

Quantification of SPECT myocardial perfusion imaging

Wanda Acampa, MD,^{a,b} Wei He, MD,^a Carmine di Nuzzo, CNMT,^a and Alberto Cuocolo, MD^{a,b}

Radionuclide myocardial perfusion imaging has been established as a noninvasive method for diagnosis of coronary artery disease.¹⁻³ The assessment of myocardial perfusion imaging can be done by either qualitative or quantitative analyses. Through use of both types of analyses, clinically useful reproducible interpretation of myocardial perfusion images requires considerable operator experience. The reasons for problems with interpretation are many. In particular, the reproducibility of interpretation of myocardial perfusion images depends on (1) experience of the reader, (2) quality of the images, (3) severity of abnormality, (4) degree of change on serial images, and (5) uniform criteria for interpretation. It has been widely accepted that quantification of myocardial perfusion significantly improves diagnostic accuracy in detecting coronary artery disease.^{4,5} Furthermore, the concept of quantification of perfusion imaging includes two significant aspects that must be taken into account. The first is methodological, and the other is more related to the clinical application of the quantification process in nuclear cardiology.

QUANTIFICATION OF MYOCARDIAL PERFUSION IMAGING

Quantitative analysis of myocardial perfusion single photon emission computed tomography (SPECT) is widely used to objectify and standardize the process of interpreting and analyzing images. It has been demonstrated that computer quantification of myocardial perfusion images provides an important means of improving consistency of interpretation.⁶ Thus different quantitative programs have been developed. At the present time, a method has not been developed for obtaining absolute or

true relative quantitative values from SPECT data; the most widely used relative approaches have involved data-based programs of quantification that emulate the physician's method of image interpretation. The concept of data-based quantification involves 3 major steps: (1) image processing to enhance the image, (2) image analysis to extract measurements for use in determining abnormality versus normality, and (3) comparison of extracted measurements to a database of results from healthy patients to quantify the degree of abnormality. The first type of software developed at Cedars-Sinai for thallium 201 imaging quantitatively compares patient's results with a database of normal values, producing a report indicating the normal and abnormal areas of the patient's study.⁷ The introduction of technetium 99m labeled tracers demonstrated an improvement in image quality useful for visual interpretation. In addition, programs for quantitative analysis of Tc-99m sestamibi myocardial perfusion SPECT, optimizing imaging acquisition and processing protocols, have been introduced.⁸ A quantitative algorithm has been developed for analysis of sestamibi images, which reduces operator interaction at the left ventricular (LV) segmentation stage by performing automatic selection of the processing parameters (ie, the images to quantitate, the LV cavity center, and the radius of search). This enhancement improves the reproducibility and objectivity of the quantitative analysis compared with previously used Tl-201 approaches.

Quantification of myocardial perfusion imaging through use of the different methods available is important and should be applied routinely for different reasons. First, quantification provides greater confidence in interpretation, as graphic display of relative count distribution serves as an objective and consistent "second observer." The normal database serves as a fixed "benchmark" against which images are compared. Moreover, it has been demonstrated that quantification provides enhanced intraobserver and interobserver reproducibility and a reproducible measure of the degree of abnormality in the detection of coronary artery disease. However, it has been recommended that in addition to using a quantitative approach, the physician should review the results and integrate them with the other information related to the study and then make a final interpretation. In fact,

From Biostructure and Bioimaging Institute of the National Council of Research, Department of Biomorphological and Functional Sciences, University Federico II, Naples,^a and IRCCS Neuromed, Pozzilli,^b Italy.

Reprint requests: Alberto Cuocolo, MD, Dipartimento di Scienze Biomorfologiche e Funzionali, Università Federico II, via Pansini 5, 80131 Napoli, Italy; cuocolo@nina.it.

J Nucl Cardiol 2002;9:338-42.

Copyright © 2002 by the American Society of Nuclear Cardiology.

