Slow bolus injection of ribose in the identification of thallium-201 redistribution following combined adenosine/dynamic exercise stress

M. G. Gunning, G. Clunie, J. Bradley, N. K. Gupta, J. B. Bomanji and P. J. Ell

Institute of Nuclear Medicine, University College London Medical School, London, U.K.

Aim A simple stress/redistribution thallium-201 myocardial perfusion imaging protocol may underestimate the degree of thallium redistribution in a defect identified on the stress images. We sought to investigate whether a slow-bolus injection of D-ribose improves the identification of thallium redistribution following combined adenosine/dynamic exercise stress.

Materials and methods Fifteen patients (10 males, five female, median age 63 years, range 50–75) were enrolled in the study. All underwent two successive adenosine plus exercise myocardial perfusion scintigraphy protocols 7–14 days apart. Adenosine was infused at 140 μg . kg⁻¹ . min⁻¹ coupled with 25 W ergometer pedalling for 6 min with 74 MBq of thallium-201 being injected at 4 min. Immediately following the stress image acquisition, patients received the one of either 60 mg . kg⁻¹ of D-ribose or normal saline, injected over 5 min. Redistribution images were acquired after 4 h. The identical stress procedure was conducted in the crossover arm of the study, and patients received the alternative test article. SPECT images were visually analysed and scored in a nine segment model by two blinded observers. In addition, circumferential profile analysis was conducted.

Results By visual interpretation 25 segments displayed redistribution of the ribose, but not in the saline study, 14 reversible segments were seen on the saline study alone, and 18 were seen on both studies (P=ns). In six patients ribose identified a greater number of redistributing segments, and in a further six patients saline identified more reversible segments. Comparison of mean values of defect extent severity and percentage reversibility scores generated from the circumferential profile analysis showed no significant difference between the two arms of the study.

Conclusion A 5 min bolus injection of D-ribose following combined adenosine/dynamic exercise stress confers little benefit on the identification of redistribution of thallium-201. These results differ from those of previous studies which showed that a 30 min infusion of D-ribose following treadmill exercise significantly enhanced thallium redistribution. The duration of the ribose infusion is likely to be an important factor influencing the effect brought to bear on the redistribution of the tracer, and should be run over 30 min, or longer.

(Eur Heart J 1996; 17: 1438–1443)

Key Words: Perfusion, ribose, scintigraphy, thallium.
redistribution of thallium on the basis of differential uptake and clearance from ischaemic versus normally perfused regions. Both Perlmutter et al. and Hegewald et al. found that a 30 min infusion of 3-3 mg \( \cdot \) kg\(^{-1}\) \( \cdot \) min\(^{-1}\) of a 10% solution of ribose (total 100 mg \( \cdot \) kg\(^{-1}\)), administered intravenously following image acquisition post-treadmill exercise, enhanced the identification of thallium redistribution in patients with coronary artery disease.

Despite these findings ribose is not widely used in clinical myocardial perfusion scintigraphy. A 5 min injection is more convenient to administer than a 30 min infusion. In this study, we sought to assess the value of a 5 min slow bolus injection of 60 mg \( \cdot \) kg\(^{-1}\) of D-ribose, administered following image acquisition post-stress (adenosine coupled with dynamic exercise) on the identification of thallium redistribution, when compared to placebo.

**Materials and methods**

**Study design**

This study as conducted as a prospective randomized double-blind crossover study. The study was approved by the Administration of Radioactive Substances Advisory Committee and the hospital’s ethical committee.

**Patient population**

Fifteen patients, 10 males and five females (median age 63 years, range 50–75), with stable angina were enrolled in the study. Referral for myocardial perfusion scintigraphy was based on clinical grounds. All patients presented with classical angina and were found to have a positive treadmill exercise test (defined as horizontal or downsloping ST-segment depression of 0.1 mV in at least one lead). Four of the patients had previously undergone coronary artery bypass surgery (>3 years previously), two patients had angiographically confirmed coronary artery stenosis and one patient had previously suffered a myocardial infarction. Patients with a history of diabetes mellitus, unstable angina, asthma or other obstructive airways disease, or those unable to undertake moderate exercise, were excluded from the study.

