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Using Quantitative Coronary Arteriography to Redefine SPECT Sensitivity and Specificity

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ABSTRACT **Previous studies looking at the sensitivity, specificity, and predictive accuracy of single photon emission computed tomography (SPECT) have been based upon the results obtained by visual interpretation of coronary arteriograms. Since the results of visual and quantitative determination of percent diameter stenosis have been shown to be statistically different, the results obtained from SPECT imaging when compared to quantitative methods for assessing coronary artery disease would be expected to provide a more correct assessment of sensitivity, specificity, and predictive accuracy. To determine the "true" sensitivity, specificity, and predictive accuracy of SPECT in diagnosing coronary artery disease, this study compared the results obtained in 44 SPECT images (20 thallium and 24 teboroxime) with the results obtained when quantitative coronary arteriography was used to analyze the coronary arteriograms. These 44 cases were then compared against 8 different definitions of significant coronary artery disease, varying from 30 to 80%, to yield 352 comparisons.**

The maximum specificity and predictive accuracy was found when 45% diameter stenosis was used to define the presence or absence of significant disease. At 45% diameter stenosis, SPECT imaging demonstrated an 86% sensitivity, 78% specificity, and 94% predictive accuracy with only 6% false positives. In 100% of the cases where 45% diameter stenosis was used to define the presence of disease and exercise failed to demonstrate ST segment changes or angina, when SPECT imaging demonstrated a perfusion defect(s), quantitative coronary arteriography agreed with SPECT imaging results. Regardless of whether 45, 50, or 55% diameter stenosis was used to define significant disease, excluding one equivocal (47% diameter stenosis) result, when exercise testing demonstrated a positive result and SPECT demonstrated no perfusion abnormalities, quantitative coronary arteriography revealed no significant coronary artery disease.

Key words: Single photon emission tomography, teboroxime, PET

INTRODUCTION

Considerable controversy has occurred over the proposed sensitivity and specificity of both single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging. The use of newer technetium tracers and rubidium-82 have added to the debate. However, despite several reports on sensitivities and specificities dating from the mid-1970s [1–3] through the mid-1980s [4,5], and studies looking at the results of intravenous pharmacologic stressors [6], the discussions to date have focused on the visual interpretation of coronary arteriograms as the principal method for determining the presence or absence of significant coronary artery disease, against which SPECT and PET imaging are compared.

In a recently published study [7], Fleming et al. looked at SPECT imaging comparing thallium-201 and technetium-99m teboroxime. When results obtained using the two nuclides were compared with results obtained using automated quantitative coronary arteriography (QCA), teboroxime while better than thallium, was not statistically better. The same study, however, demonstrated a statistical difference ($P < 0.005$) between the two tracers when compared with the "visual" interpretations of coronary arteriograms. This pointed out a major problem when using visual interpretations of coronary arteriograms to make comparisons between nuclides, or imaging modalities. Furthermore, it has been shown [8] that there are patterns in visual reporting of coronary arteriograms that can lead to erroneous conclusions

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about the number of coronary arteries "truly" diseased, the results of angioplasty, and the relative merit of nuclear tracers and imaging modalities.

In order to remove the biasing results of visual interpretation of coronary arteriograms, this study looked at the results of 44 SPECT images, which were compared with results obtained from QCA. These 44 images were then compared against 8 arbitrarily determined definitions of "significant" percent diameter stenosis to determine the "true" sensitivity, specificity, and predictive accuracy of SPECT imaging. These eight arbitrary definitions were 30, 40, 45, 50, 55, 60, 70 and 80% diameter stenosis, resulting in 352 comparisons (44 images × 8 definitions of disease). The predictive accuracy was then analyzed using Bayes' theorem. Finally, the results of exercise treadmill testing were compared with the results obtained by SPECT imaging, and flow sheets developed for 45, 50, and 55% diameter stenosis respectively.

METHODS

Study population

Subjects were enrolled if they were suspected of having coronary artery disease, and they and their private physicians agreed to participation in the study. All patients signed a consent form approved by the Institutional Review Board for the Protection of Human Subjects. The average age was 56.6 ± 11.2 years, with 62% of the subjects being male. Patients who had a history of cardiomyopathy, severe valvular disease, unstable angina, recent myocardial infarction, morbid obesity, or who were pregnant were not eligible for enrollment into the study.

