Endothelium-Dependent Arterial Vasoconstriction After Balloon Angioplasty

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To determine whether balloon angioplasty can provoke arterial vasoconstriction independent of platelet aggregation and neurogenic input, we studied the spontaneous vasomotor effects of balloon dilatation in isolated, perfused whole-vessel segments of rabbit aorta and pig carotid artery. Freshly dissected rabbit thoracic aortas were mounted in a muscle bath-perfusion chamber, perfused with physiologic saline solution at 70 mm Hg, and allowed to equilibrate. The proximal or distal half of the aortas were dilated with either a "large" (5 mm, 31–51% stretch beyond relaxed diameter) or a "small" (4 mm, 5–16% stretch) balloon angioplasty catheter with the other half of the vessel serving as the control. A similar series of experiments were performed in pig carotid arteries using "large" (6 or 8 mm, 48–90% stretch) balloon catheters. The spontaneous vasomotor effects of balloon angioplasty were examined with long-axis, high-frequency ultrasonic imaging combined with computerized edge detection image processing to measure changes in segmental internal vessel diameters. Additional experiments were carried out in rabbit aortas to determine the roles of the endothelium, extracellular calcium, indomethacin, ibuprofen, and calcium-channel blockade in modulating angioplasty-induced vasoconstriction. Significant arterial vasoconstriction was observed in the balloon angioplasty segments after dilatation with 5-mm balloons but not with 4-mm balloons. After dilatation with 5-mm balloons, the angioplasty segments' cross-sectional areas decreased by an average of 31% versus 4% for the nondilated (control) segments (p<0.0001). Similar postangioplasty vasoconstriction was observed in the pig carotid arteries (decrease in minimal vessel cross-sectional area of 41% [angioplasty segment] versus 2% [control segment]) (p<0.005). This angioplasty-induced vasoconstriction was prevented by endothelial denudation before angioplasty, removal of extracellular calcium, and pretreatment with indomethacin or ibuprofen. The vasoconstriction was only partially inhibited by calcium channel blockade with verapamil. These findings demonstrate that stretch-pressure-induced arterial vasoconstriction may occur after balloon angioplasty, independent of platelet aggregation and neurogenic input. This angioplasty-induced vasoconstriction appears to be mediated by an endothelially derived cyclooxygenase product(s). (Circulation 1989;79:899–910)

Arterial spasm after balloon angioplasty has been well documented and may be a contributing factor in abrupt vessel closure, and possibly restenosis.1–3 The exact mechanisms of enhanced vasoconstriction after balloon angioplasty have not been fully determined but may be related to enhancement of vasoconstrictor responses to 5-hydroxytryptamine and platelets,4–7 endothelial injury with resultant loss of endothelium-derived relaxant factor (EDRF),8,9 alteration of vessel wall arachidonate metabolism,10,11 or a combination. The possible contribution of pressure- or stretch-dependent, "myogenic" vasoconstriction in mediating arterial spasm after balloon angioplasty has not been previously examined. The goals of our study were to determine whether balloon angioplasty can provoke spontaneous pressure-stretch–dependent arterial vasoconstriction in perfused whole-vessel segments of rabbit aorta and pig carotid artery and to determine the characteristics of this vasoconstriction. Specifically, we tested three hypotheses: 1) balloon angioplasty can cause, in a stretch-pressure–dependent fashion, spontaneous arterial vasoconstriction independent of platelet...
aggregation and neurogenic input; 2) angioplasty-induced arterial vasoconstriction (in vitro) is dependent on the presence of extracellular calcium; and 3) this vasoconstrictor response is mediated by an endothelially derived cyclooxygenase product(s).

Methods

An ultrasonic imaging technique was used to study the segmental vasomotor effects of balloon angioplasty in isolated, perfused rabbit thoracic aortas and pig carotid arteries. This technique uses high-frequency, long-axis ultrasonic imaging of vessels suspended and perfused in a muscle bath, combined with computerized edge detection image processing to measure segmental internal vessel diameters. Dose-response curves to pharmacologic agents obtained via this method have shown a high degree of correlation with data obtained by classical tissue bath techniques with arterial ring segments and force displacement transducers. The experimental apparatus used for these studies is shown in Figure 1.

