Quantitative Planar Rest-Redistribution $^{201}$TI Imaging in Detection of Myocardial Viability and Prediction of Improvement in Left Ventricular Function After Coronary Bypass Surgery in Patients With Severely Depressed Left Ventricular Function

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Background. Although many patients with multivessel coronary artery disease (CAD) and severely depressed left ventricular (LV) function will benefit from coronary artery bypass graft surgery (CABG), surgeons may be reluctant to perform CABG on these patients without evidence of myocardial viability in regions of severe asynergy. We hypothesized that quantitative planar rest-redistribution $^{201}$TI imaging would identify viable myocardium and predict improved regional and global function after revascularization in patients with depressed LV function and CAD.

Methods and Results. Twenty-one patients (mean LV ejection fraction, $0.27\pm0.05$) were studied. Regional and global LV functions were evaluated before and 8 weeks after CABG with radionuclide ventriculography. Segments were prospectively classified as showing normal, mildly reduced, or severely reduced viability on the basis of quantitative analysis of defect severity and redistribution on planar resting $^{201}$TI imaging. By $^{201}$TI criteria, 90% of hypokinetic segments were classified with normal or mildly reduced viability. Among akinetic or dyskinetic segments, 20% had normal $^{201}$TI uptake, 53% had mildly reduced viability, and only 27% had severely reduced viability. $^{201}$TI viability criteria identified segments that improved function after CABG. Sixty-two percent of severely asynergic segments with normal viability and 54% with mildly reduced viability improved function after surgery, but only 23% with severely reduced viability improved function ($p=0.002$). When only adequately revascularized segments were considered, the predictive value of a positive preoperative viability scan for functional improvement was 73%. The greatest improvement in global LV function after CABG occurred in patients with the greatest number of asynergic segments classified as viable before surgery ($p<0.01$). In 10 patients with more than seven viable, asynergic segments, mean LV ejection fraction increased significantly after CABG ($0.29\pm0.07$ to $0.41\pm0.11$, $p=0.002$). In 11 patients with seven or fewer viable, asynergic segments, mean LV ejection fraction remained unchanged after revascularization ($0.27\pm0.05$ to $0.30\pm0.08$, $p=NS$).

Conclusions. In patients with CAD and severely depressed LV function, preoperative quantitative planar rest-redistribution $^{201}$TI imaging identifies viability in many asynergic myocardial segments, and these segments frequently improve function after CABG. The presence of numerous asynergic but viable myocardial segments before surgery correlated significantly with improvement in global LV function after bypass surgery. (Circulation 1993;87:1630–1641)

Key Words • coronary artery disease • heart failure, congestive • myocardium • radionuclide imaging

Patients with multivessel coronary artery disease (CAD) and severely depressed left ventricular (LV) function may have a survival benefit from myocardial revascularization compared with medical therapy.1–4 Surgeons are often reluctant to perform coronary artery bypass graft surgery (CABG) when the LV ejection fraction (LVEF) is significantly reduced. Although many abnormally contracting myocardial segments result from previous myocardial infarction and irreversible ventricular scarring, recent studies suggest...
that many asynergic zones have sustained metabolic activity.\textsuperscript{5-12} Hyperperfused or "hibernating" segments often improve function with enhancement of coronary blood flow.\textsuperscript{7-11} The clinical challenge is to predict which myocardial regions are viable and will improve systolic function after revascularization, thereby enhancing global LV function. Patients whose asynergy is mainly a result of irreversible myocardial injury would not be expected to improve regional and global function after revascularization.

Several approaches have been described to identify viable but asynergic myocardium. These include increased systolic contraction of premature beats on contrast ventriculography,\textsuperscript{13} inotropic stimulation during contrast ventriculography,\textsuperscript{14} low-dose dobutamine infusion with echocardiographic monitoring,\textsuperscript{15} exercise \textsuperscript{201}TI scintigraphy with or without reinfusion of a second resting dose of \textsuperscript{201}TI,\textsuperscript{16-21} 24-hour delayed \textsuperscript{201}TI imaging,\textsuperscript{22-24} positron emission tomography (PET),\textsuperscript{11,12,25,26} and \textsuperscript{123}Iiodophenylpentadecanoic acid gamma-camera imaging.\textsuperscript{27} The accuracy for predicting improved LV function after revascularization for each of these methods in patients with multivessel CAD and severely reduced ventricular function has not been well established.

Quantitative planar rest-redistribution \textsuperscript{201}TI imaging may be particularly well suited for the evaluation of myocardial viability in patients with severely reduced regional blood flow and LV systolic function, since experimental studies have suggested that myocardial uptake of \textsuperscript{201}TI is dependent on preserved regional flow and viable myocytes able to transport the cation intracellularly.\textsuperscript{28-32} Quantitative planar imaging was used because this technique has been validated\textsuperscript{33} and is highly sensitive and specific in other clinical settings such as detection of coronary disease\textsuperscript{34} and because methods for quantifying single photon emission computed tomography (SPECT) images at rest have not yet been validated. Planar imaging is suitable for assessment of viability in patients with extensive regional asynergy because large zones of myocardium are involved.

This prospective study tested the hypothesis that preserved \textsuperscript{201}TI uptake on resting quantitative planar scintigraphy would identify viability in asynergic myocardial segments and would predict improved regional and global systolic function after CABG in patients with severely reduced LVEF and multivessel CAD.

