Coronary Blood Flow

Blood Flow–Metabolism Imaging With Positron Emission Tomography in Patients With Diabetes Mellitus for the Assessment of Reversible Left Ventricular Contractile Dysfunction

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OBJECTIVES
The purpose of this study was to evaluate the predictive accuracy of positron emission tomography (PET) blood flow–F-18 fluorodeoxyglucose (FDG) imaging in coronary artery disease (CAD) patients with diabetes mellitus (DM).

BACKGROUND
Positron emission tomography accurately predicts the postrevascularization improvement in left ventricular dysfunction in unselected patients with CAD. In diabetic patients, however, poor myocardial glucose utilization may limit the accuracy of the approach.

METHODS
Forty patients (64 ± 10 years old; 19 with DM = group I; 21 without DM = group II) with reduced left ventricular ejection fraction (LVEF = 29 ± 6%) were studied with N-13 ammonia and FDG PET before coronary revascularization. Studies were performed after intravenous injection of regular insulin (group I) or oral glucose administration (group II). Blood flow–FDG mismatches and matches were identified by polar map analysis in the three vascular territories of the left anterior descending, left circumflex and right coronary artery. Wall motion and LVEF were assessed by two-dimensional echocardiography before and 158 ± 123 days after revascularization.

RESULTS
Of 107 vascular territories analyzed, 46 were classified as mismatch, 29 as match and 32 as normal. The FDG image quality, assessed by F-18 myocardium to blood pool activity ratios, and the predictive accuracy were similar in both groups; presence of a blood flow/FDG mismatch had a sensitivity of 92% (group I) and 94% (group II) and a specificity of 85% (group I) and 79% (group II) for an improvement in regional left ventricular function. A postrevascularization improvement in global left ventricular function was related to the extent of blood flow/FDG mismatch; LVEF increased from 30 ± 7% to 35 ± 7% (p = 0.017) in patients with one mismatch and from 27 ± 4% to 41 ± 7% (p < 0.001) in those with two mismatches.

CONCLUSIONS
The predictive accuracy of blood flow/FDG imaging is maintained in patients with DM when a clinically acceptable study protocol, which guarantees good FDG image quality, is used. The extent of a blood flow/metabolism mismatch is correlated with the magnitude of the postrevascularization improvement in global left ventricular function. (J Am Coll Cardiol 1999;33:1328–37) © 1999 by the American College of Cardiology

More than a decade ago Tillisch et al. (1) demonstrated that a postrevascularization improvement in regional and global left ventricular function could be predicted from patterns of blood flow and glucose utilization as evaluated with positron emission tomography (PET). Subsequent studies confirmed that maintained glucose metabolism in hypoperfused, dysfunctional myocardium, referred to as blood flow–metabolism mismatch, predicts functional recovery with an accuracy ranging from 72% to 95% (1–6). Flow–metabolism patterns therefore yield valuable diagnostic and prognostic information in patients with coronary artery disease (7–9).

Myocardial utilization of exogenous glucose can be visualized with F-18 fluorodeoxyglucose (FDG) and PET. The diagnostic quality of FDG images, and hence the accuracy

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of blood flow–metabolism images for predicting the postrevascularization outcome in left ventricular contractile function depends on myocardial glucose uptake. Typically, glucose is administered orally to stimulate insulin secretion and, thus, to enhance myocardial glucose utilization and FDG uptake. In patients with diabetes mellitus, however, reduced myocardial glucose utilization results in poor FDG uptake and image quality (10,11), which limits the diagnostic accuracy of PET blood flow–metabolism images. Because of the high prevalence of coronary artery disease in diabetic patients (12–14), they represent a substantial fraction of patients in whom identification of viable myocardium is important. Yet, the accuracy of PET blood flow–metabolism imaging has not been determined systematically in this patient group.

To improve the FDG image quality Hicks et al. (15) and Knuuti et al. (16) recommended the hyperinsulinemic–euglycemic clamp. However, the approach is labor intensive and time-consuming and therefore clinically impractical. The aims of the present study were therefore a) to evaluate in patients with diabetes mellitus the clinical and diagnostic utility of a more practical blood flow–metabolism imaging protocol and b) to assess its predictive accuracy on the postrevascularization recovery of regional and global left ventricular function.

