To determine the utility of rest-injected technetium-99m methoxybutyl isonitrile (Tc-99m isonitrile) uptake as a marker of myocardial viability, the regional uptake of this agent was compared with regional wall motion by equilibrium gated blood pool scan in 26 patients with previous myocardial infarction and with postrevascularization uptake in 8 patients after coronary bypass surgery. Rest left ventricular Tc-99m isonitrile uptake was assessed qualitatively in three coronary vascular territories as grade 0 (markedly reduced) to grade 2 (normal), and quantitatively by circumferential profile analysis. Wall motion was scored qualitatively in corresponding vascular territories as normal, hypokinetic or akinetic/dyskinetic.

There was an overall relation between qualitative Tc-99m isonitrile uptake and wall motion. Abnormal wall motion occurred in 74% of vascular territories with perfusion grade 0, in 61% of those with grade 1 and in 30% of those with grade 2; however, 26% of territories with grade 0 uptake had normal wall motion. In the territories visually assigned perfusion grade 0, quantitative isonitrile uptake (mean value ± SD) was higher when corresponding wall motion was normal or hypokinetic (62 ± 15%) than when akinesia was detected by gated blood pool scan (39 ± 16%, p < 0.02). Qualitative Tc-99m isonitrile uptake improved after coronary bypass surgery in 12 of 13 territories with reduced uptake preoperatively; this included all 5 territories with a preoperative Tc-99m isonitrile score of 0. Quantitative uptake in these regions increased from 55 ± 18% to 73 ± 21% (p < 0.01).

It is concluded that regions with a severe reduction in Tc-99m isonitrile uptake at rest may contain viable myocardium; such reduced perfusion should not necessarily be considered evidence of myocardial scar. Inferences about myocardial viability based on rest-injected Tc-99m isonitrile (as evidenced by intact wall motion) are better made using quantitative rather than qualitative image analysis.

Thallium-201 myocardial perfusion imaging has been utilized to distinguish myocardial scar from ischemia (1–4). Because thallium uptake by the myocardial cell is an active energy-requiring process, it has been generally accepted that such uptake may be used as a clinical index of myocardial viability. Conversely, the clinical dictum that a zone of markedly reduced thallium uptake on a rest injection study or lack of redistribution after a stress study connotes the presence of scar has been challenged by recent descriptions (5–8) of thallium redistribution with 24 h delayed imaging or intact metabolic function with positron emission tomography in such regions. Similarly, the resolution of apparent “persistent defects” after coronary revascularization argues that such defects should not be considered as definite evidence of myocardial scar (9,10). Reduced thallium uptake in viable myocardium may be explained either by a severe reduction in perfusion to the ischemic but viable cell or by an abnormal cellular uptake process reflecting potentially reversible metabolic derangements in severely ischemic myocardium. Recently, technetium-99m methoxybutyl isonitrile (Tc-99m isonitrile), a new myocardial perfusion agent, has been studied in patients with coronary artery disease (11). Because myocardial uptake of Tc-99m isonitrile is reportedly not dependent on active transport (12,13), we speculated that uptake after injection at rest might provide a more reliable index of viability than does thallium uptake. Specifically, in zones of markedly reduced Tc-99m isonitrile uptake, one would predict a close association between regional wall motion and uptake. This assumption regarding rest injection is of fundamental importance to the proposed use.
of stress and rest Tc-99m isonitrile imaging to distinguish ischemic from infarcted myocardium because this agent does not redistribute. Therefore, a separate rest injection is required in place of conventional “delayed” images.

To test this hypothesis, we studied rest-injected Tc-99m isonitrile perfusion scintigraphy in relation to two clinical markers of potential viability: wall motion and isonitrile uptake after revascularization. Zones with retained wall motion have viable myocardium, as do zones that improve after revascularization. Zones with akinesia are likely to contain scar. If rest isonitrile uptake reflects viability, one would expect that a severe reduction in uptake would be closely associated with absent wall motion (akinesia) in the corresponding segment; similarly, such uptake should not improve after revascularization. Alternatively, with a dissociation between uptake and viability, there would be retained wall motion, postvascularization improvement of regional Tc-99m isonitrile uptake or both. These findings would suggest that this agent is primarily a perfusion marker.

