To investigate the time course of restenosis, serial treadmill exercise testing was performed in the absence of medical therapy by 31 patients with single vessel coronary disease who underwent successful angioplasty. Exercise tests were performed before angioplasty and at 3 days and 1, 3 and 6 months after angioplasty; if the test was positive, it was repeated after administration of 10 mg of intravenous verapamil. 

At arteriography 6 months after coronary angioplasty, 17 patients (group 1) showed no restenosis but 14 patients (group 2) did. Before angioplasty all 31 patients had a positive exercise test with ST segment depression \( \leq 1 \text{ mm} \).

At 3 days after angioplasty, three patients in group 1 had a positive exercise test compared with 11 patients in group 2 (\( p = 0.08 \)). At 1, 3 and 6 months, 1 patient in group 1 had a positive exercise test compared with 14 patients in group 2 (\( p < 0.01 \)).

The heart rate-blood pressure product (beats/min; mm Hg) calculated at 1 mm ST segment depression, or at peak exercise if the test was negative, was used as an index of the ischemic threshold. In group 1 (no restenosis) the ischemic threshold increased progressively from 14,840 ± 1,075 (mean value ± SEM) before angioplasty to 21,210 ± 1,049 at 3 days and to 25,140 ± 1,177 (\( p < 0.001 \)) at 6 months. In group 2 (restenosis) the ischemic threshold increased from 16,270 ± 828 before angioplasty to 20,400 ± 984 (\( p < 0.0004 \)) at 3 days but decreased to 16,090 ± 1,298 (\( p < 0.006 \)) at 6 months. The difference in ischemic threshold between the two groups was significant (\( p < 0.05 \)) from 1 month onward. In group 2 patients the increase in ischemic threshold after verapamil was greater at 3 and 6 months after than before angioplasty (\( p < 0.01 \)).

The early high incidence of a positive exercise test indicates that the process of restenosis begins at least within 1 month of angioplasty and perhaps as early as 3 days. Furthermore, the dynamic component of the stenosis after angioplasty is greater than that of the original stenosis, as suggested by the response to verapamil.

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Restenosis remains one of the major limitations of the use of coronary angioplasty as a treatment for angina pectoris (1). The reported incidence rate (2–4) at 6 months after angioplasty has varied from 13% to 47%. Restenosis is usually associated with a positive exercise test for myocardial ischemia and accompanied by angina. Although it is already present at 3 months after angioplasty in most patients in whom restenosis occurs (5), its time course is poorly known. To this end we performed serial treadmill exercise testing without therapy and follow-up coronary arteriography in 31 patients with single vessel disease before and after successful angioplasty. In seven patients the dynamic component of restenosis was assessed by repeating each exercise test after administration of the calcium channel blocker verapamil.

Methods

Study patients. Thirty-one consecutive patients with single vessel disease underwent elective percutaneous transluminal coronary angioplasty for chronic stable angina pectoris and follow-up coronary arteriography 6 months later. There were 28 men and 3 women aged 36 to 73 years (mean 54) and all had a positive exercise test for myocardial ischemia before angioplasty. Seven patients had a previous (>6 months) Q wave myocardial infarction (five inferior, two anterior) in the region of the diseased coronary artery. Even
though seven patients had Q waves, there was enough preservation of R waves in these leads to allow analysis of ST segment changes for myocardial ischemia. No patient had evidence of left ventricular hypertrophy or conduction defects on the electrocardiogram (ECG) that could have interfered with the interpretation of ST segment changes, and no patient was taking digitalis.

**Study protocol.** The protocol was approved by the Hammersmith Hospital Research Ethics Committee and all patients gave full informed consent for the study. All patients underwent a treadmill exercise ECG during the week before angioplasty. All antianginal therapy was discontinued before the test (beta-adrenergic blocking agents were stopped for 72 h, calcium channel blockers and oral nitrates for 24 h). All patients were taking aspirin, 75 mg daily, but none received dipyridamole. Patients were free to use sublingual nitroglycerin as required, but no exercise test was performed within 2 h of its administration. In seven patients the test was repeated 1 h later after the slow intravenous administration of verapamil, 10 mg.

