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Identification of Viable Myocardium in Patients with Chronic Coronary Artery Disease Using Rest-Redistribution Thallium-201 Tomography: Optimal Image Analysis

Leonardo Pace, Pasquale Perrone-Filardi, PierPaolo Mainenti, Alberto Cuocolo, Pasquale Vezzuto, Mariella Prastaro, Andrea Varrone, Giuseppe De Luca, Andrea Soricelli, Sandro Betocchi, Massimo Chiariello and Marco Salvatore

Cattedra di Medicina Nucleare, Dipartimento di Scienze Biomorfologiche e Funzionali, Facoltà di Medicina, Università Federico II, Napoli; Centro C.N.R. per la Medicina Nucleare, Napoli; and Cattedra di Cardiologia, Dipartimento di Medicina Interna, Facoltà di Medicina, Università Federico iI, Napoli, Italy

With the widely used 50% threshold, sensitivity is high, but specificity is low in detecting viable myocardium on ^{201}Tl SPECT. In this study, we sought to identify the best threshold for semiquantitative ^{201}Tl analysis. **Methods:** Rest-redistribution ^{201}Tl SPECT was performed in 46 patients with chronic coronary artery disease before and after myocardial revascularization. Regional function was evaluated by two-dimensional echocardiography before and after myocardial revascularization using a 3-point scale (1 = normal, 2 = hypokinetic, 3 = a/dyskinetic). Myocardial segments with abnormal systolic function were defined as viable if the systolic function score decreased ≥ 1 after myocardial revascularization. A second group of 12 patients with chronic coronary artery disease constituted the validation population. Sensitivity-specificity curves, as well as receiver operating characteristic curves, for rest and redistribution images were generated by varying the ^{201}Tl uptake threshold. **Results:** A 65% threshold uptake using resting images was found to be the best for detecting a/dyskinetic segments that improve after myocardial revascularization from those that do not improve. Sensitivity was lower with a 65% threshold (75%) than with a 50% threshold (90%, $p < 0.05$), but specificity was higher (76% versus 26%, $p < 0.05$) resulting in better accuracy (76% versus 57%, $p < 0.05$) and positive predictive value (77% versus 55%), while the negative predictive value was not different (69% versus 75%, p not significant). The area under the receiver operating characteristic curve was significantly ($p < 005$) larger for rest (0.80 ± 0.05) as opposed to redistribution (0.72 ± 0.05) images. Similar results were obtained in a subgroup of patients with low ejection fraction. Significant correlations between the percentage of revascularized viable segments and both the change in ejection fraction and in postrevascularization ejection fraction were found. When these findings were applied in the validation group, a gain in specificity, accuracy and positive predictive value was obtained with the 65% threshold compared with the 50% threshold. **Conclusion:** This study demonstrated that analysis of resting images and use of the 65% ^{201}Tl uptake threshold is preferable for separating viable from not viable dyssynergic myocardial segments in patients with chronic coronary artery disease.

Key Words: myocardial viability; thallium-201; thresholds

J Nucl Med 1998; 39:1869–1874

Received Oct. 6, 1997; revision accepted Jan. 26, 1998.

For correspondence or reprints contact: Leonardo Pace, trav.priv. Sanseverino 5/A, 80128, Napoli, Italy.

Thallium-201 is being used extensively to detect viable myocardium in patients with chronic coronary artery disease. Since the study (*1*) demonstrating that up to 50% of persistent ^{201}Tl defects at 3–4 hr redistribution contain viable myocardium, modifications of the standard stress 3–4 hr redistribution approach have been proposed. Stress-redistribution-reinjection and rest-redistribution are the currently used protocols for the identification of viability using ^{201}Tl (*1–9*). Interpretation of ^{201}Tl images is enhanced by semiquantitative analysis of regional tracer uptake. In this analysis, a fixed cutoff is used to differentiate between viable and nonviable dysfunctional myocardium. Usually, a threshold value corresponding to 50% of maximal ^{201}Tl uptake has been used, although the accuracy of such a cutoff to predict the effects of revascularization on regional function is not perfect and different values of sensitivity and specificity have been reported (*9–14*). Therefore, the aim of this study was to determine the most accurate analysis of resting ^{201}Tl scintigraphy for identifying viable myocardium.