Methods

Patient Selection

Twenty-eight consecutive patients referred for CABG with ischemic cardiomyopathy and LVEF <35\% were prospectively enrolled, and none had surgery canceled because of preoperative \textsuperscript{201}TI findings. Patients with other forms of cardiomyopathy or those requiring concurrent valve replacement surgery or aneurysmectomy were excluded. Patients with depressed LVEF in whom CABG was never considered were not studied. Three patients died suddenly before follow-up, two refused further participation, and in another two patients the preoperative studies were incomplete. The remaining 21 patients constitute the study cohort. The excluded patients were not different from the study cohort with respect to important clinical or \textsuperscript{201}TI imaging parameters.

FIGURE 1. Drawing of 15-segment model used for analysis of \textsuperscript{201}TI scintigrams and radionuclide ventriculograms. Anterior, anterior projection; 45° LAO, 45° left anterior oblique projection; 70° LAO, 70° left anterior oblique projection.

Protocol

The study protocol was approved by the Human Investigation Committee of the University of Virginia, and written informed consent was obtained from all patients. Clinical data, including the presenting symptoms prompting hospitalization and history of prior infarction, angina, and congestive heart failure, were obtained before surgery. Baseline studies obtained before CABG included coronary angiography and left ventriculography, quantitative planar rest-redistribution \textsuperscript{201}TI imaging, and rest radionuclide ventriculography. Postoperative studies obtained 8 weeks (mean, 64 ± 23 days) after CABG included repeat rest-redistribution \textsuperscript{201}TI imaging and rest radionuclide ventriculography.

Cardiac Catheterization

Cardiac catheterization (10 ± 10 days before CABG) included hemodynamic assessment, coronary angiography, and left ventriculography. Each of the main epicardial coronary arteries was graded by two observers using calipers as having significant stenoses if the lesions narrowed the lumen ≥70\%. Contrast ventriculography was performed in all but two patients, and LVEF was calculated using the 30° right anterior oblique projection after a nonpremature beat by tracing end-diastolic and end-systolic frames with a computer-assisted method (IMAQS system, Trinity).

\textsuperscript{201}TI Imaging and Radionuclide Ventriculography

Quantitative resting planar \textsuperscript{201}TI imaging was performed in the fasting state for assessment of myocardial viability in all patients as previously described at our institution.\textsuperscript{33,35} Patients were imaged at rest in the anterior, 45° left anterior oblique (LAO), and 70° LAO projections 10 minutes and 3 hours after the injection at rest of 2.0 mCi of \textsuperscript{201}TI. In two patients, a left lateral projection image was also acquired to image the anterior wall optimally. In these two patients, radionuclide ventriculography was performed in the same orientation. After acquisition of the delayed \textsuperscript{201}TI image and after the intravenous injection of unlabeled pyrophosphate, [\textsuperscript{99m}Tc]pertechnetate (20 mCi) was injected, and radionuclide ventriculograms were acquired in the same projections as above. LVEF was calculated from the 45° LAO view by an automated technique.

A 15-segment model for each set of \textsuperscript{201}TI and radionuclide ventriculogram images was constructed (Figure 1). \textsuperscript{201}TI images were interpreted by two observers using consensus readings. When agreement could not be achieved, a third observer was asked to resolve the difference. This occurred in <1\% of segments analyzed.
All observers were blinded to the results of other tests and to clinical information. Each segment on $^{201}$TI images was analyzed quantitatively, and the initial (rest) images were classified as showing either normal $^{201}$TI uptake (<25% reduction), a mild defect representing a 25–50% reduction, or a severe defect representing >50% reduction in peak $^{201}$TI uptake. Delayed (redistribution) images were assessed for the presence or absence of redistribution.

$^{201}$TI images obtained 2 months after surgery were read in the same manner and then compared side by side to the preoperative image. Postoperative increases in segmental $^{201}$TI uptake of one or more grades on the initial image were classified as improved. In the analysis of global LV function, $^{201}$TI uptake was considered improved if uptake increased by one or more grades on the initial image in >50% of asynergic segments with corresponding initial $^{201}$TI defects.

The wall motion of each of the 15 radionuclide ventriculogram segments (Figure 1) was graded by two blinded observers as dyskinetic, akinetic, severely hypokinetic, mildly hypokinetic, or normal (~1 through 3, respectively). Preoperative and postoperative studies were read side by side, and observers were blinded to which of the two was the preoperative scan. LV global wall motion score was calculated as the sum of the grades of all 15 segments.

**Definition of Viability**

Three $^{201}$TI patterns of viability were prospectively defined based on the preoperative rest-redistribution images (Figure 2). Wall motion was not considered in the definition of viability. A normal pattern of viability was assigned if a segment showed normal initial $^{201}$TI uptake or demonstrated a defect of any severity with complete redistribution. A mildly reduced pattern of viability was designated if there was an initial defect of any magnitude that showed partial redistribution or if there was an initial defect that was mild (25–50% reduction in $^{201}$TI activity) and showed no redistribution. This latter pattern is often referred to as a “mild persistent defect.” A severely reduced pattern of viability was designated when a segment showed a severe defect with a >50% reduction in $^{201}$TI uptake and no evidence of redistribution on the delayed images.

Figure 3 is an example of a $^{201}$TI image showing predominantly segments with normal or mildly reduced patterns of viability. Despite an LVEF of 22% and akinesis of the anterior wall, septum, and apex and severe hypokinesis of the inferior and lateral walls, most segments show normal or only mildly reduced viability. Figure 4 is an example of a patient with the same LVEF and similar wall motion abnormalities but in whom the apex and septum have a >50% defect in $^{201}$TI uptake and no redistribution. The apex and septum were classified as exhibiting severely reduced viability by our prospective criteria.

