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Relation Between Contractile Reserve and Positron Emission Tomographic Patterns of Perfusion and Glucose Utilization in Chronic Ischemic Left Ventricular Dysfunction

Implications for Identification of Myocardial Viability

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Objectives. **This study sought to determine the incidence and extent of dobutamine-induced contractile reserve in myocardial regions characterized by classical and new positron emission tomographic (PET) patterns in patients with chronic ischemic left ventricular dysfunction.**

Background. **PET is considered the most accurate method for assessment of myocardial viability, which is traditionally identified by perfusion–metabolism mismatch.**

Methods. **In 23 patients, segmental wall thickening expressed by four echocardiographic scores at rest and during low dose (5 and 10 μg/kg body weight per min) dobutamine infusion and regional myocardial uptake of potassium-38 and fluorine-18 fluorodeoxyglucose (F-18 FDG) during glucose clamp were compared in 16 corresponding segments.**

Results. **Of a total of 368 segments, data analysis focused on 214 (58%) dyssynergic segments at baseline. Contractile reserve was identified with increasing incidence according to the six following PET patterns: 1) diminished perfusion and moderate reduction of F-18 FDG uptake (3 [11%] of 28 segments); 2) proportional reduction of perfusion and F-18 FDG uptake (10 [23%] of 43 segments); 3) perfusion–metabolism mismatch (19 [46%] of 41 segments); 4) preserved perfusion but moderate reduction of F-18 FDG uptake (13 [46%] of 27 segments); 5) preserved perfusion and F-18 FDG uptake (37 [59%] of 63 segments) compared with our normal database; and 6) normal perfusion but absolute increased F-18 FDG uptake (8 [73%] of 11 segments). In the latter category, only 7 of 24 segments had normal rest function. In dyssynergic segments with F-18 FDG uptake ≥50% supplied by vessels with ≥75% stenosis, improvement in contractility during dobutamine correlated with the presence of collateral channels.**

Conclusions. **Myocardial regions with the traditional mismatch pattern of viability show contractile reserve in slightly <50%. In segments with moderate reduction of F-18 FDG uptake, the contractile response to dobutamine is linked to the level of rest perfusion. Most segments with preserved perfusion and increased F-18 FDG uptake have impaired rest function, but contractile reserve is still present. These data suggest that in chronic ischemic left ventricular dysfunction, myocardial hibernation is a heterogeneous condition.**

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Distinguishing between necrotic tissue and noncontractile but salvageable myocardium has important implications for clinical decision making in patients with chronic coronary artery disease (CAD) and left ventricular dysfunction (1). This question may be trivial if angina is the main symptom and when left ventricular dysfunction is only moderate but is crucial in patients who present with severe ischemic left ventricular dysfunction. In most of these patients, asynergic myocardium may correspond to an admixture of areas in different states—scar, ischemia, stunning or hibernation (2). Several imaging techniques are increasingly used for assessing perfusion, membrane integrity, oxidative or anaerobic metabolism and contractile reserve (3), but there is no imaging procedure that can serve as a reference standard.

Several recent studies have suggested that low dose dobutamine echocardiography should be the preferred imaging technique for preoperative assessment of patients with severe chronic ventricular dysfunction because the presence of contractile reserve is highly predictive of early—within 1 to 3 months—improvement after revascularization (4,5). In contrast, thallium-201 single-photon emission computed tomography (SPECT) overestimates the probability of early recovery. This is not surprising because thallium-201 uptake requires only membrane integrity, whereas an inotropic response to

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Abbreviations and Acronyms

ANOVA	=	analysis of variance
CAD	=	coronary artery disease
df	=	degrees of freedom
F-18 FDG	=	fluorine-18 fluorodeoxyglucose
K-38	=	potassium-38
PET	=	positron emission tomography (tomographic)
SPECT	=	single-photon emission computed tomography (tomographic)

dobutamine requires preserved contractile material and thus a higher degree of myocyte functional integrity (6). Metabolic imaging with PET has been considered the most accurate method for identifying myocardial viability (7). Regions with a mismatch pattern—reduced perfusion but preserved fluorine-18 fluorodeoxyglose (F-18 FDG) uptake—contain predominantly viable cells and seem more likely to recover their contractile function after revascularization (8,9).

Myocardial regions with concordant reduction of perfusion and glucose utilization are considered to represent nonviable myocardium. Myocardial regions exhibiting normal perfusion are usually considered normal regardless of the extent of glucose utilization. Functional characteristics of segments with normal perfusion and increased F-18 FDG uptake are unknown. Only one study (10) has assessed the clinical significance of a moderate reduction in regional myocardial glucose utilization in regions with normal perfusion.

