Delineation of Myocardial Viability with PET

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Relative flow and metabolic imaging (the "mismatch pattern") with PET have been proposed to identify the presence of viable myocardium in patients with ischemic left ventricular dysfunction. Yet, optimal criteria to identify dysfunctional but viable myocardium and predict significant functional improvement have not been fully defined. **Methods:** Dynamic PET imaging with ^{13}N-ammonia and ^{18}F-deoxyglucose to assess absolute myocardial perfusion and glucose uptake was performed in 25 patients (20 men, 5 women; mean age 57 ± 12 yr, range 30–72 yr) scheduled for coronary revascularization because of coronary artery disease, anterior wall dysfunction and mildly depressed left ventricular ejection fraction (49% ± 11%). Global and regional left ventricular function was evaluated by contrast left ventriculography at baseline and after revascularization. **Results:** As judged from the changes in end-systolic volume and resting anterior wall motion before and after revascularization, 17 patients with improved wall motion score and decreased end-systolic volume were considered to have viable myocardium, whereas 8 patients with either no change in regional wall motion or increased end-systolic volume were considered to have nonviable myocardium. Before revascularization, viable myocardium showed higher absolute myocardial blood flow (77 ± 20 versus 51 ± 9 ml (min · 100 g)$^{-1}$, p = 0.004) and absolute regional myocardial glucose uptake (36 ± 14 versus 24 ± 11 μmole (min · 100 g)$^{-1}$, p = 0.04) than nonviable myocardium. **Conclusion:** This study identified absolute myocardial blood flow and normalized glucose extraction as the most powerful predictors of the return of contractile function after coronary revascularization in patients with ischemic anterior wall dysfunction.

Key Words: myocardial viability; myocardial metabolism; positron emission tomography; myocardial blood flow

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Accurate identification of viable but jeopardized myocardium is of paramount importance for appropriate management and risk stratification of patients with ischemic heart disease. Studies with animals (*1*) and humans (*2–5*) demonstrate that prolonged regional contractile dysfunction, due to ischemia, does not always arise from irreversible tissue damage and can be reversed by restoration of blood flow. Jeopardized myocardium that manifests such an improvement in function after revascularization is considered viable, in contrast to persistently dysfunctional myocardium that is considered nonviable and usually the consequence of a transmural infarction.

Multiple modalities have been proposed to identify jeopardized but viable myocardium. Because regional contractile ischemic dysfunction reflects underlying alterations of myocardial perfusion and metabolism, flow and metabolic imaging with PET have generated much attention. Results of earlier studies in patients with left ventricular dysfunction due to chronic coronary artery disease have indicated that PET with ^{18}F-deoxyglucose (*6–8*) or with ^{11}C-acetate (*9,10*) accurately predicted the presence of viable myocardium within dysfunctional areas. Recent observations have also suggested that PET could identify subgroups of patients at risk of subsequent cardiac morbid events if treated only medically (*11*). There are situations, however, where flow and metabolic imaging with PET may not have the same accuracy.

In patients with recent myocardial infarction, estimates of glucose uptake by PET overestimate the capacity for recovery of function after revascularization (*9,12,13*). Similarly, assessment of oxidative metabolism with ^{11}C-acetate is of limited value shortly after infarction because of the time-dependence of the return of mitochondrial function after ischemia (*14*), and because it does not provide any additional information over the measurement of absolute levels of myocardial blood flow (*15,16*). Obviously, the flow and metabolic determinants of myocardial viability are multiple and complex, making it difficult to determine which of the variables has the best accuracy if the others are not considered simultaneously in a multivariate analysis.

Accordingly, this study was designed to evaluate the flow and metabolic correlates of myocardial viability in patients with chronic anterior wall dysfunction due to severe left anterior descending (LAD) coronary artery disease more comprehensively. Specifically, we took advantage of the combined qualitative and quantitative capabilities of PET to assess, in both relative and absolute terms, regional myocardial glucose metabolism and myocardial blood flow. All flow and metabolic data were incorporated in a multivariate discriminant model to determine the best predictors of the return of function after revascularization. Because indices of global left ventricular systolic function are important prognostic indicators in patients with isch-

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TABLE 1A
Clinical and Angiographic Data before and after Revascularization

Patient no.	Age/Sex	Previous MI	% Stenosis LAD	LC	RCA	RWMS Pre	RWMS Post	EDI Pre	EDI Post	ESI Pre	ESI Post	EF Pre	EF Post	Revasc
Patients with Viable Myocardium														
1	63/F	No	100	—	—	4	3	97	72	45	26	54	64	PTCA
2	63/F	Yes	100	—	—	5	1	NA	NA	NA	NA	53	69	PTCA
3	72/M	No	100	—	70	5	3	104	96	50	39	52	59	PTCA
4	51/F	No	100	—	—	4	1	NA	NA	NA	NA	59	75	PTCA
5	64/M	Yes	100	—	—	5	3	120	112	60	46	50	59	PTCA
6	46/M	No	100	—	—	4	2	101	114	42	41	58	64	PTCA
7	63/F	Yes	100	—	—	5	3	123	156	81	66	34	58	PTCA
8	62/M	No	100	70	—	3	0	113	111	40	30	65	73	CABG
9	46/F	No	100	—	—	3	1	134	105	50	32	63	70	CABG
10	68/M	No	85	—	—	3	2	150	118	62	56	59	53	CABG
11	62/M	No	100	—	—	5	2	NA	NA	NA	NA	38	63	PTCA
12	51/M	No	100	—	—	4	0	NA	NA	NA	NA	60	75	PTCA
13	69/M	No	100	75	—	4	2	123	80	54	22	56	73	CABG
14	62/M	Yes	90	60	—	7	5	100	100	71	50	29	50	PTCA
15	42/M	No	100	—	—	4	1	70	56	38	16	46	71	PTCA
16	30/M	Yes	100	—	100	3	1	108	127	47	49	56	61	CABG
17	49/M	Yes	100	75	100	5	4	142	107	102	69	28	36	PTCA
mean ± s.d.						5 ± 1	2 ± 1	114 ± 21	103 ± 25	57 ± 18	40 ± 17	51 ± 12	63 ± 18	
Patients with Nonviable Myocardium														
18	66/M	Yes	90	—	75	6	6	101	130	60	83	41	36	PTCA
19	65/M	Yes	90	—	100	5	5	120	169	71	97	41	43	PTCA
20	38/M	Yes	90	—	—	5	7	119	146	63	66	47	55	PTCA
21	65/M	Yes	90	—	60	4	3	97	119	37	49	62	59	PTCA
22	67/M	Yes	90	60	—	5	4	116	150	70	88	40	41	CABG
23	39/M	Yes	100	—	—	9	10	171	219	122	185	29	16	CABG
24	65/M	Yes	90	—	—	5	7	118	87	51	57	57	34	PTCA
25	62/M	Yes	90	—	—	4	4	120	114	60	46	50	60	PTCA
mean ± s.d.						6 ± 2	6 ± 3	120 ± 22	142 ± 40	67 ± 25	84 ± 45	46 ± 11	43 ± 15	

