Multicenter Clinical Trial to Evaluate the Efficacy of Correction for Photon Attenuation and Scatter in SPECT Myocardial Perfusion Imaging

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Background—Soft tissue attenuation is a prominent cause of single-photon emission computed tomography (SPECT) imaging artifacts, which may result in reduced diagnostic accuracy of myocardial perfusion imaging. A method incorporating simultaneously acquired transmission data permits nonuniform attenuation correction and when incorporating scatter correction and resolution compensation may substantially reduce interpretive errors.

Methods and Results—A prospective multicenter trial was performed recruiting patients with angiographically documented coronary disease (n=96) and group of subjects with a low likelihood of disease (n=88). The uncorrected and attenuation/scatter corrected images were read independently, without knowledge of the patient’s clinical data. The detection of ≥50% stenosis was similar using uncorrected perfusion data or with attenuation/scatter correction and resolution compensation (visual or visual plus quantitative analysis), 76% versus 75% versus 78%, respectively (P=NS). The normalcy rate, however, was significantly improved with this new methodology, using either the corrected images (86% vs 96%; P=0.011) or with the corrected data and quantitative analysis (86% vs 97%; P=0.007). The receiver operator characteristic curves were also found to be marginally but not significantly higher with attenuation/scatter correction than with tradition SPECT imaging. However, the ability to detect multivessel disease was reduced with attenuation/scatter correction. Regional differences were also noted, with reduced sensitivity but improved specificity for right coronary lesions using attenuation/scatter correction methodology.

Conclusions—This multicenter trial demonstrates the initial clinical results of a new SPECT perfusion imaging modality incorporating attenuation and scatter correction in conjunction with 99m Tc sestamibi perfusion imaging. Significant improvements in the normalcy rate were noted without a decline in overall sensitivity but with a reduction in detection of extensive coronary disease. (Circulation. 1999;99:2742-2749.)

Key Words: imaging ■ perfusion ■ nuclear medicine ■ diagnosis ■ radioisotopes

Although single-photon emission computed tomography (SPECT) is an accurate, noninvasive diagnostic method for the detection of coronary artery disease, the production of image artifacts reduces the clinical impact of this technique. One of the most common artifacts results from the nonuniform reduction of photon activity caused by attenuation by soft tissue, which causes apparent perfusion defects. These false-positive perfusion studies may lead to further diagnostic evaluations, potentially increasing the risk to the patient and the burden of healthcare expenditures. Several methods have been developed to improve the recognition of soft tissue attenuation including gated SPECT and uniform photon attenuation correction algorithms. Recent advances in camera instrumentation and software development offer the potential for correction of nonuniform photon attenuation. One such method for attenuation correction involves the acquisition of transmission data and construction of an attenuation map to correct for nonuniform photon attenuation. The purpose of this trial was to determine the efficacy of attenuation correction, scatter correction, and resolution compensation, hereafter referred to as corrected imaging, in patients with known or suspected coronary disease by use of 99m Tc sestamibi perfusion imaging. Additionally, because the primary benefit of artifact reduction was believed to be decreased false-positive SPECT studies, a cohort of patients with a...
low likelihood for coronary disease was recruited to determine the comparative normalcy rates.

Methods

Patients with signs or symptoms of coronary disease and for whom coronary angiography had been performed within 3 months without a change in symptomatology or an interim cardiac event were recruited for this study. Additionally, a cohort of patients with a low likelihood of coronary artery disease (<5%) was also examined. Exclusion criteria were (1) inability or unwillingness to comply with the protocol, (2) prior bypass surgery, (3) PTCA within 1 month, and (4) known coronary artery disease (for low likelihood cohort only).

Treadmill exercise testing was performed with a Bruce protocol, which was continued for ≥1 additional minute after injection of the 99mTc sestamibi (∼25 mCi). Alternatively, pharmacological stress testing was performed with the use of standard protocols with dipyridamole or adenosine infusions. The resting study was obtained either on a separate day with 25 mCi 99mTc sestamibi or on the same day preceding the stress study with 201TI (2 to 5 mCi) or 99mTc sestamibi (8 to 12 mCi).

