off). Selection criteria was the Akaike Information Criterion (AIC) applied backward for each model tested. The final model was selected if superior in terms of AIC at a significance level of 0.05. Proportionality in hazard was carefully checked, both with visual analysis of Schoenfeld residuals and, formally, with the Grambsch-Therneau test. Thus, for the final model, multivariate HRs have been presented along with their 95% CIs. Finally, effect of mismatch on survival was modeled with a non-linear restricted cubic spline function, tested. All computations were performed with S-plus version 2000 and the Harrell's Design and Hmisc libraries (Insightful Corp., Seattle, Washington) (7). Somer's discrimination index (8) was used to evaluate goodness of fit. For all tests, a p value <0.05 was considered significant.

RESULTS

Baseline characteristics of medically treated and revascularized patients were comparable (Table 1).

The 167 patients who did not undergo revascularization and were medically treated represent our study population. Clinical characteristics of the study population, combined and stratified according to the occurrence of a mismatch pattern, are reported in Table 2. In 107 patients, no mismatch pattern was present on PET imaging, whereas 60 patients showed at least one segment with a mismatch pattern. Patients with a mismatch pattern did not differ in age, gender, previous myocardial infarction and/or previous revascularization procedures, and presence of LBBB on ECG from patients without a mismatch pattern. The prevalence of risk factors and co-morbidity was similar in the two groups. On the basis of the inclusion criteria, all patients had significant CAD on coronary angiography. In particular, three-vessel disease was present in 79 (47%) patients and was observed in 36 of 60 patients with a

JACC Vol. 46, No. 7, 2005
October 4, 2005:1264–9

Table 1. Clinical Characteristics of Medically Treated and Revascularized Patients*

	Medically Treated Patients (n = 167)	Revascularized Patients (n = 94)	p Value
Age (yrs)	66 [57, 69]	66 [58, 70]	NS
Male	89% (148)	89% (84)	NS
Hypertension	50% (83)	50% (47)	NS
Diabetes	10% (16)	12% (11)	NS
Dyslipidemia	50% (83)	65% (61)	NS
Smoking	52% (87)	75% (70)	NS
Family history of CAD	31% (51)	41% (38)	NS
NYHA functional class III to IV	62% (104)	65% (61)	NS
Previous MI	82% (137)	79% (74)	NS
Previous PTCA	5% (9)	8% (8)	NS
Previous CABG	6% (10)	6% (6)	NS
Presence of LBBB	22% (37)	17% (16)	NS
Peripheral vascular disease	4% (7)	9% (8)	NS
Severe COPD	5% (8)	5% (5)	NS
Renal failure	6% (10)	8% (8)	NS
LVEF (%)	29 [22, 34]	30 [25, 35]	NS
PET MM present	36% (60)	58% (55)	<0.001
Extent of MM (%)	13 [7, 20]	20 [10, 30]	<0.001

*Continuous variables are presented as median (first and third quartile in brackets). Categorical variables are presented as percentages (absolute number in parentheses).

CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MM = mismatch; NYHA = New York Heart Association; PET = position emission tomography; PTCA = percutaneous transluminal coronary angioplasty.

mismatch (60%) and in 43 of 107 patients without a mismatch (33%) ($p < 0.05$). Median LVEF was 29% (first quartile, 22%; third quartile, 34%), with no difference between patients with and without mismatch.

The prescribed medical treatment was as follows: angiotensin-converting enzyme inhibitors were used in 93% of patients, diuretics in 72%, aspirin and/or oral anticoagulation in 93%, nitrates in 60%, beta-blockers in 41%, calcium antagonists in 15%, digoxin in 41%, and amiodarone in 21% of patients.

Prediction of long-term outcome. During a median follow-up period of 2.1 years (first to third quartile, one to three years), a total of 40 cardiac deaths occurred in the study population (Fig. 1).

Univariable predictors of cardiac death were age, diabetes, smoking, previous myocardial infarction, presence of LBBB, three-vessel disease on angiography, and extent of a mismatch pattern on PET imaging. The simple presence of a mismatch pattern was not predictive of death (Table 3). Scar tissue (match pattern) involved a median of 30% of the left ventricle (first to third quartile, 18% to 42%) and was not a predictor of cardiac death during follow-up.