MATERIALS AND METHODS

Patient Population

Forty-six consecutive patients (45 men, 1 woman; mean age 59 ± 7 yr) with chronic coronary artery disease and regional wall motion abnormalities at both angiography and echocardiography undergoing myocardial revascularization (25 patients underwent coronary artery bypass grafting and 21 patients underwent percutaneous transluminal coronary angioplasty) constituted the reference population. All patients were in stable hemodynamic condition, and no patient had acute myocardial infarction or unstable angina for at least 1 mo before the study. Coronary angiography was performed in all patients, and it documented in all patients a significant stenosis (>50% of maximal luminal diameter) of at least one epicardial coronary artery. Eleven patients had three-vessel, 19 patients had two-vessel and 16 patients had one-vessel coronary artery disease. All patients underwent rest-redistribution ^{201}Tl imaging and echocardiography in the same day before and after (mean 40 ± 20 days) revascularization. Beta-blockers, Ca^{++}-antagonists and nitrate were discontinued in all patients at least 2 days before the pre- and postrevascularization imaging studies. Resting ejection fraction was 40% ± 11% (range 19%–55%). No patient suffered perioperative myocardial infarction, and no patient reported angina at the time of follow-up. The validation population, an additional group of patients in whom the criteria for reversible regional dysfunction were applied, included 12 consecutive patients (11 men, 1 woman; mean age 60 ± 12 yr) with chronic coronary artery disease undergoing myocardial revascularization (3 patients underwent coronary artery bypass grafting and 9 patients underwent percutaneous transluminal coronary angioplasty). At coronary angiography, 6 patients had one-vessel disease, 4 had two-vessel disease and 2 had three-vessel disease. Prerevascularization rest ejection fraction was 41% ± 13%. All patients underwent rest-redistribution ^{201}Tl imaging and echocardiography in the same day before and after (mean 60 ± 22 days) revascularization. Beta-blockers, Ca^{++}-antagonists and nitrate were discontinued in all patients at least 2 days before the pre- and postrevascularization imaging studies. No patient suffered perioperative myocardial infarction, and no patient reported angina at the time of follow-up.

Thallium-201

All patients underwent rest-redistribution ^{201}Tl SPECT after an overnight fast. Thallium-201 images were acquired 15–20 min (rest images) and 4 hr (redistribution images) postintravenous injection of 111 MBq ^{201}Tl, using a wide-field-of-view rotating gamma camera (SP4HR, Elscint, Haifa, Israel), as described previously (*15*). Briefly, 32 images (matrix 64 × 64 matrix) were acquired using a step-shoot method over a 180° semicircular orbit with a 6° increment for 30 sec each. Flood, center-of-rotation and decay correction were applied during reconstruction. Filtered backprojection with a Butterworth filter (order 5, cutoff 0.5 cm^{-1}) was used. No attenuation correction was applied. In each patient, four consecutive, three-pixel thick, midventricular slices from the short-axis series were selected for the subsequent semiquantitative ^{201}Tl analysis. For each patient, regional ^{201}Tl activity was measured. An operator-defined circular region of interest was drawn around the left ventricle, and the tomogram was divided into six sectors of equal arc representing the posterolateral, inferior, posteroseptal, anteroseptal, anterior and anterolateral myocardium. Regional ^{201}Tl activity was measured in each myocardial sector, and it was expressed as a percentage of the maximal ^{201}Tl activity for each set of images. The corresponding sectors from two consecutive short-axis tomograms were then grouped and averaged. In each patient, 12 midventricular segments were evaluated. Of these segments, 6 (2 anterior, 2 anteroseptal and 2 posteroseptal) were assigned to the territory of the left anterior descending artery, 4 (2 posterolateral and 2 anterolateral) were assigned to the territory of the left circumflex coronary artery and 2 inferior segments were assigned to the territory of the right coronary artery. The reproducibility of the ^{201}Tl analysis was assessed in 22 patients in whom quantitative analysis was repeated twice by different operators, and the average difference between the two measurements was 0.5% ± 8%. Further details on the reproducibility study have been already reported (*15*).