In the present study, consecutive patients with chronic CAD and heart failure or severe left ventricular dysfunction underwent both PET and low dose dobutamine echocardiography to evaluate the proportion of remaining viable tissue and possible indication for bypass surgery. The aims were the following: 1) to study the relation between semiquantitative measurements of regional perfusion, regional glucose utilization and corresponding echocardiographic scores of myocardial thickening at baseline and during low dose dobutamine infusion; and 2) to determine the absence and presence and, when present, the extent of contractile reserve in regions characterized by various patterns of combined perfusion and glucose utilization.

Methods

Study patients. The study included 23 patients with angiographically proved severe CAD and profound alteration of left ventricular function (22 men, 1 woman; 39 to 73 years old, mean [±SD] age 61 ± 9). Mean left ventricular ejection fraction determined by ventriculography was 29 ± 9%. Sixteen patients had three-vessel disease; five had two-vessel disease; and two had one-vessel disease. Fifty-eight percent of diseased vessels were occluded. Sixteen patients had had a previous myocardial infarction; two had had two infarctions; and one an episode of unstable angina, but not within 3 weeks of the study. Ten patients had stable angina; 18 had heart failure (New York Heart Association functional class III or IV). PET and low dose dobutamine echocardiography were performed within 1 week in patients with stable chronic CAD. All patients gave written informed consent, and the study was approved by our hospital ethics committee.

Dobutamine stress echocardiography. *Echographic examination.* Each patient underwent low dose dobutamine echocardiography. If a patient was treated by a beta-adrenergic blocking agent, the drug was stopped 48 h before the test. Two-dimensional transthoracic echocardiograms were obtained in standard views with the patient lying at rest in the left lateral position. Dobutamine was infused intravenously at 5 μg/kg body weight per min, followed by 10 μg/kg per min, each stage lasting for 3 min. The echocardiogram was obtained continuously and intermittently recorded on videotape, at least during the last minute of each stage. Digital acquisition of images was obtained at rest, at every dobutamine dose and during recovery for side by side display in quad screen format. A 12-lead electrocardiogram was monitored continuously and recorded every minute. Blood pressure was measured at each stage by sphygmomanometer.

Analysis of echocardiograms. The dobutamine echocardiographic studies were interpreted by two experienced observers (L.A.P., J.L.P.) who had no knowledge of the clinical, angiographic and PET findings. The analysis was semiquantitative, and the classical 16-segment model was used. Wall thickening of each segment was scored by a four-point scoring system: 1 = normal wall thickening; 2 = moderate hypokinesia; 3 = severe hypokinesia; and 4 = akinesia or dyskinesia. We decided to merge akinesia and dyskinesia in the only score of four for the following reasons. The echocardiographic pattern of an akinetic segment at rest becoming dyskinetic with dobutamine is related to a mechanical phenomenon (11) and does not represent ischemia. In contrast, a dyskinetic segment that would be judged akinetic with low dose dobutamine cannot be considered as having contractile reserve. We considered a segment severely hypokinetic in the presence of minimal wall thickening <2 mm, confirmed when possible by M-mode recording.

Rest dyssynergy was defined as severe segmental dysfunction, with a score of 3 or 4. Contractile reserve was judged to be present when wall thickening improved during low dose dobutamine by at least one score. A distinction was made between a small improvement of only one score and large improvement of two or more scores. Inadequately visualized segments were not scored. Discrepancies between observers were resolved by consensus. The low level of interobserver variability in our laboratory has been previously documented (12,13) and may relate to similar reading criteria. However, variability between expert interinstitutional centers may be higher (14).

PET. The combined study of regional perfusion and glucose utilization was performed at rest using potassium-38 (K-38) and F-18 FDG, respectively, and the whole-body ECAT 951/31R scanner (CTI). This equipment allows simultaneous

acquisition of 31 slices 3.4 mm apart. For optimal positioning of the heart within the field of view, a 5-min transmission scan was acquired at the beginning of the procedure. It was followed by a 30-min transmission scan used for a measured attenuation correction. The emission scans began with a perfusion study (mean injection of 518 MBq of K-38); next, after the decay of K-38 (half-life 7.6 min), 370 MBq of F-18 FDG was injected intravenously. A 20-min static scan was performed after a delay of 35 to 45 min. To provide optimal definition of the myocardial walls and standardize metabolic conditions, a hyperinsulinemic euglycemic clamp was used according to the method of De Fronzo et al. (15).

