Clinical Investigation

Coronary Artery Vasoconstriction Routinely Occurs After Percutaneous Transluminal Coronary Angioplasty
A Quantitative Arteriographic Analysis

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To determine whether percutaneous transluminal coronary angioplasty (PTCA) increases coronary artery luminal dimensions by stretching and injuring ("paralyzing") the smooth muscle of the arterial wall, we prospectively analyzed spontaneous changes and then intracoronary nitroglycerin-induced changes in segmental coronary artery diameters during the first 30 minutes after uncomplicated single-vessel PTCA in 10 patients. Five additional patients received intravenous nitroglycerin throughout the procedure to determine whether nitroglycerin could prevent vasoconstriction after PTCA. All of the patients were maintained on oral doses of diltiazem and aspirin at the time of the study. Coronary arteriography was performed at 2, 5, 15, and 30 minutes after PTCA and then 3 minutes after 300 μg i.c. nitroglycerin. Quantitative measurements (computerized edge-detection) were performed at each time, in coronary segments centered in the dilated segment, distal to the dilated segment, and in a control vessel not manipulated with the balloon catheter or guidewire. Progressive vasoconstriction (defined as a loss of diameter that was reversed by intracoronary nitroglycerin) was observed after PTCA in the dilated and distal segments (10 of 10 patients) but not in the control segment. The vasoconstriction in the dilated segment at 30 minutes (mean, 30±4%) was highly statistically significant compared with vasoconstriction at 2 and 5 minutes after PTCA (p<0.001) and compared with the control segment at 30 minutes (p<0.005). There was no significant loss of diameter after PTCA in the dilated segment in the five patients who received intravenous nitroglycerin. In conclusion, 1) spontaneous coronary artery vasoconstriction after PTCA occurs routinely at and distal to the site of balloon dilatation despite pretreatment with aspirin and calcium channel blockers; 2) coronary artery vasoconstriction after PTCA is rapidly reversed by intracoronary nitroglycerin and can be prevented by the continuous administration of intravenous nitroglycerin during and after the procedure; 3) these results are incompatible with the hypothesis that PTCA improves coronary luminal dimensions by arterial "paralysis"; and 4) these findings have implications concerning the etiology and prophylaxis of abrupt vessel closure after PTCA. (Circulation 1988;78:1323–1334)

Despite the widespread application of percutaneous transluminal coronary angioplasty (PTCA) in the treatment of obstructive coronary artery disease, little is known about the early spontaneous changes in coronary artery morphology and vasomotor behavior after this procedure is performed in humans. Similarly, some uncertainty remains about the mechanism(s) of successful PTCA.1–6 Several animal studies suggest that balloon angioplasty causes severe medial smooth muscle injury with impairment or loss of vasoconstrictor activity.6–8 It has been proposed that this arterial "paralysis," with resultant medial and adventitial stretching, contributes to the observed improvement in luminal dimensions observed after successful PTCA.1,2,7–10 In contrast, there is evidence from animal models11–13 and the clinical setting14–16 that balloon angioplasty can promote arterial spasm. Indeed, there is limited clinical evidence that angioplasty-induced vasoconstriction may contrib-
ute to acute vessel closure and possibly restenosis after successful PTCA. 16–19

The purpose of this study was to examine the changes in coronary artery dimensions after successful PTCA to determine whether PTCA increases coronary artery diameters by irreversibly stretching and injuring (‘‘paralyzing’’) the smooth muscle of the arterial wall. Accordingly, we prospectively studied spontaneous changes and then intracoronary nitroglycerin-induced changes in segmental coronary artery diameters with quantitative arteriographic techniques during the first 30 minutes after uncontrolled single-vessel PTCA in 10 patients. Five additional patients received intravenous nitroglycerin throughout the procedure to determine whether or not nitroglycerin alters the course of spontaneous changes in coronary dimensions after PTCA.

Patients and Methods

Patients

Fifteen patients scheduled for elective single-vessel PTCA were prospectively entered into the study. All patients had angina pectoris despite medical therapy. Exclusion criteria included concurrent nitroglycerin therapy, requirement for intracoronary nitroglycerin during the PTCA, repeat PTCA for restenosis, refusal to participate in the study, or technically inadequate coronary arteriography. The initial five patients composed a nonrandomized cohort. When data analysis from these five patients demonstrated consistent vasoconstriction after PTCA in the dilated segment, 10 additional patients were randomized either to receive continuous intravenous nitroglycerin during and after PTCA or to receive no intravenous nitroglycerin to determine whether intravenous nitroglycerin could inhibit vasoconstriction after PTCA. Thus, the study group consisted of an initial five nonrandomized patients, five patients randomized to receive intravenous nitroglycerin, and five patients randomized to receive no intravenous nitroglycerin.

