Quantification of the Reversibility of Stress-Induced Thallium-201 Myocardial Perfusion Defects: A Multicenter Trial Using Bull's-eye Polar Maps and Standard Normal Limits

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A multicenter trial was performed on 140 patients from four centers to determine the accuracy of quantitative analysis of stress/delayed thallium-201 myocardial tomograms using normal limits to assess the relative amount of reversibility of stress-induced defects. The patients were found to have 85 fixed and 124 reversible defects, as determined by visual interpretation. Reversibility bull's-eye polar maps were compared to gender-matched normal limits from 36 normals. Regions were identified as reversible if their normalized difference between stress and 4 hr >1.5 s.d.s from the mean normal limits. Overall agreement between experts at multicenter sites and reversibility maps was 73% for reversible defects and 80% of fixed defects. Sensitivity in detecting reversibility was highest for the left circumflex (88%) and lowest for the right coronary (60%). These results indicate that reversibility polar maps and normal limits offer an objective, accurate technique for determining the reversibility of stress-induced perfusion defects.

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In order to standardize and objectify the analysis of defect reversibility, we recently developed a computer method to quantify and display the extent that tomographic thallium myocardial perfusion defects normalize (*1*). For that study, we developed normal limits for reversibility based on the same patient population with low likelihood of disease that we previously used for determining the normal limits of the stress and delayed thallium-201 (^{201}Tl) tomographic myocardial distributions (*2*). A criteria for defect reversibility was also developed, which resulted in the best agreement between the computer output and the majority of five experts' visual assessment from our institution. The purpose of this study is to validate this previously described methodology using a prospective patient population and expert visual interpretation from four centers independent from Emory.

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METHODS

Center and Patient Selection

Centers were selected from different geographic regions based on the following criteria:

1. Each center had the same tomographic camera system (GE 400 AC/STARCAM, Milwaukee, WI) for which the computer program was written.
2. Each center's tomographic thallium studies could be interpreted by one investigator with at least 2.5 yr of expertise in the visual assessment of thallium tomograms, which was used as the gold standard for defect reversibility.

The centers were as follows: Lenox Hill Hospital, New York, New York; Ochsner Clinic, New Orleans, Louisiana; Philadelphia Heart Institute, Philadelphia, Pennsylvania; and St. Luke's Episcopal Hospital, Houston, Texas. These centers will be referred as centers A through D.

Each of the four centers contributed 35 patient cases for a total of 140 patients. These cases were selected for each center from 35 consecutive abnormal patients who were referred for assessment of known or suspected coronary artery disease (CAD) and who exhibited myocardial ^{201}Tl stress-perfusion defects both visually and from quantitative analysis using the Emory bull's-eye approach (*2*). Five additional patients from studies which were considered to exhibit artifacts due to gross patient motion were excluded. Coronary arteriographic studies were not requested in these patients since the presence of a coronary lesion cannot be used to document a fixed or reversible defect. Table 1 describes the demographic characteristics of the combined patient population and the populations on a

TABLE 1
Demographic Characteristics of Patient Population by Center

	Sex		Age		
Center	Males	Females	Mean	Range	s.d.
A	29	6	60.2	(42–76)	8.2
B	30	5	60.5	(37–73)	9.0
C	26	9	59.6	(42–77)	9.2
D	25	10	64.4	(37–78)	8.9
Combined	110	30	60.8	(37–78)	10.4

center-by-center basis. A second patient population of 36 subjects with less than 5% likelihood of CAD, previously used for development of stress and delayed normal limits files (*2*) and for normal limits of reversibility (*1*), was also used in this study.

Quantification of Defect Reversibility

Our procedures for exercise, acquisition, processing, and quantification of SPECT thallium studies has been previously described in detail (*2*). Our procedure for quantification of defect reversibility has also been described previously (*1*). Briefly, each point in the patient's normalized stress distribution array is subtracted from the corresponding point in the normalized delayed distribution array, resulting in a new array representing improvement from stress to rest or defect reversibility. For display purposes, these arrays are transformed into a polar plot known as a "reversibility bull's-eye."

