Early Detection of Restenosis After Successful Percutaneous Transluminal Coronary Angioplasty by Exercise-Redistribution Thallium Scintigraphy

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The value of exercise testing and thallium scintigraphy in predicting recurrence of angina pectoris and restenosis after a primary successful transluminal coronary angioplasty (PTCA) was prospectively evaluated. In 89 patients, a symptom-limited exercise electrocardiogram (ECG) and thallium scintigraphy were performed 4 weeks after they had undergone successful PTCA. Thereafter, the patients were followed for 6.4 ± 2.5 months (mean ± standard deviation) or until recurrence of angina. They all underwent a repeat coronary angiography at 6 months or earlier if symptoms recurred. PTCA was considered successful if the patients had no symptoms and if the stenosis was reduced to less than 50% of the luminal diameter. Restenosis was defined as an increase of the stenosis to more than 50% luminal diameter. The ability of the thallium scintigram (presence of a reversible defect) to predict recurrence of angina was 66%, vs 38% for the exercise ECG (ST-segment depression or angina at peak workload). Restenosis was predicted in 74% of patients by thallium scintigraphy, but only in 50% of patients by the exercise ECG. Thus, thallium scintigraphy was highly predictive but the exercise ECG was not ($p < 0.005$). These results suggest that restenosis had occurred to some extent already at 4 weeks after the PTCA in most patients in whom it was going to occur.

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Restenosis after primary successful percutaneous transluminal coronary angioplasty (PTCA) occurs in 19 to 36% of patients within the first 6 months after the procedure.[1-5] This restenosis may manifest itself by changes in the patient's clinical status and may be detected by noninvasive diagnostic tests or by coronary angiography. Scholl[2] and Hirzel[6] and their co-workers showed that an abnormal response on the exercise electrocardiogram (ECG) and a myocardial perfusion defect on the thallium scintigram is associated with angiographically documented restenosis of the dilated vessel or is a sign of the presence of additional disease. The present study was performed to determine the value of early noninvasive testing in the prediction of restenosis and recurrence of symptoms. The study patients had undergone technically successful PTCA, which resulted in a "complete" anatomic correction. They were all free of angina pectoris up to the time of exercise electrocardiography and thallium scintigraphy, which were performed a median of 4 weeks after PTCA. Follow-up data regarding subsequent recurrence of symptoms and repeat coronary angiography a median of 6 months after the procedure were compared in a prospective manner with the noninvasive test results obtained at 4 weeks.

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Methods

Between September 1980 and September 1983, 296 consecutive first PTCA procedures for stable or unstable angina pectoris were attempted at the Thoraxcenter; 221 were primary successes. The 162 patients from our own institution were asked to cooperate with a follow-up protocol, which included an exercise electrocardiogram and thallium scintigram 4 to 6 weeks after the procedure, a visit to the outpatient clinic at 2-month intervals and a repeat angiogram at 6 to 8 months. The 59 patients referred from institutions in other cities were excluded. One hundred twenty patients met the inclusion criteria for the present study: "complete" anatomic correction,

TABLE I Characteristics of the Angioplasty Procedure

		Group 1 Restenosis* (n = 35)		Group 2 Long-Term Success (n = 54)
Dilated vessel (n = 93)	LAD	25		34
	LCX	6		3
	RCA	5		19
	Bypass	1		0
% diameter stenosis	Pre	66 ± 15	NS	62 ± 11
	Post	33 ± 12	NS	31 ± 13
	Late	62 ± 14		31 ± 13
Pressure gradient	Before	0.64 ± 0.16 (33)	NS	0.61 ± 0.13 (55)
	After	0.19 ± 0.11 (35)	NS	0.16 ± 0.10 (55)

The translesional pressure gradient is normalized for the mean aortic pressure; numbers under parentheses refer to the number of available measurements. * Stenosis more than 50% in luminal diameter at repeat angiography.
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; NS = not significant; RCA = right coronary artery.

