Quantitative Analysis of Stress Thallium-201 Myocardial Scintigrams: A Multicenter Trial

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Previously we validated a method for quantification of ^{201}Tl myocardial stress distribution and washout in which the patient's stress and washout circumferential profiles are compared with observed normal limits. The present study reports the results of a multicenter trial in which this method, utilizing normal limits from our institution, was employed to evaluate the presence, location, and extent of coronary artery disease (CAD). The normal limits utilized were generated from 49 patients having a low likelihood of CAD. The study population included 157 patients from four centers in the United States and Canada as well as a comparative prospective population from Cedars-Sinai Medical Center (CSMC) of 51 patients with CAD, 30 patients with normal coronary arteriograms, and 30 additional low-likelihood normals. The results in the combined centers regarding overall detection of CAD revealed a sensitivity of 84% and a frequency of test normality in the patients with low likelihood of CAD of 88%, compared to a sensitivity of 82% and true normalcy rate of 83% obtained in the prospective CSMC population. The sensitivity for detecting disease increased according to the extent of angiographic CAD in both the multicenter sites and the prospective CSMC group. Regarding localization of disease, similar sensitivities and specificities for detecting disease in individual coronary arteries were found in the multicenter sites and the prospective CSMC population. The results indicate that our method for quantifying ^{201}Tl stress-redistribution scintigrams utilizing standard normal limits can be applied at other institutions using a variety of scintillation cameras with similar accuracy to that currently obtained at our institution.

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Visual interpretation of stress-redistribution thallium-201 (^{201}Tl) scintigrams is limited by observer variability, dependence on the quality of the hard copy output, and the inability to compensate for tissue cross-talk. The need to standardize the interpretation of ^{201}Tl scintigrams, and the realization that objective criteria for the detection and assessment of the extent of disease can only come from a quantitative technique, have led to the development of several computerized approaches to the problem (*1–5*). We have previously developed and validated at Cedars-Sinai Medical Center a method for the quantification of ^{201}Tl myocardial distribution and washout (*6–8*). An important feature of our analytic approach is the comparison of each patient's results to statistically derived normal limits. These limits reflect unique normal profiles of our patient population from images obtained with a specific camera-computer system. The purpose of this study was to determine whether this quantitative imaging method including these normal limits could be applied at other institutions with different patient populations and equipment.

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MATERIALS AND METHODS

Patient Selection

Included in this trial were patients from four centers

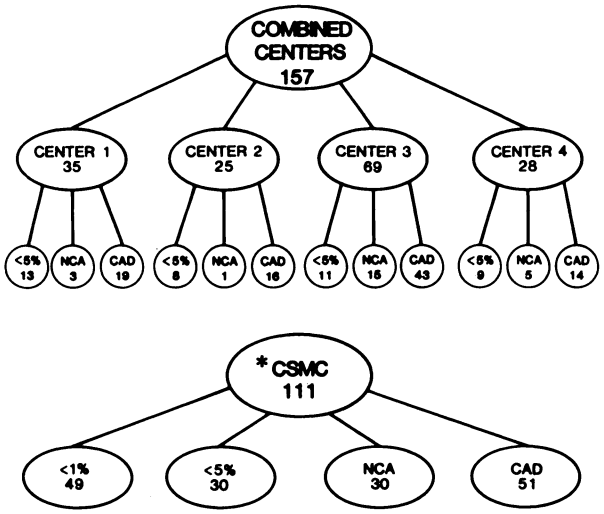

FIGURE 1
Population tree representing type and number of patients from each of multicenter sites as well as prospective Cedars population.
* Cedars-Sinai Medical Center; <1% = <1% likelihood of CAD; <5% = <5% likelihood of CAD: NCA = normal coronary arteriograms; CAD = coronary artery disease

selected from different geographical locations and having various scintillation camera systems. For purposes of comparison, a prospective population was studied from our institution (Fig. 1). The centers were as follows: the Cardiac & Vascular Diagnostic Center (affiliated with, but separate from, Cedars-Sinai Medical Center), Los Angeles, California (Center 1); Yale University School of Medicine, New Haven, Connecticut (Center 2); St. Michael's Hospital, Toronto, Ontario (Center 3); University of California at San Diego, California (Center 4).

