Prevalence of Myocardial Viability as Detected by Positron Emission Tomography in Patients With Ischemic Cardiomyopathy

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Background—Detection of myocardial viability is important in patients with ischemic cardiomyopathy. Restoration of blood flow to viable myocardium is associated with improved left ventricular function and improved patient prognosis. However, the prevalence of viable myocardium in patients with ischemic cardiomyopathy is unknown.

Methods and Results—To determine the prevalence of myocardial viability, clinical [13N]ammonia/[18F-deoxyglucose PET studies performed in 283 patients (age, 63±10 years) with ischemic heart disease (mean ejection fraction, 26±8%) were visually analyzed for the presence and extent of viable and nonviable myocardium. The myocardium was divided into 19 segments. The extent of viable myocardium was considered “functionally” significant if ≥5 segments (~25% of the left ventricular myocardium) exhibited a blood flow/metabolism mismatch and “prognostically” significant if 1 to 4 left ventricular segments did so. Of all patients, 41% had no evidence of viable myocardium, 55% had viable myocardium, and 4% had normal blood flow and metabolism within an enlarged left ventricle. Functionally significant viability was found in 27% and prognostically significant viability in 28% of the patients. Multivariate analysis revealed the presence of angina to be the only clinical parameter associated with the presence of functionally significant viability.

Conclusions—Revascularization might improve patient prognosis in 55% and result in improved left ventricular function in 27% of all patients with ischemic cardiomyopathy. (Circulation. 1999;99:2921-2926.)

Key Words: coronary disease ■ viability ■ myocardium ■ tomography ■ cardiomyopathy

Dysfunctional myocardium might exhibit improved contractile performance after revascularization if extensive areas of myocardial viability are present in hyperperfused tissue. However, even small areas of viability might be of considerable prognostic importance. Di Carli et al have recently demonstrated an increased risk for cardiac death if >5% of the left ventricle exhibits dysfunctional but viable myocardium.

The determination of presence and extent of myocardial viability is therefore important for patients with ischemic cardiomyopathy who might benefit from coronary revascularization as an alternative treatment to cardiac transplantation or medical therapy. Numerous studies have documented the value of blood flow/glucose metabolic imaging with PET in determining myocardial viability. However, the prevalence of myocardial viability in patients with ischemic cardiomyopathy is unknown.

The aim of this study was to determine with PET in patients with ischemic cardiomyopathy the prevalence of viable myocardium and to evaluate whether the presence of myocardial viability can be predicted from clinical parameters.

Methods

Study Population

The study population consisted of 283 patients (242 men, 41 women; mean age, 63±10 years) who were referred to the UCLA PET Center between June 1989 and June 1998. After approval by the UCLA Human Subject Protection Committee, clinical data were obtained retrospectively by chart review.

Of the ~700 clinically reimbursed PET studies performed in patients with ischemic heart disease since 1989, 283 were randomly selected for visual interpretation and chart review by pulling ~30 studies per year from a file cabinet. This approach provided us a representative sample of patients who had solid clinical indications for PET viability studies, ie, heart failure symptoms in the setting of ischemic heart disease. Of these patients, 21 (7.4%) had been enrolled in previous clinical PET trials from this institution. To avoid any selection bias, they were not excluded from the present study.

All patients had ischemic cardiomyopathy as documented angiographically and/or by history of myocardial infarctions. All had various degrees of congestive heart failure. Left ventricular ejection fraction, available in 208 patients (73%) from 2-dimensional echocardiography (n=57) or cine ventriculography (n=151) performed within 4±13 months of the PET study, averaged 26±8% (range, 7% to 48%). Coronary angiography, available in 201 patients (71%), revealed single-vessel disease in 8%, double-vessel disease in 22%,
PET Image Acquisition

[$^{13}$N]ammonia and $^{18}$F-deoxyglucose (FDG) were used as tracers of myocardial blood flow and glucose consumption. From January 1989 until December 1996, an ECAT/931 (CTI/Siemens; intrinsic resolution, 6 mm at full width–half maximum [FW–HM]), which acquires 15 transaxial images simultaneously, was used; since January 1997, the CTI/Siemens ECAT/EXACT HR+ (intrinsic resolution, 4.5 mm at FW–HM), which acquires 62 transaxial image planes simultaneously, was used.

