Abnormal Vasomotor Changes Early After Coronary Angioplasty
A Quantitative Arteriographic Study of Their Time Course

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Background. To study the impact of percutaneous transluminal coronary angioplasty (PTCA) on coronary vasomotion, we prospectively analyzed spontaneous changes in coronary diameter and the response to the cold pressor test and intracoronary nitroglycerin in 11 patients subjected to successful single-vessel PTCA.

Methods and Results. All antianginal medications were stopped 48 hours before each study. The minimum diameter of the PTCA segment and the diameter of a distal segment in the angioplastied vessel and of a segment in a control vessel not manipulated by the balloon catheter or guide wire were measured by computerized edge detection immediately before PTCA and 5 minutes after, 4 hours after, and 8 days after PTCA. At 4 hours, PTCA and distal segments were constricted by 38±9% and 16±5%, respectively, compared with the values at 5 minutes (p<0.01). Before angioplasty, the cold pressor test caused vasoconstriction of PTCA and distal segments by 23±6% (p<0.0001) and 15±4% (p<0.008), respectively, but no constrictor response was elicited at 5 minutes or 4 hours after angioplasty. Eight days after PTCA, the basal coronary diameters were similar to those observed 5 minutes after PTCA and the response to the cold pressor test was similar to that observed before PTCA. All segments dilated significantly with nitroglycerin at all times, and no vasoconstriction changes were found in the control segments.

Conclusions. Four hours after PTCA, transient spontaneous vasoconstriction of the PTCA and distal segments occurs, which is so intense that the cold pressor test does not cause any further constriction. These abnormalities resolve within 8 days of PTCA. (Circulation 1991;84:1198–1202)

Percutaneous transluminal coronary angioplasty (PTCA) reduces the severity of coronary stenosis by intimal and medial disruption with endothelial ablation. In a number of patients, acute occlusion or early restenosis may follow. Altered coronary vasoreactivity of the PTCA segment as a result of acute trauma might be part of the mechanism leading to these complications, as vasoconstriction soon after PTCA has recently been reported. However, little is known about the magnitude, distribution, and time course of such changes in vasoreactivity and of the response of the vessel to sympathetic stimulation.

The purpose of this study was to examine the early (4 hours) and late (8 days) effects of PTCA on the vasomotor response of coronary arteries to the cold pressor test.

Methods

Patient Population

Eleven consecutive patients with chronic stable angina and single-vessel disease requiring elective PTCA were selected for study. There were eight men and three women aged 44–67 years (mean, 56 years), all with a positive exercise test for myocardial ischemia before PTCA, and whose clinical features are shown in Table 1. One patient had an old (more than 6 months) anterior Q wave myocardial infarction in the region supplied by the diseased coronary artery. Patients with restenosis after previous PTCA were excluded from the study. No patient had evidence of left ventricular hypertrophy or conduction defects on the electrocardiogram, and no patient was taking digitalis.

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Study Protocol

The protocol was approved by the Hammersmith Hospital Research Ethics Committee, and all patients gave informed consent for the study. All antianginal therapy was discontinued before the study (β-blockers were stopped for 72 hours, calcium channel blockers and oral nitrates for 24 hours). Patients were free to use sublingual glyceryl trinitrate as required, but no study was performed within 4 hours of its administration. All patients were taking aspirin (75 mg daily), but none received dipyridamole.

Selective coronary arteriography of the vessel to be dilated was performed in multiple projections using nonionic contrast medium. The precise angles of the optimum angiographic projection were recorded, and this projection was used for all subsequent coronary arteriograms.

Coronary arteriography was performed in the basal state, at the peak of the cold pressor test (immersion of patient’s hand in a slurry of ice water for 2 minutes), and, after a 5-minute recovery period, after the intracoronary injection of 300 μg nitroglycerin. The heart rate and aortic pressure were recorded continuously.