Multivariable analysis selected age ($p = 0.005$), LBBB ($p = 0.001$), and extent of mismatch on PET imaging ($p = 0.001$) as independent prognostic indicators (Table 3). The extent of mismatch was strongly related (HR 1.36, 95% CI 1.13 to 1.64) to mortality, with an 8% increase in extent of mismatch determining a 36% increase in risk of cardiac

Table 2. Clinical Characteristics of the Medically Treated Study Population*

	Medically Treated Patients (n = 167)	Patients Without Mismatch (n = 107)	Patients With Mismatch (n = 60)	p Value
Age (yrs)	66 [57, 69]	65 [55, 69]	67 [60, 71]	NS
Male	89% (148)	89% (95)	88% (53)	NS
Hypertension	50% (83)	51% (55)	47% (28)	NS
Diabetes	10% (16)	7% (7)	15% (9)	NS
Dyslipidemia	50% (83)	51% (55)	47% (28)	NS
Smoking	52% (87)	51% (55)	53% (32)	NS
Family history of CAD	31% (51)	30% (32)	32% (19)	NS
Previous MI	82% (137)	82% (88)	82% (49)	NS
Previous PTCA	5% (9)	5% (5)	7% (4)	NS
Previous CABG	6% (10)	6% (6)	7% (4)	NS
Presence of LBBB	22% (37)	22% (24)	22% (13)	NS
Peripheral vascular disease	4% (7)	5% (5)	3% (2)	NS
Severe COPD	5% (8)	5% (5)	5% (3)	NS
Renal failure	6% (10)	6% (6)	7% (4)	NS
LVEF (%)	29 [22, 34]	28 [22, 34]	29 [23, 34]	NS

*Continuous variables are presented as median (first and third quartile in brackets). Categorical variables are presented as percentages (absolute number in parentheses). Abbreviations as in Table 1.

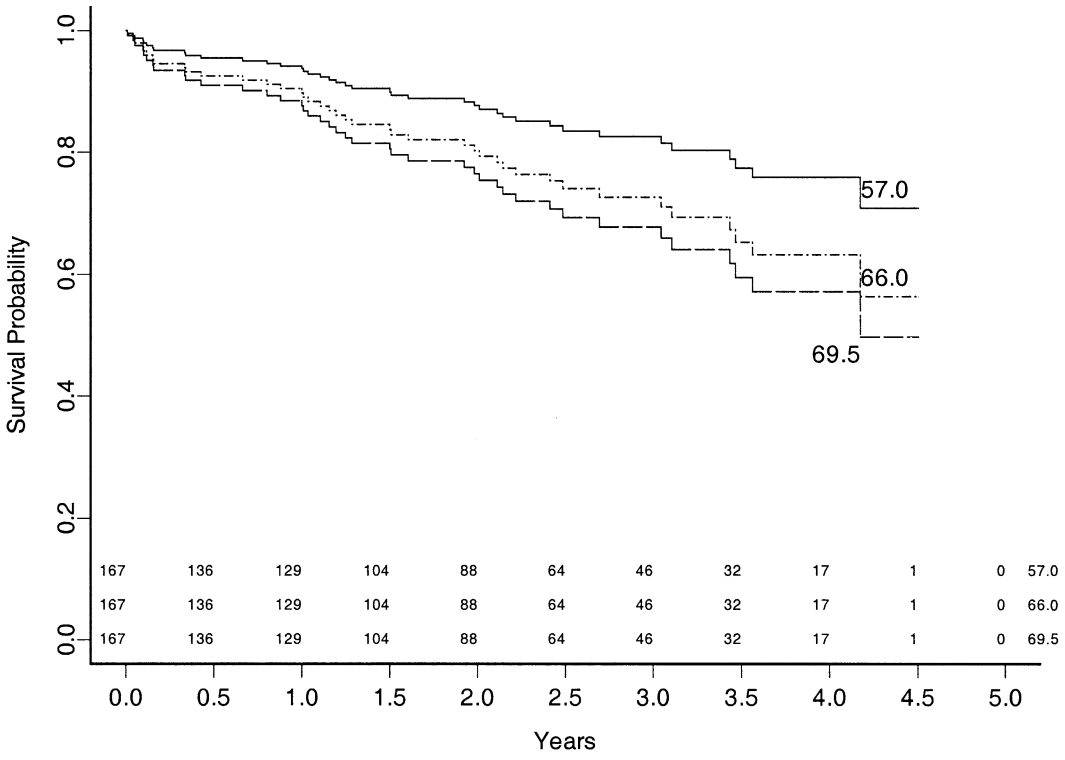

Figure 1. Kaplan-Meier survival curve with 95% confidence intervals in the medically treated patients; the number of patients at risk at the different time-intervals is indicated.

death during follow-up (Table 3, Fig. 2). To describe the relation between extent of mismatch and mortality, a plot of log-hazard versus mismatch in non-linear terms is shown in Figure 2. The risk of cardiac death is not significantly increased when the extent of mismatch is ≤20% (HR 0.97, 95% CI 0.46 to 2.05), but the risk of death is significantly increased when the extent of mismatch exceeds 20% (HR 3.21, 95% CI 1.38 to 7.49).

