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Quantitative assessment of myocardial perfusion abnormality on SPECT myocardial perfusion imaging is more reproducible than expert visual analysis

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Abstract

Background—Current guidelines of Food and Drug Administration for the evaluation of SPECT myocardial perfusion imaging (MPI) in clinical trials recommend independent visual interpretation by multiple experts. Few studies have addressed whether quantitative SPECT MPI assessment would be more reproducible for this application.

Methods and Results—We studied 31 patients (age 68 ± 13 , 25 male) with abnormal stress MPI who underwent repeat exercise ($n = 11$) or adenosine ($n = 20$) MPI within 9–22 months (mean 14.9 ± 3.8 months) and had no interval revascularization or myocardial infarction and no change in symptoms, stress type, rest or stress ECG, or clinical response to stress on the second study. Visual interpretation per FDA Guidance used 17-segment, 5-point scoring by two independent expert readers with overread of discordance by a third expert, and percent myocardium abnormal was derived from normalized summed scores. The quantitative magnitude of perfusion abnormality was assessed by the total perfusion deficit (TPD), expressing stress, rest, and ischemic perfusion abnormality. High linear correlations were observed between visual and quantitative size of stress, rest, and ischemic defects ($R = 0.94, 0.92, 0.84$). Correlations of two tests were higher by quantitative than by visual methods for stress ($R = 0.97$ vs $R = 0.91$, $P = 0.03$) and rest defects ($R = 0.94$ vs $R = 0.82$, $P = 0.03$), respectively, and statistically similar for ischemic defects ($R = 0.84$ vs $R = 0.70$, $P = \text{ns}$).

Conclusions—In stable patients having serial SPECT MPI, quantification is more reproducible than visual for magnitude of perfusion abnormality, suggesting its superiority for use in randomized clinical trials and monitoring the effects of therapy in an individual patient.

Keywords

Myocardial perfusion SPECT; quantification; reproducibility

Introduction

Serial studies of SPECT myocardial perfusion imaging (MPI) are increasingly being employed in randomized clinical trials (RCTs) for assessing effects of treatment. In recent years, these trials have increasingly relied on quantitative approaches to myocardial perfusion assessment.¹⁻⁴ Nonetheless, current guidelines of Food and Drug Administration (FDA) for evaluation of SPECT MPI in clinical trials recommend independent visual interpretation by multiple experts.⁵ Due to the subjective nature of visual interpretation, however, the visual approach is likely to have lower repeatability than objective quantitative measurements. Danias et al, for example, reported intraobserver agreement of only 65-80% for visual assessment of normal and abnormal SPECT MPI.⁶ On the other hand, the reproducibility of quantitatively analyzed SPECT MPI has been reported to be excellent (96%).⁶ Although it is recognized that quantification of myocardial perfusion images enhanced reliability and reproducibility of interpretation,⁷ few studies have compared reproducibility between visual and quantitative assessments of SPECT MPI for this application—the subject of the present study.

Methods

Study Population

We retrospectively identified all patients in our database who met the following criteria: free of known nonischemic cardiomyopathy or valvular heart disease, referred for clinically indicated rest thallium (Tl)-201/stress gated Tc-99m sestamibi SPECT MPI with exercise (n = 11) or adenosine stress (n = 20) on two separate occasions within two years between March 2000 and March 2006 with no intervening cardiac event [myocardial infarction (MI), cardiac hospitalization, or revascularization], change in symptoms, or change in reported cardiac medications at the time of the second scan, and had abnormal perfusion on the first MPI by visual analysis. Additionally, there had to be no change in stress type, rest ECG, stress ECG, or clinical response to stress at the time of the second study compared to baseline. The repeat rest/stress MPI was performed 9-22 months after the first examination (mean 14.9 ± 3.8 months).