In order to objectively identify defect reversibility, each patient's reversibility array is compared to gender-matched normal files developed from the low likelihood of CAD group in which the mean values and s.d. were established from the pooled reversibility arrays of these normal patients. Previously, we established the points representing 1.5 s.d.s above the mean normal response as our threshold for detecting reversibility in regions already identified to exhibit a stress-perfusion defect (*1*). We also established that if a stress defect was considered visually reversible by experts, in general, the extent of reversibility was at least 15% of the extent of the stress perfusion defect, although regions as small as 5% were perceived by the experts as having partial reversibility. Thus, these criteria were used in interpreting reversibility for the prospective, multicenter patient population.

Expert Review of Patient Data

Four physicians experienced in the interpretation of SPECT-thallium myocardial perfusion studies, one physician from each of the participating centers, were asked to review the standard stress and delayed tomographic slices as well as the stress and delayed bull's-eye for each of the patients in their population. These bull's-eyes included comparisons with normal files but did not include the reversibility bull's-eyes. Each reviewer was asked to identify all stress abnormalities and then score the improvement in the appropriate myocardial segment of the delayed study as none, partial, nearly complete or complete.

These experts were also asked to provide a final impression as to which coronary artery territory corresponded to the stress-perfusion defect segment and whether they considered the region to exhibit significant ischemia or mostly scar. All interpretations by each expert were limited to the patients from his institution. The coronary artery territories to which the perfusion defect could be assigned were as follow: left anterior descending (LAD), left circumflex (LCX), the indefinite vascular region perfused by the diagonal branch of the LAD (Dx) or by the LCX, the right coronary artery (RCA) and/or posterior descending artery (PDA), and the indefinite region perfused by the RCA/PDA and/or LCX. Previously, we have developed objective criteria for assigning a defect to a specific vascular territory (*2*). For purposes of statistical analysis, the results of the LAD(Dx) or LCX region were combined with the LCX results and the results of the RCA/PDA or LCX region were combined with the RCA region. The reviewers were instructed to use as a criterion for scoring significant ischemia for a stress-perfusion defect, one which normalized by delayed imaging such that the reviewer would predict that at least 25% of the defect would normalize with intervention. Otherwise, the defect should be scored as being mostly scar.

The quantitation results for all 140 patients were sent to Emory for tabulation and for comparison to each center's expert interpretation of defect reversibility. Subsequently, experts from all centers met at Emory to verify the results obtained from these comparisons and to mitigate minor differences in the assignment of vascular territories in four patients.

Comparisons of the detection of reversible and fixed segments between centers and between the vascular territories of the combined results were performed using either a chi-squared test or the Fisher's exact test and were tested at the alpha-0.05 level of significance. All p values are two-tailed and were adjusted for multiple comparisons.

RESULTS

Overall Detection of Reversibility

The physicians from the four centers who reviewed the studies of each of their populations identified 72 patients with only reversible lesions; 45 patients with only fixed lesions; 22 patients with both reversible and fixed lesions; and 1 patient with a defect due to a breast artifact. The quantitative methodology correctly identified all the involved vascular territories and lesion characteristics in 69% (50/72) of the patients with only reversible lesions; 69% (31/45) of the patients with only fixed lesions; and 45% (10/22) of the patients with both reversible and fixed lesions. These patient studies were interpreted as exhibiting 209 stress-perfusion defects. Of these defects, 124 were considered to be relatively reversible and 85 of the defects were evaluated as relatively fixed. The right-most column in Table 2 lists, on a center-by-center basis and combined results from all centers, the overall agreement between the quantitative methodology and the expert interpretation of stress defects as being reversible or fixed. Of the 91 combined defects correctly identified as reversible, 13 were detected using the threshold criteria that the reversible extent was $\geq$5% of the stress defect extent but <15%.