**Statistical Analysis**

All data were expressed as mean±SD. Preoperative and follow-up data were compared by paired Student’s $t$ test or a Fisher’s exact test where appropriate. A value of $p<0.05$ (two-sided) was considered significant. Stepwise logistic regression analysis was used to assess multivariate predictors of improvement in global LV function. Variables entered were the number of viable, asynergic segments, history of angina, presence of infarction on presentation, diabetes, and number of Q waves. The final model was chosen by a stepwise selection procedure that retained only significant vari-
ables. Odds ratios and confidence intervals were derived from the final model.36

Results

Clinical, Angiographic, and Hemodynamic Data

The clinical characteristics and cardiac catheterization data from the 21 patients are presented in Table 1. The mean age of the cohort was 64 years, and the majority were men (86%). Most (76%) had a prior history of myocardial infarction; all of these had at least one Q-wave myocardial infarction, and nine patients also had a previous non-Q-wave infarction. Nine patients (43%) had a prior history of congestive heart failure, and 16 (76%) had a prior history of angina pectoris.

At the time of the hospitalization leading directly to CABG, at which time patients were enrolled in this study, 17 (81%) had clinical congestive heart failure or pulmonary edema; only four patients (24%) were free of pulmonary congestion. Sixteen patients (76%) presented clinically with unstable ischemic syndromes; eight of these had confirmed acute myocardial infarction (three of these were Q-wave infarctions), and eight presented with unstable angina. The remaining five patients were free of angina.

Cardiac Catheterization Findings

At the time of cardiac catheterization, the mean LVEF was 0.27±0.05 (range, 0.17–0.35). Sixteen of 21 patients (76%) had >70% narrowing of all three major epicardial coronary arteries; the remaining five had disease of the left anterior descending and right coronary arteries. As summarized in Table 1, the mean pulmonary artery systolic and diastolic pressures, pulmonary capillary wedge pressure, LV end-diastolic pressure, and right atrial pressure were elevated, consistent with severe LV dysfunction.

$^{201}$TI Imaging and Wall Motion

The prospectively defined $^{201}$TI viability patterns in the 315 segments were distributed as follows: among segments with normal viability ($n=159$), 138 had normal uptake on the initial rest image, 20 had a mild initial defect with complete redistribution, and one had a severe defect with complete redistribution. Among segments with mildly reduced viability ($n=115$), 19 had a

| TABLE 1. Clinical Characteristics and Cardiac Catheterization Data From 21 Patients Referred for CABG |
| Mean age (years) | 64±8                  |
| Sex (n)         | Male 18 Female 3     |
| Cardiac history | CHF 9 (43%)           |
| Prior MI        | Q-wave 16 (76%)       |
| Non-Q-wave      | Angina 16 (76%)       |
| Prior CABG      | 2 (10%)               |
| Symptoms at presentation | CHF/pulmonary edema 17 (81%) |
| Myocardial infarction | 8 (38%)     |
| Q-wave          | 3 (14%)               |
| Non-Q-wave      | 5 (24%)               |
| Unstable angina | 8 (38%)               |
| VT              | 5 (24%)               |
| Cardiac catheterization data | Ejection fraction 0.27±0.05 |
| No. of vessels diseased per patient | 2.8±0.4 |
| PA systolic (mm Hg) | 40±15             |
| PA diastolic (mm Hg) | 21±9               |
| PCWP (mean, mm Hg) | 19±10              |
| LVEDP (mm Hg) | 28±10                |
| RA (mean, mm Hg) | 9±3                 |

CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; MI, myocardial infarction; VT, ventricular tachycardia; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; RA, right atrial.

![FIGURE 4. Initial and delayed rest-redistribution $^{201}$TI scintigrams in the anterior and 45° left anterior oblique (LAO) projection from a patient with ejection fraction and wall motion abnormalities similar to those in Figure 3, but with a large region of myocardium with severely reduced viability in the apex and septum.](image-url)
mild defect with partial redistribution, 45 had a severe defect with partial redistribution, and 51 had mild persistent defects. Severely reduced viability was seen in the remaining 41 segments.

Regional wall motion was abnormal in the majority of segments in this patient population. Sixty-five segments had normal wall motion, and 74 were mildly hypokinetic. Severely asynergy was seen in the remaining 176 segments; of these, 82 were severely hypokinetic, 87 were akinetic, and seven were dyskinetic.

Relation of Viability to Wall Motion

The relation between regional wall motion defined by radionuclide ventriculography and the preoperative $^{201}$TI pattern of viability in the 315 segments analyzed is shown in Figure 5. As expected, of the 65 segments with normal wall motion, 99% were viable by $^{201}$TI criteria; 55 (85%) of these segments showed a normal pattern of normal viability, and an additional nine (14%) had only a mild reduction in viability. Only one normally contracting segment had a scintigraphic pattern of severely reduced viability. Seventy-four segments had mild hypokinesis; almost all of these (93%) had evidence of viability by $^{201}$TI imaging, with 46 (62%) having a pattern of normal viability, 23 (31%) showing a pattern of mildly reduced viability, and only five (7%) demonstrating severely reduced viability. Eighty-two segments had severe hypokinesis; most of these (88%) were viable by $^{201}$TI criteria, with 39 (48%) having a pattern of normal viability, 33 (40%) having mildly reduced viability, and only 10 (12%) demonstrating severely reduced viability. There were 94 akinetic or dyskinetic segments; 69 (73%) of these showed evidence of viability, with 19 (20%) showing a normal pattern of viability and 50 (53%) demonstrating a mild reduction in viability. Only 25 akinetic/dyskinetic segments (27%) had a pattern of severely reduced viability. Thus, nearly three quarters of segments with either akinetic or dyskinetic wall motion were viable by $^{201}$TI criteria.