PTCA was performed by a standard technique, using the femoral approach. Heparin (10,000 units i.v.) was administered at the beginning of the procedure and maintained as an intravenous infusion of 1,000 units/hr for 12 hours after the procedure. At least two balloon inflations were used, with additional inflations as needed until the coronary stenosis had been dilated adequately. A coronary arteriogram was obtained 5 minutes after final balloon deflation and repeated at the peak of the cold pressor test and after 300 μg intracoronary nitroglycerin. The femoral artery sheath was left in place, and the patients were transferred to the coronary care unit with no medication administered except for heparin infusion. The coronary arteriogram was repeated 4 hours later in the basal state, at the peak of the cold pressor test, and after 300 μg intracoronary nitroglycerin. Dil-tiazem (60 mg) was administered orally three times daily and aspirin (75 mg) once daily for 5 days. Coronary arteriography was repeated 8 days after PTCA (without antianginal therapy for 48 hours) with a 5F Judkin diagnostic catheter. The arteriogram was recorded in the basal state, at the peak of the cold pressor test, and after 300 μg nitroglycerin.

Coronary Arteriographic Analysis

All films were analyzed by a quantitative arteriographic technique. This method, which is based on automated edge contour detection analysis (COMPUTERISED ANGIOGRAPHIC ANALYSIS SYSTEM [CAAS] VERSION 2.2; Pie Data Medical), has been described in detail. High-resolution video-converted digital images of the film frames were automatically corrected for radiographic pin cushion distortion, and the known size of the stem of the coronary catheters was used for calibration. End-diastolic cine frames were selected for analysis. Three coronary segments were analyzed in all patients: the PTCA segment, including the most severe point of the coronary stenosis as viewed in the arteriogram before PTCA; the distal segment, which was a segment distal to the PTCA segment and not manipulated by the balloon catheter; and the control segment, which was a segment not manipulated by guide wire or balloon catheter (e.g., left circumflex coronary artery when PTCA was performed in the left anterior descending artery). The analysis of the three segments was repeated for each condition (before PTCA and 5 minutes after, 4 hours after, and 8 days after PTCA, each in the basal state, during cold pressor testing, and after intracoronary nitroglycerin), and the results were expressed as minimum luminal diameter (mm) or as percentage change in minimum luminal diameter from basal.

Statistical Analysis

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

Results

Successful PTCA, defined as a reduction in stenosis diameter of less than 50%, was achieved in all 11 patients. During cold pressor stimulation, heart rate and systolic blood pressure rose significantly (p<0.001) by 16±4 beats/min and 25±4 mm Hg, respectively. Nitroglycerin produced a significant reduction in heart rate and blood pressure by 4±2 beats/min and 20±5 mm Hg (p<0.001), respectively. Chest pain associated with more than 0.15 mV ST-segment depression occurred in three patients before PTCA during cold pressor test but in none after PTCA.

Changes in Coronary Diameter

Basal coronary diameter. The basal minimum coronary diameter of the PTCA segment was 0.97±0.10 mm before PTCA, 1.83±0.08 mm at 5 minutes after (p<0.0001 versus before), 1.37±0.08 mm at 4 hours after (p<0.01 versus 5 minutes and 8 days), and

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F, female; M, male; LAD, left anterior descending coronary artery; CX, circumflex coronary artery.
1.82±0.07 mm at 8 days after PTCA (Figure 1). The basal coronary diameter of the distal segment was 2.29±0.10 mm before PTCA, 2.36±0.13 mm at 5 minutes after, 2.08±0.13 mm at 4 hours after (p<0.01 versus before and 8 days), and 2.28±0.10 mm at 8 days after PTCA (Figure 1). The basal coronary diameter of the control segment was 2.68±0.26 mm before PTCA, 2.82±0.22 mm at 5 minutes after, 2.66±0.23 mm at 4 hours after, and 2.80±0.22 mm at 8 days after PTCA (Figure 1).

Response to nitroglycerin. The change in coronary diameter after nitroglycerin with respect to basal was as follows. PTCA segment: +43±9% (p<0.006) before PTCA, +10±3% (p<0.01) at 5 minutes after, +33±6% (p<0.0001) at 4 hours after, and +9±3% (p<0.001) at 8 days after PTCA (Figure 2). Distal segment: +13±4% (p<0.01) before PTCA, +8±3% (p<0.02) at 5 minutes after, +24±7% (p<0.005) at 4 hours after, and +17±4% (p<0.02) at 8 days after PTCA (Figure 2). Control segment: +9±4% (p<0.01) before PTCA, +14±3% (p<0.008) at 5 minutes after, +14±3% (p<0.02) at 4 hours after, and +7±4% (p<0.002) at 8 days after PTCA (Figure 2).