Image Acquisition and Processing

Images were acquired with the use of a noncircular clockwise orbit with a dual detector camera (Vertex, ADAC Laboratories). A total of 64 projections were obtained (25 seconds per projection). The data were collected in 3 individual photopeaks: (1) emission, 140 keV ±10%; (2) transmission, 100 keV ±10%; and (3) scatter, 118 keV ±10%.

A centralized core laboratory received unprocessed data, and quality control was performed on images by examination of the rotating projection and summed projection images for patient motion and other technical problems. Images were reconstructed in 3 orthogonal views with multiple slices displayed on a video monitor.

The uncorrected emission data were reconstructed by a filtered backprojection method with a Butterworth filter (cutoff 0.66 Nyquist, order 5). Reconstruction of the attenuation (μ) map was performed by filtered backprojection of the transmission data after normalization to the reference scan and logarithmic inversion. The data were then filtered with a Butterworth filter (cutoff 0.5 Nyquist, order 5). The attenuation-corrected images were created starting with the filtered backprojection initial estimate follow by a maximum likelihood expectation maximization (MLEM) algorithm with 12 iterations. The iterative reconstruction filter was set to match the resolution of the corrected data with that of the uncorrected data. Scatter correction used a single energy convolution subtraction technique and was performed on the transmission data (downscatter correction) and on the 99mTc sestamibi data (photopeak correction).

Depth-dependent, nonstationary resolution compensation was achieved with a modified Wiener filter. The software for attenuation and scatter correction algorithms with resolution recovery is fully automated (Vantage, ADAC Laboratories; ExSPECT, Emory University, Atlanta, Ga). Quantification was performed with a sex-specific database composed of either 21 men or women at low likelihood for ischemic heart disease; the cutoff for abnormality of 2.5 SD, a value determined by receiver operator curve (ROC) analysis. More than 5% of the total number of pixels with a value >2.5 SD from the mean counts per pixel constituted an abnormal study when based exclusively on quantitative analysis.

Interpretation

The images were reviewed on a video monitor by 2 experienced observers without clinical data; a third reviewer was used when no consensus was reached. The perfusion images were scored semiquantitatively (0 to 4 scale) with the 20-segment model, with the summed stress score determined by adding each of the 20-segment scores on the stress images. A final diagnosis for each scan was based on 5 categories and scored with the use of a 1 to 5 numerical scale: definitely normal (1), probably normal (2), equivocal (3), probably abnormal (4), and definitely abnormal (5). When the data were dichotomized to the presence or absence of coronary artery disease, an evaluation of either definitely normal or probably normal was used to reflect the scintigraphic absence of disease. The paired, noncorrected stress/rest images were read in a blinded manner. During a second interpretation session several weeks later, the corrected images were visually interpreted. After visual assessment of the images, the interpreters were presented with the quantitative data (polar plots). These quantitative results were assessed with the visual data to obtain a combined interpretation. The quantitative results were also used exclusively for the determination of the quantitative normalcy rate.

Diagnostic End Points

The coronary angiograms were reviewed by an interventional cardiologist/cardiac radiologist at each site who was blinded to the clinical and scintigraphic data. Append ation diameter stenoses ≥50% were considered significant for the presence of coronary disease. Individual vessel correlation was also determined comparing the angiographic results with those of perfusion imaging by use of the segmental scores, in accordance with a previously defined schema. If patients had a normal overall score, they were treated as if there were no segmental abnormalities present.

Statistics

Continuous data are expressed as mean ± SD. Paired t tests were used to compare differences in continuous data and McNemar's tests were used to compare differences in paired discrete data. All statistical tests were 2-tailed, and a value of P < 0.05 was considered significant. The sensitivity was determined for whether any disease (≥1-vessel disease) was present or when multivessel disease (≥2 vessels) was noted. The normalcy rate was determined from low-likelihood subjects who had a <5% likelihood of having coronary artery disease based on age, sex, risk factors, symptoms, and ECG response to exercise. The normalcy rate was defined as the ratio of the number of subjects with definitely normal or probably normal scans divided by the total number of subjects in the cohort (×100%). Data from patients in the coronary artery disease cohort were used to calculate sensitivity and specificity. ROC analyses were based on overall diagnostic scan scores from all patients in the study, both low-likelihood and coronary artery disease cohorts. The areas under each pair of ROC curves and the significance of the difference between the areas was calculated with the use of CORROC2. Patients with single-vessel disease were excluded from sensitivity, specificity, and ROC analyses for comparisons in patients with multivessel disease.