Preoperative $^{201}$TI Imaging and Prediction of Postoperative Improvement in Regional Function

Improvement in function after CABG occurred in 19 of 74 mildly hypokinetic segments (26%), in 43 of 82 severely hypokinetic segments (52%), in 40 of 87 akinetic segments (46%), and in six of seven dyskinetic segments (86%). The prospective classification of myocardial viability predicted improvement in postoperative regional systolic function. Because improvement in normal or mildly hypokinetic segments was difficult to measure, the outcome 8 weeks after surgery of only the 176 segments with severe preoperative asynergy (severe hypokinesis, akinesis, or dyskinesis) was analyzed (Figure 6). Of the 58 severely asynergic segments showing a normal pattern of viability before surgery, 36 (62%) improved function after CABG. Of the 83 segments with a mild reduction in viability by $^{201}$TI criteria before surgery, 45 (54%) improved after CABG. In contrast, only eight of 35 segments (23%) with a severely reduced pattern of viability before surgery improved function 2 months after CABG. Compared with segments with a severely reduced pattern of viability, the segments with

Pre-operative $^{201}$TI Uptake

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<th>Condition</th>
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<th>Mildly Reduced (%)</th>
<th>Severely Reduced (%)</th>
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<tr>
<td>Normal (n=65)</td>
<td>55 (85%)</td>
<td>46 (62%)</td>
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<tr>
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<td>23 (31%)</td>
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FIGURE 5. Bar graph showing relation between preoperative regional wall motion and preoperative viability as determined by rest-redistribution thallium scintigraphic criteria in 315 segments.

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FIGURE 6. Bar graph showing correlation between improvement in regional function after coronary artery bypass surgery and preoperative $^{201}$TI uptake in the subgroup of 176 segments with severe asynergy (severe hypokinesis, akinesis, or dyskinesis). Segments with normal or mildly hypokinetic wall motion before surgery were excluded from this analysis.
normal or mildly reduced viability by $^{201}$TI criteria were significantly more likely to improve function after revascularization ($p<0.002$).

Interestingly, the percentage of segments with normal viability that improved function was comparable to the percentage of segments with mild reduction in viability that improved function. To determine whether there were any differences among the various subgroups of "viability," the 141 severely asynergic but viable segments were further analyzed according to the four possible combinations of $^{201}$TI patterns that were defined as reflecting viability. Thirty-one of 50 segments (62%) with normal initial $^{201}$TI uptake, five of eight segments (63%) with an initial defect showing complete redistribution, 29 of 50 segments (58%) with an initial defect with partial redistribution, and 18 of 33 segments (55%) with mild persistent defects improved function 8 weeks after revascularization surgery. The differences between these subgroups were not significant.

**Degree of Improvement in Function Related to Preoperative $^{201}$TI Image Patterns**

Segments with normal or mildly reduced patterns of viability had a greater degree of improvement in function after surgery than did segments with severe reduction in viability. Segments with a preoperative pattern of normal viability improved the wall motion score by $+1.0 \pm 1.1$ units, which is not significantly different from those with a mild reduction in viability, which improved by $+0.82 \pm 1.0$ units. In contrast, segments with a severe reduction in viability had significantly less improvement in wall motion score, improving by only $+0.31 \pm 0.72$ units ($p=0.0001$ compared with viable segments). Wall motion rarely returned completely to normal at 8 weeks in the 176 segments with severe hypokinesis, akinesis, or dyskinesis before surgery, and this occurred exclusively in segments with evidence of viability by $^{201}$TI criteria. Nineteen of 141 "viable" segments (13.5%) with severe asynergy at baseline showed normal systolic function 8 weeks after revascularization, whereas none of 35 segments with severe reduction in viability by $^{201}$TI criteria returned to normal function at 8 weeks ($p<0.02$).

**Postoperative $^{201}$TI Imaging and Prediction of Postoperative Regional Function**

Eighteen patients underwent repeat $^{201}$TI imaging 8 weeks after surgery to detect changes in $^{201}$TI uptake after revascularization. Of the 270 segments analyzed in this patient subgroup, 156 (58%) had severe asynergy (severe hypokinesis, akinesis, or dyskinesis) on the preoperative scan. Twenty-seven of 41 severely asynergic segments (66%) with normal $^{201}$TI uptake both before and after surgery improved function. In the 115 remaining segments with abnormal $^{201}$TI uptake before surgery, 59 improved, 39 were unchanged, and 17 had worsened $^{201}$TI uptake after surgery.

Figure 7 shows the relation between preoperative viability classification, change in postoperative $^{201}$TI uptake, and improvement in function in the 115 asynergic segments with abnormal $^{201}$TI uptake before surgery. There was a strong correlation between improvement in function and improvement in postoperative $^{201}$TI uptake ($p<0.001$). Segments with normal or mildly reduced preoperative viability with improved $^{201}$TI uptake after surgery were significantly more likely to improve function (32 of 44, 73%) than were segments without improved $^{201}$TI uptake (10 of 28, 36%) or segments with worsened uptake (three of 17, 18%). Because improved postoperative $^{201}$TI uptake is indicative of improved perfusion, these data suggest that adequate revascularization, in addition to myocardial viability, is important for improved postoperative function. In contrast, among the 26 segments classified before surgery as having severely reduced viability, 15 (58%) had improved thallium uptake after surgery. Although these segments had improved $^{201}$TI uptake after revascularization, only five of 26 segments (19%) showed a corresponding improvement in function.

