Sublingual isosorbide dinitrate to improve technetium-99m-teboroxime perfusion defect reversibility.

Sublingual Isosorbide Dinitrate to Improve Technetium-99m-Teboroxime Perfusion Defect Reversibility

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Previous studies demonstrate perfusion defect reversibility in ^{201}Tl reinjection imaging performed after the administration of nitrates. This study tests whether the acute sublingual administration of isosorbide dinitrate (ISDN) could improve the capability of ^{99m}Tc-teboroxime to detect reversibility in exercise-induced perfusion defects. **Methods:** Ten patients with previous myocardial infarction underwent exercise, redistribution and reinjection ^{201}Tl imaging, ^{99m}Tc-teboroxime exercise and rest scans. Following the latter, 5 mg sublingual ISDN were given, ^{99m}Tc-teboroxime was reinjected and images collected. **Results:** The total defect score/patient in the ^{201}Tl images was 10.5 ± 3.1 (mean ± s.d.), decreasing to 7.4 ± 2.7 after redistribution ($p < 0.02$) and to 4.8 ± 2.1 after reinjection ($p < 0.01$ versus redistribution). The total defect score in ^{99m}Tc-teboroxime exercise images was 12.7 ± 3.1 ($p < 0.05$ versus ^{201}Tl exercise), decreasing to 7.3 ± 3.3 at rest ($p < 0.01$ versus exercise, NS versus ^{201}Tl redistribution) and to 5.6 ± 2.6 in ISDN images ($p < 0.02$ versus rest, $p < 0.05$ versus ^{201}Tl redistribution, NS versus reinjection). Of the 44 abnormal segments in ^{201}Tl exercise images, the redistribution scan identified 26 defects as reversible and 18 as fixed. After reinjection, 37 defects appeared reversible and only seven fixed ($p < 0.005$ versus redistribution). Stress-rest ^{99m}Tc-teboroxime classified 33 segments as reversible and 11 as fixed (NS versus both ^{201}Tl protocols). After ISDN, the uptake score increased in 19 segments. Therefore, 37 were classified as reversible and seven as fixed defects ($p < 0.01$ versus ^{201}Tl redistribution, NS versus ^{201}Tl reinjection). **Conclusions:** Sublingual ISDN before ^{99m}Tc-teboroxime rest injection seemed to improve the tracer capability of detecting reversibility in exercise-induced perfusion defects.

Key Words: isosorbide dinitrate; technetium-99m-teboroxime; thallium-201; myocardial viability

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When using ^{99m}Tc-teboroxime, a separate injection at rest is required for the definition of the baseline uptake pattern in stress myocardial scintigraphy (*1–7*). Therefore, stress-rest ^{99m}Tc-teboroxime imaging could offer some advantages over ^{201}Tl early redistribution in differentiating between reversible and fixed defects (*6,7*). On the other hand, some features of ^{99m}Tc-teboroxime kinetics, mainly the strict relation of its uptake to coronary blood flow and the very high first-pass extraction (*4,8–10*), could unfavorably affect the capability of severely hypoperfused but viable myocardium to take up a sufficient amount of the tracer to be effectively visualized. Preliminary experiences comparing rest ^{99m}Tc-teboroxime imaging with ^{201}Tl reinjection showed the superiority of the latter in detecting perfusion defect reversibility (*11*). Theoretically, a transient improvement of rest coronary blood flow before ^{99m}Tc-teboroxime injection could increase uptake by the severely hypoperfused territories. The acute administration of nitrates was reported to improve the regional myocardial blood flow at rest (*12*) and during exercise (*13*). Furthermore, sublingual nitroglycerin was shown to increase the reversibility of perfusion defects following ^{201}Tl reinjection (*14–16*). This preliminary study aimed to test the hypothesis that the uptake of ^{99m}Tc-teboroxime in exercise-induced perfusion defects could be improved by repeating the rest injection of the tracer after the administration of ISDN.

METHODS

Patient Population and Study Protocol

The study group was recruited from patients referred to our Nuclear Medicine laboratory for ^{201}Tl exercise myocardial scintigraphy. The following inclusion criteria had to be fulfilled: history of proven prior myocardial infarction dating back no more than 2 yr and no less than 1 mo; suspected effort angina and/or ischemic electrocardiographic changes during exercise stress testing; absence of heart disease other than coronary artery disease; and willingness to participate in the study after having given informed consent. For all patients the results of a recently performed coronary angiography were available or its execution had already been planned independently of the radionuclide investigations. The final study group consisted of ten patients, all male, mean age 56.1 ± 6.7 yr. Study protocol required the withdrawal of nitrates at least 48 hr before beginning the radionuclide examinations. Exercise ^{201}Tl and ^{99m}Tc-teboroxime myocardial scintigra-

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phy were performed in random sequence and within 5 days of each other. The protocol was approved by the ethics committee of our institution.

