Comparison of $^{201}\text{Tl}$, $^{99m}\text{Tc}$-Tetrofosmin, and Dobutamine Magnetic Resonance Imaging for Identifying Hibernating Myocardium

Mark G. Gunning, MRCP; Constantinos Anagnostopoulos, MD; Charles J. Knight, MA, MRCP; John Pepper, MChir, FRCS; Elisabeth D. Burman; Glyn Davies, PhD; Kim M. Fox, MD, FRCP; Dudley J. Pennell, MD, MRCP; Peter J. Ell, MD, FRCP; S. Richard Underwood, MD, FRCP

**Background**—Both radionuclide perfusion tracers and contractile response to dobutamine have been used to identify hibernating myocardium. The aim was to compare $^{201}\text{Tl}$ (thallium) single photon emission CT (SPECT), $^{99m}\text{Tc}$-tetrofosmin (tetrofosmin) SPECT, and dobutamine cine MRI for identifying regions of reversible myocardial dysfunction.

**Methods and Results**—Thirty patients with 3-vessel coronary artery disease and impaired left ventricular function (mean LVEF, 24.0%; SD, 8.3%) scheduled for coronary bypass grafting were recruited. All underwent rest/dobutamine stress (5 to 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) cine MRI, stress/rest tetrofosmin SPECT, and stress/redistribution and separate-day rest/redistribution thallium SPECT before surgery. Stress/redistribution thallium SPECT and resting MRI were repeated after surgery. In a 9-segment model, SPECT images were scored visually for tracer uptake, which was also measured from a polar plot of myocardial counts. MRI was scored visually for endocardial motion, myocardial thickening, and thickness. Five patients died before follow-up, and 2 declined postoperative investigation. In the remaining 23 patients, mean LVEF increased from 24.0% (SD, 8.3%) to 29.7% (SD, 11.1%) ($P<0.05$). Of 207 segments analyzed, 145 had significantly abnormal wall motion before surgery, and 82 of these improved function after revascularization. The criteria for predicting recovery of severely hypokinetic segments on preoperative imaging were tracer uptake graded “moderately reduced” or better, or positive inotropic response on dobutamine MRI. Late-rest thallium images showed the highest sensitivity (76%), compared with stress-redistribution thallium (68%) and rest tetrofosmin (66%) ($P<0.05$). All 3 tracer techniques were nonspecific (44%, 51%, and 49%, respectively). Redistribution of thallium after the resting injection was insensitive (18%) but highly specific (83%). Inotropic response to dobutamine was also insensitive (50%) but specific (81%).

**Conclusions**—Radionuclide uptake is a sensitive but nonspecific predictor of myocardial functional recovery, whereas dobutamine MRI is specific but insensitive. *(Circulation. 1998;98:1869-1874.)*

Key Words: magnetic resonance imaging ■ radioisotopes ■ surgery ■ perfusion

In patients with impaired left ventricular function secondary to ischemic heart disease, it is important to identify dysfunctional but viable myocardium with the potential to improve function after revascularization, described by Rahimtoola as “hibernating myocardium.”1 Several imaging techniques have been used, including inotropic response to dipyridamole2 or to low-dose dobutamine detected by transthoracic echocardiography,3 transesophageal echocardiography,4 and cine MRI.5,6 PET is particularly accurate in identifying underperfused but metabolically active tissue, but it is not available in many centers. Single photon emission CT (SPECT) using a number of agents identifies perfusion abnormalities and can distinguish viable myocardium from scar. Conventional stress/redistribution $^{201}\text{Tl}$ (thallium) scintigraphy underestimates the amount of viable myocardium present, but delayed redistribution imaging,7 re-injection imaging,8 and resting injection are more reliable.9 Adjunctive use of nitrates10 may also improve the assessment of viability. $^{99m}\text{Tc}$-MIBI (MIBI) has also been used successfully, and it has been extensively compared with thallium.11 A newer technetium-based tracer, $^{99m}\text{Tc}$-tetrofosmin (tetrofosmin), is well established in identifying reversible ischemia,12 but its role in detection of hibernation is less clear.