Coronary angioplasty was performed by a standard technique using the femoral approach. Heparin, 10,000 IU, was administered at the beginning of the procedure and maintained as an intravenous infusion for 12 h after the procedure. During angioplasty, an intravenous isosorbide dinitrate infusion was maintained with supplementary bolus injections of intracoronary isosorbide dinitrate as required and continued for 24 h after angioplasty. Aspirin, 75 mg/day, was continued during and for 6 months after the angioplasty. Diltiazem, 180 mg/day, was started 24 h after the procedure and also continued for 6 months.

A repeat exercise test without therapy was performed at 3 days and at 1, 3 and 6 months after angioplasty. If the test was positive it was repeated 1 h later, after the slow intravenous administration of 10 mg verapamil. In all patients, follow-up coronary arteriography was performed approximately 6 months after angioplasty with use of the same radiographic projections as those obtained during the procedure.

**Exercise testing.** Exercise testing using the modified Bruce protocol was performed on a computerized treadmill system (Compusprint Inc.). Twelve lead ECG recordings and (cuff) blood pressure measurements were obtained at rest, at the end of each stage during exercise, at the point of 1 mm ST segment depression, at peak exercise and at 3 and 6 min into the recovery period. Three ECG leads were monitored continuously before and during exercise and for 6 min into recovery. All tests were performed at the same time of day for each patient. A positive exercise test diagnostic of myocardial ischemia was defined as horizontal or downsloping ST segment depression $\geq 1$ mm (0.1 mV) measured 60 ms after the J point with respect to the value at rest. The exercise test was stopped in the event of chest pain of moderate severity, ST segment depression $\geq 2$ mm or inability of the patient to exercise further.

For all exercise tests the heart rate-blood pressure product (beats/min mm Hg) was calculated at 1 mm ST segment depression, or at peak exercise when the exercise test was negative, and its value was used as an index of the ischemic threshold. The reason for stopping the test was noted.

**Cardiac catheterization.** Selective right and left coronary arteriography was performed by the Judkins technique. Each vessel was filmed in multiple projections. The coronary artery luminal diameter at the site of the original stenosis was measured from end-diastolic frames of identical projections of the arteriograms recorded before and after angioplasty and at 6 months using an automated edge contour detection analysis system (Computerised Angiographic Analysis System [CAAS] Version 2V2; Pie Data Medical) (6). High resolution video-converted digital images of the film frames were automatically corrected for radiographic pincushion distortion, and the known size of the stem of the coronary catheters was used for calibration. The results were expressed as percent diameter stenosis compared with the adjacent normal segment. Restenosis was defined, in accordance with the definition of the National Heart, Lung, and Blood Institute (2), as a loss of $\geq 50\%$ of the initial gain in luminal diameter.

**Statistical analysis.** Statistical analysis was performed by using analysis of variance or the two-tailed Student's t test for paired data as appropriate. The results are expressed as mean values ± SEM. A value of $p < 0.05$ is considered significant; p values were adjusted for the multiple test situation by the use of Bonferroni inequality.

**Results**

**Changes in coronary stenosis (Fig. 1).** Two groups were defined on the basis of the 6 month follow-up arteriogram. Group 1 consisted of 17 patients without restenosis and group 2 consisted of 14 patients (45.2%) with restenosis. The two groups were similar with respect to the severity of stenosis before and immediately after angioplasty. The stenosis severity was 67.9 ± 1.5% and 70.0 ± 2.4% before angioplasty, 31.4 ± 3.5% and 29.8 ± 2.9% immediately after angioplasty and 27.5 ± 4.0% and 62.9 ± 3.5% at 6 months in groups 1 and 2, respectively.

**Exercise tolerance and ischemic threshold.** Before angioplasty (Fig. 2). All exercise tests were positive for myocardial ischemia. There was no significant difference between the two groups in the ischemic threshold as assessed from the heart rate-blood pressure product (beats/min mm Hg); it was 14,840 ± 1,075 in group 1 and 16,270 ± 828 in group 2. In group 1 (no restenosis) the exercise test was stopped because of chest pain in nine patients and ST segment depression in five patients. In group 2 (with restenosis), the
exercise test was stopped in 12 patients because of chest pain and in 2 patients because of ST segment depression.