Coronary arteriograms and quantitative coronary arteriography

All subjects underwent conventional coronary arteriography via a Judkins approach. The images were obtained using a Philips Poly Diagnost C/Lateral ARC system with pincushion and magnification correction as previously described by Brown et al. [9]. The films were analyzed by a DEC VAX 11/780 computer and Tektronics 4207 graphics computer as previously described [7]. The percent diameter reduction in the most severely stenotic region of each of the three major coronary arteries (including branches) was reported as the percent diameter stenosis for that artery.

Exercise protocol

Each of the 44 SPECT images were acquired after individuals completed a Bruce protocol exercise treadmill study. Exercise was stopped after subjects reached 85% of their maximum predicted heart rate or when fatigue occurred. Exercise results were reported as positive if there was an ST segment depression of 1 mm, or if the subject had anginal symptoms, which were relieved with sublingual nitroglycerin. All regions of ST depression had to be recorded in two contiguous leads. Furthermore, each patient with a 1-mm ST segment depression subsequently developed 2-mm depression before stopping exercise.

SPECT imaging

Each SPECT image was obtained after the injection of either thallium-201 or technetium-99m teboroxime. SPECT imaging protocols for both thallium and teboroxime are shown in Figure 1. Image reconstructions were done in conventional short, horizontal, and vertical-long axis views. Figure 2A demonstrates the vertical long axis images for both stress and redistribution images using thallium. Figure 2B reveals vertical long axis images for teboroxime at stress and rest.

Images were analyzed by two observers blinded to clinical and QCA data. Perfusion of regions were scored on a continuous scale from 0 to 5, where 0 equaled "normal"

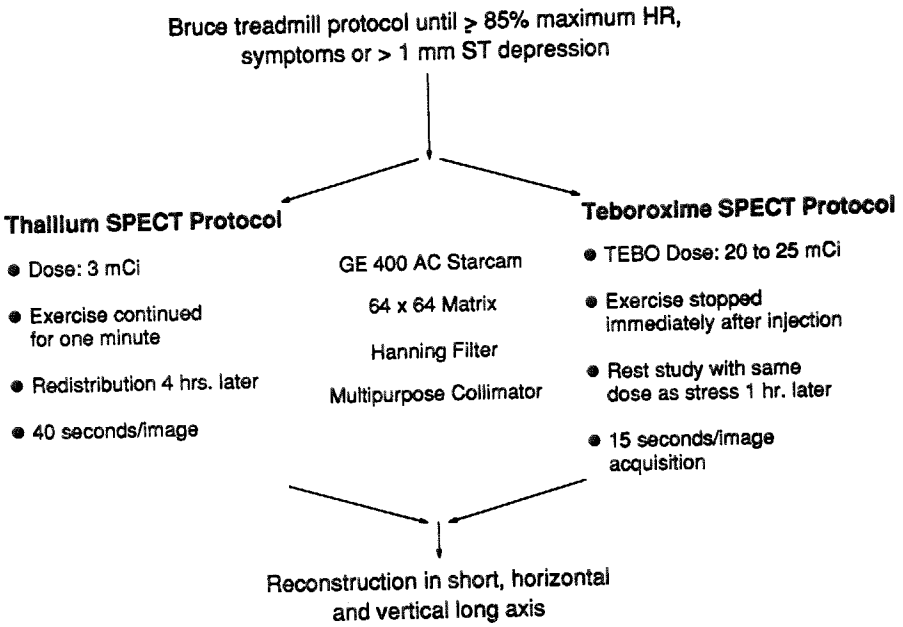

Fig. 1. Exercise and SPECT protocol. The **left side** of the diagram explains the approach used for those SPECT studies where thallium-201 was used. The **right side** of the diagram compares the method for performing teboroxime SPECT imaging with exercise treadmill testing.