Methods

All patients agreed to undergo PTCA and study procedures after being informed of the potential risks and complications, as outlined in a protocol approved by the Institutional Review Board of the Stanford University Medical Center, Stanford, California. All patients took their usual oral medications including aspirin and calcium channel blockers on the day of the procedure. After premedication with diazepam and local anesthesia with 0.25% bupivacaine, femoral artery (8F) and femoral venous (7F) sheaths were placed by single-wall entry technique. Heparin (5,000 units) was given intravenously. In those patients undergoing PTCA of the right coronary artery, a bipolar temporary pacing catheter was placed in the right ventricular apex. Selective coronary arteriography of the vessel to be dilated was performed in multiple projections with the 4–5 in. image intensifier mode and Renografin 76 at a cine rate of 30 frames/sec. The precise angle of each projection was recorded so that the projection that best demonstrated the stenosis to be dilated with minimal foreshortening could be replicated. To ensure that the changes in diameter observed after PTCA in the dilated segment were not due to a change after PTCA in luminal geometry, the spontaneous vasoconstrictor responses during the first 30 minutes after PTCA were analyzed from serial views in two orthogonal projections for the first five (nonrandomized) patients. When data analysis obtained from these five patients revealed no significant differences between the two orthogonal projections, the single best angiographic view was elected for use for subsequent studies. All injections throughout a given study were performed by the same operator to minimize variability in angiographic technique.

After a second intravenous bolus of 5,000 units heparin, coronary angioplasty was performed with either an over-the-wire balloon catheter system (13 patients) or a fixed-wire balloon catheter system (two patients). Balloon sizes were chosen to approximate the diameter of the ‘‘normal’’ coronary segment adjacent to the segment to be dilated. At least two balloon inflations were performed in each instance, with additional inflations performed as needed until the coronary stenosis had been dilated adequately according to angiographic and hemodynamic criteria.

As soon as was feasible after the final balloon inflation (mean, 2 minutes; range, 1–3 minutes), the balloon catheter was withdrawn, and selective coronary arteriography, in the previously selected projection that best demonstrated the stenosis (and the orthogonal projection [n=5], as above), was performed with the guidewire still across the dilated segment. This angiogram was designated ‘‘after PTCA 1.’’ The guidewire was withdrawn from the coronary artery, and a second angiogram after PTCA (‘‘after PTCA 2’’) was obtained (mean, 5 minutes; range, 3–6 minutes after final balloon inflation). The coronary guiding catheter was then withdrawn and replaced with an 8F right or left coronary artery Judkin’s ‘‘marker’’ catheter to be used as a reference for coronary quantification (see below). Coronary arteriograms (same projection) were repeated at 15 and 30 minutes after final balloon inflation and again 3 minutes after the administration of 300 µg i.e. nitroglycerin given immediately after the 30-minute angiogram (33 minutes after final balloon inflation). This dose of intracoronary nitroglycerin was chosen to provide a near maximal vasodilating effect. Blood pressure and heart rates were recorded immediately preceding each arteriogram (before PTCA, after PTCA 1, after PTCA 2, 15 minutes, 30 minutes, and after intracoronary nitroglycerin).

The five patients assigned to receive intravenous nitroglycerin had their blood pressure recorded immediately after the femoral sheaths were placed.
(baseline blood pressure). Before angiography, these patients received intravenous nitroglycerin, starting at a dosage of 25 μg/min and then titrated upward until there was a persistent decrease in systolic blood pressure (vs. baseline) of greater than 10 mm Hg and less than 25 mm Hg (mean blood pressure drop = 21 ± 4 mm Hg). The intravenous nitroglycerin was adjusted as needed during the study to maintain a stable hypotensive effect. The study protocol for these patients was otherwise identical to that used in the other 10 patients.