Results

A total of 397 patients were recruited for this trial. Technical limitations were present in 87 studies, largely because of issues related to gated SPECT acquisition (bad beat rejection; n = 83) and other limitations of the earliest attenuation correction hardware/software package. An additional 87 subjects were excluded before the performance of the image interpretation sessions because of missing clinical data. Coronary angiography was performed in 112 patients, of whom 96 possessed at least 1 coronary stenosis of ≥50%. This latter group constituted the angiographically confirmed coronary disease cohort and was used for calculating the diagnostic sensitivity. Single-, double-, and triple-vessel coronary disease were noted in 26, 38, and 32 patients, respectively. A significant (≥50%) stenosis was present in the left anterior descending (n = 72), left circumflex (n = 66), and right (n = 60) coronary arteries. Of the 111 low-likelihood subjects, 23 with pharmacological stress testing were excluded from the normalcy rate determination. The demographic data for the 2 study groups are depicted in the Table.
Demographics and Clinical Characteristics of Study Populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coronary Disease (n=96)</th>
<th>Low Likelihood (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (66)</td>
<td>39 (44)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>65 (68)</td>
<td>29 (33)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (19)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>40 (42)</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Family history</td>
<td>35 (37)</td>
<td>12 (16)</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>29 (30)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>History of percutaneous transluminal coronary angioplasty</td>
<td>15 (16)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>64 (67)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>Age, y</td>
<td>61.4±12.1</td>
<td>50.6±9.7</td>
</tr>
</tbody>
</table>

Patients with angiographically documented coronary artery disease had either treadmill exercise (58%) or pharmacological stress testing (45%; dipyridamole=18, adenosine=21, dobutamine=1). The coronary disease cohort developed ECG changes or chest pain in 32 and 26 patients, respectively. Imaging was performed with the dual isotope method in most cases.

Using the a priori definition of an abnormal SPECT study to include images considered equivocal, probably abnormal, or definitely abnormal, the sensitivity for the detection of coronary disease was 76% by visual interpretation of uncorrected images (Figure 1). The subsequent interpretation of the corrected images yielded a similar sensitivity (75%; P=NS). Examples of the effects of attenuation/scatter correction and resolution recovery are shown in Figures 2 and 3. When quantitative data were used along with the visual assessment of the corrected data, the combined interpretation demonstrated a sensitivity of 78% (P=NS). Therefore there were no significant differences in diagnostic sensitivity attributable to the use of correction techniques. The diagnostic scores (1 through 5) were also similar for the visually assessed uncorrected (3.9±1.5) and corrected (3.9±1.6) images and for the combined visual and quantitative analyses (3.9±1.5; all values P=NS). An analysis of patients without prior infarction (n=69) demonstrated no difference in sensitivity between the corrected and uncorrected images (both 72%). The summed stress score for the uncorrected images was higher that after correction (12.7±11.0 vs 9.6±9.4, P<0.001). The sensitivity and specificity for triple-vessel coronary disease were similar for corrected (81% and 63%, respectively) and uncorrected imaging (78% and 63%, respectively). However, the identification of multivessel disease in patients with more than 1 stenotic coronary artery decreased from 70% to 47% when correction methods were applied (P<0.01).

Only 16 patients were available for determination of specificity. This cohort demonstrated low specificity with or without correction techniques (44% vs 50%; P=NS). However, images with complete homogeneity of activity were noted in 7 patients with correction applied, in contrast to none in the usual SPECT images (P=0.008). The diagnostic value of attenuation/scatter correction for the visual interpretation of individual coronary arteries was also determined (Figure 4). Sensitivity and specificity were similar in the left anterior descending and left circumflex coronary artery territories. However, for the right coronary artery, significantly improved specificity was noted for the corrected images, but at the expense of a reduced sensitivity.