**Predictive Value of Rest-Redistribution $^{201}$TI Scintigraphy**

For a myocardial segment to improve function after revascularization, it must be viable, there must not be extensive preoperative subendocardial infarction, adequate perfusion must be restored by surgery (distal
arterial sites must be able to accept a bypass graft, and perioperative infarction or late graft closure must be avoided. In this study population, which tended to have diffuse and severe obstructive atherosclerosis, the predictive value of a positive preoperative viability test by $^{201}$TI criteria for functional improvement was 57% (81 of 141; 95% CI, 49–65%). In patients showing improvement in postoperative segmental $^{201}$TI uptake (suggesting adequate revascularization and no perioperative infarct), the predictive value of a positive preoperative viability test for functional improvement was 73% (32 of 44; 95% CI, 60–86%). Conversely, the predictive value of a negative viability test for lack of functional improvement was 77% (67 of 87; 95% CI, 69–85%).

Rest-Redistribution $^{201}$TI Scintigraphy and Prediction of Improvement in Global Ventricular Function

The effect of CABG on LVEF is depicted in Figures 8 and 9. Figure 8 is a plot of the change in LVEF versus the number of viable, severely asynergic segments based on $^{201}$TI criteria. As in previous analyses, a segment was defined as viable if it showed either a pattern of normal viability or a mild reduction of viability. As shown, the greatest increases in LVEF occurred in patients with the greatest number of viable, asynergic segments and improved postoperative $^{201}$TI uptake. It should be noted that all patients in this study population had at least one viable but asynergic segment.

Patients were divided into two groups (Figure 9). Group A consisted of 10 patients with more than seven viable, asynergic segments. Group B consisted of 11 patients with seven or fewer viable, asynergic segments. The mean preoperative LVEF did not differ between the groups (0.27±0.05 versus 0.29±0.07, respectively; p=0.02). The 8-week postoperative LVEF differed significantly between the two groups (0.41±0.11 versus 0.30±0.08, p<0.02). LVEF increased significantly after surgery only in group A (p=0.002). As depicted in Figure 8, six of 10 group A patients had >0.10 increase in LVEF after surgery, whereas no group B patients had such an increase after surgery (p<0.004). Although the two groups had similar LVEF at baseline, the preoperative global wall motion score (the sum of the 15 individual wall motion scores, Figure 10) was worse in group A than group B patients (14.3±2.7 versus 25.4±6.9, p=0.0001). Eight weeks after surgery, the global wall motion score improved significantly in group A (28.5±7.1, p<0.001) but did not change in group B (23.5±7.4, p=NS). The improvement in wall motion score from before to after surgery was significantly greater in group A (14.2±7.4 versus −1.9±7.3, p=0.0001).

Group A and group B patients were not different with respect to mean age, number with prior myocardial
infarction, number with diabetes mellitus, percent with preoperative angina or congestive heart failure, or the mean number of critically narrowed coronary arteries per patient. There was no difference between these two groups with respect to medications affecting either preload (such as lasix or nitrates) or afterload (such as angiotensin converting enzyme inhibitors) either before surgery or 8 weeks after surgery. The two groups did differ with respect to Q waves on the preoperative ECG; four of 10 group A patients (40%) had Q waves versus 10 of 11 (91%) in group B (p = 0.02). In univariate analysis, only the number of Q waves per patient (p = 0.02) and the number of viable, asynergic segments per patient (p < 0.01) were significantly associated with improvement in global LVEF. Presence of angina did not correlate with improvement in LVEF. In multivariate analysis, only the number of viable, asynergic segments per patient was an independent correlate of improvement of LVEF (r = 0.67).

Discussion
An accurate noninvasive determination of myocardial viability is important for clinical decision making to identify patients with CAD and severe LV dysfunction who will benefit most from revascularization. Clinical trials evaluating the efficacy of coronary bypass surgery have shown that patients with multivessel CAD and depressed LVEF benefit most from revascularization, even if symptoms of angina are mild or absent. Recently, there has been greater appreciation among clinicians for the phenomena of “stunned” and “hibernating” myocardium. Either of these pathophysiological states may result in profound LV dysfunction in the absence of myocardial necrosis or fibrosis. Thus, simple assessment of regional systolic function does not distinguish irreversibly injured from viable but asynergic myocardium. There are experimental and clinical data that suggest that imaging of myocardial perfusion, metabolism, or both can provide clinically pertinent information regarding myocardial viability in the presence of regional or global systolic dysfunction.

Observations in the Present Study
The findings in the present study expand the previous observations with either rest or exercise 201Tl imaging in assessing resting myocardial perfusion and viability in patients with CAD and severely depressed LVEF. As expected, nearly all segments (99%) showing normal regional wall motion were viable by 201Tl criteria, with the majority (85%) showing normal initial 201Tl uptake or complete redistribution. Similarly, most segments (90%) that were hypokinetic had evidence of preserved viability by 201Tl imaging, with 54% of these segments showing a pattern of normal viability. An important finding in this study was that 73% of akinetic or dyskinetic segments showed evidence of viability, with 20% showing normal viability and 53% demonstrating only mildly reduced viability. In this patient population, only 27% of segments that were akinetic/dyskinetic showed a pattern of severely reduced viability.

