Role of Thallium-201 and PET Imaging in Evaluation of Myocardial Viability and Management of Patients with Coronary Artery Disease and Left Ventricular Dysfunction

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The reported mortality of patients with coronary artery disease (CAD) and congestive heart failure is high but variable. In the clinical management of these patients, the available treatment choices are medical therapy, cardiac transplantation and myocardial revascularization. Myocardial revascularization has become an attractive alternative in the management of patients with CAD and poor left ventricular function because medical therapy is associated with a high mortality and cardiac transplantation is expensive and not practical due to shortage of donor hearts. Myocardial revascularization, however, should be recommended in those patients in whom the procedure is very likely to reverse regional and global left ventricular dysfunction and to improve heart failure symptoms and survival. Thallium-201 rest-redistribution myocardial scintigraphy and PET imaging of myocardial perfusion and ^{18}F-fluoro-deoxyglucose metabolism have been extensively evaluated for the assessment of myocardial viability and for prediction of recovery of regional left ventricular dysfunction following myocardial revascularization; with positive and negative predictive accuracies of 72% and 70% for ^{201}Tl rest-redistribution imaging and 83% and 84% for perfusion-metabolism PET imaging. Both modalities also are predictive of improvement in left ventricular ejection fraction after myocardial revascularization. Patients with congestive heart failure who demonstrate the PET pattern of mismatch are more likely to improve their heart failure symptoms following revascularization than those without the mismatch pattern. Furthermore, the PET pattern of mismatch identifies a subgroup of patients who are at very high risk for cardiac death on medical therapy. Survival of these patients can be significantly improved by myocardial revascularization.

Key Words: myocardial viability; left ventricular dysfunction; coronary artery disease; PET; thallium-201

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CLINICAL IMPORTANCE AND DEFINITION OF MYOCARDIAL VIABILITY

The reported mortality of patients with coronary artery disease (CAD) and congestive heart failure is high but variable, ranging from 15% to 60% per year (*1–4*). In the CASS study (*4*), mortality of medically treated patients was related to the severity of left ventricular (LV) dysfunction. The annual mortality in 77 patients with LVEF = 31%–35%, was 9%, in 113 patients with LVEF = 26%–30% was 12% and in 172 patients with LVEF < 25% was 24%. In the clinical management of patients with CAD and poor LV function, the available treatment choices, other than medical therapy, are cardiac transplantation and myocardial revascularization (coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA)). One year survival after cardiac transplantation is currently favorable at approximately 90% (*5*). Cardiac transplantation, however, cannot be performed in 90% of heart failure patients who are potentially eligible, due to the shortage of donor hearts (*6*). Moreover, cardiac transplantation is an expensive procedure.

It is well recognized that in some patients, poor LV function and heart failure may improve after myocardial revascularization. In the CASS study (*4*), CAB artery bypass surgery was beneficial in patients with severe LV dysfunction in promoting their survival and improving their functional status. In patients with LVEF < 35%, cumulative survival for as long as 6 yr was better in the subgroup who underwent myocardial revascularization as compared to those on medical therapy. Specifically, in patients with LVEF < 25%, respective mortalities in the medical and surgical subgroups were 24% versus 15% at 1 yr and 62% versus 48% at 6 yr. Myocardial revascularization, however, cannot be readily recommended in patients with poor LV dysfunction since the surgery itself is associated with 5%–37% mortality (*7–9*). Therefore, in patients with poor LV function, myocardial revascularization should be recommended to those in whom the procedure is very likely to

reverse regional and global LV dysfunction and to improve heart failure symptoms and survival.

PATHOPHYSIOLOGY OF LV CONTRACTILE DYSFUNCTION

Before discussing the methods for assessing myocardial viability, it is important to recognize that different conditions may lead to LV contractile dysfunction (dyssynergy) and these conditions are quite different with respect to potential for recovery after myocardial revascularization. In patients with CAD, LV dyssynergy may be due to: (1) transmural myocardial infarction, (2) nontransmural myocardial infarction, (3) myocardial hibernation or (4) myocardial stunning. In transmural myocardial infarction (MI), myocardial necrosis involves the full thickness of the myocardium, while in nontransmural myocardial infarction, myocardial necrosis is either limited to the subendocardium or is scattered throughout the myocardium. Revascularization is not expected to improve LV dyssynergy in these two conditions. The term hibernating myocardium was coined by Dr. Rahimtoola (*10,11*) to define abnormal LV function at rest that was due to chronic painless, persistent severe "ischemia" at rest and which was reversible. Hibernating myocardium is a result of reduced myocardial blood flow that causes decreased myocardial contractility while viability is maintained. Restoration of normal blood flow to hibernating myocardium reverses regional wall motion abnormality. Myocardial stunning results from periods of severe ischemia that are too brief to cause myocardial necrosis and may nonetheless be associated with ultrastructural and biochemical changes and, most importantly, with contractile dysfunction that persists for prolonged periods after restoration of perfusion (*12*). This situation is observed clinically when reperfusion is induced after coronary occlusion and salvages some of the jeopardized tissue. The return of contractile function in the salvaged tissue is generally not immediate and may require weeks to months.