TABLE II Exercise Test Results and Recurrence of Symptoms During Follow-Up

	Group 1 Restenosis (n = 35)		Group 2 Long-Term Success (n = 54)
Weeks after PTCA (range)	4.7 ± 2.3 (2–11)	NS	4.7 ± 1.7 (2–8)
Maximal workload (% of predicted)	96 ± 13	NS	90 ± 16
Maximal heart rate	140 ± 28	NS	149 ± 22
Abnormal exercise ECG	13		13
Angina during test	1		3
ST depression >0.1 mV	11		10
Both	1		0
Abnormal scintigram	26		9
Recurrent angina	23		6
New myocardial infarction	0		0

ECG = electrocardiogram; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

i.e., no significant residual coronary obstructions after PTCA; absence of angina until the time of exercise testing; and ability to complete the exercise test. Thirty-one patients refused to undergo repeat coronary angiography. This report is thus based on the prospective evaluations of 89 patients, 74 men and 15 women. A single stenosis was dilated in 85 patients and 2 stenoses were dilated in 4 patients. The dilated vessel was the left anterior descending artery in 59 patients, the left circumflex in 9, the right coronary artery in 24 and the distal anastomotic site of a saphenous vein bypass graft on the left anterior descending coronary artery in 1 patient. PTCA was performed according to the technique of Gruentzig,[1] with Schneider equipment through a femoral route. Details regarding the procedure used in our laboratory were described previously.[7,8] The PTCA procedure was considered successful when the residual stenosis was less than 50% in diameter with a good run off and filling of the distal vessel at angiography. In the 91 stenoses with satisfactory recordings, the residual pressure gradient (normalized for the mean aortic pressure) was less than 0.20 in 63 cases and less than 0.40 in 25 cases.

In an attempt to reduce the restenosis rate,[3,5] all patients received nifedipine, 10 mg every 2 hours for the first 8 hours after the procedure and received maintenance therapy on salicylic acid, 500 mg/day, and nifedipine, 10 mg 3 to 6 times daily, until repeat angiography was performed. Beta-blocking agents were stopped unless the patient had hypertension. Repeat angiography was performed 7.0 ± 2.3 months (mean ± standard deviation) after PTCA in the patients who remained asymptomatic and 4.9 ± 2.3 months after PTCA in patients who had recurrent angina during follow-up. Coronary angiography was performed in multiple views (including hemiaxial views for the left coronary artery) and were interpreted visually without knowledge of the initial noninvasive test results. The clinical definition of restenosis was an increase of the diameter stenosis of the dilated lesion above the 50% level. In addition, quantitative analysis of the dilated stenosis was obtained in the same angiographic projection for each angiogram by means of our computer-based coronary angiographic analysis system.[9] Based on these accurate and more objective measurements of stenosis severity,[10] the definition of restenosis used by the National Heart, Lung, and Blood Institute (NHLBI) registry[4] was applied as well, i.e., an increase in stenosis of at least 30% from the immediate post-PTCA result or the loss of at least half the initial gain in diameter.

The exercise studies were performed 4.7 ± 1.9 weeks after PTCA. The subjects performed a symptom-limited exercise test on the bicycle ergometer with stepwise increments of 20 W/min. The 3 orthogonal leads XYZ of the Frank lead system were recorded and analyzed as previously described.[11] The reported sensitivity and specificity for the diagnosis of significant coronary disease were 85% and 90%, respectively. Horizontal ST depression of 0.1 mV or greater and typical angina during exercise were considered as abnormal (or positive) responses. One minute before peak exercise, thallium, 1.5 mCi, was injected intravenously. Imaging was started 5 minutes later in 3 views: anterior, left anterior oblique 45° and 65°. Static planar images (500 kcounts full field, zoom 2 ×) were obtained after exercise and 4 hours later with a Searle Phogamma V camera. The scintigraphic images were processed on a DEC gamma-11 system with a quantification procedure developed at our institution.[12] The late image was corrected for acquisition time differences with respect to the early image. The exercise and redistribution images were registered on the basis of the detected positions of point sources taped to the patient's chest. After automated left ventricular contour detection[13] and interpolative background correction,[14] circumferential profiles were computed at 6° intervals. The profiles of the early and late images were normalized for the maximal value in the early image (100%) excluding the outflow tract of the left ventricle. The analog Polaroid® images from the gamma camera, the processed images and the circumferential profiles were analyzed prospectively on a routine basis by 3 experienced observers without knowledge of the angiographic data. The thallium uptake in a total of 11 segments was scored both in the postexercise and late images on a 5-point scale: 0 = no thallium uptake; 1 = severely abnormal; 2 = definitely abnormal; 3 = doubtfully abnormal; and 4 = normal. The following segments were defined: posteroseptal, inferior, apical and anterolateral in the anterior view; anteroseptal, apical and posterolateral in the left anterior oblique 45° view; and anterior, apical, inferior and posterior in the left anterior oblique 65° view. The scores of all segments were summed per patient and the difference between late and early postexercise sums was taken as a measure of the amount of redistribution. An increase in thallium uptake score of 2 points or more between postexercise and late images was taken as the cutoff between normal (absence of exercise-induced ischemia) and abnormal (presence of exercise induced ischemia) scintigrams. Persistent defects without redistribution were considered to represent scars

