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Tomographic Myocardial Perfusion Imaging With Technetium-99m Teboroxime During Adenosine-Induced Coronary Hyperemia: Correlation With Thallium-201 Imaging

ABDULMASSIH S. ISKANDRIAN, MD, FACC, JAEKYEONG HEO, MD, THACH NGUYEN, MD, SALLY BEER, MD, VIRGINIA CAVE, RN, DAVID CASSEL, RT, BASIL B. ISKANDRIAN, BS

Philadelphia, Pennsylvania

Single-photon emission computed tomographic imaging with technetium-99m teboroxime during exercise has been found to be feasible and the results correlate with those obtained with thallium-201. This study examined the feasibility of this technique and compared tomographic imaging with technetium-99m teboroxime during adenosine-induced coronary hyperemia with thallium-201 imaging. With the patient positioned on the imaging table, adenosine was infused at a rate of 140 μg/kg per min for 6 min. At 4 min, 20 to 25 mCi (740 to 925 MBq) of technetium-99m teboroxime was injected intravenously and imaging was started as soon as the infusion was completed with use of a 180° anterior arc and 32 stops at 10 s/stop (total imaging time 7.8 min). Rest images were obtained 60 to 90 min later with use of a similar dose of technetium-99m teboroxime. Exercise tomographic thallium images were obtained within 2 weeks of the teboroxime studies.

In the 20 patients studied, the teboroxime images were normal in 2 (50%) of 4 normal subjects and abnormal in 15 (94%) of 16 patients with coronary artery disease; 4 of the 15 had a fixed defect and 11 a reversible defect. There was agreement between teboroxime and thallium studies in 16 patients (80%), in 319 (80%) of 400 segments and in 50 (83%) of 60 vascular segments ($p < 0.05$). In two normal subjects, an apparent fixed defect involving the inferior wall was seen on the teboroxime but not the thallium images and was thought to be due to an attenuation artifact secondary to extracardiac activity in the left lobe of the liver. There were no clinically significant adverse events.

Thus, this preliminary report shows that teboroxime tomographic imaging during adenosine infusion is feasible and convenient. This method combines the strengths of both agents: a very short half-life (12 min for teboroxime and 10 s for adenosine), a rapid imaging sequence (immediately after completion of infusion), maximal coronary hyperemia and a short acquisition protocol (7.8 min). This technique should be an acceptable alternative to exercise thallium-201 imaging.

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Recently, two technetium-labeled myocardial perfusion imaging agents were approved for clinical use: technetium-99m sestamibi (hexakis 2-methoxy-2-isobutyl isonitrile) and technetium-99m teboroxime. These agents differ from each other and from thallium in many aspects involving pharmacokinetics and physical characteristics necessitating different imaging protocols (1–6). Unlike thallium, teboroxime (Cardiotec, Squibb Diagnostics) is lipophilic, neutrally charged and not dependent on an enzymatic mechanism for uptake. Furthermore, the dose and energy level of teboroxime are much higher than those of thallium-201. Teboroxime has a very short half-life; the effective half-life in humans is approximately 12 min, which mandates a rapid imaging protocol (7,8).

We previously showed (6) that single-photon emission computed tomographic (SPECT) imaging with a single-head gamma camera is feasible with teboroxime exercise testing if imaging is started as soon as the exercise is terminated and the imaging protocol is modified to considerably decrease the acquisition time. We showed that decreasing the imaging time from 40 s/stop as used with thallium to 10 s/stop is sufficient to produce high quality teboroxime images. This procedure effectively reduces the total time for 180° SPECT imaging using the "step and shoot" protocol from 24 to 7.8 min. With continuous acquisition, the imaging time may be shorter, but this option is not available in our system.