BASIS FOR USE OF THALLIUM-201 AND PET METABOLIC TRACERS FOR ASSESSMENT OF MYOCARDIAL VIABILITY

Thallium-201

Thallium-201 is a potassium analogue and its ultimate distribution following intravenous administration is primarily intracellular (*13*). Transport of thallium across the cell membrane has been reported to occur partly via an ouabain inhibitable mechanism, presumed to be the sodium-potassium ATPase pump (*13*). Following intravenous injection, the initial distribution of ^{201}Tl in the myocardium is related to the regional myocardial blood flow and extraction fraction of the myocardium for ^{201}Tl which is 87% (*14*) at normal flow rates. Thus, initial ^{201}Tl myocardial defects, whether injection is made at rest, during exercise or following administration of coronary vasodilator, are produced primarily by regional deficits in myocardial blood flow distribution. In clinical situations, the additional role played by myocardial ischemia or drugs in introducing image defects (by altering extraction fraction) is unclear but appears to be insignificant.

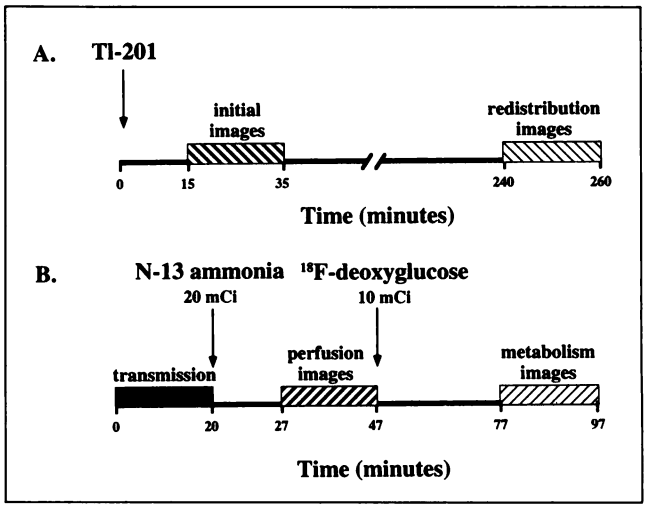

FIGURE 1. Protocols for imaging myocardial viability using ^{201}Tl rest-redistribution scintigraphy and positron emission tomographic imaging of myocardial perfusion and metabolism.

Following the initial distribution, ^{201}Tl concentration in the normal and defect region changes as a function of time. This change is referred to as redistribution. Pohost and colleagues (*15*) showed that in patients with exercise-induced myocardial defects, delayed ^{201}Tl images revealed disappearance of the initial perfusion defects. Reversibility of the initial ^{201}Tl defect generally results from slower clearance of ^{201}Tl from the defect region as compared to the normal zone. Defect reversibility on a rest-redistribution ^{201}Tl study may result from clearance of ^{201}Tl from the normal zone and net accumulation of ^{201}Tl in the defect region over time.

The preferred protocol for assessment of regional myocardial viability with ^{201}Tl is rest-redistribution imaging (Fig. 1). With this protocol, hibernating myocardium would appear as an area with reduced ^{201}Tl uptake on the initial rest image because of reduced regional myocardial blood flow at rest. However, this initial defect is expected to reverse on the redistribution image since, as stated above, ^{201}Tl redistributes in viable myocardial regions. When myocardial dyssynergy is caused by transmural myocardial infarction, a severe ^{201}Tl defect is noted on the resting image that fails to redistribute. In nontransmural myocardial infarction, regional uptake of ^{201}Tl is reduced, in proportion to the volume of myocardial necrosis, and defect intensity remains unchanged on the redistribution image.

When in addition to myocardial viability, stress-induced "ischemia" is being evaluated, ^{201}Tl should be injected during stress and various reinjection/redistribution protocols should be utilized to evaluate reversibility of the initial defect. It should be noted that when ^{201}Tl is injected during exercise or pharmacologic stress, it is not possible to de-

termine to what extent a reversible defect represents hibernating myocardium versus stress-induced "ischemia." For this reason, reversible and nonreversible stress/redistribution defects have a highly variable predictive value for recovery of regional LV dysfunction.

