Scintigraphic quantification of myocardial ischemia: a new approach

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ABSTRACT This study was undertaken to develop a quantitative scintigraphic measurement of ischemia. We recorded $^{201}$TI scintigrams by the seven-hole tomographic technique immediately after exercise and 3 hr later in 15 normal subjects with a low likelihood of coronary disease and in 55 catheterized patients with chest pain. Circumferential profiles of the initial and 3 hr tracer distribution and of the 3 hr clearance rate were generated for each of three left ventricular sections. A circumferential profile of the 3 hr clearance rate (initial counts minus 3 hr counts divided by initial counts, expressed as percent) was also generated for each of these sections. A scintigraphic ischemic score (SIS) was then derived by summing for the three sections the area (in arbitrary units) between the exercise and 3 hr profiles and the area by which the clearance profile fell below the lower limits of normal for clearance derived from the normal subjects. This summed area was then normalized for the level of stress by dividing by the product of the exercise duration (in minutes) and the fraction of age-predicted maximum heart rate achieved. This SIS was above the 95% confidence limits derived from the normal subjects in 44 of 46 (96%) patients with the significant coronary disease and in only one of nine with less than a 50% obstruction. The SIS was $52 \pm 58, 233 \pm 220, 427 \pm 325$, and $826 \pm 551$ U (mean $\pm$ SD) for patients without coronary disease and for those with one-, two-, and three-vessel disease, respectively. The intergroup differences were statistically significant, but there was considerable overlap among individual patients. More importantly, the SIS correlated significantly with a coronary arteriography score designed to reflect the potential for ischemia based on the coronary anatomy ($r = .78$, $p < .001$) and with an index of ischemia generated from the exercise electrocardiogram ($r = .72$, $p < .001$). These findings suggest that a continuous and quantitative scintigraphic index of myocardial ischemia can be derived from analysis of the postexercise distribution and clearance of $^{201}$TI. Such an index should be valuable in determining prognosis and choosing therapy for patients with coronary artery disease and in assessing their response to therapeutic interventions.


THALLIUM-201 ($^{201}$TI) scintigraphy is widely used to detect coronary disease, usually in conjunction with exercise testing. In addition, many groups have evaluated its ability to localize obstructed vessels and to estimate the extent of anatomic involvement. Unfortunately, the scintigraphic results with these latter applications have often been disappointing, at least in part because of the relative nature of the conventional interpretation criteria, which occasionally make it difficult to recognize generalized disease. Most recently a combined spatial and temporal approach has been used to evaluate $^{201}$TI-perfusion scintigrams. This technique has provided an additional sensitivity, especially in the evaluation of patients with extensive disease.

Previous studies have always assessed scintigraphic findings in relation to the anatomic extent of disease, usually classifying patients by number of obstructed vessels without reference to the viability of the perfused myocardium, the severity of the stenosis, or the presence of collaterals. Thus, there is often a poor correlation between coronary anatomy and either symptomatic or electrocardiographic evidence of ischemia. Furthermore, the relationship between the coronary anatomy and the clinical course of ischemic heart disease, while significant, is relatively crude. It would be valuable to have a quantitative measurement...
of myocardial ischemia, which could then be studied as a prognostic tool and as a method for evaluating therapeutic interventions.

With this in mind, we developed a quantitative scintigraphic index of ischemia based on the change in the relative distribution of $^{201}$TI on postexercise and delayed scintigrams, the rate of tracer clearance, and the level of treadmill exercise performed. This index was then applied to a group of patients undergoing catheterization for evaluation of chest pain. Although no absolute standard for quantitation of myocardial ischemia is available, this scintigraphic index was validated by correlating it with both a new coronary anatomy score designed to reflect the potential for ischemia and a previously described quantitative exercise electrocardiographic index of ischemia.

**Methods**

**Patients.** The study population consisted of 59 male subjects drawn from a group of 63 consecutive patients who had not previously undergone coronary artery revascularization and who were evaluated for chest pain both by coronary arteriography and exercise $^{201}$TI scintigraphy within a 2 month period. These patients did not have any intervening symptomatic or electrocardiographic changes. Four of the 63 patients were excluded because of concomitant cardiac diseases that might have produced or exacerbated ischemia (aortic valve disease in two, idiopathic cardiomyopathy in one, and a coronary arteriovenous fistula in one). Since we have previously shown that inadequate levels of stress invalidate quantitation of $^{201}$TI clearance, 13 four additional subjects who did not meet our previously stated criteria of exhibiting an ischemic electrocardiographic response, developing an exercise induced scintigraphic defect, or achieving 85% of age-predicted maximum heart rate (MPHR) are discussed only briefly.