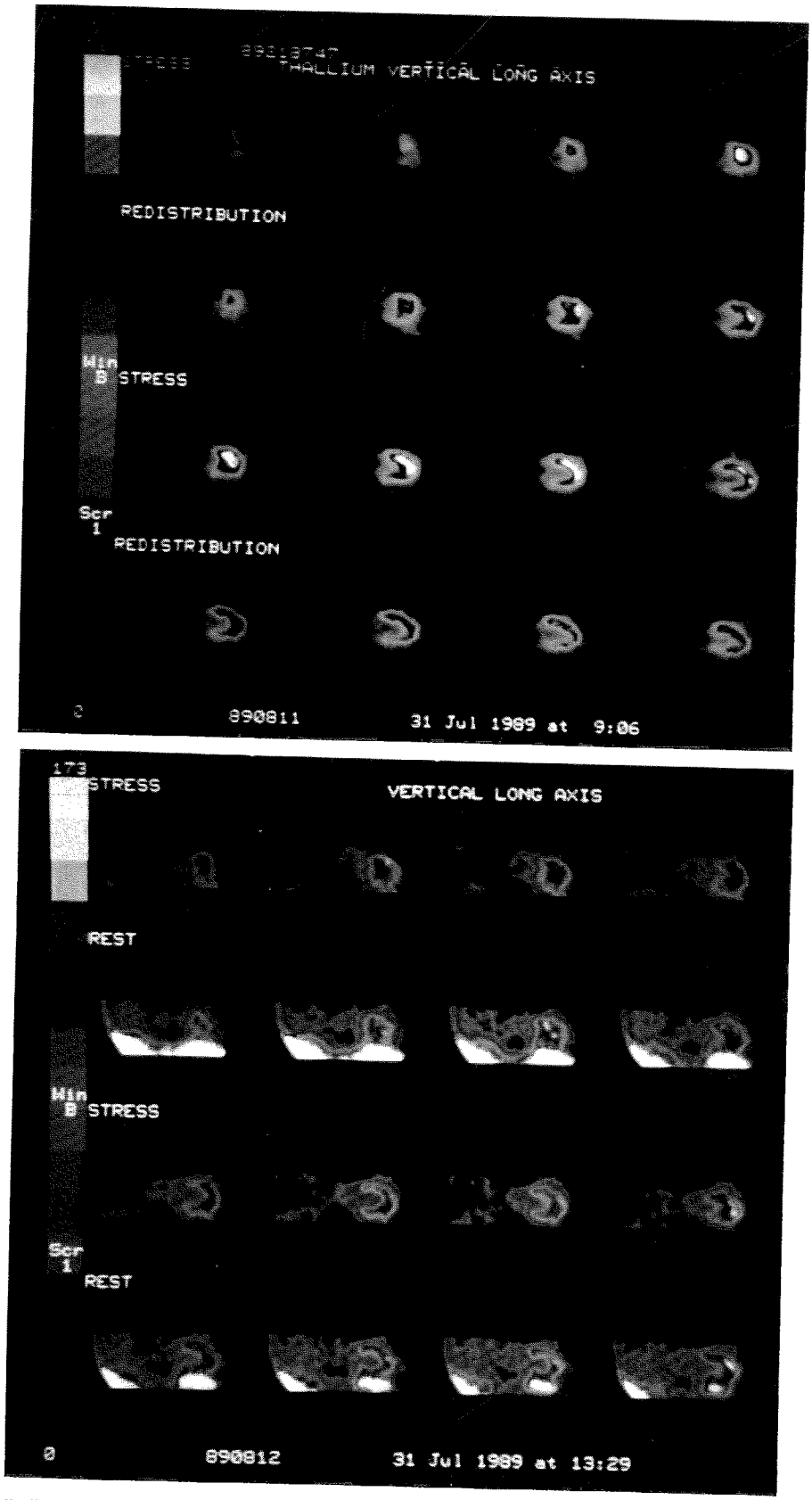

Fig. 2. **A.** Stress and redistribution SPECT images of thallium-201 using reconstructed vertical long axis views. The images are graded qualitatively **(on a gray scale)** on a continuum from regions of highest tracer uptake (white), to regions of lowest uptake (black). **B.** Stress and rest SPECT images of technetium-99m teboroxime using reconstructed vertical long axis views. The images are quantitatively graded in a manner identical to the thallium images in **A.** Note the hepatobiliary uptake of teboroxime on the rest images associated with the relatively short biologic half-life of 5.3 min.

perfusion, 1 represented "probably normal" perfusion, 2 was "equivocal," and 3 to 5 defined "mild," "moderate," and "severe" defects. Eight regions were analyzed per image including anterior, anterolateral, posterolateral, posterior, inferior, posteroseptal, anteroseptal, and apex. Averaged values from two observers ranging from 0 to 2 were reported as not significant for perfusion abnormalities. Mean values from 3 to 5 were reported as remarkable for the presence of perfusion deficits. Segments were matched to the region of arterial distribution as described previously [7].

Order of testing

The order of QCA and SPECT imaging occurred randomly to prevent any biasing of entry into the study. Studies were completed without any intervening changes in the patients condition or electrocardiogram.