Imaging and Stress Protocol

Patients were injected intravenously at rest with Tl-201 (3-4.5 mCi) and SPECT MPI was initiated 10 minutes after injection.⁸ Exercise or adenosine with or without low-level treadmill exercise protocols were then performed as previously described,⁹ with stress injection of Tc-99m sestamibi (25-40 mCi). SPECT MPI image acquisition was initiated 15-30 minutes after exercise or 30-60 minutes after adenosine stress and performed as previously described.^{10,11} While the patients had both supine and prone post-stress imaging, for purposes of this study only supine images were interpreted. No attenuation or scatter correction was employed. Twelve-lead electrocardiography (ECG) was monitored continuously during stress tests. SPECT tomograms were reconstructed and reoriented using an automatic algorithm as previously described.¹¹

Visual Perfusion Defect Interpretation of SPECT MPI

Visual semiquantitative interpretation was assessed per the FDA Guidance, using 17-segment, 5-point scoring system (0 = normal, 4 = absent tracer uptake) by two independent

expert readers with adjudication of discordant segments by a third expert.⁵ The readers were provided with computer-derived 17-segment scores which are based on the average deviation from the normal limits of the polar map pixels corresponding to the segment. The expert interpreter modified the segmental scores based on their visual interpretation, according to standard practice.⁸ Readers were blinded regarding clinical information and final diagnosis. As recommended by the Guidance,⁵ the studies were evaluated individually in a mixed, random sequence and not side by side. A summed stress score, summed rest score, and summed difference score were obtained by adding the scores of 17 myocardial segments.^{12,13} The scores were normalized to percent of the total myocardium involved with stress, rest, and ischemic defects by dividing the summed scores by 68, the maximum potential score (4×17), and multiplying by 100, respectively.¹⁰ Image quality was assessed as excellent, good, fair, and poor by an experienced imaging cardiologist.

Automated Quantification of SPECT MPI

The quantitative perfusion variable employed was total perfusion deficit (TPD),¹⁴ which is the computer derived analog of the percent myocardium abnormal by visual analysis, representing both defect extent and severity. TPD was calculated as the percentage of the total surface area of the left ventricle below the predefined uniform average deviation threshold¹⁴ using QPS software^{13,15} (Figure 1). TPD was measured at stress and rest, and ischemic TPD was calculated from the difference (stress TPD minus rest TPD).

Quantitative Measurement of Transient Ischemic Dilation (TID) Ratio

TID ratio was assessed using the automatic quantitation algorithm and operating on the summed perfusion data.¹² After calculation of endocardial volumes, the algorithm derives the TID ratio as the ratio of left ventricular cavity volumes at stress to those at rest.

Statistical Analysis

All continuous variables are expressed as mean $\pm$ standard deviation. Univariate analyses of continuous variables were performed using the paired *t* test for the comparison of two studies. Univariate analyses of categorical variables were compared using the χ^2 test. Simple linear regression analysis was used to compare sequential changes in perfusion variables between two studies and between visual and quantitative assessments. Pearson correlation coefficients were calculated and pairwise compared using the test for two independent samples (MedCalc Software, Version 9.4.2.0, Mariakerke, Belgium). The Bland-Altman method was applied to determine the reproducibility between quantitative and visual methods.¹³ The 95% limits of agreement served to determine the threshold of absolute change of perfusion abnormality in successive studies, beyond which exceeds the variability of the test and reflects a true change in perfusion defect. In order to test reproducibility, reproducibility coefficient and analysis of variance estimator of intraclass correlation coefficient were also determined.¹⁶ A probability value <0.05 was considered statistically significant.

Results

Clinical Characteristics

Patient characteristics at study 1 and study 2 are illustrated in Table 1. By study design, there was no difference in the numbers of patients with prior MI or revascularization at the time of the two studies. There were high frequencies of diabetes, hypertension, hypercholesterolemia, angina symptoms, and abnormal resting ECG. All variables at study 2 are same as or similar to study 1 ($P = \text{ns}$) except older age ($P < 0.001$). In one patient, digoxin was no longer a medication at the time of the second study and another patient did

not use beta-blocker at the second study. None of patients reported being under the influence of nitrates or calcium-channel blockers at the time of the two studies.

SPECT MPI Results

The visual and quantitative perfusion results of serial studies are shown in Table 2. By design, all of the patients had stress abnormality by visual analysis, at baseline. More than 70% of patients had over 10% myocardium abnormal at stress, over half of the patients had >5% myocardium abnormal at rest, and over 80% had >5% ischemic myocardium. The quantitative results showed similar distributions of abnormalities of stress, rest, and ischemic abnormality. As expected in patients with stable clinical conditions, in the overall group, neither visual nor quantitative perfusion findings were significantly changed at the time of study 2 (all $P = \text{ns}$).

Regarding image quality, no study was considered poor on either first or second study. In 27 of the 31 patients (87%), the studies were good or excellent on both examinations. In 2/31 patients, one examination was considered of fair quality, and in the remaining two patients, both studies were of fair quality.