The final group of 55 patients included nine with no significant coronary disease (defined as an obstruction greater than 50% of the luminal diameter) and 4, 12, and 30 with one-, two-, or three-vessel involvement, respectively. Twenty-three of the 46 coronary disease patients had electrocardiographic or ventriculographic evidence of prior myocardial infarction.

A group of 15 male subjects with a mean age of 44 years (range 38 to 56) and who were considered to have a very low likelihood of having significant coronary artery disease was studied for comparison. Results of medical history and physical examination were negative in all and all had normal plasma lipid levels. In addition, they performed treadmill exercise tests to at least their MPHR and aerobic capacity, and their rest and exercise blood pool scintigrams were normal (as evidenced by a resting ejection fraction above 0.55, with a rise in ejection fraction of at least 0.05 U and no segmental wall motion abnormalities).

**Exercise electrocardiography.** $^{201}$TI scintigraphy was performed in conjunction with treadmill testing. Patients exercised in the postabsorptive state by the Bruce protocol to a symptom-limited maximum, and all tests were discontinued for either chest pain or fatigue. Leads $V_1$, $V_4$, and $aVF$ of the electrocardiograph were monitored simultaneously and continuously during the entire period of exercise and recovery.

A continuous printout of the signal-averaged values for J point deflection and ST segment slope was obtained with a commercially available computer-assisted exercise system (CASE, Marquette Electronics). From these data, a treadmill exercise score (TES) was calculated according to previously published methods. 12 In brief, the areas of J point deviation from baseline and ST segment slope from baseline were algebraically summed for both leads $V_4$ and $aVF$. This summed area becomes progressively more negative with increasing J point deflection and with increasing degrees of downsloping ST segment depression, and thus produces an electrocardiographic measure of ischemia. The total summed area for both leads is then divided by the duration of exercise (in minutes) and the fraction of the MPHR is obtained as shown below.

$$TES = \frac{\text{Area (J point + ST) \, V_4 + area (J point + ST slope) \, aVF}}{\text{Exercise duration \times fraction MPHR}}$$

Thus, the absolute value of TES is greater in subjects who exhibit poor exercise capacity.

The TES was further refined by adjusting the area of ST depression for the magnitude of the QRS voltage exhibited in the particular monitored lead. 14 Thus, the area contribution of $V_4$ was normalized to a mean R wave voltage of 1.2 mV and that in aVF was averaged to a mean R wave voltage of 0.8 mV (only if R in aVF exceeded 0.8 mV). These values for R wave voltage were the medians for 100 subjects in our laboratory and the adjusted TES was calculated as

$$TES = \frac{\text{Area (J point + ST slope) \, V_4 \times \frac{12}{RV_4}} + \text{area (J point + ST slope) \, aVF \times \frac{8}{RaVF}}{\text{Exercise duration \times fraction MPHR}}$$

**Scintigraphic procedure.** Two millicuries of $^{201}$TI was injected through an indwelling intravenous cannula at near maximal exercise, which was then continued for one additional minute. Following a 5 min monitored recovery period, patients were promptly taken to the imaging room. Scintigraphy was performed by the seven-pinhole tomographic technique described by Vogel et al. 15, 16 All studies were performed by one experienced technologist. Acquisition was terminated after 750,000 counts were obtained, and delayed scintigraphy was performed 3 hr later. The orientation of the camera was carefully noted to ensure its reproducibility. Patients were instructed to limit their activity and food consumption during the intervening period.

Twelve sections, beginning 7.5 cm from the collimator and at nominal intervals of 1.25 cm, were reconstructed with the algorithms developed by Vogel et al. 15, 16 Three sections were chosen for quantitative analysis: an apical section (the first section that revealed a left ventricular cavity), a basal slice (the last section before the image fragmented, usually section 7 or 8), and a midventricular slice located midway between these. A mean value for paraventricular background was subtracted automatically. No smoothing was performed since linear tomography entails considerable averaging among adjacent pixels.

