Are regions of ischaemia detected on stress perfusion scintigraphy predictive of sites of subsequent myocardial infarction?

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SUMMARY To determine the relation between scintigraphic regions of stress-induced ischaemia and subsequent myocardial infarction, a select group of 21 patients was investigated. Each patient had undergone stress perfusion scintigraphy before myocardial infarction was recorded. After acute infarction, thallium-201 perfusion scintigraphy was performed in 16 patients (76%) and ⁹⁹ᵐTc (stannous) pyrophosphate in 14 patients (67%). All patients had at least one post-myocardial infarction scintigram and nine (42%) had both perfusion scintigraphy and infarct imaging.

Nineteen patients (90%) had scintigraphic evidence of stress-induced ischaemia pre-infarction. Scintigraphic regions of infarction were compared with regions of previously demonstrated stress-induced ischaemia. In 11 patients (53%) the myocardial infarction was more extensive; in one of these patients, reimaged one week before myocardial infarction, and in four others (19%) there were matching defects; in three patients (14%) the infarction was less extensive, and in two patients (9%) the infarction was less extensive but also involved regions not previously shown to develop ischaemia. In the final patient (5%) there was no match.

Stress perfusion scintigraphy was generally abnormal before acute infarction in this group of patients. Acute infarction frequently involved regions previously shown to develop stress-induced ischaemia, though these often underestimated the extent of myocardium at risk.

Stress myocardial perfusion scintigraphy has been well documented to be both sensitive and specific to the diagnosis of coronary disease.¹⁻³ Scintigraphy complements the findings of stress electrocardiography⁴⁻⁵ and aids the documentation of ischaemia in association with an otherwise uninterpretable electrocardiogram.⁶⁻⁷ There is little information available, however, regarding the overall predictive value of scintigraphy.

We sought to assess one aspect of scintigraphic prediction—whether by identifying areas of ischaemia stress scintigraphy would also predict the site of any subsequent infarction. To this end we studied a

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selected group of patients who had previously undergone stress scintigraphy and who had later suffered an infarction with scintigraphy on a second occasion soon afterwards.

Patients and methods

The study population consisted of all 21 patients retrospectively identified to have undergone clinically indicated stress perfusion scintigraphy before a documented myocardial infarction over a six year period at the University of California Medical Center, San Francisco. Each had undergone further myocardial perfusion scintigraphy with thallium-201 (²⁰¹Tl) or infarction scintigraphy with technetium ⁹⁹ᵐTc (stannous) pyrophosphate after infarction, again as clinically indicated. Pre- and post-infarction scintigrams were analysed to compare regions of ischaemia and infarction. There were 15 men and 6 women, with a mean age of 64 years and an age range of 50 to
77 years. Nineteen patients each had one documented myocardial infarction and two patients had two infarctions during the period between scintigrams. Six events were perioperative and occurred during or within the first week after coronary artery bypass graft surgery. Of the 23 myocardial infarctions, 20 were documented by at least two of the following criteria: (1) a history of prolonged chest pain, (2) the development of new electrocardiographic Q waves of 0-04 second duration or greater, or persistent ST depression and/or T wave inversion, and (3) a rise in the level of serum CK with a positive MB fraction. Three of the perioperative infarctions were additionally confirmed by positive infarct imaging with Tc-99m (stannous) pyrophosphate.

GRADED EXERCISE TREADMILL TESTING
All patients underwent stress perfusion scintigraphy in the fasting state a variable time before the clinical episode of infarction. Cardiac drugs were continued before the exercise study if clinically indicated. Ten patients were on propranolol at the time of stress testing. After giving informed consent, each patient had a standard 12 lead electrocardiogram followed by continuous monitoring with a CM5 bipolar precordial lead early, and by a 12 lead system later in the study period at rest, while standing, with hyperventilation and during maximal treadmill exercise, conducted according to the Bruce protocol. All patients exercised until the appearance of limiting symptoms. In the absence of resting ST-T wave abnormalities a test was considered positive for ischaemia if 1-0 mm or more of horizontal or downsloping ST segment depression compared with baseline, 0-08 second from the J point, developed during exercise or recovery. In the presence of baseline ST-T wave abnormalities as occurred in the setting of left ventricular hypertrophy, left bundle-branch block, and drug effect, the exercise electrocardiogram was considered "non-diagnostic".

