Inappropriate Constriction of Small Coronary Vessels as a Possible Cause of a Positive Exercise Test Early After Successful Coronary Angioplasty

Hassan El-Tamimi, MD; Graham J. Davies, MD, FRCP; Piyamitr Sritara, MD; David Hackett, MD; Filippo Crea, MD, FACC; and Attilio Maseri, MD, FRCP

Background. The mechanism responsible for exercise-induced myocardial ischemia early after successful coronary angioplasty (PTCA) is poorly understood.

Methods and Results. Twelve patients who underwent one-vessel PTCA were studied. Exercise testing was performed before and on day 7 after PTCA, which was repeated after 10 mg sublingual isosorbide dinitrate if the test was positive. Quantitative coronary arteriography was also performed on day 8 after PTCA in the basal state, after intracoronary infusion of 0.9% saline, 1, 5, 10, and 20 μg ergonovine, and after 300 μg nitroglycerin. All patients had a positive exercise test before PTCA but on day 7, six patients had a positive exercise test (group 1) and six patients (group 2) had a negative exercise test. In group 1, all positive exercise tests on day 7 became negative when repeated after isosorbide dinitrate. Intracoronary ergonovine was associated with a dose-dependent constriction of the PTCA segment, a segment distal to it, and a control segment, with no significant difference in the magnitude of the response between the two groups; maximum constriction for group 1 was 19±3%, 23±2%, and 16±3% (p<0.001 versus basal), and in group 2 was 20±4%, 18±4%, and 9±2% (p<0.01 versus basal). No angina, ischemic ST segment changes, occlusive, or subocclusive spasm occurred in any patient of either group.

Conclusions. We could find no evidence that exercise-induced myocardial ischemia early after PTCA is related to the presence of fixed angiographic restenosis or to dynamic constriction of any epicardial coronary segment. Therefore, inappropriate small coronary vessel constriction responsive to nitrates should be considered as a possible alternative explanation. (Circulation 1991;84:2307–2312)

A positive exercise test early after successful percutaneous transluminal coronary angioplasty (PTCA) in patients with one-vessel coronary artery disease has been reported in a proportion of patients ranging from 37 to 54%.1,2 This relatively high proportion of positive tests is in sharp contrast with the reported incidence of restenosis at 1 month of only 12%.3 This obvious discrepancy suggests a dynamic rather than organic limitation of residual coronary flow reserve during exercise. This apparent paradox of a positive exercise test in the absence of restenosis could be explained by dynamic changes in caliber at the site of the residual stenosis after PTCA or to an abnormality of small coronary vessels. To investigate these possible mechanisms, we tested the coronary vascular reactivity to ergonovine and to nitroglycerin in the PTCA segment, a segment distal to it, and a control epicardial coronary segment of patients with positive and negative exercise tests 1 week after PTCA. We were unable to detect differences in the vasomotor response of any of these segments.

Methods

Study Patients

Twelve consecutive stable angina patients (nine men and three women aged 44–65 years; mean, 56 years) with one-vessel disease and a positive exercise test for myocardial ischemia who had elective successful PTCA were studied. None of the patients had suffered a myocardial infarction. Exclusion criteria
included the need to use intracoronary nitroglycerin during PTCA, repeat PTCA, or technically inadequate coronary arteriography. 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. All anti-anginal therapy was discontinued before the study (β-blockers were stopped for 72 hours, calcium channel blockers and oral nitrates for 24 hours). All patients were on 75 mg aspirin daily but none was on dipyridamole or digitalis. They all gave written informed consent to participation.

Study Protocol

All patients underwent a treadmill exercise ECG during the week before PTCA both before and 1 hour after sublingual administration of 10 mg isosorbide dinitrate.

Selective coronary arteriography of the vessel to be dilated was performed in multiple projections, and the single best projection was selected for use for subsequent studies. Two angiograms of the study vessel with nonionic contrast medium were performed in the basal state and after 300 μg of intracoronary nitroglycerin.

