Clinical Utility of Technetium-99m-Teboroxime Myocardial Washout Imaging

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The purpose of this study was to evaluate the clinical utility of ^{99m}Tc-teboroxime myocardial washout imaging. The differential washout after a single tracer injection has been proposed as an alternative for characterization of the perfusion defects. **Methods:** Fifty-six patients received 5-min adenosine infusion. The stress dose of ^{99m}Tc-teboroxime was injected at 4.5 min and stress imaging with a single-headed SPECT gamma camera was started at 6 min, washout imaging followed immediately. At 20 min, the rest tracer dose was injected at rest and imaging was started at 21.5 min. The reversibility of the perfusion defects on the washout and rest images was compared visually and quantitatively. **Results:** There was no statistical difference in the number of stress defects that improved on the washout and rest images. The visual interpretation of the perfusion abnormalities was confirmed by quantitative analysis of relative segmental activity. **Conclusion:** Thus, ^{99m}Tc-teboroxime-adenosine washout myocardial perfusion imaging can be safely and quickly accomplished. Detected reversibility of the perfusion defects did not significantly differ from reversibility observed on the rest images.

Key Words: technetium-99m-teboroxime; washout imaging; adenosine stress

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Technetium-99m-teboroxime is a newer myocardial perfusion imaging agent characterized by high myocardial extraction which is proportional to the blood flow, and also by rapid myocardial clearance (*1,2*). Its use requires initiation of imaging early after tracer injection and also rapid completion of the image acquisition. Successful imaging has been accomplished with planar imaging (*3,4*), single-headed and multiheaded (*5,6*) SPECT imaging. When used in conjunction with treadmill exercise, the use of ^{99m}Tc-teboroxime remains a challenge particularly for SPECT imaging: the hyperventilating patient with possible ischemic chest pain, ECG changes or arrhythmia, needs to be imaged immediately after stepping off the treadmill.

The use of the short-acting coronary vasodilator adenosine offers an alternative; after prepositioning the patient on the imaging table, vasodilator infusion, tracer injection and repeat imaging can be accomplished in a rapid sequence (*7*). Also, the patient can be monitored without interruption for the entire duration of the test.

The observation of differential flow dependent regional uptake of ^{99m}Tc-teboroxime is used for diagnosis of coronary artery disease. Comparison of the stress and rest images, which requires administration of two doses of the tracer, is used for further characterization of the stress-induced perfusion defects. It has also been suggested that differential regional washout of ^{99m}Tc-teboroxime can be used to distinguish ischemia from scar (*6,8*). This approach requires injection of one dose of the tracer only, similar to ^{201}Tl imaging. However, the sequential ^{99m}Tc-teboroxime images are obtained in a rapid succession.

The first goal of our study was to test the logistical feasibility and image quality of this approach to myocardial perfusion imaging. The second goal was to compare the characterization of stress perfusion defects as fixed or reversible by the two-injection method (stress-rest) to the single-injection method (stress-washout).

METHODS

Patients

We studied 56 patients (29 males and 27 females), with a mean age of 68 ± 10 yr (range 40–88 yr). The indication for the myocardial perfusion study was screening for the presence of coronary artery disease in 35 patients (62%). Sixteen patients had chest pain suggestive of ischemic origin and 19 had multiple risk factors, the most frequent being peripheral vascular disease, cerebrovascular disease, diabetes mellitus and hypertension. In 21 patients (38%), the indication was for evaluation of severity of known coronary artery disease. The diagnosis was established by documented history of a myocardial infarction (n = 10), coronary angioplasty (n = 3), coronary artery bypass graft surgery (n = 5) and/or presence of a Q-wave on the rest ECG (n = 7). All patients were taking medication chronically: 18 (32%) were taking beta-blockers, 24 (43%) calcium channel blockers, 23 (41%) nitrates, 14 (25%) diuretics, 8 (14%) angiotensin-converting-enzyme inhibitors and 6 (11%) were taking digoxin. Only six patients (11%) were not taking any of the above drugs. All patients were unable to exercise adequately on a treadmill. Patients with unstable anginal symptoms, history or clinical finding of broncho-constriction and patients currently treated with methylxanthines or oral dipyridamole were excluded. Consumption of caffeine-containing beverages was discontinued for at least 12 hr. All patients signed an institutionally approved informed consent for this study.