Echocardiography

Two-dimensional echocardiography was performed with a 2.5-MHz transducer and a commercially available scanner (Sonos 1000, Hewlett-Packard, Andover, MA) under resting conditions. Echocardiographic studies were acquired in the left lateral decubitus position and recorded on 12.5-mm VHS videotape. Echocardiography was repeated with the same modalities 40 ± 20 days after revascularization. Echocardiographic images were analyzed off-line from the videotape playback by two operators unaware of the scintigraphic results. To allow a more accurate matching of the echocardiographic and the scintigraphic data, only two short-axis midventricular images were evaluated in each patient. Each of them was divided into six segments as recommended by the American Society of Echocardiography (*16*), representing the posteroseptal, anteroseptal, anterior, anterolateral, posterolateral and inferior segments. Thus, regional function was evaluated in 12 myocardial segments corresponding to ^{201}Tl segments. For each myocardial segment, wall motion and systolic wall thickening were graded semiquantitatively using a 3-point scoring system where 1 indicated normal; 2, hypokinesia (severely reduced wall thickening and inward wall motion; and 3, a/dyskinesia (absence of wall motion and of systolic thickening or dyskinesia). An a/dyskinetic myocardial segment was defined viable if its systolic function score decreased ≥1 after myocardial revascularization. To assess the reproducibility of the echocardiographic analysis, prerevascularization and postrevascularization echocardiograms were read in random order by the same observers at least 2 mo after the initial reading, and the segmental exact score agreement was 82%. Further details on the reproducibility study have been previously reported (*15*).

Statistical Analysis

Sensitivity was defined as the number of a/dyskinetic myocardial segments classified as viable by ^{201}Tl divided by the number of segments showing improvement of contractile function after revascularization. Specificity was defined as the number of a/dyskinetic myocardial segments classified as nonviable by ^{201}Tl divided by the number of segments not showing improvement of contractile function after revascularization. Accuracy was defined as the number of a/dyskinetic myocardial segments correctly detected as being either viable or nonviable by ^{201}Tl divided by the total number of a/dyskinetic segments. Positive predictive value (PPV) was defined as the number of a/dyskinetic segments classified as viable by ^{201}Tl that improved after revascularization divided by the total number of a/dyskinetic segments classified as viable by ^{201}Tl. Negative predictive value (NPV) was defined as the number of a/dyskinetic myocardial segments classified as nonviable by ^{201}Tl that did not improve after revascularization divided by the total number of a/dyskinetic segments classified as nonviable by ^{201}Tl. All these figures of merit were computed by varying uptake thresholds of ^{201}Tl. Receiver operating characteristic (ROC) curves were generated and their areas were computed. Differences between proportions were assessed using the McNemar's Test. The Student's t-test, with the Bonferroni's correction when indicated, was used to assess differences in mean values. Linear regression was used when appropriate. A probability (p) value of less than 0.05 was considered significant.

RESULTS

Reference Population

Of the 552 myocardial segments analyzed, 276 showed normal wall motion, 144 were hypokinetic and 132 were a/dyskinetic at baseline echocardiography. Of the 132 a/dyski-

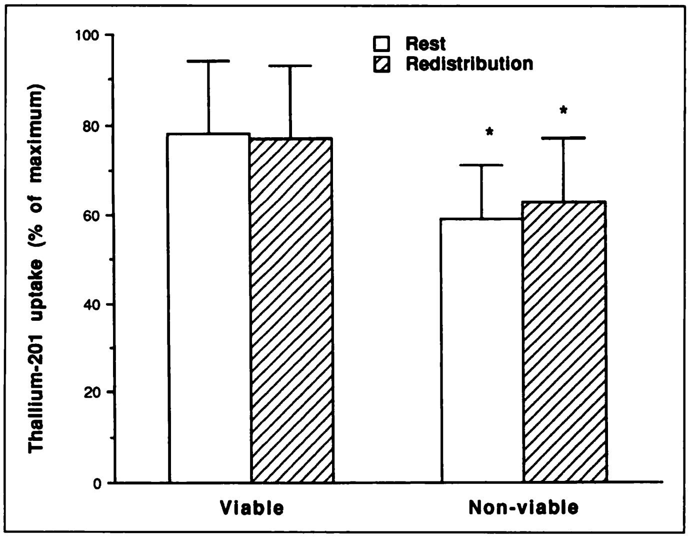

FIGURE 1. Rest and redistribution ^{201}Tl uptake in preoperative SPECT study in a/dyskinetic myocardial segments with and without functional improvement after revascularization. *p < 0.05 versus viable.