Repeatability of Perfusion Abnormality by Visual and Quantitative Analyses

Figures 2, 3, and 4 illustrate interstudy results of visual and quantitative perfusion for stress, rest, and ischemic. The correlations by visual interpretation were high for stress ($r = 0.91$), good for rest ($r = 0.82$), and fair for ischemic ($r = 0.70$) percent myocardium abnormal, respectively (all $P < 0.001$). The correlations by quantitative data were all higher with r values of 0.97, 0.94, and 0.84, for stress, rest, and ischemic TPD, respectively (all $P < 0.0001$). When compared, the correlations of serial tests between quantitative and visual assessments were significantly different for stress and rest defects (both $P = 0.03$) but not for ischemic defect ($P = \text{ns}$).

The differences of visual and quantitative assessments between two studies by Bland-Altman analyses are shown in Table 3. Both methods demonstrated no significant differences ($P = \text{ns}$) between studies. The mean differences, 95% limits of agreement, and standard deviations were smaller by quantification compared with visual findings. The repeatability coefficients (the maximum difference likely to occur between measurements) were smaller by quantification (6.4) than those by visual analysis (11.8) indicating improved reproducibility. Similarly, when assessed by the intraclass correlation coefficients, quantification demonstrated better reproducibility than visual method with higher values in matched stress, rest, and ischemic defects sizes with correlations of 0.90, 0.82, and 0.67, compared to 0.97, 0.94, and 0.83, respectively.

The estimated thresholds of true change for stress, rest, and ischemic defects were 11%, 13%, and 9% for visual analysis, respectively, and the corresponding thresholds for quantitative TPD were all less than 7%.

Comparison of Visual and Quantitative Perfusion

Figures 5, 6, and 7 illustrate correlations and differences between methods for stress, rest, and ischemic percent myocardium abnormal and percent TPD on study 1. Close correlations were seen with all of the measurements, ranging from a high of $r = 0.94$ for stress to $r = 0.84$ for ischemic abnormality. By using Bland-Altman analyses, the mean paired absolute difference between two methods were all small, -0.6% , 0.5% , and -0.3% for stress, rest, and ischemic defects, respectively ($P > 0.05$).

Repeatability of TID Measurements

The mean TID ratio by quantification between two studies was similar (1.28 ± 0.12 vs 1.23 ± 0.11 , $P = \text{ns}$). However, the correlation was only fair (Pearson correlation = 0.47, $P = 0.008$, 95% limits of agreement = -0.19 - 0.28). The estimated threshold of true change for quantitative TID was $<10\%$.

Discussion

The intent of this study was to compare the repeatability of quantitative and visual analyses of myocardial perfusion. As a group, in these patients with stable coronary artery disease (CAD) selected for lack of interval change in clinical parameters, serial SPECT MPI studies over a 9-22 month interval showed no statistically significant change in quantitative or visual assessments of myocardial perfusion. Correlations of the magnitude of stress and rest perfusion abnormality between the serial tests were significantly higher by quantitative than by visual methods (both $P = 0.03$). These findings support our hypothesis that objective quantitative analysis would be more reproducible than subjective visual analysis.

Comparison with Prior Studies

To our knowledge, this is the first study directly comparing the reproducibility of visual and quantitative measurements of rest and stress SPECT MPI. There are few previous studies evaluating variability for sequential MPI. Mahmarian et al reported the reproducibility of myocardial perfusion defects by serial exercise thallium-201 SPECT.⁶ These authors also found that mean defect sizes of scar and ischemia were not significantly different between studies. Quantitative analysis was highly reproducible with variability $<10\%$ in total perfusion defects. An early study from our laboratory reporting the reproducibility of quantitative exercise SPECT MPI found that the variability for defect extent was 7.2% .¹⁵ In the present study, we found the reproducibility thresholds for quantitative stress, rest, and ischemic TPD were all $<7\%$ and smaller than the thresholds for visual percent myocardium abnormal (9 - 13%). These findings are concordant with previous reports. The greater reproducibility observed in the current study compared to the study by Mahmarian et al may be due to the use of automatic quantitative software not available at the time of their study.