Thallium-201 Myocardial Scintigraphy

After overnight fasting, the patients underwent a symptom-limited exercise in upright position using a bicycle ergometer, starting with a 30 W work load, which was increased by 30 W every 3 min. Thallium-201 (74 MBq) was injected at peak effort and the patient kept exercising for a further 60 sec. Early and 4-hr redistribution scans were collected. After redistribution imaging, 55 MBq of ^{201}Tl were reinjected at rest, followed by image acquisition 30 min later (*17*). Three-view (best septal and steep left anterior oblique and anterior) planar studies were collected using either a Siemens Rotacamera or an Elscint Apex SP4 camera, equipped with a low-energy all-purpose parallel hole collimator, using two 20% energy windows centered at the 70 and 167 keV photopeaks of ^{201}Tl. The acquisition time was 400 sec per view for each study, using a zoom factor and a 128 × 128 computer matrix.

Technetium-99m-Teboroxime Myocardial Scintigraphy

On a separate day, exercise stress testing was performed in the same manner and at peak exercise 555 MBq of ^{99m}Tc-teboroxime were injected. After injection the exercise was continued for an additional 30 sec and imaging was started immediately using the same gamma camera, collimator, zoom factor and computer matrix of the ^{201}Tl study for each patient. A 20% energy window centered at the 140 keV photopeak of ^{99m}Tc was employed. The same three planar views of the ^{201}Tl study were acquired, beginning with the steep left anterior oblique projection, followed by the best septal left anterior oblique and by the anterior view. Acquisition time was 60 sec each for the first two views and 120 sec for the last one. Image collection was always completed within 7 min of tracer injection. Approximately one hr later an equal tracer amount was injected at rest and the baseline images were collected using the same procedure. Forty min after rest imaging sublingual ISDN (5 mg) was given. A dose of 555 MBq of ^{99m}Tc-teboroxime was then injected as soon as a 10 mmHg systolic blood pressure drop was measured and a new set of rest images was immediately collected using the above described procedure.

Image Evaluation

Both ^{201}Tl and ^{99m}Tc-teboroxime studies were evaluated in random order, blindly and independently by two experienced observers. Disagreements were solved by consensus with the help of a third reviewer. Analog images on x-ray film and digital computer displays were used. No smoothing or background subtraction was performed. Each scan was divided into seven segments (three segments/view, with the apical segment common to all three views) (*18*). Tracer uptake was visually graded using the following scoring scheme: 0 = normal; 1 = slightly, but clearly reduced uptake; 2 = moderately reduced; 3 = severely reduced and 4 = absent uptake. The score of the abnormal segments in each scan was summed up to give the total defect score. Each abnormal segment in the stress images was then evaluated for defect reversibility by comparing its score with that of the related redistribution or reinjection ^{201}Tl scans and, respectively, ^{99m}Tc-teboroxime rest or ISDN images. Those segments with unchanged or higher scores were classified as fixed and those with score decrease were classified as reversible.

Statistical Analysis

All data are expressed as the mean ± s.d. Continuous variables were compared using the Student's t-test for paired data. The total defect scores obtained in the various scans were compared using the Wilcoxon ranks test for paired data. The defect classification obtained by the two tracers using the different imaging protocols was compared using the McNemar chi square test for related proportions. A p value <0.05 was considered significant.

RESULTS

Patient Population

Eight patients showed electrocardiographic signs of previous anterior and two of previous inferior myocardial infarction. None of the patients had symptoms or signs of left ventricular dysfunction. A wall motion abnormality (either hypokinesia or akinesia) was demonstrated in all infarcted territories using contrast ventriculography, however, the left ventricular ejection fraction was >50% in all patients. Using a 50% vessel lumen narrowing as the angiographic threshold for the diagnosis of significant coronary artery disease, three patients were found to be affected by one-vessel, two by two-vessel and five by three-vessel disease during coronary angiography.

During the two stress tests, similar durations (^{201}Tl 10.5 ± 2.9 min versus ^{99m}Tc-teboroxime 10.3 ± 2.7, ns) and double product values (^{201}Tl 21679 ± 3992 bpm × mmHg versus ^{99m}Tc-teboroxime 22937 ± 3355, ns) were achieved, and the same end point was reached in each patient.

