Reproducibility of Quantitative Planar Thallium-201 Scintigraphy: Quantitative Criteria for Reversibility of Myocardial Perfusion Defects

Stephen L. Sigal, Robert Soufer, Robert C. Fetterman, Jennifer A. Mattera, and Frans J. Th. Wackers

Departments of Medicine, Section of Cardiovascular Medicine, and Diagnostic Radiology, Cardiovascular Nuclear Imaging Laboratory, Yale University School of Medicine, New Haven, Connecticut

Fifty-two paired stress/delayed planar ^{201}Tl studies (27 exercise studies, 25 dipyridamole studies) were processed twice by seven technologists to assess inter- and intraobserver variability. The reproducibility was inversely related to the size of ^{201}Tl perfusion abnormalities. Intraobserver variability was not different between exercise and dipyridamole studies for lesions of similar size. Based upon intraobserver variability, objective quantitative criteria for reversibility of perfusion abnormalities were defined. These objective criteria were tested prospectively in a separate group of 35 ^{201}Tl studies and compared with the subjective interpretation of quantitative circumferential profiles. Overall, exact agreement existed in 78% of images (kappa statistic k = 0.66). We conclude that quantification of planar ^{201}Tl scans is highly reproducible, with acceptable inter- and intraobserver variability. Objective criteria for lesion reversibility correlated well with analysis by experienced observers.

J Nucl Med 1991;32:759–765

Planar thallium-201 (^{201}Tl) imaging after exercise (*1–3*) or after administration of dipyridamole (*4,5*) has proven to be useful in the detection of functionally significant coronary artery disease. Furthermore, semiquantitative information, such as the number, extent, and severity of ^{201}Tl perfusion abnormalities has been shown to correlate with the severity of coronary artery disease (*6*) and, most importantly, with risk for future cardiac events (*7,8*).

Quantitative analysis has improved the interpretation of stress ^{201}Tl scintigraphy by reducing inter- and intraobserver variability and enhancing detection of coronary artery disease over visual analysis (*9–12*). This is accomplished by quantification of myocardial distribution of ^{201}Tl in comparison to a normal data base and by analysis of ^{201}Tl kinetics (*13–15*). Usually this information is displayed as either circumferential or transverse count profiles. Despite the objective nature of the quantitative technique, the ultimate interpretation of a clinical ^{201}Tl study is, in part, still subjective, since it is based upon inspection of the analogue images and the quantitative data.

The goals of this study were: (1) to assess the reproducibility of this computer method for quantifying myocardial perfusion abnormalities for both treadmill exercise and pharmacologic stress studies; and (2) to establish limits of variability in quantitative measurement of lesion size to provide objective guidelines for reversibility.

PATIENTS AND METHODS

Development of Quantitative Criteria for Reversibility

Study Material. The study material consisted of 52 planar ^{201}Tl studies of patients who had diagnostic ^{201}Tl imaging between May 1988 and September 1989. These studies were selected from a larger number of studies to represent approximately equal numbers of normal, postinfarct, and ischemic studies. Twenty-seven patients underwent symptom-limited treadmill exercise testing (standard Bruce protocol); twenty-five patients had pharmacologic stress testing with intravenous dipyridamole (0.568 mg/kg over 4 min).

Imaging Protocol. At peak exercise or 4 min after completion of dipyridamole infusion, 2.5 mCi of ^{201}Tl was injected intravenously. In the case of exercise studies, the patient was encouraged to exercise for two additional minutes.

Planar myocardial imaging was begun within 5 min of ^{201}Tl injection, using a single crystal gamma camera (Siemens LEM, Siemens Medical Systems, Inc., Iselin, NJ) equipped with a low-energy, all-purpose, parallel-hole collimator interfaced with a dedicated minicomputer (Picker PCS-512, Picker Instruments, Inc., Highland Heights, OH). Images were obtained in the left anterior oblique, left lateral and anterior projections. Each view was acquired for 8–10 min with a minimum of 600,000 counts in the field of view. Delayed imaging was performed 2–2.50 hr postinjection at identical projections. Thus, a total of 312 images were obtained: 162 views in 27 three-view paired exercise and delayed studies and 150 views in 25 three-view paired dipyridamole and delayed studies. The images were acquired in a 128 × 128 matrix (word mode) and stored on floppy disk for later retrieval and processing.