**METHODS**

**Study population.** The study population consisted of 40 consecutive patients with coronary artery disease. All patients underwent coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Regional and global left ventricular function was assessed with two-dimensional echocardiography before and after revascularization. Patients were grouped according to presence or absence of diabetes mellitus (Table 1). Group I consisted of 19 patients with previously diagnosed diabetes mellitus; the diagnosis of diabetes mellitus was based on a fasting plasma glucose level of >120 mg/dl. There were 14 male and 5 female subjects with a mean age of 64 ± 11 years. Seventeen patients had non–insulin-dependent (NIDDM) and two patients insulin-dependent diabetes mellitus (IDDM, patients 12 and 19 in Table 1). Group II consisted of 21 patients (19 male, 2 female, mean age 65 ± 9 years) with coronary artery disease but without diabetes (fasting plasma glucose concentrations less than 120 mg/dl).

The two groups were similar in age, gender, New York Heart Association (NYHA) heart failure symptoms, coronary arteriographic findings and left ventricular ejection fraction (LVEF; Table 1). Fourteen patients in group I and 14 in group II had prior myocardial infarctions, coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Heart failure symptoms (NYHA) class III or IV were present in 14 patients in group I and 16 patients in group II. Further, one patient in each group suffered from chronic renal failure.

Coronary angiography was performed within three months, and two-dimensional echocardiography and PET imaging 31 ± 53 days before revascularization. All group I patients had three-vessel disease; in group II, three patients had double-vessel and 18 patients had triple-vessel disease.

**Positron emission tomography.** All patients fasted overnight. Myocardial blood flow and exogenous glucose utilization were determined noninvasively with N-13 ammonia, FDG and a Siemens/CTI ECAT 931/8 or ECAT EXACT HR plus whole body positron emission tomograph (17–19). The images were reconstructed using a Shepp filter with a cutoff frequency of 0.3 cycles per pixel, resulting in an effective in–plane resolution of 10.5 mm at full width at half maximum (17,20). Both patient groups underwent the same study protocol; initial acquisition of transmission images for 20 min was followed by static perfusion imaging for 20 min after intravenous N-13 ammonia (15 mCi) and by static glucose metabolism imaging for 20 min, which began 35 to 60 min after intravenous FDG (10 mCi).

**Patient preparation for FDG imaging.** Plasma glucose was measured immediately before the 20-min transmission scan followed by immediate oral glucose and/or intravenous insulin administration. Baseline plasma glucose levels averaged 86 ± 10 mg/dl (range 60 to 102 mg/dl) in nondiabetic patients. These patients received an average of 55 g (range 40 to 100 g) of glucose orally to stimulate insulin secretion, thereby enhancing myocardial glucose and FDG uptake. In the diabetic patients, plasma glucose averaged 200 ± 87 mg/dl (range 100 to 410 mg/dl; p = 0.0001 vs. nondiabetic). According to our clinical study protocol, diabetic patients were subdivided into two groups—patients with plasma glucose >150 mg/dl and those with plasma glucose ≤150 mg/dl.

In 15 diabetic patients, plasma glucose was >150 mg/dl. Therefore, only (regular) insulin was administered intravenously to enhance the uptake of FDG into myocardium and to accelerate its clearance from blood. Initially 4 IU insulin was injected. Glucose measurements and insulin injections were then repeated every 20 min until plasma glucose levels declined to ≤140 mg/dl or by at least 20%; only at that time was the FDG image acquisition started. These patients received a mean of 6 ± 6 IU insulin intravenously.

In four diabetic patients baseline plasma glucose was ≤150 mg/dl (mean 125, range 100 to 140 mg/dl). Therefore, an initial injection of 2 to 4 IU of intravenous insulin...
was combined with the oral administration of 25 g glucose to avoid hypoglycemia.

**Positron emission tomography image analysis.** The transaxially acquired image sets were reoriented into six short axis cuts which were then assembled into polar maps of the distribution of N-13 ammonia and of FDG in the left ventricular myocardium (17,21). Vascular territories were classified as showing normal or reduced perfusion based on the N-13 ammonia polar maps; N-13 activity concentrations within 2 SDs of the mean of a database of normal measurements were considered normal (17). Extent and

### Table 1. Patient Characteristics, Left Ventricular Function and PET Blood Flow–Metabolism Patterns

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*Excluded from analysis because of graft occlusion or because territory was not revascularized. EF = left ventricular ejection fraction; F = female; LAD = left anterior descending artery; LCX = left circumflex coronary artery; M = male; m = match; mm = mismatch; n = normal; PET = positron emission tomography; RCA = right coronary artery; RWM = regional wall motion.