TABLE III Positive and Negative Predictive Values of the Noninvasive Tests

	Restenosis					
	50% Diameter		NHLBI Criteria*		Recurrent Angina	
	Present (n = 35)	Absent (n = 54)	Present (n = 37)	Absent (n = 52)	Present (n = 29)	Absent (n = 60)
Predictive value	+	−	+	−	+	−
Exercise ECG						
ST segment	55 (12/22)	66 (44/67)	55 (12/22)	63 (42/67)	32 (7/22)	67 (45/67)
ST and/or AP	50 (13/26)	65 (41/63)	54 (14/26)	63 (40/63)	38 (10/26)	70 (44/63)
Thallium scintigraphy	74 (26/35)	83 (45/54)	74 (26/35)	80 (43/54)	66 (23/35)	89 (48/54)

Positive (+) and negative (−) predictive values of respectively abnormal and normal tests are percentages.

* An increase in stenosis of 30% or more from the immediate post-PTCA result and/or the loss of at least half the initial gain in diameter.

AP = angina pectoris; ECG = electrocardiogram; NHLBI = National Heart, Lung, and Blood Institute.

without exercise-induced ischemia. With this analysis, the previously reported sensitivity and specificity for the diagnosis of significant coronary artery obstructions were 80 and 88%, respectively.[12] The patients were followed up in the outpatient clinic until occurrence of typical angina pectoris or a new myocardial infarction. The follow-up duration was 6.4 ± 2.5 months. No patient died during this period.

Results are presented as mean ± standard deviation. The *t* test for paired or unpaired data was used whenever appropriate. The positive predictive value for restenosis (or recurrent angina) was calculated as the frequency of restenosis (or recurrent angina) in those with abnormal test results. The negative predictive value for the absence of restenosis (or recurrent angina) was calculated as the frequency of long-term success in those with normal test results. Differences between correct and incorrect classifications by exercise ECG vs thallium were evaluated by the McNemar test.

Results

The characteristics of the PTCA procedure are listed in Table I for 2 groups: patients with restenosis of the dilated vessel, i.e., diameter stenosis at repeat angiography more than 50% (n = 35), and patients with long-term success (n = 54). There was no significant difference between these 2 groups in the pressure gradient across the stenosis either before or after PTCA. The exercise test results and the recurrence of symptoms during the follow-up are summarized for both groups in Table II. The mean timing of exercise testing after PTCA and the resultant maximal workloads and heart rates achieved were similar for both groups. Ninety-two percent of the patients reached 80% of their predicted maximal workload. An abnormal exercise ECG was observed in 26 patients: 21 had ST-segment depression, 4 had angina at peak workload and 1 patient had both.