Quantitative Analysis of Images. Software for computer processing and quantitative analysis has been previously described (*15*). Briefly, an elliptical reference region was placed around the

Received Jun. 1, 1990; revision accepted Oct. 30, 1990.

For reprints contact: Frans J. Th. Wackers, MD, Yale University School of Medicine, Cardiovascular Nuclear Imaging Laboratory, TE-2, 333 Cedar St., New Haven, CT 06510.

heart for interpolative background correction. The generated background image was subtracted from the unsmoothed analog images. A modified background subtraction algorithm was employed (*16,17*). A region of interest was defined around the left ventricle. The technologist identified the long-axis and apex of the ventricle. The exercise and delayed images were automatically aligned for small differences in position. Circumferential count distribution profiles were then generated displaying mean count density in 36 equal segments. The segment with the highest mean count density was designated as 100%, and the mean count densities in all remaining segments were displayed relative to this maximal value. This allowed comparison of the relative distribution of ^{201}Tl uptake in serial studies.

Curves defining the lower limit of normal for ^{201}Tl distribution in each view (mean − 2 s.d., derived from a normal database of 28 subjects with less than 3% likelihood of coronary artery disease) were displayed simultaneously with the patient data for each image (mean counts per 10-degree angle). The size of myocardial perfusion abnormalities was determined by integrating the hypoperfused area under the lower limit of normal curve. This area was expressed as a proportion (×100) of the total potentially visualized normal myocardium (Fig. 1). The value obtained is defined as the defect integral. It is unitless and reflects both the extent and severity of the myocardial perfusion abnormalities. We have shown previously (*18*) that the defect integral measured in this manner increases as the visual interpretation of defect severity increases (Fig. 2).

Assessment of Inter- and Intraobserver Variability. Inter- and intraobserver variability were assessed by having seven experienced technologists process 312 ^{201}Tl scintigrams (52 paired three-view stress and delayed studies) in duplicate. The technologists were blinded to the patient's clinical data and previous quantitative processing results. Repeat analyses by a single technologist were separated by at least 2 wk. The defect integral for each stress or delayed image was compared to that obtained on reprocessing

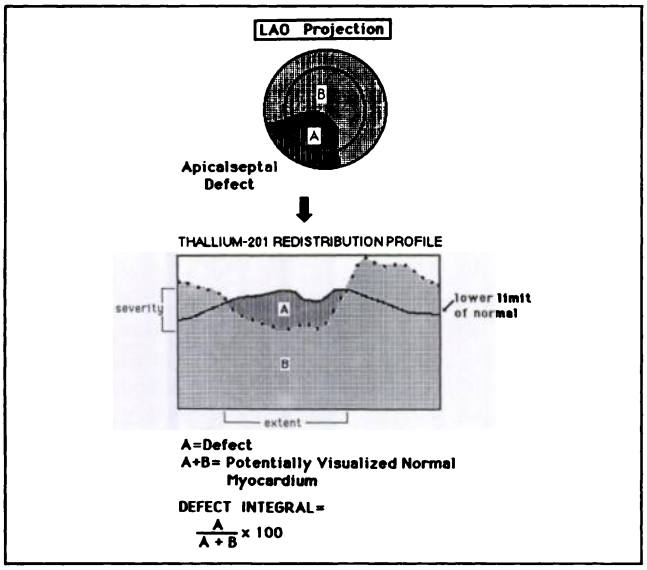

FIGURE 1. Method of quantification of planar ^{201}Tl myocardial perfusion defects. The defect integral is a dimensionless quantity representing both the extent and severity of the defect, as compared to a normal database.