TABLE 2
Detection of Perfusion Defect Reversibility by Center

	LAD		RCA		LCX		Overall	
Center	Reversible	Fixed	Reversible	Fixed	Reversible	Fixed	Reversible	Fixed
A	6/9 (67)	3/6 (50)	9/11 (82)	9/13 (69)	3/3 (100)	5/7 (71)	18/23 (78)	17/26 (65)
B	6/8 (75)	11/14 (79)	2/7 (29)	14/15 (93)	4/4 (100)	6/6 (100)	12/19 (63)	31/35 (89)
C	14/15 (93)	1/2 (50)	7/8 (88)	5/6 (83)	8/8 (100)	4/4 (100)	29/31 (94)*	10/12 (83)
D	14/19 (74)	1/2 (50)	10/21 (48)	8/9 (89)	8/11 (73)	1/1 (100)	32/51 (63)*	10/12 (83)
Combined	40/51 (78)	16/24 (67)	28/47 (60)†	36/43 (84)	23/26 (88)†	16/18 (89)	91/124 (73)	68/85 (80)

Number in parentheses = %Agreement.
*† $p < 0.05$.

Of these 13, 10 were evaluated by the experts as partially reversible, 1 as nearly completely reversible, and 2 as completely reversible. Of the 15 combined defects incorrectly identified as reversible, only 3 were missed using the ≥5% reversible (but <15%) extent threshold criteria. Of these three defects, two were evaluated by the experts as fixed and one as partially reversible (but did not fulfill the criteria for significant ischemia).

The high rate of detecting reversibility (94%) on the patient population of center C was determined to be significantly different from that of center D (63%). No difference in the overall detection of fixed defects reached statistical significance.

Detection of Reversiblity by Vascular Territory

Table 2 shows the agreement between experts and the quantitative methodology by vascular territory on a center-by-center basis. None of these results were determined to be significantly different. The bottom row in Table 2 compares agreement between experts and the quantitative methodology for the combined results from all centers by vascular territory. The LCX territory showed the best overall agreement for both the identification of reversible and fixed defects. The highest rate of detecting reversibility in the LCX territory (88%) was determined to be significantly different from the lowest rate found for the RCA territory (60%). None of the differences in the rate of detecting fixed defects in the vascular territories reached statistical significance. The results presented in Table 2 are rearranged in Figure 1 to better illustrate the regional characteristics. Only three total defects (reversible or fixed) in the LCX territory showed disagreement between the computer and expert interpretation as to reversible or fixed. Of the eight reversible defects in the LAD territory incorrectly identified by the computer as fixed, six were evaluated by the experts as located in the septum and partially reversible. Of the eight nonischemic LAD defects incorrectly identified by the computer as reversible, seven were evaluated by the experts to be partially reversible but not fulfilling the criteria for significant ischemia and one was evaluated as fixed. Of these eight defects, seven were located in the anterior wall and one in the septum. All of the 17 reversible defects in the RCA territory incorrectly identified by the computer as fixed were found to be associated with one or more of the following conditions:

1. The reversibility bull's-eye showed improvement in a region inside the region corresponding to the stress-perfusion defect as defined by the stress blackout bull's-eye map but not reaching statistical significance (≥1.5 s.d.).
2. The reversibility bull's-eye showed improvement in a region which reached statistical significance but located just outside the stress-perfusion defect as defined by the blackout bull's-eye map.

DISCUSSION

This multicenter trial was undertaken to validate the accuracy of our previously developed quantitative reversibility methodology in a prospective patient population from multiple geographic regions. Reversibility as assessed by the computer methodology was compared to visual assessment of reversibility by expert

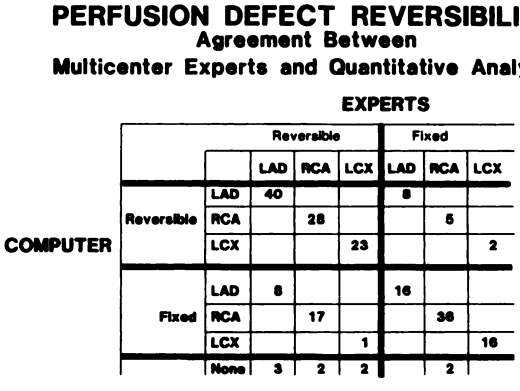

FIGURE 1
Regional characteristics of detecting reversibility. Combined results from all centers illustrating the regional characteristics, in terms of vascular territory, of identifying stress-perfusion defects as reversible or fixed.

observers from different backgrounds. Our results in the present validation are somewhat poorer although not significantly different from those reported by Klein et al. (*1*) in testing this technique using a pilot group. Klein et al. (*1*) reported a rate of agreement with the experts in identifying reversible defects in 82% (14/17) of the cases, whereas we report a 73% rate. Klein also reported a rate of identifying fixed defects in 81% (25/31) of the cases. We report an 80% rate. The major differences in these studies is that previously we used a retrospective pilot group in order to establish the quantitative criteria applied in this prospective multicenter trial.