### Table 1. Patient Characteristics, Left Ventricular Function and PET Blood Flow–Metabolism Patterns
severity of perfusion defects were determined for each of the three coronary vascular territories and the entire left ventricular myocardium; extent reflects the hypoperfused area as the fraction of pixels of a vascular territory or the entire left ventricle, and severity reflects the average percent reduction of the relative N-13 ammonia uptake less than 2 SDs below the normal mean (17).

The FDG uptake was normalized to myocardium with normal blood flow and a difference polar map (N-13 ammonia–FDG) created for comparison with a normal database (17). Perfusion defects were then subclassified into those with blood flow–metabolism mismatches and matches. Mismatch was defined as relative difference between the relative F-18 and N-13 concentrations greater than 2 SDs above the normal mean and match as a concordant reduction of both N-13 and F-18 activity by more than 2 SDs below the normal mean (17). A vascular territory was considered to exhibit the match or mismatch pattern only if more than 15% of that territory was hypoperfused (22).

To assess the FDG image quality, regions of interest (50 pixels each) were placed in the left ventricular cavity in the center of the blood pool and in left ventricular segments with normal myocardium (based on normal resting perfusion assessed by N-13 ammonia) on midventricular short-axis slices. Counts per pixel were averaged, and a myocardium to blood pool activity ratio was calculated by dividing the myocardial by the blood pool activity counts. Regions of interest (ROIs) were not placed in the interventricular septum or in match territories to avoid artificially elevated (right ventricular activity spillover into the septum) or decreased (match) myocardium to blood pool activity ratios.

The diagnostic image quality was also assessed by visual inspection by three independent readers (C.K.H., D.H.M., J.C.) who were blinded to clinical data.

Two-dimensional echocardiography. Regional wall motion was evaluated with two-dimensional echocardiography from four- and two-chamber, and apical long-axis views. Echocardiograms were analyzed by clinical cardiologists who were blinded to the PET data. Regional wall motion was graded in six myocardial segments (anterior, anterolateral, inferolateral, inferior, inferoseptal, anteroseptal) on a 4-point scale where 0 = normal, 1 = mild hypokinesis, 2 = severe hypokinesis and 3 = akinesis or dyskinesis. The six myocardial segments were assigned to one of the three vascular territories as follows: the anteroseptal and anterior wall to the left anterior descending coronary artery, the anterolateral and inferolateral wall to the left circumflex and the inferior and inferoseptal wall to the right coronary artery. Wall motion scores in each of the two segments per vascular territory were averaged. The left ventricular ejection fraction was determined with a standard echocardiography package using the Simpson rule (23). Follow-up echocardiography was performed 156 ± 118 (range 25 to 365) days after revascularization in group I and 160 ± 130 (range 25 to 380) days after revascularization in group II (p = NS). Changes by at least one grade in the motion score in a coronary vascular territory were considered significant.

**Statistical analysis.** Mean values are given with SD. Mismatch segments with functional improvement after revascularization were considered as true positive and those without improvement as false positive. Likewise, segments with match and without functional improvement were considered as true negative and those with functional improvement as false negative. Sensitivity, specificity, predictive values and accuracy were calculated (24). Dysfunctional segments with normal blood flow were treated separately, as their functional outcome may be related to the underlying pathophysiologic mechanism (see Discussion).

Comparison of continuous data within one group was performed using Student t test for paired data, comparisons between groups by unpaired t test or, for comparisons between more than two groups, by analysis of variance (ANOVA) followed by Bonferroni’s modified t test. Nonparametric testing (Fisher exact test) was used for comparison of sensitivity, specificity, accuracy and number of mismatches, matches and normal territories between groups. Nonparametric testing (chi-square, runs test) was also employed a) to evaluate whether presence of a certain blood flow–metabolism pattern in one coronary territory was independent of blood flow and metabolism in the other territories in a given patient and b) to assess potential trends and correlations of postrevascularization changes in wall motion between the three coronary vascular territories in each patient. Regression analysis employed nonweighted least-square fitting. A p value of <0.05 was considered significant.