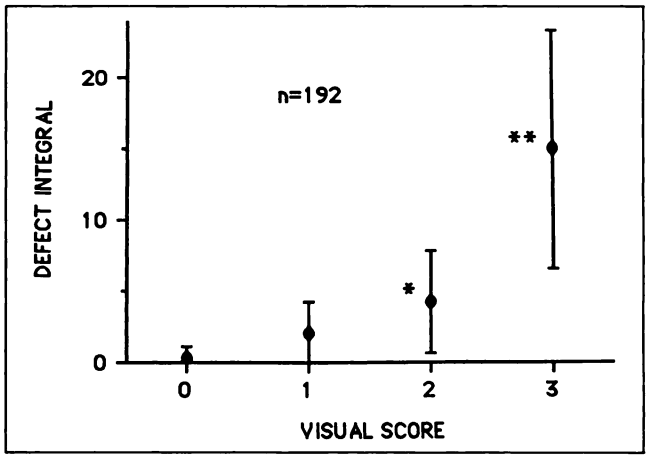

FIGURE 2. Comparison of visual scoring of ^{201}Tl defect severity with quantitative measurements of defect size. Visual scores are defined as 0 = normal, 1 = minimal defect, 2 = moderate defect, and 3 = severe defect.

of the same image. The reproducibility of processing was analyzed separately for exercise and dipyridamole studies.

The ^{201}Tl images were subsequently divided into four subgroups based upon the magnitude of the initial lesion integral. These groups were arbitrarily defined as follows: normal (defect integral 0), small (1–5), medium (6–15), and large (>15). Inter- and intraobserver variability were determined for each of these subgroups.

Criteria for Reversibility. Since exercise and delayed ^{201}Tl images are processed by the same technologist in standard clinical practice, intraobserver variability was used to define objective criteria for lesion reversibility. A study was considered "normal" when there was no defect quantitatively (i.e., all portions of the circumferential profiles were above the lower limit of normal). A study was considered "probably reversible" if the decrease in lesion size was between 1 and 2 s.d. more than the mean intraobserver variability for defects of that size. A study was considered to show "definite reversibility" if the change was greater than 2 s.d. above the mean variability. A study was considered to show a "fixed" abnormality if the change between images was less than 1 s.d. above the mean variability.

Application of Quantitative Criteria for Reversibility

An additional 35 planar ^{201}Tl studies were selected at random between January and June 1989 to evaluate the applicability of the quantitative criteria established above in comparison to standard techniques of determining reversibility. These patients underwent the same stress and imaging protocol previously described. Each of the 105 paired exercise and delayed images generated was evaluated by the objective quantitative criteria developed above, as well as by subjective analysis of circumferential profiles. In the latter approach, both the analog images and the circumferential profiles were examined by an experienced reader, as has been done routinely in our institution over the past seven years. On the basis of this "subjective quantitative analysis," the studies were categorized as "normal," "probably reversible," "definitely reversible," or "fixed" defects.

Statistical Analysis. The reproducibility of processing was analyzed separately for exercise and dipyridamole studies. For assessment of *interobserver variability*, the repeat measurements by

six technologists were compared to that of a seventh technologist (J.A.M.). Thus, there were 972 comparisons for exercise studies and 950 comparisons for dipyridamole studies. To assess *intraobserver variability*, repeat measurements by each of the seven technologists were used (1134 comparisons for exercise studies and 1050 comparisons for dipyridamole studies). Individual differences on repeat processing by each technologist for each image were meaned to calculate the mean variability. In addition, the difference between repeat measurements was expressed as a percentage of the larger measurement for defect size. Relationships between repeat measurements of the defect integral were examined using Pearson's correlation coefficients. Categorization of the change between paired images as evaluated by different methods was compared using chi-square analysis for repeated measures and the kappa statistic, k. Comparisons between groups of data were performed by one-way analysis of variance (ANOVA) and by Tukey's HSD test for multiple means. A value of $p < 0.05$ was considered significant.

RESULTS

Intraobserver Variability of Defect Quantification

Individual correlation coefficients for repeat measurements by each technologist ranged from 0.94 to 0.97 for exercise studies and from 0.85 to 0.92 for dipyridamole studies. The mean difference in defect integral obtained on repeat processing of the same image by each technologist ranged from 1.2 to 1.8 for exercise studies and from 0.3 to 0.6 for dipyridamole studies. The defect integrals measured by each technologist did not differ significantly among the seven technologists, as measured by Tukey's HSD test for multiple comparisons of means. There was also no statistically significant variation in the average difference in measured defect integral on reprocessing by any one technologist compared to any other technologist. When measurements by each technologist were combined, the overall correlation coefficient (r) was 0.96 for exercise studies (Fig. 3A) and r = 0.89 for dipyridamole studies (Fig. 3B).