Two groups of patients were studied from the four centers. Group A, "low-likelihood" normals, consisted of 41 patients referred for ^{201}Tl scintigraphy in an attempt to rule out the presence of coronary artery disease (CAD). These patients were classified as normals by having <5% likelihood of CAD as determined by sequential Bayesian analysis of age, sex, symptom classification, and the results of exercise electrocardiography (*9*). Group B consisted of 116 patients referred for assessment of known or suspect CAD who underwent both ^{201}Tl scintigraphy and coronary arteriography. These patients were further separated into two subgroups. The first subgroup consisted of 24 patients whose coronary arteriographic studies were considered free of significant disease: 20 had normal coronary arteriograms (NCA), two minimal intimal irregularities (up to 25% narrowing), and two mild coronary lesions (25–49% narrowing). The second subgroup consisted of 92 patients whose arteriographic findings revealed ≥50% luminal stenosis of at least one of the three major coronary arteries. Of this group of patients, 41 had historical or ECG evidence of prior myocardial infarction.

The Cedars-Sinai Medical Center prospective population was also divided into two groups as at the other centers: CSMC Group A consisted of 30 patients with <5% likelihood of CAD. Group B consisted of 81 patients undergoing ^{201}Tl scintigraphy and coronary angiography. Thirty were classified as angiographically normal, of whom 26 had normal coronary arteriograms (NCA), two minimal intimal irregularities (up to 25% narrowing), and two mild coronary lesions (25–49% narrowing). The other 51 patients had arteriographic findings of ≥50% luminal stenosis of at least one of the three major coronary arteries. These patients were chosen consecutively to reflect the proportion of patients with single-, double-, and triple-vessel disease previously observed in the entire CSMC population undergoing ^{201}Tl stress-redistribution scintigraphy and coronary angiography. Twelve of these patients had evidence of prior myocardial infarction (MI). Beta-blocking medications were withheld for at least 24 hr in all patients. From all groups, patients achieving ≤85% of maximal predicted heart rate were excluded due to the potential impact of the low heart rate achieved on myocardial washout of ^{201}Tl. Normal limits were generated from a separate population of 49 "low-likelihood normals" who were patients studied at CSMC classified as normal by having less than 1% likelihood of CAD. This group included 36 males and 13 females ranging in age from 26 to 70 yr (mean age 47 yr). The demographic and angiographic characteristics of the patient popula-

TABLE 1
Demographic and Angiographic Characteristics of Patient Population

	Group A					Group B									
						NCA					CAD				
		Mean		Sex			Mean		Sex			Mean		Sex	
Center	N	age	Range	M	F	N	age	Range	M	F	N	age	Range	M	F	PMI
1	13	49	34–63	10	3	3	53	45–68	2	1	19	62	34–74	18	1	6
2	8	38	32–43	7	1	1	51	—	1		16	45	38–56	12	4	2
3	11	45	29–64	6	5	15	49	32–63	9	6	43	52	34–65	34	9	24
4	9	57	40–76	4	5	5	66	60–69	2	3	14	56	39–78	12	2	9
Combined	41	48	29–76	27	14	24	53	32–69	14	10	92	53	34–78	76	16	41
Cedars	30	52	29–75	19	11	30	50	30–73	15	15	51	59	30–77	44	7	12

TABLE 2
Equipment and Energy Window Used by Each Center

Center	Camera	80 keV	167 keV	Collimator
1	Siemens Orbiter	20%		All purpose
2	Siemens LEM	25%		High resolution
3	GE Portable	20%		High resolution
4	Picker Dynamo	25%		General purpose Medium resolution
CSMC	Siemens LEM	25%	10%	High resolution

tion on a center-by-center basis are presented in Table 1.