K-38 is a cationic positron-emitting tracer that behaves like thallium-201 and rubidium-82 (16). Intracellular transport of the tracer is mediated by the sodium–potassium transmembranous ion exchange system. On extraction by the myocardial cells, the tracer has a prolonged retention time that, with its rapid blood flow clearance, provides high image quality of the heart.

Image processing and data analysis. For systematic analysis of results, transaxial images were reoriented into 12 short-axis images of the heart using a dedicated SUN work station (SUN Microsystem Inc.). Reoriented short-axis images served as input function data in a semiautomated program providing polar coordinate maps of myocardial tracer uptake. The endocardial and epicardial edges of the myocardium were manually defined with circles by the operator (P.G.M.). The posterior intersection of the right and left ventricles was also drawn. A radius was then automatically interpolated between the center of the circles and this point of intersection. In each plane, the radius served as the beginning of a circumferential profile of activity along to 60 equidistant radii. The program automatically searches for a mean of the maximal activity recorded in a 3 × 3-pixel area along each radius. Regional data were displayed on a coordinate polar map. The polar map was subsequently divided in 16 segments corresponding to the echographic segmentation of the heart used for comparative analysis. In each patient, the myocardial segment characterized by the highest number of counts in the perfusion scan was used as the normal reference segment for that patient. K-38 activity in all other segments was then expressed as a percentage of the activity measured in the reference segment. Relative segmental F-18 FDG uptake was assessed using the identical method, giving a value of 100% to the reference segment obtained in the perfusion scan ("normalization" of data).

Reference values. Because reference values for perfusion and glucose utilization change from one laboratory to another, we established our normal values in 10 normal subjects with a low likelihood of CAD. All subjects were studied using a hyperinsulinemic euglycemic clamp. Data analysis was performed using polar map displays. In this group of control subjects, the relative segmental activity of K-38 and F-18 FDG uptake averaged 84 ± 10% and 93 ± 9%, respectively. On the basis of these data, perfusion and glucose utilization were considered abnormal if values fell outside 2 SD of the mean relative segmental tracer activity measured in our control group: The thresholds values were 64% for perfusion and 75% for glucose utilization.

Table 1. Categories of Perfusion and Uptake Patterns

Category	Pattern	K-38 Uptake	F-18 FDG Uptake
1	"Necrotic pattern"	<64%	<50%
2	Reduced perfusion and moderately reduced F-18 FDG uptake	<64%	Between 50% and 75%
3	"Mismatch pattern"	<64%	>75%
4	Normal perfusion and moderately reduced F-18 FDG uptake	≥64%	Between 50% and 75%
5	"Normal pattern"	≥64%	Between 75% and 111%
6	Normal perfusion and high F-18 FDG uptake	≥64%	>111%

F-18 FDG = fluorine-18 fluorodeoxyglose; K-38 = potassium-38.

Patterns of perfusion and glucose utilization: criteria of viability. For the purpose of data analysis, the myocardial segments were separated into six different categories. The first three were characterized by reduced perfusion and increasing levels of F-18 FDG activity, whereas in the last three, the perfusion was within normal limits, and F-18 FDG uptake increased from category to category. Table 1 summarizes this classification.

With PET, a dyssynergic segment was considered viable in the presence of F-18 FDG uptake ≥50%. With echocardiography, a dyssynergic segment was considered viable when the score at rest was ≤3, with improvement of contractility by at least one score during dobutamine infusion.

Statistical analysis. Results are expressed as mean value ± SD. In a recent study that compared the patterns of perfusion and metabolism in dobutamine-responsive myocardium, Sawada et al. (17) verified that a segment by segment analysis of the data was appropriate in the absence of any consistent intrapatient correlation of the segment data. Because our analysis was similar to that performed by Sawada et al. (17), we also used the segment as the unit of analysis. Differences in K-38 and F-18 FDG uptake between groups of segments were compared by analysis of variance (ANOVA), followed by the Bonferroni modified *t* test when significant differences were indicated by ANOVA. The chi-square test was used to compare proportions between categories; $p < 0.05$ was considered statistically significant.