Exercise-induced ischemia as assessed by the thallium redistribution was observed in 35 patients. During the follow-up, angina recurred in 29 patients. No patient had a new myocardial infarction in the territory of the dilated vessel. The positive and negative predictive values of each single test are shown in Table III. Thallium was superior to the exercise ECG both for the prediction of recurrent stenosis and recurrent angina (both $p < 0.005$). The predictive value for recurrent stenosis of the 4 combinations of test results is shown in Figure 1. An abnormal scintigraphic response was associated with a high incidence of restenosis, which was not influenced by the result of the exercise ECG: 71% of restenoses when both tests were abnormal vs 76% when tests were discordant. Conversely, a normal scintigraphic response was associated with a low incidence of restenosis, which was also not influenced by the result of the exercise ECG: 14% of restenosis when both tests were normal and 25% when tests were discordant.

The value of combined noninvasive test results for the prediction of recurrent angina is shown in Figure 2. Angina recurred in 64% of patients with both tests abnormal and in 67% of patients with only thallium abnormal. In the presence of a normal scintigraphic response, the recurrent angina was about 10%, regardless of the result of the response on the exercise ECG.

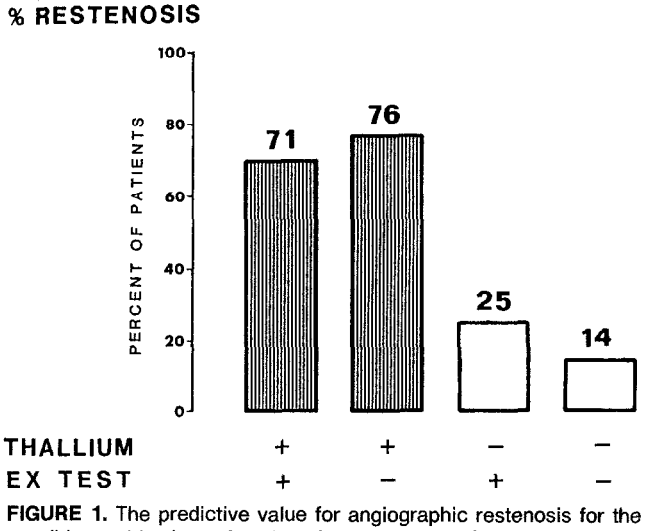

FIGURE 1. The predictive value for angiographic restenosis for the possible combinations of noninvasive test results: (+) = abnormal test and (−) = normal test; EX TEST = exercise electrocardiogram. **Shaded columns** represent the patients with abnormal scintigraphic responses. Both test results were abnormal in 14 and normal in 42 patients; only thallium was abnormal in 21 and only exercise ECG in 12 patients.

By the NHLBI definition of restenosis based on the quantitative analysis of the angiograms, only 6 patients were categorized in another group; 37 had restenosis by these criteria. The predictive value of the noninvasive tests was not significantly different: 54% restenosis when the exercise ECG was abnormal vs 74% restenosis when the scintigram was abnormal (Table III).

Discussion

The present report demonstrates that early assessment of myocardial perfusion by exercise thallium scintigraphy has a high predictive value for restenosis and recurrence of angina in patients who underwent a technically satisfactory PTCA. Previous studies[2,6,15–17] assessing the results of PTCA by noninvasive tests have focused on the reversibility of the ischemic changes after a successful procedure and on their induction at the time of recurrence. However, more recently, DePuey et al[18] reported that failure to increase ejection fraction or the development of a new regional wall motion abnormality during exercise radionuclide ventriculography early after PTCA predicted restenosis at 4 to 12 months in 73% of 41 patients. Their findings and those of the present study suggest that restenosis had occurred to some extent already at 4 weeks in most patients in whom it was documented later. This observation raises speculations about the underlying mechanism of restenosis after dilatation. Fibrocellular proliferations as a reparative response to coronary wall laceration has been described in necropsy studies[19] and may represent the pathologic substrate of early restenosis. In analogy with aortic dissection, exposure of vascular smooth muscle cells to blood may trigger an exuberant tissue reaction, leading to obliteration of the false channel and eventually of the functional lumen. Preliminary data[20] from experimental angioplasty in pigs suggest that balloon dilatation is a potent stimulus to early platelet deposition and subsequent intimal hyperplasia. In this model, the reparative process was observed as early as 2 weeks after the procedure. If present in patients, such ongoing processes may have induced the observed perfusion abnormalities. Since only successful cases were included and the decrease in stenosis severity and in the transstenotic pressure gradient were comparable in patients with restenosis and long-term success, there is no evidence that recurrence occurred predominantly in patients in whom the dilatation was incomplete. In this study, the high predictive value of the perfusion scintigram contrasts with the poor predictive value of the exercise electrocardiographic response, especially for the prediction of restenosis.