PTCA was then performed by a standard technique, using the femoral approach. Heparin 10,000 IU was administered through the femoral venous sheath at the beginning of the procedure and maintained as an intravenous infusion for 12 hours after the procedure. PTCA was performed with a monorail balloon catheter system (ACS). At least two balloon inflations were performed in each instance, with additional inflations performed as needed until the coronary stenosis had been adequately dilated. A coronary arteriogram of the study vessel was obtained 5 minutes after the final balloon inflation and after 300 μg of intracoronary nitroglycerin. Medical therapy was initiated with diltiazem 60 mg three times daily for 5 days plus aspirin 75 mg daily.

Seven days after PTCA, an exercise test without drug therapy was performed and if positive was repeated 1 hour later after sublingual administration of 10 mg isosorbide dinitrate.

Coronary arteriography was performed 8 days after PTCA without drug therapy using a 5F femoral diagnostic catheter in the basal state, after 0.9% saline infusion, after 1, 5, 10, and 20 μg of intracoronary ergonovine, and after 300 μg of intracoronary nitroglycerin.

Exercise Testing

Exercise testing was performed using the modified Bruce protocol on a computerized treadmill system (Marquette Case 12). Twelve-lead ECG recording and cuff blood pressure measurement were obtained at rest, at the end of each minute during exercise, at the point of 1 mm (0.1 mV) ST segment depression, at peak exercise, and 3 and 6 minutes into the recovery period. Three ECG leads (I, V₃, and V₅) were monitored continuously before and during exercise and for 6 minutes 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 1 mm or greater measured 60 msec after the J point with respect to the resting value. The exercise test was stopped in the event of chest pain of moderate severity, ST segment depression 2 mm or greater, or inability of the patient to exercise further.

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

Quantitative Coronary Angiographic Analysis

The coronary arteriograms were analyzed with use of a computerized automatic analysis system (CAAS, Pie Data Medical), which has been described in detail in a previous report. End-diastolic frames from each arteriogram were selected by a cardiologist and analyzed by a technician. Both were unaware of the study protocol or the sequence of infusions. Coronary arterial segments were selected between identifiable branching points. The angiographic catheter was used as a scaling device and this, together with pincushion distortion correction, allowed the diameters to be recorded as absolute values (expressed in millimeters). The response of discrete stenotic segments was studied by measuring the minimal diameter in the stenotic segment and the reference diameter proximal to the stenosis at baseline and after each intervention. To construct segmental dose–response curves, segments 5 mm in length from the distal portions of the artery under study and a middle portion of a control artery were analyzed at baseline and after each intervention.

Statistical Analysis

Statistical analysis was performed by analysis of variance or the two-tailed Student's t test for paired data as appropriate. A value of p<0.05 was considered significant. Results are expressed as mean±SEM.

Results

Successful PTCA, defined as a reduction in stenosis diameter to less than 50%, was achieved in all 12 patients. Two groups were defined on the basis of their exercise test response 7 days after PTCA. Group 1 consisted of six patients with a positive exercise test and group 2 consisted of six patients with a negative exercise test. The clinical characteristics of the two groups are shown in Table 1.

Exercise Testing

Before PTCA. All patients had a positive exercise test. In group 1, the exercise test was stopped because of chest pain in all patients. In group 2, the
The ischemic positive and because of silent ST patients of 2.5 min x ST mm were similar (7±1 and 7±1 minute, respectively) (Figure 1).

After nitrate administration, one test out of six in group 1 and three out of six in group 2 became negative. The ischemic threshold increased to 18,050±1,522 beats/min x mm Hg in group 1 (p<0.05) and to 19,310±1,522 beats/min x mm Hg in group 2 (NS). The exercise time to 1 mm ST segment depression increased to 9±1 minute (p<0.05) and 9±0.9 minute (p<0.05) for group 1 and group 2, respectively. Both ischemic threshold and exercise time to 1 mm ST segment depression were similar in the two groups (Figure 1).

Seven days after PTCA. In group 1, all exercise tests were positive by definition. Five patients were stopped because of chest pain and one because of silent ST segment depression of 2.4 mm. The ischemic threshold increased from 14,405±1,217 beats/min x mm Hg before PTCA to 20,742±948 beats/min x mm Hg (p<0.005), whereas exercise time to 1 mm ST segment depression did not change (7±1.1 versus 6±1 minute, respectively, NS). In group 2, all exercise tests were negative and stopped because of fatigue. The rate–pressure product increased from 17,526±1,738 beats/min x mm Hg before PTCA to 24,300±1,315 beats/min x mm Hg (p<0.003) and the exercise duration from 7±1 to 12.7±0.5 minute (p<0.005) (Figure 1). The resting rate–pressure product for group 1 was 14,645±932 beats/min x mm Hg and for group 2 was 9,490±1,213 beats/min x mm Hg (p<0.01).