netic myocardial segments, 94 underwent myocardial revascularization, and 48 of them (51%) improved thereafter. Thallium-201 uptake at rest before revascularization was significantly ($p < 0.001$) higher in segments improving after revascularization (78% ± 16%) as opposed to those that did not improve (59% ± 12%) (Fig. 1). Similarly, significantly ($p < 0.005$) higher ^{201}Tl uptake at redistribution before revascularization was found in segments improving after revascularization (77% ± 16%) as opposed to those not improving (63% ± 14%) (Fig. 1). Of these 94 a/dyskinetic myocardial segments, 74% had rest ^{201}Tl uptake < 80% and 50% had rest ^{201}Tl uptake < 65%. Figure 2 shows the ROC curves for rest and redistribution images. To compare the accuracy of rest images to those of redistribution, the areas under the ROC curves were computed. Using rest images, the ROC curve area was significantly ($p < 0.05$) greater (0.80 ± 0.05) than for redistribution images (0.72 ± 0.05, respectively). It appears that, for both sets of images, a threshold value of 65% of maximal activity provided the best combination of sensitivity and specificity. As reported in Table 1, when using rest images the 65% threshold resulted in significantly higher values of specificity, accuracy and PPV compared to the conventional 50% threshold, with lower sensitivity and NPV. Similarly, when using redistribution images specificity substantially increased from 28% with the 50% cutoff to 63% with the 65% cutoff ($p < 0.05$), although at the expense of reduced sensitivity (Table 1).

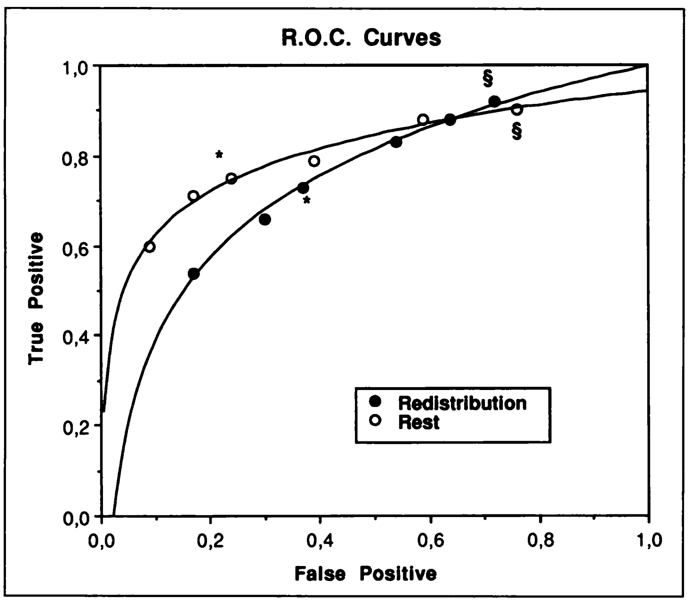

FIGURE 2. ROC curves for rest and redistribution ^{201}Tl imaging. *65% threshold; §50% threshold.

In the 48 a/dyskinetic segments improved at follow-up, rest ^{201}Tl uptake did not change significantly from pre- (78 ± 16) to post- (76% ± 16%) revascularization, also it did not change in segments that did not improve (59% ± 12% versus 61% ± 12%) and in segments that were not revascularized (from 57% ± 21% to 56% ± 20%). However, postrevascularization rest ^{201}Tl uptake was significantly ($p < 0.05$) higher in revascularized segments (n = 48) improving thereafter (76% ± 16%) as opposed to those (n = 46) not improving (61% ± 12%) and in those (n = 38) not revascularized (56% ± 20%). In addition, of the 94 a/dyskinetic revascularized segments, 30 had postrevascularization rest ^{201}Tl within normal limits (i.e., ≥80%) and 27 (90%) of them showed improved function thereafter, while of the remaining 64 only 21 (33%) had functional improvement ($p < 0.05$). On the other hand, of the 38 nonrevascularized a/dyskinetic segments, 4 (11%) had postrevascularization rest ^{201}Tl uptake ≥ 80%.