Our results in this multicenter trial are not significantly different from those reported by Kiat et al. (*3*), using a prospective population, in which a 72% (55/76) rate of agreement with experts in identifying reversible defects and a 83% (54/65) rate in identifying nonreversible (fixed) defects was reported.

To date, there are no other reports on the accuracy of quantitative reversibility by vascular territory or myocardial segment. Our quantitative results showed that the vascular region supplied by the LCX exhibited the best agreement with experts for both reversible and fixed perfusion defects. Moreover, our results also showed that the vascular regions supplied by the LCX and the anterior wall supplied by parts of the LAD and its diagonal branches were the most sensitive for detecting reversibility while the vascular region supplied by the RCA and septal branches of the LAD were the least sensitive. These results are consistent with our normal limits file for reversibility (*1*). The significantly lower rate of detecting reversibility on the patient population of center D or compared to center C was probably due to a difference in their higher prevalence of reversible defects (51 versus 31) and the fact that the expert from center D tended to relate more subtle reversibility with significant ischemia.

We chose to analyze the regional characteristics of the quantitative reversibility methodology using vascular territories (LAD, RCA, etc.) rather than myocardial segments. This decision was based on our ultimate goal of validating (and utilizing) this approach not only in terms of how well it can predict whether a stress-perfusion defect reverses or remains fixed by delayed imaging but, more importantly, how well it can predict whether a stress-perfusion defect is associated with disease in a vessel resulting in myocardial ischemia or scar. A preliminary abstract of this application was reported by Luna et al. (*4*), who applied our reversibility algorithm to a group of patients who underwent exercise and delayed thallium myocardial imaging before and after revascularization to see if reversibility pre-revascularization could predict which defects would or would not improve post-revascularization. In that study, a small group of 25 patients yielded a 64% sensitivity for detecting ischemia (which improved or resolved after revascularization) and a 91% specificity for detecting scar. One common limitation between the study by Luna et al. (*4*) and this multicenter trial is that no analysis of late reversibility at 8–24 hr is performed, mostly due to the unavailability of these late normal limits. It has been reported that many stress-perfusion defects which do not redistribute by 4 hr will redistribute at a later time (*5,6*). Thus, analysis of reversibility at 8–24 hr could potentially be more sensitive for detecting ischemia. Since revascularization is performed on a vessel-by-vessel basis, it was advantageous to perform the analysis by vascular regions, particularly since we have objective criteria for assigning these regions. For similar reasons, we chose to use in the present analysis the expert observers' prediction of significant ischemia or scar from the visual patterns of reversibility rather than the more commonly used scoring scheme (no redistribution, partial, nearly complete, and complete redistribution). We have empirically found that different experts mean different things by partial redistribution, using it to apply to a broad range of reversibility patterns. For example, partial redistribution is used to mean some of the following observed patterns:

1. The entire stress-perfusion defect clearly improves by delayed imaging but not enough to be called nearly complete.
2. One part of the defect clearly improves by delayed imaging (such as the periphery) but the rest remains clearly fixed.
3. The defect appears different in the stress versus delayed imaging, but it has not clearly improved.

Thus, it is understandable that most of the regions of disagreement between quantitative analysis and the experts were associated with regions visually assessed as partially reversible by the experts and of 5%–14% extent of reversibility by the quantitative analysis.

The multicenter trial results presented in this report indicate that the method of quantitative analysis of reversibility previously developed by us, including the normal limits generated from the patient population at Emory, may be used clinically by other centers to assess (in an objective, standardized manner) whether stress-perfusion defects significantly reverse or remained fixed at the time of delayed imaging. This method should be of particular value to diagnosticians with limited experience in interpreting thallium tomograms as a tool for learning what degree of visual reversibility is considered to be significant using objective criteria. The accuracy of this analysis for identifying and quantifying the extent of myocardial ischemia or scar needs to be further evaluated on a large group of patients undergoing thallium-201 myocardial perfusion imaging before and after revascularization.

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