In assessment of the predictive value of 201Tl scintigraphic viability criteria for predicting functional improvement after revascularization, a myocardial segment must not only contain viable tissue but must also be adequately revascularized to improve regional function. The patient cohort described in this study, however, had severe diffuse obstructive CAD, and vessels supplying many segments were suboptimal for the distal bypass graft anastomosis. When only preoperative myocardial viability criteria were considered, the predictive value of a positive preoperative viability test for functional improvement was 57%. When adequacy of revascularization is considered (as reflected by the postoperative 201Tl image), the predictive value of a positive preoperative viability test for functional improvement was 73%. This emphasizes the importance of assessing the likelihood that revascularization will be successful before CABG is considered for these patients.

Resting 201Tl imaging parameters correlate with improvement in global LVEF after CABG. The greater the number of viable, asynergic segments, the greater was the improvement in LVEF. Patients with more than seven viable, asynergic segments had significant postoperative increases in LVEF, whereas those with seven or fewer viable segments had no postoperative improvement in LVEF. As depicted in Figure 7, six of the 10 patients with more than seven viable, asynergic segments demonstrated a >0.10 increase in LVEF after revascularization, whereas no patient with seven or fewer viable, asynergic segments by 201Tl criteria had such improvement in LVEF after surgery.

Thus, our findings demonstrate that improvement in both regional and global LV function is related to the
extent of myocardial viability as evaluated on preoperative rest-redistribution $^{201}$Tl imaging. These observations are consistent with previous experimental data demonstrating that stunned or hibernating myocardial regions without histological evidence of necrosis show preserved membrane extraction of $^{201}$Tl as long as some regional blood flow is preserved. Our data also correlate well with assessments of viability using metabolic techniques in similar patient groups. Perrone-Filardi et al reported that 74% of akinetic or dyskinetic segments were viable by [$^{18}$F]fluorodeoxyglucose uptake and PET criteria in patients with coronary artery disease and reduced LV function, whereas Murray et al demonstrated viability in 73% of severely asynergic segments using [$^{13}$I]iodophenylpentadecanoic acid imaging at rest. Similarly, our results are consistent with previous observations that preoperative increased [$^{18}$F]fluorodeoxyglucose uptake relative to flow on PET images in severely asynergic segments predicted improved improvement in regional and global function after revascularization. Additionally, our observations are in agreement with those of Mori et al., who showed that $^{201}$Tl rest-redistribution correlated with improved wall motion in segments with severe asynergy and that segments with mild persistent $^{201}$Tl defects were more likely to improve function than were segments with severe persistent defects.

Clinical Implications

The finding that rest-redistribution $^{201}$Tl imaging can identify patients likely to improve function has important clinical implications. Depression of LVEF and multivessel CAD are important variables predictive of adverse outcome in medically treated patients with CAD. Results of both randomized and nonrandomized trials comparing the outcome of medically and surgically treated patients demonstrate that the relative survival benefit in the surgical group is greatest when ventricular function is depressed. Despite this survival advantage, the 5-10-year mortality rate in surgical cohorts in these studies is not optimum. In the study by Alderman et al from the Coronary Artery Surgery Study (CASS) registry, there was approximately 40% mortality during a 7-year follow-up in patients with a resting LVEF ≤25% undergoing CABG. In the CASS randomized study, minimally symptomatic patients with three-vessel disease and resting LVEF ≤50% who were randomized to surgery had 25% mortality at 10 years. One possible explanation for this high mortality rate in surgical cohorts with multivessel disease and depressed LV function is that some patients without residual viable myocardium were revascularized and, thus, may have had no survival benefit. The LV dysfunction in those patients may be a result of extensive irreversible damage, and they succumb to fatal ventricular arrhythmias or progressive congestive heart failure. Perhaps the subgroup of patients with depressed LVEF who demonstrate improved survival with bypass surgery has more hibernating but viable myocardium as the cause of LV dysfunction.

Hibernating or Stunned Myocardium

"Hibernating myocardium," a term first used by Rahimtoola, describes a state of persistently impaired LV function in the basal state attributable to a chronic reduction in coronary blood flow. Hibernation implies that if myocardial blood flow is enhanced or the oxygen supply–demand relation is improved, then function will improve. Stunned myocardium, in contrast, describes a state of abnormal contraction after an episode of ischemia despite restoration of adequate blood flow. Although the design of the present study did not allow differentiation of hibernating from stunned myocardium, the patients enrolled in the present study did have evidence of hibernating myocardium. They had symptoms and signs of ischemic cardiomyopathy with multiple regional wall motion abnormalities and extensive multivessel CAD. Only 21% of myocardial segments had normal contraction before surgery and many segments (89 of 176, 50%) with severe asynergy before surgery improved systolic function after coronary revascularization. LVEF increased significantly after CABG for the group as a whole, and approximately 50% of the patients had an improvement in LVEF of ≥0.05 after revascularization.

Experimental Basis for $^{201}$Tl Scintigraphy for Detection of Myocardial Viability

The finding of preserved $^{201}$Tl uptake in severely asynergic segments is consistent with the kinetics of $^{201}$Tl uptake and washout. After intravenous injection, the myocardial uptake of $^{201}$Tl is proportional to regional blood flow and the extraction fraction of $^{201}$Tl by the myocardium. The first-pass extraction fraction for $^{201}$Tl under normal basal flow conditions is approximately 85%. The $^{201}$Tl extraction and cellular washout kinetics are unaltered in experimental canine models of stunned myocardium characterized by severe postischemic dysfunction occurring either after repetitive 5-minute periods of flow reduction or after 15 minutes of coronary occlusion followed by reperfusion.