After nitrate administration, all positive exercise tests in group 1 became negative. Peak rate–pressure product increased to 26,445±942 beats/min x mm Hg (p<0.001) and the exercise duration to 10.4±0.9 minute (p<0.001) (Figure 1).

Angiographic Findings
In groups 1 and 2, there was no significant difference in the severity of stenosis at the PTCA site before PTCA and 5 minutes after and 8 days after PTCA.

Before PTCA. In groups 1 and 2, the basal minimum luminal diameter of the PTCA segment was 1.08±0.15 mm and 0.79±0.13 mm, respectively; it increased to 1.26±0.13 mm (p<0.001) and 1.18±0.05 mm (p<0.001) after nitroglycerin (Figure 2). The basal luminal diameter of the distal segment was 1.51±0.11 mm and 1.36±0.10 mm, respectively; it increased to 1.79±0.15 mm (p<0.001) and 1.75±0.13 mm (p<0.001) after nitroglycerin (Figure 2). The basal luminal diameter of the control segment was 2.60±0.23 mm and 3.19±0.29 mm, respectively; it increased to 2.95±0.18 mm (p<0.01) and 3.43±0.31 mm (p<0.02) after nitroglycerin (Figure 2).

<table>
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Group 2

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F, female; M, male; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.
Five minutes after PTCA. In groups 1 and 2, the basal luminal diameter of the PTCA segment was 1.84±0.13 mm and 1.80±0.11 mm, respectively; it increased to 2.01±0.11 mm (p<0.01) and 2.0±0.05 mm (p<0.02) after nitroglycerin (Figure 2). The basal luminal diameter of the distal segment was 1.56±0.14 mm and 1.42±0.17 mm, respectively; it increased to 1.84±0.17 mm (p<0.001) and 1.77±0.14 mm (p<0.001) after nitroglycerin (Figure 2). The basal luminal diameter of the control segment was 2.57±0.21 mm and 3.23±0.28 mm, respectively; it increased to 2.96±0.17 mm (p<0.01) and 3.56±0.29 mm (p<0.01) after nitroglycerin (Figure 2).

Eight days after PTCA. The intracoronary infusion of 0.9% saline was not associated with significant change in epicardial lumen diameter or the severity of stenosis.

In groups 1 and 2, the basal luminal diameter of the PTCA segment was 1.83±0.09 mm and 1.97±0.10 mm, respectively; it decreased to 1.48±0.01 mm (p<0.001 versus basal) and 1.57±0.11 mm (p<0.006 versus basal) after the highest dose of ergonovine and increased to 1.97±0.10 mm (p<0.01 versus basal) and 2.09±0.08 mm (p<0.02 versus basal) after nitroglycerin in groups 1 and 2 (Figure 2). The basal luminal diameter of the distal segment was 1.44±0.11 mm and 1.45±0.12 mm, respectively; it decreased to 1.11±0.08 mm (p<0.01 versus basal) and 1.15±0.11 mm (p<0.02 versus basal) after the highest dose of ergonovine and increased to 1.80±0.17 mm (p<0.001) and 1.83±0.14 mm (p<0.001) after nitroglycerin (Figure 2). The basal luminal diameter of the control segment was 2.53±0.22 mm and 3.20±0.29 mm, respectively; it decreased to 2.13±0.20 mm (p<0.007 versus basal) and 2.93±0.30 mm (p<0.002 versus basal) after the highest dose of ergonovine and increased to 2.81±0.20 mm (p<0.001) and 3.47±0.30 mm (p<0.001) after nitroglycerin (Figure 2).

Symptoms and ECG Changes
No symptoms or ECG changes or occlusive or subocclusive coronary spasm occurred in any patient of either group.