PET

With PET, positron-emitting radionuclides are utilized to obtain tomographic images of regional myocardial perfusion, metabolism and receptor density. Four different PET approaches have been utilized for assessment of myocardial viability: (1) perfusion-FDG metabolism imaging, (2) determination of oxidative metabolism with ^{11}C-acetate, (3) uptake and retention of ^{82}Rb and (4) the water perfusable tissue index.

By far, myocardial viability has been more extensively evaluated with myocardial perfusion-FDG metabolism PET method than other PET protocols. Therefore, myocardial perfusion-FDG metabolism PET protocol will be the focus of this review. With this protocol, regional myocardial perfusion is first evaluated with ^{13}N ammonia, ^{82}Rb or ^{15}O water. Subsequently, ^{18}F 2-fluoro 2-deoxyglucose (FDG) is used to assess regional myocardial glucose utilization. Regional myocardial distribution of all the three PET perfusion tracers has been shown to be related to regional myocardial blood flow and extraction fraction of the myocardium for a given tracer, which has been well characterized (*16–22*). These tracers, however, have different imaging characteristics; the physical half-life of ^{13}N-ammonia is relatively longer (10 min) than those of ^{82}Rb (75 sec) and ^{15}O-water (2 min), allowing longer imaging time and higher image count density with ^{13}N-ammonia. Since ^{15}O-water exchanges rapidly between blood and surrounding tissue, blood-pool subtraction techniques are needed to delineate myocardial uptake of ^{15}O-water, further complicating the clinical imaging protocol and reducing ^{15}O-water myocardial image quality. Nitrogen-13-ammonia and ^{15}O-water are cyclotron produced while ^{82}Rb may be produced by a portable generator.

FDG is a glucose analogue which crosses the capillary and sarcolemmal membrane at a rate proportional to that of glucose. Following myocardial uptake, FDG is phosphorylated to FDG-6-phosphate and is then trapped in the myocardium because unlike phosphorylated glucose, it is a poor substrate for glycogen synthesis, the fructose phosphate shunt and glycolysis (*23,24*). Regional myocardial uptake of FDG therefore reflects relative distribution of regional rates of exogenous glucose utilization (*23–26*). In the fasting state, fatty acids are the preferred myocardial substrate for ATP production and FDG is taken up very little if any by the myocardium (*26,27*). In ischemic myocardial regions, however, regional substrate utilization shifts from fatty acid oxidation to glucose utilization (*28–30*). Hibernating myocardium therefore would demonstrate increased FDG uptake in the fasting state, unlike the surrounding normal myocardium. In the postprandial state, the normal myocardium shifts from fatty acid to glucose as the primary substrate for ATP production; thus hibernating and normal myocardium both would demonstrate FDG uptake. Therefore, preserved or even enhanced FDG uptake in dysfunctional myocardial regions represents presence of myocardial viability. It is possible that membrane-related ATP glycolytically derived is essential for cell survival (i.e., maintenance of transmembrane ion concentration gradients) which may indeed account for the enhanced FDG uptake (*31*).

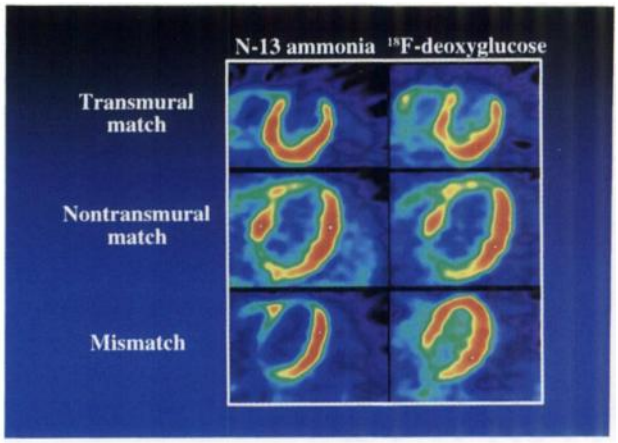

FIGURE 2. Positron emission tomographic patterns of myocardial viability using perfusion-FDG imaging.

With the PET perfusion-metabolism protocol (Fig. 1), when FDG is injected in the postprandial state, three different patterns of myocardial viability may be observed (Fig. 2). Regional myocardial perfusion and FDG uptake may be concordantly reduced or absent, the so-called perfusion metabolism "match" pattern. Based on the severity of perfusion and FDG deficit, the "match" pattern may be categorized as transmural match (absent or markedly reduced perfusion and FDG uptake) or nontransmural match (mildly to moderately reduced perfusion and FDG uptake). We have used these two terms to indicate that transmural match implies presence of transmural myocardial infarction while nontransmural match suggests the presence of a mixture of viable and nonviable tissue in a given myocardial region and thus nontransmural myocardial necrosis. When regional myocardial FDG uptake is disproportionately enhanced as compared to regional myocardial blood flow, the pattern is termed perfusion-metabolism "mismatch." This PET pattern is thought to represent hibernating myocardium. Regional dysfunction due to myocardial stunning may be manifested by normal blood flow and normal, enhanced or reduced glucose utilization.