Exercise and Imaging Procedure

All of the centers followed the exercise and imaging protocol utilized at our institution. The patients were stressed using a multistage treadmill test, performed according to the Bruce protocol. Exercise was maximal to at least 85% of the patient's maximal predicted heart rate or terminated only after the patient developed chest pain, exhaustion, serious arrhythmia, or hypotension. A dose of 2 mCi ^{201}Tl was injected at near maximal exercise, and the patients continued to exercise for 45–60 sec after injection. Following exercise, multiple-view myocardial scintigrams were obtained serially, beginning 6 min and then 3–6 hr after the injection of thallium. During each phase of imaging, 10-min images were obtained in the anterior, 45°, and 85° left anterior oblique (LAO) projections. For the 85° LAO position, the patients were placed with the left side up (right decuitus position). The following format was used for positioning in order to compensate for varying orientations of the heart in the chest. The exact angle for "45° LAO" imaging was determined by a film taken for 2 min between 3 and 5 min postinjection ("positioning LAO"). The angle used was that which provided the shortest dimension between the septal and posterolateral walls. This is similar to the best septal image utilized for equilibrium blood-pool scintigraphy. The actual angle used for each view was determined from the angle of the positioning view. The "anterior view" angle = "45° LAO" angle −45°. The "85° LAO angle" = +5°, with the patient in the right decubitus position (actually an 85° LAI view). The detector was positioned against the chest wall, resulting in slight cephalad orientation in most patients. The sequence of images was "position LAO," ant, 45° LAO, 85° LAO. Imaging was performed using a scintillation camera with an unshielded high- or medium-resolution collimator, and no hardware or software zooming. The scintillation camera utilized had to be able to resolve clearly the 1 cm lines of the gold-195 New England Nuclear line source. All data was collected using a 128 × 128 matrix format and stored on magnetic tape. In females, care was taken to position the left breast out of the field of view for stress and delayed imaging. Imaging was performed using various camera systems at the different centers, as listed in Table 2.

Image and Curve Processing

Each center sent the patients' raw scintigraphic data to our institution for quantitative analysis by the method previously reported and validated by our group (*6,7*). Briefly, the quantitative ^{201}Tl analysis involves the following: After pre-processing the images with an interpolative background subtraction algorithm and a nine-pointed weighted filter, maximum-count circumferential profiles are generated comprised of 60 radii spaced at 6° intervals plotted clockwise as a function of angle from 0 to 360°. The profiles are normalized to 100% and aligned so that the apex corresponds to 90°. In addition to distribution profiles, washout circumferential profiles are calculated as percent washout from stress to the delayed interval. The following improvements have been implemented in the method since the initial publication: There is less operator interaction due to a more reproducible technique for apical selection, and a more comprehensive hard copy report form (*8*) has been developed. Normal limits were generated by using the 49 normals previously studied at CSMC computing the mean and standard deviation (s.d.) for each of the 60 angular locations on a point by point basis from the stress and washout profiles for all three views. The washout normal limits varied for each patient according to the actual time between the stress and delayed views. This time was used to interpolate the normal washout circumferential profiles from 4 hr to the actual time used in a given patient based on the $T_{1/2}$ of 12.4 hr between 3 and 6 hr (*10*). Abnormal ^{201}Tl distribution and washout are identified by comparing each patient's profiles to the corresponding limits of normal. Based on our previous studies (*8*), the threshold for a perfusion defect or a washout abnormality was 2.5 s.d. below the mean. The criterion for abnormality previously developed for detection of disease requires at least three contiguous abnormal points (18° arc) on either the stress or washout profile (*6*). In addition, to be considered abnormal, the patient needs at least two abnormal 18° arcs in the combined initial distribution and washout profiles in the three views. The criteria for abnormality and threshold were chosen as those providing the best tradeoff in sensitivity and specificity as determined in a previous report (*6,8*).