After a 20-minute transmission scan, [$^{13}$N]ammonia (10 to 15 mCi) was injected, and 5 minutes later, a 20-minute image of the myocardial [$^{13}$N]ammonia distribution was obtained. Forty to 50 minutes later, 10 mCi of FDG was injected, and after an uptake period of 40 minutes, a 20-minute image of the exogenous myocardial glucose use was acquired.

To obtain high-quality glucose metabolic studies, the patients were studied after an overnight fast. Blood glucose levels were measured before administration of FDG. If serum glucose levels were <120 mg%, 50 g glucose was administered orally. Patients with glucose levels between 120 and 150 mg% were imaged without oral glucose loading. If serum glucose levels were >150 mg%, insulin was administered until serum glucose had declined by ≥20%. Once glucose levels had declined by 20%, FDG was administered intravenously. Patients with insulin-dependent diabetes mellitus were asked to adhere to their regular diet and insulin regimen. Patients on oral antidiabetic medication were asked to remain fasted after midnight and to take their oral antidiabetic medication.

Visual Analysis of PET Images

The left ventricle was divided into 19 segments: the basal, middle, and apical portions of the anterior septum and anterior wall; anterolateral and inferolateral walls; and inferior wall and inferior septum; and the apex as a single myocardial segment. Two readers (Drs Auerbach and Czernin) who were unaware of the patients’ histories consensually graded [$^{13}$N]ammonia and FDG uptake defects on a 4-point scale: 0 = normal, 1 = mildly reduced, 2 = moderately reduced, and 3 = severely reduced.

Myocardium was defined as normal if the [$^{13}$N]ammonia uptake was scored as 0 regardless of FDG uptake. A concordant reduction in [$^{13}$N]ammonia and FDG activity scores was classified as blood flow/metabolism match indicating scar tissue, subsequently referred to as nonviable myocardium. A reduction in [$^{13}$N]ammonia uptake more severe than the reduction in glucose metabolic activity by ≥1 point was defined as a blood flow/metabolism mismatch, subsequently referred to as viable myocardium.

Failure to revascularize viable myocardium of any extent might be associated with poor patient prognosis, whereas only extensive areas or myocardial viability encompassing 20% to 30% of the left ventricular myocardium is associated with functional improvement after revascularization. Therefore, the terms “functionally” and “prognostically” significant viability were introduced as follows: Viability in ≥5 of the 19 myocardial segments (≥26% of the left ventricular mass) was considered functionally significant, and viability found in 1 to 4 left ventricular segments was considered prognostically significant.

Statistical Analysis

All continuous data are presented as mean ± SD. The paired t test was used for comparisons within individuals. Stepwise multiple regression and all-possible subsets regression with Mallow’s $C_p$ criterion were performed to assess the relationships among independent variables and the presence of viability. Additionally, stepwise logistic regression was performed to determine which independent variables might be associated with the presence of viable myocardium. The BMDP statistical software package was used for data analysis. The Wilcoxon rank-sum test was used to compare relative reductions in myocardial blood flow between viable and nonviable myocardium. The chi-square test was used to compare the frequency of possible flow reductions occurring in viable and nonviable myocardium. A value of P < 0.05 was considered statistically significant.

Results

Prevalence of Viability

Of the 283 patients, 116 (41%) exhibited nonviable myocardium, 156 (55%) had viable myocardium of various extents, and 11 (4%) had enlarged but normally perfused myocardium. Functionally significant and prognostically significant viability occurred in 27% and 28% of the study population, respectively (Figure 1). Interestingly, only 21 of the 283 patients (7%) had viable tissue without evidence of additional nonviable myocardium. Viable and nonviable myocardium coexisted in 135 patients (48%). All of the 11 patients with normal blood flow/metabolic patterns had markedly enlarged left ventricles.

Resting Blood Flow and Viability

Thirty percent of all viable segments had mild, 42% had moderate, and 27% had severe reductions in myocardial blood flow. Mild, moderate, and severe reductions were found in 20%, 28%, and 52% of nonviable segments, respectively (all P < 0.0001). Overall, myocardial blood flow was less severely reduced in viable than in nonviable myocardium (1.97 ± 0.76 versus 2.3 ± 0.78, P < 0.0001) (Figure 2). However, there was considerable overlap in the degree of flow reductions between viable and nonviable myocardium.