We also investigated (9) the results of SPECT thallium imaging during coronary hyperemia induced by adenosine, an important short-acting coronary vasodilator with a half-life of <10 s. Our results show that adenosine-thallium imaging is a highly accurate method for detecting coronary artery disease. Wilson et al. (10) showed that the degree of coronary hyperemia induced by intravenous adenosine at the currently recommended dose is comparable to that

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Address for reprints: Abdulmassih S. Iskandrian, MD, Philadelphia Heart Institute, Presbyterian Medical Center, 39th and Market Streets, Philadelphia, Pennsylvania 19104.

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Table 1. Clinical Characteristics of the 20 Study Patients

	No. (%)
Age (yr) (mean ± SD)	60 ± 10
Hypertension	9 (45)
Diabetes mellitus	2 (10)
ECG Q wave MI	8 (40)
Nitrates	11 (55)
Beta-adrenergic blocking agents	11 (55)
Calcium channel blocking agents	15 (75)

ECG Q wave MI = electrocardiographic Q wave myocardial infarction.

achieved by intracoronary papaverine and is roughly fourfold higher than the rest flow in normal coronary arteries.

An important and unique characteristic of teboroxime is that its extraction remains very high (>90%) even at very high flow rates such as those achieved with adenosine (7). In this respect the agent is significantly different from technetium-99m sestamibi and thallium.

The purposes of this study, therefore, were to examine the feasibility of SPECT teboroxime imaging during adenosine-induced coronary hyperemia and to compare the results with those obtained with exercise SPECT thallium imaging.

Methods

Study patients (Table 1). There were 20 patients (17 men and 3 women); 4 of these patients had either normal coronary angiograms (n = 2) or <5% pretest probability of coronary artery disease (n = 2). The remaining 16 patients had coronary artery disease defined either by coronary angiography showing ≥50% stenosis in one or more major coronary arteries (n = 14) or by previous Q wave myocardial infarction (n = 2). There were two patients with previous coronary artery bypass grafting and recurrent angina due to graft occlusion documented on repeat angiography. None of the patients had unstable angina, recent myocardial infarction, active bronchospastic disease, hypersensitivity on a previous exposure to adenosine or second degree or greater atrioventricular block. The selection was based primarily on the willingness of the patients and their referring physicians to participate in the study. All patients signed a consent form approved by the Institutional Review Board of the medical center.

Study design. At the time of the activation of this protocol, both adenosine and teboroxime were investigational agents. All xanthine-containing medications and oral dipyridamole were discontinued for ≥24 h before the adenosine-teboroxime testing. Caffeine-containing beverages were withheld on the morning of the test. All cardiac medications were continued until the day of the stress test.

Adenosine infusion and imaging. The adenosine infusion protocol is similar to that used with thallium-201 (11). In brief, two intravenous lines were started, one to infuse the adenosine, the second to inject the teboroxime. The patients were positioned on the imaging table, adenosine infusion was performed under constant electrocardiographic (ECG) monitoring and blood pressure was obtained every minute during the infusion and for 5 min after the infusion. Adenosine was infused at a rate of 140 μg/kg per min for 6 min; after 4 min, 20 to 25 mCi of technetium-99m teboroxime (740 to 925 MBq) was injected. As soon as the infusion was completed, imaging was started. Single-photon emission computed tomographic (SPECT) imaging was performed with use of a 180° anterior arc from 45° left posterior oblique to 45° right anterior oblique and 32 stops at 6° angles at 10 s/stop. A standard filtered-back projection technique was employed with use of a Butterworth filter with a power of 10 and a cutoff frequency of 0.3 cycle/cm. From the original transaxial tomograms, oblique angled tomograms in the short- and long-axis views were obtained at 6 mm/slice. The rest images were obtained with a second injection of 20 to 25 mCi of technetium-99m teboroxime 60 to 90 min after the stress study and were processed in a fashion similar to that of the stress images.