Statistical analysis

SPECT sensitivity and specificity were determined for each of the 44 images using different levels of percent diameter stenosis, ranging from 30 to 80%, to define the presence of significant disease. Chi-square analyses were done to determine differences in SPECT imaging results at 45, 50, and 55% diameter stenosis. The predictive accuracy was subsequently determined for 45, 50, and 55% diameter stenosis using Bayes' theorem. Three flow sheets demonstrating the results obtained through a combination of treadmill testing and SPECT imaging for 45, 50, and 55% diameter stenosis were then developed.

RESULTS

Exercise results

As outlined in Table I, approximately 48% of the individuals demonstrated significant ST segment changes during or after exercise. No individuals demonstrated ST segment changes "only" after exercise and no dysrhythmias occurred. Angina occurred in 43% of subjects and was relieved with one (0.4 mg) or two sublingual nitroglycerin. The maximum rate-pressure product and heart rate achieved were comparable to those reported in other studies. All subjects exercised to fatigue or symptom limitation, and no one was stopped at the arbitrary 85% of maximum predicted heart rate.

Interobserver variability

The variability noted between observer interpretation of SPECT imaging is noted in Table II, with results listed for both stress and rest/redistribution readings. As previously reported [7], there are no statistically significant differences in the ability of observers to read SPECT thallium and SPECT teboroxime images. These results demonstrate complete agreement, or a difference of only one observer score (on a scale of five) in approximately 80% of the segments read. Observers agreed within two scores in approximately 90% of the segments. As pointed out in Table II, there were no differences in interobserver variability scoring of stress versus rest/redistribution images.

TABLE I. Results of exercise testing in 44 SPECT studies

Maximum heart rate (beats/min)	134 ± 13.5
Rate-pressure product[a]	22,710 ± 4,018
Exercise ECG response	
Positive (%)	21 (47.7%)
Negative (%)	23 (52.3%)
Angina during exercise (%)	19 (43.2%)

[a]Maximum systolic blood pressure × maximum heart rate. Values are mean ± standard deviation.

TABLE II. Interobserver variability in SPECT image interpretation

Interobserver difference[a]	Stress	Rest redistribution	Statistical difference
0 (no difference)	58%	59%	NS[b]
1	21%	21%	NS
2	10%	10%	NS
3	4%	4%	NS
4	4%	4%	NS
5	3%	2%	NS

[a]Observer scores differed from 0 to 5 based upon a 0 to 5 scale of severity of perfusion defects.
Abbreviations: NS, not statistically significant.

TABLE III. SPECT sensitivity and specificity as determined by varying percent diameter stenosis necessary to define significant coronary artery disease

	Percent diameter stenosis							
	30	40	45	50	55	60	70	80
Percent sensitivity	77	81	86	90	93	93	100	100
Percent specificity	60	71	78	69	59	59	57	44

SPECT sensitivity and specificity

The calculated sensitivity and specificity of varying levels of percent diameter stenosis are reported in Table 3. When 30% diameter stenosis was used as the arbitrary definition of disease, SPECT sensitivity was 77% and specificity was 60%. Sensitivity increased as the definition of a significantly diseased vessel increased from 30 to 80% diameter reduction. Sensitivity reached 90% when stenosis was defined as 50% diameter stenosis or greater. The specificity reached a maximum of 78%, when 45% diameter stenosis was used to define significant disease. In this case, seven of nine individuals defined as free of significant disease by QCA were free of perfusion abnormalities. These results are depicted in Figure 3.

The results of chi-square analysis shown in Table IV demonstrate no statistical differences between the results obtained by defining disease as either 45 or 50% diameter stenosis and no differences between results obtained by defining disease as either 50 or 55% diameter stenosis. However, there was a statistical difference ($P < 0.025$) between the sensitivity and specificity obtained by SPECT when disease was defined as 45 versus 55% diameter stenosis. This was due to the significantly higher specificity associated with 45% diameter stenosis. When disease was defined as being present with a 45% diameter narrowing or greater, there were 9 cases by QCA where disease was absent and SPECT imaging reported normal perfusion in 7 of these 9. At 50%, there were 13 cases free of disease, with 9 having normal studies. For 55% diameter narrowing, there were 17 cases free of significant disease, with 7 having normal SPECT perfusion images.