CABG = bypass surgery; Cx = circumflex artery; EDI (ml/m^2) = end-diastolic volume index; EF (%) = ejection fraction; ESI (ml/m^2) = end-systolic volume index; LAD = left anterior descending coronary artery; NA = not available; MI = myocardial infarction; Pre/Post = before and after revascularization; PTCA = balloon angioplasty; Revasc = revascularization procedure; RCA = right coronary artery; RWMS = regional wall motion score. There was a statistically significant difference in baseline left ventricular function between the two groups. No statistical analysis was applied to the differences in left ventricular function after revascularization, which are built in by the study design.

emic left ventricular dysfunction, improvement in both regional and global left ventricular function was required to identify the presence of viable myocardium (*17*).

METHODS

Patients

The individual clinical characteristics of the patients are summarized in Tables 1A and 1B. The total study population consisted of 25 nondiabetic patients (20 men, 5 women; mean age 57 ± 12 yr, range 30–72 yr) with chronic left anterior wall dysfunction and well-defined coronary anatomy. The baseline PET data of 13 patients have been included in previous reports from our group (*15,18*). By reviewing all diagnostic coronary angiograms performed at two clinical sites, we prospectively selected patients having isolated severe anterior wall dysfunction due to proximal (LAD) coronary artery disease. Fourteen patients had sustained a previous anterior myocardial infarction, the most recent occurring 11 days before the tomographic study. Subsequent to the PET study, all patients underwent complete coronary revascularization. The decision to revascularize was based on clinical criteria and not on the results of the PET study. Coronary artery bypass surgery (CABG) was performed in seven patients, with the use of the internal mammary artery to graft the LAD, and percutaneous transluminal coronary angioplasty (PTCA) was performed in the remaining 18 patients. The adequacy of revascularization was based on the results of the follow-up angiographic study, performed prospectively in every patient 6 to 9 mo after revascularization. This study protocol was approved by the Ethical Committee of our institutions and no complications resulted from any part of the study.

Cardiac Catheterization

Selective coronary arteriography and left ventriculography were performed from the femoral approach an average of 17 days before the PET study (range 1–40 days) and again 6 to 9 mo after revascularization. Significant disease was defined as a greater than 70% luminal diameter stenosis in any major coronary branch. Sixteen patients showed complete occlusion of the proximal LAD. The remaining nine patients had severe proximal LAD stenosis (75%–90% luminal diameter stenosis). Fifteen patients had single-vessel disease, nine patients had two-vessel disease, six of whom had right coronary and three left circumflex coronary

TABLE 1B
Flow and Metabolic Data

Patient no.	MBF	rel NH_3	rMGU	rel FDG	FDG/NH	rMGU/MBF
Patients with Viable Myocardium						
1	99	91	19	135	1.49	0.19
2	67	57	41	138	2.46	0.61
3	75	80	63	98	1.17	0.84
4	45	34	26	182	6.07	0.58
5	49	69	30	61	0.90	0.61
6	102	80	47	86	1.10	0.46
7	93	58	14	101	1.53	0.15
8	57	88	32	91	1.03	0.56
9	72	67	41	101	1.50	0.57
10	110	81	41	109	1.34	0.37
11	90	89	30	82	0.91	0.33
12	62	69	57	100	1.47	0.92
13	96	82	37	119	1.45	0.39
14	73	50	22	107	2.26	0.30
15	89	85	51	96	1.13	0.57
16	87	75	41	91	1.20	0.47
17	49	57	23	96	1.75	0.47
mean ± s.d.	77 ± 20	71 ± 16	36 ± 14	105 ± 27	1.69 ± 1.21	0.49 ± 0.20
Patients with Nonviable Myocardium						
18	37	39	32	42	1.11	0.86
19	50	71	27	77	1.08	0.54
20	45	71	15	81	1.16	0.33
21	56	61	23	149	2.45	0.41
22	56	52	28	112	2.17	0.50
23	48	46	3	137	3.01	0.06
24	68	55	37	33	0.60	0.39
25	47	50	25	98	1.92	0.53
mean ± s.d.	51 ± 9	56 ± 11	24 ± 11	91 ± 41	1.69 ± 0.83	0.45 ± 0.23

FDG/NH = mismatch ratio; MBF ($ml \cdot min^{-1} \cdot 100\ g^{-1}$) = myocardial blood flow; rel FDG (%) = relative FDG uptake; rel NH3 (%) = relative ammonia uptake; rMGU ($\mu mole\ min^{-1} \cdot 100\ g^{-1}$) = regional myocardial glucose uptake. Units of rMGU/MBF are μmole/ml.

artery disease. Only one patient had three-vessel disease. None of the patients had left main stenosis.