Tissue Collection and Preparation

We used the thoracic aortas from 45 New Zealand White rabbits (females, 1–3 kg) and seven pig common carotid arteries from adult Yorkshire pigs (females, 33–45 kg). All studies were performed in compliance with the Stanford University Panel on Animal Laboratory Care guidelines. The rabbits were killed by cerebral concussion, and their thoracic aortas, approximately 4 cm in length, were dissected free. The swine were anesthetized with 1% halothane general anesthesia. The common carotid arteries were dissected free, transected at their origin and at the carotid bifurcation, and removed. The arteries were mounted in the muscle bath by tying the proximal and distal ends of the vessel to the tapered and adjustable vessel attachment pieces using 2.0 silk suture, as shown in Figure 1. The arteries were suspended to approximate their original in vivo length. The vessels were bathed in physiologic saline solution with the following composition (mM): NaCl 24, KCl 4, MgSO4 1.2, CaCl2 2, dextrose 5, NaHCO3 24, and NaH2PO4 1.2. The pH was kept constant at 7.40–7.45, and the muscle bath solution was warmed to 36–37°C and aerated with 95% O2–5% CO2. All perfusates were heated to 36–37°C by passage through a capillary tubing network within the outer heating bath, and then delivered to the proximal vertical port via standard polyvinyl chloride intravenous tubing.

To permit perfusion at physiologic pressures and flow rates without side branch leakage, all of the small lumbar arteries arising from the posterior aspect of the rabbit aortas were cauterized with a miniature, battery-powered surgical cautery device (Accu-Temp, Concept, Clearwater, Florida). The cautery was performed at a minimum distance of 0.5 mm from the lumbar artery takeoff to ensure that there would be no thermal damage to the thoracic aorta. The pig common carotid artery lacks side branches and, therefore, did not require cautery before study.

Balloon Angioplasty Studies

After mounting, the arteries were perfused with recirculating oxygenated physiologic saline solution at a flow rate maintained at 50–60 ml/min by a constant flow (nonpulsatile) peristaltic pump. Vessel perfusion pressure was maintained at a constant 70 mm Hg throughout each study via minor adjustments in outflow resistance. Minor vessel length adjustments were made to ensure that there was no resting longitudinal tension at this vessel perfusion pressure. The vessels were allowed to equilibrate for 45 minutes before experimental manipulation. After equilibration perfusion, a 10 mHz ultrasonic transducer (Diasonics 200 RF) was positioned approximately 1 cm above the artery, in contact with the muscle bath solution. The transducer head was aligned along the vessel so as to optimize the long-axis image of the upper and lower vessel walls. Gain settings were held constant throughout the experiment. This system provided a uniform, sharp vessel wall image of at least 3 cm of vessel length at short focal distances (less than 1 cm). Once the vessel was optimally imaged, real-time ultrasonic vessel wall images were recorded to determine the control vessel internal diameter. All ultrasonic images were recorded with a 3/4-in. videocassette tape recorder (Sony U-matic, VO-5800).

Balloon angioplasty was then performed in the proximal vessel segment relative to perfusate flow,
FIGURE 2. Bar charts of immediate vasoconstrictor effects of balloon angioplasty in rabbit aortas. Mean segmental cross-sectional areas ± SEM (y axis), before (pre) and 5 minutes after (post) balloon angioplasty (x axis). Panel A: Effects of balloon angioplasty with a 4-mm balloon catheter are shown for the control (nondilated) segments and the balloon injured segments (n = 5). Panel B: Effects of balloon angioplasty with a 5-mm balloon catheter (n = 7). Panel C: Immediate vasomotor effects of 5-mm balloon angioplasty in a calcium-free bath (− calcium, n = 4) are compared with the responses with calcium present (+ calcium, n = 7). Panel D: Effects of 5-mm balloon angioplasty in vessel segments with (+ endothelium, n = 7) and without (− endothelium, n = 6) intact endothelium.

with the balloon catheter introduced via the proximal central port. Three 60 second inflations to 6 atm, each separated by 15 seconds, were performed with catheters with a balloon length of 2.0 cm. Vessel perfusion was, by necessity, discontinued during balloon inflations since the vessel lumen was totally occluded by the inflated balloon. For the rabbit aorta experiments, angioplasty was performed with balloon angioplasty catheters having an inflated balloon diameter of 4 mm (n = 5) (Lo Profile II, USCI) or 5 mm (n = 7) (Dotter Polyethylene Dilatation Catheter, Cook). The ratio of inflated balloon diameters to control internal vessel diameter for the rabbit aortae was 1.1–1.2 for the 4-mm balloon experiments and 1.3–1.5 for the 5-mm balloon experiments. The pig carotid artery angioplasty was performed with balloon angioplasty catheters with an inflated diameter of either 6 (n = 3) or 8 mm (n = 4). The balloon size was specifically selected to obtain a ratio of inflated balloon size to control internal vessel diameter of 1.5–1.9:1 in pig carotid arteries ranging in size from 3.5 to 5.1 mm in diameter.