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Study Protocol

Adenosine (Medco Research Inc., Los Angeles, CA) was infused in an incremental fashion: the initial concentration was 80 mcg/kg/min, which was increased in 1-min intervals to 110, 140 and 170 mcg/kg/min, respectively. A stress dose of ^{99m}Tc-teboroxime (Cardiotec, Squibb Diagnostics, Princeton, NJ) was injected at 4.5 min into the contralateral arm vein. The adenosine infusion was discontinued at 5 min. A 4-min stress SPECT imaging acquisition was started at 6-min. A washout imaging acquisition followed at 11 min and was completed at 15 min. At 20 min, a resting dose of ^{99m}Tc-teboroxime was injected, and the final, or resting, imaging was started 1.5 min later at 21.5 min and was completed at 25.5 min. The total dose of ^{99m}Tc-teboroxime did not exceed 50 mCi. The stress and rest doses were approximately even. In all patients a 12-lead ECG was continuously monitored and recorded every minute for the whole duration of the test. The blood pressure was measured every minute for the first 6 min and then every 4 min until it returned to the baseline.

Image Acquisition, Processing and Analysis

A single-headed gamma camera (Apex 409, Elscint, Hackensack, NJ) was equipped with a high-resolution collimator. The acquisition was continuous over a circular 180° arc from the LPO to the RAO position, divided into sixty 64 × 64 pixel frames without zoom. Reconstruction of all sets of images was identical: a filtered backprojection was performed with a combined Hanning and ramp filter followed by a three-point temporal filter between the slices. The transaxial images were reoriented into short axis, horizontal and vertical long axis slices, each 2-pixels thick.

The myocardium was divided into six segments (anterior, lateral, inferior, posterior, septal and apical). Each segment was subjectively evaluated for the presence of a perfusion defect by an experienced reader blinded to any clinical information or to the result of another diagnostic procedure. A 0–3 scale was used to grade the defects (0 = normal, 1 = mild, 2 = moderate, 3 = severe). A normalization of the compared sets of images to the hottest pixel in the myocardium was used in patients whose liver intensity exceeded the myocardial intensity. The change of at least one grade between the stress and washout images and stress and rest images was noted.

On a separate occasion, and in an identically blinded fashion, the three sets of images were quantified. The hottest pixel was identified in each anterior, lateral, inferior, posterior and septal segments in four short-axis slices. A mean value for each segment was then normalized to, or divided by, the highest segmental intensity present. Thus, the highest possible intensity ratio was 1.00.

Statistical Analysis

A chi-squared test was used to test group differences for the categorical variables. Paired and unpaired t-tests were used for comparison of continuous variables. A p value of <0.01 was considered to be significant.

RESULTS

Hemodynamic and ECG Changes

The myocardial perfusion study was completed without complications in all patients. The heart rate was 71 ± 12 at rest, and increased to 84 ± 22 bpm at peak effect of adenosine. The systolic blood pressure decreased from 151 ± 26 to 135 ± 26 mmHg and the diastolic blood pressure decreased from 83 ± 12 to 73 ± 22 mmHg. Of the 56 patients studied, 27 (48%) complained of chest pain during the adenosine infusion. Nine of 42 patients developed more than 1 mm horizontal ST depression during the stress. In 14 patients, abnormalities on resting ECG or use of digoxin precluded analysis of adenosine-induced ST segment changes.

SPECT Imaging

In all patients the quality of stress, washout and resting images was good, comparable to conventional ^{201}Tl SPECT images.

Visual Analysis. Myocardial perfusion during the adenosine infusion was considered normal in 2 patients and abnormal in 54. Of the 336 analyzed segments in 56 patients, 165 segment were normal, 92 had mild, 28 moderate and 48 severe perfusion defects on the stress images. Three

TABLE 1
Sequential Changes in Perfusion Defects Present on the Stress Images

	Normal No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)
No. of segments	165	92	28	48
Improved				
Washout	—*	30 (33)	11 (39)	19 (40)
Rest	—*	35 (38)	12 (43)	19 (40)
No change				
Washout	158 (96)	58 (63)	13 (47)	29 (60)
Rest	158 (96)	51 (55)	13 (46)	29 (60)
Worse				
Washout	3 (2)	4 (4)	4 (14)	—*
Rest	7 (4)	5 (5)	2 (7)	—*
Unable to analyze				
Washout	4 (2)	0 (0)	0 (0)	0 (0)
Rest	0 (0)	1 (2)	1 (4)	0 (0)

*Not applicable. There was no significant difference between the number of improved segments in any of the perfusion defect categories on the washout and rest images.