MYOCARDIAL PERFUSION SCINTIGRAPHY
Myocardial perfusion scintigraphy was performed in all patients before infarction and in 16 patients after infarction. Stress perfusion scintigraphy was performed after the injection of 2-0 mCi of thallium-201 during peak exercise. Exercise was continued for another 30 to 60 seconds and scintigraphy begun within 10 minutes of completion of exercise. Our imaging technique evolved over the period of the study with the development of the method. Images were obtained in the anterior, 45° left anterior oblique, and left lateral projections early in the study. Later studies included 30° and 60° left anterior oblique projections. Imaging was performed with an Ohio Nuclear Series 120 scintillation camera, using a converging collimator in the early part of the study period, and a high sensitivity parallel hole collimator later. A 20% window was centred at 80 keV. Images were taken to 300 000 counts in the anterior projection, and to equal time in the remaining projections. Patients with abnormal exercise scintigrams returned four hours later for a redistribution study or within a week for a rest perfusion study. Rest perfusion scintigraphy was performed as above, with imaging initiated 10 minutes after radionuclide administration.

Two observers agreed on the interpretation of the original unenhanced analogue images without knowledge of the patient's clinical, electrocardiographic, or angiographic findings. Scintigrams were considered abnormal when relatively decreased perfusion of a region of the left ventricular image was present. Isolated linear apical defects and lone defects of the inferior wall in the left lateral projection are often seen in healthy persons, and so were not considered abnormal. A positive stress perfusion scintigram indicative of exercise-induced ischaemia was defined as a defect in the stress myocardial image not present at rest or redistribution. A positive perfusion scintigram indicative of infarction was defined as a defect in the stress perfusion image which persisted on redistribution, or as a defect in the resting myocardial image.

MYOCARDIAL INFARCTION SCINTIGRAPHY
Myocardial infarction scintigraphy was performed in 14 patients after myocardial infarction. For each study 15 mCi of 99mTc (stannous) pyrophosphate manufactured according to the method of Huberty and co-workers were administered intravenously and images obtained on Polaroid prints two to four hours later to 300 000 counts in anterior, 45° left anterior oblique, and left lateral projections, using a portable Ohio Nuclear Series 120 of Searle Pho Gamma V scintillation camera with a high resolution collimator. Two independent observers with no knowledge of the clinical history or other laboratory findings agreed on the interpretation of each scintigram.

IMAGE INTERPRETATION
All perfusion and infarct scintigrams were interpreted for regional abnormalities. The regional method of scintigraphic interpretation is shown in Fig. 1. In the anterior projection of perfusion and infarct scintigrams—anterolateral, apical, and inferior regions were identified. In the left anterior oblique projections—septal, inferopapical, and posterolateral regions were identified, and in the left lateral projection—anteroapical, and inferior regions were evaluated. Regional abnormalities on post-infarction scintigrams were compared with those of scintigraphic stress-induced ischaemia before infarction. A
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Fig. 1 Regional methods of scintigraphy interpretation: left ventricular regions. Shown are diagrammatic representations of scintigraphic regions in $^{201}$TI perfusion and $^{99}$Tc (stannous) pyrophosphate scintigrams used for the assessment of abnormalities. In the anterior projection, anterolateral, apical, and inferior regions are identified. In the left anterior oblique projections, posterolateral, inferoapical, and septal regions are identified. As projections are rotated more laterally, inferior, apical, and anterior regions are identified. Regions are illustrated for anterior, and left anterior oblique $45^\circ$ and $60^\circ$ projections.

A post-infarct scintigram was classified as “matching” when scintigraphic abnormalities of myocardial infarction involved the same regions as earlier ischaemia. A post-infarct scintigram was classified as “more extensive” when scintigraphic abnormalities involved all previously ischaemic regions plus any that were previously unaffected or that occurred where there had been no documented ischaemia. A scintigram was called “less extensive” when abnormalities involved some but not all of the previously ischaemic regions, and “less extensive+” if it also involved any previously non-ischaemic regions. A scintigram
showed “no match” if the infarct involved regions that failed to correspond to any previously demonstrated ischaemic regions.

Results

A complete summary of results is shown in the Table. Each of the 21 patients underwent stress perfusion scintigraphy for clinical indications and later suffered myocardial infarction. Two patients, cases 1 and 2, each experienced two myocardial infarctions and one of these, case 1, had two stress perfusion scintigrams, one before the first infarction, the other before the second infarction. One further patient, case 3, had two stress perfusion scintigrams before a single myocardial infarction. After infarction, each patient underwent further myocardial perfusion and/or infarction scintigraphy as clinically indicated. The initial stress perfusion scintigram was performed before myocardial infarction, with a mean time from scintigraphy to infarction of 11.5 months (range one day to 56 months).