PREDICTION OF POTENTIAL FOR RECOVERY OF REGIONAL LV DYSSYNERGY FOLLOWING REVASCULARIZATION

Rest-Redistribution Thallium-201 Imaging

As shown in Table 1, three studies have reported the utility of rest-redistribution ^{201}Tl imaging for predicting recovery of regional LV dyssynergy following revascularize-

TABLE 1
Predictive Accuracies of Thallium-201 Rest-Redistribution Myocardial Perfusion Imaging for Recovery of Regional Left Ventricular Dyssynergy after Myocardial Revascularization

Author, year	Reference	Number of patients (segs)	Predictive accuracy	
			Positive	Negative
Mori, 1991	32	17 (51)	11/14 (85%)	23/37 (62%)
Alfieri, 1993	33	13 (120)	92/100 (92%)	14/20 (70%)
Ragosta, 1993	34	21 (176)	81/141 (57%)	6/6 (100%)
Total		51 (274)	184/255 (72%)	64/92 (70%)

Ref = reference number, segs = segments.

tion. In the study of Mori et al. (*32*), 51 myocardial regions were identified in 17 patients with prior anterior wall myocardial infarction which were supplied by at least 90% stenosed left anterior descending coronary arteries. Regional wall motion was assessed one week prior to and six weeks after revascularization in all patients. Eleven of 14 myocardial regions with ^{201}Tl redistributions showed improvement of regional wall motion after revascularization (positive predictive accuracy of 85%). In this study, 23 of 37 myocardial regions without ^{201}Tl redistribution did not show improvement of regional wall motion after revascularization (negative predictive accuracy of 62%). In the study of Alfieri et al. (*33*), 128 kinetic myocardial regions in 13 patients with CAD and LV dysfunction were evaluated. None of these 120 regions had clinical evidence of myocardial infarction and all were supplied by coronary arteries having at least 75% stenosis and which were deemed graftable prior to enrollment of patients into the study. Regional wall motion was assessed in all patients prior to and (3 to 12 mo) after CABG. Reversible rest-redistribution ^{201}Tl defects predicted improvement of regional wall motion in 92% of segments and nonreversible rest-redistribution ^{201}Tl defects predicted lack of improvement in regional wall motion in 70% of regions. In a recent study from Ragosta et al. (*34*), 21 patients with LV dysfunctions (LVEF < 35%, average 27% ± 5%) underwent rest-redistribution planar ^{201}Tl imaging and regional wall motion analysis prior to and 2 mo after CABG surgery. In this study, regional myocardial viability was defined by one of four criteria: normal ^{201}Tl uptake, reversible defects, partially reversible defects and mild defects that were nonreversible. Of a total of 176 segments with severe asynergy, 141 showed one of the four patterns of myocardial viability and 57% showed improvement in regional wall motion after revascularization. The positive predictive accuracy of the four patterns of myocardial viability were not significantly different from one another: 62% for normal thallium uptake patterns, 63% for reversible defects, 58% for partially reversible defects and 55% for mild but nonreversible defects. Of the 35 segments which were classified by rest-redistribution ^{201}Tl study as nonviable (severe defects which were nonreversible), 77% did not show improvement in regional wall motion after revascularization. The positive predictive accuracy of the four different patterns of myocardial viability were not significantly different from one another: 62% for normal thallium uptake, 63% for reversible defects, 68% for partially reversible defects and 55% for mild nonreversible defects.

Overall, these three studies (*32–34*, Table 1) suggest that rest-redistribution ^{201}Tl imaging has an average positive predictive accuracy of 72% and a negative predictive accuracy of 70% for improvement of regional LV dyssynergy following myocardial revascularization. The results, however, are variable from study to study, with positive predictive accuracies ranging from 57% to 92% and negative predictive accuracies ranging from 62% to 77%.