Exercise testing. All patients also underwent exercise thallium-201 imaging within 2 weeks (mean 7 ± 8 days) of the adenosine-teboroxime studies using a standard protocol previously described from our laboratory (12). Briefly, 3 mCi (111 MBq) of thallium-201 was injected at peak exercise, tomographic images were obtained within 5 min of termination of the exercise with use of 32 stops at a 180° anterior arc with 40 s/stop. The Ramp-Hanning filter was used for reconstruction. Delayed (4 h) images were obtained after reinjection of 1 mCi of thallium-201 to obtain the reinjection images. The thallium and teboroxime images were interpreted by consensus of two readers (A.I. and J.H.) who had no knowledge of the clinical data or thallium results. The perfusion pattern was assessed in 20 segments in three short-axis slices and one vertical long-axis slice at the mid-ventricular level. The short-axis slices were chosen at the apical, mid and basal levels of the left ventricular cavity; each slice was divided into six segments, one anterior, one inferior, two septal and two lateral. The apex was interpreted from the mid-vertical long axis in two segments (anterior and inferior). The perfusion pattern in each segment was assessed as either normal or abnormal (reversible, partially reversible or fixed abnormality).

Statistical analysis. The results were expressed as mean values ± SD when appropriate. Discrete and continuous variables were compared by using the chi-square or the Student's *t* test as appropriate. A probability value <0.05 was considered statistically significant.

Results

The hemodynamic and ECG responses to exercise and adenosine infusion are shown in Table 2. The peak heart rate and systolic blood pressure, as expected, were significantly higher during exercise. The side effects of adenosine in this small sample size are shown in Table 3. Most side effects

Table 2. Hemodynamic and Electrocardiographic Responses to Exercise and Adenosine Infusion in 20 Patients

	Exercise	Adenosine	p Value
Peak heart rate (beats/min)	131 ± 24	84 ± 16	0.0001
Blood pressure (mm Hg)			
Peak systolic	179 ± 23	123 ± 16	0.0001
Peak diastolic	87 ± 13	74 ± 11	0.0003
ST segment depression	4 (20%)	3 (15%)	NS

were transient and none required reversal with aminophylline.

Results of technetium-99m teboroxime imaging. The teboroxime images were normal in two of four patients without significant coronary artery disease. In the other two patients, an apparent fixed defect was seen in the inferior wall on both adenosine and rest images. The teboroxime images were abnormal in 15 (94%) of 16 patients with coronary artery disease, showing a fixed abnormality in 4 patients and a reversible abnormality (with or without an associated fixed abnormality) in 11 patients. There were 14 patients with an inferior defect; 12 of these patients had a corresponding thallium defect. Of the remaining two patients, one had isolated left anterior descending artery disease and one had residual stenosis after angioplasty of the right coronary artery. Figure 1 shows representative images of fixed, partially reversible and reversible defects.

Liver uptake. In most patients, the liver teboroxime uptake did not interfere with the quality of the SPECT images. However, as mentioned earlier, in two patients, an apparently fixed abnormality was seen involving the inferior wall in both the rest and the adenosine images. In these two patients, the left lobe of the liver was prominent and very close to the inferior surface of the left ventricle. The rest studies demonstrated more intense liver teboroxime uptake than did the adenosine studies because they were performed after the adenosine studies and therefore demonstrated residual liver uptake from the latter studies. Intense uptake in the left lobe of the liver was not seen in the patients with coronary artery disease. Furthermore, most patients with an inferior wall abnormality on teboroxime images also had a corresponding abnormality on thallium study. Nevertheless, attenuation artifacts in the inferior wall should be considered in patients with coronary artery disease who also have intense uptake in the left lobe of the liver.

Table 3. Side Effects of Adenosine in 20 Patients

	No. (%)
Chest pain	8 (40)
Dyspnea	9 (45)
Flushing	13 (65)
Gastrointestinal discomfort	1 (5)
2° or 3° AV block (transient)	1 (5)
Severe hypotension	0
Ventricular arrhythmias	0
Headache	1 (5)

AV = atrioventricular.

