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Assessment of "Silent" Restenosis and Long-Term Follow-Up After Successful Angioplasty in Single Vessel Coronary Artery Disease: The Value of Quantitative Exercise Electrocardiography and Quantitative Coronary Angiography

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Exercise electrocardiographic (ECG) testing during follow-up after coronary angioplasty is widely applied to evaluate the efficacy of angioplasty, even in asymptomatic patients. One hundred forty-one asymptomatic patients without previous myocardial infarction underwent quantitative exercise ECG testing and quantitative coronary angiography 1 to 6 months after successful angioplasty in single vessel coronary artery disease to 1) determine the value of exercise ECG testing to detect "silent" restenosis, and 2) assess the long-term prognostic value of exercise ECG testing and coronary angiography.

The prevalence of restenosis (defined as ≥50% luminal narrowing at the dilation site) was 12% in this selected study group. Of 26 patients with an abnormal exercise ECG (ST segment depression ≥0.1 mV), only 4 (15%) showed recurrence of stenosis. Sensitivity and specificity for detection of restenosis were 24% and 82%, respectively.

One hundred thirty-four patients (95%) were followed up 1 to 64 months (mean 35) after exercise ECG testing and coronary angiography. Thirty-two patients (24%) experienced a cardiac event: in 25 patients (78%) the initial event was recurrent angina pectoris (New York Heart Association class III or IV) and in 7 patients (22%) it was myocardial infarction, although cardiac death did not occur. The mean interval between exercise ECG testing and the initial cardiac events was 14 months (range 1 to 55), whereas 47% of the initial events took place ≤6 months after exercise ECG testing. An abnormal exercise test result and angiographic restenosis had, respectively, a predictive value of 36% and 41% and a relative risk of 1.7 and 1.9. Gender, age and extent of ST segment depression were not related to the occurrence of cardiac events.

Thus, exercise ECG testing is not the technique of choice to detect silent restenosis after coronary angioplasty of single vessel coronary artery disease. An abnormal exercise test result and angiographic evidence of restenosis had only limited value in predicting long-term outcome in this patient group.

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In the last decade, percutaneous transluminal coronary angioplasty has become an important interventional tool for managing patients with coronary artery disease. One of the major drawbacks of coronary angioplasty is the relatively frequent recurrence of stenosis at the dilation site, usually within 6 months of the procedure (1–8). Recurrence of a flow-limiting stenosis can usually be identified by symptoms of chest pain similar to those that occurred before angioplasty, commonly after a symptom-free period. In addition to the medical history, exercise electrocardiographic (ECG) testing is generally performed as a noninvasive approach to confirm the recurrence of a coronary artery obstruction because it is a relatively simple, safe and inexpensive test.

Because most patients undergoing coronary angioplasty have single vessel coronary artery disease (9) and because inclusion of subjects with prior myocardial infarction will

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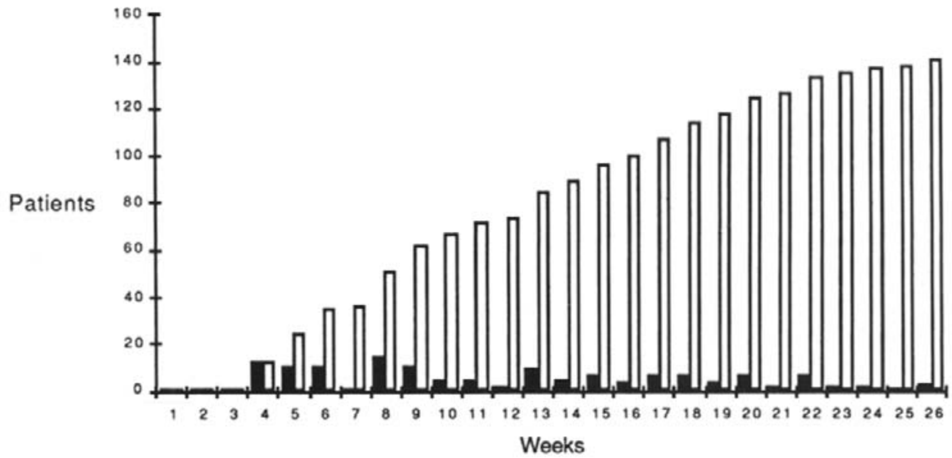


Figure 1. Time distribution of exercise electrocardiographic testing in 141 patients after coronary angioplasty. **Filled bars** represent number of tests performed per week and **open bars** the cumulative number of tests performed.