Exercise-Redistribution/Reinjection Thallium-201 Imaging

Three studies have compared the 4-hr ^{201}Tl redistribution and ^{201}Tl reinjection protocols for prediction of improvement in regional LV dysfunction after myocardial revascularization (*35–37*). Dilsizian et al. (*35*) showed that of 23 dyssynergic myocardial segments which were nonreversible or partially reversible on stress-4-hr redistribution images, 10 did not show improvement of regional wall motion following myocardial revascularization (negative predictive accuracy of 43%). Low negative predictive accuracies were also reported by other investigators: 53% (16/14 segments) by Ohtani et al. (*36*) and 48% (12/25 segments) by Tamaki et al. (*37*). In these three studies, lack of defect reversibility after ^{201}Tl reinjection predicted a higher percentage of LV regions that did not improve after myocardial revascularization; 100% (8/8), 75% (12/16), and 75% (6/8), respectively (*35–37*). In the study of Ohtani et al. (*36*), the accuracy of the ^{201}Tl reinjection protocol for predicting normal or improved wall motion after revascularization was 73% (33/45 segments), however, 26% of all segments analyzed in this study had normal wall motion before surgery. As mentioned earlier, reversible defects on stress-redistribution/reinjection ^{201}Tl images do not distinguish stress-induced ischemia from hibernating myocardium. Therefore, the predictive accuracy of reversible ^{201}Tl defects, when ^{201}Tl is injected during stress, is expected to be highly variable, depending on the study population.

Myocardial Perfusion-FDG Metabolism Imaging with PET

Table 2 summarizes the results from seven studies reporting the value of myocardial perfusion-FDG metabolism match and mismatch patterns for predicting postrevascularization improvement of regional LV contractile dysfunction (*37–43*). A total of 356 dyssynergic myocardial segments were reported in 135 patients. The average reported positive and negative predictive accuracies for the PET mismatch pattern were 83% (186/225) and 84% (110/131), respectively. The positive predictive accuracies ranged from 72% to 95% and the negative predictive accuracies ranged from 75% to 100%. In three studies (*37,39,40*), FDG

TABLE 2
Predictive Accuracies of Perfusion-FDG Metabolism PET Imaging for Recovery of Regional Left Ventricular Dyssynergy After Myocardial Revascularization

Author, year	Reference	Number of patients (segs)	Predictive Accuracy	
			Positive	Negative
Tillisch, 1986	38	17 (67)	35/41 (85%)	24/26 (92%)
Tamaki, 1989	39	20 (46)	18/23 (78%)	18/23 (78%)
Tamaki, 1991	37	11 (56)	40/50 (80%)	6/6 (100%)
Lucignani, 1992	40	14 (54)	37/39 (95%)	12/15 (80%)
Carrel, 1992	41	23 (23)	16/19 (84%)	3/4 (75%)
Gropler, 1992	42	16 (53)	19/24 (79%)	24/29 (83%)
Gropler, 1993	43	34 (57)	21/29 (72%)	23/28 (82%)
Total		135 (356)	186/225 (83%)	110/131 (84%)

TABLE 3
Accuracy of Thallium-201 Rest-Redistribution Scintigraphy for Predicting Improvement (by at least 5%) in LVEF After Myocardial Revascularization

Author, year	Reference	Number of patients (segs)	Predictive accuracy	
			Positive	Negative
Iskandrian, 1983	47	26	12/16 (75%)	8/10 (80%)
Mori, 1991	32	17	4/7 (57%)	8/10 (80%)
Ragosta, 1993	34	21	7/10 (70%)	8/11 (73%)
Total		64	23/33 (70%)	24/31 (77%)

uptake was assessed in the fasting state, while the remaining four studies (*38,41–43*) evaluated regional myocardial FDG uptake in the glucose-loaded state. Theoretically, fasting FDG studies may demonstrate small, but functionally insignificant, amounts of hibernating myocardium because of low myocardial background activity (no FDG uptake by the surrounding normal and nonviable myocardial segments). Although this has been thought to diminish the positive predictive accuracy of fasting FDG studies for recovery of regional LV dysfunction, the average reported positive predictive accuracy for fasting FDG studies is 85% and appears to be similar to the average positive predictive accuracy of postglucose loading FDG studies, i.e., 81%. Different approaches to the analysis of perfusion and metabolism pattern, however, may affect the predictive accuracy. Gropler et al. (*43*) first normalized the relative uptake of perfusion tracer and FDG to their respective highest tracer activity concentrations and then evaluated ratios of FDG-to-perfusion image as criteria for match and mismatch. This approach differs from the original one which normalized the myocardial FDG uptake to the myocardial region with the highest perfusion (upper 10% of tracer concentration) and defined match and mismatch by differences between FDG and perfusion rather than ratios. The "ratio" approach had an even lower positive predictive accuracy (52%) when myocardial segments with milder degrees of regional contractile dysfunction were included in the analysis.