Mean absolute intraobserver difference for all comparisons was 1.5 ± 1.9 for exercise studies (median = 1) and 0.4 ± 0.8 for dipyridamole studies (median = 0) ($p < 0.001$, unpaired t-test). However, the defects in the exercise studies evaluated were significantly larger than those in the dipyridamole studies chosen (7.8 ± 8.6 versus 0.9 ± 1.8, $p < 0.001$). To correct for this difference, intraobserver variability was also expressed as a percentage of the defect size. Overall variability was 20% ± 36% for exercise studies and 22% ± 29% for dipyridamole studies (p = ns, unpaired t-test).

Mean absolute difference on repeat processing by the same technologist varied with the initial size of the defect integral ($p < 0.001$, ANOVA) (Fig. 3C). Larger initial defects were associated with greater mean *absolute* difference on reprocessing than were smaller defects. The mean absolute differences for each group of defect sizes differed significantly from each other ($p < 0.001$, Tukey's HSD test). However, when expressed as a *relative* percentage of the defect integral, larger defects (defect integral > 5) had less variation on repeat processing than did smaller defects (defect integral 1 − 5) ($p < 0.001$, Tukey's HSD test). Moreover, there was no significant difference in intraobserver variability between exercise and dipyridamole studies for defects of similar size, when considered as a relative percentage difference (p = ns, Tukey's HSD test) (Fig. 3D).

Interobserver Variability of Defect Quantification

The defect integrals measured by each of six technologists for each ^{201}Tl image were compared to that obtained

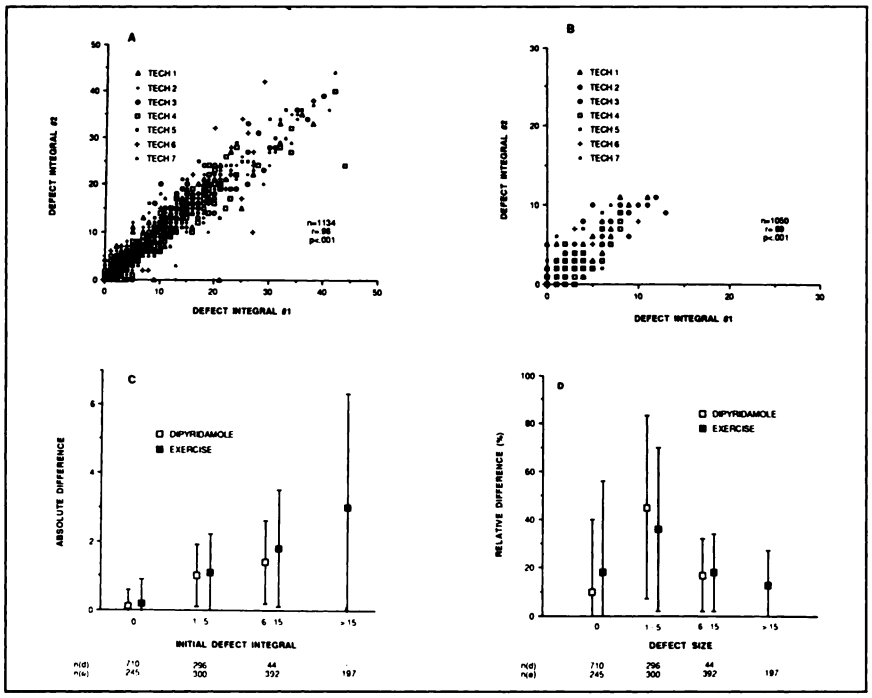

FIGURE 3. Intraobserver variability. (A) Correlation between exercise/delayed defect integrals at original measurement (defect integral #1) and at repeat processing (defect integral #2) by each of seven technologists. (B) Correlation for dipyridamole studies. (C) Absolute difference (mean ± s.d.) at repeat processing of defects of different sizes (see text); ■ represents exercise studies; □ represents dipyridamole studies; n(e) = number of exercise images in each range group; and n(d) = number of dipyridamole images in each range group. (D) Relative (percentage) difference (mean ± 1 s.d.) at repeat processing of defects of different sizes (see text).