Myocardial Perfusion Imaging

Exercise ^{201}Tl images showed a mean of 190K counts over the myocardium, redistribution images a mean of 140K counts, and reinjection images a mean of 175K counts. The image quality of the ^{99m}Tc-teboroxime studies was poorer, with a mean of 50K counts over the myocardium on exercise scan. This increased to 75K counts in rest and to 100K counts in ISDN images. Furthermore, a high liver activity was found in the ^{99m}Tc-teboroxime images. Although this was reported to impair the evaluation of the inferior wall (*18*), particularly in the steep left anterior oblique view, by collecting this projection first, the assessment of the inferior wall uptake score was performed in all patients without problems. Disagreements in scoring were rare: 29 in a total of 420 assigned scores (6.9%) never exceeding 1 score unit. Figure 1 shows a typical example of the images obtained in our study. The scintigraphic results of the patient population are summarized in Table 1 and in Figure 2.

All patients had abnormal ^{201}Tl exercise scans and the total defect score/patient was 10.5 ± 3.1. In the redistribution images the total defect score decreased to 7.4 ± 2.7 ($p < 0.02$ versus exercise). After reinjection, a further decrease to 4.8 ± 2.1 ($p < 0.01$ versus both exercise and redistribution) was observed. Of the 44 abnormal segments in the ^{201}Tl stress images, 26 were classified as reversible and 18 as fixed when compared with the redistribution scan. After reinjection, the uptake score improved in 24 segments and the final classification was 37 reversible and 7 fixed defects ($p < 0.005$ versus redistribution).

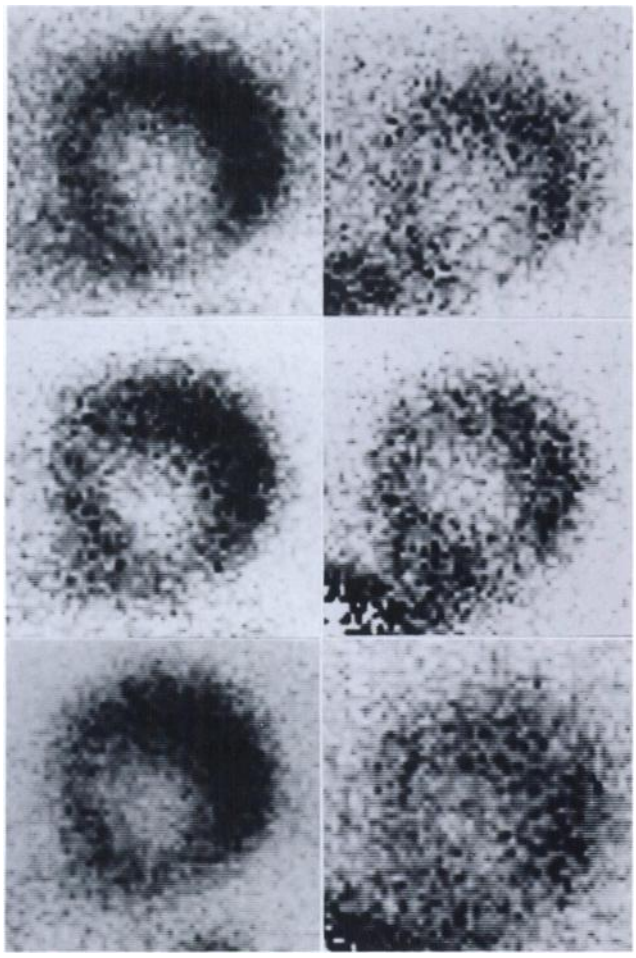

FIGURE 1. Best septal left anterior planar view of a patient with three-vessel disease and previous myocardial infarction. Thallium-201 images on the left and digital ^{99m}Tc-teboroxime images on the right. A clear-cut defect of the septal and apical wall is detected in the exercise scans (upper row); which is significantly reduced in the ^{201}Tl redistribution and ^{99m}Tc-teboroxime rest images (middle row), and has almost disappeared in the ^{201}Tl reinjection and ^{99m}Tc-teboroxime images after ISDN (lower row).

The overall agreement between ^{201}Tl and ^{99m}Tc-teboroxime stress images in detecting perfusion defects was good ($p = 0.37$). More specifically, a disagreement was observed only in five of 70 segments: ^{99m}Tc-teboroxime uptake was normal in one segment with a ^{201}Tl grade 2 defect and was abnormal (grade 1) in four segments with normal ^{201}Tl uptake.