1071-3581/2002/\$35.00 + 0 43/1/123917

doi:10.1067/mnc.2002.123917

integrating quantitative with qualitative visual analysis generally aids in the interpretation of myocardial perfusion imaging. Whereas visual interpretation is subjective and more prone to observer variability, quantitative analysis offers an objective approach, providing a more accurate means to assess the extent, severity, and reversibility of perfusion defects or to estimate their functional significance. Moreover, quantitative techniques are well suited to analyzing a study objectively over a period of time or after medical or surgical intervention. Interpretation of myocardial perfusion SPECT images should always start with visual inspection of images (ie, unprocessed planar images and tomographic slices). Images should be inspected for overall quality and the presence of possible artifacts. It is important to realize that artifacts, such as those caused by attenuation resulting from overlying soft tissue or diaphragm or those resulting from patient motion, often have an unpredictable effect on the appearance of reconstructed slices. Although a normal database, to a certain extent, incorporates normal variation, computer quantification per se should not be expected to distinguish between true perfusion defects and artifacts. Quantitative display then serves to confirm the visual impression. Quantitative analysis should not and cannot be expected to provide entirely new information. This process was described by Wackers et al⁹ as “quantitative analysis with visual overread.” It must be considered that even when quantification of perfusion defects with good image quality is used, the full diagnostic clinical potential of myocardial perfusion images may be realized only with good standardization of interpretation to better optimize the clinical use of myocardial SPECT imaging.

CLINICAL USE OF QUANTIFICATION OF MYOCARDIAL PERFUSION IMAGING

Detection of Coronary Artery Disease

It has been widely demonstrated that computer quantification of myocardial perfusion images enhances overall accuracy in the detection of coronary artery disease. A review of the literature showed that the overall sensitivity and specificity of planar Tl-201 imaging by visual analysis were 83% and 90%, respectively.¹⁰ The introduction of quantitative analysis of SPECT Tl-201 images greatly improved overall diagnostic accuracy. In particular, the overall sensitivity to detect coronary artery disease was 89%, with a specificity of 89%.¹¹ Tamaki et al,¹² in a direct comparison between quantitative and qualitative analysis for evaluation of coronary artery disease using Tl-201 imaging, showed better sensitivity with the use of quantitative analysis than with qualitative analysis (91% and 80%, respectively), without a signif-

icant difference in specificity. It must be considered that when quantification of myocardial perfusion study alone is used, it tends to find more perfusion defects than physicians find with visual inspection alone. This may result in an increase in sensitivity at a tradeoff of lower specificity. Specificity may also be decreased by the inability of commercial systems to incorporate automated quality control to account for conditions that result in myocardial regions with count variations due to artifacts. However, the use of quantification specificity can be increased by having generated a gender-matched normal database that accounts somewhat for differences in normal distribution resulting from anatomic differences. This is particularly true when Tc-99m-based myocardial perfusion tracers that generate excellent image quality and reduced scatter are used.

Detection of Myocardial Viability

It has been demonstrated that the use of quantification is also important in the detection of myocardial viability. Quantitative analysis measures the amount of regional myocardial tracer activity and evaluates the extent of dysfunctional myocardium with preserved tracer uptake. In anterior wall biopsy specimens, a direct relationship between the amount of fibrosis and regional sestamibi uptake at quantitative analysis has been shown.¹³ In particular, sestamibi activity lower than 50% was associated with greater extent of fibrosis, as compared with tracer uptake greater than 50%. However, it should be taken into account that the predictive values for recovery of LV function are not dichotomous but exist on a continuous scale. A direct relation between viable myocardium (defined as improved wall motion after coronary revascularization) and the magnitude of regional tracer activity has been clearly demonstrated.^{14,15} Udelson et al¹⁴ compared regional activities of Tl-201 and sestamibi after resting injection in patients with regional or global LV dysfunction using both quantitative and qualitative analysis and assessed the comparative abilities of both tracers to predict recovery of severe regional dysfunction after coronary revascularization. Concordance between the 2 tracers was found with both analyses.¹⁴ However, the authors did not perform a direct comparison between quantitative and qualitative analysis. Subsequent studies have clarified that analogous to data showing that quantitative analysis of Tl-201 content within irreversible defects more accurately discriminates viable from nonviable myocardium, quantitative analysis of sestamibi activity within a visually apparent defect may also contain such information.^{15,16} Therefore quantitative analysis of regional tracer activity may improve the diagnostic accuracy of