**Thallium scintigraphy**

Patients attended for two successive adenosine plus dynamic exercise, stress myocardial perfusion scans, 7–14 days apart. Anti-anginal medications were not discontinued during the study, and care was taken to ensure that medications were not altered in the interim period between scans. Symptoms were recorded on both attendances to ensure that no deterioration or focal events, such as episodes of unstable angina, had occurred in the interval between scans.

**Stress study**

Patients abstained from food, and caffeine-containing beverages overnight prior to thallium scintigraphy. Stress was conducted by infusing 140 \( \mu \)g \( \cdot \) kg\(^{-1}\) \( \cdot \) min\(^{-1}\) of adenosine through a peripheral intravenous cannula, coupled with 25 W of ergometer cycling for a period of 6 min. Blood pressure, pulse and an electrocardiogram were recorded before, every 2 min during, and immediately after, the stress procedure. At 4 min, 74 Mbq of thallium-201 were administered through the intravenous cannula. Images were acquired within 5 min of completion of stress, on a dual-headed Optima gamma camera (IGE). Acquisition was conducted through an arc of 180°, from 45° right anterior oblique to 45° left posterior oblique involving 64 projections of 20–25 s per stop. Two low energy, high resolution collimators were used and energy peaks set at 72 keV and 169 keV, with 20% windows and no offset, were employed.

Data were recorded and processed on an IGE-Star 4000i computer utilizing a Hanning pre-filter with a cut-off frequency of 0.8 cycles. cm\(^{-1}\) and a Ramp filter during the back-projection algorithm. The reconstructed transaxial slices were than reoriented into the vertical and horizontal long, and short axes. In addition, circumferential count profile curves of relative thallium activity for the post-stress, and resting images were generated.

**Test article administration**

Patients were randomized to one of two treatment arms in the first period and crossed over to the alternate treatment arm in the second period. The test articles were administered in a double-blind fashion. Immediately following the stress image acquisition, patients received one of either 60 mg \( \cdot \) kg\(^{-1}\) of D-ribose in a 10% solution or placebo (normal saline). Both were given by a slow intravenous bolus over 5 min. Between this administration and the resting image acquisition, patients were instructed not to eat, but permitted to drink either water or a single beverage containing no caffeine or sugar and a record was made of this. Patients were requested to remain in the institution during this period, in order to avoid exertion during the redistribution phase. Any adverse effects following test article administration were recorded. Rested images were acquired at 4 h post-stress.

**Crossover study**

At 7–14 days, patients underwent the identical stress procedure, receiving the alternative test article immediately following the stress image acquisition. They were requested to drink the same caffeine-free, sugar-free beverage as recorded on the first study, at the same interval following stress.

**Thallium-201 image analysis and interpretation**

SPECT images were reviewed visually by two physicians, and scored with the observers blinded to the results.
identity of the images in respect of the administration of the test articles. Images were analysed in the nine segment model (basal and apical segments of each of the septum, anterior, inferior and lateral walls with the apex as the ninth segment) and scores were allocated by consensus between the two observers. A third observer mediated in the event of disparity. Grading of thallium distribution in each segment was assigned as follows: 4, normal; 3, mildly reduced; 2, moderately reduced; 1, severely reduced; and 0, absent tracer uptake. In order to evaluate reproducibility of the visual scoring system, eight of the 15 patients were scored twice.

Change in thallium distribution between the stress and resting images within defects, was scored as follows: C, complete (improvement in uptake from grades ≤3 following stress, to grade 4 after redistribution); NC, near complete (improvement from grade ≤2 to grade 3); P, partial (improvement from grade 0 or 1, to grade 1 or 2); R, reverse redistribution (decrease in tracer uptake grading on redistribution compared with stress); F, fixed (no change in tracer distribution noted).

In addition polar map analysis was conducted using a computer-assisted algorithm comparing stress and redistribution images. Initial stress defects were defined as regions with thallium activity >2-5 standard deviations below the mean value for normal patients on the computer database (normal database Institute of Nuclear Medicine, University College London Medical School). Extent of a defect was defined as the number of pixels which displayed activity >2-5 standard deviations below the mean. Severity was defined as the overall number of standard deviations deficit in activity within the collection of pixels comprising the defect. Only defects identified on both the ribose and the saline stress studies were considered in the analysis, and defects at the extreme apex or base of profiles were not included.