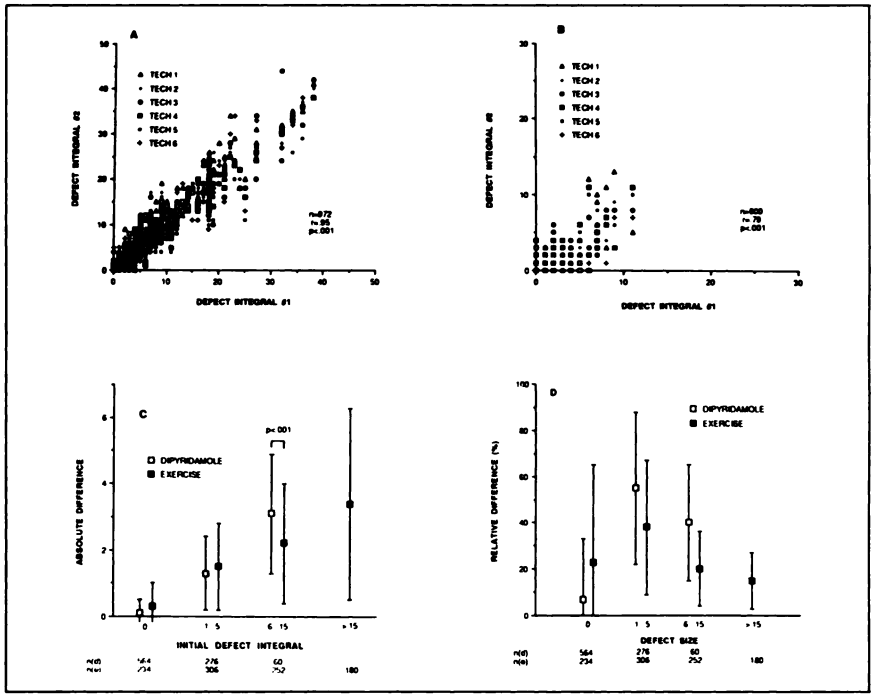

FIGURE 4. Interobserver variability. (A) Correlation between the exercise/delayed defect integral at original measurement by a single technologist (defect integral #1) and at repeat processing by each of six other technologists (defect integral #2). (B) Correlation for dipyridamole studies. (C) Absolute difference (mean ± 1 s.d.) at repeat processing of defects of different sizes (see text); ■ represents exercise studies; □ represents dipyridamole studies; n(e) = number of exercise images in each range group; and n(d) = number of dipyridamole images in each range group. (D) Relative (percentage) difference (mean ± s.d.) at repeat processing of defects of different sizes (see text).

by the reference technologist (J.A.M.). The individual interobserver correlation coefficients for each technologist ranged from 0.94 to 0.97 for exercise studies and from 0.73 to 0.86 for dipyridamole studies. Mean differences in defect integral obtained on repeat processing by each technologist ranged from 1.5 to 2.0 for exercise studies and from 0.6 to 0.8 for dipyridamole studies. There was no significant difference in the average difference of measured defect integral on reprocessing by any one technologist compared to any other technologist. When measurements by each technologist were combined, an overall correlation coefficient of r = 0.95 was obtained for exercise studies (Fig. 4A), and r = 0.79 for dipyridamole studies (Fig. 4B).

Mean absolute interobserver difference for all comparisons was 1.8 ± 2.0 for exercise studies (median = 1) and 0.7 ± 1.2 for dipyridamole studies (median = 0) ($p < 0.001$, unpaired t-test). Expressed as a percentage of defect size, overall variability was 24% ± 38% for dipyridamole studies and 26% ± 29% for exercise studies (p = ns, unpaired t-test).

As with intraobserver variability, interobserver variability varied with the initial size of the defect integral ($p < 0.001$, ANOVA) (Fig. 4C). Larger initial defects were associated with greater mean *absolute* difference on reprocessing than were smaller defects. The mean absolute differences for each group of defect sizes differed significantly from each other ($p < 0.001$, Tukey's HSD test). However, when expressed as a *relative* percentage of the defect integral, larger defects (defect integral > 5) had less variation on repeat processing than did smaller defects (defect integral 1 − 5) ($p < 0.001$, Tukey's HSD test) (Fig. 4D). In those studies with zero initial defect integral (normal), there was significantly more interobserver variability in exercise studies compared to dipyridamole studies (23% ± 42% versus 7% ± 26%, $p < 0.001$). Conversely, for small defects (defect integral 1 − 5) and for moderately large defects (defect integral 6 − 15) there was greater interobserver variability for dipyridamole studies ($p < 0.001$, Tukey's HSD test).