**RESULTS**

**Effects of glucose load and insulin administration.** Plasma glucose levels declined in group I patients to 136 ± 38 mg/dl (range 75 to 200) after insulin injection (p < 0.05 vs. baseline) and were similar to those in group II after oral glucose administration (139 ± 20 mg/dl) (Fig. 1).

The time from oral glucose administration (in nondiabetic patients) or first insulin injection (in diabetic patients) to the beginning of the FDG PET imaging was similar for both groups (121 ± 32 min in group I vs. 111 ± 21 min in group II, p = 0.22).

**F-18 Fluorodeoxyglucose PET image quality.** The diagnostic quality of the FDG images was considered sufficient in all studies by the three independent readers. This is also reflected by comparable F-18 myocardium to blood pool activity ratios for both patient groups (2.70 ± 0.74 in group I and 3.09 ± 0.79 in group II, p = NS). The myocardium to blood pool ratios in the two patients with IDDM were 2.9 and 3.3 respectively, and thus were similar to those observed in NIDDM patients.
Coronary revascularization and regional wall motion analysis. In group I, all patients underwent coronary artery bypass surgery (CABG). The mean number of grafts per patient was 4.2 ± 0.9. One patient had mitral valve replacement, another one aneurysmectomy in addition to bypass surgery. In group II, 18 patients underwent coronary artery bypass surgery; the mean number of grafts per patient was 4.1 ± 0.9. Two patients had aneurysmectomy or endoaneurysmorrhaphy in addition to bypass surgery. In one of these patients (Table 1, number 10), the postsurgical coronary angiogram revealed occlusion of the left anterior descending artery graft (excluded from analysis), whereas the other graft was patent. Two patients had single-vessel percutaneous transluminal coronary angioplasty only, and one patient had angioplasty of the left anterior descending artery and the left circumflex coronary artery. The time interval between blood flow–FDG PET and coronary revascularization was similar for both study groups (25 ± 32 vs. 20 ± 43 days, p = NS).

There were a total of 120 coronary vascular territories (three per patient). Eight territories exhibited normal wall motion and normal perfusion; these were excluded from analysis. Of the remaining 112 territories with abnormal wall motion, one hypokinetic territory was excluded because of postoperative graft occlusion (see above) and four other territories were excluded because they had not been revascularized.

The remaining 107 territories, that is, 53 in group I and 54 in group II, were analyzed (Fig. 2). In group I, 9 territories showed akinesis, 32 severe hypokinesis and 12 mild hypokinesis. In group II, 6 territories showed akinesis, 42 severe hypokinesis and 6 mild hypokinesis (Table 1). Seventy-five of the 107 dysfunctional territories had abnormal resting perfusion on polar map analysis; the extent of perfusion defects in these 75 territories averaged 57 ± 19% per coronary artery territory in group I and 61 ± 25% in group II (p = NS). The extent of the preoperative perfusion defects was similar for territories with match or mismatch pattern (51 ± 26% vs. 51 ± 22%; p = NS) and tended to correlate with the severity of wall motion abnormalities (r = 0.3, p = 0.04). Neither extent nor severity of perfusion defects correlated with the magnitude of a postoperative improvement in regional wall motion (r = 0.04, p = NS).

The presence of a certain pattern of blood flow and metabolism in a given vascular territory was independent of blood flow–metabolism patterns in the other two vascular territories of the same patient (p = 0.24, NS).

Predictive accuracy of myocardial blood flow–metabolism patterns. POSTSURGICAL CHANGES IN WALL MOTION ABNORMALITIES. A blood flow–metabolism mismatch was present in 46 territories (in 27 patients), whereas 29 territories (in 19 patients) exhibited a match (Fig. 2). Forty mismatch territories (in 25 patients) showed improvement in regional wall motion after revascularization, whereas six (in five patients) did not. Thus, the overall sensitivity and specificity of the mismatch pattern for an improvement in regional wall motion were 93% and 81%, respectively. Positive and negative predictive values were 87% and 90%, and the overall predictive accuracy of the test
was 88%. The mean extent of a mismatch in a given vascular territory was similar in both groups (45 ± 22% in group I vs. 58 ± 31% in group II; p = NS). No trend or correlation was found regarding postrevascularization changes in wall motion between the three coronary vascular territories per patient, that is, changes in wall motion in one territory did not predict similar changes in the other two coronary territories in a given patient (p = 0.27 and 0.67, respectively).