Danias et al reported interobserver agreement by visual assessment of myocardial perfusion of only 65% to 80% ($\kappa = 0.32$ - 0.60).¹⁷ Recently, Cerqueira et al also reported visual observer agreement. In their study, while the agreement rate was high in patients with no ischemia, it was lower in patients with moderate to large ischemia (80% vs 50%).¹⁸

Relationship to the COURAGE Nuclear Sub-study and Clinical Implications

In the COURAGE nuclear sub-study comparing ischemia reduction in patients randomized to percutaneous coronary intervention (PCI) and optimal medical therapy (OMT) compared to patients randomized to OMT alone, a threshold of 5% ischemic myocardium was employed as the threshold for significant change. The primary end point, significant ischemia reduction, occurred in 33% of PCI + OMT patients compared with 19% of OMT patients ($P = 0.0004$).² The results of the current study showing a reproducibility threshold of $<7\%$ ischemic myocardium generally support the findings of the COURAGE nuclear sub-study, but suggest that a slightly higher threshold for significant ischemia reduction may be appropriate in future studies using SPECT MPI.

From a clinical perspective, the type of assessment made in the COURAGE nuclear sub-study is frequently employed in clinical practice to determine whether patients with ischemia are improving or worsening after being placed on treatment. The findings of the present study that threshold for significant change is substantially lower with quantitative

TPD than with visual assessment suggest that this type of objective, quantitative assessment of ischemia may be more effective in assessing the effects of therapy in individual patients than visual analysis alone.

Implications for Clinical Trial Design

By current FDA guidance, visual assessment of SPECT MPI is the standard for randomized clinical trials. As previously shown, the results of this study demonstrated excellent correlation between visual and quantitative measurements of myocardial perfusion on SPECT MPI and, importantly, showed improved reproducibility for the quantitative measurements. If confirmed in larger multicenter studies, it would appear reasonable that the Agency might consider quantitative analysis as the standard in future trials. While “over-read” by an experienced observer will still be needed to identify artifacts such as attenuation or patient motion and to verify computer derived myocardial contours, subjective semiquantitative visual interpretation may no longer be needed for SPECT MPI in randomized clinical trials. This change in trial design could substantially lower the work involved in the interpretation of SPECT MPI using multiple expert readers, and the improved reproducibility of the measurements could reduce the number of patients required for statistical power.¹⁹

Study Limitations

The major limitation of this study is its retrospective nature. Thus, compared to a study prospectively designed to assess reproducibility of the perfusion measurements, there was greater opportunity for actual differences in the true amount of ischemia due to change in the underlying disease process, patient medications at the time of testing, and patient's clinical state. We attempted to select patients whose clinical state and medications were unchanged at the time of their second study. We also could not exclude the possibility that some change in the patients' clinical state that was not captured in our assessment at the time of the repeat study actually prompted the referral for the second examination. The need for careful selection of the patients for this lack of clinical change resulted in the second major limitation of the paper—the small number of patients included. The readers were provided with computer-derived suggested scores as their starting place in interpretation. The true visual reproducibility without computer-derived scores may not be as high as shown in this study. We chose this approach, however, as it is the method used in clinical practice and is in conformance with the FDA Guidance.⁵ Furthermore, the quantitative method for assessment of interval change employed did not utilize the “change” software recently incorporated into the software package from our institution which eliminates the need for each component (rest and stress) of each study to be compared to normal limits.²⁰ We chose to study the more standard TPD variables due to their more widespread use in clinical practice and clinical trials.²

Conclusion

The present study demonstrates that defect extent by visual and quantitative analysis is highly correlated. In patients with stable CAD having serial SPECT MPI, quantitative assessment is more reproducible than visual interpretation for magnitude of MPI abnormality, suggesting its superiority for use in randomized clinical trials.

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Figure 1.

A figure illustrating the concept of total perfusion deficit (TPD).¹⁴ A circumferential profile for one short axis slice is shown with corresponding normal limits. The areas below the normal limit curve but above the circumferential profile curve for a given slice define perfusion deficit in a given slice. These areas are computed for all circumferential profiles in the myocardium and summed forming TPD.

Figure 2.

Correlation of stress perfusion defects by visual (left) and quantitative (right) analyses between study 1 and study 2. $P = 0.03$ for the comparison between visual and quantification. % myo = percent of myocardium abnormal; TPD = total perfusion deficit.

Figure 3. Correlation of rest perfusion defects by visual (left) and quantitative (right) analyses between study 1 and study 2. $P = 0.03$ for the comparison between visual and quantification. Abbreviations as in Figure 2.