In one study (*44*), FDG was injected after exercise rather than at rest in 16 patients. The reported positive and negative predictive accuracies with this approach were 68% and 79%, respectively. As with reversible exercise ^{201}Tl defects, postexercise myocardial uptake of FDG is expected to be observed in regions with exercise-induced ischemia as well as hibernating myocardium, resulting in lower positive predictive accuracy for recovery of LV dysfunction. In another study (*45*), regional FDG uptake, without comparison to perfusion, was used to predict recovery of regional myocardial dyssynergy. These investigators performed ROC analysis of various thresholds for normalized regional FDG uptake and determined that a 85%–90% value yielded a sensitivity of 85% and specificity of 84% for detection of regional functional recovery after revascularization. Reanalysis of these data shows that this threshold is associated with a positive predictive accuracy of 70% (23/33) and a negative predictive accuracy of 93% (53/57) for prediction of functional recovery after revascularization. It should be noted that it would not be possible to determine whether myocardial perfusion is concordantly reduced (nontransmural match pattern) or myocardial perfusion is more severely reduced (mismatch pattern) without comparing regional FDG uptake to regional myocardial perfusion. As stated earlier, such distinction is important, because the former is not expected to demonstrate recovery after myocardial revascularization. In the study of Lucignani et al. (*40*) and a preliminary report from Vom Dahl et al. (*46*), a "hybrid" imaging approach was used in which myocardial perfusion was assessed by ^{99m}Tc-sestamibi SPECT and myocardial metabolism was evaluated by FDG PET imaging. Vom Dahl and colleagues reported positive and negative predictive accuracies of 77% and 88% for postrevascularization recovery of regional LV dysfunction.

PREDICTION OF POTENTIAL FOR RECOVERY OF LV EJECTION FRACTION FOLLOWING REVASCULARIZATION

Rest-Redistribution Thallium-201 Imaging

In 1983, Iskandrian and colleagues (*47*) reported on rest-redistribution ^{201}Tl scintigraphy for prediction of improvement in LVEF following coronary artery bypass surgery in 26 patients with abnormal preoperative LV function (LVEF < 50%). In this study, various criteria for myocardial viability were used. In 20/26 patients who had perfusion defects on the initial ^{201}Tl image, the positive and negative predictive accuracies of defect reversibility for improvement in LVEF were 67% and 57%, respectively. When normal patterns of ^{201}Tl uptake and abnormal regional ^{201}Tl washout in nonreversible defects were considered as additional criteria for myocardial viability, the positive and negative predictive accuracies increased to 75% and 80%, respectively. These results and those of two subsequent studies are summarized in Table 3. In the study

TABLE 4
Value of Perfusion-Metabolism PET Studies for Predicting Improvement in LVEF After Myocardial Revascularization

Author, year	Reference	Number of patients	Patients with mismatch		Patients without mismatch	
			Pre	Post	Pre	Post
Tillisch, 1986	38	17	30 ± 11	45 ± 14	30 ± 11	31 ± 12
Besozzi, 1992	48	56	29 ± 12	41 ± 11	43 ± 10	39 ± 16
Depre, 1993*	49	23	43 ± 18	52 ± 15	35 ± 9	24 ± 8

*LVEF data are not part of the published abstract, but were presented at the 1993 American Heart Association Meeting.
Pre = prerevascularization LVEF. Post = postrevascularization LVEF.

of Ragosta et al. (*34*), 21 patients with LVEF < 35% were evaluated and the criterion for "significant" myocardial viability was selected as presence of at least seven viable myocardial segments demonstrating either normal ^{201}Tl uptake, a reversible defect, a partially reversible defect or a nonreversible mild defect. The positive and negative predictive accuracies for at least a 5% increase in LVEF were respectively 70% and 73% (Table 3) and for at least a 10% increase in LVEF were respectively 60% and 100% (*34*). Overall, as shown in Table 3, the average literature positive and negative predictive accuracies of ^{201}Tl rest-redistribution scintigraphy for prediction of postrevascularization improvement (by at least 5%) in LVEF are respectively 70% and 77%.

Myocardial Perfusion-FDG Metabolism Imaging with PET

Literature reports on the value of PET for predicting improvement in LVEF are predominantly presented as a comparison between pre- and postrevascularization LVEFs in patients with and those without significant perfusion-FDG metabolism mismatch. The results are summarized in Table 4 for three studies (*38,48,49*). In all three studies, the average LVEF significantly increased from pre- to postrevascularization in patients who had the PET pattern of perfusion-metabolism mismatch. In contrast, the average LVEF remained unchanged or decreased in patients who did not have the PET pattern of perfusion-metabolism mismatch.

PREDICTION OF POTENTIAL FOR IMPROVEMENT IN HEART FAILURE FOLLOWING REVASCULARIZATION

Since most patients with poor LV function suffer from heart failure symptoms, an important goal in assessing myocardial viability is to predict recovery of heart failure symptoms following myocardial revascularization. There are no reported studies, to our knowledge, that evaluates the role of ^{201}Tl myocardial imaging for this purpose. However, this question has been addressed by two groups of investigators, using myocardial perfusion-FDG metabolism PET imaging.