Minimal Changes Needed to Define Reversibility of Defects

Based upon the mean absolute difference in defect integral on reprocessing by the same technologist, confidence limits of reversibility were established. Intraobserver variability was chosen, since it duplicated the standard practice

TABLE 1
Summary of Intraobserver Variability and Definitions of Reversibility for Varying Sizes of Defect Integrals

	Initial stress defect integral		
	1–5	6–15	>15
Intraobserver variability mean ± s.d.	1.1 ± 1.2	1.8 ± 1.7	2.9 ± 3.1
Minimum change needed to indicate probable reversibility* (Minimum change as a percentage of defect)	2 (70%)	4 (34%)	6 (27%)
Minimum change needed to indicate definite reversibility† (Minimum change as a percentage of defect)	4 (100%)	5 (50%)	9 (41%)

* Probable reversibility defined as mean intraobserver variability plus 1 s.d. for a defect of a given size.

† Definite reversibility defined as mean variability plus 2 s.d. for a defect of a given size.

TABLE 2
Comparison of Objective and Subjective Quantitative Analyses for 105 Paired Stress/Delayed Images

Subjective quantitative analysis	Objective quantitative analysis: Normal	Probably reversible	Definitely reversible	Fixed
Normal	18	—	4	2
Probably reversible	—	5	1	8
Definitely reversible	2	—	11	1
Fixed	1	2	2	48

Exact agreement in 82 of 105 views (78%); $k = 0.66$; $p < 0.001$.

of a single technologist processing serial images (initial and delayed) from a single patient study. Table 1 summarizes numerically the magnitude of change required in each subgroup to exceed average intraobserver variability. As shown above, these limits vary according to the size of the initial defect. The mean variability plus one standard deviation rounded to the nearest whole number established the definition for "probably" reversible defect, and the mean variability plus two standard deviations defined "definitely" reversible defect.

Application of Quantitative Criteria for Reversibility

As summarized in Table 2, there was close overall agreement between subjective analysis of circumferential profiles and the use of the developed objective quantitative criteria, with concordance in 82 of 105 images (78%), and a kappa statistic $k = 0.66$ ($p < 0.001$). When all defect integrals of ≤5 were excluded from analysis (given their significantly greater variability on repeat processing) there was concordance in 33 of 40 images (83%; $k = 0.63$, $p < 0.001$). In the seven cases of disagreement in defects >5, subjective interpretation of profiles suggested partial reversibility, while the defects were fixed (change between images less than mean variability +1 s.d.) by quantitative criteria.

Of the 35 patients studied, 6 underwent dipyridamole testing, while 29 underwent treadmill testing with ^{201}Tl injected at peak exercise. The small number of dipyridamole studies included in this group precludes any definitive analysis of a difference in the applicability of the technique to these two populations.

DISCUSSION

In the present study, we established the limits of reproducibility of measuring defect size on planar ^{201}Tl scintigrams and provided objective standards for reversibility of perfusion abnormalities. Although these results pertain to the use of our specific software for quantitative image analysis, similar findings may be expected from use of other computer programs that are based on the same concept.

The usefulness of quantitative ^{201}Tl scintigraphy as a sensitive and specific method of detecting coronary artery disease is well established (*13–15*). Quantitation has improved reproducibility and enhanced confidence in detection of coronary artery disease (*9,10*). However, quantitative techniques involve several operator-dependent processing steps, each of which has the potential to add variability to the results (Table 3). Although the method is considered "quantitative," the *interpretation* of processed results in clinical practice is largely subjective. Until recently, in our laboratory, interpretation consisted of visual inspection of analog images and circumferential profiles without well-defined specific quantitative criteria for reversibility.

TABLE 3
Processing Steps and Potential Sources of Variability*

Processing step	Degree of variability	Practical measures to minimize variability
1. Placement of elliptical region for interpolative background subtraction	Minor to Major	Standardization
2. Definition of ROI around left ventricle	Major	Simultaneous drawing on exercise and rest iso-color boundary
3. Autoregistration for position difference of left ventricle on exercise and rest images	Minor	Automation (Manual override exception)
4. Identification of apex, long-axis, and alignment of normal database	Minor	Marking long-axis
5. Generation of distribution profiles	None	Automation
6. Computation of defect size (segmental, total)	None	Automation

* Using the Yale quantitative ^{201}Tl analysis software.