Coronary Arteriographic Analysis

All films were analyzed by quantitative arteriographic techniques. This method, which uses automated computerized edge detection of a digitized cineangiographic image, has been described in detail in a previous report. This system uses a 35-mm cine film transport mechanism mounted on a moveable stage (Vanguard Instruments, Melville, New York). Well opacified end-diastolic cine frames were selected, as described, and magnified (×3.5) with the appropriate coronary segment centered in the image field. The image was digitized (Model 5524, DeAnza Systems, Fremont, California) with the video processor controlled by a Hewlett-Packard 2100 computer (Andover, Massachusetts). The digitizer has a spatial resolution of 480 × 512 pixels and 8-bit gray scale resolution. With this cine film digitizing system at ×3.5 magnification, an average 3-mm diameter coronary vessel segment occupies a width of 30 pixels. The digitized image was displayed on a graphics computer terminal linked to a light pen. Magnification correction was achieved with a cylindrical tantalum marker of known diameter that is attached to the tip of the coronary catheter in the field of view. Because all views were obtained at precisely reproduced angles, table and intensifier heights, and without patient movement, the marker catheter in the 15-minute angiogram (first view with marker catheter) could be reliably used for magnification correction in all of the analyzed angiograms (before PTCA, after PTCA 1, after PTCA 2, 15 minutes, 30 minutes, and after intracoronary nitroglycerin). This technique was validated by the finding of no statistically significant differences in luminal diameter measurements of angiograms at 30 minutes and after intracoronary nitroglycerin when using the 15-minute marker compared with the “appropriate” 30-minute or after intracoronary nitroglycerin markers for calibration. After the segment length was designated on the computer terminal, the light pen was used to manually trace the margins of the appropriate vessel segment and to indicate the fiducial point. The maximum derivatives of the density profile perpendicular to these manually defined margins are defined as the computer-generated vascular boundaries. With these computer-generated vascular boundaries, the minimum, maximum, and mean diameters of the vessel segment were calculated. Occasionally, the computer algorithm was unable to resolve vessel boundaries in areas of crossing vessels, particularly strong random variation in quantum mottle, or where there was haziness in the dilated segment after PTCA. Manual editing of short segments of the boundary with the light pen is then used to correct the computer-generated boundary. Manual modification of the computer-generated vessel boundary generally did not exceed 10% of the vessel segment length. The resolution of this system has been demonstrated to be ±0.06 mm.

Three coronary segments were analyzed in patients undergoing PTCA in the left coronary artery system as illustrated in Figure 1A. Segment 1 (dilated segment) was defined as the 5-mm segment centered on the narrowest point of the coronary stenosis as viewed in the arteriogram before PTCA. Segment 2 (distal segment) was chosen to be a clearly identifiable 5-mm long segment distal to the dilated segment not manipulated by the balloon catheter. Segment 3 (control segment) was defined as a clearly identifiable 5-mm long segment in the left coronary artery that was not manipulated by guidewire or balloon catheter (e.g., left circumflex coronary artery when PTCA was performed in the left anterior descending coronary artery). For the six patients undergoing right coronary artery PTCA, only segments 1 and 2 could be analyzed because there was no equivalent control segment (see Figure IB).

All cine films were analyzed independently by two investigators. The precise locations of segments 1, 2, and 3 were defined and recorded by a “road map” drawing so that both investigators analyzed essentially identical segments for each cine film analyzed. The two film readers analyzed the mean and minimum segmental diameters in each of three consecutive end-diastolic frames (marked automatically on the cine film by an electrocardiographic marker) for each 5-mm long segment, at each time and condition (i.e., before PTCA, after PTCA 1, after PTCA 2, 15 minutes, 30 minutes, and after intracoronary nitroglycerin). The final segmental vessel diameters (mean and minimum) for each condition were defined as the mean of the six end-diastolic measurements (three from each cine film reader). The mean interobserver variability in the measurement of minimal segmental vessel diameter, analyzed for the first 100 segments was ±0.07 mm (±4.3%). For the purposes of determining percent vasoconstriction, the segmental vessel diameters measured from the after intracoronary nitroglycerin angiogram were defined as the maximally vasodilated state.

Statistics

Data are presented as the mean±SEM unless otherwise stated. The changes in minimum vessel diameter in each segment for each condition and the changes in blood pressure for the randomized patients were compared by a one-way analysis of variance by repeated measures (Fisher’s PLSD and Scheffe’s F test). The comparisons of percent vaso-
Constriction between segments at a given time and condition were performed with a Student's paired t test. A p value less than 0.05 was considered statistically significant.

Drugs

Nitroglycerin for intracoronary and intravenous administration was prepared by the addition of 25 mg nitroglycerin (Tridil) to 250 ml normal saline, yielding a final concentration of 100 μg/ml. Immediately after the 30-minute arteriogram, 3 ml of this solution was injected into the right or left coronary artery diagnostic catheter, which was then flushed with 3 ml normal saline solution.