Comparison between adenosine-teboroxime and exercise thallium imaging. Thallium images were normal in two patients without significant coronary artery disease; in one subject with left bundle branch block, a reversible septal abnormality was noted. The thallium images were abnormal in 14 (88%) of 16 patients with coronary artery disease. Of these, 3 had a fixed and 11 a reversible perfusion defect. There was agreement between the teboroxime and thallium images in 16 patients (80%) (Fig. 2); in 50 (83%) of 60 vascular territories and in 319 (80%) of 400 segments (Fig. 3) ($p < 0.05$ for each).

Discussion

Technetium-99m teboroxime imaging. This technetium-labeled perfusion imaging agent is a neutral lipophilic complex of a class known as boronic acid adducts of technetium dioxime complexes (1–4). It has a higher extraction fraction than thallium but a shorter retention time. Unlike thallium and technetium-99m sestamibi, the teboroxime has a very high extraction fraction at high flow rates such as those achieved during adenosine infusion. The washout is biexponential, with an effective half-life of 12 min in humans. There is evidence that differential washout from normal and ischemic myocardium may be present, allowing the detection of reversible and fixed defects from a single study (13); however, the accepted clinical protocol requires the use of two studies, one during stress and one at rest. The differential washout may also suggest that single-photon emission computed tomographic (SPECT) imaging, which requires approximately 8 min for completion, tends to underestimate the degree of ischemia. This obviously requires further studies, especially with multihead gamma cameras that can complete the tomographic imaging within a much shorter period of time.

The rapid teboroxime clearance requires that imaging be performed as soon as possible (<2 min) after termination of exercise. Planar imaging is ideal with this imaging agent because each image may be acquired in 40 to 60 s (total acquisition time 3 min) (14). Such an imaging sequence might permit acquisition of both initial and delayed images within 10 min (13,14). We have found (6) our modification of the SPECT imaging protocol by considerably shortening the acquisition time to be very effective for obtaining high quality images with teboroxime. The added advantages of this technique during adenosine infusion are that the patient can be positioned on the imaging table during the infusion and imaging can be started as soon as possible after completion of the infusion, thereby optimizing the interval between injection and imaging.

Pharmacologic stress testing with adenosine. Adenosine is a potent vasodilator in most vascular beds, but in the renal afferent arterioles and hepatic veins it produces vasoconstriction (9,15). Intravenously administered adenosine is