Clinical Characteristics and Prevalence of Viability

Multiple regression analysis revealed no statistically significant relationship between the presence of viability and any of the following factors: patient age, sex, history of revascularization and myocardial infarction, diabetes mellitus, angina,
Figure 2. Myocardial [13N]ammonia uptake score in viable and nonviable myocardium. Tracer uptake as index of blood flow was more severely reduced in nonviable than viable myocardium (2.3±0.78 vs 1.97±0.76; P<0.0001). Note considerable overlap in relative tracer uptake reductions between nonviable and viable tissue.

angiographic extent of disease, left ventricular size, and left ventricular ejection fraction. Functionally significant viability occurred in 30% of patients with and 35% of those without histories of revascularization, 28% with and 34% of those without histories of infarction, and 27% of patients with and 28% of those without diabetes mellitus (all P=NS).

Logistical regression analysis determined that in patients with anginal symptoms, functionally significant viability was more prevalent than prognostically significant viability (P=0.038). A history of myocardial infarction tended to be associated with nonviable tissue by PET (P=0.051).

Clinical Management Decisions
A clinical management decision was available for 110 patients (39%). Of these, 55 underwent coronary revascularization, 19 had cardiac transplantation, and 36 remained under medical treatment (Figure 3).

Prewascularization and postrevascularization ejection fraction were available in 14 of 25 patients with functionally significant, 4 of 12 patients with prognostically significant viability, and 6 of 18 patients without viable myocardium. They improved significantly only in patients with functionally significant viability (26±8% to 33±9%, P=0.0024), not in those with prognostically significant viability (39±5% versus 40±10%, P=NS) and those without viable myocardium (32±10% versus 33±8%, P=NS). The extent of myocardial viability by visual analysis (ie, the number of myocardial segments exhibiting a blood flow/metabolism mismatch pattern) tended to be correlated with changes in left ventricular ejection fraction after revascularization (r=0.36, P=0.083).

Of the 19 patients who underwent cardiac transplantation, 3 had functionally significant, 5 had prognostically significant, and 11 had no evidence of myocardial viability. Of the 36 patients who remained on medical therapy, 9 had functionally significant, 6 had prognostically significant, and 21 had no evidence of myocardial viability.

Discussion
Coronary revascularization might prognostically benefit all patients with viable myocardium (55%) and result in improvements in left ventricular function in 27% of all patients with ischemic cardiomyopathy.1–5,12

Importantly, myocardial viability cannot be predicted from clinical parameters.

Prevalence of Myocardial Viability
The prevalence of myocardial viability in patients with ischemic heart disease and compromised left ventricular function is unknown. Christian et al13 measured ejection fraction in 86 patients with ischemic cardiomyopathy (mean left ventricular ejection fraction, 39±8%) who underwent revascularization without a specific presurgical viability assessment. Functional improvement was observed in 21% of the patients after revascularization,13 suggesting the presence of extensive areas of presurgical viability.

Using PET, Go et al14 studied 155 patients and observed the blood flow/metabolism mismatch pattern in 29% of patients. In their study, the extent of viable myocardium was considered significant if 12.5% of the left ventricular mass exhibited a blood flow/metabolism mismatch pattern. Because this threshold is lower than the cutoff point for functionally significant viability in the present study, a higher prevalence of viable myocardium would have been expected. However, this previous and the present investigations yielded similar prevalence data. One explanation is that the former study included only patients with a history of myocardial infarction, a clinical parameter that tended to be associated with a lower prevalence of myocardial viability in the present investigation.

Using symptomatic improvement as the study end point, Di Carli et al12 determined that viability encompassing ≥18% of the left ventricular myocardium identified best those patients who exhibited improvements in heart failure symptoms after revascularization. A similar threshold was established by Hausmann et al,15 who used 2-dimensional echocardiography and 201Tl SPECT imaging to predict functional improvement after bypass surgery. However, most studies selecting post-surgical changes in ejection fraction as a study end point used a somewhat higher threshold. For instance, Tillisch et al1 and Louie et al2 demonstrated that 2 of 7 left ventricular segments

Figure 3. Clinical management decisions. Clinical management decision was available for 110 patients. Sixty-eight percent of patients with functionally significant viability underwent revascularization (CABG/PTCA), 24% remained on medical treatment, and 8% went on to heart transplantation (HTX). Of patients with prognostically significant viability, 52% percent were revascularized, 26% were treated medically, and 22% underwent heart transplantation. Thirty-six percent of patients without viable myocardium were revascularized, 42% were treated medically, and 22% underwent cardiac transplantation.
(28.5%) needed to exhibit viability by PET to expect a postsurgical improvement in left ventricular function.