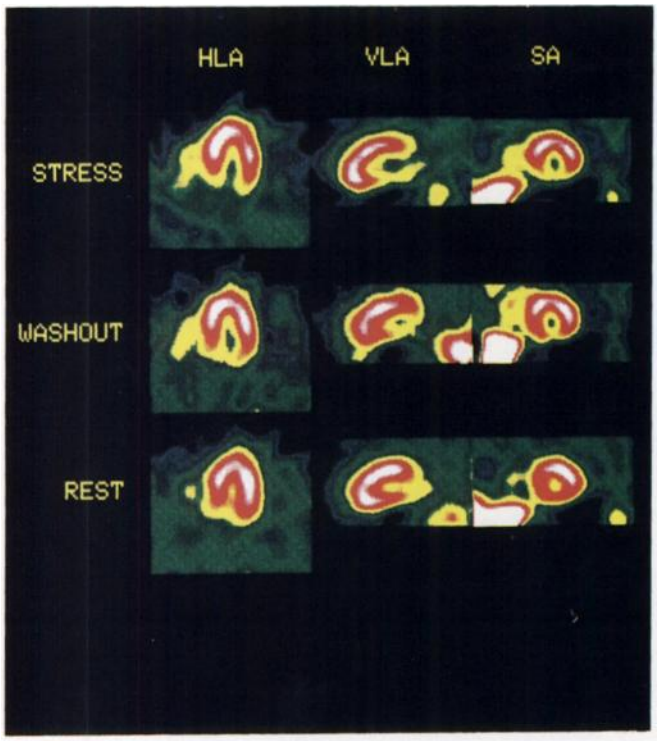

FIGURE 1. Comparison of selected slices from stress, washout and rest images in horizontal long-axis (HLA), vertical long-axis (VLA) and short-axis (SA). Concordant improvement is seen in the anterior and lateral wall segments on the washout and rest images.

(0.9%) inferior wall segments could not be evaluated because of overlapping liver activity. The number of improved segments in all categories was similar on the washout and the rest images (Table 1). Also, the number of segments with worsened perfusion was similar on the washout and rest images (11 versus 14 segments). An additional seven segments could not be analyzed on at least one set of images due to overlapping liver activity. Four of those segments were considered normal on the stress images, thus the clinical test evaluation was possible in 330 of 336 segments (98%). An example of reversibility of the perfusion defects on the washout and rest images is shown in Figure 1.

Quantitative Analysis. Sequential changes in the intensity ratio were compared in normal, ischemic and infarcted segments as diagnosed visually on the stress and rest images (Tables 2, 3 and 4). No change was detected in the normal segments between the stress and washout images, there was a trend towards improvement between the stress and rest images (Table 2). Statistically significant improvement was present in the ischemic segments, both on the washout and rest images (Table 3). No change was detected in the infarcted segments (Table 4).

DISCUSSION

The current study confirms the feasibility of rapid acquisition of high-quality ^{99m}Tc-teboroxime-adenosine myocardial perfusion images with a single-headed SPECT camera (*7*). In addition, we have expanded the protocol by adding a washout acquisition and have shown that good quality SPECT washout images can be obtained as well. The detection of perfusion defects reversibility was similar using the washout images and the rest images regardless of the initial depth of the defect. The visual assessment of the changes was confirmed by quantification of the sequential relative intensity ratios in normal, ischemic and infarcted segments.

We used 4-min continuous acquisition for imaging, which is considered acceptable in view of the fast-changing myocardial activity (*9*). Since the first-pass extraction of the tracer is very high and continued myocardial extraction is unlikely (*10*), the delayed imaging likely reflects differential washout only. The washout of ^{99m}Tc-teboroxime has been shown to be slower from myocardium supplied by a stenotic coronary artery as compared to the segments supplied by a nonobstructed artery (*6,8*). Thus, faster washout from normal segments and slower washout from hypoperfused segments appear to explain the appearance of defect reversibility on the washout images. Similar observation was recently made by Weinstein et al. (*11*) in 68 patients who underwent exercise stress test and planar imaging immediately and early after stress and at rest, after a second ^{99m}Tc-teboroxime injection.