Results

The patient and PTCA procedural data (n=15) and the initial improvement in luminal diameters after PTCA are shown in Tables 1 and 2, respectively, for each of the three patient groups (nonrandomized, without intravenous nitroglycerin, and with intravenous nitroglycerin). There were no significant differences in the historical characteristics between the groups. None of the patients had a history suggestive of variant angina pectoris. All of the patients were taking diltiazem and aspirin on a long-term basis (>2 weeks) at similar dosages at the time of entry into the study (see Table 1), and they received their usual oral dosages of these medications before undergoing PTCA. One of the patients in the intravenous nitroglycerin group took 80 mg aspirin/day, with the remaining 14 patients receiving 325 mg/day. The diltiazem was given in dosages (t.i.d. or q.i.d.) of 30 mg (n=1), 60 mg (n=13), or 90 mg (n=1). Primary angiographic success, defined as a reduction in stenosis diameter to less than 50%, was achieved in all 15 patients. There were no major complications associated with any of these procedures (i.e., no myocardial infarction, death, or need for coronary artery bypass surgery).

Coronary Vasoconstriction After PTCA

Spontaneous coronary artery vasoconstriction after PTCA was observed in the dilated coronary artery segment (segment 1) in five of five of the nonrandomized patients and in all of the patients randomized (n=5) to receive no intravenous nitroglycerin (Table 2). There were no significant differences in the percent vasoconstriction in the dilated segment at each time when measured in two orthogonal projections for the first five (nonrandomized) patients (see Figure 2). Figure 3 summarizes the spontaneous vasoconstricor responses during the first 30 minutes after PTCA in segments 1 (dilated), 2 (distal to the dilated segment) and 3 (control) for the 10 patients who did not receive intravenous nitroglycerin during and after the procedure. For a given segment (i.e., 1, 2, or 3), there were no significant differences in vasoconstricor responses in the nonrandomized compared with the randomized (without intravenous nitroglycerin) cohorts. In the earliest angiogram after PTCA (after PTCA 1), there was evidence of a mild degree of stretching (3±3%) beyond the maximally relaxed (after intracoronary nitroglycerin) diameter in the dilated segment (segment 1). After this early “stretching,” the dilated segment demonstrated progressive vasoconstriction of 5%, 27%, and then 30% (vs. after intra-
coronary nitroglycerin) at about 5, 15, and 30 minutes after PTCA, respectively. This loss of diameter (i.e., vasoconstriction) was reversed after the administration of intracoronary nitroglycerin at 30 minutes after PTCA. The amount of vasoconstriction observed 15 and 30 minutes after PTCA in the dilated segment (segment 1) was significant when compared with the degree of vasoconstriction measured in the arteriograms after PTCA (about 2 and 5 minutes) (p<0.001, ANOVA) and compared with the vasoconstriction of the control segment at 15 and 30 minutes (p<0.005, paired t test). An example of the spontaneous vasoconstriction observed in the dilated segment after PTCA and its reversal by intracoronary nitroglycerin is shown in Figure 4.

A lesser, but significant, degree of spontaneous reversible vasoconstriction was observed in the distal segment (segment 2) in all 10 of these patients during the first 30 minutes after PTCA. The distal segment demonstrated 7%, 17%, and 22% vasoconstriction (vs. after intracoronary nitroglycerin) at about 5, 15, and 30 minutes after PTCA, respectively. The vasoconstriction observed at 15 and 30 minutes after dilatation in the distal segment was significantly greater than that seen in the arteriograms after PTCA (1 and 2) (p<0.01, ANOVA) and compared with the vasoconstriction of the control segment at 15 and 30 minutes (p<0.01, paired t test).

Effects of Intravenous Nitroglycerin

The patient and procedural characteristics of the patients randomly assigned to receive intravenous nitroglycerin (n=5) or not receive intravenous nitroglycerin (n=5) are shown in Table 1. There were no significant differences in the initial results of PTCA in these two groups (Table 2). The initial “baseline” blood pressures in the two groups were not significantly different (mean; 126/83, without intravenous nitroglycerin; 124/76 mm Hg, with intravenous nitroglycerin). After the initiation of intravenous nitroglycerin (average final dosage, 66±7 μg/min) in the group with intravenous nitroglycerin, there was a significant decrease in systolic blood pressure (21±2 mm Hg), with smaller decreases in diastolic (5±1 mm Hg) and mean (9±1 mm Hg) arterial pressures. There were no significant changes in blood pressure from before PTCA to 30 minutes after PTCA in either the cohorts with or without intravenous nitroglycerin. There was, however, a decrease in systolic blood pressure (123±9 mm Hg to 115±9 mm Hg) after the administration of intracoronary nitroglycerin in the group without intravenous nitroglycerin (p<0.01, ANOVA) but not in the group with intravenous nitroglycerin.