**Quantitative analysis of $^{201}$TI scintigrams.** The quantitative analysis procedures were developed before the evaluation of this patient population. These incorporated the circumferential profile approach to the assessment of radiotracer distribution and clearance previously used by Burow et al., 17 Vogel et al., 16 and Garcia et al. 8 In addition, the normalization for level of stress developed for the TES (see above) was used. 12 This method is described in detail below.

After the center of the ventricle was chosen manually, circumferential profiles displaying normalized maximal pixel ac-
FIGURE 1. Circumferential profiles of the initial postexercise (solid line) and 3 hr (interrupted line) \(^{201}\)TI distribution, normalized to the radian of maximal pixel activity. The stippled area indicates the distribution and amount of relative increase in uptake over time, while the small hatched area of 350 degrees is an area with a relative decrease in activity. The redistribution area is defined as the algebraic sum of these two areas. These profiles are from a midventricular section in a patient with three-vessel disease.

activity at 6 degree intervals were generated for each radian, as described by Vogel et al.\(^{13,16}\). The area of redistribution was computed automatically as the algebraic sum of the areas for the initial and 3 hr profiles (in arbitrary units of percent times degrees), as illustrated in figure 1.

The 3 hr clearance rates were calculated by our previously published methods, which were modified for tomographic scintigrams from those of Garcia et al.\(^8\). This rate was calculated radian by radian by subtracting the 3 hr activity (in counts/min of acquisition time) from the initial activity (same units) and dividing the difference by the initial activity (same units). This was multiplied by 100 to express the 3 hr clearance rate as a percent. For each section a circumferential profile of the 3 hr clearance rate was generated (figure 2). The abnormal clearance area was then computed automatically as the area in which this curve fell below the curve representing the 95% confidence limits for clearance derived from 15 previously studied normal subjects with a low likelihood of coronary disease, again expressed in arbitrary units of percent times degrees. This abnormal clearance area was considered to be 0 if the patient profile showed that the clearance rate was entirely above the normal limits. In patients with old myocardial infarction, the clearance rates were not used in the calculation of infarcted regions, defined as those with 3 hr profiles remaining below the normal limits.

A scintigraphic ischemic score (SIS) was then derived by the same approach used for the TES according to the equation below:

\[
SIS = \frac{\text{Redistribution area} + \text{abnormal clearance area}}{\text{Exercise duration} \times \text{fraction MPHR}}
\]

This is illustrated in figure 3. In 30 subjects the SIS was derived independently by two observers — one a cardiologist and the other a nuclear medicine technologist.

Angiographic analysis. The coronary arteriograms were analyzed by a cardiologist who was blinded to the scintigraphic and exercise electrocardiographic results. In determining the number of involved vessels, any lesion greater than 50% of the luminal diameter was considered significant.

In addition, a coronary arteriography score (CAS) was developed in an attempt to translate the coronary anatomic findings into a quantitation of the myocardium in jeopardy for ischemia. Each major branch was individually graded on a 10-point scale, as indicated in table 1. The majority of patients had eight scorable branches: two from the right coronary artery (the posterior descending and a low posterolateral), two from the left circumflex artery (two obtuse marginal arteries), and four from the left anterior descending coronary artery (the proximal septal perforator, two diagonal, and the distal left anterior descending arteries). Any proximal lesion was considered to place all distal portions of the vessel in jeopardy. For instance, a 90% obstruction at the origin of the left anterior descending coronary artery would yield a score of 32 (8 points times four branches). The number and identity of the major branches was assessed on a patient-by-patient basis, and the score of those with a greater or lesser number of major branches was normalized to a maximum score of 80.

To make the score more reflective of the potential to develop ischemia, branches supplying infarcted segments, as defined by the presence of akinesis or dyskinesis on the left ventriculogram and Q waves on the electrocardiogram, were scored as 0. The scores of branches that filled well (full opacification before the proximal vessel emptied) from nonjeopardized collaterals were reduced by 50%.

Statistical methods. All data are expressed as mean ± SD. The significance of differences in quantitative indices between the various anatomic subsets of patients (normal subjects, patients without vessel disease, and those with one-, two-, or three-vessel disease) was determined by one-way analysis of variance and the Newman-Keuls multiple-range test. The correlations between the various ischemic indices were studied by least squares linear regression analysis and the t statistic.