The total defect score/patient in the ^{99m}Tc-teboroxime exercise images was 12.7 ± 3.1 ($p < 0.05$ versus ^{201}Tl exercise). In the rest images this value decreased to 7.3 ± 3.3 ($p < 0.01$ versus exercise, NS versus ^{201}Tl redistribution). After ISDN, the total defect score was 5.6 ± 2.6 ($p < 0.02$ versus rest, $p < 0.05$ versus ^{201}Tl redistribution, NS versus ^{201}Tl reinjection). Of the 47 segments with a perfusion defect in the exercise images, 34 were classified as reversible and 13 as fixed by the rest ^{99m}Tc-teboroxime images. In the ^{99m}Tc-teboroxime study after ISDN, the uptake score was found to be improved in 20 segments. Thus, 39 were classified as reversible and 8 as fixed (ns versus rest).

For a better direct comparison of ^{99m}Tc-teboroxime with ^{201}Tl data concerning defect reversibility, the analysis was restricted to the 44 segments with an abnormal ^{201}Tl exercise scan. Of these, 33 were classified as reversible and 11 as fixed by the sequence of stress and rest ^{99m}Tc-teboroxime images (NS versus both ^{201}Tl redistribution and reinjection). In the rest ^{99m}Tc-teboroxime images obtained by reinjecting the tracer after ISDN, however, the classification of 4 segments, all included in the patients' infarcted territories, was changed from fixed to reversible. Therefore, the same ultimate result was obtained as that in ^{201}Tl reinjection (37 reversible and 7 fixed segments, NS) and a significant difference was achieved compared to ^{201}Tl redistribution ($p < 0.01$).

DISCUSSION

Early redistribution images with ^{201}Tl are known to underestimate the reversibility of stress-induced perfusion

TABLE 1
Scintigraphic findings in the patient population

Patient no.	^{201}Tl			^{99m}Tc-teboroxime		
	EX	RED	REINJ	EX	REST	ISDN
1	5 (4)	3 (3)	3 (3)	11 (4)	5 (4)	3 (3)
2	10 (4)	10 (4)	7 (4)	12 (4)	10 (4)	8 (4)
3	9 (3)	5 (3)	2 (2)	11 (3)	3 (3)	1 (1)
4	11 (4)	9 (4)	5 (4)	12 (4)	7 (4)	6 (4)
5	8 (4)	8 (4)	4 (3)	9 (4)	4 (3)	5 (3)
6	12 (5)	5 (4)	4 (4)	13 (4)	5 (3)	4 (3)
7	12 (5)	9 (5)	6 (5)	20 (7)	13 (6)	9 (6)
8	17 (6)	12 (6)	9 (6)	16 (7)	10 (5)	7 (5)
9	11 (4)	6 (4)	3 (3)	11 (5)	6 (4)	3 (3)
10	10 (5)	7 (5)	5 (4)	12 (5)	10 (5)	8 (5)

EX = exercise; RED = redistribution; REINJ = reinjection; ISDN = rest imaging after ISDN. For each set of images, the total defect score and the number of abnormal segments (in parentheses) is reported.

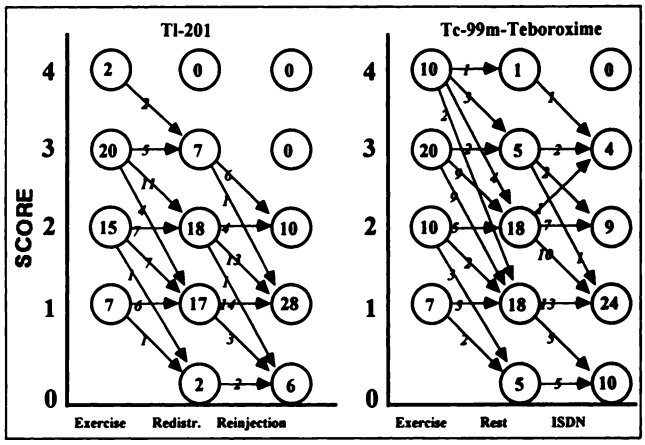

FIGURE 2. Plot of the defect score of the abnormal segments in exercise imaging and their changes in redistribution (Redistr.) and reinjection images (^{201}Tl, left panel) and in the rest and ISDN images (^{99m}Tc-teboroxime, right panel), respectively. The number of segments having a particular score is written in the circles; the small italic number written on each arrow shows how many segments underwent a score change indicated by the arrow itself.