Methods

Study patients. This two part study was performed in the previously described 38 patients (14) with known prior myocardial infarction who underwent clinically indicated coronary angiography and perfusion scintigraphy with rest-injected Tc-99m methoxybutyl isonitrile. Part I involved the 26 patients who also had equilibrium gated blood pool ventriculography. Part II involved the eight patients who had a second perfusion scan performed at rest after coronary bypass surgery. No patients with recent acute myocardial infarction or unstable angina were included. Isonitrile imaging was performed at least 2 weeks after myocardial infarction, within 1 week of angiography and within 1 month of coronary revascularization in the surgical cohort. All patients gave informed consent as part of a protocol approved by the Subcommittee on Human Studies at the Massachusetts General Hospital on October 26, 1986.

Coronary angiography. Selective coronary angiography was performed in standard orthogonal projections. Percent diameter coronary stenosis was scored for all major epicardial vessels by two experienced observers who were unaware of patient data. The presence or absence of collateral vessels was assessed, with the quality of collateral perfusion scored with use of a binary (poor versus good) system that reflected the degree of distal filling. In cases of disagreement, consensus was established by a third observer.

Technetium-99m isonitrile scintigraphy. After an overnight fast, all patients received an intravenous injection of Tc-99m isonitrile (20 mCi) at rest. Eight minute planar images were subsequently collected in three standard projections: anterior, “best septal” left anterior oblique and left lateral. Technetium-99m isonitrile uptake was scored by two observers who did not know the angiographic data as absent or markedly reduced (grade 0), reduced (grade 1) or normal (grade 2). The scoring was assigned on a standard segmental basis (three segments per view), and each segment was subsequently assigned to a coronary vascular territory (see Fig. 1 and 2 in Part I) (14). Assignment of apical left ventricular perfusion defects was variable and based on the results of coronary angiography and adjacent perfusion abnormalities. Disagreements in scoring or assignment were resolved by consensus with a third observer. The score assigned to a given coronary vascular territory reflected the maximal defect assigned to any segment within that territory.

Quantitative evaluation of the Tc-99m isonitrile images was performed with use of a computer-assisted circumferential profile analysis originally developed for application to thallium-201 images (15, 16). An ellipse was fitted around the left ventricular activity by an experienced technologist; areas of excessive background that might be “oversubtracted” by standard algorithms were excluded at the discretion of the operator (17). Myocardial activity was then divided into 15 sectors of equal length along the left ventricular perimeter for each projection; basal and valve plane sectors were excluded because of known interobserver variability in qualitative scoring of these segments (15). The activity within each sector was expressed as a percent of the peak activity in that projection. The sectors were then grouped to correspond to the standard perfusion image segments and assigned to a coronary vascular territory as previously described (14). Each territory was assigned a value to correspond to that of the sector with the lowest uptake.

By quantitative techniques, an abnormal vascular territory was defined as exhibiting peak Tc-99m isonitrile activity ≥2 SD below normal (that is, <67% peak activity) as previously described (14); for postcoronary artery bypass studies, improvement was defined as an increment in peak Tc-99m isonitrile activity >10% compared with the preoperative study. The segments and territories with abnormal Tc-99m isonitrile uptake by quantitative techniques were subdivided for analysis into those with <50% and those with ≥50% peak activity; this subdivision follows from previous work (10) with thallium in preoperative and postoperative patients.

Radionuclide ventriculography. Radionuclide ventriculography was performed utilizing Tc-99m-labeled red blood cells according to a previously described protocol (18). Data were acquired in the anterior, “best septal” left anterior oblique and left posterior oblique projections. A 3 point scoring system was independently applied by two observers as follows: grade 0 = akinetic/dyskinetic, grade 1 = hypokinetic and grade 2 = normal. Regional wall motion was determined on a segmental basis, and subsequently assigned to a coronary vascular territory. The score for a vascular territory represented the maximal defect assigned to any of
Table 1. Qualitative Technetium-99m (Tc-99m) Isonitrile Uptake in Relation to Regional Wall Motion in 78 Vascular Territories

<table>
<thead>
<tr>
<th>Tc-99m Isonitrile Uptake Grade</th>
<th>Regional Wall Motion (% of territories)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>0 (n = 27)</td>
<td>26</td>
</tr>
<tr>
<td>1 (n = 18)</td>
<td>39</td>
</tr>
<tr>
<td>2 (n = 33)</td>
<td>70</td>
</tr>
</tbody>
</table>

the segments constituting that territory. Again, disagreements were resolved by three person consensus.

Statistics. All quantitative data are presented as mean values ± 1 SD.