The spontaneous vasoconstrictor responses after PTCA in segments 1 (dilated), 2 (distal), and 3 (control) in the groups with and without intravenous nitroglycerin are shown in Figure 5. In contrast to the patients not receiving intravenous nitroglycerin, the group receiving intravenous nitroglycerin demonstrated no significant spontaneous vasoconstriction after PTCA in segments 1 and 2. The differences in vasoconstriction between the patients with and without intravenous nitroglycerin in segments 1 and 2 at 15 and 30 minutes were highly significant (p<0.001). There was no significant increase after PTCA in vasoconstriction observed in the control segment of either the group with or without intravenous nitroglycerin.

Discussion

Relatively little is known about the short-term effects of PTCA on human coronary artery smooth muscle vasmotor reactivity. Animal studies in normal rabbit aorta,10 normal and diseased rabbit iliac arteries,5,6,9,23 and normal dog carotid arteries7 demonstrate that balloon angioplasty is capable of injuring or tearing medial smooth muscle, resulting in impairment or loss of vasoconstrictor responses. However, it is not entirely clear from these studies whether balloon angioplasty routinely causes severe medial injury, or whether the injury seen in these
animal models was due to some degree of balloon oversizing as compared with balloons that are used clinically, or possibly to an enhanced susceptibility to medial injury in these animal vessels. The possibility that angioplasty-induced arterial paralysis in animal models is the result of overstretching is suggested by the discrepancies between the severe histopathological medial injury observed in many of the animal models5–7,9,23 compared with the milder arterial disruption described in human postmortem studies.24–30 For example, Casteneda-Zuniga et al23 found that angioplasty-induced arterial paralysis was associated with histopathological features of smooth muscle cell lysis with "corkscrew" nuclei, whereas Kohchi et al25 did not find such signs of medial smooth muscle injury or loss in postmortem human arteries that had been recently dilated in vivo. In an in vitro model of balloon angioplasty in rabbit aorta and pig carotid arteries, only severe degrees of arterial stretching (e.g., >60–70% beyond physiological relaxed diameter) produced significant impairment of arterial vasoconstrictor responsiveness.13

In contrast to the findings of angioplasty-induced arterial paralysis cited above, there is evidence in both animal models11–13 and in the clinical setting14–19,21,22 that balloon angioplasty can promote arterial spasm. The results of this study support the latter view by demonstrating that human coronary artery smooth muscle retains both vasoconstrictor and vasorelaxant behavior after PTCA when balloons are chosen to approximate the size of the adjacent "normal" vessel. More importantly, the findings indicate that in the absence of ongoing nitroglycerin therapy, dilated coronary segments may exhibit marked spontaneous vasoconstriction.

**Mechanisms of Coronary Vasoconstriction After PTCA**

The dilated coronary artery segment (segment 1) consistently demonstrated a spontaneous loss of diameter (mean, 33±4%) from the time of the first arteriogram after PTCA (about 2 minutes after final balloon deflation) compared with the arteriogram taken 30 minutes after the final balloon deflation. In the most extreme case, there was a 46% loss of diameter at 30 minutes. The observation that nearly all of this loss in diameter was reversed after an intracoronary injection of nitroglycerin and was prevented by the administration of intravenous nitroglycerin strongly suggests that these spontaneous changes in segmental coronary artery diameter were due to vasoconstriction. Similar observations have been reported by Redd et al.,17 who found that spontaneous increases in trans-stenotic pressure gradients after PTCA could be reversed, in some cases, by nitroglycerin. Although it is recognized

