Accurate detection of dysfunctional but viable myocardium has become an important component of the clinical assessment of patients with ischemic left ventricular dysfunction. Several noninvasive modalities, including positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose, thallium-201 (Tl) single-photon emission computed tomography (SPECT) and dobutamine echocardiography, have been developed during the past decade to detect myocardial viability. Recent studies have suggested that stress-redistribution-reinjection imaging, rest-redistribution imaging, rest technetium-99m sestamibi and tetrofosmin SPECT identify viable myocardium better than stress redistribution imaging. PET is still recognized as a more reliable method to evaluate myocardial viability than SPECT, but because PET is not commonly available, it is necessary to develop a more accurate and convenient method for detecting viable myocardium using SPECT. In 1993, Tartagni et al found that continuous infusion of Tl with a low dose of insulin in a glucose–potassium solution enhanced the cellular uptake of the radiotracer in severely ischemic regions, but little is known about the usefulness of this method in predicting functional recovery. The present study was designed to (1) compare the regional Tl uptake between glucose–insulin–Tl (GI-Tl) infusion SPECT and reinjection imaging and (2) compare the accuracy of predicting functional recovery by GI-Tl SPECT, reinjection imaging and low-dose dobutamine echocardiography in the same patients.

Methods

Patients

Patients with coronary artery disease and resting regional left ventricular dysfunction were screened for enrollment in the study. Patients with unstable angina, uncontrolled heart failure, atrial fibrillation, and technically inadequate echocardiographic images were excluded. Twenty patients (17 men, 3 women; mean age, 66 years; Table 1) constituted the final study group. All patients had regional wall motion abnormalities on rest echocardiography: 14 patients had acute myocardial infarction (AMI <4 weeks before the study), 6 had stable angina pectoris with (n=3) or without (n=3) a previous (>6 months) MI. Of the 14 patients with AMI, 10 underwent primary percutaneous transluminal coronary angioplasty within 12 h of the onset of symptoms. Repeat angiography in the chronic phase revealed significant (≥75%) restenosis in 1 of the 10 patients, who then...
underwent coronary artery bypass grafting. The remaining AMI patients, who did not undergo emergency coronary angioplasty in the acute phase, had significant coronary artery stenoses in the infarct-related vessels in the chronic phase. These 4, together with the 6 patients with stable angina underwent an elective revascularization procedure: 9 underwent percutaneous transluminal coronary angioplasty, and one underwent coronary artery bypass grafting. All 20 patients were clinically stable, and none experienced unstable angina or a recurrent myocardial infarction during the entire study period. All patients underwent the myocardial scintigraphic studies and the low dose dobutamine echocardiography during the same hospital period. Informed consent was obtained from each patient.

**TI SPECT**

After overnight fasting, patients underwent treadmill exercise testing according to the standard Bruce protocol, with continuous monitoring of the electrocardiography (ECG), heart rate and symptoms. At peak exercise, 74 MBq of Tl was injected intravenously, and the patients continued to exercise for an additional 60 s. After cessation of exercise, TI SPECT images were obtained with a Toshiba GCA-602A digital gamma camera equipped with a high-resolution low-energy collimator (energy peak 72 keV; energy window ±20%). Thirty images were acquired over a 180° arc from the 50° right anterior oblique position to the 40° left posterior oblique position, with each image being recorded 2 s later (2nd image).

**Quantitative TI Analysis**

TI scintigraphy was analyzed quantitatively by an experienced observer blinded to all other data. Regional TI uptake was assessed using the same 9 myocardial segments model as for 2-dimensional echocardiography (Fig 1). Basal and mid-ventricular short-axis tomograms were divided into 4 segments representing the anterior, septal, inferior and lateral myocardium. Apical TI activity was measured from the vertical long-axis tomogram. A 10×10-mm region of interest was placed in the area of worst color-coded uptake, and the percentage of maximal count activity was derived in each of the 9 segments. For GI-Tl SPECT, images with a higher regional TI uptake between the 1st and 2nd images were selected and compared with the reinjection TI images.

**Dobutamine Stress Echocardiography**

All patients were allowed to take their prescribed medications, except for β-adrenergic blocking agents, which were withdrawn for at least 48 h before the investigation. Two-dimensional echocardiograms were obtained in the left-lateral position during both rest and dobutamine infusion, using commercially available echocardiographic systems (Toshiba SSH-160A) equipped with a 2.5 MHz transducer. Short-axis images at the levels of the mitral valve and mid papillary muscle, and apical 2-chamber and 4-chamber images, were acquired and recorded on a VHS videotape in a baseline study, after which dobutamine infusion was started at an initial dose of 5 μg·kg⁻¹·min⁻¹ for 3 min and then increased to 10 μg·kg⁻¹·min⁻¹ for an additional 3 min. Two-dimensional echocardiography was repeated at the end of each dobutamine infusion level. Patients underwent...
continuous ECG monitoring, and their blood pressure was recorded at 1.5 min intervals with an automated cuff. The criteria for stopping dobutamine infusion included hypotension, angina, significant ventricular arrhythmias and worsening of wall motion.