All post-infarction scintigrams were performed within four months of infarction. Seventeen post-infarction perfusion scintigrams were performed in 16 patients including one patient, case 1, who was studied before each of two myocardial infarctions. Stress scintigrams with redistribution images were performed in seven of these patients. The mean time from infarction to perfusion scintigraphy was 3.2 weeks, range one day to four months.

99mTc (stannous) pyrophosphate infarct imaging was performed after infarction in 14 patients. The mean time from infarction to imaging was four days (range one to 11 days). All but two infarct scintigrams were performed within five days of infarction. In these two patients, positive pyrophosphate scintigrams were obtained on days 9 and 11.

All patients had at least one post-infarction scintigram. Nine of the 21 patients had both myocardial

<table>
<thead>
<tr>
<th>Stress testing Class.</th>
<th>Heart rate (% MPHR)</th>
<th>ECG</th>
<th>Time to myocardial infarction</th>
<th>Scintigraphy Pre-MI</th>
<th>Post-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case no.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>150 (87%)</td>
<td>±</td>
<td>12 mth</td>
<td>An I</td>
<td>An I S</td>
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<td>2</td>
<td>150 (87%)</td>
<td>±</td>
<td>4 mth</td>
<td>An S</td>
<td>An Ap I P-L S</td>
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<tr>
<td>3</td>
<td>129 (86%)</td>
<td>+</td>
<td>8 mth</td>
<td>An S</td>
<td>An Ap S P-L</td>
</tr>
<tr>
<td>4</td>
<td>147 (98%)</td>
<td>±</td>
<td>14 mth</td>
<td>I</td>
<td>An Ap I S</td>
</tr>
<tr>
<td>5</td>
<td>78 (52%)</td>
<td>±</td>
<td>37 mth</td>
<td>Ap</td>
<td>Ap</td>
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<td>6</td>
<td>125 (94%)</td>
<td>±</td>
<td>15 mth</td>
<td>Ap S</td>
<td>An-L Ap S</td>
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<tr>
<td>7</td>
<td>130 (71%)</td>
<td>+</td>
<td>7 mth</td>
<td>O</td>
<td>P-L</td>
</tr>
<tr>
<td>8</td>
<td>111 (80%)</td>
<td>±</td>
<td>3 wk</td>
<td>P-L</td>
<td>Ap I P-L</td>
</tr>
<tr>
<td>9</td>
<td>114 (76%)</td>
<td>±</td>
<td>10 mth</td>
<td>P-L</td>
<td>Ap I P-L</td>
</tr>
<tr>
<td>10</td>
<td>154 (88%)</td>
<td>-</td>
<td>56 mth</td>
<td>O</td>
<td>P-L</td>
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<tr>
<td>11</td>
<td>142 (85%)</td>
<td>-</td>
<td>19 mth</td>
<td>I</td>
<td>P-L</td>
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<td></td>
<td>92 (65%)</td>
<td>±</td>
<td>17 mth</td>
<td>S</td>
<td>An Ap I S</td>
</tr>
<tr>
<td>16*</td>
<td>42 (30%)</td>
<td>±</td>
<td>1 wk</td>
<td>Ap</td>
<td>Ap</td>
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<tr>
<td>17</td>
<td>107 (61%)</td>
<td>±</td>
<td>16 mth</td>
<td>An Ap I</td>
<td>An Ap I</td>
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<tr>
<td>18*</td>
<td>118 (72%)</td>
<td>±</td>
<td>8 mth</td>
<td>An Ap</td>
<td>An Ap</td>
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<td></td>
<td>131 (85%)</td>
<td>±</td>
<td>23 mth</td>
<td>I P-L</td>
<td>I P-L</td>
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<tr>
<td></td>
<td>134 (87%)</td>
<td>+</td>
<td>6 mth</td>
<td>I P-L</td>
<td>I P-L</td>
</tr>
<tr>
<td>19*</td>
<td>145 (90%)</td>
<td>±</td>
<td>3 wk</td>
<td>An Ap</td>
<td>An Ap</td>
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<td></td>
<td>130 (85%)</td>
<td>+</td>
<td>1 d</td>
<td>Ap I P-L</td>
<td>Ap I</td>
</tr>
<tr>
<td>20</td>
<td>122 (82%)</td>
<td>±</td>
<td>4 wk</td>
<td>Ap I P-L</td>
<td>Ap I</td>
</tr>
<tr>
<td>21*</td>
<td>84 (53%)</td>
<td>±</td>
<td>5 wk</td>
<td>I S</td>
<td>P-L</td>
</tr>
</tbody>
</table>