The myocardial clearance of ^{99m}Tc-teboroxime is biexponential, with an approximately 10-min half-life of its first major component (*1*). Therefore, the second dose can be injected shortly after completion of the early imaging. Also, since the vasodilatory effect of adenosine lasts less

TABLE 2
Sequential Changes in the Intensity Ratio in Segments Assessed Visually as Normal from the Stress and Rest Images

Localization	No.	Stress	Washout	Rest	P_1	P_2
Anterior	38	0.92 ± 0.07	0.92 ± 0.09	0.93 ± 0.09	0.83	0.42
Lateral	35	0.93 ± 0.17	0.93 ± 0.18	0.97 ± 0.05	0.88	0.13
Interior	13	0.80 ± 0.15	0.79 ± 0.14	0.87 ± 0.11	0.78	0.04
Posterior	11	0.69 ± 0.13	0.74 ± 0.18	0.75 ± 0.12	0.24	0.08
Septal	40	0.96 ± 0.06	0.92 ± 0.15	0.96 ± 0.07	0.05	0.44
All	137	0.90 ± 0.14	0.90 ± 0.15	0.93 ± 0.10	0.33	0.02

N = number of segments; P_1 = stress versus washout; and P_2 = stress versus rest.

TABLE 3
Sequential Changes in the Intensity Ratio in Segments Assessed Visually as Ischemic from the Stress and Rest Images

Localization	No.	Stress	Washout	Rest	P_1	P_2
Anterior	13	0.77 ± 0.13	0.86 ± 0.13	0.88 ± 0.08	0.04	0.002
Lateral	11	0.57 ± 0.27	0.77 ± 0.17	0.77 ± 0.17	0.04	0.05
Interior	10	0.68 ± 0.14	0.74 ± 0.14	0.79 ± 0.13	0.06	0.01
Posterior	8	0.45 ± 0.22	0.61 ± 0.14	0.58 ± 0.14	0.15	0.21
Septal	7	0.75 ± 0.12	0.80 ± 0.09	0.88 ± 0.06	0.06	0.05
All	49	0.66 ± 0.21	0.77 ± 0.16	0.79 ± 0.16	0.0001	<0.0001

No. = number of segments; P_1 = stress versus washout; and P_2 = stress versus rest.

than 1 min after the termination of the infusion, the rest images reflect coronary flow distribution at rest.

So far, the use of ^{99m}Tc-teboroxime during adenosine vasodilation has been reported in only a limited number of patients (*6,7*). In our series, the hemodynamic effect of adenosine infusion was well tolerated. The side effects, if present, were of short duration and only reassurance and encouragement were needed to complete the protocol in all patients. We consider the incremental adenosine infusion more flexible and possibly better tolerated than the more often used single concentration (140 mcg/kg/min). The patients undergoing pharmacological stress tests are usually older and sicker than their counterparts who can exercise. The gradual increase of the adenosine concentration prevents a sudden drop in blood pressure and thus allows completion of the test which may otherwise have been aborted.

The infusion of adenosine was stopped 1 min before imaging was started. Since the hemodynamic changes and the side effects almost completely resolve within a minute after stopping the infusion, the patient's discomfort during acquisition was minimal and blood pressure monitoring could be safely interrupted during the imaging. The patients remained on the imaging table for the entire duration of the test which lasted less than 30 min. The advantage was superior reproducibility of the positioning and fast throughput for the laboratory. The brevity of the test was well received. For some of our patients, the completion of a much longer, two-part ^{201}Tl or ^{99m}Tc-sestamibi protocol would have been more difficult.

The time of ^{99m}Tc-teboroxime injection 30 sec before discontinuation of the adenosine infusion was arbitrarily chosen. We wanted to avoid premature discontinuation of the adenosine infusion and possible loss of the coronary vasodilatory effect prior to the tracer injection. Also, we did not want to continue the infusion beyond the first-pass extraction in order to avoid accelerated washout of the tracer.