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**TABLE 2. Coronary Artery Diameters in the Angioplasty Segment**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Before PTCA</th>
<th>After PTCA</th>
<th>After PTCA 1</th>
<th>After PTCA 2</th>
<th>15 min</th>
<th>30 min</th>
<th>After intracoronary NTG</th>
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<tbody>
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<td>Without intravenous NTG</td>
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<td>With intravenous NTG</td>
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<td>1.29</td>
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PTCA, percutaneous transluminal coronary angioplasty; before PTCA, angiography before crossing lesion; after PTCA 1, angiogram taken 1–3 minutes after final balloon inflation with guidewire still in dilated vessel; after PTCA 2, angiogram performed 2–6 minutes after final balloon inflation, guidewire removed; 15 min, angiogram 15 minutes after final balloon inflation; 30 min, angiogram 30 minutes after final inflation; after intracoronary NTG, angiogram taken 3 minutes after 300 μg of intracoronary nitroglycerin (33 minutes after final balloon inflation); without intravenous NTG, patients randomized to receive no intravenous nitroglycerin during and after the PTCA; with intravenous NTG, patients randomized to receive continuous intravenous nitroglycerin during and after the PTCA.
changes in vessel diameter were due to the effects of intracoronary contrast injections because repeated administration of intracoronary contrast material has either minimal or no detectable effects on large coronary artery diameters.\textsuperscript{31,32} It is not possible to determine from this study whether the vasoconstriction in the dilated segment was due to enhanced sensitivity to normal vasoconstricting stimuli or whether it represents a normal, or possibly subnormal, response to a potent vasoconstricting stimulus, although the latter appears more likely.

There are many potential mechanisms and mediators that have been proposed to explain the clinical observation of arterial spasm after balloon angioplasty. Animal studies suggest that balloon angioplasty may promote arterial vasoconstriction by impairment of the ability to degrade vasoactive substances such as serotonin,\textsuperscript{33–35} release of vasoactive substances from aggregating platelets at the site of endothelial injury,\textsuperscript{36–38} loss of endothelium-derived relaxant factor,\textsuperscript{39} adrenergic nerve dysfunction,\textsuperscript{40} alterations in vessel wall arachidonate metabolism,\textsuperscript{41} and stimulation of stretch-dependent myogenic tone.\textsuperscript{13} One cannot directly determine from this study which, if any, of these mechanisms is responsible for the segmental vasoconstriction observed in the dilated segment. However, the clinically relevant observation that pretreatment with calcium channel blockers (diltiazem) did not prevent vasoconstriction after PTCA suggests that this vasospasm is either receptor-mediated or myogenic or both because these two mechanisms promote smooth muscle calcium entry that is not significantly blocked by conventional calcium channel blocking agents.\textsuperscript{42,43} Arterial spasm after angioplasty that is resistant to calcium channel blocking agents has been previously described in animals\textsuperscript{11} and after PTCA in humans.\textsuperscript{44} A caveat to these observations regarding the inefficacy of calcium channel blocking agents is that one cannot necessarily dismiss the etiological role of coronary artery spasm in restenosis,\textsuperscript{38} based upon clinical studies showing that nifedipine and diltiazem do not alter restenosis rates.\textsuperscript{45,46}

Unlike orally administered calcium channel blockers, intravenous nitroglycerin appears to be effective in both the prevention and reversal of angioplasty-induced vasoconstriction. Although it is likely that adequate doses of orally or topically administered nitroglycerin preparations would be as effective as intravenous nitroglycerin in preventing vasoconstriction after PTCA, these routes of administration were not evaluated in this study. The efficacy of nitroglycerin in this setting is consistent with its role as a nonspecific vasodilator that modifies the production of substances that regulate myoplasmic calcium homeostasis.\textsuperscript{13,42}

\textbf{Implications: Mechanisms of Balloon Angioplasty}

A number of mechanisms have been proposed to explain the improvement in luminal dimensions that intravascular thrombus formation may occur despite full heparinization, it is unlikely that the loss of coronary artery diameter after PTCA was primarily the result of thrombus formation because no intraluminal filling defects were identified even in those cases in which orthogonal projections were analyzed. More importantly, nitroglycerin was very effective in both reversing and preventing the loss of diameter after PTCA, a finding that would not be expected if the luminal compromise were due primarily to thrombus. It is acknowledged, however, that in a few of the cases the diameter after intracoronary nitroglycerin was smaller than that observed immediately after PTCA and that this small nonreversible component of the diameter loss may be explained in some cases by intravascular thrombus.