Contrast left ventriculography, in the 30° right anterior oblique projection, was performed in every patient. Left ventricular volumes and ejection fraction were measured from the first well-opacified sinus beat, excluding premature depolarization and the subsequent sinus beat. Left ventricular volumes were calculated at end-diastole (R wave of the electrocardiogram) and end-systole (minimal volume) using a standard Simpson's method. Regional ventricular wall motion was reviewed by two experienced observers blinded to the clinical and PET data. Each ventricular silhouette was divided into five segments (anterobasal, anterolateral, apical, inferior and posterobasal). Regional wall motion in each segment was defined as hyperkinetic (−1), normal (0), hypokinetic (1), akinetic (2) or dyskinetic (3). A regional wall motion score for the LAD-dependent segments was calculated by summing the two anterior and apical segments.

As judged from angiographic analysis, dysfunctional myocardium at baseline was defined as viable if the wall motion score improved by at least one full grade and if end-systolic volume decreased after revascularization; it was defined as nonviable if regional wall motion did not improve and/or if end-systolic volume increased after revascularization. Changes from dyskinesis to akinesis were not considered an improvement.

PET

Imaging was performed an average of 18 days (range 1–55 days) before coronary revascularization. Acquisitions were obtained with an ECAT III (CTI, Knoxville, TN) one-ring tomograph, the characteristics of which have been previously described (*19*). Measurements were performed with a stationary ring and images were reconstructed with an inplane resolution of 8 mm FWHM. The collimator aperture was set at 30 mm, resulting in a slice thickness of 15 mm FWHM. Regular calibration of the tomograph versus a well counter was performed by measuring a uniform cylindrical phantom (diameter 20 cm) filled with a solution of ^{68}Ge. All patients were studied after overnight fasting. To standardize the dietary state and enhance myocardial glucose uptake, a venous line was inserted in the antecubital vein and was continuously perfused using a 10% dextrose in water solution (15 μmole/kg/min). Each patient was carefully positioned in the tomograph. Serial transmission scans, at different levels, were obtained to allow subsequent correction for photon attenuation. All transmission scans were viewed prior to collection of emission data to verify proper positioning of the patient. The selected imaging plane corresponded to a midventricular plane. Correct positioning was maintained throughout the study with the use of a light beam and indelible felt pen marks on the torso.

Myocardial perfusion was assessed with ^{13}N-ammonia and exogenous glucose uptake with ^{18}F-deoxyglucose (FDG). The trac-

ers were injected intravenously by means of an infusion pump. After collection of attenuation data, 10–15 mCi ^{13}N-ammonia were injected over a 20-sec period. Beginning with tracer injection, 28 serial cross-sectional images were acquired in a decay-compensated mode for 10 min. After a 50-min interval for decay of ^{13}N radioactivity to baseline levels, 15 mCi [^{18}F]FDG was infused over 60 sec, followed by acquisition of 34 serial cross-sectional images for 45 min.

For analysis, each reconstructed tomographic image was corrected for physical decay. Nine 3.6-cm^3 volumes of interest were assigned to each image of the left ventricular myocardium and another volume was assigned to the center of the left ventricular blood pool. Three of these volumes of interest were located in the interventricular septum, three others in the anterior wall and the remaining three in the lateral free wall of the left ventricle. Counts as well as deadtime loses were corrected for partial volume and spillover effects using a specially developed Monte Carlo simulation (*15*).

Circumferential Profiles. Nitrogen-13-ammonia and [^{18}F]FDG cross-sectional images were analyzed with an operator-interactive computer program using circumferential profiles. The program normalized ^{18}F and ^{13}N counts within a given myocardial cross-section to maximal activity in the same ventricular slice. Each cross-section of the left ventricle was then divided into serial 30° segments. Activity within each segment was expressed in relative terms (reported as relative ^{18}F and ^{13}N uptake) as the percentage of maximal activity normalized to peak ^{13}N-ammonia segmental activity at the same level. A pattern of flow-metabolism mismatch was considered to be present when the segmental FDG-to-ammonia activity ratio exceeded 1.2 (*15*). Regions of interest (ROIs) in tomograms obtained after administration of ^{13}N-ammonia were subdivided to encompass ROIs in remote and risk tissue. Remote (normal) regions are identified as the three 30° segments from the lateral free wall. In five patients, this region was supplied by a diseased circumflex coronary artery. None of these patients, however, had sustained a previous posterior myocardial infarction. Risk regions are identified as the three 30° segments from the anterior wall.

Quantitation of Tomographic Data. Data were quantified as previously described (*15,18*). One midventricular transaxial slice per patient was analyzed for dynamic studies. Regional myocardial perfusion was quantified by use of a three-compartment model developed by Hutchins et al. (*20*) and validated by Bol et al. (*21*). No correction for circulating metabolites was applied (*21*). Patlak graphic analysis was used to estimate absolute regional myocardial glucose uptake (*22*). Glucose extraction was calculated as the ratio of regional myocardial glucose uptake to regional myocardial blood flow. Normalized glucose extraction was calculated as the ratio of absolute glucose extraction in the ischemic region to that in the remote region. The results are reported as the average value of the four regions from the lateral free wall and the basal septum for remote (normal) segments and of the three regions from the anterior wall for risk segments.