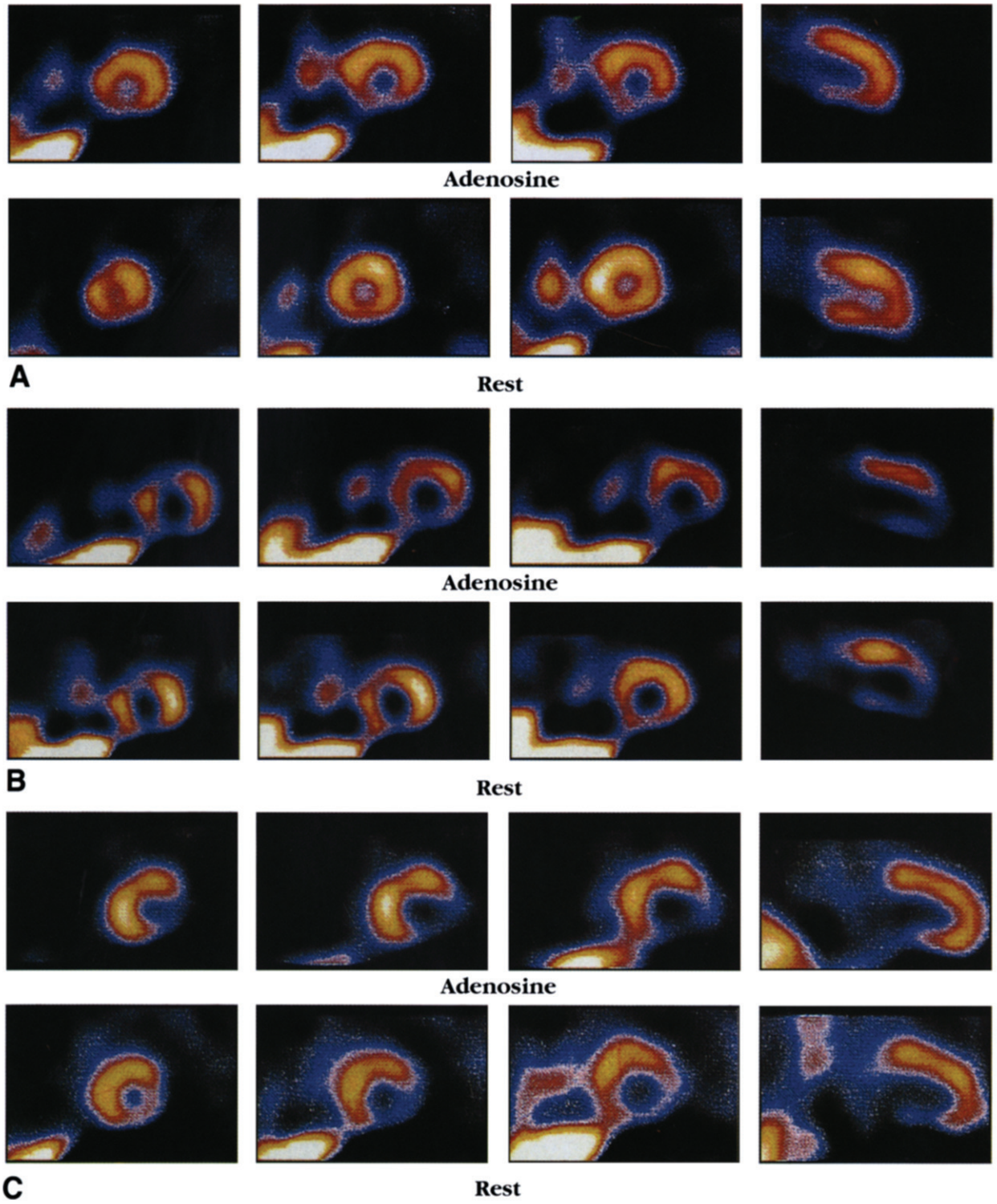


Figure 1. Single-photon emission computed tomographic (SPECT) adenosine-teboroxime images (**upper panels**) and rest images (**lower panels**) showing defects. Three short-axis slices at apical, mid and basal levels and one vertical long-axis slice at the mid-ventricular level are shown. **A**, Reversible defects. **B**, Fixed and reversible defects. **C**, Fixed defect.

rapidly cleared from the circulation through cellular uptake primarily by erythrocytes and vascular endothelial cells. Adenosine is thought to exert its pharmacologic effects through activation of purine receptors (cell surface A_1 and A_2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current, reducing calcium uptake, and activation of adenylate cyclase through A_2 receptors in the smooth muscle cells. Intravenously administered adenosine is rapidly metabolized either through phosphorylation to adenosine monophosphate by

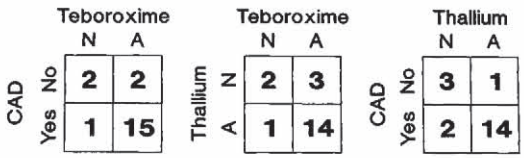


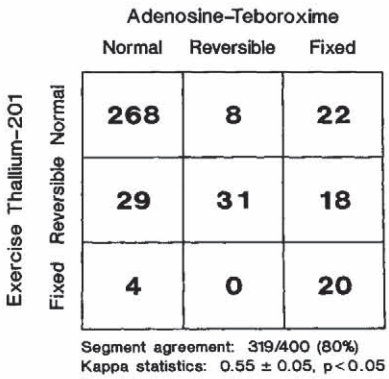
Figure 2. Correlation between adenosine-teboroxime imaging, exercise thallium imaging and presence or absence of coronary artery disease (CAD). A = abnormal; N = normal.