(falsely) increase the accuracy of exercise tests and will influence the long-term prognosis (10), we studied a selected patient group without angina pectoris and without prior myocardial infarction after successful coronary angioplasty for single vessel and single lesion coronary artery disease.

The purpose of the present study was twofold: to 1) assess the diagnostic value of exercise ECG testing for "silent" restenosis, and 2) determine the long-term prognostic value of an abnormal exercise test result and of angiographically proved restenosis.

Methods

Study patients. Of 500 consecutive patients who underwent initial successful coronary angioplasty, 141 met the specific inclusion criteria for the present study: angioplasty for single vessel disease, no other significant lesions, no historical or ECG evidence of prior myocardial infarction, absence of typical angina pectoris before follow-up investigation, ability to perform the exercise ECG test, and a diagnostic exercise ECG, that is, without left ventricular hypertrophy, bundle branch block or a digitalis effect.

The study group consisted of 117 men and 24 women with a mean age of 55 ± 9 years (range 31 to 75). The dilated vessel was the right coronary artery in 24 patients (17%), left anterior descending coronary artery in 96 (68%) and left circumflex coronary artery in 21 (15%).

The Committee on Human Research at our institution approved the study protocol. All patients gave informed consent for follow-up coronary angiography and exercise ECG testing within 1 to 6 months after coronary angioplasty and at long-term follow-up study.

Coronary angioplasty procedure. Coronary angioplasty by a femoral route was performed according to the technique of Gruentzig et al. (11). Details of the procedure used in our laboratory have been described previously (12,13). Patients received maintenance therapy of aspirin, 500 mg/day. All antianginal medication was withheld, but beta-adrenergic blocking agents for hypertension were continued throughout the follow-up investigations. Successful coronary angioplasty was defined as 1) <50% diameter residual stenosis on visual inspection of the coronary angiogram immediately after angioplasty, and 2) absence of recurrence of angina pectoris, repeat angioplasty, coronary bypass surgery, myocardial infarction or cardiac death at the time of short-term follow-up exercise ECG testing and coronary angiography.

Quantitative coronary angiography. Repeat coronary angiography was performed a mean of 92 ± 46 days after coronary angioplasty in multiple left and right anterior oblique projections, including views with cranial and caudal angulation. Quantitative analysis of the coronary angiogram was performed with the computer-based Cardiovascular Angiography Analysis System (CAAS) previously described in detail (14–17). A coronary artery stenosis was considered significant if the luminal diameter was narrowed by ≥50%.

Quantitative exercise electrocardiography. The exercise test was performed a mean 87 ± 48 days (range 1 to 6 months) after coronary angioplasty (Fig. 1). The mean interval between exercise ECG testing and repeat coronary angiography was 4 ± 12 days. The subjects performed a symptom-limited exercise test on a bicycle ergometer with stepwise increments of 20 W/min. The three orthogonal XYZ leads of the Frank lead system were recorded and analyzed in a quantitative manner as previously described (18). Horizontal ST segment depression ≥0.1 mV was considered an abnormal test response.

Long-term follow-up. Patients were followed up for ≥12 months after the short-term follow-up exercise ECG test. In patients with a cardiac event, follow-up was considered terminated, even if this event occurred <12 months after the exercise ECG test. A second cardiac event in the same patient was noted when it occurred <3 months after the first event and was considered to be related to that event (for example, angina pectoris and subsequent reintervention). The information was obtained by clinic visit, questionnaire and telephone interview with the patient or referring cardi-

Table 1. Results of Quantitative Exercise Electrocardiography Compared With Quantitative Coronary Angiography in 141 Patients After Coronary Angioplasty

Characteristic	Result	95% CL
Prevalence of restenosis	12% (17/141)	7% to 17%
Sensitivity	24% (4/17)	7% to 50%
Specificity	82% (102/124)	76% to 89%
PVP	15% (4/26)	4% to 35%
PVN	87% (102/115)	83% to 94%
Accuracy	75% (106/141)	68% to 82%

Numbers in parentheses represent number of events per number of patients. CL = confidence limit; PVP = predictive value of an abnormal test result; PVN = predictive value of a normal test result.

ologist. Cardiac events were classified as recurrent angina pectoris (New York Heart Association functional class III or IV), reintervention by repeat angioplasty or coronary artery bypass graft surgery, myocardial infarction and cardiac death.