Results

Scintigraphic findings. Figure 4 illustrates the relationship of the redistribution area and abnormal clearance area to the coronary anatomy. The redistribution area became progressively larger for patients with zero-, one-, two-, or three-vessel disease (438 ± 428, 846 ± 370, 1150 ± 903, and 1367 ± 927 U, respec-
tively). However, there was considerable overlap between the groups; only the difference between patients with insignificant disease and those with three-vessel disease achieved statistical significance (p < .05). If an upper limit of normal is derived based on the 95% confidence band from the normal subjects, only one patient without significant disease was abnormal, but 21 of 46 (46%) of the patients with significant obstruction also fell within the normal range.

As can be seen from the right panel in figure 4, abnormal clearance was unusual without advanced disease. The abnormal clearance area was 5 ± 8 U for the normal subjects and 6 ± 10, 200 ± 354, 1074 ± 1239, and 1794 ± 1194 U for patients without disease and with one-, two-, or three-vessel disease, respectively. While it is noteworthy that values in no patient without vessel disease and in only one with single-vessel disease exceeded the 95% confidence limit of normal, there was considerable overlap between the two- and three-vessel disease group. The only intergroup differences that achieved statistical significance were those between the three- and both the insignificant obstruction and one-vessel disease groups (p < .001).

When the distribution and abnormal clearance areas were summed, the differences between the groups increased (figure 5, left). The summed area for the normal subjects averaged 425 ± 295 and the patients without obstructions and with one-, two-, or three-vessel disease had summed areas of 434 ± 438, 1169 ± 625, 1970 ± 1665, and 3162 ± 1086 U, respectively. Only one patient without significant disease had an area that exceeded the 95% confidence limit derived from normal subjects, in contrast to 34 of 46 (74%) of those with significant obstructions.

The right panel of figure 5 illustrates the SIS findings when the combined redistribution and abnormal clearance areas were normalized for the level of stress. The SIS in the normal subjects was 36 ± 27 U, compared with 52 ± 58, 233 ± 220, 427 ± 325, and 826 ± 551 U for patients without stenoses and those with one-, two-, or three-vessel disease, respectively.

The differences in SIS between the insignificant disease and one- or two- and three-vessel disease groups were each significant at least at the p < .05 level. The SIS was lower in the infarct patients than in the coronary disease patients without prior infarction (563 ± 362 vs 914 ± 872 U, p < .05). In the noninfarct patients SIS was 51 ± 58 U for patients without disease, 408 ± 178 U for those with one- or two-vessel disease, and 1037 ± 935 U for those with three-vessel disease, the latter value being significantly higher than the others. In the infarct patients the difference between one- or two-vessel disease and three-vessel disease groups (323 ± 294 vs 698 ± 347 U) was also significant (p < .01).

Again, only one chest pain patient without significant coronary disease had an SIS that exceeded the 95% confidence limits derived from the normal subjects but, after taking into account the degree of stress, 44 of 46 (96%) coronary disease patients exceeded this limit; the remaining two patients had old myocardial infarctions. This improved sensitivity of the SIS compared with various other area quantification methods is illustrated in figure 6.

As was noted in Methods, 4 patients with inadequate levels of stress were not included in these quantitative differences.
analyses. Three of these had coronary disease (two with three-vessel disease and one with single-vessel disease), but one did not. All had clearance profiles falling below the normal limits in the distribution of all three vessels. Because of their low exercise levels each would have had an SIS of above 200 U.

Relationships of the SIS to arteriographic and electrocardiographic measures of ischemia. Although patients with three-vessel disease had a higher SIS than those with less diffuse disease, the overlap between groups was obvious. Since the CAS was designed to provide a quantitative measure more reflective of potential ischemia than a simple classification based on the number of involved vessels, the relationship between the SIS and the CAS was examined. Figure 7 shows this correlation, which was highly significant ($r = .78$, $p < .001$) and was higher than those between the redistribution area, the abnormal clearance area, or the combined areas and the CAS (table 2). The correlation between SIS and CAS remained high if the noninfarct and previous infarct patients are examined separately as well ($r = .77$, $p < .001$ for no infarct; $r = .79$, $p < .001$ for old infarct).