Results

Patients. Table 2 presents clinical characteristics of the patients and summarizes the overall results of the two techniques used to detect myocardial viability. Patients had a mean follow-up period of 48 ± 8 months after PET and dobutamine echocardiography. According to PET, an admixture of viable and necrotic myocardium was observed in 13 patients; viability alone was present in 9 and necrosis alone in 1. Low dose dobutamine echocardiography showed the presence of viable tissue alone in 1 patient and necrosis alone in 4; 18 patients

Table 2. Clinical Characteristics of 23 Study Patients

Pt. No.	Age (yr)/ Gender	LVEF (%)	No. of Diseased Vessels	No. of Dyssynergic Segments	PET		Echo		Therapy and Follow-Up
					Viability	No. of Viable Segs	Viability	No. of Viable Segs	
1	69/M	23	2	8	+	7	+	7	CABG; alive, no improvement of LV function
2	67/M	34	3	8	+	8	+	2	CABG; alive, no symptoms
3	45/M	37	3	7	+	7	+	7	CABG; alive, no symptoms
4	59/M	23	3	9	−	0	−	0	Tx; excellent outcome
5	54/F	33	2	11	+	11	+	6	Cardiac death before scheduled CABG
6	63/M	23	3	7	+	2	+	4	CABG; cardiac death
7	39/M	19	3	9	+	9	+	8	Medical therapy; cardiac death
8	67/M	17	3	9	+	6	+	1	Medical therapy; noncardiac death
9	73/M	24	3	9	+	9	+	2	Medical therapy; cardiac death
10	70/M	26	2	7	+	4	+	2	CABG; noncardiac death
11	47/M	40	2	9	+	9	+	7	CABG; alive, no symptoms
12	55/M	47	3	8	+	8	+	2	Medical therapy; cardiac death
13	48/M	15	3	10	+	10	+	8	CABG; alive, no symptoms
14	55/M	14	3	13	+	8	+	4	CABG; alive no symptoms
15	64/M	24	3	11	+	5	−	0	Medical therapy; cardiac death
16	70/M	34	3	7	+	6	−	0	Medical therapy; alive
17	55/M	31	3	11	+	11	+	8	Medical therapy; cardiac death
18	61/M	36	3	12	+	10	+	8	CABG; alive, no symptoms
19	63/M	17	3	10	+	8	+	2	CABG; alive, alteration of LV function
20	68/M	27	1	12	+	11	+	9	Medical therapy; noncardiac death
21	67/M	32	3	9	+	7	+	4	Medical therapy; alive
22	69/M	38	2	10	+	7	+	2	Medical therapy; alive
23	69/M	43	1	6	+	2	−	0	Medical therapy; alive

CABG = coronary artery bypass graft surgery; Echo = dobutamine echocardiography; F = female; LV = left ventricular; LVEF = left ventricular ejection fraction; M = male; PET = positron emission tomography; Pt = patient; segs = segments; Tx = transplantation; + = present; − = absent.

had both viable and necrotic myocardium. PET and dobutamine echocardiography yielded concordant identification of viability or necrosis in 20 patients (87%).

Surgical revascularization was performed in nine patients with viable myocardium detected by both PET and dobutamine echocardiography and in one patient with viable tissue demonstrated by dobutamine echocardiography only. During follow-up, cardiac death was registered in four medically treated patients who had viable myocardium demonstrated by PET and dobutamine echocardiography.

Distribution of perfusion and F-18 FDG uptake in dyssynergic segments. Of 368 segments, 323 were correctly imaged for comparative PET and echographic data analysis. Two hundred fourteen segments (66%) had severe rest dyssynergy (echographic score 3 or 4); 43 (20%) were identified as "necrotic" (category 1); reduced perfusion with moderate reduction of F-18 FDG uptake was observed in 29 (14%) (category 2); 41 (19%) had the "mismatch pattern" (category 3); 27 (13%) showed normal perfusion with moderately reduced F-18 FDG uptake (category 4); 63 (29%) were classified as "normal" (category 5); and 11 (5%) showed normal perfusion with high F-18 FDG uptake (category 6).

Segmental perfusion and F-18 FDG uptake versus contractile response during low dose dobutamine infusion. Among the 214 dyssynergic segments at baseline, 118 (55%) did not have improved contractility during a low dose dobutamine infusion. Improvement of contractility by one echographic score was observed in 21 dyssynergic segments (10%) and by two or more scores in 75 (35%). As shown in Figure 1, perfusion, as assessed by K-38 uptake, was significantly higher ($p < 0.001$) in dyssynergic segments with improvement in contractility by at least one score during dobutamine than in those without contractile reserve. No significant difference in perfusion level was documented between segments that had improved contractility by one and two or more scores. When F-18 FDG uptake was related to the presence and extent of contractile reserve, there was a significant difference in tracer uptake between nonresponsive segments and segments with improved contractility by at least two scores during low dose dobutamine infusion only. As shown in Figure 2, the proportion of dyssynergic segments that showed a positive inotropic response to dobutamine increased with the level of regional perfusion (chi-square 44.7, degrees of freedom (df) 3, $p < 0.001$) or F-18 FDG uptake (chi-square 4 5.3, df 3, $p < 0.001$). One-fifth of dyssynergic segments with severe reduction of perfusion or F-18 FDG uptake (tracer uptake <50%) had contractile reserve, whereas one-third of segments with moderately reduced perfusion (between 50% and 63%) or F-18 FDG uptake (between 50% and 75%) demonstrated a positive response to dobutamine. When perfusion or F-18 FDG uptake