The progressive loss of diameter during a 30-minute period after PTCA cannot be explained by "elastic recoil" because this phenomenon should occur almost instantaneously after the final balloon deflation and would not be reversed or prevented by nitroglycerin. The spontaneous loss of diameter in the dilated segment also cannot be explained by hemodynamic factors because blood pressure was essentially constant during the serial arteriograms and because the control segment showed no similar loss of diameter. Finally, it is doubtful that the
observed after successful balloon angioplasty. Initially, Lee et al.\textsuperscript{24} and Dotter and Judkins\textsuperscript{47,48} proposed that the improvement was the result of plaque compression, although this has been difficult to demonstrate in animal and cadaver models of balloon angioplasty.\textsuperscript{2,5,9,49,50} Other studies suggest that longitudinal plaque extrusion\textsuperscript{47} or loss of plaque material secondary to embolic debris or both\textsuperscript{51} may explain some of the luminal improvement. More recently, studies in cadaver tissue\textsuperscript{2,50,51} and cholesterol-fed rabbits\textsuperscript{5,9} suggest that luminal improvements after balloon angioplasty are primarily the result of intimal splitting, subintimal dissection, and irreversible stretching of the medial and adventitial layers. The extrapolation of the findings of irreversible medial stretching from the cadaver tissue and cholesterol-fed rabbits to balloon angioplasty as it is applied clinically is uncertain because cadaveric medial smooth muscle is incapable of contracting once stretched, and modest balloon oversizing may explain the loss of smooth muscle viability in cholesterol-fed rabbits (as discussed above). In addition, the experimental lesions produced in cholesterol-fed rabbits may bear relatively little resemblance to the advanced atherosclerotic lesions treated by balloon angioplasty in humans.\textsuperscript{52,53}

The frequent finding of transmural medial tearing with pseudoaneurysm formation in several of these

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Bar graph of spontaneous vasoconstrictor responses after percutaneous transluminal coronary angioplasty (PTCA) in the angioplasty, distal, and control segments during the first 30 minutes after PTCA. Vertical bars represent percent vasoconstriction for each segment, defined as the percent change in minimal segmental vessel diameter at each time compared to the minimal segmental diameter 3 minutes after the administration of 300 \(\mu\)g i.c. nitroglycerin. Vasoconstriction of the angioplasty segment at 15 and 30 minutes after PTCA was significantly greater than that in the post-PTCA 1 (about 2 minutes after final balloon inflation) and post-PTCA 2 (about 5 minutes after final balloon inflation) arteriograms (\(p\) values as shown). Vasoconstriction in the angioplasty segment was also significantly greater than that in the control segment at 15 minutes (\(p<0.01\) ) and 30 minutes after PTCA (\(p\) value as shown). NA, not applicable.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Arteriograms of spontaneous, reversible vasoconstriction in the angioplasty segment after percutaneous transluminal coronary angioplasty (PTCA). All images are end-diastolic frames viewed in the same projection and magnification and shown after computerized edge-detection image processing. Panel A: High-grade stenosis of the right coronary artery before PTCA. Panel B: End-diastolic frame of the same vessel segment approximately 3 minutes after the final balloon inflation. Panel C: Same vessel segment 30 minutes after the final balloon inflation, with nearly a 50\% loss of segmental vessel diameter compared with vessel in Panel B. Panel D: Same segment 3 minutes after administration of 300 \(\mu\)g i.c. nitroglycerin (33 minutes after final balloon inflation), with return to diameter similar to that of vessel in Panel B.}
\end{figure}
FIGURE 5. Bar graphs of segmental coronary vasoconstrictor responses after percutaneous transluminal coronary angioplasty (PTCA) in patients randomized to receive (+IV Nitroglycerin) or not receive (−IV Nitroglycerin) intravenous nitroglycerin during and after PTCA. Vertical bars represent percent vasoconstriction for each coronary segment (angioplasty, distal, and control), defined as the percent change in minimal segmental vessel diameter at each time compared with the minimal segmental diameter 3 minutes after the administration of 300 μg i.c. nitroglycerin. In the −IV Nitroglycerin patients, significant increases in vasoconstriction were observed at 15 and 30 minutes after PTCA compared with the post-PTCA 1 and post-PTCA 2 arteriograms in the angioplasty and distal segments (p<0.01, as shown) but not in the control segment. There were no significant post-PTCA changes in vasoconstriction in the angioplasty, distal, or control segments in the patients who received intravenous nitroglycerin. NS, not statistically significant.

cadaver and rabbit studies contrast with the typically modest medial injury described in other cadaver studies, in which balloon sizes were

FIGURE 6. Diagrams of proposed mechanisms of balloon angioplasty. Panel A: High-grade eccentric coronary stenosis has been crossed by the guidewire and balloon catheter before balloon inflation. Panel B: Balloon is inflated. Panel C: Immediately after the final balloon inflation, there is intimal splitting to the internal elastic lamina with “release” of the cicatrizong effects of the intima and modest arterial “stretching.” Panel D: Approximately 30 minutes after the final balloon inflation, the dilated segment with a relatively intact medial smooth muscle layer spontaneously constricts, possibly secondary to the release of vasoactive substances released from aggregating platelets. Panel E: Vessel relaxes after the administration of intracoronary nitroglycerin, with improvement in luminal dimensions resulting from intimal splitting, subintimal dissection, and “release” of the media from the underlying noncompliant intima.