All low-likelihood patients had exercise testing performed, with 94% of these subjects achieving at least 85% of their age-adjusted maximum heart rate. No subject developed exercise-induced ECG changes, but 5 (6%) did experience noncardiac chest pain; the age and sex of the subjects still permitted classification as a low-likelihood subject. The normalcy rates for uncorrected, corrected-visual, and corrected-combined are depicted in Figure 5. Within the low-likelihood cohort, significantly more studies were interpreted as normal or probably normal with either visual only corrected (96% P=0.0114) or combined visual/quantitative corrected interpretation (97%; P=0.0067) than with uncorrected imaging (86%). However, if the equivocal category was included in the normal group, no statistical improvement in normalcy was noted with attenuation correction. Automated quantitative analysis of the corrected images yielded a normalcy rate of 92% (P=NS compared with the visual only or combined readings). The overall diagnostic score was significantly lower (“more normal”) when attenuation correction was used for the evaluation of these low-likelihood subjects; 1.3±0.6 for corrected-visual and 1.3±0.6 for corrected-combined versus 1.7±0.9 for uncorrected (P<0.001). The summed stress score was lower for the corrected data than with standard SPECT imaging (0.6±1.4 vs 1.6±2.0, P<0.001).

To assess overall diagnostic performance, ROC curves were generated, with the addition of low-likelihood patients to the coronary artery disease cohort as a measure of “specificity.” The curves for the detection of coronary artery disease (≥50% stenosis) are displayed in Figure 6A. For the
analysis of multivessel disease, the ROC determinations were performed in 2 ways. First, patients with 2 or more diseased vessels were compared with patients without documented coronary artery disease and demonstrated slight improvement of the ROC areas with correction (0.91 vs 0.85; \( P \leq 0.04 \)) (Figure 6B). In the second analysis, the ROC areas were compared in patients with 2 or more diseased vessels with those with either single-vessel disease or no disease and demonstrated only a minor trend for improvement of ROC area with corrected imaging (0.85 vs 0.82; \( P=0.09 \)).

**Discussion**

The results of the current investigation demonstrate that the normalcy rate of tomographic myocardial perfusion imaging is significantly improved by the use of attenuation and scatter correction with resolution compensation. False-positive perfusion images were reduced by more than 4-fold, from 14% to 3% and the confidence for the presence of a normal image was increased, as reflected in the diagnostic scores. This was done without sacrificing the overall sensitivity for the detection of coronary disease, although a reduction in the detection of right coronary lesions was noted. Furthermore, the extent of disease detected was lower with corrected imaging, as manifest by the lower summed stress scores and reduced detection of multivessel disease.

Photon attenuation from overlying soft tissue constitutes a major problem for SPECT perfusion imaging. Although the true prevalence of soft tissue artifacts is unknown, estimates have ranged from 20 to 50%.\(^2\)\(^6\)\(^2\)\(^7\) A number of techniques have been shown to be useful in recognizing these artifacts, such as a review of the projection data,\(^1\)\(^3\)\(^2\)\(^8\) gated SPECT imaging,\(^1\)\(^3\)\(^2\)\(^8\) prone imaging,\(^2\)\(^9\) incorporation of clinical patient data,\(^3\)\(^0\) and quantitation.\(^2\)\(^1\) However, techniques incorporating attenuation and scatter correction have held the promise of depicting true coronary perfusion and theoretically improving the diagnostic value of modern perfusion imaging beyond any currently available method.

**Attenuation Correction**

Although methods for the uniform correction of attenuation were initially promising,\(^4\) the thorax possesses significant nonhomogeneity of soft tissue attenuation and negate the
value of these algorithms. To perform nonuniform attenuation correction, the generation of a patient specific attenuation map is of critical importance. Integrated SPECT systems incorporating the use of an external transmission source in a variety of configurations have been used with variable success. The development of nonuniform attenuation correction methods has been facilitated by improved computer systems and provide the ability to successively approximate true tracer distribution by iterative reconstruction techniques.

Current Trial
The system examined in this trial used a camera with 2 detectors separated by 90 degrees and a shuttered Gd-153 line source positioned 180 degrees across from each detector. The Gd-153 rod moves across the field of view during the acquisition of the emission data, providing the transmission data required for the construction of the attenuation map by use of a scanning, electronic photopeak window. This eliminates the need for additional imaging time and reduces the potential for misregistration of the emission and transmission data sets. As the entire field of view is utilized, truncation, a potential source of error, is reduced. Promising clinical results using a similar method for attenuation correction as in the current trial, but without scatter correction or resolution compensation, were reported for a small group of patients undergoing Tc tetrofosmin imaging.