sestamibi imaging in the identification of patients with dysfunctional but still viable myocardium who may benefit from coronary revascularization procedures. Recently, a direct comparison between visual and quantitative analysis of sestamibi SPECT was performed in the detection of dysfunctional but viable myocardium in patients with chronic ischemic LV dysfunction undergoing coronary revascularization procedures.¹⁵ According to the results of Udelson et al,¹⁴ quantitative analysis showed better identification of segments that have the most probability to improve function after coronary revascularization. In fact, sensitivity was significantly lower when visual analysis was used, as compared with quantitative analysis.¹⁵ Moreover, the most significant result was that when visual analysis was compared with quantitative analysis using the best cutoff point for sestamibi (<55%), sensitivity was significantly higher at quantitative analysis, but there was no statistical difference in specificity. On the other hand, visual analysis as compared with quantitative analysis using the cutoff point of 50% showed higher specificity. These observations, according to the results of previously published data,¹⁶ emphasize the importance of using the most appropriate threshold for each tracer to identify preserved myocardial viability in the presence of severe LV dysfunction when a quantitative approach is used. In fact, despite the fact that myocardial viability has been considered not to be a dichotomous variable, the use of the best cutoff point may be helpful to efficiently utilize myocardial perfusion imaging in the detection of myocardial viability. We have postulated that quantitative analysis seems unnecessary in patients with evidence of viability at visual analysis.¹⁵ In fact, in our study the majority of the akinetic or dyskinetic segments with preserved sestamibi activity at visual analysis demonstrated functional recovery after revascularization.¹⁵ On the other hand, quantitative analysis may provide important information in identifying viable myocardium in regions with a severe reduction of tracer uptake at visual inspection. In fact, a substantial number of dysfunctional segments with no evidence of viability at visual analysis exhibit preserved tracer uptake at quantitative analysis and improved wall motion after revascularization.¹⁵ Finally, it should be considered that in the presence of an intermediate level of tracer uptake at rest (defined as being in the 40%-60% range of peak activity), the probability of a favorable outcome is also intermediate and further information may be needed to make an appropriate clinical decision.¹⁷ This may include a stress study to determine whether inducible ischemia is present or a metabolic study that evaluates the presence of mismatch between reduced flow and preserved or enhanced glucose metabolism.

Prognosis and Risk Assessment

SPECT imaging provides important prognostic information in patients with either known or suspected coronary artery disease. An important significance has been given to the evaluation of the extent of myocardial perfusion defects. For example, in patients with known coronary artery disease and LV dysfunction, it has been shown that the greater the extent of viability is, the better the outcome after coronary revascularization.¹⁸ For assessment of the extent of perfusion defects by quantitative analysis, the following different approaches have been proposed: (1) the number of segments with perfusion defects divided by the total number of segments, (2) summed stress score, and (3) polar maps. The polar map method relies on computer-derived quantitative measurements of the defect size expressed as a percentage of the LV myocardium. The summed stress score depends on the presence and degree of perfusion abnormality in each of 20 segments scored visually.

For prognostic evaluation, it has been demonstrated that both qualitative and quantitative exercise Tl-201 SPECT studies are useful in stratifying patients into low-, intermediate-, and high-risk groups.¹⁹ However, only 39% of the patients could be stratified into the low- and high-risk groups by means of qualitative analysis, whereas 79% of the patients were stratified into the low- and high-risk groups based on the quantitative method. The remaining patients, 61% by the qualitative method and 21% by the quantitative method, were in the intermediate-risk group and had an intermediate event-free survival.¹⁹ Therefore a high percentage of patients in the intermediate-risk group may limit the clinical usefulness of the qualitative method in the decision-making process. These findings may be of considerable importance, considering that the management of patients in the intermediate-risk group is not clear, as compared with patients in the low-risk (medical therapy) and high-risk (revascularization therapy) groups.

A factor that should be considered is that not all of the studies reporting on the prognostic effectiveness of myocardial perfusion scintigraphy have been based on visual assessments of experienced expert readers. Less experienced observers may have difficulty reproducing the expert-derived results. Berman et al,²⁰ in a comparison of quantitative and semiquantitative visual analysis (the visual evaluation was performed by expert readers) of extent, severity, and reversibility of myocardial perfusion defects, showed a close correlation for all of these criteria to assess the prognostic value of SPECT imaging. In particular, the various objective quantitative indices performed equally well, as compared with analogous consensus expert visual analyses for assessment of prognosis. With both quantitative and semiquantitative visual