The relationship between the SIS and an electrocar-

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Left, The relationship of the redistribution area to the gross coronary anatomy. The NLS are volunteers with a low likelihood of coronary disease and 0VD, 1VD, 2VD, and 3VD indicate the number of obstructed vessels in the chest pain patients. The dashed line is the upper 95% confidence limit for the NLS and the open squares indicate the patients with previous myocardial infarction. The plot on the right was constructed with the format used for the abnormal clearance area.

![Figure 5](http://circ.ahajournals.org/)

**FIGURE 5.** The same format used in figure 4 is used to show the relationship of the combined area and the SIS to the number of involved vessels. The SIS provides the best separation between patients with and without significant disease. The means for no, one-, two-, and three-vessel groups differ significantly (see text), but individual overlap is apparent.
FIGURE 6. The sensitivity and specificity of the various quantitative measurements for diagnosing significant coronary disease. The 95% confidence limits derived from the normal subjects were used. The SIS was more sensitive than the redistribution area and the summed area methods.

A scintigraphic measure of ischemia, the TES, is illustrated in figure 8. Only 40 points are plotted since the TES could not be derived in the 15 patients with intraventricular conduction abnormalities. The correlation between these two indices was also highly significant (r = .72, p < .001). Again, this was a closer correlation than that between the other scintigraphic measurements and the TES. For patients without old infarcts, this correlation coefficient was .78 (p < .001) and for patients with old infarcts it was .75 (p < .001).

The SIS incorporated a double normalization for the level of stress by including a division by both the fraction of MPHR and the duration of exercise. The correlations with the CAS and TES were also examined if only the fraction of MPHR correction was used. In this case the relationship between the scintigraphic index and CAS was equally good (r = .77, p < .01), but the correlation with the TES was much poorer (r = .54, p < .01; table 2). This latter finding is not surprising since the TES also incorporates the double normalization.

Reproducibility of the SIS. In 30 patients for whom SIS was calculated twice by the same observer, the mean variation was 40 U (6%). In the same patients the variability between two observers was 27 U (4%).

Discussion

Background. Many previous articles have evaluated TI scintigraphy in coronary disease. The sensitivity of this technique has generally been high, but studies examining its ability to define the extent of disease have shown a consistent tendency toward underestimation. Thus, a number of reports have found that only 50% to 70% of diseased vessels are detected and the accuracy of scintigraphic examination in the diagnosis of critical disease such as left main or three vessel involvement has been limited.

A number of factors are probably responsible for this discordance between the scintigraphic findings and gross assessments of coronary anatomy. Most promi-
TABLE 2

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<th>Correlation of scintigraphic measurements with CAS and TES</th>
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Despite the drawbacks of the scintigraphic method, it is also likely that some discrepancies between results obtained by this method and the usual assessments of coronary anatomy result from the fact that two different manifestations of coronary disease are being examined. Scintigraphy detects heterogeneity of myocardial perfusion, which may be an indication of ischemia. The usual classification of coronary anatomy into categories based on the number of obstructed vessels may, in fact, be a poor indicator of the potential for ischemia. Previous scintigraphic-anatomic correlation studies have suggested that a high-grade stenosis (usually greater than 80% to 90%) is required before a defect is apparent and experimental studies provide some support for this finding. Furthermore, whatever the severity of the stenosis, the severity of the ischemia is likely to be less if the subserved region is either infarcted or well collateralized.

Since many of the important clinical manifestations of coronary disease are likely to reflect the severity of the ischemia or the amount of jeopardized myocardium rather than simply the degree of anatomic involvement, a method for quantitating ischemia could be invaluable. Our study was undertaken to develop such an index with some of the newer scintigraphic approaches such as tomographic reconstruction, quantitative analysis, and measurement of radiotracer clearance rates. Also, the level of stress that was required to produce the given scintigraphic abnormalities in each patient was incorporated into our scintigraphic index.
of ischemia, since we have previously found this approach to be valuable in quantifying exercise-induced electrocardiographic abnormalities.\textsuperscript{12}