Data Analysis

The computerized quantitative ^{201}Tl analysis in this multicenter trial was accomplished with the computer operator blinded to the clinical status of the patients and the angiographic results. As independent party, New England Nuclear (NEN), was responsible for collection of all results. First, the quantitative ^{201}Tl results of patients included in the multicenter trial and

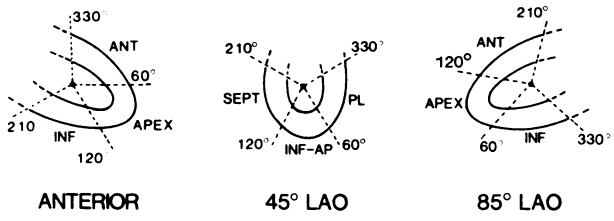

FIGURE 2
Each view is divided into three regional areas for localizing disease. All profiles are aligned in that apex always corresponding to 90° in each view

processed at our institution were sent to NEN. Then, from each of the centers the coronary arteriogram reports and all clinical and electrocardiographic data were furnished to the radiopharmaceutical company. After all data were received, NEN then released to our institution the patient classification data from which the results were tabulated and verified.

The data were analyzed to determine the ability of the quantitative ^{201}Tl approach to answer several questions regarding the presence or extent of CAD. The overall detection of CAD was determined by whether the above-noted criterion for abnormality was present in patients in each of the two groups of normals (less than 5% likelihood, normal coronary arteriograms) or the patients with significant CAD. In this latter category, the true-positive rate for overall detection of disease was further subdivided based on angiographic findings of single-vessel, double-vessel, or triple-vessel disease to determine whether the degree of angiographic involvement was related to the frequency of disease detection.

Regarding the identification of individual coronary stenoses, three regions in each view were assessed as illustrated in Fig. 2. The profile in each view which corresponded to the arc from 210–330° was considered to represent the inflow and outflow tract. The arc from 60–120° was designated as representing the apex in the anterior and 85° LAO views and to represent the inferoapical area in the 45° LAO view. These apical regions were considered for overall detection of disease, but not assigned to an individual coronary artery.

For localization of anatomic disease, the anterior wall (anterior and 85° LAO views) and interventricular septum (45° LAO view) were considered to represent the distribution of the left anterior descending (LAD) coronary artery, the inferior wall (anterior and 85° LAO views), the distribution of the right coronary artery (RCA), and the posterolateral wall (45° LAO view) the left circumflex (LCX) distribution. The involved coronary arteries were considered diseased if the major vessel or one of its major branches had ≥50% luminal diameter narrowing.

The ability of the technique to correctly identify multiple-vessel disease was also assessed. Multivessel disease was considered to be present when the major trunk or major branch of any two of the major coronary arteries had ≥50% luminal diameter narrowing.

Statistical Methods

Sensitivities and specificities between the centers and CSMC were compared using either the 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. Ninety-five percent confidence intervals for sensitivity and specificity were calculated from the binomial distribution, and in cases where appropriate, using a normal approximation.

RESULTS

Overall Detection of CAD

For overall detection of CAD, the sensitivity, specificity, and frequency of test normality in the patients with low likelihood of CAD are shown for each center in Table 3. Figure 3 compares these same variables in the

TABLE 3
Overall Detection of CAD: True-Positive and True-Negative Rates for Each Center

	True negative				True positive							
Center	<5%†		NCA‡		SV§		DV¶		TV**		Total	
1	11/13	(85)*	0/3	(0)	5/5	(100)	2/2	(100)	11/12	(92)	18/19	(95)
2	8/8	(100)	1/1	(100)	2/2	(100)	7/8	(88)	6/6	(100)	15/16	(94)
3	10/11	(91)	8/15	(53)	15/26	(58)	7/8	(88)	8/9	(89)	30/43	(70)
4	7/9	(78)	3/5	(60)	5/5	(100)	4/4	(100)	5/5	(100)	14/14	(100)
Totals	36/41	(88)	12/24	(50)	27/38	(73)	20/22	(87)	30/32	(94)	77/92	(84)

* Number in parentheses = %.
† = Low-likelihood normals.
‡ NCA = Normal coronary arteriograms.
§ SV = Single-vessel disease.
¶ DV = Double-vessel disease.
** TV = Triple-vessel disease.