The diameter of the distal coronary artery after nitroglycerin was similar before PTCA and 5 minutes after, 4 hours after, and 8 days after PTCA. Therefore, this diameter can be assumed to represent the relaxed state of the vascular segment. Compared with this maximally relaxed state, the diameter in the basal state indicates the extent of constriction present in the basal state in the different conditions (Figure 3). Compared with this maximally dilated state, the degree of constriction at 4 hours after PTCA in the distal vessel was significantly greater than before PTCA and 5 minutes after and 8 days after PTCA but did not correlate with the severity of the preexisting stenosis (Figure 4).

Response to the cold pressor test. The change in coronary diameter from basal in response to cold pressor testing was as follows. PTCA segment:
FIGURE 4. Scatterplot showing relation between lesion severity and degree of vasoconstriction in distal segment 4 hours after percutaneous transluminal coronary angioplasty. There is no significant association between lesion severity and severity of vasoconstriction.

-23±6% (p<0.0001) before PTCA, -8±4% (p=NS) at 5 minutes after, +10±2% (p<0.002) at 4 hours after, and -15±3% (p<0.001) at 8 days after PTCA (Figure 2). Distal segment: -15±4% (p<0.008) before PTCA, -4±2% (p=NS) at 5 minutes after, +2±1% (p=NS) at 4 hours after, and -9±1% (p<0.001) at 8 days after PTCA (Figure 2). Control segment: -4±3% (p=NS) before PTCA, +4±4% (p=NS) at 5 minutes after, -9±2% (p=NS) at 4 hours after, and -6±6% (p=NS) at 8 days after PTCA (Figure 2).

Discussion

This study shows that diffuse transient coronary artery constriction in the angioplastied vessel can be detected 4 hours after PTCA and is associated with loss of the response to the cold pressor test. These transient changes are detectable both at the site of PTCA and in the distal segment but not in the nondilated artery. This vasomotor abnormality is no longer detectable 8 days later when the response to the cold pressor test has reverted to that observed before PTCA. In our study, no nitroglycerin had been administered in the 4 hours preceding each angiogram except for that recorded 5 minutes after PTCA, and all antianginal medications were discontinued for at least 24 hours before each study.

Spontaneous Basal Coronary Vasomotor Changes

The dose of intracoronary nitroglycerin used in our study can be assumed to cause maximal relaxation of smooth muscle of epicardial coronary arteries. Therefore, the decrease in caliber at this maximal vasodilation indicates the basal level in vasoconstrictor tone. The caliber of the distal vessels before PTCA and 8 days after PTCA were similar, indicating a similar degree of constriction from the maximal dilated state. They were less constricted 5 minutes after PTCA, compatible with persisting effect of nitroglycerin administration before PTCA but markedly constricted 4 hours after PTCA. The caliber of the vessel at the site of successful PTCA was also significantly smaller at 4 hours after PTCA than at 5 minutes after and 8 days after PTCA. For both the PTCA and distal segments, the reduction in diameter was nearly 30%; that is similar to that induced by ergonovine in normal and diseased coronary arteries in patients who do not have variant angina.

This increase in resting coronary tone could result from a myogenic response to the sudden increase of pressure after the relief of the stenosis by PTCA, as recently proposed by Fischell. However, in our patients the degree of constriction did not correlate with the severity of the stenosis, contrary to the findings of Fischell et al 30 minutes after PTCA. This increase of basal tone 4 hours after PTCA could have a number of alternative explanations. It could be caused by an intense constrictor stimulus resulting from PTCA-induced nerve damage, by increased vasoactivity to physiological constrictor stimuli such as serotonin released by platelets adhering and aggregating at the PTCA site (it was recently shown that serotonin causes intense constriction in atherosclerotic arteries), or by lack of the dilator effect of endothelium-derived relaxing factor (EDRF). The latter hypothesis assumes that functionally intact endothelium was present at the site of dilatation before PTCA and that the endothelial function becomes impaired after PTCA. PTCA might have impaired the function of the vasa vasorum, which are known to be considerably increased in number at the site of atheromatous plaque.