In the group I (diabetic) patients, there were 25 territories (in 15 patients) with flow–metabolism mismatches and 13 (in 10 patients) with matches (Fig. 3A). Postoperatively, regional wall motion improved in 23 territories (in 14 patients) with mismatch but only in two territories (in two patients) with match. Sensitivity and specificity of the flow–metabolism mismatch pattern for predicting the postsurgical outcome in myocardial dysfunction were 92% and 85%, respectively. Positive and negative predictive values were 92% and 94% with an overall predictive accuracy of 86%.

In the group II (nondiabetic) patients, 37 territories were analyzed: 21 territories (in 11 patients) with a blood flow–metabolism mismatch and 16 territories (in 10 patients) with a match pattern. Regional wall motion improved following revascularization in 18 territories, 17 of them with a mismatch pattern (in 11 patients) and one with match (Fig. 3B). Wall motion remained unchanged or deteriorated in 19 territories. Four had a blood flow–metabolism mismatch, and 15 had a match. Two patients in this group (numbers 13 and 19) underwent aneurysmectomy or endoaneurysmorrhaphy in addition to coronary revascularization. Postsurgically, the respective mismatch territories demonstrated complete or almost complete recovery of wall motion. Sensitivity and specificity of the mismatch pattern for an improvement in regional wall motion were 94% and 79%, respectively. Positive and negative predictive values were 81% and 94% with an overall predictive accuracy of 86%.

Sensitivity, specificity, predictive values and accuracy of the mismatch pattern for functional improvement after coronary revascularization did not differ between group I and group II patients.

**CHANGES IN GLOBAL LEFT VENTRICULAR FUNCTION.** For the whole patient population the left ventricular ejection fraction improved significantly from 29.5 ± 5.9% to 37.0 ± 8.4% (p < 0.01). The improvement was similar in group I and group II patients (p < 0.01 for both; Table 1).

The amount of reversibly dysfunctional myocardium appears critical for a postoperative improvement in global left ventricular function. This study found a linear correlation between the extent of mismatch and the postsurgical improvement in left ventricular function (y = 6.5x – 0.6, r = 0.56, p = 0.0017). As depicted in Figure 4, the left ventricular ejection fraction improved in patients with one mismatch (n = 13) by 18% from 30.0 ± 6.8% to 35.3 ± 5.9% (p = 0.017), in those with two mismatches (n = 12) by 51% from 27.1 ± 4.4% to 40.8 ± 7.3% (p = 0.0001) and in those with three mismatches (n = 3) by 53% from 30 ± 10% to 46 ± 10% (p = 0.012).

**Dysfunctional myocardium with normal blood flow and glucose metabolism.** As shown in Figure 2, there were 32 territories (15 in group I and 17 in group II) with mild to moderate hypokinesis (n = 31) or akinesia (n = 1) but normal blood flow and glucose metabolism. After revascularization, eight of these territories showed functional improvement; 24 demonstrated no change (n = 21) or worsening (n = 3) in regional wall motion. The lack of functional improvement was not related to the time of
follow-up (181 ± 126 days vs. 131 ± 120 days, p = 0.24) or any demographic parameter. Thus, blood flow–metabolism imaging did not predict the postsurgical outcome of hypokinetic or akinetic myocardium with normal resting perfusion.

**DISCUSSION**

In the present study, the predictive accuracy of PET myocardial blood flow–FDG imaging for an improvement in left ventricular dysfunction after coronary revascularization was similar in diabetic and nondiabetic patients and in agreement with early observations in unselected patient populations. The study demonstrates therefore that the predictive accuracy of myocardial blood flow–FDG imaging by PET is maintained in patients with diabetes mellitus when an appropriate study protocol is used. F-18 Fluoro-deoxyglucose images of good diagnostic quality can be obtained in diabetic patients without the need for a glucose–insulin clamp by using small intravenous doses of regular short-acting insulin. Thus, PET imaging of blood flow and glucose metabolism can be used to identify reversibly dysfunctional myocardium in patients with diabetes mellitus.

**Methodological considerations.** Diabetic patients characteristically demonstrate FDG images of poor diagnostic quality because of high blood pool and low myocardial tracer activity, resulting in a high proportion of uninterpretable studies (10,25).