Statistical Analysis

Values are expressed as mean ± 1 s.d. An exact Fisher test was used to assess differences in categorical variables. A Mann-Whitney rank-sum test was used to assess differences in continuous variables between patients with and without evidence of myocardial viability. All tests were two-tailed and a probability value greater than 0.05 was considered indicative of a statistically non-significant difference. The nine previously defined PET variables were submitted for stepwise linear discriminant analysis with a forward selection procedure. Variables were entered until no F-to-enter statistics were significant at the 5% level and until the mean-squared error reached a minimum (*23*). The power of the discriminant function was assessed by the canonical correlation. Based on the results of the discriminant analysis, an equation was built that provided maximal separation between patients with and without viable myocardium. A jackknife-validation procedure was performed to reduce bias in the evaluation of the number of patients correctly classified into each group (*24*). The predictive accuracy of the discriminant function was determined by the Cohen's kappa coefficient.

RESULTS

Clinical and Angiographic Characteristics

Coronary artery bypass surgery was performed in 7 patients using the internal mammary artery to graft the LAD, and PTCA was performed in the remaining 18 patients. None of the patients suffered from perioperative or post-angioplasty myocardial infarction. As judged from the follow-up angiographic results, which were obtained prospectively in all patients 6–9 mo after revascularization, complete revascularization was achieved in all patients undergoing bypass surgery and in 8 of 18 patients undergoing PTCA. In the remaining 10 patients, a restenosis had occurred at the site of the initially successful angioplasty. In eight of these patients, the restenosis was moderate (50%–75% luminal diameter stenosis), whereas in two other patients reocclusion or severe restenosis (75%–95% luminal diameter stenosis) of the LAD had occurred. Regional wall motion score and global left ventricular function improved in eight patients despite restenosis, including the two patients with reocclusion or severe restenosis.

According to the changes in resting anterior wall motion and end-systolic volume before and after revascularization, the patients were categorized into two groups: Group 1: (viable) 17 patients (15 men, 2 women, mean age 56 ± 12 yr, range 30–72 yr) with improved anterior wall motion score (−2.47 ± 0.94 grade) and end-systolic volume (−15 ± 11 ml/m^2); Group 2: (nonviable) 8 patients (7 men, 1 woman, mean age 58 ± 12 yr, range 38–67 yr) with an increase in end-systolic volume (+17 ± 22 ml/m^2) and variable changes in anterior wall motion score (three patients with no changes, two patients with improvement by only 1 grade and three patients with deterioration). Before revascularization, anterior wall motion score, left ventricular volumes, left ventricular ejection fraction and coronary anatomy were similar among the two patient groups (p = ns, Table 1). There was, however, a significantly greater proportion of patients with previous myocardial infarction in the nonviable group (100 versus 35%, $p < 0.01$). As shown in Figure 1, an inverse correlation was observed between the changes in global ejection fraction and the improvement in regional wall motion score after revascularization ($r = -0.73$, $p < 0.001$).

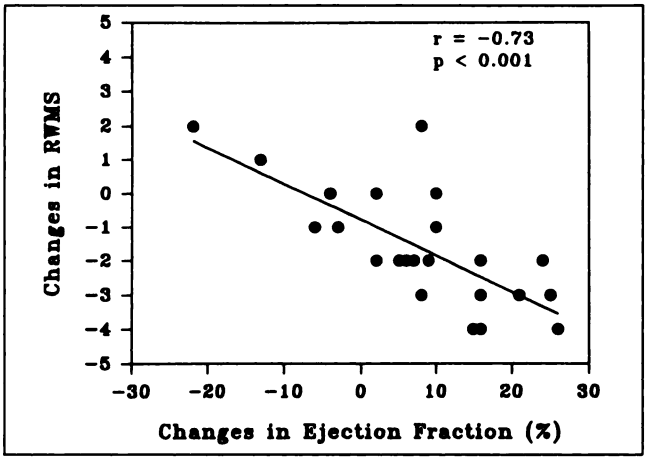

FIGURE 1. Scatter plot shows the relation between changes in regional wall motion score and changes in global left ventricular ejection fraction following revascularization.

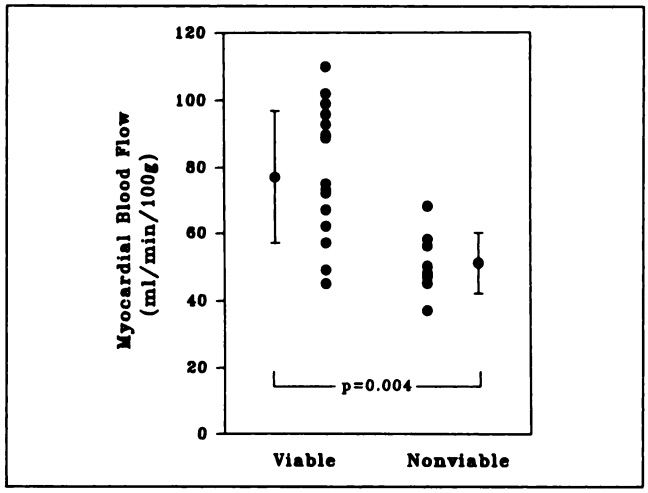

FIGURE 2. Dot plot shows individual absolute myocardial blood flow in patients with and without viable myocardium. Note that patients with viable myocardium had significantly higher levels of absolute myocardial blood flow than patients without viable myocardium.