Patients with significantly depressed left ventricular function are likely to benefit most from the identification of hibernating myocardium, and this study was designed to compare the value of low-dose dobutamine cine MRI, stress/redistribution and separate-day rest/redistribution thallium scintigraphy, and stress/rest tetrofosmin imaging in these patients.
Methods

Patients
Thirty patients with ischemic LV dysfunction were identified prospectively (27 male; median age, 61 years; range, 40 to 70 years). They were selected from the waiting list for coronary bypass surgery, and the 2 main inclusion criteria were left ventricular ejection fraction (LVEF) ≤35% and dyspnea as a dominant symptom. All patients had 3-vessel coronary artery disease (defined as >70% luminal diameter stenosis), and all had suffered previous myocardial infarction. Patients with significant valve disease, uncontrolled atrial fibrillation, permanent pacemaker, or previous coronary bypass surgery were excluded.

Imaging
Preoperative assessment was performed within 3 months of surgery and postoperative assessment between 3 and 6 months after surgery. Preoperative assessment included stress/redistribution thallium SPECT, separate-day rest/redistribution thallium SPECT, stress/rest tetrofosmin SPECT, and cine MRI at rest and during infusion of low-dose dobutamine. Postoperative assessment included stress/redistribution thallium SPECT, rest MRI, and x-ray coronary angiography. One week before the postoperative studies, medication was adjusted to be the same as for the preoperative studies.

No cardiac events were reported between preoperative assessment and surgery.

Magnetic Resonance Imaging
MRI was performed with a 1.5-T system (Picker International Inc, HPQ). Cine gradient echo images were acquired in the vertical and horizontal long-axis planes and in basal and apical short-axis planes. Echo time was 4.6 ms; flip angle, 25°; 12 frames per cardiac cycle; 2 averages of 128 phase encoding steps; slice thickness, 10 mm; and field of view, 400 mm. A 5-mm presaturation band was placed on either side of the slice to depress signal from blood and to give a “black-blood” cine. Preoperative images were acquired at rest and during a peripheral infusion of dobutamine at 5 and 10 mg/min. Postoperatively, only resting images were acquired.

Thallium Scintigraphy
Stress was performed with adenosine infused at 140 μg·kg⁻¹·min⁻¹ for 6 minutes combined with bicycle exercise at 25, 50, and 75 W in 2-minute stages if tolerated. Thallium (80 MBq IV) was injected at 4 minutes, and a dual-headed gamma camera (IGE Optima) was used to acquire images 5 minutes after completion of stress (stress images) and again 4 hours later (distribution images). The rest study was conducted on a separate day with 80 MBq of thallium at rest followed by immediate (early rest) and 4 hour delayed (late-rest) imaging. Acquisitions were over an arc of 180° from right anterior oblique to left posterior oblique with 64 projections of 20 or 25 seconds each. Low-energy, high-resolution collimators were used, and the 72- and 169-kVp peaks of thallium were acquired with 20% windows. Data were processed with a Hanning prefilter with a cutoff frequency of 0.8 cycles/cm and a ramp filter during back-projection. The transaxial tomograms were reoriented into the vertical and horizontal long-axis and short-axis planes.

Tetrofosmin Scintigraphy
Adenosine with submaximal exercise was used in a manner identical to that used for thallium scintigraphy. Tetrofosmin (250 MBq) was given during stress, and the images were acquired 30 minutes later without a fatty meal. A matched protocol similar to that for thallium was used, with 64 projections of 20 to 25 seconds each using high-resolution collimators and a 20% energy window centrally placed around the 140-keV photopeak. Four hours after the stress injection, 750 MBq of tetrofosmin was injected at rest, and images were acquired 30 minutes later. Image processing was identical to that described for the thallium images.