chosen to match the adjoining normal segment, with other reports of balloon angioplasty in the rabbit model of atherosclerosis and with the histology of human postmortem arteries that were studied after angioplasty in vivo. Of all the postmortem studies in humans, only one case report, in which the balloon was intentionally oversized, clearly identified severe medial injury after PTCA. The most reproducible finding in successful balloon angioplasty, as determined by postmortem studies of in vivo human angioplasty is intimal splitting and plaque fracture, often to and occasionally through
The internal elastic lamina. These studies have not clearly identified medial and adventitial stretching as a major determinant of successful balloon angioplasty. Our findings of preserved arterial vasmotion after balloon angioplasty is inconsistent with the hypothesis that angioplasty routinely improves luminal dimensions by irreversibly stretching and severely injuring the media. It is most likely, as suggested by Block, that the splitting of the plaque, particularly when it involves the separation of the intima from the media along the internal elastic lamina, ‘releases’ the cicatrizing effect of the plaque on the media, allowing it to passively distend (in response to hydrostatic forces) to achieve a normal or even slightly larger than normal medial diameter. A revised hypothesis of the mechanisms of successful balloon angioplasty based on these observations is illustrated in Figure 6.

Implications: Etiology of Abrupt Occlusion After PTCA

The routine finding of arterial vasoconstriction in the dilated coronary artery segment also has significant implications regarding the etiology of abrupt vessel closure after successful PTCA. Acute coronary artery occlusion after successful PTCA occurs in 2–10% of patients, typically within 3–6 hours of the procedure. The mechanisms of acute occlusion are likely multifactorial and may include mechanical obstruction due to intimal flap, platelet aggregation followed by intracoronary thrombus formation, or coronary artery spasm or all three. The contribution of arterial vasoconstriction in acute vessel closure is strongly suggested by observations that both acute occlusions and rising trans-stenotic pressure gradients after PTCA can be reversed with vasodilators. The risk of abrupt occlusion appears to be closely correlated with a suboptimal short-term PTCA result as determined by percent stenosis after PTCA, trans-stenotic pressure gradient, or the presence of a large intimal flap or all three. It is reasonable to assume that the degree of vasoconstriction routinely observed in the dilated segment in this study (20–46% decrease in minimal diameter during the first 30 minutes after PTCA) may play an important contributing role in acute vessel occlusion in the setting of a suboptimal PTCA result.

The route and timing of nitroglycerin administration varies greatly from one institution to another. The results of this small trial suggest that systemic administration of nitroglycerin, during and after PTCA, in doses sufficient to reduce systolic blood pressure by about 20 mm Hg effectively prevents coronary vasoconstriction. Based upon these observations, we now administer relatively high doses of systemic nitrate therapy in the setting of suboptimal PTCA results, and we continue this therapy for a minimum of 12–24 hours after the PTCA. The question of whether or not sustained high-dose nitrate therapy can affect the incidence of abrupt vessel closure after PTCA will require a larger, randomized clinical trial.

Summary

Spontaneous coronary artery vasoconstriction after PTCA occurs routinely at, and distal to, the site of balloon dilatation despite pretreatment with aspirin and calcium channel blockers. The mechanism of this vasospasm is not known, but it may be due to the release of vasoactive substances from aggregating platelets at the site of intimal injury or myogenic vasoconstriction or both. This coronary artery vasoconstriction is rapidly reversed by intracoronary nitroglycerin and can be prevented by the continuous administration of intravenous nitroglycerin during and after the procedure. The results of this study are incompatible with the hypothesis that PTCA improves coronary luminal dimensions by arterial paralysis and irreversible medial and adventitial stretching. Finally, these findings suggest that coronary vasoconstriction plays a role in abrupt vessel closure after PTCA.

Acknowledgments

We thank Marc Gradman, MD, for his assistance in patient recruitment and participation in the study protocol, and Mary Toews for manuscript preparation.

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KEY WORDS • spasm • coronary artery • balloon angioplasty • nitroglycerin
Coronary artery vasoconstriction routinely occurs after percutaneous transluminal coronary angioplasty. A quantitative arteriographic analysis.

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Circulation. 1988;78:1323-1334
doi: 10.1161/01.CIR.78.6.1323

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