Study Limitations

Our prospective study was designed to test the feasibility of a new imaging protocol. It was not designed to compare the findings with another imaging modality. Also, the findings are limited to a small group of patients with high pre-test probability of presence of multivessel coronary artery disease. Another limitation is the inability to evaluate segments obscured by intense or overlapping liver activity. This occurred in 3 of 56 patients (5%). A similar problem is encountered with ^{99m}Tc-sestamibi. However, unlike ^{99m}Tc-sestamibi, no corrective maneuvers such as repeat prone or upright imaging can be used with ^{99m}Tc-teboroxime, because the time window for the image acquisition is very limited.

Conclusions and Clinical Implications

It is feasible and safe to complete SPECT myocardial perfusion stress and rest imaging with ^{99m}Tc-teboroxime and adenosine within 30 min. Images obtained using a single-headed camera with continuous acquisition are of good quality and are satisfactory for clinical use. The additional acquisition of washout images is easily accomplished. In our patients, the diagnostic information obtained from the stress-rest images was already available

TABLE 4
Sequential Changes in the Intensity Ratio in Segments Assessed Visually as Infarcted from the Stress and Rest Images

Localization	No.	Stress	Washout	Rest	P_1	P_2
Anterior	5	0.71 ± 0.21	0.77 ± 0.19	0.73 ± 0.20	0.40	0.54
Lateral	10	0.70 ± 0.18	0.70 ± 0.21	0.73 ± 0.17	0.90	0.32
Interior	30	0.61 ± 0.19	0.60 ± 0.22	0.63 ± 0.18	0.78	0.49
Posterior	33	0.53 ± 0.23	0.57 ± 0.20	0.55 ± 0.18	0.29	0.38
Septal	9	0.83 ± 0.08	0.77 ± 0.18	0.82 ± 0.06	0.19	0.78
All	87	0.62 ± 0.22	0.63 ± 0.22	0.64 ± 0.19	0.62	0.16

No. = number of segments; P_1 = stress versus washout; and P_2 = stress versus rest.

from the stress-washout images.

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REFERENCES

1. Leppo JA, Meerdink DJ. Comparative myocardial extraction of two technetium-labeled BATO derivatives (SQ30217, SQ32014) and thallium. *J Nucl Med* 1990;31:67–74.
2. Stewart RE, Schweigert M, Hutchins GD, et al. Myocardial clearance kinetics of technetium-99m-SQ30217: a marker of regional myocardial blood flow. *J Nucl Med* 1990;31:1183–1190.
3. Seldin DW, Johnson LL, Blood DK, et al. Myocardial perfusion imaging with technetium-99m SQ30217: comparison with thallium-201 and coronary anatomy. *J Nucl Med* 1989;30:312–319.
4. Hendel RC, McSherry B, Karimeddini M, Leppo JA. Diagnostic value of a new myocardial perfusion agent, teboroxime (SQ30217) utilizing a rapid planar imaging protocol: preliminary results. *J Am Coll Cardiol* 1990;16: 855–861.
5. Iskandrian AS, Heo J, Nguyen T, Mercuro J. Myocardial imaging with ^{99m}Tc-teboroxime: technique and initial results. *Am Heart J* 1991;121:889–894.
6. Chua T, Kiat H, Palmas W, et al. Regional washout of ^{99m}Tc-teboroxime is slowed in ischemic, non-infarcted myocardium [Abstract]. *Eur J Nucl Med* 1992;19:628.
7. Iskandrian AS, Heo J, Nguyen T. Tomographic myocardial perfusion imaging with technetium-99m teboroxime during adenosine-induced coronary hyperemia: correlation with thallium-201 imaging. *J Am Coll Cardiol* 1992; 19:307–312.
8. Gray WA, Gewirtz H. Comparison of ^{99m}Tc Teboroxime with thallium for myocardial imaging in the presence of a coronary artery stenosis. *Circulation* 1991;84:1796–1807.
9. O'Connor MK, Cho DS. Rapid radiotracer washout from the heart: effect on image quality in SPECT performed with a single-headed gamma camera system. *J Nucl Med* 1992;33:1146–1151.
10. Rumsey WL, Rosenspire KC, Nunn AD. Myocardial extraction of teboroxime: effects of teboroxime interaction with blood. *J Nucl Med* 1992;33:94–101.
11. Weinstein H, Dahlberg ST, McSherry BA, Hendel RC, Leppo JA. Rapid redistribution of teboroxime. *Am J Cardiol* 1993;71:848–852.