For comparison, in the 94 revascularized patients, 12 (13%) cardiac deaths occurred during follow-up. The cardiac death rate was significantly less in the revascularized patients as compared with the medically treated patients (13% vs. 24%, $p < 0.05$). In particular, the cardiac death rate was significantly higher in viable patients who were treated medically as compared with viable patients who underwent revascularization (28% vs. 15%, $p < 0.05$). In the

Table 3. Univariable and Multivariable Analysis*

	No Event (n = 127)	Event (n = 40)	Univariable Analysis			Multivariable Analysis		
			HR	95% CI	p Value	HR	95% CI	p Value
Age (yrs)	64 [55, 69]	68 [61, 72]	2.0	1.2–3.4	0.005	2.1	1.2–3.7	0.005
Male	90% (114)	85% (34)	1.2	0.5–2.8	NS			
Hypertension	45% (56)	25% (10)	0.5	0.2–0.9	0.03			
Diabetes	7% (9)	18% (7)	2.8	0.9–4.7	0.08			
Dyslipidemia	58% (74)	22% (9)	0.2	0.1–0.4	<0.001			
Smoking	38% (48)	80% (32)	5.8	2.7–12.6	<0.001			
Previous MI	13% (17)	32% (13)	2.2	1.1–4.2	0.02			
Previous PTCA	6% (8)	2% (1)	0.5	0.1–3.3	NS			
Previous CABG	6% (7)	8% (3)	1.1	0.3–3.7	NS			
Presence of LBBB	17% (21)	40% (16)	2.0	1.1–3.9	0.03	3.4	1.6–7.2	0.001
LVEF (%)	29 [22, 34]	27 [25, 30]	0.8	0.5–1.4	NS			
3-vessel disease	37% (47)	55% (22)	2.4	1.3–4.4	0.04			
PET MM present	34% (43)	42% (17)	1.4	0.7–2.6	0.07			
Extent of MM (%)	10 [7, 20]	15 [7, 30]	1.2	1–1.36	0.05	1.36	1.1–1.6	0.001
Extent of scar (%)	30 [18, 42]	30 [18, 30]	1.0	0.51–2.0	NS			

*Study population (n = 167), stratified according the occurrence of cardiac death. Continuous variables are presented as median (first and third quartile in brackets). Categorical variables are presented as percentages (absolute number in parentheses). Univariable hazard ratios (HR) are presented with their 95% confidence intervals (CI). Multivariable model for hard events: HR for LBBB and extent of mismatch (MM) have been computed, adjusting the respective values in the interaction term (coefficient −0.083, SEM 0.0294, p = 0.0047) at 0. After 500 bootstrap replications, Somer's discrimination index was estimated as Dxy = 0.35.

Abbreviations as in Table 1.

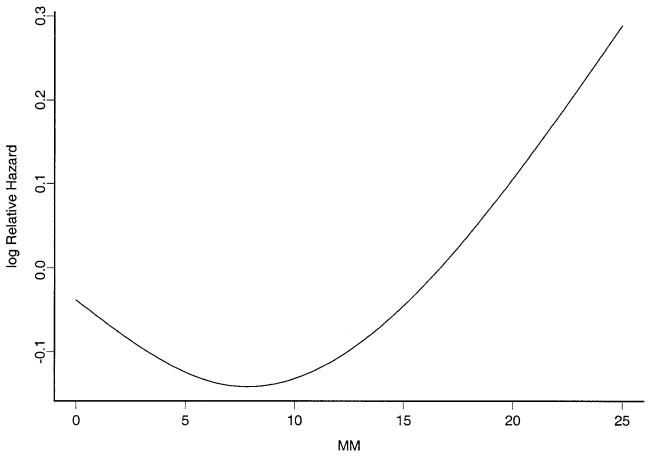

Figure 2. Plot of log-hazard versus mismatch (MM) in non-linear terms. The graph indicates a non-significant effect on risk of having a mismatch with an extent ≤20% compared with 0% (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.46 to 2.05), whereas the effect is significant when the extent of mismatch exceeds 20% (HR 3.21, 95% CI 1.38 to 7.49).

revascularized patients, there was a trend toward better survival in patients with viable myocardium as compared with nonviable myocardium (3.5-year survival, 85% and 75%, respectively, p = NS).