Statistical analysis. The results of exercise ECG testing were compared with those of coronary angiography with respect to the following characteristics: sensitivity, specificity, predictive value of an abnormal test result, predictive value of a normal result and diagnostic accuracy. Values are expressed as mean values ± SD. To determine the prognostic value of the variables, relative risk ratios were calculated. The 95% confidence limits for all comparisons were calculated (19).

Results

Short-term follow-up coronary angiography and exercise ECG testing (Table 1). At follow-up coronary angiography the prevalence of restenosis was 12% (17 of 141 patients). No complications occurred during exercise testing. In none of the patients was exercise-induced systolic hypotension or ST segment elevation observed. The exercise test result was abnormal in 26 patients (18%); of these, restenosis was present in 4 (15%). One hundred fifteen patients had a normal exercise test result; of these, restenosis was absent in 102 (87%). The predictive values of the test in this study group and the sensitivity and specificity are shown in Table 1. Three of the 17 patients with restenosis experienced angina pectoris during the exercise ECG test.

Analysis of false negative and false positive test results (Tables 2 and 3). Patients with false negative and false positive test results are described in Tables 2 and 3. The mean percent diameter stenosis in the true positive and in the false negative groups were not statistically different (59% versus 57%).

Four patients with a false negative test response were taking beta-blocking medication. Only two of these patients did not achieve the maximal predicted heart rate. In two patients not taking medication, inadequate exercise capacity was a possible cause for an incorrect normal test result. Disease confined to a side branch was observed in two

Table 2. Patients (n = 13) With False Negative Test Results According to the Criterion of ≥50% Coronary Diameter Narrowing

Pt.	Vessel (segment)	Age (yr)/ Gender	%DS	AP	BB	%MPH	Reason
1	LAD	51/M	52.5	–	–	105	–
2	LAD	36/M	52	–	–	98	BD/DD
3	RCA	62/M	51	–	–	91	–
4	LAD	58/F	58	–	–	99	BB
5	LCx	69/M	52.5	–	–	76	HR
6	RCA	50/M	51	–	+	108	BB
7	LAD	57/M	100	–	–	91	–
8	LAD	55/M	51.3	–	–	75	HR
9	RCA	56/M	55.3	–	–	74	HR
10	LCx	49/M	59.3	–	+	72	BB/HR
11	LCx	68/M	54.5	+	–	107	BD/DD
12	LAD	56/M	55.4	–	+	59	BB/HR
13	LAD	63/M	52	+	–	105	–

AP = angina pectoris during the test; BB = administration of beta-adrenergic blocking agents; BB/DD = coronary branch or distal disease; F = female; HR = low heart rate (<90% of maximal predicted heart rate); LCx = left circumflex coronary artery; M = male; %DS = percent diameter stenosis; %MPH = percent maximal predicted heart rate; Pt. = patient; RCA = right coronary artery; + = present; – = absent.

Table 3. Patients (n = 22) With False Positive Test Results According to the Criterion of ≥50% Coronary Diameter Narrowing

Pt.	Vessel (segment)	Age (yr)/ Gender	%DS	AP	%MPH
1	RCA	63/M	20.5	–	112
2	RCA	59/M	2	–	141
3	RCA	66/M	38.5	–	104
4	LCx	45/M	47.5	–	99
5	LAD	63/M	44.5	–	105
6	LAD	45/M	45.5	–	105
7	LAD	59/M	33.5	–	124
8	LAD	70/M	10	+	117
9	LAD	52/M	37.5	+	90
10	LAD	62/F	38.9	–	91
11	RCA	59/M	29.9	–	121
12	LCx	60/M	31.5	+	73
13	LAD	53/M	32.7	–	83
14	LAD	67/M	40.8	–	134
15	LAD	58/M	21.3	+	113
16	LCx	56/M	24.8	–	118
17	LAD	65/F	26.6	+	119
18	LAD	50/M	41.6		78
19	LAD	67/M	25.2	–	103
20	LAD	68/M	23.4	–	100
21	RCA	65/F	13.5	–	133
22	LCx	60/M	48.7	–	124

Abbreviations as in Table 2.