Image Analysis
MR images were analyzed by 2 experienced observers independently and without knowledge of the findings of the other imaging techniques. A 9-segment model of the LV was used, with basal and apical parts of the septum and anterior, lateral, and inferior walls, together with the apex. Endocardial motion was scored visually on a 5-point scale, systolic myocardial thickening on a 4-point scale, and diastolic myocardial thickening on a 3-point scale (Table 1). Functional recovery was defined as ≥1 class improvement on postoperative MRI. Left ventricular volumes were calculated at end diastole and end systole by a biplane area-length technique. Stroke volume and LVEF were derived.

Radionuclide images were analyzed in a similar fashion by 2 observers unaware of the findings of MRI. Tracer uptake was scored in the 9 segments on a 5-point scale (Table 1) in which the grades corresponded roughly to uptake of 100% to 70%, 69% to 50%, 49% to 30%, 29% to 10%, and 0% to 0% of maximum but taking into account normal variations such as inferior attenuation. In addition, quantitative analysis was performed by dividing a polar representation of the whole myocardium into the corresponding 9 segments and calculating the mean uptake in each of the segments as a percentage of maximum uptake within the heart.

Postoperative coronary arteriograms were analyzed by a single observer unaware of the other imaging findings. Criteria were defined prospectively for the preoperative detection of hibernating myocardium (Table 3). Criteria 1 through 3 were based on the assumption that uptakes of thallium and tetrofosmin 4 hours after stress or rest injection reflect the amount of viable myocardium present. If an area with significant viable myocardium has severely reduced function, then it may be hibernating. Criterion 4 is similar to criterion 1 but in addition requires evidence of redistribution between early and late-rest thallium images, which is a marker of reduced perfusion at rest. Reversible ischemia, in segments in which resting tracer uptake was moderately reduced or better, was defined as improvement in tracer uptake of ≥1 grade between stress and rest images in the case of tetrofosmin. Segments were excluded from analysis if the postoperative redistribution thallium score was ≥2 grades less than the preoperative score, because this implies perioperative myocardial damage or inadequate revascularization (5 segments excluded), and segments were also excluded if, on postoperative angiography, the coronary artery was not successfully bypassed (2 segments).

Statistics
Summary data were expressed as mean±SD. Changes in LVEF were compared by a paired t test. Mean segmental tracer uptake was compared by ANOVA. Agreement between observers for visual scoring of the images was evaluated by a weighted κ statistic, for which absolute agreement was weighted as 1, disagreement by 1 class as 0.5, and disagreement by >1 class as 0. Sensitivity,
Results

There was good agreement between observers for scoring of tracer uptake (total agreement, 73%; $\kappa=0.77$) and moderate agreement for scoring of MR wall motion (61%; $\kappa=0.54$), thickness (55%; $\kappa=0.41$), and thickness (60%; $\kappa=0.41$).

Five patients died during the study, 2 perioperatively and 3 postoperatively. Two patients declined follow-up, and therefore, 23 patients completed the study. Median time to follow-up imaging was 5 months (range, 3 to 6 months). For those completing the study, mean LVEF increased from 24.0% (SD, 8.3%) to 29.7% (SD, 11.1%) ($P<0.05$). For those patients who died, the mean LVEF was 17% (SD, 6%).

In the 23 patients with complete imaging data, 207 segments were analyzed. Before surgery, 145 segments had wall motion scores of $\leq1$ (severe hypokinesia), and 82 of these improved after revascularization by $\geq1$ wall motion grade. These segments were classified retrospectively as hibernating, and this classification was taken as the standard against which the ability of the imaging techniques to predict hibernation was compared. Few segments improved from a wall motion score of $-1$ to 0, but the majority of segments that recovered function were graded as severely hypokinetic.

Specificity, and predictive values were calculated with conventional formulas, and these were compared by McNemar’s test.

<table>
<thead>
<tr>
<th>Improvement in wall motion after revascularization</th>
<th>Preoperative Wall Motion Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 grade</td>
<td>$-1$  0   1   2</td>
</tr>
<tr>
<td>2 grades</td>
<td>2     21  39   4</td>
</tr>
<tr>
<td>3 grades</td>
<td>2     12  12   $\cdots$</td>
</tr>
<tr>
<td>Total</td>
<td>4     27  51   4</td>
</tr>
</tbody>
</table>

$-1$ indicates dyssyntetic; 0, akinetic; 1, severely hypokinetic; and 2, mildly hypokinetic.