For the wall motion study, each coronary vascular territory was assigned a qualitative score (normal, hypokinetic, akinetic/dyskinetic). Qualitative and quantitative Tc-99m methoxybutyl isonitrile uptake scores (Tables 1 and 2, respectively) are presented for each wall motion score in the corresponding coronary vascular territory. The quantitative data were compared by one-way analysis of variance in two paired wall motion groups (normal versus hypokinetic, hypokinetic versus akinetic/dyskinetic). Assessment of Tc-99m isonitrile uptake as a predictor of retained wall motion was performed by comparing binary uptake scores (≥50% versus <50%) to a binary wall motion assignment (normal/hypokinetic versus akinetic/dyskinetic) using Fisher's chi-square test.

For the pre- versus postcoronary bypass study, each patient provided "corresponding" segments for comparison. Thus, the data were grouped and compared by Fisher's chi-square test.

Results

Wall Motion Study

Regional Tc-99m isonitrile uptake versus wall motion. The qualitative and quantitative scoring data relating Tc-99m methoxybutyl isonitrile uptake to scintigraphic regional wall motion in 78 vascular territories are shown in Tables 1 and 2. When regional perfusion, as evidenced by Tc-99m isonitrile uptake, was visually normal, corresponding regional wall motion was present (normal or hypokinetic) in 94% of cases.

When regional perfusion was mildly to moderately reduced, wall motion was detectable in 72% of cases. When regional perfusion was markedly reduced by qualitative analysis, regional contraction was detected in 52%. When the quantitative Tc-99m isonitrile score was <50%, wall motion was present in only 11% of territories, in contrast to 89% of territories with uptake ≥50% (p < 0.02). Thus, there is a general relation between both qualitative and quantitative Tc-99m isonitrile uptake and regional wall motion.

Regional coronary perfusion versus wall motion. A more detailed analysis of the 27 coronary vascular territories assigned a qualitative uptake of grade 0 is shown in Table 3. There was a relation between coronary anatomy and wall motion. Of the 14 territories with akinesia, 12 were supplied by a vessel with total occlusion. Of the 14 territories in which wall motion was present (hypokinetic or normal), 8 were supplied by a vessel with subtotal stenosis and 6 by a vessel with total occlusion. In five of the latter six cases, collateral filling of the distal coronary vessel was detected at angiography. Thus, angiographic evidence of intact perfusion was detected in 13 of 14 territories manifesting a dissociation between flow and wall motion.

There was also a relation between quantitative isonitrile uptake and wall motion in territories assigned an uptake of grade 0. For grade 0 territories with intact wall motion (normal or hypokinetic), the mean quantitative Tc-99m isonitrile score was 62 ± 15%, in contrast to 39 ± 16% in akinetic grade 0 territories (p = 0.02). Quantitative profiling allowed for detection of preserved wall motion in grade 0 territories (Table 4). When the quantitative Tc-99m isonitrile score was

<table>
<thead>
<tr>
<th>Wall Motion</th>
<th>Normal/Hypokinetic (n = 14)</th>
<th>Akinetic/Dyskinetic (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary anatomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% occlusion</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Good collateral vessels</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Poor collateral vessels</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>75% to 90% stenosis</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Quantitative Technetium-99m Isonitrile Uptake in Relation to Regional Wall Motion

<table>
<thead>
<tr>
<th>Regional uptake (%) peak activity</th>
<th>Normal/Hypokinetic (%)</th>
<th>Akinetic/Dyskinetic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (≥ 50%)</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>Grade 2 (&lt; 50%)</td>
<td>9</td>
<td>91</td>
</tr>
</tbody>
</table>

p < 0.01, grade 1 vs. 2.

Table 3. Relation of Wall Motion and Coronary Anatomy in Grade 0 Technetium-99m Isonitrile Vascular Territories

Table 2. Quantitative Technetium-99m (Tc-99m) Isonitrile Uptake in Relation to Regional Wall Motion

<table>
<thead>
<tr>
<th>Tc-99m Isonitrile Uptake (% of peak)</th>
<th>Normal (Group I)</th>
<th>Hypokinetic (Group II)</th>
<th>Akinetic/Dyskinetic (Group III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>84 ± 10*</td>
<td>71 ± 15*</td>
<td>47 ± 21</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.001, I vs. II; †p < 0.001 II vs. III. Data are reported as mean ± standard deviation.
$<50\%$; akinesia was present in 91% of such territories, in contrast to 23% of territories (3 of 13) with $\approx50\%$ peak activity ($p<0.01$). In a subset of 20 patients with Q wave infarction, 8 demonstrated retained wall motion in the infarct zone; 7 of these 8 patients had a peak Tc-99m isonitrile score $\approx50\%$.