**EUGLYCEMIC HYPERINSULINEMIC CLAMP.** Previously, the euglycemic–hyperinsulinemic clamp technique has been proposed for improving the image quality of cardiac FDG studies. The clamp technique aims at achieving stable plasma glucose concentrations, a prerequisite for quantitative analysis of glucose utilization, but also improves myocardium to blood pool F-18 activity ratios and hence the FDG image quality (15,16). Preliminary data suggest that with the clamp technique comparable predictive accuracies of blood flow–FDG imaging can be achieved for diabetic (70%) and nondiabetic patients (67%) (26). However, the technical demands of the clamp method may preclude its routine use in the clinical setting.

**NICOTINIC ACID DERIVATIVES.** Alternatively, the nicotinic acid derivative acipimox has been used to improve myocardial FDG image quality (27–29). The agent inhibits lipolysis and lowers circulating free fatty acid levels, which in turn promotes myocardial glucose uptake (29–31). In a small number of patients, Knutti et al. (27) compared myocardial glucose uptake during glucose–insulin clamp and after oral administration of acipimox. In patients with NIDDM, acipimox and the clamp technique reduced plasma glucose concentrations to similar levels. Image quality and identification of regions as normal, match, or mismatch were similar with both techniques. In eight nondiabetic patients, Bax et al. (28) compared FDG images obtained with single photon emission computed tomography after acipimox, after oral glucose loading and using the clamp technique. Again, both the clamp technique and acipimox achieved similar image quality, and both were slightly superior to oral glucose loading. However, acipimox is not widely available in many countries. Use of another more widely available nicotinic acid derivative, niacin, which lowers plasma free fatty acids and enhances myocardial glucose uptake and metabolism, does not yield superior image quality compared with oral glucose load or insulin injections (32). More important, no study to date has systematically explored whether the reported improvement in FDG image quality with acipimox translates into a superior predictive accuracy of FDG imaging for the improvement in regional and global left ventricular dysfunction.

**BOLUS INSULIN INJECTION.** The current study examined the feasibility of another approach for enhancing myocardial FDG uptake, that is, titration of plasma glucose levels with small intravenous doses of regular, short-acting insulin (10,11). As the results demonstrate, the approach yielded FDG images of good diagnostic quality. Myocardium to blood pool activity ratios in diabetic patients were similar to those in nondiabetic patients. In addition, the time interval from study initiation to FDG image acquisition was not longer for diabetic than for nondiabetic patients, implying that the approach is feasible in the clinical setting.

The concept of bolus insulin injections is not new (33). However, no systematic comparison of image quality and predictive accuracy of blood flow–metabolism imaging between diabetic and nondiabetic patients has been reported previously. Hence, the current study is the first to document that the presence of diabetes mellitus per se does not compromise the predictive accuracy of blood flow–metabolism mismatch patterns when an appropriate study protocol is used, and that clinical FDG imaging can be performed without using the rather labor-intensive glucose–insulin clamp technique; positive and negative predictive value and the predictive accuracy of the mismatch pattern for a recovery of left ventricular dysfunction were similar in diabetic and nondiabetic patients and consistent with data previously reported in unselected patient populations (1–6,34). The proposed protocol for clinical FDG imaging might be of even greater importance because many centers are now starting to employ FDG single photon emission computed tomography imaging for the assessment of myocardial viability.

**STUDY POPULATION.** The study population is representative of that referred consecutively to the PET clinic for the assessment of myocardial viability. There were only two patients with IDDM; 17 patients had NIDDM. This distribution of diabetic patients is consistent with the prevalence of diabetes mellitus in the United States. Insulin-dependent diabetes occurs in approximately 10% of the diabetic population; NIDDM is present in the remaining
90% (35,36). The small number of patients with IDDM precludes a meaningful statistical comparison between both types of diabetes. However, the present data suggest that the proposed standardization protocol is equally effective in patients with NIDDM and with IDDM.

**Predictive accuracy of blood flow–metabolism imaging.** The predictive accuracy of the blood flow–metabolism mismatch pattern in the current study compares well with that in previous reports (1–6,34). Nevertheless, several reasons may account for false positive studies, that is, a lack of functional improvement in segments with mismatch. First, ventricular function after bypass surgery recovers only slowly, sometimes over a period of several months (37–39). Thus, measures of outcome are critically related to the time of follow-up. However, the lack of functional recovery in the present study was not related to the time of echocardiographic follow-up, which was similar for patients with and without functional improvement (196 ± 134 days vs. 122 ± 57 days, p = 0.15). Echocardiography was performed in two patients on day 25 after revascularization; both demonstrated a significant improvement at that time. Also, in 14 of 15 patients with more than one mismatch, most territories showed functional improvement. Differences in follow-up time periods are therefore unlikely to account for the lack of functional recovery in some mismatch segments.