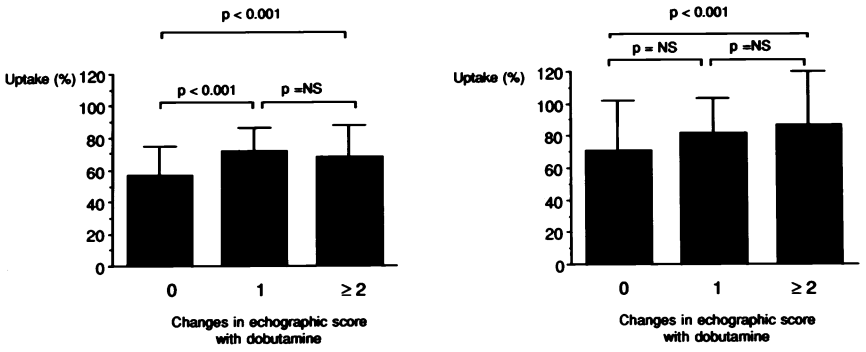


Figure 1. K-38 (**left**) and F-18 FDG (**right**) uptake (mean value ± SD) in dyssynergic segments versus change in echocardiographic score with low dose dobutamine.

was within normal limits, 60% of dyssynergic segments had contractile reserve.

Contractile reserve in six categories of perfusion and F-18 FDG uptake. As shown in Figure 3, the majority of segments (33 [77%] of 43) considered necrotic by PET (category 1) showed no decrease in myocardial thickening during low dose dobutamine infusion. In categories characterized by moderately reduced F-18 FDG uptake, the response to dobutamine depended on the level of segmental perfusion. Reduction of perfusion with moderately reduced F-18 FDG uptake (category 2) was associated with contractile reserve in only 11% of segments, whereas preserved perfusion with moderate reduction of F-18 FDG uptake (category 4) was associated with the presence of contractile reserve in 48% of segments ($p < 0.05$). Nineteen (46%) of 41 segments with a mismatch pattern (category 3) had increased wall thickening during dobutamine infusion. The largest number of segments (37 of 214) responding to dobutamine administration had normal perfusion and F-18 FDG uptake (category 5). The highest proportion of segments with contractile reserve (73%) was observed in segments characterized by normal perfusion and high F-18 FDG uptake (category 6).

Changes in contractile score during low dose dobutamine test in segments with a mismatch pattern (category 3). Figure 4 presents the contractile score change for each segment with a perfusion–metabolism mismatch during low dose dobutamine infusion. Only 3 segments with a mismatch pattern had normal rest wall thickening (score 1), whereas 41 were dyssynergic (score ≥3). The response to low dose dobutamine infusion was markedly heterogeneous among these dyssynergic segments. With dobutamine, 5 segments (12%) normalized their contractility (score 1); 12 (30%) became moderately hypokinetic (score 2); and 24 (58%) remained dyssynergic (score ≥3).

Changes in contractile score during low dose dobutamine test in segments with normal perfusion and high F-18 FDG uptake (category 6). Figure 5 presents the contractile score change for each segment in category 6 during low dose dobutamine infusion. Of the 24 segments that presented with normal perfusion and high F-18 FDG uptake, only 7 (29%) had normal rest wall thickening (score 1); 6 were moderately hypokinetic (score 2); and 11 (46%) were dyssynergic (score ≥3). With dobutamine, 8 (73%) of the dyssynergic segments showed the presence of contractile reserve either by normalizing myocardial wall thickening (5 segments) or by a change to moderate hypokinesia (3 segments). Only three segments remained dyssynergic (score ≥3).

Correlation between PET and echocardiographic patterns with angiographic data. In the presence of severe coronary artery stenosis (≥75%), detection of viability by low dose dobutamine echocardiography in dyssynergic segments with F-18 FDG evidence of viability (F-18 FDG uptake ≥50%) depended on the presence of collateral channels. Indeed, 44 (86%) of 51 dyssynergic segments viable according to PET that did not have improved contractility during low dose dobutamine were supplied by a severely stenosed artery without collateral vessels. Conversely, in the presence of severe coronary stenosis with collateral vessels, 44 (78%) of 56 dyssynergic segments with PET evidence of viability had improved contractility during dobutamine infusion.