adenosine kinase or deamination to inosine by adenosine deaminase. The half-life is <10 s. In 132 patients with coronary artery disease, defined as ≥50% diameter stenosis in one or more major coronary arteries, and 16 patients with normal coronary angiograms, SPECT thallium imaging during adenosine infusion at a rate of 140 μg/kg per min for 6 min resulted in high quality tomographic images and a high degree of sensitivity and specificity (16). The sensitivity was 87% in the 54 patients with one-vessel disease, 92% in the 37 patients with two-vessel disease and 98% in the 41 patients with three-vessel disease. The specificity was 88% in the 16 patients with normal coronary angiograms.

Rationale for using teboroxime with adenosine. The combination of teboroxime imaging during adenosine-induced coronary hyperemia appears to offer the maximal advantages of both agents. Thus, studies can be performed with the patient on the imaging table and imaging can be started immediately after injection; the degree of coronary hyperemia is maximal with adenosine; the extraction of teboroxime is high at the high flow rates achieved with adenosine; both imaging agents have a very short half-life (<10 s for adenosine and 12 min for teboroxime); and the imaging protocol is short (<10 min). We were also encouraged by our initial feasibility studies suggesting that teboroxime can be imaged with use of SPECT techniques and our high degree of accuracy in detecting coronary artery disease using SPECT thallium imaging during adenosine infusion (6,16).

Results of the present study. Our results suggest that SPECT imaging with teboroxime during adenosine infusion is feasible, produces high quality images and results in data that generally correlate quite well with those obtained with thallium-201 (Fig. 1 to 3). Uptake of teboroxime in the liver is considerable because of the hepatic clearance of the teboroxime and because adenosine, unlike exercise, does not result in a redistribution of regional cardiac output. The latter mechanism also explains the considerable thallium uptake in the liver during adenosine thallium imaging. In two patients intense uptake of teboroxime in the left lobe of the liver resulted in an apparent fixed perfusion defect involving the inferior wall. This reconstruction artifact, which is caused by extracardiac activity, is similar to that observed in the spine during bone scanning in the presence of intense uptake in the bladder (17). In general, the hepatic uptake of teboroxime, like the hepatic uptake of thallium during adenosine studies (in contrast to exercise studies), does not interfere with SPECT imaging. Nevertheless, uptake of teboroxime in the liver is probably greater than that of thallium during adenosine studies because teboroxime, unlike thallium, is cleared through the liver. Examination of the raw data is helpful in ascertaining whether the abnormality is due to artifact. Most patients with coronary artery disease had abnormal teboroxime and thallium images, with good agreement between the two methods in defining the presence and nature of perfusion abnormality as fixed or reversible (Fig. 2, 3).

Figure 3. Correlation between teboroxime and thallium images in a segment by segment analysis. The segments were considered normal, fixed or reversible.



Our study was a feasibility evaluation of the imaging technique; it was limited by a small sample size and was not designed to address the issues of specificity and sensitivity. Discussion of these issues should await further studies in a much larger group of patients. On a theoretic basis, the combination of teboroxime imaging during adenosine-induced coronary hyperemia appears to be an attractive techniques for detecting of mild or moderate coronary artery disease, which requires not only the presence of maximal coronary hyperemia in the normal artery, but also a tracer that has a high extraction fraction in the presence of high flow state. The application of this technique to the study of progression and regression of coronary atherosclerosis is another area that needs further study.

Conclusions. Our preliminary results suggest the feasibility of performing SPECT imaging with teboroxime during adenosine infusion with use of a single-headed gamma camera. It is hoped that these results will stimulate further research in comparing adenosine with exercise teboroxime imaging, as well as imaging with thallium or technetium-99m sestamibi during adenosine-, dipyridamole- or dobutamine-induced coronary hyperemia.

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