Estimates of Myocardial Perfusion and Metabolism before Revascularization

Individual tomographic measurements of myocardial perfusion and metabolism before revascularization are shown in Table 1. Mean values for these measurements in remote normal and ischemic regions in groups of patients with and without viable myocardium are presented in Table 2. Before revascularization, dysfunctional but viable myocardium exhibited significantly higher absolute myocardial blood flow (77 ± 20 versus 51 ± 9 ml (min · 100 g)$^{-1}$, p = 0.004, Fig. 2) than nonviable myocardium. Absolute regional myocardial glucose uptake (36 ± 14 versus 24 ± 11 μmole (min · 100 g)$^{-1}$, p = 0.04, Fig. 3) was also slightly higher in viable compared with nonviable myocardium.

To explore possible reasons for interpatient variability in blood flow in normal remote myocardium, absolute levels of perfusion were compared with the rate-pressure product as an index of myocardial oxygen demand. A linear relation was observed between rate-pressure product and myocardial blood flow (r = 0.56, p < 0.01). In contrast, blood flow (r = 0.35, p = ns) was unrelated to the rate-pressure product in dysfunctional segments.

As shown in Figure 4, the FDG over ammonia activity ratio did not differ among patients with and without viable myocardium. A flow-metabolism mismatch pattern was present in 11 of 17 patients with viable myocardium (sensitivity 65%) and 4 of 8 patients with nonviable myocardium (specificity 50%). The overall accuracy was 60%. It should be pointed out, however, that 8 of 17 (47%) patients with viable myocardium and no patients with nonviable myocardium had normal perfusion at rest, defined as

TABLE 2
Myocardial Blood Flow and Regional Glucose Uptake in 25 Patients Based on Changes in Regional Wall Motion Score and End-Systolic Volume before and after Revascularization

	Region	Viable (n = 17)	Nonviable (n = 8)
Myocardial blood flow (ml (min · 100 g)$^{-1}$)	Remote	97 ± 18	87 ± 18
	Anterior	77 ± 20***	51 ± 9***‡
Myocardial glucose uptake (μmole (min · 100 g)$^{-1}$)	Remote	36 ± 18	37 ± 28
	Anterior	36 ± 14	24 ± 11†
Glucose extraction (μmole/ml)	Remote	0.39 ± 0.22	0.42 ± 0.31
	Anterior	0.49 ± 0.20**	0.45 ± 0.23
FDG/Ammonia	Anterior	1.69 ± 1.21	1.69 ± 0.83
Rate-pressure product (bpm × mmHg)		9944 ± 1976	7516 ± 890†

*p < 0.05, **p < 0.01, ***p < 0.001 versus remote from the same group.
†p < 0.05, ‡p < 0.01 versus anterior from the viable group.

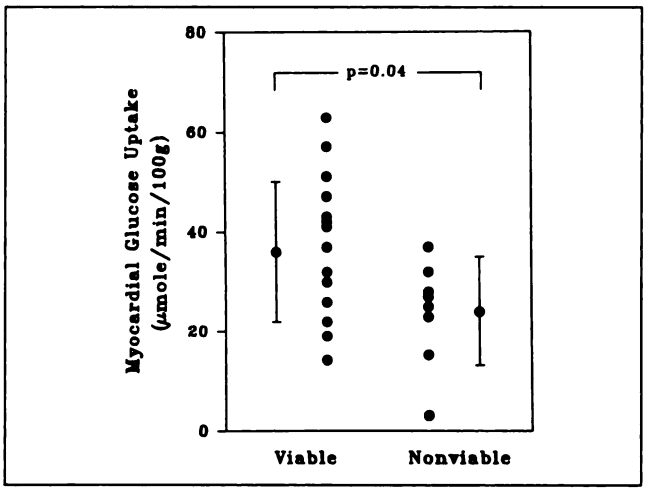

FIGURE 3. Dot plot shows individual absolute regional myocardial glucose uptake in patients with and without viable myocardium. Note that patients with viable myocardium had significantly higher levels of absolute regional myocardial glucose uptake than patients without viable myocardium.

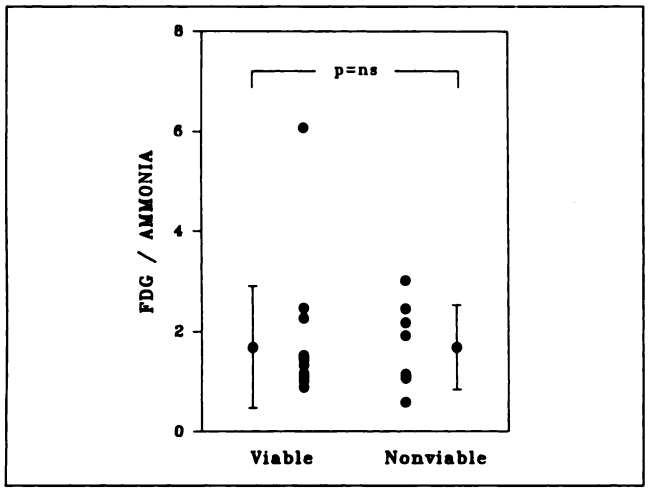

FIGURE 4. Dot plot shows individual FDG over ammonia activity ratio (mismatch ratio) in patients with and without viable myocardium. There was no difference in the matching between flow and metabolism among the two groups of patients.

>80% of maximal perfusion (*15,18*) (p = 0.05). If only patients with relative hypoperfusion in anterior regions (<80% of maximal perfusion) are considered, eight patients with viable myocardium (sensitivity 89%) and four patients with nonviable myocardium (specificity 50%) showed a flow-metabolism mismatch pattern in the anterior region. Overall accuracy improved to 77%.