Reversibility within the defect on the redistribution images was defined as regions with thallium activity >2-5 standard deviations. Percentage reversibility was defined as the proportion of number of pixels within any given defect which displayed reversibility multiplied by 100.

**Statistical analysis**

The number of reversible defects identified by visual inspection on the ribose and saline studies, were compared using McNemar’s paired chi-squared test. The mean values of extent, severity and percentage reversibility scores of defects obtained from polar map analysis were compared between the two studies using the paired Student’s t-test. Haemodynamic characteristics during the stress procedure were compared using the paired t-test. Agreement for repeated measurements of the visual scoring to thallium uptake was compared using the kappa statistic. Statistical significance was considered where \( P<0.05 \).

**Results**

**Haemodynamics**

The results are illustrated in Table 1. No significant difference was found between mean values of peak heart rate, increment in heart rate, increment in systolic blood pressure, peak rate-pressure product, and increment in rate–pressure product between the ribose and saline studies.

**Thallium images**

**Visual interpretation and scoring**

Segmental scoring of the images yielded the following results. In the ribose study, 62 normal segments, 18 fixed defects, 43 reversible defects (of which 29 were completely reversible, nine nearly completely reversible, and five partially reversible) were identified. Twelve segments displayed reverse redistribution. In the placebo (saline) arm of the study, 72 normal segments were identified, 21 fixed defects, 32 reversible defects (of which 20 were completely reversible, 10 nearly completely reversible, and two were partially reversible). Ten segments displayed reverse redistribution (see Table 2).

Twenty-five segments displayed redistribution on the ribose study, but not on the saline study, while 14 reversible segments were identified on the saline but not on the ribose study. Eighteen segments displayed redistribution in both arms of the study, while no redistribution was identified in either study in 78 segments (\( \chi^2 =2.56, df=1, P>0.05 \)). These results are displayed in Table 3.

In addition the findings were analysed on a patient-by-patient basis. In six patients ribose studies
Studies of thallium redistribution showed that the administration of ribose solution was found to be greater in three defects in the ribose study alone, and in one, it was identified only in the saline study. No significant difference was found when comparison was made of these values between the ribose and saline studies.

### Table 2 Comparison of visual interpretation and scoring of SPECT images between the ribose and saline arms of the study

<table>
<thead>
<tr>
<th></th>
<th>Ribose</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>Fixed</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Reverse redistribution</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Reversible:</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>Complete reversibility</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Nearly complete reversibility</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Partial reversibility</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3 Results of segmental analysis of total of 135 segments 4 h post-stress: ribose compared with saline

<table>
<thead>
<tr>
<th></th>
<th>Ribose arm of the study</th>
<th>Saline arm of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>+RD</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>-RD</td>
<td>25</td>
<td>78</td>
</tr>
</tbody>
</table>

+RD = reversible defect present; -RD = reversible defect absent. P > 0.05.

### Table 4 Extent, severity and percentage reversibility scores of ribose and saline studies on quantitative imaging

<table>
<thead>
<tr>
<th></th>
<th>Ribose</th>
<th>Saline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent (± SE)</td>
<td>74±1 ± 10.5 pixels</td>
<td>75±2 ± 13.5 pixels</td>
<td>ns</td>
</tr>
<tr>
<td>Severity</td>
<td>302.6 ± 51</td>
<td>317.2 ± 76.8</td>
<td>ns</td>
</tr>
<tr>
<td>Percentage reversibility</td>
<td>21.9 ± 6.1%</td>
<td>15.5 ± 5.7%</td>
<td>ns</td>
</tr>
</tbody>
</table>

identified more reversible segments than saline studies, in six patients saline studies identified more reversible segments. In three patients no difference was noted in the number of segments. For repeated visual scoring of eight of the 15 patients (72 segments) total agreement was 92% with a corresponding kappa value of 0.87.

### Polar map analysis

Seventeen defects were identified by quantitative processing. In three of these, reversibility was identified in the ribose study alone, and in one, it was identified only in the saline study. Where six reversible defects were common to both studies, the degree of reversibility was found to be greater in three defects in the ribose study, and higher in three defects in the saline study. No reversibility was shown on quantitative assessment in seven defects. Mean values for extent, severity and percentage reversibility of defects are shown in Table 4. No significant difference was found when comparison was made of these values between the ribose and saline studies.