Hemodynamic Parameters
There was no significant change in heart rate or systolic blood pressure associated with intracoronary infusion of saline or incremental concentra-
tions of ergonovine in any patient. Nitroglycerin produced a significant reduction in blood pressure by 20±5 mm Hg and an increase in heart rate by 14±2 beats/min.

Discussion

This study shows that in anginal patients with one-vessel disease, exercise-induced myocardial ischemia may occur early after successful PTCA in the absence of restenosis. In fact, the severity of the residual coronary stenosis in our patients with a positive result of exercise testing was mild and similar to that observed in patients with a negative result of the test. Because coronary angiography was not performed during the exercise test in this study, the theoretical possibility that the exercise-induced myocardial ischemia was caused by functional alterations of large epicardial coronary arteries cannot be excluded. However, this possibility would appear to be very unlikely because in our patients with a positive exercise test result, the reactivity of large epicardial coronary vessels to the intracoronary administration of ergonovine (a vasoconstrictor stimulus stronger than exercise) was similar to that observed in patients with a negative exercise test result, and coronary spasm did not occur in any patient of either group. Functional alterations of large epicardial coronary arteries were observed by Fischell et al⁶ immediately after successful PTCA. However, these authors observed vasoconstriction of the coronary segments distal to the dilated site. Because the degree of vasoconstriction was correlated with the severity of the stenosis before PTCA,⁶ they concluded that the vasoconstriction was due to “resetting” of the autoregulatory responsiveness of distal coronary segments in response to the abrupt increase of pressure caused by PTCA. We believe that the exercise-induced myocardial ischemia observed in our patients, however, is unlikely to be due to this mechanism because we have previously observed that the functional abnormalities of coronary segments described by Fischell et al are no longer present 1 week after PTCA.⁷ The positive response to exercise testing observed in our patients is unlikely to be accounted for by anatomical or functional alterations of large epicardial coronary arteries; therefore, it might be due to alterations of small coronary vessels. This hypothesis would be consistent with the observation by Wilson et al⁸ of a reduction of coronary flow reserve unrelated to the severity of the residual coronary stenosis when assessed using intracoronary papaverine and a Doppler catheter immediately after PTCA. Because this alteration was not present 6–8 months after PTCA, they concluded that it was a transient perturbation secondary to PTCA. The results of our study do not allow us to discern whether the alteration of the coronary circulation responsible for the positive response to exercise testing early after PTCA was caused or just unmasked by the procedure. The former possibility is supported by the transient nature of the abnormal small coronary vessel reactivity described by others.⁸,⁹ The latter possibility is suggested by the observation that, in patients who had a negative exercise test early after PTCA, nitrate administration did not improve the ischemic threshold (as reflected by the rate–pressure product at the onset of ischemia) before PTCA, whereas in group 1 patients, nitrate administration improved the ischemic threshold both before and after PTCA. It is possible, therefore, that the functional improvement obtained with nitrates in group 1 before PTCA was caused not only by stenosis dilatation as currently believed but also by dilatation of abnormally constricted small vessels and that, in these patients, the partial improvement of ischemic threshold by PTCA was due to abolition of one mechanism of ischemia (epicardial stenosis) but not of the other (abnormal small vessel constriction). In a previous study¹⁰ performed in a highly selected group of anginal patients characterized by total occlusion of a coronary branch and lack of angiographically detectable stenoses in the remaining coronary branches, we demonstrated that functional alterations of small coronary arteries can play an important role in the modulation of myocardial ischemia.

A limitation of this study is the small number of subjects, which, in particular, does not allow us to draw conclusions about the incidence of a positive result of exercise testing early after PTCA in the absence of restenosis.

Thus, the present investigation, in which successful stenosis dilation allowed us to eliminate the confounding effects of coronary stenoses on myocardial ischemia, suggests that functional alterations of small coronary arteries can modulate residual coronary flow reserve and also cause or contribute to the development of myocardial ischemia after PTCA. Further studies are warranted to elucidate the incidence, time course, and mechanisms of such alterations and the reason for the intriguing observation that an early positive exercise test result after PTCA predicts late restenosis, as we have shown in a previous study.¹

References


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**KEY WORDS**

- coronary angioplasty
- small vessel
- exercise testing
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