Stepwise Linear Discriminant Analysis

Analysis of Factors Associated with Improved Global and Regional Left Ventricular Function after Coronary Revascularization. To further define the variables associated with the return of global and regional ventricular function after coronary revascularization, all available prerevascularization PET flow and metabolic data were proposed for inclusion in a multivariate discriminant model. As mentioned above, myocardial viability was defined on the basis of combined improvement in global and regional function. Among the nine PET variables analyzed (absolute and normalized [% of absolute remote values] myocardial blood flow, absolute and normalized myocardial glucose uptake, absolute and normalized glucose extraction, relative ammonia and FDG uptake, mismatch ratio), both absolute and normalized levels of resting myocardial perfusion, absolute regional myocardial glucose uptake and normalized glucose extraction were related to the presence of viable myocardium (Table 3).

Among the PET variables, stepwise linear discriminant analysis selected absolute resting myocardial blood flow and normalized glucose extraction as independent predictors of the presence of viable myocardium (Table 3). Of these two factors, myocardial perfusion was the most significant (p = 0.004). According to myocardial blood flow alone and a cutoff value of 64 ml (min · 100 g)$^{-1}$ (from discriminant analysis), 12 of 17 patients with viable myocardium (sensitivity 70%) and 7 of 8 patients with nonviable myocardium (specificity 88%) were correctly categorized by PET. Overall accuracy of absolute myocardial blood flow measurements was 76%. As shown in Figure 5, discriminant function improved the ability to identify patients in whom ventricular function is likely to recover following revascularization. Consideration of normalized glucose extraction in addition to absolute myocardial blood flow enabled correct classification in 14 of 17 patients with viable myocardium (sensitivity 82%) and 7 of 8 patients with nonviable myocardium (specificity 88%). Overall accuracy improved to 84%. To further refine our ability to classify an individual patient into groups with and without viable myocardium, the 95% confidence interval on the discriminant line was determined. Accordingly, 16 of 25 patients (64%) were correctly classified, 2 of 25 were incorrectly classified and 7 of 25 were unclassified (28%). Thus, in patients outside the 95% confidence bands, correct classification was achieved with 89% accuracy.

Similar results were obtained in the subgroup of patients with resting underperfusion (defined as <80% ammonia uptake) in the anterior region. Twelve of these patients had

TABLE 3
Stepwise Linear Discriminant Analysis of the Factors Associated with Improvement in Global and Regional Function after Coronary Revascularization

	Step	F-to-enter	p value
PET Variables in Univariate Analysis			
Absolute myocardial blood flow		12.21	<0.01
Normalized myocardial blood flow		11.09	<0.01
Relative ^{13}N-ammonia uptake		6.20	<0.05
Normalized absolute glucose extraction		5.97	<0.05
Absolute regional glucose uptake		5.19	<0.05
Normalized absolute glucose uptake		4.39	<0.05
Discriminant Analysis			
Absolute myocardial blood flow	1	12.21	<0.01
Normalized absolute glucose extraction	2	6.36	<0.05

Normalized is the percentage of remote absolute values.

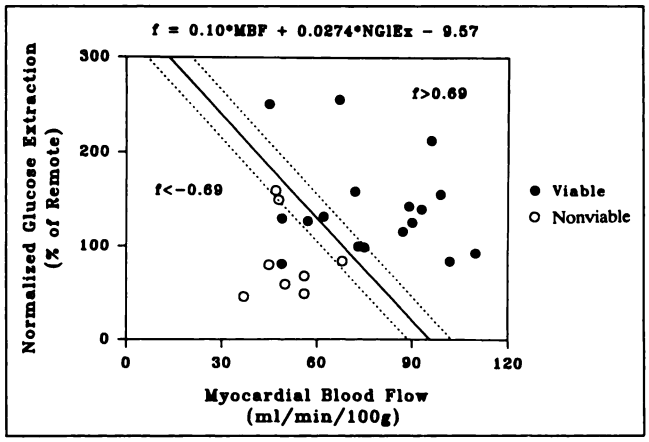

FIGURE 5. Scatter plot of the relation between normalized glucose extraction and myocardial blood flow and superimposition of the discriminant function and its 95% confidence limits. [●] Patients with and [○] without viable myocardium.

TABLE 4
Myocardial Blood Flow and Regional Glucose Uptake in 25 Patients Based on Changes in Regional Wall Motion Score before and after Revascularization

	Region	Improved wall motion (n = 19)	No improvement in wall motion (n = 6)
Myocardial blood flow (ml (min · 100 g)$^{-1}$)	Remote	98 ± 18	83 ± 16
	Anterior	75 ± 20***	49 ± 10***‡
Myocardial glucose uptake (μmole (min · 100 g)$^{-1}$)	Remote	35 ± 18	40 ± 32
	Anterior	35 ± 13	23 ± 12
Glucose extraction (μmole/ml)	Remote	0.38 ± 0.21	0.47 ± 0.35
	Anterior	0.49 ± 0.19*	0.45 ± 0.27
FDG/Ammonia	Anterior	1.75 ± 1.15	1.48 ± 0.86
Rate-pressure product (bpm × mmHg)		9837 ± 1969	7383 ± 1009†

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus remote from the same group.
†$p < 0.05$, ‡$p < 0.01$ versus anterior from the viable group.

TABLE 5
Stepwise Linear Discriminant Analysis of the Factors Associated with Improvement in Regional Function after Coronary Revascularization

	Step	F-to-enter	p value
PET Variables in Univariate Analysis			
Absolute myocardial blood flow		8.90	<0.01
Normalized absolute blood flow		6.42	<0.05
Normalized absolute glucose uptake		6.18	<0.05
Relative [^{18}F]FDG uptake		4.61	<0.05
Relative ^{13}N-ammonia uptake		4.08	<0.05
Discriminant Analysis			
Absolute myocardial blood flow	1	8.90	<0.01
Relative [^{18}F]FDG uptake	2	5.29	<0.05

viable myocardium and eight had nonviable myocardium. Among these patients, viable myocardium also showed higher prerevascularization absolute anterior myocardial blood flow (72 ± 19 versus 51 ± 9 ml (min · 100 g)$^{-1}$, p = 0.008), normalized myocardial blood flow (0.74 ± 0.13 versus 0.60 ± 0.11, p = 0.03) and regional myocardial glucose uptake (38 ± 15 versus 24 ± 11 μmole (min · 100 g)$^{-1}$, p = 0.03) than nonviable myocardium. Among these parameters, discriminant analysis selected absolute myocardial blood flow as the only independent predictor of return of function after revascularization.