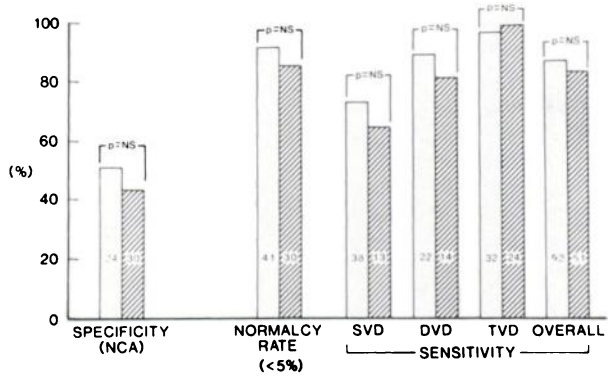

FIGURE 3
Overall detection of CAD. Comparative results between multiple centers and prospective CSMC population for single-, double-, and triple-vessel, and overall detection of CAD as well as specificity in NCA population and normalcy rate in low-likelihood population. □ Multicenter: ▨ CSMC

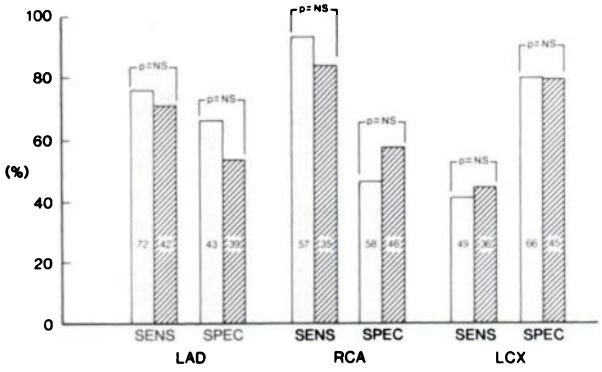

FIGURE 4
Comparative results between multiple centers and prospective CSMC population for localization of CAD in LAD, RCA, and LCX coronary arteries. □ Multicenter, ▨ CSMC

combined multicenters and the prospective CSMC populations. The results reveal a lower normalcy rate in the NCA population as compared to the <5% likelihood population (50% compared with 88%, respectively) in the combined multicenters as compared with 43% and 83%, respectively, in the prospective CSMC population (p = N.S. between multicenter and CSMC centers). The sensitivity of the program for overall detection of coronary disease was 84% in the combined multicenters as compared with 82% in the prospective CSMC group (p = N.S.). The sensitivity for overall detection of CAD increased according to the angiographic extent of disease: In the multicenter trial patients, the sensitivity was 73, 87, and 94% for detecting CAD in single-, double-, and triple-vessel disease [(SVD), (DVD), (TVD)] patients respectively, compared with 62, 79, and 96% in the prospective CSMC group (p = N.S. between multicenter and CSMC centers). Patients with single-vessel disease comprised a larger proportion of Center 3's CAD population (58%), which probably explains the decreased overall sensitivity for disease detection of that center.

Localization of Disease

With respect to localization of individual coronary stenoses, the sensitivity and specificity for disease in each of the three major coronary arteries are shown in Table 4 for the individual centers and are compared in Fig. 4 between the combined multicenters and the CSMC prospective group. There was no significant difference between the combined multicenter trial and CSMC prospective data for sensitivity or specificity of any vessels. The results indicate that the highest sensitivity of the program for localization of disease is obtained in the RCA and the highest specificity in the LCX.

