Reduced variability of interpretation and improved image quality with a technetium 99m myocardial perfusion agent: Comparison of thallium 201 and technetium 99m–labeled tetrofosmin

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Background. The purpose of this study was to determine the relative image quality and interobserver variability among four readers for 201Tl and 99mTc-labeled tetrofosmin myocardial perfusion images. 99mTc-labeled perfusion agents, with near-optimal physical characteristics for gamma camera imaging, may allow for superior image quality and improved consistency of interpretation. However, most studies to date have demonstrated only similarity in the diagnostic accuracy between technetium agents and thallium. Tetrofosmin is a recently developed 99mTc-labeled agent that has shown promising results in early clinical trials.

Methods and Results. A multicenter, open-label trial was performed during which treadmill exercise thallium and tetrofosmin scintigraphy was performed within a 2-week period of each other in 216 subjects. Image quality was evaluated subjectively and scans were interpreted in a blinded, independent fashion by four readers. Perfusion abnormalities were graded as consistent with ischemia, infarction, or mixed and were described both globally and regionally. Interobserver variability was assessed by use of the k statistic, and receiver-operator curves were compared for each observer for the diagnostic accuracy of each agent. More tetrofosmin images were of excellent quality than with thallium (52% vs 28%; p < 0.05), and when differences in quality were noted between the agents, tetrofosmin was more often superior (p < 0.0001). The interobserver variability was lower with tetrofosmin scintigraphy because generally higher k values were noted, especially in the lateral wall. Higher receiver-operator curve areas indicative of improved diagnostic accuracy were noted among the four readers for tetrofosmin in 80% of vascular territories.

Conclusions. 99mTc-labeled tetrofosmin scintigraphy yields images of improved quality compared with thallium, and there is an overall improvement in the consistency of image analysis associated with the use of tetrofosmin. (J NUCL CARDIOL 1994;1:509-14.)

Key Words: tetrofosmin • thallium • myocardial perfusion imaging • radioisotope • coronary artery disease

The development of 99mTc-labeled myocardial perfusion agents has been heralded as a major advance in nuclear cardiology. The physical properties of 99mTc suggest that these agents offer significant advantages compared with 201Tl, including a shorter half-life, which permits the administration of a larger...
amount of activity, with greater photon flux and count density. Furthermore, the higher photon energy of technetium may result in a decrease in soft-tissue attenuation. These factors theoretically should translate into improved image quality and more consistent information regarding myocardial perfusion. However, other than the relative diagnostic accuracies of $^{201}$Tl and $^{99m}$Tc-labeled agents,\textsuperscript{1-3} little comparative information is available.

$^{99m}$Tc-labeled tetrofosmin ($^{99m}$Tc-tetrofosmin) is a recently developed cationic, lipophilic myocardial perfusion agent.\textsuperscript{4,5} Initial results from clinical trials have demonstrated high-quality images and good correlation with $^{201}$Tl scintigraphy for the detection of coronary artery disease.\textsuperscript{6} These findings are similar to the diagnostic concordance demonstrated between thallium and sestamibi\textsuperscript{1,2} and between thallium and teboroxime.\textsuperscript{3}

To generalize the results of clinical research studies in specialized laboratories to all laboratories performing nuclear cardiology studies, the images must be highly reproducible and there should be minimal variation of interpretation. Reduced variability of image readings should lead to more uniform diagnostic interpretation throughout the entire medical community. The goals of this study were to examine subjectively the quality of $^{99m}$Tc-tetrofosmin images in contrast to $^{201}$Tl scans and to determine if differences exist in image quality and interobserver variability between the two agents.

**METHODS**

The data for this investigation were derived from the Phase III Multicenter Tetrofosmin Trial, an international, multicenter investigation comparing $^{99m}$Tc-tetrofosmin with $^{201}$Tl perfusion imaging.\textsuperscript{6} Each participating center received approval for this research protocol by the various human subjects’ research committees. This study enrolled a cohort of patients with coronary artery disease who underwent both treadmill exercise thallium and tetrofosmin scintigraphy within a 2-week period. Postexercise planar thallium imaging was performed after the injection of 2.0 to 3.5 mCi $^{201}$Tl, with redistribution or reinjection imaging 2½ to 4 hours later. After obtaining written, informed consent, tetrofosmin imaging was performed in a stress-rest sequence after the injection of 5 to 8 mCi and 15 to 24 mCi for stress and rest scanning, respectively. Three planar views (best septal left anterior oblique [LAO], anterior, and left lateral) were obtained by the sites located in the United States, whereas four planar views (anterior, 40-degree LAO, 70-degree LAO, and left lateral) were acquired by the European investigators. To maintain consistency, the 40-degree LAO view was used as the best septal planar view, and a total of three planar views were used for data analysis.

All studies were forwarded to a central laboratory and processed in a uniform manner. The gray-scale images were displayed on glossy paper. Quantitative information was also available with circumferential count distribution profiles referenced to appropriate normal data files and was used by each reader along with the images to formulate a final impression. Four experienced readers (R.H., P.R., A.L., and F.W.) interpreted each stress/rest image set in an independent manner, blinded to the clinical data and the corresponding scintigraphic study. The image quality was graded subjectively as excellent, good, or poor. Uninterpretable scans were noted and excluded from analysis. The images were categorized as either normal perfusion or showing fixed (scar), reversible (ischemia), or mixed (partially reversible) perfusion defects. Perfusion defects were defined as mild, moderate, or severe. In addition, regional analysis was performed as described previously, based on five major territories: anterior, lateral, inferior, septum, and apex.\textsuperscript{6}

Interobserver variability was determined with the $\kappa$ statistic.\textsuperscript{8,9} Agreement was categorized as poor, fair, moderate, good, or excellent based on $\kappa$ values of 0.20 or less, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and greater than 0.80, respectively.\textsuperscript{9,10} In the subset of patients in whom coronary angiography data were available ($n = 115$), the diagnostic accuracy of image interpretation was assessed by receiver-operator characteristic curves (ROCs), with 75% or greater coronary stenosis used as the threshold for the presence of disease.\textsuperscript{11} The ROCs were based on stress perfusion defects, which were categorized as mild, moderate, or severe for ROC analysis.

**RESULTS**

Two hundred forty-one patients were enrolled in the Tetrofosmin Multicenter Study. Complete data from 216 patients who underwent both thallium and tetrofosmin imaging were available for comparison, 113 from the European centers and 103 from the United States sites. Information on image quality was collected in 212 patients.

Analysis of image quality (Figure 1) reveals that more images were categorized as “excellent” with the tetrofosmin images than with thallium (52% vs 28%; \( p < 0.05 \)). There was no difference in image quality information based on whether the image was obtained after stress or at rest. Furthermore, the scoring of image quality was similar irrespective of the projection (anterior, LAO, or left lateral). The relative quality of tetrofosmin and thallium images is displayed in Figure 2. When a difference in image quality was noted between the tetrofosmin and thallium scans, more tetrofosmin images were superior in each view (\( p < 0.0001 \)). This was also true for the overall comparative quality analysis.

The $\kappa$ value, a measure of agreement between the four observers, was generally higher for the tetrofos-