Figure 4.

Correlation of ischemic perfusion defects by visual (left) and quantitative (right) analyses between study 1 and study 2. $P > 0.05$ for the comparison between visual and quantification. Abbreviations as in Figure 2.

Figure 5. Correlation (left) and differences (right) of stress perfusion defects by visual and quantitative analyses on study 1. Quant = quantitative; other abbreviations as in Figure 2.

Figure 6. Correlation (left) and differences (right) of rest perfusion defects by visual and quantitative analyses on study 1. Abbreviations as in Figure 5.

Figure 7. Correlation (left) and differences (right) of ischemic perfusion defects by visual and quantitative analyses on study 1. Abbreviations as in Figure 5.

Table 1
Characteristics of patients (n = 31)

Characteristic	Study 1	Study 2
Age	68 ± 13	69 ± 13 [*]
Male	25 (81%)	25 (81%)
Body mass index 30 kg/m ²	13 (42%)	12 (39%)
Prior myocardial infarction	19 (61%)	19 (61%)
Prior revascularization	19 (61%)	19 (61%)
Diabetes	10 (32%)	12 (39%)
Hypertension	24 (77%)	25 (81%)
Hypercholesterolemia [†]	25 (81%)	22 (71%)
Smoking	2 (6%)	0 (0%)
Angina	13 (42%)	13 (42%)
Shortness of breath	1 (3%)	1 (3%)
Digoxin [‡]	3 (10%)	2 (6%)
Nitrate [‡]	0 (0%)	0 (0%)
Beta-blocker [‡]	1 (3%)	0 (0%)
Calcium-channel blocker [‡]	0 (0%)	0 (0%)
Abnormal resting ECG	27 (87%)	27 (87%)
Ischemic stress ECG	3 (10%)	3 (10%)
Positive clinical response	2 (6%)	2 (6%)
Exercise test	11 (35%)	11 (35%)

^{*} $P < 0.001$ vs Study 1.

[†] Self-reported history of hypercholesterolemia; reduced frequency on the 2nd examination likely due to misinterpretation of the question.

[‡] Under the influence of this medication. *ECG*, Electrocardiogram.

Table 2
Visual and quantitative perfusion results of serial studies (n = 31)

	Study 1	Study 2
Visual stress percent myocardium	18.9 ± 10.4%	19.4 ± 12.4%
5%	31 (100%)	30 (97%)
>10%	23 (74%)	23 (74%)
>20%	16 (52%)	14 (45%)
Visual rest percent myocardium	11.4 ± 9.3%	11.9 ± 10.7%
5%	20 (65%)	20 (65%)
>10%	14 (45%)	14 (45%)
Visual ischemic percent myocardium	7.6 ± 4.6%	7.7 ± 6.5%
5%	25 (81%)	24 (77%)
>10%	9 (29%)	7 (23%)
Quantitative stress TPD	18.8 ± 11.6%	19.1 ± 12.4%
5%	27 (87%)	27 (87%)
>10%	21 (68%)	21 (68%)
>20%	15 (48%)	16 (52%)
Quantitative rest TPD	10.9 ± 9.3%	10.7 ± 9.8%
5%	20 (65%)	17 (55%)
>10%	14 (45%)	16 (52%)
Quantitative ischemic TPD	7.9 ± 4.8%	8.5 ± 5.3%
5%	24 (77%)	24 (77%)
>10%	6 (19%)	9 (29%)

$P > 0.05$ for all comparisons between two studies. *TPD*, Total perfusion deficit.

Table 3
Differences of visual and quantitative assessments between two studies by Bland-Altman analyses

	Bias (SD)	95% Limits of agreement	Range	Repeat coefficient	Intraclass coefficient
% Myo stress	-0.55 (5.19)	-10.7, 9.6	2.9-39.7	10.1	0.90
% Myo rest	-0.48 (6.11)	-12.5, 11.5	0-31.6	11.8	0.82
% Myo ischemic	-0.08 (4.67)	-9.2, 9.1	1.5-27.2	9.0	0.67
Stress TPD	-0.35 (3.15)	-6.5, 5.8	0.7-35.9	6.1	0.97
Rest TPD	0.21 (3.30)	-6.3, 6.7	0-27.3	6.4	0.94
Ischemic TPD	-0.56 (2.92)	-6.3, 5.2	0.7-24.6	5.7	0.83