**Echocardiographic Analysis**

Undigitized echocardiographic images were analyzed off-line from the videotape playback by continuous display by 2 independent operators unaware of the scintigraphic results. To match the TI data, short-axis echocardiographic images were divided into 4 myocardial segments corresponding to the scintigraphic segments. The apex was considered a single myocardial region in the echocardiographic analysis, as it was for TI analysis.13,16 Wall motion and systolic thickening were graded semiquantitatively with a scoring system in which 4 = dyskinetic or akinetic, 3 = severely hypokinetic, 2 = hypokinetic and 1 = normal. Improved wall motion was indicated by a decrease in score of at least 1 grade at any stage of the dobutamine infusion compared with the baseline study. Follow-up echocardiography was repeated at a mean of 116 days later. Reversible dysfunction was defined as improved wall motion (a reduction in segmental score of at least 1 grade) at late follow-up compared with the baseline study. Disagreement in interpretation was resolved by consensus.

**Statistical Analysis**

Continuous variables are expressed as mean ± SD. Comparison of proportions was analyzed using the chi-square test or Fisher’s exact test where appropriate. Comparison of regional tracer uptake was analyzed with the paired t-test. Sensitivity and specificity for prediction of functional recovery were calculated with standard formulae. For GI-TI SPECT and reinjection imaging, receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic performance in predicting functional recovery using the computer program CORROC developed by Metz.17 We defined the optimal cutoff as the point that minimized diagnostic errors (ie, the sum of false-positives plus false-negatives).18 All tests were 2-tailed, and p<0.05 was considered significant.

**Results**

**Comparison of GI-TI SPECT and Reinjection Imaging by Quantitative Analysis**

Nine of the 10 AMI patients who underwent emergency coronary angioplasty showed a persistent patency of the infarct-related vessel on the TI SPECT images. The impaired wall motion of the infarcted lesion in these patients was followed after emergency coronary angioplasty to evaluate stunning. The remaining 11 patients (1 with restenosis after emergency coronary angioplasty, 4 AMI patients who did not undergo emergency coronary angioplasty and 6 patients with stable angina) had significant stenoses on the TI SPECT images and their impaired wall motion was re-evaluated after elective coronary angioplasty or bypass grafting for hibernation and/or stunning. Of 180 segments analyzed by echocardiography, 64 (36%) had abnormal wall motion in the baseline study and were the focus of assessment of the reversibility of impaired wall motion in this study. At late follow-up (mean, 116 days later), 33 of the segments showed improvement in the wall motion abnormality, but 31 segments did not. Quantitative regional activities for both GI-TI SPECT and reinjection TI imaging are shown in Fig 2. In all dysfunctional segments, the regional TI activity of GI-TI SPECT (62±17) was higher than for reinjection imaging (55±18, p<0.01). In segments with functional recovery, the regional TI activity of GI-TI SPECT was significantly higher than that of reinjection imaging (p<0.05), although there were no significant differences in the segments without recovery.

**Prediction of Regional Functional Recovery**

The ROC curves for predicting reversible dysfunction
are shown in Fig 3. The area under the fitted curve for GI-Tl (0.75±0.06) was greater than that for reinjection imaging (0.68±0.07). The optimal cutoff values to identify wall motion reversibility were considered to be 55% of peak activity for GI-Tl SPECT and 50% for reinjection imaging. At this cutoff point, the sensitivity and specificity for detection of functional recovery were, 85% and 61% for GI-Tl SPECT, and 73% and 61% for reinjection imaging respectively. Of the 28 segments judged to be nonviable (<50% of peak activity) by reinjection imaging, 7 segments were considered viable and 21 nonviable by GI-Tl SPECT. Of the 7 segments that were considered viable by GI-Tl SPECT, 5 segments (71%) had functional recovery. However, of the 21 segments considered nonviable by GI-Tl SPECT, only 4 (19%) recovered function (p<0.05, Fig 4). Dobutamine echocardiography had the same sensitivity (85%), but lower specificity (48%) than GI-Tl SPECT. In addition, the subset of patients undergoing revascularization procedures was analyzed using ROC curve (Fig 5). The area under the fitted curve was 0.79±0.08 for GI-Tl SPECT and 0.76±0.09 for reinjection imaging. In this subset, the sensitivities for GI-Tl SPECT, reinjection imaging and dobutamine echocardiography to assess functional recovery were 92%, 83% and 79%, respectively; specificities were all the same value (64%).