Thus, the current arbitrary definition of "functionally" significant viability (≥5 of 19 segments, or ≈25%) appears to reflect previous reports with reasonable accuracy. This classification was chosen to emphasize that extensive areas of myocardial viability are associated with improvements in contractile function,1,2,6,16,17 higher daily life activity levels, and reduced heart failure symptoms.12 After revascularization, it takes into account that the presence of any amount of myocardial viability might have important prognostic implications: Medically treated viable myocardium is associated with an increased risk of cardiac death or myocardial infarction, as demonstrated by Eitzman and coworkers.5 In their study, 6 of 18 medically treated patients (33.3%) with evidence of viability by PET died during a 12-month follow-up period, and 3 other patients suffered myocardial infarction. In contrast, only 1 of 26 patients with PET evidence of viability who underwent revascularization died, and no myocardial infarction occurred in this subgroup. Consistently, Lee et al4 reported that during a 17±9-month follow-up period, 48% of medically treated patients with evidence of myocardial viability by PET had ischemic cardiac events as opposed to only 8% of those who underwent revascularization. However, these authors did not observe increased mortality in patients with viable myocardium who remained under medical treatment.

Important information was provided by Di Carli et al,2 who concluded that even the presence of small amounts (>5%) of myocardial viability by PET identifies a high-risk subgroup with a poor 1-year survival.

The findings of the present study support the validity of the term "functionally" significant viability. The left ventricular ejection improved only in those patients who had ≥5 viable segments, not in those who had smaller areas or no myocardial viability. Nevertheless, the term "prognostically" significant viability awaits further prospective validation.

In 4% of the patients (n=11), left ventricular enlargement was the only abnormal PET finding. No significant abnormalities in blood flow or glucose use were noted. Importantly, only 4 of these patients underwent additional pharmacological stress studies during intravenous dipyridamole. Three of these patients exhibited stress-induced ischemia. Thus, myocardial stunning might have accounted for the impaired left ventricular function in these patients. However, normally perfused, normometabolic, yet dysfunctional myocardium does not necessarily denote viable tissue (ie, reversible contractile dysfunction). Ventricular remodeling in patients with ischemic or hypertensive heart disease or an additional myopathic component might account for this finding.18,19 In fact, 2 of the 11 patients had histories of ethanol abuse, and 2 others had prior cancer chemotherapy.

Relationship Between Resting Blood Flow and Myocardial Viability

The degree of flow reductions has been proposed as a marker of myocardial viability. Gewirtz et al20 reported that myocardial segments with blood flows <0.25 mL·min⁻¹·g⁻¹ rarely exhibited substantial glucose metabolic activity and were therefore likely to represent scar tissue. Both viable and nonviable myocardium was found in segments with blood flows ranging from 0.25 to 0.39 mL·min⁻¹·g⁻¹. Similarly, Duvernoy et al21 observed that intermediate reductions in relative blood flow discriminated poorly between viable and nonviable myocardium. Go et al22 failed to find any correlation between the relative severity in decreased perfusion and myocardial viability in irreversible perfusion defects.

The present study confirms these previous observations. Relative resting blood flow was significantly lower in nonviable than in viable myocardium. However, the considerable overlap in relative blood flow indicates that relative perfusion imaging without metabolic imaging cannot reliably distinguish between viable and nonviable myocardium.

Relationship Between Clinical Parameters and Myocardial Viability

The present study revealed that the prevalence of myocardial viability is independent of the patient’s sex, age, history of revascularization, diabetes mellitus, extent of coronary artery disease, left ventricular size, or left ventricular ejection fraction. This observation is in agreement with a previous report that failed to demonstrate a significant relationship between myocardial viability and these clinical variables.12,13 However, logistical regression analysis identified the presence of angina as a significant discriminator between functionally and prognostically significant viability. In fact, angina occurred in 38% of patients with extensive areas of viability but in only 18% of those with smaller, prognostically significant amounts of myocardial viability. Thus, the presence of anginal symptoms is related to the presence of functionally significant myocardial viability. A similar trend was observed for history of myocardial infarction, which, not surprisingly, tended to be associated with predominantly nonviable tissue.