In 26 patients who underwent revascularization in the distribution of resting a/dyskinesia ejection fraction increased from 38% ± 11% to 45 ± 11, and 17 of them had a significant (i.e., ≥5%) increase in ejection fraction thereafter. A significant positive correlation was found between the percent of revascularized segments with prerevascularization rest ^{201}Tl uptake ≥ 65 and both the postrevascularization ejection fraction (Fig. 3) and the change in the ejection fraction (Fig. 4).

Of the 46 patients, 20 had prerevascularization ejection fraction < 40% (mean 30% ± 6%). Of the 240 segments analyzed in this subgroup, 70 were a/dyskinetic and 54 of them were revascularized. Of these 54 segments, 20 (37%) improved after revascularization. Rest ^{201}Tl uptake was significantly ($p < 0.0001$) higher in the 20 segments with improved function after

TABLE 1
Prediction of Recovery of Function with Rest-Redistribution Thallium-201 SPECT in A/Dyskinetic Segments

	Rest ^{201}Tl			Redistribution ^{201}Tl		
	Threshold 50%	Threshold 65%	p value	Threshold 50%	Threshold 65%	p value
Sensitivity	90%	75%	<0.05	92%	73%	<0.05
Specificity	24%	76%	<0.05	28%	63%	<0.05
Accuracy	57%	77%	<0.05	61%	68%	ns
PPV	55%	77%	<0.05	57%	67%	ns
NPV	69%	75%	ns	76%	69%	ns

PPV = positive predictive value; NPV = negative predictive value; ns = not significant.

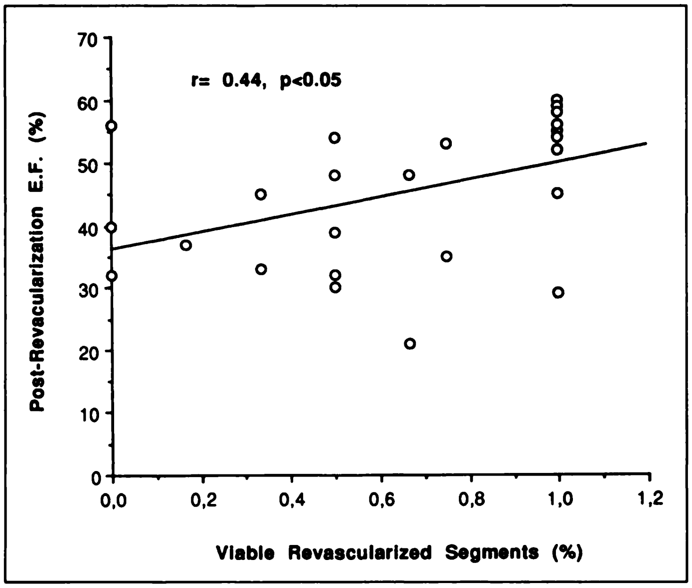

FIGURE 3. Relationship between percent of viable revascularized territory and postrevascularization ejection fraction.

revascularization as opposed to the 24 without such improvement (75% ± 58% versus 58% ± 11%, respectively). Similarly, redistribution ^{201}Tl uptake was higher in segments improving as opposed to those not improving (77 ± 17 versus 62% ± 13%, respectively, $p < 0.001$). The ROC curve for rest and redistribution images are shown in Figure 5. The area under the ROC curve for rest images was larger than that for redistribution images (0.77 ± 0.07 versus 0.72 ± 0.07, respectively), but this difference was not statistically significant. Again, as in the whole group of patients, a 65% threshold offered the best values of sensitivity, specificity and accuracy (Table 2). In particular, using rest data, sensitivity using a 65% threshold (i.e.,75%) was not significantly different from that obtained using a 50% threshold (i.e., 90%). However, both specificity and accuracy were significantly ($p < 0.05$) higher using a 65% threshold (85% and 81%, respectively) than using a 50% threshold (26% and 50%, respectively). As a consequence, PPV was significantly ($p < 0.05$) higher with the 65% threshold (75%) as opposed to the 50% threshold (42%).