A unique aspect of this multicenter trial was the application of scatter correction and depth-dependent resolution compensation into the attenuation correction algorithm. As photons interact with tissue and have some reduction of energy, they may still be included in the counting as the result of the width of the energy window, potentially interfering with the accurate generation of the attenuation map. In fact, attenuation correction without scatter correction may even promote artifact production.

Comparison With Other Attenuation-Correction Methodologies
Although attenuation correction has been under development for more than 3 decades, a clinically applicable system has only recently been developed. Some systems have been shown in preliminary reports to be highly prone to artifacts or are simply ineffective. One of the most encouraging methods was used by Ficaro and colleagues, who reported the results of attenuation correction in phantoms and patient cohorts with a custom designed system. Using a unique
3-detector system and a transmission source of $^{241}$Am, these investigators showed a significant improvement in the diagnostic accuracy of $^{99m}$Tc sestamibi SPECT imaging. Although no significant increase was noted in sensitivity, as found in the current study, marked improvement in specificity was noted. Similarly, in a group of 59 low likelihood patients, an increase in the normal rate from 88% to 98% was shown using visual assessment; improvement of a similar magnitude was found in the current multicenter trial.

Cost-Effectiveness

The value of these correction techniques is due to improved normalcy determination, as traditional SPECT imaging is limited by the frequent appearance of nonhomogenous tracer distribution. The improved identification of imaging artifacts will decrease the number of false-positive interpretations and could lead to fewer inappropriate coronary angiograms. However, underestimation of disease extent and the resultant failure to detect a high-risk patient may actually increase costs. The modern era mandates that any technological advance requiring additional expenditures be placed in a cost-effectiveness construct; thus further examination of the economic impact of this new technology appears prudent.

Limitations

Technical problems with the initial software were present early in this study, accounting for a number of acquisition errors. These were predominately caused by the difficulty in obtaining transmission and emission data during a gated SPECT acquisition. These problems were resolved, and no patients were excluded because of software problems in the second half of the trial.

Our pilot studies demonstrated that “blinding” to whether or not attenuation correction was performed was virtually impossible because of the image characteristics associated with attenuation correction (ie, enhanced appearance of the right ventricle). Therefore, a potential but unavoidable and unintentional bias may be present in the interpretation of the images. An optimal design of a future study might include a larger number of patients, with both the uncorrected and corrected images being blindly interpreted during a single reading session.
The current trial used sex-specific populations for the derivation of the separate male and female normal databases. The reason for differences, even after attenuation and scatter correction, is not apparent and is different from the use of a single map as reported by Ficaro et al.5,6 The probable explanation is that residual attenuation and scatter may be present, accounting for sex differences.

This trial compared the traditional method of SPECT image reconstruction (filtered backprojection) directly to attenuation/scatter correction with resolution recovery with MLEM reconstruction. Thus no comparison of MLEM reconstruction with or without correction methods was performed as part of this trial. However, previously noted changes in image appearance from the use of MLEM did not affect diagnostic accuracy, as preliminary work revealed that changes in the normalcy value of imaging with attenuation correction may exacerbate this problem in such patients.5,32 An additional concern is the apparent decrease in delineation of disease extent, as manifest by the reduction in the summed stress score and the lowered sensitivity for multivessel disease with attenuation/scatter correction. This may have important prognostic ramifications.

Gated SPECT also offers the opportunity for improved recognition of soft-tissue attenuation artifacts.3,28 Although gated SPECT is now feasible simultaneously with correction, only a subgroup of patients in this study were acquired with gated SPECT, and the trial design did not allow the determination of the added value of correction over gated SPECT or which technique may be more valuable.

Conclusions
The current multicenter trial demonstrates the potential value of a new SPECT perfusion imaging modality incorporating attenuation and scatter correction in conjunction with 99mTc sestamibi perfusion imaging. Significant improvements in the normalcy rates were noted without a decline in overall sensitivity. However, there is underestimation of disease extent.

Acknowledgments
This project was supported by an Advanced Clinical Research Program Grant from ADAC Laboratories. The authors wish to thank Michele Parker, RN, MS, for assistance with the statistical analysis and Jaime Tecson and Gerrard Silagan for technical assistance.

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_Circulation_. 1999;99:2742-2749
doi: 10.1161/01.CIR.99.21.2742

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/21/2742

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