analysis, hard event rates of approximately 1% with normal scan and 5% with abnormal scan ($P < .05$) were observed over the 20-month follow-up period. Multivariate analysis showed the same incremental prognostic value of quantitative defect extent and summed stress score after clinical and exercise variables were considered. By either method of defining defect severity, patients had low event rates with a mildly abnormal scan and high event rates with a moderately to severely abnormal scan. Thus it must be stressed that in either manner in which the myocardial perfusion defect extent is evaluated, the clinical result obtained from SPECT imaging does not change. There was no significant difference in the distribution of events in each group with matched quantitative and semiquantitative visual scan results. However, a significantly higher proportion of the population was categorized as normal by the semiquantitative visual method than by quantitative analysis. Because a single reader interprets images in most clinical settings, the fact that quantitative analysis was nearly equivalent to consensus visual analysis takes on greater clinical importance. It should be noted, however, that with the current quantitative method, a greater proportion of patients were categorized as low risk by semiquantitative visual analysis than by quantitative analysis. This result may be related to the lack of incorporation of artificial intelligence for the recognition of artifacts with the current quantitative methods. Evidence supporting this explanation is seen in the stronger correlation of quantitative analysis with expert visual analyses in men than in women. In fact, although the authors used gender-matched normal limits for quantification, the program does not account for differences between women in breast size and breast attenuation, which creates a problem in recognition of marked breast attenuation as an artifact.²⁰ With expert visual analysis, on the other hand, this pattern is frequently identifiable. The reliance on semiquantitative visual inspection by experts has limited the degree to which the results from individual centers can be generalized to all laboratories. Thus, for prognostic assessment and risk stratification also, the visual overread after quantitative analysis seems to be the best approach to interpret myocardial perfusion defects through use of SPECT imaging.

ARTIFICIAL INTELLIGENCE APPROACHES

Over the past years, artificial intelligence methods have been investigated. Most of these approaches have used the polar map output of well-established database quantification programs as input to the decision-making process. In the artificial neural network approach, the concept is to try to emulate the central process of pattern

recognition tasks.^{10,21} Repeated recognition trials run using sample perfusion data as input and corresponding coronary angiography results as output to modify the strength between input and output nodes. In this manner, the network is trained and the input data eventually predict the output. In the case-based reasoning approach, the algorithm searches a library of patient cases to find the ones that best match those of the patient study being analyzed.⁵ More recently, another artificial intelligence approach that has been investigated for this purpose is the knowledge-based expert system.²² In expert systems, a knowledge base of heuristic rules is obtained from human experts, capturing how they make their interpretations. These rules are usually expressed in the form of if/then expression. It has been demonstrated that automatic computer-assisted interpretation of myocardial perfusion SPECT studies by an expert system agrees well with the interpretations of expert nuclear medicine physicians and exhibits diagnostic accuracy consistent with that of the experts when coronary angiography is used as the gold standard.²² There are continuing efforts to investigate how to further improve the diagnostic performance of this approach.

Berman et al²⁰ showed that the information obtained from a myocardial perfusion study through use of semiquantitative visual analysis by experts may be achieved by more widely applicable, objective quantitative analysis. It may be of particular clinical importance in laboratories with less experienced visual interpreters. The reliance on semiquantitative visual inspection by experts has limited the degree to which published results can be generalized to all laboratories.

REPRODUCIBILITY OF SPECT IMAGING

The clinical usefulness of an imaging modality depends on the reproducibility of interpretation within the same laboratory and in different centers. Wackers et al⁹ demonstrated that standardization of image display and computer quantification resulted in better overall agreement between centers. Therefore, when either visual or quantitative analysis is used in a nuclear cardiology laboratory, the reproducibility of SPECT imaging must be assessed to best standardize study interpretation. In fact, measurement error can seriously affect image interpretation. It is important to evaluate the degree of such error by calculating a reliability index. Many of the indices available can be viewed as versions of the interclass correlation coefficient, which may be used to provide measures of reliability, typically as a ratio of the variance of interest over the sum of the variance of interest plus error.^{23,24}

Acknowledgment

The authors have indicated they have no financial conflicts of interest.