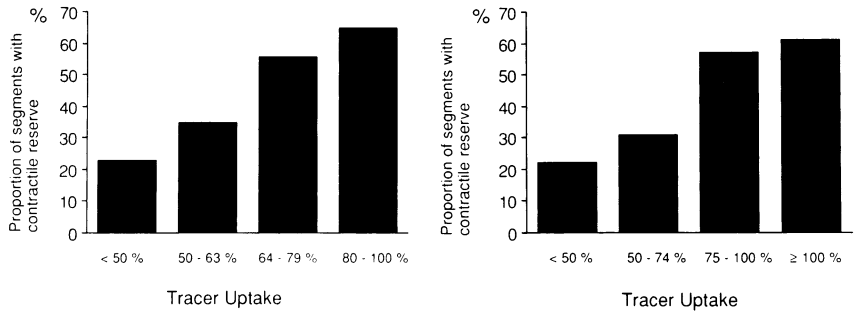


Figure 2. Relation between the proportion of dyssynergic segments with contractile reserve and the level of perfusion (**left** [K-38]) or F-18 FDG (**right**) uptake.

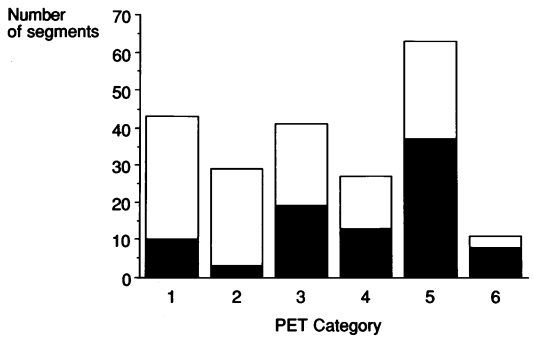


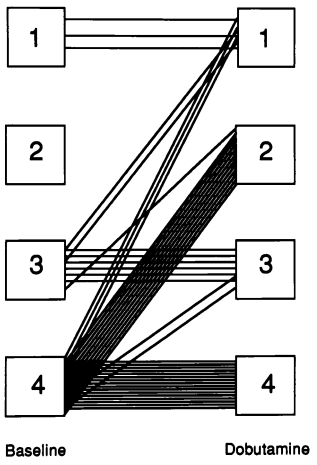
Figure 3. Distribution of segments with **(solid portions)** and without **(open portions)** contractile reserve according to the six categories of perfusion and F-18 FDG uptake.

Discussion

The main findings of this study are that 1) contractile reserve is observed in <50% of segments showing a mismatch between perfusion and glucose utilization, a pattern considered reliable as a sign of viability; 2) the contractility of most segments with preserved perfusion and increased glucose utilization is impaired in basal conditions but improves during inotropic stimulation; 3) the functional significance of myocardial regions with moderately reduced glucose utilization depends on the level of rest blood flow; 4) dobutamine-induced contractile reserve may be observed in the presence of several patterns of perfusion and glucose utilization, most probably corresponding to different myocardial states, such as stunning and hibernation, associated with a variable amount of nontransmural infarction; and 5) in regions perfused by a severely stenosed vessel, contractile reserve of segments with F-18 FDG evidence of viability depends on collateral circulation.

Inotropic stimulation of myocardium in the presence of perfusion metabolic mismatch. Of the 41 dyssynergic segments with flow–metabolic mismatch, contractile reserve was present in only 19 (46%). Several reasons may explain why >50% of such segments remained akinetic throughout dobutamine infusion: 1) Some improvement may have occurred but was too small or too brief to be detectable. 2) Beta-blockers were withheld before the echocardiographic test but not before PET. The increase in rest heart rate resulting from beta-blocker withdrawal determined a new perfusion–contraction match that could have resulted in a reduced inotropic response in these myocardial regions (18). 3) The absence of contractile reserve may be related to morphologic alterations, in particular, a significant reduction of contractile material. Myocardial biopsy samples from patients with prolonged reversible contractile dysfunction have indeed demonstrated ultrastructural changes in myocytes: cellular swelling, abnormalities of the mitochondria, increased glycogen content and, importantly, severe reduction in the number of myofibrils (19). Consequently, recruitable contractile reserve cannot be present in these conditions.