Sinusas et al examined $^{201}$Tl uptake in a canine model intended to simulate "short-term" hibernating myocardium, defined as proportionally reduced regional contraction and reversible contractile dysfunction resulting from a brief period of reduced coronary blood flow. Myocardial $^{201}$Tl uptake was preserved during a sustained reduction in regional blood flow despite the corresponding systolic dysfunction.

$^{201}$Tl Redistribution and Viability

After initial myocardial uptake of $^{201}$Tl after intravenous injection, there is a continuous exchange of $^{201}$Tl between perfused, viable myocardium and the blood pool. This process of continuous exchange forms the basis of $^{201}$Tl redistribution, which results in delayed defect resolution and can be observed when $^{201}$Tl is administered during transient underperfusion of the myocardium or with a chronic reduction in myocardial blood flow (rest-redistribution). Redistribution can occur only if myocardium supplied by a stenotic artery is viable, with an intact sarcolemmal cell membrane. When extensive necrosis is present, no delayed $^{201}$Tl redistribution is seen in the zone of irreversibly injured myocardial tissue. Partial redistribution can be seen when there is a mixture of necrosis and reversibly ischemic myocardium, as may occur when a region composed of normal and necrotic myocardium is supplied by a severely stenotic artery. It may also occur in the setting of severe underperfusion in which the pro-
cess of redistribution is incomplete at the time of delayed imaging. In the clinical setting, improved detection of defect reversibility on exercise imaging has been reported either by late (24-hour) imaging or by reinjection of $^{201}$TI in the resting state after acquisition of the 2.5–4-hour images.17–24

Rest-redistribution $^{201}$TI imaging has been reported previously in patients with severe chronic stable angina or unstable angina to assess regional myocardial perfusion before and after revascularization. Most patients in these prior studies did not have severe depression of LV function, and the predominant symptom was angina. Berger et al45 reported that 76% of scan segments in 29 patients with either severe stable angina or unstable angina showed $^{201}$TI defects at rest with delayed redistribution. Of these segments, 77% showed reversion to normal initial $^{201}$TI uptake at rest after bypass surgery. Improved wall motion on postoperative ventriculograms corresponded to scan segments showing improved $^{201}$TI uptake. Of patients showing rest-redistribution before surgery, 80% showed a ≥0.05 increase in LVEF after surgery. In contrast, only 22% of patients with persistent defects before surgery showed comparable improvement. The data presented in the present study in patients with poor ventricular function are consistent with these prior observations in patients with severe angina.

**Persistent $^{201}$TI Defects and Myocardial Viability**

It is clear that some persistent $^{201}$TI defects may not represent solely irreversibly injured myocardium. In a previous study from our institution,16 45% of persistent defects (thought to represent scar) on preoperative exercise $^{201}$TI imaging showed significant improvement in $^{201}$TI uptake after surgery. The defects that normalized after surgery were usually mild, with no more than a 25–50% reduction in $^{201}$TI activity relative to normal zone activity. In contrast, severe persistent defects (>50% reduction in regional $^{201}$TI activity) rarely improved after revascularization. Most defects showing partial redistribution before surgery had enhanced $^{201}$TI uptake on postoperative exercise imaging.

Berger et al45 using the same $^{201}$TI protocol as used in the present study, also showed that mild resting persistent defects were more likely to show enhanced $^{201}$TI uptake after bypass surgery compared with severe resting persistent defects. Liu et al46 also reported that many persistent $^{201}$TI defects on 3-hour delayed images normalized after revascularization. In a study from the National Institutes of Health (NIH), most mild persistent $^{201}$TI defects showed evidence of myocardial viability as assessed by PET.19 [18F]Fluorodeoxyglucose uptake on PET imaging was seen in 91% of mild persistent defects and 84% of moderate persistent defects in that study. They found that the greater the defect severity, the less evidence of viability by PET criteria. Tamaki et al47 also showed increased [18F]fluorodeoxyglucose uptake indicative of viability in defects showing a mild reduction in perfusion as assessed by [$^{13}$N]ammonia imaging. These data support the criteria for normal viability or mildly reduced viability by $^{201}$TI imaging used in the present study.

**Limitations of the Study**

The study population was a selected group referred for CABG and not a consecutive group of patients with CAD and congestive heart failure. Seventy-six percent were experiencing angina, and 38% had a recent myocardial infarction. Patients without evidence for viability by $^{201}$TI imaging might not have been referred for surgery and therefore would not have been identified for study recruitment. The applicability of this study to a cohort of patients not referred for surgery is less certain. Our data would suggest, however, that patients with few viable, asynergic myocardial segments are unlikely to have an improved postoperative ejection fraction or improved global wall motion scores. Additionally, the mean LVEF for the patient cohort reported in the present study was 27%, and most patients presented with heart failure or pulmonary edema. The mean LV end-diastolic pressure was 28 mm Hg. Thus, this group of patients had severe LV dysfunction, permitting the testing of the hypothesis that rest-redistribution $^{201}$TI imaging would identify those viable but asynergic myocardial segments that would improve systolic function after surgery. Viable but asynergic segments might have been less prevalent if more patients with ischemic cardiomyopathy who were not experiencing angina had been enrolled. However, it should be emphasized that the presence of angina did not correlate with improvement in global LVEF in our study. In multivariate analysis, only the number of viable, asynergic segments per patient was an independent correlate of improvement of LVEF.