Three days after angioplasty. In group 1 the exercise test was negative, and 14 patients stopped exercise because of fatigue; the remaining 3 patients had a positive test and stopped because of ST segment depression. In group 2, the exercise test was negative in 3 patients who stopped because of fatigue; it was positive in the remaining 11 patients, of whom 4 stopped exercise because of chest pain, 4 because of ST segment depression and the remaining 3 because of fatigue. The predictive value of a positive test for restenosis was 79%; that of a negative test was 82%. Both groups showed a significant increase in the ischemic threshold compared with that before angioplasty; it increased from 14,840 ± 1,075 to 21,210 ± 1,049 (p < 0.0001) in group 1 and from 16,270 ± 828 to 20,400 ± 984 (p < 0.0004) in group 2. The difference between the two groups was not significant (Fig. 2).

One month after angioplasty. In group 1 all exercise tests were negative, and all patients stopped with fatigue. In group 2, 1 patient had a negative exercise test and stopped with fatigue; the test was positive in 13 patients, of whom 5 stopped with chest pain, 5 with ST segment depression and 3 with fatigue. The predictive value of a positive test for restenosis was 100% and that of a negative test was 94%. Group 1 showed a further increase in ischemic threshold compared with that at 3 days; the threshold increased from 21,210 ± 1,049 to 23,300 ± 1,077 (p < 0.02), but it remained almost unchanged in group 2, from 20,400 ± 984 to 20,870 ± 830 (p = NS). The difference between the two groups was significant (p < 0.05) at this stage (Fig. 2).

Three months after angioplasty. In group 1 all exercise tests were negative and all patients stopped with fatigue. In group 2 the exercise test was negative in 1 patient, who stopped with fatigue; it was positive in 13 patients, of whom 6 stopped with chest pain, 6 with ST segment depression and 1 with fatigue. The predictive value of a positive test for restenosis was 100% and that of a negative test was 94%. In group 1, the ischemic threshold increased from 23,300 ± 1,077 at 1 month to 24,480 ± 965 at 3 months (p = NS), but it decreased in group 2 from 20,870 ± 830 at 1 month to 18,800 ± 1,636 (p = NS). The difference between the two groups was significant (p < 0.004) (Fig. 2).

Six months after angioplasty. In group 1, all exercise tests were negative and all patients stopped with fatigue. In group 2, the exercise test was negative and stopped with fatigue in 1 patient, but was positive in 13 patients; 5 stopped with chest pain, 7 with ST segment depression and 1 with fatigue. The predictive value of a positive test for restenosis was 100% and of a negative test it was 94%. In group 1, the ischemic threshold increased from 24,480 ± 965 at 3 months to 25,140 ± 1,177 at 6 months (p = NS). However, in group 2 it decreased further from 18,800 ± 1,636 at 3 months to 16,090 ± 1,298 (p < 0.0006). The difference between the two groups was significant (p < 0.0001) (Fig. 2).

Initial response to coronary angioplasty. When compared with the value before angioplasty, ischemic threshold improved (by ≥2,000 beats/min·mm Hg) in 23 of the 31 patients at 3 days after angioplasty, whereas it did not improve significantly in the other 8 patients. However, these latter
angioplasty. This study shows that the predictive value of a positive exercise test with respect to restenosis is high from 3 days after angioplasty onward. Even at 3 days, 11 of the 14 patients who were later found to have developed restenosis already had a positive exercise test, indicating that their coronary flow reserve was already impaired. From 1 month onward, 13 of the 14 patients who developed restenosis had a positive exercise test. It is therefore quite clear that either restenosis or the processes that lead or predispose to it are already present within days of the procedure. Whether fixed anatomic restenosis, enough to limit coronary flow reserve and result in a positive exercise test, is already present at 3 days after angioplasty is not clear from this study, but certainly the efficacy of the angioplasty in reducing the stenosis was similar in both groups as evidenced by the stenosis severity immediately after the balloon dilation.