References

1. Pohost GM, Zir LM, Moore LM, et al. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 1979;55:294-302.
2. Zaret BL, Rigo P, Wackers FJT, et al. Myocardial perfusion imaging with Tc-99m tetrofosmin. Comparison to TI-201 imaging and coronary angiography in a phase III multicenter trial. *Circulation* 1995;91:313-9.
3. Iskandrian AS, Heo J, Kong B, et al. Effects of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients. *J Am Coll Cardiol* 1989;14:1477-86.
4. Kahn JK, McGhie I, Akers MS, et al. Quantitative rotational tomography with TI-201 and Tc-99m 2-methoxy-isobutyl-isonitrile. A direct comparison in normal individuals and patients with coronary artery disease. *Circulation* 1989;79:1282-93.
5. De Pasquale EE, Nody AC, DePuey EG, et al. Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease. *Circulation* 1988;77:316-27.
6. Van Train KF, Garcia EV, Cooke CD, Areeda JS. Quantitative analysis of SPECT myocardial perfusion imaging. In: DePuey EG, Garcia EV, Berman DS, editors. *Cardiac SPECT imaging*. Volume 3. Philadelphia: Lippincott Williams and Wilkins; 2001. p. 42-64.
7. Garcia EV, Van Train KF, Maddahi J, et al. Quantification of rotational thallium-201 myocardial tomography. *J Nucl Med* 1985;26:17-26.
8. Garcia EV, Cooke CD, Van Train KF, et al. Technical aspects of myocardial SPECT imaging with technetium-99m sestamibi. *Am J Cardiol* 1990;66:23E-31E.
9. Wackers FJTh, Bodenheimer M, Fleiss JL, Brown M. Factors affecting uniformity in interpretation of planar TI-201 imaging in a multicenter trial. The Multicenter Study on Silent Myocardial Ischemia (MSSMI) Thallium-201 Investigators. *J Am Coll Cardiol* 1993;21:1064-74.
10. Maddahi J, Garcia EV, Berman DS, Waxman A, Swan HJC, Forrester J. Improved noninvasive assessment of coronary artery disease by quantitative analysis of regional stress myocardial distribution and washout of thallium-201. *Circulation* 1981;64:924-35.
11. Kaul S, Boucher CA, Newell JB. Determination of the quantitative thallium imaging variables that optimize detection of coronary artery disease. *J Am Coll Cardiol* 1986;7:527-37.
12. Tamaki N, Yonecura Y, Mukai T, et al. Stress thallium-201 transaxial emission computed tomography: quantitative versus qualitative analysis for evaluation of coronary artery disease. *J Am Coll Cardiol* 1984;4:1213-21.
13. Maes AF, Borges M, Flameng W, et al. Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT. Correlation with histologic and positron emission tomographic studies and functional follow-up. *J Am Coll Cardiol* 1997;29:62-8.
14. Udelson JE, Coleman PS, Metherall J, et al. Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with thallium-201 and ^{99m}Tc-sestamibi. *Circulation* 1994;89:2552-61.
15. Acampa W, Petretta M, Florimonte L, Scotto di Santolo M, Cuocolo A. Sestamibi SPECT in the detection of myocardial viability in patients with chronic ischemic left ventricular dysfunction: comparison between visual and quantitative analysis. *J Nucl Cardiol* 2000;7:406-13.
16. Cuocolo A, Acampa W, Nicolai E, Pace L, Petretta M, Salvatore M. Quantitative thallium-201 and technetium-99m sestamibi tomography at rest in detection of myocardial viability in patients with chronic ischemic left ventricular dysfunction. *J Nucl Cardiol* 2000;7:8-15.
17. Proceedings of the 4th Invitational Wintergreen Conference. Wintergreen, Virginia, USA. July 12-14, 1998. *J Nucl Cardiol* 1999;6:93-155.
18. Beller GA. Selecting patients with ischemic cardiomyopathy for medical treatment, revascularization, or heart transplantation. *J Nucl Cardiol* 1997;4:S152-S157.
19. Cohen Y, Acio E, Jaekyeong H, Hughes E, Narula J, Iskandrian AE. Comparison of the prognostic value of qualitative versus quantitative stress tomographic perfusion imaging. *Am J Cardiol* 1999;83:945-8.
20. Berman DS, Kang X, Van Train KF, et al. Comparative prognostic value of automatic quantitative analysis versus semiquantitative visual analysis of exercise myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol* 1998;32:1987-95.
21. Van Train KF, Maddahi J, Berman DS, et al. Quantitative analysis of tomographic stress thallium-201 myocardial scintigrams: a multicenter trial. *J Nucl Med* 1990;31:1168-79.
22. Garcia EV, Cooke CD, Folks RD, et al. Diagnostic performance of an expert system for the interpretation of myocardial perfusion SPECT studies. *J Nucl Med* 2001;42:1185-91.
23. Fleiss JJ. *Statistical methods for rates and proportions*, 2nd ed. New York: Wiley & Sons; 1981. p. 217-225.
24. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420-8.