defects (*17,19–23*). Therefore, either late redistribution or rest-reinjection images are needed to exclude the presence of reversibility. Indeed, these have become widely used methods for the detection of viable hibernating myocardium (*17,19–23*). The currently available ^{99m}Tc-labeled myocardial perfusion tracers require a separate injection at rest for baseline imaging. This could theoretically enhance their capability for demonstrating the reversibility of stress-induced defects. Some reports suggested that rest ^{99m}Tc-teboroxime imaging is superior to early ^{201}Tl redistribution (*6,7*). On the other hand, the few available data demonstrate that rest ^{99m}Tc-teboroxime imaging is less effective than ^{201}Tl reinjection for the recognition of defect reversibility (*11*). Similar data have been reported using rest ^{99m}Tc-sestamibi (*24*). Various approaches have been proposed to overcome this limitation of ^{99m}Tc-labeled agents, including the simultaneous evaluation of left ventricular function to assess wall motion of the hypoperfused territories (*4*). This is possible by the acquisition of first-pass radionuclide angiocardiography during tracer injection (*25,26*). Alternatively, with ^{99m}Tc-sestamibi, gated imaging can be used (*27*). As regards ^{99m}Tc-teboroxime, the analysis of myocardial washout has been suggested in order to differentiate between viable and non-viable tissue (*9,10*). Another approach is that of performing the tracer rest injection under a stimulation that can improve, at least transiently, the coronary blood flow in hypoperfused territories. Recent data suggest that the acute administration of nitrates may favorably affect coronary blood flow mainly, but not exclusively, through the improvement of collateral circulation (*28,29*). As far as perfusion imaging is concerned, various reports have shown that the acute administration of nitrates increases uptake of ^{201}Tl or enhances its redistribution, so that the detection of defect reversibility is improved (*12–16*). Based on this information, the present preliminary study is the first undertaken to test the possible influence of the acute administration of sublingual nitrates on the rest uptake of ^{99m}Tc-teboroxime and, consequently, on its ability to differentiate between reversible and fixed perfusion defects.

On the basis of our results, the slight superiority of rest ^{99m}Tc-teboroxime over early ^{201}Tl redistribution imaging to differentiate between reversible and fixed defects was confirmed. On the other hand, after ^{201}Tl reinjection, a significant decrease of the defect score was demonstrated both compared to the ^{201}Tl redistribution and the ^{99m}Tc-teboroxime rest images. Furthermore, the ^{201}Tl reinjection images were able to detect reversibility in a larger number of segments than both ^{201}Tl redistribution and rest ^{99m}Tc-teboroxime. The main result of this study, however, was that in the rest ^{99m}Tc-teboroxime images collected injecting the tracer after the acute administration of ISDN, the uptake score was found to have improved in almost half of the stress-induced defects. Accordingly, the total defect score decreased significantly compared to both the ^{99m}Tc-teboroxime rest and the ^{201}Tl redistribution images, and it was no longer statistically different from the ^{201}Tl reinjection value. Furthermore, the final classification of fixed or reversible segments in the ^{99m}Tc-teboroxime ISDN scans was the same as in ^{201}Tl reinjection imaging. These data support the initial hypothesis of the possible favorable role of acute nitrate imaging in enhancing the recognition of defect reversibility using ^{99m}Tc-labeled perfusion agents.

These data must however be evaluated with the utmost caution owing to the several limitations of this preliminary study. First, the patient population is extremely small. Second, although they were all affected by prior infarction, the patients were not studied because of symptoms or signs of left ventricular dysfunction, but because of suspect effort angina. Therefore, the indication for myocardial perfusion imaging was not the possible detection of viable hibernating myocardium. Actually, the majority of territories with uptake defects in the stress images were ischemic. Accordingly, in most of these segments the tracer uptake was found to be improved, albeit still abnormal, both in the ^{201}Tl redistribution and in the usual rest ^{99m}Tc-teboroxime images. So, viability had already been demonstrated without the need for further scans. This implies that our results must only be considered from the point of view of the imaging technique and should not be analyzed in clinical terms, since neither the ^{201}Tl reinjection nor the ISDN ^{99m}Tc-teboroxime images influenced patient management in this population. It must also be taken into account that our results are based on the simple visual evaluation of the tracer uptake and not on quantitative data. However, similar limitations are present in other reports about the issue of defect reversibility and myocardial viability (*16,24*). Finally, the possibility of an apparent increase in myocardial activity, because of the partial volume effect due to the improvement of either wall motion or thickening induced by the ISDN, cannot be excluded (*30*). Nevertheless, from a practical point of view, this mechanism would also imply

the presence of viable myocardium in the involved territory.

CONCLUSION

The reinjection of ^{99m}Tc-teboroxime after administration of ISDN could improve the ability to differentiate between reversible and fixed perfusion defects. This could be of value in the detection of myocardial viability, although this hypothesis cannot be demonstrated by the present study because of patient selection criteria. Nevertheless, further studies on wider populations, including patients with the clinical suspicion of hibernating myocardium, are warranted.

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