**Postcoronary Artery Bypass Study**

**Regional Tc-99m isonitrile perfusion score.** Technetium-99m isonitrile uptake studies were available before and after coronary artery bypass grafting in eight patients. Two of 120 segments available for comparative uptake scoring were excluded for technical reasons. Of the remaining 118 segments, 55 were scored as normal on the preoperative study and remained so after surgical revascularization (Table 5). Sixty-three segments were assigned an abnormal qualitative uptake score on the baseline study: 36 (57%) demonstrated improved uptake postoperatively; 29 (46%) were scored as normal at repeat imaging. Of 18 segments with grade 0 uptake preoperatively, 11 (61%) showed improvement after revascularization, with 4 segments (22%) scored as normal on the postintervention study. When the grade 0 segments were analyzed quantitatively, there was a significant improvement in Tc-99m isonitrile uptake ($55 \pm 18\%$ before vs $73 \pm 21\%$ after operation; $p=0.03$), thereby corroborating the subjective data. A representative example is shown in Figure 1. This improvement occurred more frequently in segments with a higher uptake value preoperatively. Eighty percent of myocardial segments with a quantitative preoperative score between 50% and 67% of peak activity improved postoperatively to a range of $58 \pm 5\%$ to $80 \pm 12\%$ ($p < 0.001$); in contrast, only 39% of segments with a preoperative score $<50\%$ improved significantly after revascularization (to a range of $45 \pm 5\%$ to $62 \pm 18\%$; $p=0.03$).

**Correlation with coronary vascular anatomy.** When considered according to coronary vascular anatomy, qualitative Tc-99m isonitrile uptake improved in 12 of 13 vascular territories with a reduced preoperative score; all 5 territories assigned a preoperative uptake of grade 0 showed postoperative improvement (Fig. 2). Furthermore, of the eight coronary vascular territories with an abnormal quantitative preoperative score ($<67\%$ of peak activity; that is, $>2$ SD below normal), seven (88%) demonstrated a significant increase in the postoperative score to a range of $51 \pm 9\%$ to $75 \pm 8\%$ ($p < 0.001$).

![Figure 1. Perfusion studies using rest-injected technetium-99m isonitrile in a patient before (A) and after (B) coronary bypass surgery, demonstrating improved qualitative perfusion on the postoperative study (inferior wall, anterior projection).](image)
Discussion

Technetium-99m (Tc-99m) methoxybutyl isonitrile has been reported to be analogous to thallium-201 chloride in that it accumulates in myocardium in proportion to regional blood flow. The prolonged retention of Tc-99m isonitrile by the myocardium and the lack of significant redistribution underlie the potential application of this agent in patients to assess myocardial perfusion at times remote from initial injection. Preliminary data suggest that stress- or rest-injected Tc-99m isonitrile imaging is comparable with thallium imaging for the detection of ischemia and infarction.

Technetium-99m isonitrile uptake as a marker of viable myocardium. The present data demonstrate that if one equates reduced perfusion at rest as measured by Tc-99m isonitrile uptake in patients with infarction, the presence of viable myocardium in these territories is underestimated. In approximately 50% of regions in which Tc-99m isonitrile uptake at rest was graded visually as being markedly reduced, wall motion was present by radionuclide ventriculography; in 25% of such cases, regional contraction was normal. These data approximate results previously reported by Gibson et al. (10), who compared regional thallium uptake with regional wall motion (contrast ventriculography). These investigators (10) reported that the quantitative severity of a persistent thallium defect was related to the presence or absence of regional contraction as follows: wall motion was present in 59% of a group with a less severe defect compared with 14% of those with a more severe defect (more severe defined as < 50% of peak myocardial activity in a given projection).

We applied a similar quantitative “profile” to the subset of patients with a qualitative Tc-99m isonitrile uptake of grade 0. Although the numbers are limited, our data similarly suggest that quantitation helps to discriminate preserved wall motion in regions with severe qualitative abnormalities of rest-injected Tc-99m isonitrile uptake. Specifically, isonitrile uptake < 50% of peak myocardial activity predicted absent wall motion in the left ventricular segment under consideration and failure to improve after coronary artery bypass grafting. There is a trend for Tc-99m isonitrile uptake of 50% to 67% to be associated with retained viability as evidenced by retained preoperative wall motion and improved uptake after revascularization. Finally, Tc-99m isonitrile uptake > 67% appears to be associated with a normal qualitative perfusion score and normal regional contraction.