Possible pathophysiologic mechanisms. It would be quite reasonable to hypothesize that the early positive exercise tests were due partly to a dynamic component such as vasoconstriction (7,8) because the vessel wall damage associated with balloon angioplasty is likely to lead to platelet adhesion and aggregation (9–12) and the local release of vasoconstrictor substances (13,14). Furthermore, the local migration of vascular smooth muscle cells into the intima and their proliferation in response to platelet-derived growth factor (9,15) would provide a mechanism for vasoconstriction and also form part of the fibromuscular response to balloon dilation that ultimately constitutes the anatomic lesion in restenosis (16). A recent study by Fischel et al. (7) clearly demonstrated spontaneous coronary artery constriction immediately after angioplasty, and persistence of this tendency for several days could explain the occurrence of a positive exercise test 3 days after angioplasty (as found in our study) even if anatomic restenosis had not occurred to a degree comparable with that of the preexisting stenosis.

Comparison with other studies. In our study a relatively homogeneous group of patients was selected on the basis of single vessel disease and a positive exercise test before angioplasty, with all exercise tests performed without therapy. Therefore, precise comparison cannot be made with the results of other studies. However, the results of our study are consistent with those of Wijns et al. (5), who found 74% of exercise tests positive at 4 weeks after angioplasty (as found in our study) even if anatomic restenosis had not occurred to a degree comparable with that of the preexisting stenosis.

Discussion

Predictive value of a positive exercise test 3 days after angioplasty. This study shows that the predictive value of a positive exercise test with respect to restenosis is high from
thus significant fixed residual stenosis might have been responsible for the impairment of coronary flow reserve, at least in some of these patients.

Perhaps the definitive study on the anatomic aspect of restenosis was reported recently by Nobuyoshi et al. (19). The study involved serial follow-up coronary arteriography in 229 patients subjected to angioplasty and found an actuarial restenosis rate of 43% at 3 months and of 52.5% at 1 year, although the restenosis rate at 1 month was only 12.7%. These findings suggest that the relatively high frequency of positive exercise tests at 1 month in our study could represent either a dynamic change in stenosis severity occurring during exercise or an increase in resistance in the smaller vessels. With regard to the latter hypothesis a reduced coronary flow reserve immediately after angioplasty was found by Wilson et al. (20) using the technique of intracoronary Doppler flow velocity measurement and papaverine-induced maximal vasodilatation. In that study the impairment of coronary flow reserve found in 17 of 31 patients was unrelated to the severity of the epicardial vessel stenosis and had either resolved at an average of 7.5 months after angioplasty or persisted in association with restenosis where it correlated significantly with the severity of restenosis. The results of their study, however, require further validation because the assessment of coronary flow reserve by this technique did not take into account the basal level of flow, which might have been elevated immediately after angioplasty. Such further validation and confirmation of these findings would suggest that a regional increase in small vessel resistance might contribute to the early limitation of coronary flow reserve.

Effect of verapamil. In our study, the magnitude of the change in ischemic threshold induced by verapamil was significantly greater at 3 and 6 months after angioplasty compared with that observed before angioplasty. This finding is of interest because the effect of verapamil on ischemic threshold has been used in previous studies to assess the magnitude of the dynamic component of coronary stenosis. Intravenous calcium blocking agents have been shown to slightly dilate both the normal and stenotic segments of coronary arteries (21) and to prevent exercise-induced vasoconstriction (22) and coronary vasospasm (23). The results of our study suggest that the restenotic coronary artery might constrict more during exercise than would the atherosclerotic artery before angioplasty. This finding would be consistent with the cellular nature of the restenotic lesion, whose cellular component contains mainly smooth muscle cells. This restenotic lesion, therefore, might induce coronary obstruction not only by its physical presence but also by an enhanced constrictor response to exercise.

Clinical implication. These results indicate the value of ECG exercise stress testing in the early identification of those patients with single vessel disease who are in the process of developing restenosis. Routine follow-up coronary arteriography would appear to be of little value in the event of a persistently negative exercise stress test. Our results also indicate that little value, in terms of exercise tolerance, is obtained from angioplasty in patients whose ischemic threshold (blood pressure-heart rate product) is already high before angioplasty. In fact, a high proportion of patients with restenosis were found in this group and in some of them the ischemic threshold had fallen at 3 days after angioplasty to a level below that observed before angioplasty. In these patients with a high ischemic threshold and good effort tolerance before angioplasty the severity of coronary stenosis was very similar to that of the other patients, therefore, the coronary arteriogram should not be used in isolation when selecting patients who are likely to benefit from angioplasty.

References