Table 4. Prognostic Value of Exercise Electrocardiography, Coronary Angiography, Gender, Age and Dilated Coronary Artery in 134 Patients With Follow-Up Study

Characteristic	Events	RR	95% CL
Exercise ECG			
Abnormal	36% (9/25)	1.706	0.90–3.22
Normal	21% (23/109)	—	—
Coronary angiography			
≥50% DS	41% (7/17)	1.927	0.99–3.75
<50% DS	21% (25/117)	—	—
Gender			
Male	24% (27/112)	1.061	0.46–2.45
Female	23% (5/22)	—	—
Age (yr)			
≥60	19% (9/48)	0.701	0.35–1.39
<60	27% (23/86)	—	—
Dilated artery			
LAD	20% (18/91)	—	—
RCA	33% (8/24)	1.685	0.84–3.40
LCx	32% (6/19)	1.596	0.73–3.49

Events = recurrent angina pectoris (New York Heart Association class III or IV), repeat coronary angioplasty, coronary artery bypass graft surgery and myocardial infarction; RR = relative risk; other abbreivations as in Tables 1 and 2.

patients with a normal exercise ECG (posterolateral branch of the left circumflex coronary artery and first diagonal branch of the left anterior descending coronary artery). When considering the distribution of restenosis in the separate coronary arteries, a normal ST response during exercise was found in 7 of 10 patients with a lesion in the left anterior descending coronary artery, 3 of 4 patients with a lesion in the left circumflex coronary artery and 3 of 3 patients with a lesion in the right coronary artery.

Female gender appeared not to be correlated with a false positive response, as the proportion of women with a positive test but without restenosis did not differ from the proportion of women in the entire study group (14% versus 17%). Five of the 22 patients with an abnormal exercise ECG but without angiographic restenosis experienced angina pectoris during the test.

Long-term follow-up (Tables 4 and 5). Long-term follow-up was obtained in 134 patients (95%) (22 women [16%] and 112 men [84%]) with a mean age of 55 ± 9 years (range 31 to 75). During an average follow-up period of 35 months (range 1 to 64), 32 (24%) of these patients experienced a cardiac event (Fig. 2). In 25 patients the initial event was recurrent class III or IV angina pectoris and in 7 patients it was acute myocardial infarction. The mean interval between the exercise ECG and the initial cardiac event was 14 months (range 1 to 55); 47% of the initial events took place ≤6 months after the exercise ECG (Fig. 3). The incidence of cardiac events in relation to gender, age, repeat coronary angiography and the results of exercise ECG testing is presented in Table 4. The relative risk of a further cardiac event was 1.71 for an abnormal exercise ECG response and 1.95 for the presence of angiographic restenosis. The extent of ST segment depression (Table 5), gender and age were not significantly related to the occurrence of events. Patients with left anterior descending coronary artery dilation experienced less cardiac events in comparison to those with angioplasty of the right coronary artery and left circumflex coronary artery (Fig. 4).

Table 5. Degree of ST Segment Depression and Subsequent Cardiac Events in 134 Patients With Follow-Up Study

ST Depression (mV)	Events	95% CL
<0.1 (normal)	21% (23/109)	13% to 29%
≥0.1 (abnormal)	36% (9/25)	18% to 57%
0.1–0.2	50% (6/12)	21% to 79%
0.2–0.3	33% (3/9)	7% to 70%
≥0.3	0% (0/4)	0% to 60%

Definitions and abbreviations as in Tables 1 and 4.