The data regarding correct identification of patients with multivessel disease are shown in Table 5. The sensitivity for correct identification of multivessel disease was 71% in the multicenter trial compared with 79% in the CSMC prospective population (p = N.S.). The specificities for correct identification of the absence of multivessel disease were 57 and 63% for the multicenter trial and CSMC prospective populations, respectively (p = N.S.).

DISCUSSION

We have previously shown that the quantitative method presented in this paper provides an accurate and objective approach for the interpretation of stress-redistribution ^{201}Tl myocardial scintigrams at our institution (CSMC). This multicenter trial evaluation was undertaken to determine whether this quantitative

TABLE 4
Localization of CAD: Sensitivity and Specificity for Each Center

Center	LAD				RCA				LCX			
	Sens.		Spec.		Sens.		Spec.		Sens.		Spec.	
1	13/19	(68)	2/3	(67)	13/14	(93)	1/8	(13)	4/13	(31)	6/9	(67)
2	13/14	(93)	2/2	(100)	11/11	(100)	1/5	(20)	7/9	(78)	2/7	(29)
3	18/28	(64)	19/30	(63)	18/23	(78)	20/35	(57)	8/19	(42)	34/39	(87)
4	10/11	(91)	6/8	(75)	9/9	(100)	5/10	(50)	1/8	(13)	11/11	(100)
Total	54/72	(75)	29/43	(67)	51/57	(89)	27/58	(47)	20/49	(41)	53/66	(80)

TABLE 5
Sensitivity and Specificity for Correct Identification of Multivessel CAD for Each Center

	Center 1		Center 2		Center 3		Center 4		Combined		CSMC	
Sensitivity*	8/14	(57)	11/14	(79)	13/17	(76)	7/9	(78)	39/54	(72)	30/38	(79)
Specificity†	1/8	(13)	1/3	(33)	26/41	(63)	7/10	(70)	35/62	(57)	27/43	(63)

* Sensitivity = No. of patients with multivessel quantitative ^{201}Tl abnormalities/no. of patients with multivessel disease.
† Specificity = No. of patients without multivessel quantitative ^{201}Tl abnormality/no. of patients with NCA or 1-vessel CAD.

method could be employed with the same success at institutions from other geographical locations using differing scintillation camera systems.

With respect to sensitivity (in the patients with CAD), specificity (in the patients with NCA), and frequency of normalcy (in the patients with a <5% likelihood of CAD), the results of the multicenter trial were similar to the CSMC results both on an individual site and combined basis (Table 3 and Fig. 3). Additionally, it is observed that as the angiographic extent of disease increases, a corresponding increase in sensitivity of disease detection was achieved.

Regarding detection of disease in individual coronary arteries, similar sensitivities and specificities were again obtained in the comparison of the results of the multicenter and CSMC centers. In all centers the highest sensitivity for the test was obtained when evaluating the RCA and LAD, and in general the highest specificity was obtained for the LCX. The principal reason for highest specificity in the LCX territory is likely that this is the only myocardial territory with very little overlap in planar imaging with other vascular distributions. The lowest sensitivity for this vessel is related to the fact that this territory is examined "en face," and in only one view, whereas that of the RCA is examined in a perpendicular fashion from two views and that of the LAD in perpendicular (anterior and 85° LAO views) and "en face" (45° LAO) manners. A technical factor also relates to these different sensitivities and specificities. Our previous work (*8*) had demonstrated that the widest range in all three views between the mean and lower limit of normal occurs in the region between 330 and 60° on the 45° LAO view, which is the only zone where the LCX territory is sampled. This lower threshold for abnormality results in a higher specificity and lower sensitivity for the test in this area.

The program's accuracy is correctly identifying patients with or without multivessel disease was found to be not significantly different in the multicenter or prospective CSMC populations (Table 5).