DISCUSSION

It has been postulated that the presence of viable myocardium represents an unstable situation, prone to ischemic and arrhythmic events in patients who do not undergo revascularization; on the basis of this hypothesis, the extent of jeopardized, viable myocardium might be of less importance than the simple presence of viable tissue. The results of the current study, however, indicate that not simply the presence of a perfusion-FDG mismatch but rather the extent of mismatch determines the long-term mortality in patients with ischemic cardiomyopathy who are medically treated.

The identification of residual viability is a key element for optimal management of patients with ischemic cardiomyopathy, who represent a high-risk population that, even when revascularized, showed a 13% death rate during follow-up in our series. In patients with a LVEF <35%, the perioperative and in-hospital mortality are lower and one-year survival is better when the need for revascularization is guided by pre-operative assessment of viability (9). Conversely, patients with viable myocardium who do not undergo revascularization seem to have poor outcome. Pooling of the five available prognostic studies with FDG PET (10–14) revealed a mean death rate of 17% (ranging from 0% to 33%) in 75 medically treated patients who had viable tissue on FDG PET. The main shortcoming of these previous reports lies in the retrospective, non-randomized character of the studies and the limited number of patients per study. In addition, the reasons why patients with viable myocardium did not undergo revascularization are not clear from the studies, and it has been suggested that the high event rate might not be due to viability (progressing to scar tissue) but rather due to the presence of excessive co-morbidity (which might also be the reason why the patients did not undergo revascularization).

The issue of what drives mortality in the medically treated patients is an important one and was the topic of the current study. Forty of 167 medically treated patients died during the median follow-up of 2.1 years, resulting in a comparably high mortality rate (21% per year), as reported in the previous studies. Univariable analysis identified many variables associated with a higher event rate (Table 2), but only age, the presence of LBBB on the ECG, and the extent of mismatch on PET were the variables that remained predictive on multivariable analysis. These observations suggest that co-morbidity does not primarily drive mortality in patients with ischemic cardiomyopathy but, indeed, it is the extent of viable myocardium that does so. In fact, small areas (<20%) of viable myocardium did not affect prognosis significantly, but when the mismatch area exceeded 20% of the myocardium, a steep increase in mortality was observed (Fig. 2). The previous studies did not specifically focus on the extent of viable myocardium that was associated with an increased event rate; these previous studies only showed the increased event rate in the viable, medically treated patients. Di Carli et al. (12) showed that patients with 5% viability of the left ventricle already had a high event rate when medically treated. Still, the mean extent of viability in the medically treated patients was 17 ± 15%, and also, that study was not specifically designed to address what extent of viability is associated with a high event rate.

None of the traditional clinical data (e.g., previous infarction, LVEF, three-vessel disease) remained predictive in the multivariable analysis; this finding is probably related to the fact that the majority of patients in the current study had severely depressed LVEF, frequently secondary to previous infarction, and extensive three-vessel CAD. Moreover, our results confirm previous observations that patients with CAD and concomitant LBBB have increased cardiovascular mortality as compared with patients without LBBB (15). Left bundle branch block is a commonly observed ventricular conduction disturbance occurring in patients with reduced LV function, and it might adversely affect prognosis in different manners. Experimentally induced LBBB causes structural changes such as eccentric hypertrophy and determines unequal synthesis of stress kinases and calcium-handling proteins (16,17). Also, asynchrony in ventricular activation and pressure generation might result in ineffective LV ejection, reduced LV filling time, and worsening of mitral regurgitation (18).

Another important observation in our study was that the extent of scar tissue was not predictive of death. Beanlands et al. (19) demonstrated recently that, besides viability, the extent of scar tissue was an independent predictor of improvement in LVEF after revascularization. Patients with viability demonstrated improvement in LVEF post-revascularization, but the improvement in LVEF was neg-

atively affected by the presence of extensive scar tissue. In that study, however, no survival data were presented. In the current study, it was demonstrated that the extent of scar tissue did not negatively affect survival, but this observation might be due to the fact that the majority of patients had extensive scar tissue.

It should be mentioned that only 41% of the patients used beta-blockers, the same percentage as receiving digoxin. With changing insight in medical therapy, the current percentage of patients with ischemic cardiomyopathy using beta-blockers is expected to be higher.

Study limitations. The same limitation as with all prognostic viability studies applies to the current study: it is non-randomized study, although the patients were prospectively followed-up. A difference in time period since the index MI in patients with and without mismatch was not prospectively assessed.

Conclusions. Positron emission tomography remains a powerful tool for risk stratification of patients with ischemic cardiomyopathy who do not undergo surgical revascularization. Patients with large areas (>20% of the LV) of viable myocardium on PET imaging have a high mortality during follow-up. It is not any viability but, rather, extensive viability that determines prognosis in patients with ischemic cardiomyopathy who are medically treated.

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