An early attempt by other investigators to use computer algorithms to discriminate between normal and abnormal planar images (*12*) was associated with a relatively high incidence of false-positive exams. Recently, Garcia et al. developed objective criteria for reversibility of myocardial perfusion defects on SPECT (*19*). These criteria for tomography were based upon the performance of "expert" readers. In contrast, the criteria developed herein are based upon intraobserver variability in image processing.

Measurements of Variability and Objective Criteria for Reversibility

Establishing the limits of reproducibility of measured defect size allows the establishment of criteria to discriminate between processing variability and true reversibility. The magnitude of absolute variation in defect integral increased with larger defect integrals (Table 1). However, when considered as a percentage of defect size, variability decreased with larger defects.

To apply these criteria for reversibility, adjustments for lesion size therefore should be made. As detailed in Table 1, in small lesions (defect integral 1–5), a minimum change in defect integral of 2 (70% relative difference) is required to detect reversibility with confidence, while large defects (defect integral >15) require a minimum change of 6 in defect integral (27% relative difference) to demonstrate reversibility. In clinical practice, we find it easier to express changes as relative percentages of the initial defect size (Table 1). Empirical analysis of the interpretation pattern of an "expert" reader indicates that in clinical practice "probable reversibility" indeed represents the minimal requirement for the interpretation of myocardial ischemia.

Comparison of Reproducibility in Exercise and Dipyridamole Studies

The mean and range of defect sizes in the dipyridamole studies was smaller than exercise studies. This reflects the overall patient referral pattern in our laboratory. Dipyridamole studies are usually obtained as preoperative screening tests for asymptomatic or minimally symptomatic patients with peripheral vascular disease. Intraobserver variability was similar for both exercise and dipyridamole studies. Interobserver variability for defect integrals of 0 (normal images) was greater for exercise studies than for dipyridamole studies. Conversely, for defect integrals of 6–15, there was greater interobserver variability for dipyridamole studies compared to exercise studies. Since a set of initial and delayed images is always processed by the same technologist in clinical practice, the differences observed for interobserver variability between exercise and dipyridamole studies did not impact upon the development of criteria for reversibility based upon intraobserver variability.

Application of Objective Criteria for Reversibility

A gold standard does not exist for determining reversibility of ^{201}Tl myocardial perfusion abnormalities. In the past several years, our experience with quantitative ^{201}Tl imaging has shown excellent agreement with visual analysis of analog images. When this approach (based upon the experience of "expert" readers) was compared to the quantitative criteria developed in the present study on the basis of the reproducibility of the method, a good overall agreement exists ($k = 0.66$).

Most cases of disagreement between quantitative and subjective analysis involved very small defects. Each of the four images judged to be normal subjectively, but to have objective evidence of reversibility, had initial defect integrals of 1. Similarly, the two images judged to be normal by subjective criteria, but fixed by objective analysis, had initial defect integrals of 1 and 2.

In contrast, seven of the eight images judged to be probably reversible by subjective analysis, but fixed by objective criteria, had moderately large initial defect integrals (range 6–19). In these cases, the degree of quantitative change between paired stress and delayed views fell within the range of intraobserver variability (mean variability + 1 s.d.) for defects of that size.

In very small defects (defect integral ≤2), it appears that our objective criteria cannot differentiate between statistical noise in the data and true defect reversibility. In this situation, one should rely upon visual inspection of the images in addition to quantitative data. When defects are larger, there is good agreement between objective and subjective interpretation of quantitative profiles. Because small changes in images may be apparent visually, reversibility may be suggested by subjective analysis when the difference between images is within the limits of intraobserver variability for reprocessing. Whether this represents increased sensitivity or decreased specificity of subjective analysis cannot be determined without an independent method of determining the presence of viable myocardium.

CONCLUSION AND CLINICAL IMPLICATIONS

In conclusion, objective criteria for reversibility of planar myocardial perfusion defects were established, based upon the variability of the technique. These objective criteria agree well with subjective interpretation using presently available techniques. The use of such objective criteria should further improve reproducibility and consistency in evaluation of coronary artery disease by ^{201}Tl stress imaging. They should also allow objective determination of change between serial scintigrams over time, or after interventions aimed at improvement of myocardial perfusion.