There are several statements concerning normal and abnormal populations which can be derived from these results. It appears that standard normal limits derived in one laboratory with a single camera-computer system can be used for detection of CAD in different locations with differing equipment. This is reflected in the fact that similar sensitivities for disease detection were obtained both overall and according to extent for CAD. The overall sensitivity in a given center, however, will depend on the prevalence of extensive disease in that particular site. For example, if the CAD population being studied is comprised mostly of single-vessel disease patients, then the overall sensitivity achieved would likely be in the 60–70% range. If triple-vessel disease is predominant, then a 90% sensitivity for overall CAD detection would be expected. It is important to emphasize that the success of the standard (CSMC) normal limits approach requires the use of standardized acquisition and processing protocols. Imaging for different times (for example, 8 min rather than 10 min) or with different sequences of views (for example, 45° LAO first) would be expected to reduce the accuracy of this approach.

Two different normal populations were evaluated in this paper, patients with a low likelihood of coronary artery disease and patients with normal coronary arteriograms. These two populations represent two distinctly different limits of normalcy (*11*). The quantitative ^{201}Tl analysis was highly specific in the low-likelihood normals but had much lower specificity in the patient group with NCA. We have previously reported this falloff in specificity in the NCA group as observed in our patients undergoing exercise radionuclide ventriculography (*12*) as well as stress-redistribution ^{201}Tl scintigraphy (*13*). The reason for the marked decline in specificity of exercise nuclear cardiologic procedures in the patients with normal coronary arteriograms has been a subject of considerable interest in our institution (*12*). The principal factor which appears to be operating to reduce specificity is post-test referral bias, a bias in the patient population which naturally follows the widespread clinical acceptance of a test. In the case of ^{201}Tl testing, patients who have normal stress-redistribution studies are considered unlikely to have coronary artery disease, and even if coronary disease is present, likely to have a good prognosis (*14–16*). Thus, in clinical practice, patients with suspected coronary artery disease who have normal ^{201}Tl studies are preferentially selected not to have coronary angiography. Patients with abnormal ^{201}Tl studies, in contrast, are preferentially referred for catheterization. Over time, if measured only in the catheterized patients following this referral bias, apparent specificity will be far lower than the true specificity of the test as could be measured

from unbiased populations. With exercise radionuclide ventriculography, we have recently reported this "post-bias" specificity to be as low as 21%, and with ^{201}Tl imaging to be as low as 40% (*13*). In the current multicenter trial, the specificity of the quantitative ^{201}Tl analysis was in this same range, both in the multicenters and the prospective CSMC populations. If only positive test responders were catherized, this referral bias in theory would ultimately lead to a 100% sensitivity for a test and a 0% specificity, regardless of the true sensitivity and specificity of the modality. It is important to realize that in any given clinical site in which this referral bias is operative, it may be impossible to evaluate the true specificity of a study which leads to catherization (such as quantitative thallium analysis) by using patients with normal coronary arteriograms.

The fact that, given this post-test referral bias, a substantial proportion of NCA patients have abnormal ^{201}Tl scintigraphy tests can be explained by a variety of pathophysiological mechanisms. Although technical artifacts with ^{201}Tl imaging may play a role in some patients, it is likely that most patients with ^{201}Tl abnormalities but normal coronary arteriograms do have true perfusion defects. In this regard, Vogel and associates found perfusion abnormalities by quantitative digital subtraction coronary angiography in 100% of patients with abnormal ^{201}Tl studies and normal coronary arteriograms (*17*). The organic basis of the discrepancy between ^{201}Tl studies and visually interpreted coronary arteriograms is not always known. A great deal of interest has been placed in the inaccuracy of visual interpretation of coronary arteriography (*18–20*). Furthermore, conditions such as vessel overlap (*21,22*) or diffuse atherosclerosis (*23,24*) can result in underestimation of the severity or even false-negative coronary arteriograms (*23–26*). Additionally, patients might have exercise-induced coronary artery spasm (*27*) or occult cardiomyopathy (*28*).