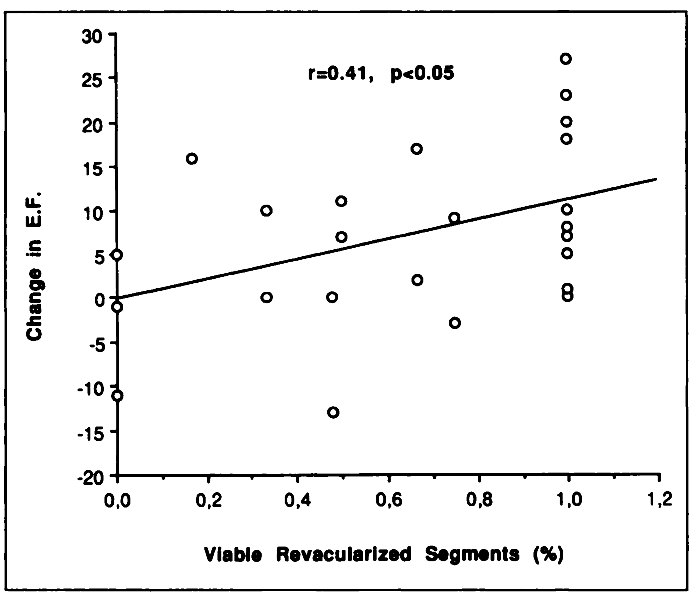

FIGURE 4. Relationship between percent of viable revascularized territory and change in ejection fraction.

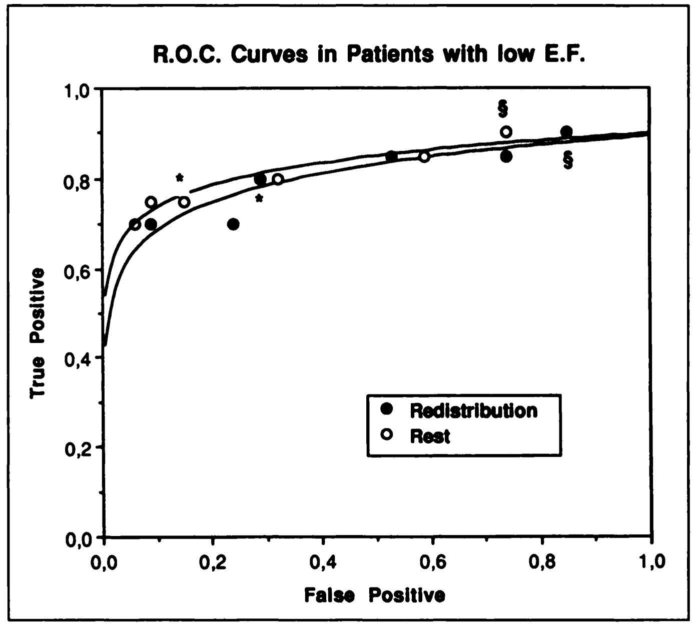

FIGURE 5. ROC curves for rest and redistribution ^{201}Tl imaging in patients with low ejection fraction. * 65% threshold; § 50% threshold.

Validation Population

Of the 144 segments analyzed in this additional group of patients, 68 showed normal wall motion, 24 were hypokinetic and 52 were a/dyskinetic at baseline echocardiography. Of the 52 a/dyskinetic segments, 42 underwent myocardial revascularization, and 26 of them (50%) improved thereafter. ^{201}Tl uptake at rest before revascularization was significantly ($p < 0.01$) higher in segments improving after revascularization (78 ± 10) as opposed to those that did not (60 ± 11). Similarly, significantly ($p < 0.05$) higher ^{201}Tl uptake at redistribution before revascularization was found in segments improving after revascularization (77 ± 13) as opposed to those that did not (67 ± 12). Table 3 shows the results obtained in this group of patients when using the 50% and 65% thresholds. Specificity, accuracy and PPV were significantly higher with the 65% threshold as opposed to the 50% threshold, while sensitivity and NPV were not different.