Discussion
Regional Activity of GI-Tl SPECT and Reinjection Imaging
In this study, quantitative assessment showed that GI-Tl SPECT had a higher regional tracer uptake than thallium reinjection imaging, which is consistent with the previous observation by Tartagni et al, who reported enhanced Tl uptake compared with reinjection or rest-redistribution imaging using a similar protocol. However, they did not evaluate whether increased regional Tl uptake improves the predictive value of functional recovery, so we prospectively compared GI-Tl SPECT with conventional reinjection Tl SPECT in relation to functional recovery. The present study showed that in the segments with functional recovery the regional activities of GI-Tl SPECT were significantly higher than those of reinjection imaging, although there were no significant differences in the segments without recovery.

Diagnostic Accuracy of GI-Tl SPECT and Reinjection Imaging in Predicting Functional Recovery
In this study, ROC curves were used to compare the accuracy of GI-Tl SPECT and reinjection imaging for predicting functional recovery. The area under the curve for GI-Tl SPECT was greater than that for reinjection imaging, which suggests that GI-Tl SPECT has higher sensitivity and higher specificity over a range of different cutoff values than reinjection imaging. Several recent studies have evaluated the diagnostic accuracy of Tl scintigraphy for assessing improvement in regional function after revascularization and have shown that reinjection imaging has a high sensitivity (80–95%), but a relatively low specificity (38–50%). Galassì et al have shown that quantitative reinjection imaging provides concordant information regarding myocardial viability compared with rest-redistribution Tl SPECT. The following 3 reasons may explain why Tl SPECT had high sensitivity, but poor specificity in the previous studies. First, the existence of membrane integrity is not always followed by functional recovery, so Tl imaging potentially overestimates functional recovery. Second, the follow up period may have been too short to allow complete recovery of all dysfunctional but viable segments; in some patients, functional recovery may occur after more than 6 months. Finally, the previous studies may have selected a cutoff point that maximized the true positive rate, that is, sensitivity, which results in lower specificity. If a cutoff point that makes the test sensitive enough to detect as many viable segments as possible is selected, the number of false-positive diagnoses unavoidably increases. However, false-positive diagnoses as well as false-negative diagnoses should be equally avoided, so we defined the optimal cutoff as the point that minimizes diagnostic errors. Using ROC curves, we selected the optimal cutoffs of 55% and 50% of peak activity for GI-Tl SPECT and reinjection imaging, respectively, and at this cutoff point, the sensitivities for GI-Tl SPECT and reinjection imaging were 85% and 73%, respectively, and the specificities were both 61%. The difference in sensitivity between GI-Tl SPECT and reinjection imaging can be explained by the following: of the 28 segments judged to be nonviable by reinjection imaging, 7 were considered viable by GI-Tl SPECT, and of these 7 segments, 5 (71%) had functional recovery. These results strongly suggest that GI-Tl SPECT is more accurate than reinjection imaging in assessing functional recovery.

Insulin acts on cations by increasing membrane conductance through activation of the Na/K ATP-sensitive pump. In addition, slow Tl infusion may improve the detection of viable myocardium. Therefore, slow infusion of a glucose – Tl – potassium solution may enhance radiotracer uptake in myocardial cells where perfusion is low and/or membrane pumps are functioning poorly.

Dobutamine Echocardiography
We also compared Tl scintigraphy with dobutamine echocardiography and found a sensitivity of 85% and specificity of 48% for dobutamine echocardiography, which is a relatively low specificity compared with previous studies. We assessed the change in wall motion abnormalities during low-dose dobutamine infusion only, which may have resulted in lower diagnostic accuracy for the assessment of functional recovery. In contrast with our result, recent studies indicate that dobutamine echocardiography has a higher predictive accuracy than Tl scintigraphy, but the accuracy and reproducibility of stress echocardiography strongly depend on operator experience and echocardiographic image quality, features which limit the availability of dobutamine echocardiography.

Study Limitations
(1) The study group was a heterogeneous population that included patients who had stunned and/or hibernating myocardium, which would influence the absolute value of the predictive accuracy. However, this aspect would affect all 3 techniques and should therefore not have changed the relative accuracy of the techniques. Indeed, the relation between ROC curves in all 20 patients and in the subgroups undergoing the revascularization procedure did not change.
(2) Misalignment between the echocardiographic and scintigraphic segments can not be excluded, even though we used the same 9-segment model for both studies, which would minimize the misalignment.
(3) We selected the images with a higher regional Tl uptake between the 1st and 2nd images. Additional studies are necessary to distinguish between these 2 phases.
Conclusions

Continuous infusion of a GI-Tl solution enhances regional uptake compared with conventional post-stress reinjection imaging. This study suggests that GI-Tl SPECT is superior to reinjection imaging and dobutamine echocardiography in predicting functional recovery after ischemic left ventricular dysfunction.

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References