Clinical Management Decisions

The presence of myocardial viability influenced the clinical decision making. Sixty-eight percent of patients with functionally significant, 52% of those with prognostically significant, but only 36% of those without viability underwent revascularization (Figure 3). However, the reasons for these clinical management decisions remain poorly understood. Discrepancies between the original clinical and the retrospective interpretation of the PET studies accounted for 4 of the 12 patients with functionally significant viability who remained under medical therapy. Inadequate target vessels, systemic diseases such as cancer or diabetes with renal failure, or patient refusal might have accounted for the others. Conversely, several patients without extensive myocardial viability underwent coronary revascularization. Again, discrepancies between the original clinical and the retrospective interpretations (n=6), a history of angina pectoris (n=10) or stress-induced ischemia on perfusion images (n=3), and aneurysmectomy or concomitant repair of dysfunctional valves (n=4) probably influenced some of these clinical management decisions. It is therefore important to note that not all patients with PET viability are surgical candidates.
conversely that clinical symptoms such as angina result in revascularization even in the absence of PET viability.

**Study Limitations**

This study has several limitations. The current prevalence data might not apply to the general population of heart failure patients; they might be biased toward the most severely compromised patients. Future studies are required to determine the prevalence of viable myocardium in larger groups of patients with coronary artery disease and relatively maintained left ventricular function.

All limitations pertaining to retrospective investigations apply to this study. A clinical history was available in only 60% and the clinical management decision in only 37% of the patients. Changes in left ventricular ejection after revascularization could be determined only in 24 patients. However, the contribution of PET to clinical management decisions was available in 110 patients, representing the largest patient population to date in which this issue has been investigated.

Another limitation is that insufficient clinical outcome data were available to further validate the concept of “prognostically significant” viability. However, 3 independent studies have previously concluded that nonrevascularized viable myocardium of any extent is associated with adverse cardiac events and/or a higher incidence of cardiac death.1-3

The PET studies were interpreted visually. No semiquantitative polar map analysis was performed. This method was chosen because the original visual clinical image interpretation clearly directed patient management toward revascularization, transplantation, or conservative treatment. Nevertheless, because no clinical attempt was made to “quantify” the extent of viability, the imaging studies had to be to be reinterpreted, which raises issues regarding the reproducibility of visual image analysis. To determine whether the original clinical and current image interpretations differed significantly, the extent of viability was estimated from the conclusion of the original clinical readout: Viability was considered functionally significant if revascularization was recommended, prognostically significant if small areas of viability were mentioned but no revascularization was recommended, and absent if no viability was mentioned in the original report. Discrepancies between the original and current interpretations that would have led to different clinical recommendations were found in <5% of all studies, suggesting a low interobserver variability of visual image interpretation.

To further validate the visual image analysis approach, we examined the pathology reports available for 10 of the 19 explanted hearts. These reports described areas of extensive myocardial infarctions but did not provide detailed histopathological evaluations of noninfarcted myocardium. A blood flow/metabolism match pattern predicted the location of myocardial infarctions by pathological inspection in 8 of the 10 patients. In the 2 remaining patients, PET predicted normal or viable tissue, whereas the pathology report revealed nontransmural myocardial infarctions. These results are in keeping with previous studies suggesting a high negative predictive value of the blood flow/metabolism match pattern for myocardial viability.

Further support for the validity of the current approach was recently provided by Duvernoy et al.,23 who demonstrated that polar map analysis and visual analysis yielded similar results for determining myocardial viability. Moreover, the currently reported prevalence of functionally significant myocardial viability of ≈25% is consistent with previous reports.13,14 Finally, the significant improvement in left ventricular ejection fraction after revascularization, observed only in patients with functionally significant viability, validates the current approach.

**Clinical Implications**

Functionally significant viability can be expected in 25% of all patients with ischemic heart disease and left ventricular dysfunction who might be suitable candidates for coronary revascularization.

Most common among the clinical tests for assessing myocardial viability are 2-dimensional echocardiography during inotropic stimulation,24-26 various SPECT imaging protocols using 201Tl as a marker of cell membrane integrity,27-30 and PET with tracers of myocardial blood flow and glucose use.1,17,31-34 These tests differ in diagnostic accuracy and costs. The current data should serve as useful prerequisites for determining the cost-effectiveness of noninvasive tests aimed at identifying those patients with left ventricular dysfunction who might benefit from coronary revascularization.

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