Figure 4. Schematic representation of wall thickening scores at baseline and during low dose dobutamine infusion for segments showing a mismatch pattern (category 3).



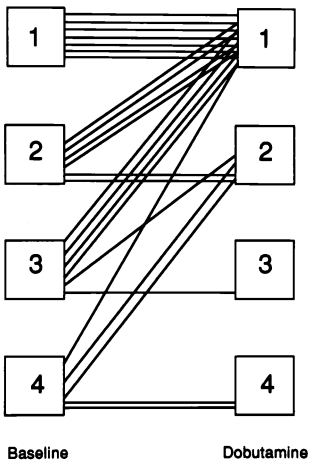


Figure 5. Schematic representation of wall thickening scores at baseline and during low dose dobutamine infusion for segments showing normal perfusion with high F-18 FDG uptake (category 6).

Significance of increased F-18 FDG uptake in regions with normal perfusion. The significance of a new PET pattern—abnormally high F-18 FDG uptake in regions with normal rest blood flow—has not yet been evaluated. This pattern was found in 24 segments in 13 patients. Only 7 of these 24 segments had normal contractility at rest. In the other 17 segments, mechanical function was impaired in basal conditions, most of them exhibiting contractile reserve. Of the 11 segments with severe dysfunction at rest (score 3 or 4), 8 retained contractile reserve, with an improvement of two scores in 7 segments during low dose dobutamine infusion. These imaging characteristics—impaired contractility, preserved perfusion at rest and increased glucose utilization—in patients in stable clinical condition are compatible with mechanical and metabolic myocardial adaptation to chronic coronary stenosis. Our findings are similar to those of Liedtke et al. (20) in an experimental pig model. In their pig model of partial coronary stenosis for 4 days, regional systolic shortening decreased by 54% despite maintenance of normal rest coro-

nary flow and myocardial oxygen consumption at aerobic levels. This was accompanied by altered metabolism: a decrease in fatty acid oxidation and a multifold increase in glycolysis (20). These results can also be compared with the observations of Vanoverschelde et al. (21) in patients with dysfunctional collateral-dependent myocardium. They found that rest blood flow was not significantly decreased but that flow reserve was blunted. Myocardial hibernation was initially considered a consequence of sustained hypoperfusion, but there are now recent data (21–23) suggesting that at least part of hibernation may be interpreted as a cumulative effect of multiple episodes of myocardial stunning or as a state of chronic stunning. Our observations demonstrate the coexistence in the same patients of hibernating regions with preserved F-18 FDG uptake, some with normal perfusion and others with insufficient blood flow.

Significance of reduced regional F-18 FDG uptake. Moderate reduction (from 50% to 75%) of F-18 FDG uptake was found in 56 of 214 dyssynergic segments, and contractile reserve was present in only 14 (25%), together with preserved perfusion in the majority of corresponding segments. The clinical significance of reduced myocardial glucose utilization in regions with normal perfusion has been investigated in only one study (10) in patients with chronic CAD. This pattern was frequent: 65% of patients, with the majority of segments exhibiting abnormal contractility at rest and inducible ischemia during exercise. Perrone-Filardi et al. (10) speculated that these regions represent an admixture of fibrotic and reversibly ischemic myocardium. As an alternative explanation, they also proposed that reperfused stunned myocardium may characterize regions with reduced F-18 FDG associated with preserved perfusion. Stunned myocardium retains contractile reserve: We found a low proportion of similar segments with contractile reserve, thus failing to confirm the latter hypothesis proposed by Perrone-Filardi et al. (10).

Contractile reserve in several myocardial states. A positive inotropic response to catecholamine stimulation in dyssynergic segments at baseline implies the preservation of some flow reserve, together with at least partial myocyte integrity and recruitable contractile material. On the basis of the findings of the present investigation, it appears that the presence of contractile reserve in patients with chronic CAD and severe ventricular dysfunction is not specific for a single myocardial state. Indeed, improvement in systolic thickening during low dose dobutamine infusion was observed, albeit in different proportions, in four of the six PET categories. A majority of dyssynergic segments with "normal" PET findings, exhibited contractile reserve; this pattern suggests the presence of myocardial stunning. The absence of contractile reserve in a significant proportion of segments with normal PET findings may be explained by several factors: the low dobutamine dose used in this study, mechanical forces such as tethering (24) or beta-receptor downregulation in patients with heart failure.