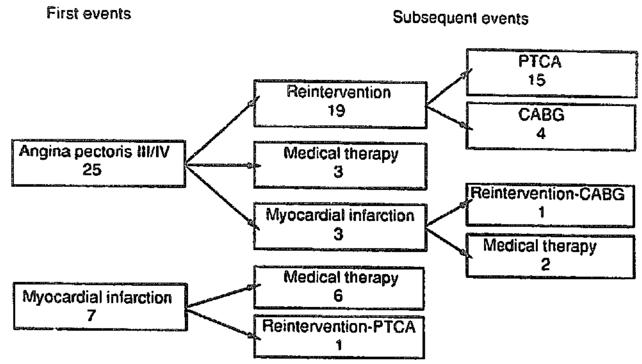
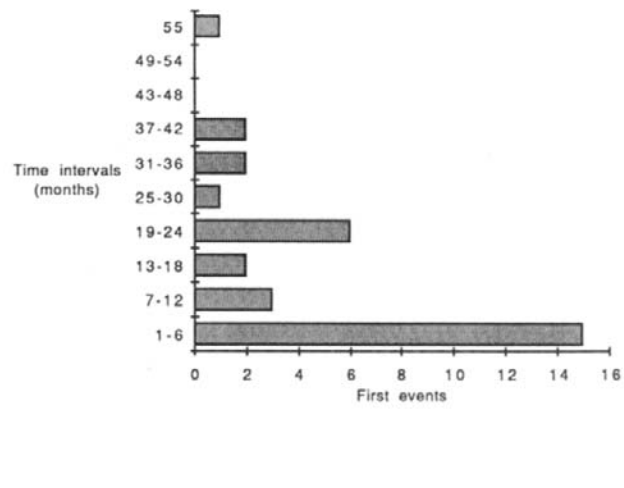


Figure 2. Number of first and subsequent cardiac events in 141 patients. CABG = coronary artery bypass graft surgery; III/IV = New York Heart Association class III or IV; PTCA = percutaneous transluminal coronary angioplasty.

Figure 3. Time distribution of the 32 first cardiac events during long-term follow-up.



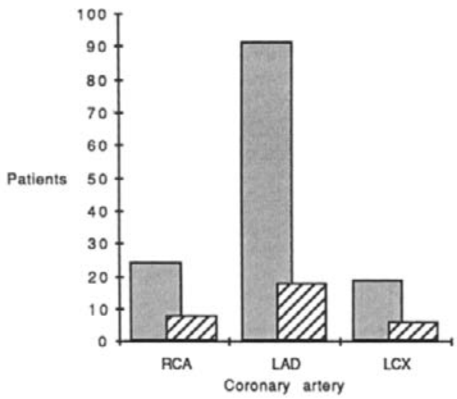


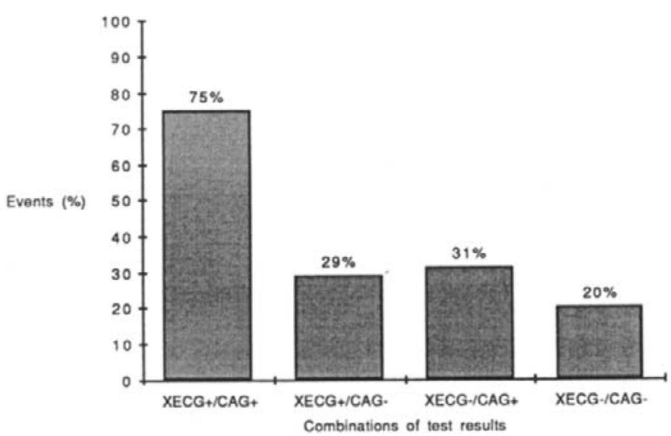
Figure 4. Relation between the distribution of dilated vessels (shaded bars) and the occurrence of cardiac events (hatched bars). LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

The combination of results of exercise ECG testing and coronary angiography and their prognostic content is depicted in Figure 5. Only four patients had both an abnormal exercise ECG test and restenosis. Three (75%) of these four patients experienced a cardiac event (recurrent angina pectoris in two and myocardial infarction in one). Thirty-four patients had discordant test results. Six (29%) of 21 patients with an abnormal exercise ECG test without restenosis and 4 (31%) of 13 patients with restenosis and normal exercise response had events during the follow-up period. The incidence of cardiac events was lowest in patients in whom both test results were normal (19 [20%] of 96 patients).