Correlation of technetium-99m isonitrile uptake and coronary perfusion. All 14 vascular territories with marked reduction in qualitative rest Tc-99m isonitrile uptake and preserved wall motion were supplied by coronary vessels with > 75% stenosis. Six of 14 territories were supplied by a totally occluded vessel, and 5 of these 6 territories had evidence of collateral flow. These data suggest that the discrepancy between coronary perfusion and regional wall motion is most likely to occur in regions of reduced but still present perfusion. The data also suggest that some patients with severe coronary artery disease have regions of under-perfused but potentially viable myocardium that are clinically “silent.” Whether this phenomenon reflects true “silent” ischemia as it is currently conceived or “hibernating” myocardium will require further investigation (22, 23). Conversely, the application of quantitative “profiles” as a means of detecting potential viability in akinetic segments cannot be assessed from these data.

Our data are consistent with the concept that accumulation of a perfusion agent is a two stage process, with delivery as a prerequisite to uptake. In the presence of high grade coronary stenosis, inadequate delivery rather than impaired uptake appears to determine Tc-99m isonitrile accumulation. Thus, despite the potential practical benefit of an agent whose uptake is not energy dependent, rest-injected Tc-99m isonitrile imaging reflects perfusion; like thallium studies, it may not provide an accurate index of viability in situations with severe limitation in perfusion.

Limitations of the study. Several limitations of the present study merit comment. First, work by Braunwald and coworkers (22, 24) has demonstrated that wall motion is an inadequate index of myocardial viability; akinesia does not necessarily imply scar. However, the concept of the “stunned” or “hibernating” myocardium is not relevant to the main theme of the present investigation—that there is preservation of wall motion in territories with markedly reduced Tc-99m isonitrile uptake. In addition, we excluded patients with recent ischemic injury in an effort to minimize the potential dissociation between perfusion and function. In the chronic setting, the presence of akinesia is more likely to reflect irreversible dysfunction and scar (9). It would be of interest to assess the possible value of quantitative Tc-99m isonitrile analysis as a means of predicting recovery of function in akinetic territories. However, we did not have sufficient post-revascularization wall motion data to investigate this issue.

Second, given the limitation inherent in using wall motion as a clinical marker of myocardial viability, it would have been preferable to assess systolic thickening by two-dimensional echocardiography. In analyzing regional wall motion by radionuclide ventriculography, it is possible that motion could be imparted to a noncontracting segment by the surrounding myocardium. Unfortunately, echocardiographic data were not available.

Third, the improvement in tracer uptake after revascularization may have only reflected improved coronary flow and may not have been a marker of myocardial viability. Although true in the strictest sense, recent experimental data (25) suggest to the contrary that postreperfusion uptake of
Tc-99m isonitrile reflects infarct size in nonviable regions. Other studies (26-28) in animal models of ischemia and infarction indicated that cell viability is necessary for myocardial Tc-99m isonitrile uptake as an index of myocardial salvage.

Fourth, although we applied widely accepted segmentation schemes to the scintigraphic data, the actual anatomic relation between the perfusion and wall motion studies is imprecise. It would have been preferable to assess perfusion and wall motion utilizing tomographic rather than planar techniques to match regions more precisely. In addition, tomography may be preferable to planar techniques for analysis of Tc-99m isonitrile images (31). However, many centers continue to utilize planar images and, given the fact that only large vascular territories were considered, a planar image analysis is defensible.

Conclusions. There is a general correlation between the qualitative rest technetium-99m isonitrile uptake score and regional wall motion. When regional perfusion is normal visually or exceeds 67% of peak activity quantitatively, regional wall motion is preserved. However, when qualitative perfusion is severely reduced, wall motion is absent in only 50% of the territories and, in fact, remains normal in 25%. A rest perfusion defect does not necessarily mean scar. In such instances, quantitative analysis appears to be helpful in assessing potential viability. Technetium-99m methoxybutyl isonitrile is primarily a perfusion and not a viability tracer and, therefore, is helpful in the characterization of myocardial viability. Indeed, the use of visual analysis of regional Tc-99m isonitrile uptake on planar images should be made with caution.

References
isotrile on myocardial viability after an ischemic insult (abstr). Circulation 1986;74(suppl II):II-256.