Abbreviations: MPHR, maximum predicted heart rate; Pre-MI, regions of stress-induced ischaemia before infarction; Post-MI, regions of scintigraphic abnormality after infarction; *, patient experiencing perioperative myocardial infarction; +, positive stress electrocardiogram; -, negative stress electrocardiogram; ±, indeterminate stress electrocardiogram; An, anterior wall involvement; An-L, anterolateral; Ap, Apical; I, inferior; P-L, posterolateral; S, septal.
perfusion scintigraphy and $^{99m}$Tc (stannous) pyrophosphate imaging. Among those who had both myocardial perfusion and infarct imaging, in every case regions of abnormality on infarct scintigraphy corresponded to abnormalities on the rest or redistribution perfusion scintigram.

On stress perfusion scintigraphy before infarction only 10 of the 21 patients attained 85% or more of maximum predicted heart rate. Of the 11 patients who did not reach this level, six were on propranolol. Exercise tolerance was limited by symptoms of pain, fatigue, or dyspnoea and, in one patient (case 4), the second pre-infarct study was limited by the development of complete heart block. Nineteen patients showed stress-induced perfusion abnormalities. Two patients failed to show any abnormalities on stress perfusion scintigraphy. One of these (case 6) attained only 71% of maximum predicted heart rate with a positive stress electrocardiogram while the other patient (case 9) achieved 88% maximum predicted heart rate without significant electrocardiographic changes 56 months before infarction. Both tests were terminated because of fatigue in the absence of chest pain. A third patient (case 4) showed no scintigraphic abnormality when studied initially at 52% of predicted heart rate before infarction but did show an abnormality at a subsequent stress test before infarction. Overall, pre-infarction stress electrocardiograms were positive for ischaemia in six patients, negative in two patients, and indeterminate in 13 patients. One patient (case 6) died two days after infarction. $^{99m}$Tc (stannous) pyrophosphate imaging performed one day earlier localised the infarction to inferior and posterolateral regions. This was confirmed at necropsy.

Six patients had historical and electrocardiographic evidence of myocardial infarction before their initial stress perfusion scintigram. In each case it was possible to localise the site of infarction as a non-reversible scintigraphic defect before the post-scintigraphic event. These defects were not included in the evaluation of areas of ischaemia or subsequent infarction.

Regions of infarction were more extensive than prior regions of stress-induced ischaemia in 11 patients (Fig. 2). One of these, case 4, when reimaged one week before infarction, and four other cases, showed a match between the extent of scintigraphic infarction and the prior region of stress-induced ischaemia (Fig. 3). Infarction was less extensive than prior regions of stress-induced ischaemia in three patients while in two patients scintigraphic infarction involved only some of the previously noted ischaemic regions as well as other regions not previously shown to be ischaemic. In the final patient, who experienced a perioperative infarction, there was no match between ischaemic and infarcted regions. Of the six patients who failed to achieve an optimal heart rate response while on beta blockers, three showed stress induced defects more extensive than those seen after subsequent infarction.

**Discussion**

A relatively small, select population was analysed in an attempt to define some aspects of the relation between the abnormalities on stress perfusion scintigraphy and subsequent infarction. While there are many questions that might be addressed regarding this relation, those posed in this study are limited by the nature of the population investigated. The patients studied were unusual in that they were noted to experience an acute myocardial infarction some time after stress perfusion scintigraphy performed during the course of standard clinical follow-up. Each patient underwent subsequent scintigraphic assessment again for clinical reasons. We did not evaluate the clinical course of all patients studied with stress scintigraphy and so cannot comment on the overall incidence of infarction in such patients. Nor could we assess from our data the relative risks for infarction of patients with negative versus positive scintigrams, nor with normal versus abnormal electrocardiograms. While
positive stress electrocardiograms are known to be related to many times greater risk of coronary events than are negative stress electrocardiograms,\textsuperscript{10} determination of the prognostic significance of stress scintigraphy requires a long-term evaluation of large populations. The population studied here, however, was an unusual one and was chosen based on the performance of scintigraphy in patients with confirmed infarction and earlier stress scintigraphy. With this population, some important observations can be made particularly regarding the relation between localisation of reversible ischaemia and subsequent regions of myocardial infarction.