SPECT predictive accuracy

As shown in Table V, when the prevalence of disease is taken into account, Bayes' theorem can be applied to the

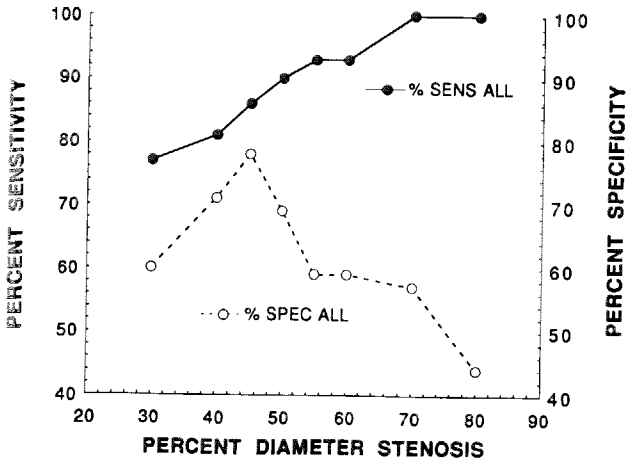

Fig. 3. Comparison of percent sensitivity and specificity to percent diameter stenosis. The percent sensitivity (●) and percent specificity (○) are plotted against percent diameter stenosis. Percent diameter stenosis represents a varying definition of significant disease e.g., at 30% diameter stenosis, the results of SPECT imaging provides a sensitivity of 77% and a specificity of 60%. When the definition of significant disease is changed to 70% diameter stenosis, the reported sensitivity and specificity of SPECT imaging become 100% and 57%, respectively. Note that the best specificity occurs at 45% diameter stenosis.

results obtained in this study, and sensitivity, specificity, and predictive values for SPECT imaging can be determined based upon the results of quantitative analysis of coronary arteriograms. From this, the number of false positives obtained using SPECT imaging can be determined. The highest predictive value, like specificity, was obtained when disease was defined as 45% or greater reduction in diameter. This resulted in a 6% false positive rate. As expected, the number of false positives increased as the percent diameter stenosis used to define significant disease increased.

Treadmill testing and SPECT

From this study, three flow sheets were developed (Figs. 4–6) which demonstrate the results obtained from both the treadmill and SPECT components of the study. Each figure represents a different result using the arbitrary definitions (45, 50, or 55% diameter stenosis) of significant disease.

Figure 4 shows the results of treadmill and SPECT imaging studies in which significant disease was defined as 45% diameter stenosis or greater. In 92% of the cases, where both treadmill and SPECT studies were positive, QCA indicated anatomic disease. In only one case, where the treadmill test was positive and the SPECT image was equivocal, did QCA indicate disease. In that case, the lesion had a 47% diameter stenosis in the anterior descending artery. In all cases where the treadmill study was negative and the SPECT image revealed a perfusion defect, anatomic disease was present.

In Figures 5 and 6, the results are shown for treadmill and SPECT studies in which significant disease was defined as 50 and 55% diameter stenosis, respectively. In 88% of the cases where treadmill and SPECT studies were positive, anatomic disease was present. In 100% of the cases where the treadmill was positive and the SPECT image was normal, significant coronary disease was absent. The presence of a positive finding during the exercise portion of the study added no additional information. When the treadmill study revealed no electrocardiographic changes and/or there were no anginal symptoms, and the SPECT image demonstrated a perfusion defect, QCA detected anatomic disease in 88% (Fig. 4) and 75% (Fig. 5) of the cases.

TABLE IV. Chi-square values of different sensitivity and specificity

	50% diameter stenosis	55% diameter stenosis
45% diameter stenosis	2.92 (P = NS)	9.97 ($P < 0.025$)
50% diameter stenosis	NA	3.02 (P = NS)

Abbreviations: NA, not applicable; NS, not statistically significant.

DISCUSSION

Previous discussions focusing on the sensitivity and specificity of SPECT (including those comparing it to PET imaging) have looked at results obtained from comparisons with visual reporting of disease from arteriograms. However, as previously demonstrated [8], the results of visual estimates follow patterns that can result in potential errors in interpreting results obtained with nuclear images. The use of reproducible and accurate methods to measure coronary arteriograms is one way in which these errors may be reduced and was used in this study to determine the "true" sensitivity, specificity, and predictive accuracy of SPECT imaging. Another recent study [10] pointed out that the use of electrocardiographic criteria may be of "minimal" value in the clinical determination of myocardial area at risk and can be influenced by multiple factors, giving "large" standard errors.