DISCUSSION

Semiquantitative rest-redistribution ^{201}Tl imaging is used to predict improvement of regional perfusion and of regional and global left ventricular function after revascularization (*9–14,17–21*). Current interpretation is based on semiquantitative analysis of redistribution images. Usually, an uptake ≥ 50% of the maximal activity in a territory showing systolic dysfunction is considered predictive of functional improvement after revascularization (*9–14*). The accuracy of such a cutoff, however, is not perfect. In particular, the use of a 50% threshold results in very high sensitivity but suboptimal specificity and positive predictive accuracy. In fact, many dysfunctional segments with ^{201}Tl uptake greater than 50% of maximal activity do not recover after revascularization.

The first major finding of this study is that relatively small changes in the cutoff selected to detect viability substantially impact the accuracy in predicting the effects of revascularization. Using an uptake of ^{201}Tl ≥ 65% on resting images as the cutoff, specificity increased from 24% (using a conventional 50% cutoff) to 76% and PPV from 55% to 77%, with a decrease in sensitivity. Using quantitative planar rest-redistribution ^{201}Tl and a 50% threshold, Ragosta et al. (*9*) found a PPV of 57% and an NPV of 77%. More recently, using quantitative SPECT

TABLE 2
Prediction of Recovery of Function with Rest-Redistribution Thallium-201 SPECT in A/Dyskinetic Segments: Analysis in Patients with Ejection Fraciton <40%

	Rest ^{201}Tl			Redistribution ^{201}Tl		
	Threshold 50%	Threshold 65%	p value	Threshold 50%	Threshold 65%	p value
Sensitivity	90%	75%	ns	90%	80%	ns
Specificity	26%	85%	<0.05	15%	71%	<0.05
Accuracy	50%	81%	<0.05	43%	74%	<0.05
PPV	42%	75%	<0.05	38%	59%	ns
NPV	82%	85%	ns	71%	86%	ns

PPV = positive predictive value; NPV = negative predictive value; ns = not significant.

rest-redistribution ^{201}Tl and a 55% threshold Matsunari et al. (*14*) obtained a very high sensitivity (92%) but a quite low specificity (33%). The results of the present article using a 50% threshold are very similar to those reported by these and other authors (*9–14*). It has been reported that, by varying the threshold, substantial changes in predictive accuracy are obtained (*20*). Qureshi et al. (*20*) found that lowering the threshold from 65% to 50% resulted in increased sensitivity but decreased specificity. In particular, when using a 65% threshold they found similar values of sensitivity (71%) and specificity (67%) to those reported in this study. On the other hand, Udelson et al. (*19*) found a PPV of 75% and an NPV of 92%. Some differences in the population studied, with a lower incidence of three-vessel disease and higher values of ejection fraction in this study, could explain this difference. Actually, when we analyzed a subgroup of patients with a low ejection fraction (mean 30% ± 6%) a PPV of 75% and an NPV of 85%, much closer to those reported by Udelson et al. (*19*), were found.

The second major finding of this study is that semiquantitative analysis of resting images, obtained 15–20 min after ^{201}Tl injection, provides better accuracy than redistribution images, as demonstrated by the significantly larger area under the ROC curve. This finding can be explained by considering the pathophysiology of chronic reversible regional dysfunction. It has been demonstrated that reversible contractile dysfunction can be sustained by either reduced perfusion (i.e., hibernation) or repetitive stunning of territories with normal perfusion at rest and impaired coronary reserve (*24–26*). In dysfunctional hypoperfused regions, reduction of blood flow delays the intrinsic washout rate of ^{201}Tl, which is the main determinant of ^{201}Tl redistribution images (*24–25*). Thus, it is conceivable that, due to the relative nature of ^{201}Tl measurements, ^{201}Tl uptake at redistribution may be increased when compared with regions with normal washout rate, thus overestimating the amount of viable tissue. If this is the case, initial ^{201}Tl uptake after rest tracer injection would contain more information on myocardial viability in patients with chronic coronary artery disease. However, hypoperfusion at rest may not occur even in territories supplied by severely stenosed vessels (*26*). When hypoperfusion at rest is not present, regional dysfunction may be sustained by repetitive episodes of ischemia leading to impaired coronary reserve. In this case, represented in our study by a small percentage of dysfunctional segments with ^{201}Tl uptake ≥ 80%, redistribution of ^{201}Tl was not expected, limiting the additional diagnostic value of delayed images after injection at rest.