ACKNOWLEDGMENTS

The authors wish to thank Kathleen Davis, CNMT, Diana Errico, RT(N), Celeste Jochimson, CNMT, Edwin Levine, RT(N), Michael McMahon, CNMT, Mark Saari, CNMT, and Peter Vitols, RT(N) for their excellent technical assistance in

performing this study. We also appreciate the advice and assistance of Emanuel Lerner, MA with the statistical analyses.

REFERENCES

1. Ritchie JL, Trobaugh GB, Hamilton GW, et al. Myocardial imaging with thallium-201 at rest and during exercise: comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* 1977;56:66–71.
2. Bailey IK, Griffith LSC, Rouleau J, et al. Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* 1977;55:79–87.
3. Ritchie JL, Zaret BL, Strauss HW, et al. Myocardial imaging with thallium-201: a multicenter study in patients with angina pectoris or acute myocardial infarction. *Am J Cardiol* 1978;42:345–350.
4. Josephson MA, Brown BG, Hecht HS, et al. Noninvasive detection and localization of coronary artery stenoses in patients: comparison of resting dipyridamole and exercise thallium-201 myocardial perfusion imaging. *Am Heart J* 1982;103:1008–1018.
5. Leppo J, Boucher CA, Okada RD, et al. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. *Circulation* 1982;66:649–657.
6. Reisman S, Berman D, Maddahi J, et al. The severe stress thallium defect: an indicator of critical coronary stenosis. *Am Heart J* 1985;110:128–134.
7. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. *J Am Coll Cardiol* 1983;1:994–1001.
8. Wackers FJ, Russo DJ, Russo D, Clements JP. Prognostic significance of normal quantitative planar thallium-201 scintigraphy in patients with chest pain. *J Am Coll Cardiol* 1985;6:27–30.
9. Trobaugh GB, Wackers FJ, Sokole EB, et al. Reproducibility of thallium-201 myocardial imaging: an inter-institutional study of observer variability. *J Nucl Med* 1978;19:359–363.
10. Atwood JE, Jensen D, Froelicher V, et al. Agreement in human interpretation of analogue thallium myocardial perfusion images. *Circulation* 1981;64:601–609.
11. Watson DD, Campbell NP, Read EK, Gibson RS, Teates CD, Beller GA. Spatial and temporal quantitation of planar thallium myocardial images. *J Nucl Med* 1981;22;577–584.
12. Garcia E, Maddahi J, Berman D, Waxman A. Space/time quantitation of thallium-201 myocardial scintigraphy. *J Nucl Med* 1981;22:309–317.
13. Berger BC, Watson DD, Taylor GJ, et al. Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease. *J Nucl Med* 1981;22:585–593.
14. Maddahi J, Garcia EV, Berman DS, et al. Improved noninvasive assessment of coronary artery disease by quantitative analysis of regional stress myocardial distribution and washout of thallium-201. *Circulation* 1981;64:924–935.
15. Wackers FJ, Fetterman RC, Mattera J, Clements JP. Quantitative planar thallium-201 stress scintigraphy: a critical review of the method. *Semin Nucl Med* 1985;15:46–66.
16. Sinusas AJ, Beller GA, Smith WH, et al. Quantitative planar imaging with technetium-99m-methoxyisobutyl isonitrile: comparison of uptake patterns with thallium-201. *J Nucl Med* 1989;30:1456–1463.
17. Koster K, Wackers FJTh, Mattera JA, Fetterman RC. Quantitative analysis of planar technetium-99m-sestamibi myocardial perfusion images using modified background subtraction. *J Nucl Med* 1990;31:1400–1408.
18. Sigal SL, Mattera JA, Fetterman RC, Wackers FJ. Virtue and limitations of quantification of extent and severity of planar Tl-201 perfusion defects [Abstract]. *J Nucl Med* 1989;30:863.
19. Garcia E, DePuey G, Sonnemaker R, et al. Quantification of the reversibility of stress-induced Tl-201 myocardial perfusion defects: a multicenter trial using bullseye polar maps and standard normal limits [Abstract]. *Circulation* 1989; 80:II–209.