In this current study, 352 comparisons (44 SPECT images × 8 different definitions of significant disease) were

TABLE V. Determination of predictive value of SPECT using varying percent diameter stenosis to define significant disease

	Percent prevalence of disease present by QCA	Percent SPECT sensitivity	Percent SPECT specificity	Predictive value of SPECT study by Bayes' theorem	Number of false positives per 100 studies
45% diameter stenosis[a]	80	86	78	0.94	6
50% diameter stenosis[a]	73	90	69	0.89	11
55% diameter stenosis[a]	61	93	59	0.78	22

[a]Percent diameter stenosis as defined by quantitative coronary arteriography (QCA).

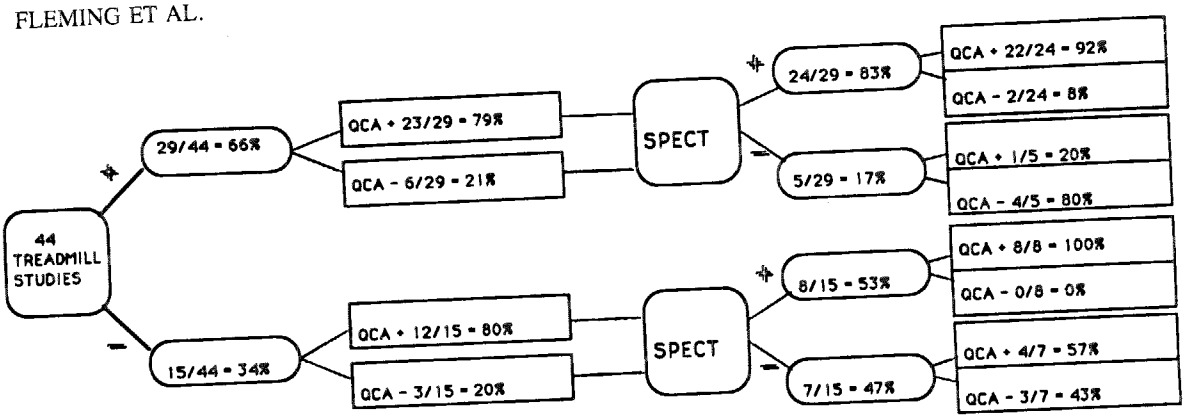

Fig. 4. Results of exercise treadmill testing and SPECT imaging. The results depicted in this diagram reveal the results of exercise treadmill and SPECT studies, using 45% diameter stenosis as the definition of significant anatomic disease. Notice that, with the exception of one equivocal study, if SPECT and treadmill studies had varying results, then results of QCA were consistent with results obtained by SPECT imaging.

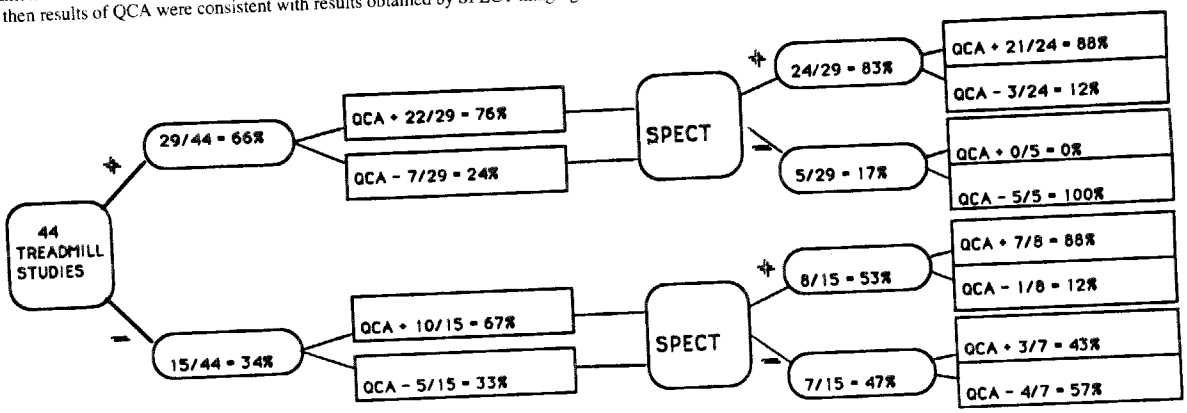

Fig. 5. Results of exercise treadmill testing and SPECT imaging. The results depicted in this diagram reveal the results of exercise treadmill and SPECT studies, using 50% diameter stenosis as the definition of significant anatomic disease.