Discussion

Methodologic considerations: coronary angiography. In the last decades, several noninvasive tests for the detection of ischemic heart disease have been introduced. The most important of these are the ECG stress test and the radionuclide imaging test. To assess the diagnostic value of these noninvasive tests, the coronary angiogram has been used as the reference standard for many years. However, visual analysis of the coronary angiograms is characterized by a high intraobserver and interobserver variability and by a poor correlation between the percent diameter stenosis and the functional significance of the obstruction in patients with multivessel coronary artery disease (20). In this context it is surprising to find sensitivity and specificity values in the 90% range for exercise radionuclide studies with visual analysis of the coronary angiograms (21–23). Recently, the use of visual analysis of the coronary angiogram as a reference standard for noninvasive tests for the detection of coronary artery disease has been questioned by several investigators (24–27). To some extent the aforementioned problems inherent in the use of the coronary angiogram can be solved with a quantitative analysis system as used in the present study. The 50% diameter stenosis threshold introduced by Gould et al. (28) in 1974, when quantitatively estimated, is still valid when applied in patients with a single lesion in single vessel coronary disease (29).

Figure 5. Combinations of the results of exercise electrocardiography (XECG) and coronary angiography (CAG) and their prognostic value. + = positive; − = negative.



Patient selection. With conventional exercise protocols, ECG leads and ECG criteria, exercise ECG testing is characterized by a high specificity and a moderate sensitivity (30). Moreover, its sensitivity increases with the extent of coronary artery disease, which implies a low sensitivity in patients with single vessel disease (31–33). This is an important fact to bear in mind when the exercise ECG is used to evaluate the results of coronary angioplasty because most patients undergoing angioplasty have single vessel disease (9). We preferentially studied only patients with single vessel disease and initially successful coronary angioplasty. In single vessel disease with a single lesion, only this stenosis can be held responsible for an abnormal ECG test response, whereas in multivessel disease the responsible lesion is not always easily identifiable. Moreover, coronary angioplasty in multivessel disease will not result in complete revascularization in a large number of cases. The absence of clinical or ECG evidence of a previous myocardial infarction was necessary to avoid a falsely increased accuracy of the test in these patients (10). Importantly, patients were referred for the exercise ECG test and the coronary angiogram at the same time (directly after successful coronary angioplasty) to avoid selection bias (34).

Noninvasive tests for the detection of restenosis. The occurrence of coronary restenosis is dependent on the definition of restenosis. Some definitions described by our group (14) are very attractive when the goal is to detect significant changes on follow-up quantitative angiography. However, for the purpose of comparing angiographic appearance with the results of noninvasive tests that study the manifestations of myocardial ischemia (for example, ECG changes, perfusion abnormalities or wall motion abnormalities), angiographic thresholds must indicate impaired flow during maximal physical stress testing.

Previous studies from our institution (35) and others (36) indicated that thallium-201 imaging and radionuclide angiography after symptom-limited exercise were highly predictive of restenosis after coronary angioplasty, whereas exercise ECG testing had limited value. Most of these studies included a heterogeneous patient group (prior myocardial infarctions, multivessel disease, multivessel dilations, anginal symptoms), from which it is inappropriate to draw conclusions regarding the significance of exercise ECG testing after coronary angioplasty.

Our study attempted to evaluate the value of symptom-limited quantitative exercise ECG testing compared with quantitative coronary angiography in a selected patient group. The incidence rate of restenosis was 12% in these asymptomatic subjects. The results showed a very low sensitivity of the exercise ECG test, which reflects the limitations of exercise ECG testing in detecting single vessel coronary artery disease. The specificity of the exercise ECG test was comparable with commonly reported findings. Eighteen percent of patients with stenosis experienced angina pectoris during exercise ECG testing, although they did not report chest pain until the time of the test. The exertion during the exercise ECG test was probably more strenuous than during daily life.