Criterion 1 (late-rest thallium) was most sensitive (76%), followed by criterion 2 (redistribution thallium) (68%) and criterion 3 (rest tetrofosmin) (66%) ($P<0.05$). All 3 criteria were nonspecific, however (44%, 49%, and 51%, respectively, $P>0.05$). Criterion 4, which was similar to criterion 1 but required rest-redistribution of thallium in addition, was very insensitive (18%) but specific (83%). Agreement between late rest thallium uptake and dobutamine MRI is shown in Table 4. Reverse-redistribution from the stress thallium images was identified in only 7 segments, and 5 of these had improved function after surgery. Inotropic response to dobutamine was also insensitive (endocardial motion, 50%; myocardial thickening, 45%) but specific (81% and 83%, respectively). The sensitivity was lower in akinetic/dyskinetic (38%) than in severely hypokinetic segments (57%). The presence of a reversible stress-induced perfusion abnormality on either thallium or tetrofosmin imaging (Table 5) did not appear to aid the prediction of functional recovery.

The mean summed segmental thallium score was 23.8 (of a maximum 36) for the 23 patients who were followed up and 20.5 for the 5 patients who died. These results are based on semiquantitative visual analysis, the method used most widely in clinical practice, but we also investigated the value of quantitative analysis. In segments with a wall motion score $\leq1$, mean segmental uptake of late-rest thallium was greater than redistribution thallium and rest tetrofosmin uptake, although the differences were not statistically significant.

| TABLE 2. Number of Segments Improving Function After Revascularization, According to Preoperative Wall Motion Score |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Improvement in wall motion after revascularization | Preoperative Wall Motion Score |
| 1 grade                                           | $-1$  0   1   2             |
| 2 grades                                          | 2     21  39   4            |
| 3 grades                                          | 2     12  12   $\cdots$     |
| Total                                             | 4     27  51   4            |

$-1$ indicates dyssyntetic; 0, akinetic; 1, severely hypokinetic; and 2, mildly hypokinetic.

| TABLE 3. Six Criteria Defined Prospectively and Tested for the Preoperative Prediction of Hibernating Myocardium |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Criterion | Sensitivity, % | Specificity, % | Positive PA, % | Negative PA, % |
| 1 Late rest Tl $\geq2$, and rest motion $\leq1$    | 76     | 44     | 64     | 58     |
| 2 Redistribution Tl $\geq2$, and rest motion $\leq1$ | 68     | 49     | 64     | 54     |
| 3 Rest Tl $\geq2$, and rest motion $\leq1$        | 66     | 51     | 64     | 53     |
| 4 Late rest Tl $\geq2$, and rest motion $\leq1$, and late rest Tl > early rest Tl | 18     | 83     | 58     | 44     |
| 5 Rest motion $\leq1$, and stress motion $\geq2$   | 50     | 81     | 77     | 54     |
| 6 Rest thickening $\leq1$, and stress thickening $\geq2$ | 45     | 83     | 77     | 54     |

Tl indicates thallium; Tl, tetrofosmin; and PA, predictive accuracy. Scores are based on the definitions in Table 1.
Hibernation was defined as a wall motion score of $\leq 1$, with mean segmental tracer uptake greater than an arbitrarily defined threshold. This threshold was varied to generate receiver operating characteristic (ROC) curves (Figure 2). The largest sum of sensitivity and specificity was obtained at 60% uptake of thallium (sensitivity, 72%; specificity, 58%) and 64% uptake of tetrofosmin (sensitivity, 64%; specificity, 62%). The areas under the ROC curves were the same for late-rest thallium (0.65) and for rest tetrofosmin (0.63), implying no difference between the tracers in overall performance.