Myocardial stress perfusion scintigraphy was generally abnormal in patients who suffered myocardial infarction within 32 months. While stress electrocardiography was less useful and only positive for ischaemia in six patients or 29\% of those studied here, many patients presented with indeterminate electrocardiographic findings which were often the initial indication for scintigraphy. Myocardial infarction generally involved regions of previously demonstrated ischaemia. In 18 of 19 patients with positive stress perfusion scintigraphy, the regions of infarction corresponded with some or all of those previously shown to be ischaemic. Regions of stress-induced ischaemia, however, often underestimated regions of subsequent infarction in the group as a whole.

The subgroup of six patients who had perioperative myocardial infarctions presented a spectrum of findings. Among these was the only patient in the series to show no anatomical match between an area of
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stress-induced ischaemia and the region of subsequent infarction. This suggests that the infarction occurred in an area not previously noted to become ischaemic but spared an area which had previously become ischaemic. Such might be the case, for example, if revascularisation aided previously ischaemic regions but surgery provided no benefit or reduced perfusion in a less severely affected bed, probably perfused by a stenotic vessel, but not previously associated with ischaemia.

In other cases regional infarction appeared to involve the area of earlier ischaemia to a greater or lesser extent. Frequently areas of infarction involved regions beyond those noted to be ischaemic, consistent with the previously noted hypothesis that perfusion scintigraphy does not identify the full extent of myocardium at risk.4 11 12 Such underestimation may be the result of the relative nature of stress perfusion scintigraphy itself. It has been established that scintigraphic global sensitivity for coronary disease detection is greater than regional sensitivity and the method can generally detect approximately 50% of involved vessels.11 12 Thereby, only the most severely diseased vessels are likely to produce recognisable defects. New methods employing radial analysis of washout data may help to identify such areas at risk.13 There is also no reason to believe that all regions distal to a significant lesion become ischaemic at stress for much depends on the level of stress achieved. Alternatively, underestimation of the region of subsequent infarction may relate to the underestimation of the amount of myocardium at risk. Massie and co-workers11 and others14 have shown that the ability to demonstrate a region of stress-induced ischaemia is significantly related to the level of stress. Not all patients achieved a satisfactory level of exercise. It is likely that with higher levels of exercise, scintigraphic evidence of further regions of ischaemia would be apparent. Furthermore, progression of coronary disease between initial scintigraphic study and subsequent infarction may in part explain this disparity. Infarction involving only a part of the region previously noted to be ischaemic could similarly reflect infarction in the area of a distal or branch vessel rather than the main stem which gave rise to the larger ischaemic zone. It could alternatively indicate the interm development of collateral vessels and a margin of protection or the inability of the post-infarct scintigram to identify regions of subendocardial involvement.

Although two of the three negative stress scintigrams obtained before infarction were associated with a suboptimal stress and heart rate response, the level of stress achieved did not appear to affect the relation between the extent of scintigraphic ischaemia and subsequent infarction. In addition, the interval between stress scintigraphy and infarction did not affect this relation.

Collateral vessels have been said to affect the sensitivity of stress evaluation.15 The influence of collaterals on scintigraphic abnormalities was evaluated in the seven patients who suffered perioperative infarctions and had undergone angiography before surgery. All these patients had triple vessel disease and six showed evidence of collateral circulation. In this small group of patients the presence of collateral circulation did not appear to influence the distribution of scintigraphic regions of ischaemia or subsequent infarction. The one patient without collaterals was the only patient in the series with disparate regions of ischaemia and infarction, suggesting that the scintigraphic findings could relate to the isolated nature of the affected bed.

Although all patients had myocardial scintigraphy after infarction, not all had repeat myocardial perfusion scintigraphy, as five patients had only 99mTc (stannous) pyrophosphate infarct imaging. Though previous studies using a comparison of both radiotracers in patients with acute infarction have shown some minor discrepancies when comparing the size of infarction, the studies generally agreed on the region of involvement.16 17 as did each of our studies in the nine patients assessed here by both methods.

Although preliminary, the study confirms the expectation that thallium stress perfusion scintigraphy is generally abnormal in patients who subsequently suffer myocardial infarction and that regions of infarction tend to involve those of demonstrated ischaemia. The latter often underestimate the region of subsequent infarction. The study population is a relatively small select patient group which prohibits overall conclusions regarding the risk of findings on stress perfusion scintigraphy for subsequent infarction and other aspects of prognosis. The data presented, however, constitute initial observations on the relations between the incidence and extent of perfusion scintigraphic abnormalities and subsequent infarction. A prospective study involving a larger population is needed to obtain more qualitative and quantitative data regarding this relation, an important one for assessing the prognostic significance of the scintigraphic estimation of ischaemic myocardium.

References


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