Analysis of Factors Associated with Improved Regional Wall Motion after Coronary Revascularization. Because in many previous reports viable myocardium has been identified solely on the basis of an improvement in regional wall motion, the determinants of the return of regional function, irrespective of the evolution of global left ventricular function, was also investigated. Nineteen of 25 patients showed improved regional wall motion score at the follow-up study. As shown in Table 4, patients with improved wall motion after revascularization showed higher absolute and normalized levels of resting myocardial perfusion and higher FDG uptake in the anterior region than patients without. Among the PET variables, stepwise linear discriminant analysis also selected absolute resting myocardial blood flow and relative FDG uptake as independent predictors of return of regional function (Table 5). Based on myocardial blood flow alone and a cutoff value of 62 ml (min · 100 g)$^{-1}$ (from discriminant analysis), 12 of 19 patients with viable myocardium (sensitivity 63%) and 5 of 6 patients with nonviable myocardium (specificity 83%) were correctly categorized by PET. Overall accuracy of absolute myocardial blood flow measurements was 68%. The discriminant function improved the ability to identify patients likely to recover regional ventricular function following revascularization correctly classified 16 of 19 patients with viable myocardium (sensitivity 84%) and 5 of 6 patients with nonviable myocardium (specificity 83%). Overall accuracy improved to 84%.

DISCUSSION

Previous studies have demonstrated that accurate preoperative prediction of the reversibility of regional wall motion abnormalities could be achieved with PET assessment of myocardial blood flow and metabolism (*6–10*). Optimal criteria for identification of dysfunctional but viable myocardium have not yet been fully defined. It remains unclear, for instance, which PET parameter is the most relevant to the return of function after successful coronary revascularization. It is also largely unknown whether quantitation of flow and metabolism in absolute terms, which requires modeling and computational capabilities as well as dynamic imaging, would improve predictive accuracy compared with relative imaging. The present study addresses both issues. By using multivariate analysis, we observed that, in patients with LAD coronary artery disease and sustained anterior wall dysfunction, postoperative improvement in both regional and global left ventricular function was best predicted by a discriminant function that combines preoperative measurements of absolute levels of myocardial blood flow and normalized myocardial glucose extraction in the area of dysfunction. The discriminant function identified the presence of viable myocardium with a sensitivity of 82%, a specificity of 88% and an overall accuracy of 84%.

Defining Myocardial Viability

Earlier studies have indicated that indices of global systolic function, such as end-systolic volume and ejection fraction, were strong predictors of survival in patients with chronic left ventricular dysfunction due to coronary artery disease (*17*). In these patients, coronary revascularization by either CABG or PTCA has been shown to improve ventricular function (*6*), and to some extent, to prolong survival (*25*). It has been recently shown that the degree of improvement in global left ventricular function following coronary revascularization was intimately related to the

amount of salvageable myocardium, indicating that some threshold amount of viable tissue is needed to affect global left ventricular function (*6*), and presumably prognosis. Therefore, we defined the presence of viable myocardium in an individual patient on the basis of improvement in both regional and global left ventricular function.

Myocardial Glucose Metabolism to Predict the Presence of Viable Myocardium

Because glucose is the main substrate under ischemic conditions, PET with [^{18}F]FDG has been proposed for delineating the presence of residual metabolic activity within dysfunctional myocardial segments of patients with coronary artery disease. Results of studies using PET with FDG showed that the persistence of residual glucose utilization in hypoperfused segments (the relative flow-metabolism mismatch) identified those likely to resume satisfactory contractile function following revascularization (*6–8*). With this approach, myocardial viability could be detected with a sensitivity of 75%–85% and specificity of 78%–92% (*6,7*).

At first glance, the results of the present study (sensitivity 65% and specificity 50%) might appear to contradict those of earlier reports. They are, however, in agreement with results of previous studies, indicating that PET with FDG may overestimate both the amount and extent of viable myocardium in patients studied both early (*9,12,13*) and later (*26*) after myocardial infarction. Schwaiger et al. (*12*) observed that the functional outcome of infarcted segments with a flow-metabolism mismatch pattern was quite variable. Similarly, Piérard et al. (*13*) demonstrated that the presence of a flow-metabolism mismatch pattern in recently infarcted segments was of limited value to predict the recovery of contractile function after successful revascularization. Gropler et al. (*9*) reached similar conclusions. It must be emphasized that these three studies dealt mainly with patients studied early (usually within 1 wk) after infarction. Their findings may not therefore be applicable to ours; our study was targeted more towards patients with chronic coronary artery disease. Nonetheless, our findings agree with the data reported by vom Dahl et al., who studied patients with chronic left ventricular ischemic dysfunction (*26*), thus suggesting that overestimation of the capacity for recovery with PET and FDG is not limited to the immediate postinfarction period and may extend into the first weeks after the initial event.