Eitzman and colleagues (*50*) used PET to assess myocardial viability in 82 patients with poor LV function (average LVEF = 34%). Improvement in heart failure, by at least one class, was related to the PET pattern (presence or absence of mismatch) and type of treatment (revascularization or medical therapy). More patients in the subgroup with mismatch who underwent revascularization than the other subgroups had improvement in the heart failure class (*50*). Di Carli et al. (*51*) performed perfusion-FDG metabolism PET studies in 93 patients with LV dysfunction (average LVEF = 25%) who had follow-up for an average of 13.6 mo and of whom 66 had severe heart failure symptoms. In the medically treated patients as a group, the severity of heart failure symptoms did not change significantly during the follow-up period. In contrast, a significant improvement in heart failure symptoms was observed only in the subgroup of patients with mismatch who underwent revascularization (*51*). Stated differently, in the 34 patients with heart failure who underwent revascularization, 71% of the subgroup with PET mismatch pattern prior to surgery had improvement in heart failure symptoms, while only 31% of patients without PET mismatch pattern had improvement in heart failure symptoms (Fig. 3).

These data suggest that the PET pattern of myocardial viability not only predicts recovery of regional and global LV dysfunction after myocardial revascularization, but it also identifies the subgroup of patients with poor LV function and heart failure who are most likely to show relief of heart failure symptoms as a result of revascularization.

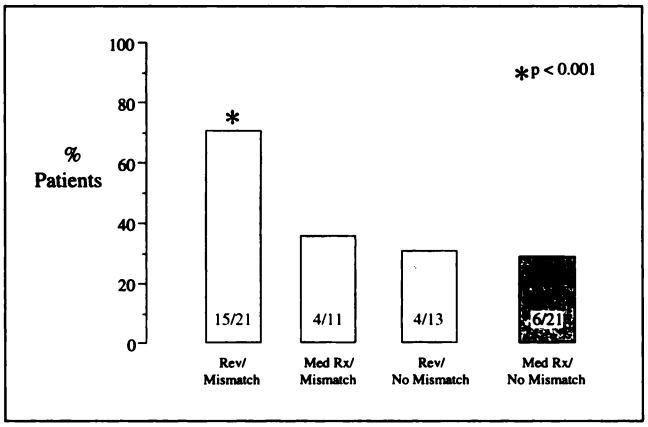

FIGURE 3. Prediction of improvement in heart failure symptoms on medical therapy or after myocardial revascularization by perfusion-FDG PET patterns of myocardial viability. The data are derived from Di Carli et al. (*51*).

TABLE 5
The Relationship Between Perfusion-Metabolism PET Patterns of Myocardial Viability, Type of Treatment and Mortality in Patients with CAD and LV Dysfunction

Author, year	Reference	Number of patients	Patients with mismatch		Patients without mismatch	
			Med	Rev	Med	Rev
Eitzman, 1992	50	83	33% (6/18)	4% (1/26)	8% (2/24)	0% (0/14)
Di Carli, 1993	51	93	41% (7/17)	12% (3/26)	9% (3/33)	6% (1/17)

Med = medical therapy, Rev = myocardial revascularization. The percentages under each type of treatment represent mortality rates during the follow-up period.

PREDICTION OF POTENTIAL FOR IMPROVEMENT IN SURVIVAL FOLLOWING REVASCULARIZATION

A major goal of noninvasive diagnostic procedures in the assessment of CAD is to evaluate prognosis and to assess the potential of survival benefit from a treatment plan. Since survival of patients with LV dysfunction relates to the resting LVEF, it may be implied that rest-redistribution ^{201}Tl scintigraphy and perfusion-FDG metabolism PET imaging, by predicting improvement in LVEF also predict survival after myocardial revascularization. Although this hypothesis has not been evaluated by rest-redistribution ^{201}Tl scintigraphy, it has been addressed by two reports using perfusion-FDG metabolism PET imaging.

Eitzman et al. (*50*) evaluated survival of 82 patients with LV dysfunction during an average follow-up period of 12 mo. Of the 44 patients who demonstrated the PET pattern of mismatch, 18 underwent medical therapy and 26 were revascularized. Of the remaining 38 patients who did not have the PET pattern of mismatch, 24 underwent medical therapy and 14 were revascularized. Table 5 summarizes cardiac mortality in the four subgroups and shows that the highest mortality (33%) was noted in the subgroup with PET mismatch who underwent medical therapy. Mortality rate was significantly lower in patients with the PET mismatch pattern who were revascularized. Di Carli et al. (*51*) evaluated survival of 93 patients with LV dysfunction (average LVEF = 25%) during an average follow-up period of 13.6 mo. Patients were categorized into four subgroups based on the presence or absence of the PET mismatch pattern and the type of treatment (medical therapy versus myocardial revascularization). As shown in Table 5, findings were similar to those of Eitzman and associates in that the subgroup with PET pattern of mismatch on medical therapy had the highest mortality of 41%. Of note, in the subgroup with PET pattern of mismatch who underwent revascularization, mortality was significantly lower at 12%.