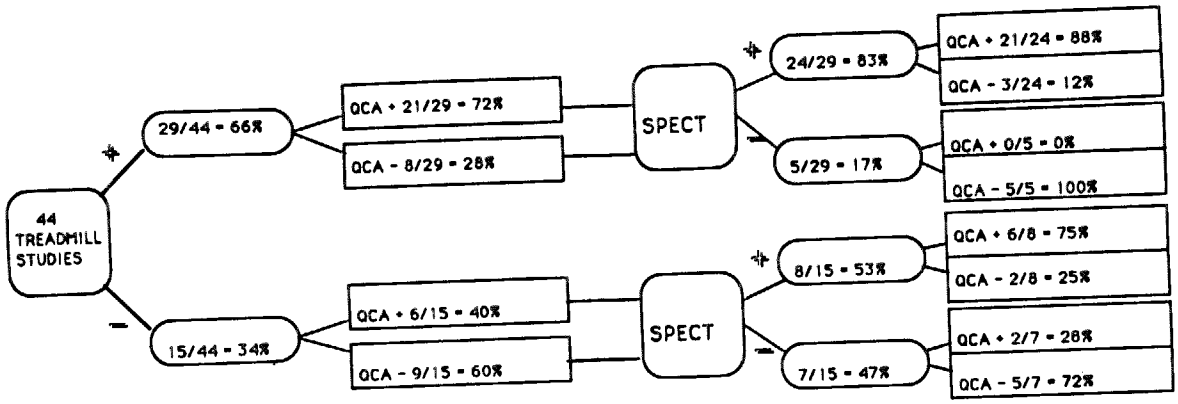

Fig. 6. Results of exercise treadmill testing and SPECT imaging. The results depicted in this diagram reveal the results of exercise treadmill and SPECT studies, using 55% diameter stenosis as the definition of significant anatomic disease.

made with results obtained from coronary arteriograms as analyzed by QCA. The definition of significant coronary artery disease by percent diameter stenosis was varied to determine the impact of results obtained by SPECT perfusion imaging studies over a wide range of arbitrarily defined disease. The maximum predictive value and specificity occurred when significant disease was defined as a 45% or greater reduction in arterial diameter. With the exception of one equivocal study, using 45% diameter stenosis as the definition of significant disease, when results of the exercise component of the study and the SPECT perfusion image disagreed, QCA always agreed with the results obtained with SPECT imaging. The result of a positive exercise stress test adds little if any benefit to the study, and increases the

potential risk to the patient, when compared to pharmacologic stressors.

The results obtained using 45% diameter stenosis as the definition of disease were not statistically different from those obtained using 50% diameter stenosis, but were different ($P < 0.025$) from results obtained using 55% diameter stenosis. This may in part be due to the smaller number of normals present when disease was defined as 45% diameter stenosis. It may, however, also represent the "true best" definition for the ability of SPECT imaging to provide specificity and predictive accuracy. The resultant predictive value of the SPECT images was 94%, with a 6% false-positive rate. The number of false positives increased to 11 and 22% when significant disease was defined as 50 and 55% diameter stenosis respectively.

CONCLUSIONS

The use of arbitrary definitions can sometimes be confusing, and it may be better to remind ourselves that coronary atherosclerosis is a continuum, not a finite phenomenon. However, in the realm of clinical decision-making, some point is frequently necessary at which action must be taken or disease is considered to be "significant." Since decisions about patient care, as well as comparisons of imaging modalities and nuclear tracers, are based upon such definitions of disease, we must be certain of the accuracy and reproducibility of these terms.

This study used the accuracy and reproducibility of QCA to redefine the sensitivity, specificity, and predictive accuracy of SPECT imaging. This study suggests that the best results for SPECT imaging occurred when disease was defined as the presence of a lesion with 45% diameter stenosis or greater, and that such a definition gives SPECT imaging a 94% predictive accuracy. SPECT imaging may play a more important role in the screening of individuals with "moderate" coronary artery disease, since its highest predictive accuracy with least false negatives appears to be in the 45 to 50% diameter stenosis range in this study. A comparison study using a quantitative method to assess coronary artery disease is necessary for comparing other nuclides or other imaging modalities. Further work needs to be done including sensitivity, specificity and predictive accuracy of SPECT using pharmacologic stressors, IPPA, and PET imaging.

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