However, possible differences in the magnitude and extent of structural alterations between territories with and without improvement in contractile function cannot be excluded with certainty. For instance, histomorphologic studies have shown that the extent of fibrotic tissue in a given myocardial segment is directly related to the magnitude of recovery of contractile function (40,41). Other factors such as the fraction of abnormal myocytes also affect magnitude and possible time course of the functional recovery (40,42,43).

**Dysfunctional myocardium with normal perfusion and glucose metabolism.** Thirty-two territories exhibited normal perfusion and FDG utilization despite abnormal regional wall motion; mild to moderate hypokinesis was noted in 31 territories and akinesia in one territory. Only eight (25%) territories had improved wall motion after revascularization. These findings could reflect either ventricular remodeling or repetitively stunned myocardium. Ventricular remodeling is a dynamic process that is initiated by a loss of contractile tissue due to myocardial infarction or chronic coronary artery disease. Subsequently, the excessive workload and compensatory hypertrophy of the residual viable tissue can lead to structural and functional alterations of the remote myocardium (44,45). It is possible that in the current patient population with end-stage coronary artery disease and severely impaired left ventricular function a number of segments with normal blood flow and metabolism did in fact represent remodeled myocardium. It is currently unknown whether such remodeled myocardium can undergo structural and functional improvements after revascularization. Alternatively, dysfunctional myocardium with normal blood flow at rest might also result from repeated stunning (34,46–48). In this scenario, coronary revascularization prevents further ischemic episodes and allows recovery of contractile function. Demonstration of stunning as a possible explanation would have required an additional stress perfusion study, which was not performed in the current patient population. Nevertheless, because of the severity of coronary artery disease in our study population, stunning is likely to account at least in some segments with normal and perfusion metabolism at rest for the reversible dysfunction. The current findings imply that PET images of blood flow and metabolism acquired only at rest do not elucidate mechanisms of contractile dysfunction and do not discriminate fully between reversible and irreversible dysfunction in normally perfused myocardium.

**Study limitations.** The present study has some limitations. It was performed retrospectively, and only those patients who eventually underwent coronary revascularization were included. However, several studies have shown that a significant percentage of patients with viable myocardium do not undergo coronary revascularization (7–9,49,50). This is because the presence of viable myocardium is only one of several criteria that determine the therapeutic approach.

Second, the majority of the group I patients in the current study had NIDDM. Further evaluation of the proposed standardization approach seems warranted in those with IDDM.

Third, potential misalignments between PET and echocardiographic images cannot be excluded entirely, yet data for the overall accuracy of the test are in concordance with previous reports. We chose rather large myocardial regions of interest, that is, the three coronary vascular territories, which would diminish the occurrence of major misalignments between PET and echocardiography data.

Last, PET and echocardiography were performed within 4 weeks of each other. Nevertheless, it is reasonable to expect that the PET data do reflect myocardial blood flow and glucose utilization also at the time of echocardiography, because relevant changes are unlikely to occur within 4 weeks in patients with chronic coronary artery disease. Specifically, none of the patients experienced a change in his clinical status between the two studies. In contrast, the time between PET and coronary revascularization varied between one day and seven months and subsequent ischemic events might have altered the PET results. Yet, the majority of patients underwent bypass surgery within 1 month’s time, and three of four patients undergoing revascularization more than 120 days after PET died in fact show an improvement in regional and global left ventricular function.

**Clinical implications.** Our results indicate that blood flow–metabolism imaging with PET accurately predicts the outcome of myocardial dysfunction after coronary revascularization in patients with diabetes mellitus. Good FDG
image quality can be achieved using a clinically feasible and practical protocol with intravenous administration of small doses of regular insulin titrated against plasma glucose levels. Using this approach, the predictive accuracy of blood flow–metabolism patterns for the postrevascularization outcome of regional wall motion abnormalities is preserved. Further, the extent of a blood flow–metabolism mismatch is directly related to the magnitude of postsurgical improvement in global left ventricular function.

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