In the study by Di Carli et al. (*51*), univariate analysis indicated that the extent of mismatch was the only predictor of survival. Heart failure class, current constructive pulmonary disease, sex, age, prior myocardial infarction, presence of Q-waves on resting ECG, diabetes, hypertension, presence of angina, LVEF, extent of PET matched and revascularization were not predictors of survival in the univariate analysis. A stepwise Cox model analysis was performed to determine the prognostic contribution of mismatch when covariates with borderline significance in the univariate analysis were included in the model. The extent of mismatch and revascularization were the only predictors of survival. The relative risk (hazard) of cardiac death associated with mismatch increased by 3.5% with each unit of increment in the percent extent of mismatch, i.e., the more extensive the mismatch, the higher the risk of dying during the follow-up period. In contrast, revascularization was associated with a positive effect on survival, decreasing the risk of cardiac death by 28%. These data were further analyzed to assess the value of mismatch for risk stratification of patients on medical therapy and myocardial revascularization using life-table analysis. Figure 4 shows that the estimated annual survival of patients with mismatch was lower than that of patients without mismatch (log-rank test, $p = 0.007$). Furthermore, the annual survival probability of patients without mismatch was similar between the revascularized and medical therapy subgroups.

CONCLUSIONS

Rational management of patients with CAD and poor LV function relies on proper identification of the subgroup at high risk and those who have the highest potential of benefiting from a particular type of treatment. It is now well recognized that patients with CAD and LV dysfunction have a high but viable mortality on medical therapy. Many of these patients who have intractable heart failure are considered candidates for cardiac transplantation. Despite favorable survival after cardiac transplantation, this procedure cannot be performed in 90% of heart failure patients who are potentially eligible due to a shortage of donor hearts. Cardiac transplantation is also an expensive procedure. Thallium-201 rest-redistribution myocardial scintigraphy and perfusion-FDG metabolism PET imaging may be used to identify presence of hibernating myocardium. Both ^{201}Tl and PET imaging methods have high accuracies for predicting recovery of regional and global LV dysfunction following revascularization. The positive and negative predictive accuracies of PET is higher than ^{201}Tl imaging in this regard. In patients with poor LV function, the PET pattern of perfusion metabolism mismatch is also predictive of improvement in heart failure

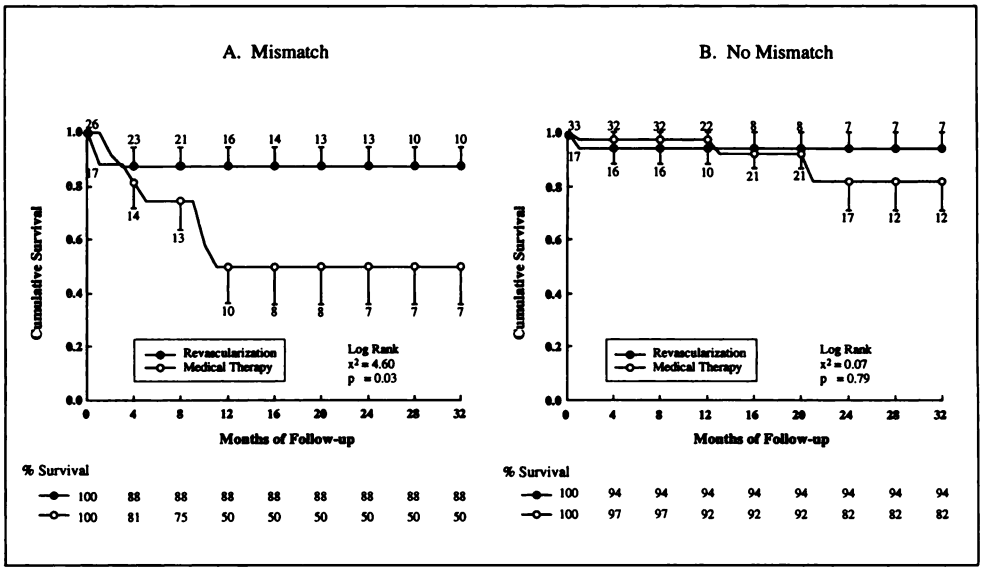

FIGURE 4. Cumulative survival of patients, by presence or absence of positron emission tomographic mismatch and mode of treatment. Reprinted with permission from the American College of Cardiology (*American Journal of Cardiology* 1993: in press).

symptoms and survival benefit after myocardial revascularization. These data suggest that a rational approach may be developed for cost-effective management of patients with CAD and poor LV function.

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