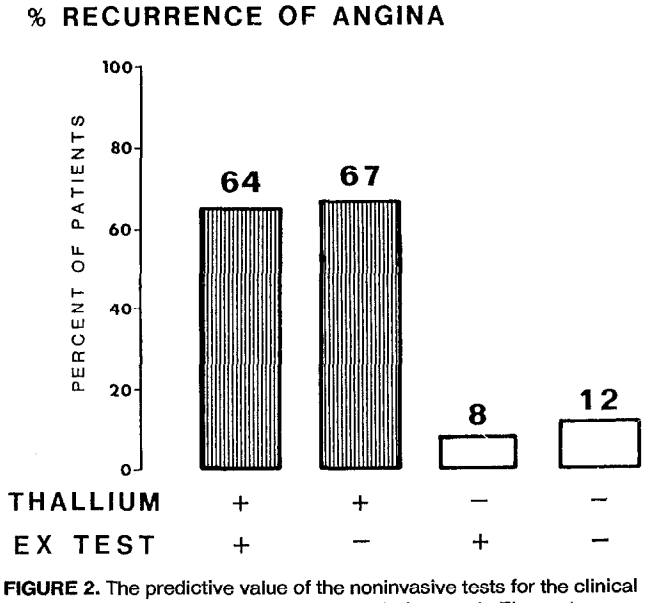

FIGURE 2. The predictive value of the noninvasive tests for the clinical endpoint (recurrent angina); other abbreviations as in Figure 1.

This could be explained by a lower sensitivity of the exercise ECG compared with thallium scintigraphy in the detection of moderate coronary artery narrowing. The combination of a normal exercise ECG with a reversible thallium perfusion abnormality could be an early indicator of the presence of a noncritical stenosis, still insufficient to induce ST-segment depression during exercise.[21] Indeed, 66% of the patients with an initially abnormal scintigram became symptomatic at a later stage during the follow-up period.

The problem of defining restenosis is not trivial. Applying the stringent criteria of the NHLBI registry to visual estimations of stenosis severity has major limitations, due to the large intra- and interobserver differences in interpretation, especially for stenoses between 20 and 80%.[22] Therefore, the stenoses were analyzed by computerized edge detection. Although this method may not be optimal after angioplasty,[9] it provides an objective and quantitative measurement, avoiding unintentional bias in reading the angiograms. This complex definition of restenosis resulted however in similar findings as the usual clinical approach based in the presence or the absence of a hemodynamically significant stenosis (>50% luminal diameter). By this clinical definition, restenosis of the dilated artery was observed in 39% and recurrent angina pectoris in 33% of the patients.

The true incidence of recurrence is probably lower because most of the patients who refused to undergo repeat angiography were asymptomatic. The patient population is thus biased in favor of those with recurrent stenosis. The clinical implication of these findings for the routine management of patients who undergo PTCA remains to be established. Certainly we share with DePuey et al[18] the conclusion that an abnormal noninvasive test early after PTCA in an asymptomatic patient is an indication for close clinical monitoring in view of the high chance of recurrence of symptoms. We believe that decisions to perform repeat angiography, followed by a redilatation when restenosis is found, should primarily be based on the severity of angina rather than on the results of the testing procedure. This is analogous to the issue of bypass surgery for documented coronary artery disease in asymptomatic patients, particularly since no benefit of surgical intervention over pharmacologic treatment was shown in mildly or nonsymptomatic patients.[23] Until the outcome

of prophylactic PTCA is studied, the procedural complications and incomplete success rates militate against performing PTCA when diagnostic testing reveals restenosis in the absence of symptoms.

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