Myocardial regions with increased F-18 FDG uptake relative to perfusion probably correspond to hibernating myocardium. In this situation, basal preserved perfusion in some segments and reduced perfusion in others probably represent two different aspects of hibernation. Contractile reserve is highly frequent when perfusion is normal at rest and glucose utilization is enhanced, whereas it is observed in <50% of regions with abnormal perfusion. Such a relation between K-38 uptake and the proportion of segments with contractile response to dobutamine is also found in regions with moderately reduced F-18 FDG uptake, which have been thought to represent an admixture of subendocardial necrosis and subepicardial viable tissue (10). These findings are in agreement with the results of Panza et al. (6) who demonstrated a relation between the magnitude of thallium-201 uptake with SPECT using a stress–redistribution–reinjection protocol and the inotropic response to dobutamine with transesophageal echocardiography.

Among the segments with concordant decreases in both perfusion and glucose utilization, suggesting irreversibly damaged myocardium, improvement of thickening with dobutamine was found in 23%. Our results are in agreement with those recently published by Sawada et al. (17), which showed that 29% of segments classified nonviable by PET were viable by dobutamine echocardiography. In patients with a previous myocardial infarction, perfusion and glucose uptake may be below normal limits in the absence of complete transmural necrosis. We previously observed (25) residual contractile reserve in some patients with a recent myocardial infarction who exhibited this PET pattern. There is no other rational explanation for this finding, which may also be related to suboptimal anatomic correspondence between the two imaging techniques, in some patients.

Limitations of the study. Several limitations should be acknowledged: Only a limited number of our patients underwent coronary artery bypass graft surgery. Consequently, we cannot compare the relative ability of PET and dobutamine echocardiography for predicting improvement of regional contractility after revascularization. The respective proportion of functional recovery in the different PET patterns cannot be described.

We used only low dose dobutamine infusion at 5 and 10 μg/kg per min for detection of contractile reserve, which represents the first (13) and most frequently used protocol (4,26–28). Other investigators (29,30) have demonstrated the usefulness of additional higher doses for optimal evaluation. Recent experimental data (30) suggest that in the absence of beta-blockers, 15 μg/kg per min is the optimal dobutamine dose needed to elicit maximal thickening of stunned myocardium. We could not identify a biphasic response with our dobutamine protocol. This biphasic response has been shown (29) to have the highest predictive value for recovery of function after angioplasty. Although high dose dobutamine echocardiography appears to be safe in patients with chronic CAD, we preferred to avoid higher doses for safety reasons. Worsening of function after earlier improvement indicates ischemia and is included within the criteria for stopping the dobutamine infusion. However, persistent akinesia does not exclude the presence of viable myocardium, as shown by our

results. In this case, maintenance of high dobutamine doses may be deleterious, and myocardial ischemia may remain undetected.

The assessment of contractile reserve was based on qualitative criteria. Quantitative measurement of systolic wall thickening may provide more reliable information but is not yet available in clinical practice. Application of quantitative methods is difficult; endocardial or epicardial dropout is frequent on stop frame images; manual tracing of the endocardial and epicardial contours involves a subjective component; and assessment of end-diastolic and end-systolic images alone lacks the visual integration of information throughout the cardiac cycle and from multiple views.

Absolute myocardial blood flow and glucose utilization were not calculated. However, it is not the rule to use absolute values of flow and glucose utilization in a clinical setting. Semiquantitative data analysis was performed, and a normal data base was used to define normal limits. Fixed threshold values used to define normality may represent too strict criteria and may not reflect physiologic variability of myocardial perfusion or glucose utilization. However, this situation does not affect the conclusions of the present analysis, which showed that myocardial regions with different perfusion–metabolic patterns may have a similar contractile response to dobutamine.

Finally, the assessment of myocardial contractility, perfusion and glucose utilization was performed with two different techniques. Although every effort was made to match the echocardiographic and PET results, it is possible that misalignment occurred to some extent and partially contributed to our observations.

Conclusions. The present study shows fair concordance between PET and dobutamine echocardiography for identification of myocardial viability in most patients with chronic ischemic left ventricular dysfunction. Our results indicate that the interpretation of PET findings should not be restricted to the three traditional patterns of normal, mismatch and necrotic tissue. Myocardial regions exhibiting normal rest perfusion have a different functional status, depending on the magnitude of glucose utilization. Contractile reserve is observed with a variable incidence in the presence of several PET patterns, probably corresponding to different myocardial states. Most segments exhibiting preserved perfusion and increased F-18 FDG uptake have impaired contractility at baseline, but contractile reserve is present, suggesting the presence of hibernating myocardium. The present study supports the concept that myocardial hibernation is a heterogeneous condition.

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