Real-time ultrasonic vessel images were observed continuously during and after angioplasty, with vessel images recorded during balloon inflations, immediately after balloon catheter removal, and at the time of maximal vasoconstriction, when present, after angioplasty. Images were also recorded at 15, 30, and 45 minutes after the final balloon inflation.

Calcium Depletion Experiments

A parallel series of experiments were carried out with 5-mm balloon catheters in rabbit aortae
(n=4) with calcium-free (EGTA) physiologic saline solution in both the muscle bath and vessel perfusate to determine the role of extracellular calcium in mediating balloon angioplasty-induced vasoconstriction. Tissue preparations for these experiments were as described above. The aortas were bathed and perfused with physiologic saline solution identical to that described above with the exception that CaCl₂ was deleted and 0.5 mM EGTA was added to the solution. Balloon angioplasty was performed as described and vessel images recorded, as above, for 45 minutes. After 45 minutes, 60 mM KCl was added to the perfusate and images recorded at 5-minute intervals for 15 minutes to determine whether potassium chloride-mediated contraction had been blocked. At 60 minutes postangioplasty, the calcium-free solution was replaced with calcium-replete physiologic saline solution and the vessels were allowed to equilibrate for 15 minutes. Sixty millimeters of potassium chloride was added to the calcium replete perfusate and vessel contractility recorded at 5-minute intervals for a final 15 minutes.

**Endothelial Denudation Experiments**

To determine the role, if any, of the endothelium in mediating balloon angioplasty-induced arterial vasoconstriction, a second series of parallel experiments were performed in rabbit aortas (n=6) with 5 mm-balloon catheters, after mechanical denudation of the endothelium. After harvesting the rabbit aortas, the aortas were cannulated with a small glass rod (outer diameter, 2 mm) and gently rolled on moistened filter paper to mechanically denude the endothelium. The aortas were then mounted in the muscle bath and the experimental protocol carried out as described above. Sixty minutes after the final balloon inflation, the effects of vessel perfusion with increasing log-doses of phenylephrine (10⁻⁸ to 10⁻⁴ M) were examined and compared with nondenuded rabbit aorta to ensure that mechanical endothelial denu-
vation had not impaired normal smooth muscle vasoconstrictor responsiveness. The effectiveness of endothelial denudation by this technique was histologically confirmed by scanning electron microscopy as described below.

Cyclooxygenase Inhibition and Calcium Blockade Experiments

Another set of parallel experiments were performed in rabbit aortas with 5-mm balloon catheters after incubation and perfusion with the cyclooxygenase inhibitors, indomethacin \((n=7)\), and ibuprofen \((n=7)\) to determine the role, if any, of arachidonic acid metabolite(s) in mediating balloon angioplasty-induced arterial vasoconstriction. In these experiments, the aortas were perfused with physiologic saline solution containing \(5.0 \times 10^{-6}\) M indomethacin or \(1.0 \times 10^{-5}\) M ibuprofen for a minimum of 30 minutes before balloon angioplasty. The experimental protocol was otherwise identical to that described above for the balloon angioplasty studies.

A final series of experiments were performed in rabbit aortas \((n=9)\) with 5-mm balloon angioplasty catheters after pretreatment with verapamil. In these experiments, the vessels were perfused with physiologic saline solution containing \(1.0 \times 10^{-5}\) M verapamil for a minimum of 30 minutes before balloon angioplasty. The experimental protocol was otherwise identical to that described above for the balloon angioplasty studies.

Data Collection and Computerized Edge Detection

Mean and minimum internal vessel diameters of the control (nonmanipulated) and balloon angioplasty segments, measured over a 1-cm length, were determined by computerized edge detection image processing of the two-dimensional ultrasonic images. The application of this computerized edge detection system to analyze internal vessel diameters from long-axis ultrasonic vessel wall images has been previously described in detail.12,13 With this system, repeated determinations of mean internal vessel diameter over a given 1-cm segment of rabbit aorta demonstrated by an interobserver variability of less than 0.05 mm. The overall resolution of the imaging and image-processing system has been calculated to be \(\pm 0.22\) mm with a 10-mHz transducer. Mean and minimal vessel cross-sectional areas were calculated from the measurements of internal vessel diameter with the formula: area = \(\pi (1/2 \cdot \text{diameter})^2\).

Histologic Examination

At the conclusion of the experiments, one ring segment, \(\sim 2\) mm in length, was cut from both the control and the balloon angioplasty segments. The ring segments were fixed in 1% glutaraldehyde in 0.067 M cacodylate buffer, prepared by methods described by Christensen and Garbarsch,14 and examined by scanning electron microscopy, to assess endothelial integrity.