Our study indicates that semiquantitative analysis of initial ^{201}Tl uptake provides similar or better diagnostic accuracy than analysis of delayed images for identifications of reversible dysfunctional myocardium. This has relevant clinical implications as it makes unnecessary the acquisition of a second delayed set of images, with obvious advantages for the patient and the nuclear medicine laboratory.

It has been suggested that the likelihood of functional improvement is influenced by the postrevascularization perfusion status (*9,19*). In this study, segments with reversible dysfunction had higher postrevascularization ^{201}Tl uptake than those with irreversible dysfunction and those nonrevascularized. However, ^{201}Tl uptake at rest did not change significantly from pre- to postrevascularization in segments with improved function. This is explained by the relatively high (mean 78%) ^{201}Tl uptake by these segments before revascularization. In addition lack of spatial resolution prevents the assessment of subendocardial perfusion. Thus, even in segments where transmural ^{201}Tl uptake did not change, flow redistribution with increased subendocardial perfusion after revascularization cannot be excluded. In this study, 90% of a/dyskinetic segments with postrevascularization ^{201}Tl uptake ≥ 80% improved their function thereafter as compared to 33% of a/dyskinetic segments that did not reach normal ^{201}Tl uptake. These findings, like those previously reported (*9,19*), indicated that adequacy of postrevascularization perfusion is an important factor in the recovery of regional contractile dysfunction.

TABLE 3
Prediction of Recovery of Function with Rest-Redistribution Thallium-201 SPECT in A/Dyskinetic Segments: Analysis in Validation Population

	Rest ^{201}Tl			Redistribution ^{201}Tl		
	Threshold 50%	Threshold 65%	p value	Threshold 50%	Threshold 65%	p value
Sensitivity	100%	96%	ns	96%	85%	<0.05
Specificity	13%	69%	<0.05	25%	50%	<0.05
Accuracy	67%	86%	<0.05	69%	71%	ns
PPV	65%	83%	<0.05	68%	73%	ns
NPV	100%	92%	ns	80%	67%	<0.05

PPV = positive predictive value; NPV = negative predictive value; ns = not significant.

Study Limitations

Our study was conducted in a population with a relatively wide range of left ventricular dysfunction. Therefore, it would be important to confirm this observation in a more select population with severely impaired left ventricular function. Differences of ROC curve areas could be accounted for by greater noise content of redistribution images. However, in our population the total myocardial counts of short-axis rest and redistribution were not statistically different (92135 $\pm$ 22897 versus 91853 $\pm$ 21699, respectively, p not significant). In this study, apical myocardium was not included in the segmental analysis since the attribution of the apex to a vascular territory is uncertain and this may have interfered with the postrevascularization analysis. In addition, comparison of short-axis tomograms obtained from two different modalities (i.e., echocardiography and ^{201}Tl tomography) allows the minimization of the misalignment of segments. Although the 65% threshold found to be the best predictor of outcome after revascularization is in line with other published studies, it would be helpful for each nuclear medicine laboratory to make an internal data analysis to select the best cutoff for their particular institution. Both technical and pathophysiological factors inherent to count recovery, resolution, attenuation and scatter correction (or not) and the clinical characteristics of the patients studied may account for variations in the most accurate cutoff among different institutions.

CONCLUSION

Optimal interpretation of ^{201}Tl imaging at rest for the identification of myocardial viability can be accomplished by measuring the regional uptake of tracer early after injection and by selecting the most appropriate cutoff to differentiate reversible from irreversible regional contractile dysfunction.

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