These limitations in currently studied NCA patients led to our choice of patients with a low likelihood for CAD as the basis for our normal limits and as a group in whom the true normalcy rate of our quantitative thallium analysis could be assessed. We chose this group rather than normal volunteers for two reasons. First, this represented a potential normal population in whom the ^{201}Tl study was being performed on a clinical basis, avoiding the difficulties inherent in recruiting normal volunteers for the study. Second, the low-likelihood approach allowed for evaluation of patients in an older age group and with more symptoms than are found in normal volunteers. Thus, the low-likelihood normals are closer to the kinds of patients being evaluated for CAD by ^{201}Tl testing than are young, healthy volunteers. In our study, a high true normalcy rate was found for the low-likelihood normals, both in the multicenters as well as the prospective CSMC population.

The original publication concerning this quantitative method (*7*) reported that a sensitivity of 93% and a normalcy rate of 91% could be obtained with this technique. This current paper is reporting a sensitivity of 82% and a normalcy rate of 83%. The different extent of disease distributions within the two prospective CSMC populations are likely responsible for the change in sensitivity. The original manuscript dealt with a prospective population comprised of 7/45 (16%) SVD, 11/45 (24%) DVD, and 27/45 (60%) TVD. In contrast, the current prospective population was comprised of 13/51 (25%) SVD, 14/51 (28%) DVD, and 24/51 (47%) TVD patients. The decrease in the normalcy rate (in the low-likelihood normals) is likely due to differences in the "normal patients" being analyzed. This paper studied patients who had a <5% likelihood of CAD, whereas the previous paper analyzed patients with <1% likelihood of CAD.

The primary goal of this investigation was to evaluate the "universal" application of normal limits. To eliminate interobserver variability from this evaluation, a single operator was responsible for all of the processing. An additional multicenter trial has been established in an attempt to evaluate the effect various computer operators have on the accuracy of this approach. This ongoing trial currently is comprised of 13 different sites involving computers from three different manufacturers. Preliminary results of these unpublished studies involving 122 CAD, 20 NCA, and 30 patients with a low likelihood of CAD suggest that the accuracy of this technique remains the same even when various computer operators process the data.

The multicenter trial results presented here indicate that the standard normal limits derived from our institution may be used successfully to quantitate ^{201}Tl stress-redistribution scintigrams acquired at centers located in different geographic regions and using differing camera systems. The accuracy in the multiple centers is as high as we are currently obtaining in our own population. The approach provides objective analysis of the presence and location of CAD, complementing subjective visual analysis.

Future Directions

Currently, the program considers regions as simply normal or abnormal. In the future, determination of the degree by which a given region falls below normal will allow for a probabilistic statement regarding the likelihood for abnormality in a given region. Furthermore, this approach will allow for assessment of the severity of the underlying perfusion deficit, potentially providing greater information regarding severity of CAD and prognosis than is currently available from the dichotomous classification of results. Preliminary work in this area has been conducted by Bassir et al. at our institution (*29*). Additionally, it will be necessary to develop

separate normal limits for rest-redistribution ^{201}Tl studies (*30*) as well as studies with alternative stimuli for increased myocardial blood flow (e.g., dipyridamole testing). It would not be expected that the stress-redistribution normal limits could be applied in these other forms of imaging. Regarding localization of disease, refining the model for predicting the angiographic correlates of quantitative perfusion abnormalities requires future development. In its current form, the program does not differentiate ischemic compared with infarcted tissue. The algorithm addressing this issue by analyzing the presence or absence of redistribution is currently in the later stages of in-house validation. Finally, since tomography shows promise in increasing the ability for localizing disease and providing an estimate of the percentage of abnormal myocardium, it will be important to apply the quantitative technique to tomographic ^{201}Tl scintigrams. Our preliminary work on quantitative tomography was recently reported in the *Journal* (*31*), and is currently undergoing the stage of in-house prospective validation.

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