Reflex Sympathetic Stimulation by the Cold Pressor Test

It has recently been reported that the response to the cold pressor test is represented by approximately 12% dilatation of basal diameter in normal human coronary arteries and approximately 9% constriction at the site of atheromatous irregularity or stenosis. However, in patients with coronary disease, both dilatation and constriction of apparently normal coronary segments have been reported. The endothelium appears to play a key role in determining the response to sympathetic stimulation. In the dog, the vasodilator response to epinephrine is changed to a constrictor response after removal of the endothelium, and endothelial integrity plays an important role in preventing α-adrenergic constriction. The mechanism of this modulation by endothelium may be flow-related, shear-stress–induced release of EDRF, as flow usually increases during the cold pressor test, or EDRF release induced by stimulation of α-2 receptors on endothelial cells.

In our study, reflex constriction occurred at the PTCA and distal segments before PTCA and at 8 days after PTCA. The distal segment constricted in response to the cold pressor test in all patients before and 8 days after PTCA, irrespective of whether its angiographic outline was smooth or irregular. By contrast, there was no significant constriction of
these segments to cold pressor testing at 5 minutes after PTCA. This is likely to be related to a persistent residual vasodilator effect by nitroglycerin administered before PTCA. At 4 hours after PTCA, the cold pressor test elicited vasodilation despite the recent disruption of the endothelium. Such a paradoxical vasodilatory response could be related to passive distension of the arterial wall caused by the marked increase of the arterial blood pressure.

**Oclusive Coronary Artery Spasm at the Site of PTCA**

Oclusive coronary artery spasm accounted for 20% of the acute complications in the National Heart, Lung, and Blood Institute PTCA registry.

However, in our study, no oclusive spasm was seen either within 5 minutes or at 4 hours after PTCA, nor was it induced by the cold pressor test. Therefore, acute endothelial damage alone appears to be insufficient to provoke oclusive spasm by itself or in response to physiological constrictor stimuli such as the cold pressor test. Thus, oclusive spasm at the site of PTCA is presumably the result of an inherent local hyperreactivity of vascular smooth muscle not present in other coronary segments as typically the case in variant angina or to very efficacious, nonphysiological constrictor stimuli.

**Vasomotor Response at 8 Days**

The resolution of the vasomotor abnormalities observed in our study within 8 days of PTCA might be, in part, related to endothelial regeneration. Confluence of endothelial cells over a 1.5-cm segment has been reported 7–10 days after denudation of the rat carotid artery by a stream of dry air, although the cell layer was not morphologically indistinguishable from normal until 1 month. In another study of endothelial regeneration in rabbit aorta, it was found that the rate of regeneration was variable and might last as long as 36 weeks. These conflicting results, the difficulty in extrapolating experimental results to humans, and the inability to explain the alterations of vasomotor tone observed in our study entirely on the basis of endothelial dysfunction do not allow us to draw precise conclusions about the role of endothelium regrowth in normalization of the vasomotor function 8 days after PTCA.

**Conclusions**

Intense coronary constriction of the PTCA and distal coronary segments can be detected 4 hours after PTCA, which prevents further constriction by physiological nervous stimulation; this constriction is undetectable at 8 days after PTCA. The cause of this early constriction is not clear. A reflex increase of myogenic tone seems unlikely because it was not related to the severity of the pre-PTCA stenosis. Mechanical damage to vasa vasorum, stimulation of perivascular nerves, or release of vasoconstrictor substances by activated platelets are possible alternative explanations. The cold pressor test failed to induce oclusive spasm at the PTCA site even at 4 hours, suggesting that the occurrence of spasm is related to a local hyperreactivity to constrictor stimuli similar to that observed in variant angina.

**References**


**KEY WORDS**  
- coronary angioplasty  
- vasoconstriction  
- cold pressor
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