**Findings of the present study.** The validation of a quantitative index of ischemia in human subjects presents a logical dilemma because of the absence of a reference standard. For this study we first made the crude assumption that the severity of ischemia should increase with the number of vessels involved, although considerable overlap was expected. We then set out to develop a more “physiologic” approach to assessing the potential for anatomic coronary artery disease to produce ischemia. This was accomplished by grading each major coronary branch, or stated another way, the blood supply to each major myocardial segment. The scale chosen was heavily weighted toward severe stenoses, since both clinical observations and experimental study results suggest that these have a greater potential for producing ischemia. Finally, we made the assumption that nonviable myocardial regions and those that were well collateralized were less likely to become ischemic, and therefore made corresponding adjustments in the CAS. Gensini et al.\textsuperscript{29} have derived a similar arteriographic score and found it useful in determining prognoses. To further validate the physiologic relevance of the scintigraphic measurements of ischemia, we also examined their relationship to an independent electrocardiographic index of ischemia, the TES.\textsuperscript{12}

Our findings corroborate and extend several observations that have been made previously with less quantitative approaches. The presence of extensive redistribution, that is, areas of initially reduced relative \textsuperscript{201}TI uptake that become less abnormal in relation to the remaining myocardium in delayed scintigrams, is a specific indicator of coronary involvement. However, the degree of redistribution alone was not an accurate indicator of ischemia. Thus, some change in radiotracer distribution in the direction of redistribution was present in normal subjects. Conversely, in the coronary patients assessment of redistribution alone underestimated the prevalence and extent of disease in many patients, even in those without previous myocardial infarction. This underestimation is apparent whether one examines the number of vessels involved or the correlations with the CAS or TES.

Quantitation of \textsuperscript{201}TI clearance abnormalities separated out most patients with multivessel disease from those with no or one-vessel involvement. However, the correlations between clearance abnormalities and both the CAS and TES were both relatively poor, suggesting that this measurement alone did not provide a good index of ischemia.

The sum of the quantitative redistribution and clearance abnormalities improved the assessment of the extent of coronary involvement and the correlations with the angiographic and electrocardiographic indices of ischemia. However, the SIS, which relates this combined measurement to the level of stress, provided the best sensitivity for diagnosing coronary disease, the best separation in relation to the number of vessels involved, and the best correlations with both the CAS and TES. Noteworthy is the fact that these correlations between SIS and both the CAS and TES remain highly significant when the infarct and noninfarct patients are considered separately or combined, suggesting that ischemia can be quantified in the former group despite the presence of fixed scintigraphic defects. The good correlation between a scintigraphic score incorporating only the heart rate normalization factor and the CAS suggests the double normalization may not be essential to assess ischemia. However, since the TES provides an independent method of validating the SIS and itself employs the correction for exercise duration in addition to that for heart rate, the data are represented with both correction factors.

One advantage of the SIS is that it is derived automatically once the observer has indicated the center point of the left ventricle on each section. This approach is well suited for quantitation of tomographic reconstructions since, with proper positioning of the camera and collimator, there is less interpatient variation of the orientation of the left ventricle and the “doughnut” appearance of each section lends itself to circumferential profile analysis. However, success with any tomographic method and with the seven-pinhole technique in particular requires a careful and consistent approach to the details of patient and collimator positioning. If the detector is not aligned perpendicularly to the long axis of the left ventricle, artifactual defects can arise. If the distance between the heart and the detector varies between studies, defects may appear in different sections. In this context, it is worth noting that all of these studies were performed by one experienced technician who carefully noted and reproduced the angulation and positioning of the camera. Although not tested in this study, the same quantitative approach to the measurement of ischemia could probably be applied to carefully performed planar scintigrams without any major changes in the results. More importantly, this technique should lend itself well to the analysis of tomographic scintigrams obtained by
rotational tomography, which has proven very promising in preliminary studies. By this latter technique, Z-axis resolution should be more satisfactory and reconstructions could be performed in different planes.

**Implications.** The development of a quantitative index of myocardial ischemia derived from exercise and delayed 201Tl scintigrams provides a new noninvasive tool that can be widely used clinically. Because an independent corroborative technique does not exist, we cannot conclude that it rigorously quantifies myocardial ischemia. However, the significant correlations between the SIS and indices of ischemia based on coronary anatomy and exercise electrocardiography suggest that the SIS is an effective measure of myocardial ischemia.

The availability of a scintigraphic technique for quantifying ischemia will facilitate the performance of more refined clinical studies to evaluate the relationship of this index to the clinical course of coronary disease. If the severity of ischemia is of prognostic importance, this measurement might then provide an objective method for choosing and evaluating therapy.

**References**

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