Because functional improvement after CABG requires adequate revascularization and lack of postoperative graft occlusion, the adequacy of revascularization must be considered in determination of the predictive value of the $^{201}$TI scintigrams. Because coronary angiography was not done routinely in this study, postoperative $^{201}$TI imaging was used as a surrogate. New $^{201}$TI defects observed on postoperative scans were assumed to be secondary to intraoperative or early postoperative myocardial injury. Although this is an imperfect technique, improvement in $^{201}$TI uptake does suggest that a segment has been adequately revascularized. The converse, however, may not be true, since persistent defects may not improve despite adequate revascularization when they represent mixtures of normal with necrotic tissue.

The discordance between postoperative $^{201}$TI patterns and postoperative changes in function has several potential explanations. In the present study, there were segments with severe defects that improved $^{201}$TI uptake after CABG without showing a corresponding improvement in systolic function. Edwards et al57 showed that severe subendocardial hypoperfusion can cause akinesis or dyskinesis even with preservation of normal subepicardial blood flow. Thus, despite enhanced $^{201}$TI uptake in epicardial regions, systolic function may not improve after an episode of subendocardial infarction or when severe subendocardial hypoperfusion persists. In our patient cohort, segments with previous subendocardial infarction perfused by persistently stenotic vessels could show some enhanced perfusion after revascularization, predominantly in epicardial layers, but function might not improve. Similarly, if subendocardial flow remained persistently depressed without necrosis because of inadequate revascularization, function might not improve despite some increased postoperative $^{201}$TI uptake.

Lack of 100% concordance between perfusion patterns, baseline function, and functional changes after CABG should be anticipated. Radionuclide ventricul-
grams and $^{201}$TI scintigrams performed at different times cannot be precisely registered such that segments on the functional study correspond exactly to segments on the perfusion study. Tethering may account for unexpected improvement in a nonviable segment when an adjacent viable segment improved function. Cardiac surgery is known to result in new septal wall motion abnormalities that are not caused by perfusion abnormalities. In our study, however, all septal segments had wall motion abnormalities before surgery, and the $^{201}$TI viability classifications correlated well with improvement in function, especially in septal segments with severe preoperative asynergy. Another limitation of the study is the use of a semiquantitative method to determine the degree of LV systolic dysfunction on serial radionuclide angiography. Fully quantitative methods for determination of regional LVEF by gated blood pool imaging, however, are not very accurate or reproducible. Wall motion was graded by two observers who were blinded both to patient identity and to which study was preoperative and which was postoperative.

The quantitative planar $^{201}$TI scintigraphy used in this study has been validated for measurement of residual $^{201}$TI uptake on rest scintigrams and identification of subtle degrees of redistribution. No significant disadvantages of using quantitative planar rest-redistribution imaging compared with SPECT imaging for assessing viability and improvement in ventricular function have been reported. The main potential advantage of SPECT imaging compared with planar techniques is the detection of circumflex coronary artery stenoses and improved delineation of small defects. Because the angiographic extent of disease was known and the areas of functional asynergy were extensive, the improved identification of small defects with SPECT is perhaps less important in this patient group. Had SPECT imaging been used, some additional myocardial segments, particularly in the circumflex coronary artery zone, might have been identified as showing perfusion abnormalities. Even so, quantitative $^{201}$TI SPECT imaging has not yet been validated for accurately measuring the degree of residual $^{201}$TI uptake at rest, and the viability data in asynergic segments reported in this study with planar imaging techniques correspond closely to published reports using metabolic techniques.

Imaging at 24 hours has been used primarily after exercise scintigraphy to identify redistribution that was not evident 4 hours after $^{201}$TI injection. The potential benefit of 24-hour imaging after $^{201}$TI injection at rest, however, has not been extensively investigated. Because $^{201}$TI redistribution is an exponential process, most redistribution occurs in the first 3 hours after injection. In addition, imaging 24 hours after rest $^{201}$TI injection may be particularly problematic because of low counting statistics, high background activity, and more image noise. It is unlikely that acquiring a third resting image at 24 hours would have added significantly to the detection of reversible defects, and it could have resulted in more false-positive findings.

No long-term follow-up was done to determine whether group A patients with substantial preserved viability by $^{201}$TI criteria had a better outcome than group B patients who had less evidence for viability. The number of patients in each group was too small to obtain valid follow-up prognostic information.

Conclusions

This study demonstrates that many severely asynergic myocardial segments show preserved $^{201}$TI uptake at rest in patients with multivessel CAD and a markedly depressed LVEF. Demonstration of preserved viability by the $^{201}$TI criteria defined in this study is predictive of improvement in global LV function after coronary bypass surgery. The presence of numerous asynergic but viable myocardial segments correlated significantly with postoperative improvement in global LV function. Three forms of management are available to patients with coronary artery disease and severely reduced LVEF: medical therapy, CABG, or heart transplantation. Because availability of donor hearts is limited, an accurate noninvasive determination of myocardial viability is important to identify those patients still likely to benefit from CABG. Rest-redistribution $^{201}$TI imaging may be clinically useful in the selection of patients who would benefit most from CABG despite a low ejection fraction and congestive heart failure. Further studies in a larger number of patients are required to assess whether this imaging approach is also predictive of long-term benefit and survival.

Acknowledgments

We are grateful for the superb editorial assistance provided by Jerry Curtis in preparing this manuscript and to the cooperation we received from our cardiovascular surgical colleagues. We would like to thank Ellen Vinson, the nuclear cardiology laboratory of the University of Virginia Medical Center, and the nursing staff in the coronary care unit for their expertise and assistance.

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Quantitative planar rest-redistribution 201Tl imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function.

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_Circulation_. 1993;87:1630-1641
doi: 10.1161/01.CIR.87.5.1630

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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