### Discussion

**Rationale behind study**

A simple stress/redistribution thallium myocardial perfusion scintigraphy protocol has been shown by several investigators to underestimate the potential degree of redistribution in any given defect, and moreover to underestimate the amount of viable myocardium present. As alluded to earlier alternative protocols have therefore been applied in order to overcome this shortcoming, involving either late imaging, thallium reinjection, or separate day resting injection. Studies assessing the value of such protocols in predicting improvement of function of myocardium following revascularization have reported a positive predictive accuracy of between 57 and 92% for prediction of segmental improvement. With the more recent application of positron emission tomography in myocardial viability assessment, reported positive predictive values for regional improvement post-revascularization have been slightly higher than thallium; 72.95%.

He et al. assessed the value of nitrates in augmenting the sensitivity of reinjection imaging, and found that a single dose of isosorbide mononitrate administered immediately following post-stress imaging improved the identification of viable segments. Clearly there is a need to develop a single day thallium protocol which is rapid, involves a single injection of thallium, but overcomes the short-comings of a simple stress/redistribution protocol. The use of a 30 min ribose infusion has not been widely applied in clinical thallium myocardial perfusion studies, despite evidence supporting its value in enhancing redistribution. As a 5 min administration of ribose solution is more convenient than a 30 min infusion, our study sought to assess whether the rate of infusion had any bearing on the effects of thallium redistribution.

**Ribose and its effects on thallium kinetics**

5-phosphoribosyl-1-pyrophosphate is an important precursor in purine and pyrimidine nucleotide synthesis. Previous studies on rat models have shown that the rate-limiting step in the oxidative pentose phosphate pathway can be bypassed by an infusion of ribose which leads to an elevation in levels of 5-phosphoribosyl-1-pyrophosphate and ribose-5-phosphate. Applied to thallium kinetics, an infusion of ribose in an animal model has been shown to enhance the rate of clearance of thallium from normally perfused myocardium more than from transiently ischaemic tissue; with a net effect of accelerating redistribution. This may be as...
a result of increasing intracellular adenosine triphosphate levels, and augmentation of the Na/K adenosine triphosphate pump. Perlmutter et al.\cite{9}, and Hegewald et al.\cite{10} applied this in two studies of patients with coronary artery disease, where a 30 min infusion of ribose (100 mg . kg$^{-1}$) was administered following a treadmill stress procedure at thallium injection. Perlmutter found that ribose infusion was associated with approximately a two-fold enhancement of identification of reversible segments when compared to saline infusion in the same subjects, and this feature of facilitation of thallium redistribution was noted in 13 of the 17 patients studied. Hegewald found that ribose identified approximately double the number of redistributing segments when compared to saline. Moreover ribose was superior at 4 h, when compared to both 4 h and 24 h redistribution images following saline infusion. Importantly, very few segments were identified by either of these investigators, where redistribution was found to be present in the saline arm of the study but not in the ribose arm (one and three, respectively).

Comparison with previous studies

The results of our study suggest that ribose administered as a 5 min slow-bolus injection does not confer great advantage on the identification of thallium redistribution; these findings differ from the results of studies cited above. On visual analysis and segmental scoring, the overall number of redistributing segments in the ribose arm of the study was higher at 43, compared to 32 in the saline arm, but importantly, as shown in Table 3, 14 segments showed redistribution on the saline study alone, and 25 with ribose alone. This differs from the studies of Perlmutter and Hegewald where very few segments were identified which showed redistribution with saline and not ribose\cite{8,10}. The results of the quantitative analysis of our study further support the suggestion that little improvement in thallium redistribution is brought about by a 5 min injection of ribose. While more defects showed redistribution with ribose alone (three) compared to saline alone (one), equal numbers of defects showed greater degree of reversibility in the alternate arms of the study (three in each). No statistical difference was identified when values of the quantitative analysis were compared between the treatment arms, as illustrated in Table 4.