In the present study, 20 of 25 (80%) patients with chronic ischemic regional dysfunction had either normal perfusion at rest or a flow-metabolism mismatch pattern in the anterior wall. Thus, only four patients (instead of eight) would have been considered to have nonviable myocardium had we used the concept of flow-metabolism mismatch as the reference standard. Although it is possible that the suboptimal results of FDG imaging in some earlier reports reflected inadequate revascularization, poor myocardial protection, coronary artery graft closure or restenosis, we believe they are more likely the manifestation of the exquisite sensitivity of FDG imaging, which could detect even small, perhaps subepicardial, portions of myocardium not materially contributing to contraction when revascularized.

Myocardial Blood Flow to Predict the Presence of Viable Myocardium

Previous studies assessing relative perfusion with ^{201}Tl (*27,28*) have indicated that tracer uptake was maintained to levels close to normal in dysfunctional but metabolically active myocardium. Studies with PET and ^{15}O-water demonstrated that at least 70% of the wall thickness had to be normally perfused before revascularization for normal function to resume following revascularization (*29,30*). Few studies, however, evaluated the accuracy of absolute myocardial blood flow measurements for predicting the reversibility of dysfunction in patients undergoing coronary revascularization (*18,31*). Gewirtz et al. (*31*) recently showed that the presence of viable myocardium was very unlikely if basal myocardial blood flow was <25 ml $(\text{min} \cdot 100\ \text{g})^{-1}$. In the present study, however, none of the patients, even in the nonviable group, exhibited such a large flow deficit. Obviously, this could be due to the fact that our patients had a milder degree of left ventricular dysfunction, less severe coronary artery disease and higher collateral flow to the dysfunctional area than those studied by Gewirtz et al.

Although we cannot entirely dismiss this possibility, we believe that the most likely explanation for the differences among the two studies lies in the way finite resolution effects were considered. Indeed, in calculating their flows, Gewirtz et al. did not differentially correct for partial volume effects in remote normal and dysfunctional areas. This likely led to significant underestimation of absolute flow values in the dysfunctional segments. On average, the sole loss of systolic wall thickening is expected to result in a 20%–25% underestimation of regional counts. The degree of underestimation can even be larger in the presence of significant wall thinning.

By contrast, in our study, individual recovery coefficients were computed for each myocardial ROI, with a previously validated approach (*15,21*). These individual recovery coefficients were then used to correct regional time-activity curves for partial volume effects, which resulted in higher flow values in both types of dysfunctional segments. Accordingly, among all absolute and relative PET variables investigated in our study, absolute myocardial blood flow was the single most powerful predictor of viability. Twelve of the 17 patients with viable myocardium and only 1 of the 8 patients with nonviable myocardium had flow values within the 95% confidence limits of normal for our laboratory. Thus, the predictive value of a normal flow value for identification of viable myocardium in our population was >93%. Additional information is thus required only in patients with reduced absolute blood flow values. In these patients, assessment of regional glucose extraction appears to be the most useful.

Study Limitations

The present study has some limitations that should not be ignored. We evaluated myocardial viability in a cohort of selected patients with mildly depressed left ventricular function. Therefore, this patient population may not reflect the patients who would benefit most from PET imaging for further treatment planning. Caution should therefore be exercised before transposing the results of this study to patients with more severely depressed left ventricular function. In these patients, a similar degree of functional reversibility may not be achievable, as other factors such as extensive left ventricular remodeling, markedly elevated myocardial wall stresses and functional mitral regurgitation, may also play an important role in the pathophysiology of left ventricular dysfunction.

As with previous studies from our laboratory, data were acquired with a single-slice PET camera. Although static images from several different levels of the left ventricular myocardium were usually obtained, only one tomographic level was used for dynamic imaging. It is therefore assumed that this tomographic level was representative of the entire anterior ischemic area. Only patients having stable coronary artery disease and left ventricular dysfunction were enrolled in this study. Although 14 patients had sustained at least one previous myocardial infarction, the most recent occurring 11 days before the PET study, no patient was studied during the acute phase of infarction (< 3 days). Therefore, our results can only be applied to patients with chronic coronary artery disease and presumably not to patients with recent (< 3 days) myocardial infarction.

Regional myocardial glucose uptake was assessed during intravenous glucose load. Like oral glucose loading, intravenous glucose load results in only a moderate increase of plasma insulin concentrations (to about 35 μU/ml). This probably explains the intermediary values for regional glucose uptake in the remote normal segments. It has been suggested that the hyperinsulinemic-euglycemic glucose clamp technique (*32*) might be preferable in this respect. How it will influence the predictive accuracy of FDG imaging is largely unknown and requires study. Finally, because of the necessary aerobic nature of cardiac contraction, some authors have proposed assessing myocardial oxidative metabolism with PET and ^{11}C-acetate as an alternative to FDG. Studies in both experimental animals (*33*) and in humans (*9,10,34*) have shown that maintenance of oxidative metabolism in dysfunctional myocardium portended its functional recovery after revascularization. In the present study, we did not systematically assess oxidative metabolism. Definite conclusions regarding the relative power of flow measurements compared with measurements of oxidative metabolism in differentiating viable from nonviable myocardium cannot be drawn from our data. Nonetheless, because myocardial blood flow and oxygen consumption are closely coupled in both viable and nonviable myocardium (*15,16*), it is likely that both measurements will have similar predictive accuracy for identification of myocardial viability.

CONCLUSION

This study identified absolute myocardial blood flow and normalized glucose extraction as the most powerful predictors of the return of contractile function after coronary revascularization in patients with ischemic anterior wall dysfunction, many of whom had a previous infarction. In this population, assessment of flow and metabolism in absolute terms appears to be superior to relative flow-metabolism mismatch for identification of viable myocardium.

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FIRST IMPRESSIONS

Does this anterior pelvic image demonstrate an area of focused activity in the left side of the scrotum, suggesting a testicular lesion? For acquisition information, turn to page 1679.