Assessing the prediction of improvement with respect to individual patients showed that preoperative identification of inotropic response in 1 segment predicted functional improvement in at least 1 segment in 17 patients (sensitivity, 89%; specificity, 50%), rest thallium uptake predicted improvement in 19 patients (sensitivity, 100%; specificity, 50%), and resting tetrofosmin uptake also predicted improvement in 19 patients (sensitivity, 100%; specificity, 50%). Improvement was not always observed in the predicted segment with this approach, hence the need for segmental analysis to accurately assess the value of the imaging modalities in identifying hibernation.

**Discussion**

**Comparison of Radionuclide and Functional Techniques**

We have shown that the use of radionuclide tracers to assess viability and MRI to assess function provides a sensitive but nonspecific method of predicting recovery of function after revascularization. Conversely, contractile reserve in response to dobutamine to assess viability provides a specific but insensitive predictor of recovery of function. These findings agree with some studies but disagree with others. For instance, La Canna and colleagues found that low-dose dobutamine echocardiography was both sensitive (87%) and specific (82%) for the detection of hibernation, and Alfieri and colleagues found sensitivity of 91% and specificity of 78%, compared with rest-redistribution thallium, which had a sensitivity of 93% and specificity of 44%. Vanoverschelde and colleagues report high sensitivity and specificity values for both dobutamine echocardiography (88% and 77%) and thallium scintigraphy (72% and 73%). The explanation for these differences is most likely patient selection, and our own population had lower mean LVEF (24%) than those of La Canna (33%), Alfieri (35%), and Vanoverschelde (36%). It is conceivable that patients with more severely reduced left ventricular function have more profound and possibly irreversible ultrastructural changes in areas of hibernation, such as loss of contractile protein, and this would lead to reduced specificity of the radionuclide techniques.

We infused dobutamine at 5 to 10 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$. Some authors advocate the use of higher rates of dobutamine infusion to provoke a biphasic response. Afridi and colleagues found that identification of this phenomenon improved the prediction of functional recovery; however, the technique had not been described when our study was carried out. It is recognized that functional recovery may occur later
than 6 months after revascularization, and thus our specificity for radionuclide techniques might have improved if follow-up had been conducted after 1 year.

Two relevant precautions were taken. First, we excluded segments from analysis if postoperative thallium uptake was not improved or if the relevant coronary artery was not successfully bypassed (assessed by postoperative arteriography). This is important because it cannot be assumed that surgery successfully improves perfusion to all segments. Second, we ensured that preoperative and postoperative function studies were performed with the patients on the same medication. Changes in medication are usual after successful surgery, and this alone might lead to changes in both global and regional function.

**Thallium Uptake and Hibernation**

Thallium is concentrated in viable myocytes, partly by passive diffusion down an electrochemical gradient and partly by active uptake with the ATPase-dependent sodium-potassium exchange pump. Both of these mechanisms require a viable cell membrane, and so thallium is a marker of membrane and hence cell viability. Because of avid extraction on its first passage, however, its initial distribution reflects viability modulated by perfusion. Thus, regional uptake reflects viability reliably only after complete redistribution. Redistribution can be a slow phenomenon, and it may depend on resting perfusion. Imaging 4 hours after a stress injection can therefore underestimate the amount of viable myocardium. This problem can be overcome in a variety of ways, including late redistribution imaging (24 or 72 hours), reinjection of thallium at rest after a preceding stress injection, or separate-day resting injection. All of these protocols provide a more reliable estimate of viability, and our results confirm greater sensitivity for the detection of hibernation with late-rest thallium images (76%) compared with stress-redistribution images (68%).

Another criterion that has been used in thallium imaging to detect hibernating myocardium is redistribution acquired early and late after a resting injection (rest-redistribution). Such redistribution implies reduced perfusion at rest, and this is one of the possible mechanisms leading to hibernation. Alfieri and colleagues found that rest-redistribution of thallium had a sensitivity of 93% and a specificity of 44% for the prediction of recovery of function after revascularization. In contrast, we found only a small number of hibernating segments that showed this phenomenon, and the finding had a low sensitivity but high specificity in our population. The discrepancy may be the result of patient selection, but it could also arise from the semiquantitative scoring system that we used, in which small changes of uptake may be insufficient to increase uptake score. Other authors have also reported a relatively low prevalence of rest redistribution, consistent with our findings.