If the results of the studies of Perlmutter et al.\cite{9} and Hegewald et al.\cite{10} are more suggestive of ribose-enhancing thallium redistribution than our own, it is worthwhile clarifying difference in methodology which might account for this disparity. The administration of ribose in the previous studies was carried out over 30 min as opposed to a slow bolus over 5 min, which our investigation aimed to assess. This may be the key issue in explaining the less pronounced influence of ribose in our study. In their study of a pig model, Angello et al.\cite{8} assessed the percentage thallium redistribution during, at the end, and 1 h following a 30 min infusion of ribose and compared the findings with saline infusion. What was noteworthy from the results was that ribose-treated animals had significantly greater thallium redistribution during and at the end of infusion, than the saline-treated group. This effect occurred predominantly during the infusion period because at 1 h post-infusion, there was no longer a significant difference in % redistribution between the groups. It would seem, therefore, that the duration of the ribose infusion has significant influence on the effect on thallium kinetics, and hence on the enhancement of redistribution.

The studies also differ in the choice of dose of ribose. The overall dose in the studies by Perlmutter and Hegewald was 100 mg . kg$^{-1}$, over 30 min, as opposed to 60 mg . kg$^{-1}$ over 5 min in our study. In their study of a pig model, Angello et al.\cite{8} found that the infusion of ribose (100 mg . kg$^{-1}$ over 30 min) provoked a mild drop in serum glucose from 101 to 87 mg . dl$^{-1}$ which was not seen on the saline study and accordingly the serum insulin levels were higher in the ribose group. Hegewald et al.\cite{10} also reported lower serum glucose and higher insulin levels during ribose infusion (100 mg . kg$^{-1}$ over 30 min). Our study involved a more rapid infusion than previously described, and therefore the lower dose of 60 mg . kg$^{-1}$ was chosen as a precaution against provoking hypoglycaemia. While serum glucose and insulin levels were not measured in this investigation, symptom monitoring yielded no reports of adverse effects during or after the ribose infusion. Based on this, it is possible that a higher dose of ribose could be administered over 5 min without adverse effect, but monitoring of serum glucose during this procedure would be advisable.

Lastly an additional feature differentiating the methodology of this study from that of previous investigations, is the choice of combined adenosine/dynamic exercise stress, as opposed to treadmill exercise. The combined pharmacological/dynamic exercise stress procedure was easily reproducible, as the end point was not limited by patient symptoms or compliance. Therefore on each visit to the institution the subjects in this study underwent identical stress conditions and received the thallium dose at exactly 4 min stress; this is reflected in the fact that there is no significant difference in the haemodynamic data recorded during the two treatment arms of this study (see Table 1). Because the half-life of adenosine is so short (<10 s)\cite{21}, and the test article administration was conducted approximately 15 min after the adenosine infusion was terminated, it is unlikely that the adenosine had any bearing on the effects of ribose on thallium redistribution in this study.

Neither our study, nor the studies of Perlmutter et al.\cite{9}, or Hegewald et al.\cite{10}, evaluate the role of ribose in the detection of viable myocardium with thallium-201. No 'gold standard' exists for identifying viable myocardium, and, while the observation of preserved regional systolic function confirms preserved viability, the observation of asynergy does not preclude it. Hegewald et al.\cite{10} correlated thallium-201 defect reversibility with intact resting regional wall motion. To clarify
whether the finding of augmented thallium-201 redistribution with ribose infusion is representative of reversibly ischaemic and viable myocardium, this technique could be validated against alternative imaging techniques, such as 18F-FDG PET, and/or regional function imaging following coronary revascularization where asynergy has been identified. This might provide the substrate for further studies.

Study limitations

The number of patients enrolled in the study was small, but due to the design as a crossover study, each patient operated as his/her control. The finding of a greater degree of redistribution of thallium in a number of defects in the saline study rather than the ribose study, is not easily explained from a mechanistic point of view. It is possible that some variation would be found if studies were repeated in the same patients using saline on two occasions, in spite of identical stress conditions. This validation was not carried out in this study as it would require additional radiation exposure for the subjects involved.

Conclusion

A 5 min bolus injection of 10% ribose solution only marginally improves the identification of thallium-201 redistribution following combined adenosine/dynamic exercise myocardial perfusion scintigraphy. This is the first study in which the use of ribose has not been shown to markedly enhance thallium-201 redistribution following cardiac stress. We conclude that both the rate of redistribution with ribose infusion is representative of reversibly ischaemic but viable myocardium by thallium-201 imaging for assessing viability of severe asynergic regions.

References