When analyzing the false negative test results of the exercise test, the use of beta-adrenergic blocking agents, inadequate heart rate response and coronary branch disease were possible explanations for the normal response in some patients. Two of the 13 patients with restenosis and a normal exercise ECG complained of chest pain during the test, suggestive of myocardial ischemia. A possible explanation for some of the false positive results is that subcritical stenoses (<50% diameter narrowing at quantitative angiography) sometimes have hemodynamic significance related to several variables, such as fluid velocity and viscosity, entrance angle to the stenosis, length of the narrowing and exit angle (27), which were not taken into consideration in our angiographic analysis. Five (23%) of 22 patients without angiographic restenosis but with an abnormal exercise test result experienced angina pectoris during the test, which may indicate myocardial ischemia. In these patients the qualification "false positive" is probably incorrect.

Long-term prognosis. It has been shown (35–37) that exercise testing in conjunction with radionuclide studies early after successful angioplasty is predictive of restenosis or recurrence of angina pectoris, in contrast to exercise electrocardiography alone. Some studies have incomplete follow-up data in asymptomatic patients, and most patient groups studied consist predominantly but not solely of patients with single vessel coronary artery disease. Deligonul et al. (38) found that a positive exercise ECG within 1 month of successful coronary angioplasty was predictive of subsequent cardiac events in patients with multivessel disease but not in patients with single vessel disease. Our present study describes the prognostic value of an exercise ECG beyond 1 month (1 to 6 months) of successful coronary angioplasty of single vessel disease. Because previous myocardial infarction and subsequent left ventricular impairment is known to influence the long-term prognosis independently, only patients without a previous myocardial infarction were studied.

The incidence of cardiac events in this group was not negligible (24%), although recurrent angina pectoris constituted 78% of the first events and cardiac death did not occur during follow-up. About 50% of the cardiac events took place within the first 6 months of follow-up and they probably represent early restenosis after coronary angioplasty, whereas events occurring later are more likely to reflect the natural history of coronary artery disease. Although patients with an abnormal exercise test result experienced more cardiac events than patients with normal test results, the predictive value of an abnormal exercise ECG for subsequent cardiac events was only 36%. Thus, the absence of prognostic value of early exercise ECG testing after coronary angioplasty reported by Deligonul et al. (38) does not apply if the exercise test is performed >1 month after the intervention. Accordingly, angiographic restenosis was equivalently predictive of subsequent cardiac events. Age and gender were not predictive of events, whereas patients with left anterior descending coronary artery angioplasty experienced fewer events than did patients with right coronary artery and left circumflex coronary artery angioplasty. This surprising finding can be explained by patient selection, as restenosis in the left anterior descending coronary artery with concurrent impairment of flow in a large perfusion area may become clinically evident and compel reintervention at an early stage. As a consequence, some of these patients were not included in this study.

Clinical implications. It can be considered a limitation of this study that patients with evident angina pectoris were excluded because they underwent repeat coronary angiography and subsequent redilation at an early stage, often without performing an exercise test. Perhaps stenoses in this group were more severe and a higher proportion of abnormal exercise ECG responses could have been observed in these patients if they had been tested. Exclusion of these patients may have influenced the sensitivity of the test in a negative way. This theoretic limitation does not apply as the purpose of our study was to evaluate subjects without evident angina pectoris.

Exercise ECG testing in asymptomatic patients with the aforementioned profile had an extremely low sensitivity for the detection of restenosis, whereas the differences between the pretest and post-test probabilities were negligible. An abnormal exercise ECG response and angiographic restenosis at short-term follow-up (1 to 6 months) were predictive of subsequent cardiac events in the long term, although the predictive values (36% and 41%, respectively) of abnormal test results are too low to have practical implications, as it is unclear how the prognosis can be influenced in these patients. Further studies are needed to determine whether other noninvasive tests, such as ambulatory ECG monitoring or perfusion imaging techniques, are more sensitive in detecting silent restenosis and whether these tests are better at predicting long-term outcome.

Two emergent questions are not answered by the presented data: 1) should we perform coronary angiography in asymptomatic patients with an abnormal exercise ECG after single vessel angioplasty? and 2) will the long-term prognosis be favorably influenced by repeat angioplasty in patients with silent restenosis on routine coronary angiography given the inherent procedural risks and considerable chance of recurrent stenosis?

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