A reduction in relative segmental thallium uptake with time ("reverse redistribution") has been proposed as a marker of viability and hence potentially of use for detecting hibernation. Provided that the appearance is not the result of artifact, the phenomenon occurs most commonly in regions of partial-thickness infarction with a patent artery, although it may also occur in areas supplied by severely stenosed or occluded arteries. Although such areas clearly contain viable myocardium, the value of the observation for predicting hibernation is uncertain. We found reverse redistribution infrequently (7 of 207 segments with severely impaired function), and so the finding was very insensitive (if specific) for detecting hibernation.

We found that preoperative reversible radionuclide perfusion abnormality after stress was a poor predictor of functional recovery. This observation is surprising in view of conventional theory that myocardial hibernation represents a state of reduced coronary flow reserve, and therefore, reversible ischemia would be expected under conditions of stress. A simple explanation might be that some of the segments studied with appreciable tracer uptake displayed impaired contractility as a manifestation of global left ventricular impairment. Nevertheless, the identification of segments with moderately well-preserved, nonreversible tracer uptake appears to be a reliable marker for hibernation. Furthermore, reversible ischemia could feasibly be identified in the epicardial and midwall region segments, with an appreciable degree of fibrosis in the subendocardial region. The fibrosis might therefore prevent improvement in function after revascularization. Clearly, this is an area that merits further study.

**Comparison of Thallium- and Technetium-Based Tracers**

Both MIBI and tetrofosmin have been used successfully for the detection and assessment of coronary stenoses. Neither of the technetium-based tracers, however, redistributes significantly after injection, and this is a theoretical disadvantage in assessment of viability in myocardium that might be underperfused at rest. Some studies suggest that thallium is superior for the detection of viable myocardium. The consensus appears to be that the theoretical disadvantage of nonredistribution is balanced by the superior imaging characteristics of technetium, and recent studies have shown that the 2 agents are equivalent, particularly if MIBI is given under nitrate cover. There is less experience with tetrofosmin for the detection of viable and hibernating myocardium.

We have shown higher sensitivity of thallium uptake for detecting hibernation (76%) than tetrofosmin (66%), although both agents were nonspecific. This finding agrees with previous studies in which we have shown greater uptake of thallium than MIBI in a significant proportion of segments with uptake <50% of maximum. It is not certain whether this is the result of failure to redistribute in areas of reduced perfusion (a problem that could be overcome by giving the agent under nitrate cover) or whether it is the result of the different energies of thallium and technetium (which might be overcome by using different thresholds for the definition of viability). Our use of tetrofosmin injected at rest without nitrate cover may certainly have prejudiced the sensitivity of tetrofosmin, but the study was begun before the potential role of nitrates in this setting was appreciated.

**Clinical Application**

We have compared the value of imaging techniques in predicting recovery of segmental left ventricular function. We found that radionuclide techniques are sensitive but nonspecific, whereas the converse is true for dobutamine MRI. In clinical assessment of patients with ischemic left ventricular dysfunction, if the prevalence of myocardial hibernation is
relatively low, the first-line investigation should be highly sensitive. Identification of hibernation may then be verified by use of a more specific technique. With this approach, the relative merits of radionuclide scintigraphy and dobutamine MRI may be applied to full advantage. However, we acknowledge that improvement in regional and global contractility is not the only clinical end point of successful revascularization. Previous reports have shown that the identification of myocardial hibernation may predict improvement in functional status. Moreover, several authors have suggested that revascularization of patients with impaired LV function but with appreciable hibernating myocardium leads to improved survival compared with medical therapy. When viewed in this context, the low specificity of the radionuclide techniques may prove to be less relevant.

Acknowledgments

Dr Gunning was supported by CORDA, a UK charity. The authors wish to thank S. Eastick and J. Francis for technical assistance.

References

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_Circulation_. 1998;98:1869-1874
doi: 10.1161/01.CIR.98.18.1869

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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