In two separate rabbit aorta preparations, the control and balloon angioplasty (5-mm balloon catheter dilatation) ring segments were harvested within 5 minutes after balloon inflation and studied by scanning electron microscopy to assess endothelial integrity at the time of maximal spontaneous vasoconstriction.

Statistical Analysis

The Student’s \(t\) test for paired means was used to compare the mean and minimum vessel cross-sectional areas of the control and balloon angioplasty segments immediately after balloon angioplasty. Analysis of variance (repeated measures) was used to compare the changes in mean and minimum vessel cross-sectional areas in the balloon angioplasty segments before and immediately after balloon angioplasty; the differences in vasoconstriction after 4- versus 5-mm balloon inflations; the effects of indomethacin, ibuprofen, and verapamil on vasoconstriction; and phenylephrine dose-responses of rabbit aortas with intact endothelium versus those with denuded endothelium. Unless otherwise stated, data are presented as mean \(\pm\) SEM.

Drugs

1-Phenylephrine hydrochloride, EGTA, potassium chloride, indomethacin, ibuprofen, and verapamil were obtained from Sigma Chemical Company, St. Louis, Missouri. Nitroglycerin was obtained from Parke-Davis, Morris Plains, New Jersey. All drugs were prepared fresh on the day of the experiments. Phenylephrine, EGTA, nitroglycerin, potassium chloride, and verapamil were all dissolved initially in distilled water and then added in precalculated (small) volumes to physiologic saline to achieve the desired drug concentration in each perfusate. Indomethacin and ibuprofen were first dissolved in 5 ml ethanol, which was then added in precalculated (small) volumes to physiologic saline to achieve the desired drug concentrations.

Results

Stretch-Pressure–Induced Arterial Vasoconstriction in Rabbit Aorta

In the 4-mm balloon experiments \((n=5)\), the rabbit aortas had a control diameter of 3.56 \(\pm\)0.31 mm and were stretched by an average of 12% (range, 5–16%) beyond their relaxed internal vessel diameter. In the 5-mm balloon experiments \((n=7)\), the rabbit aortas had a control diameter of 3.59 \(\pm\)0.43 mm and were stretched by an average of 39% (range, 31–51%) beyond their relaxed internal vessel diameter. The maximal spontaneous vasoconstrictor responses of the balloon angioplasty and control segments after dilatation with 4- and 5-mm balloons are shown in Figures 2A and 2B, respectively. Significant arterial vasoconstriction, defined
as a spontaneous decrease of 15% or more of the segmental cross-sectional area, was observed in all aortas after 5-mm balloon dilatation (e.g., Figure 3) but occurred in only one of five aortas after 4-mm balloon dilatation. After dilatation with 5-mm balloons, the angioplasty segments’ cross-sectional areas decreased by an average of 31±3% (9.96±0.54 to 6.87±0.59 mm²) compared with 4±2% (10.12±0.56 to 9.73±0.61 mm²) for the nondilated (control) segments (p<0.0001, paired t test), and 6±2% (10.03±0.52 to 9.44±0.63 mm²) for the balloon angioplasty segment after 4-mm balloon angioplasty (p<0.01, ANOVA). Maximal vasoconstriction was typically observed within the first 2–5 minutes after the final balloon inflation. Five of the seven aortas dilated with 5-mm balloons relaxed spontaneously to 90% or more of the preangioplasty vessel diameter during the 45-minute postangioplasty observational period. The time course of this spontaneous reversal of the vasoconstriction correlated with the posttraumatic loss of endothelium as determined by scanning electron microscopy (Figures 4A, 4B, and 4C). In two aortas, there was only partial relaxation at 45 minutes. The persistent vasoconstriction in these two aortas was completely and rapidly (≤5 minutes) reversed by vessel perfusion with 10⁻⁵ M nitroglycerin.

Role of the Extracellular Calcium

The calcium depletion experiments were performed in rabbit aortas (n=4) with 5-mm balloons causing an average arterial stretching of 41% (range, 26–47%) beyond the relaxed (preangioplasty) internal vessel diameter (control diameter, 3.53±0.37 mm). The results of these experiments are shown in Figure 2C. When calcium was removed from the muscle bath and perfusate, there was a 6±2% increase in the cross-sectional area (10.57±0.72 to
11.18 ± 0.74 mm²) of the balloon angioplasty segment after balloon dilatation (p < 0.001 compared with angioplasty segment after dilatation with calcium present). There was no significant vessel contraction after the addition of 60 mM KCl in the presence of EGTA (no extracellular calcium present). After the muscle bath and perfusate solutions were replaced with standard calcium containing physiologic saline solution, the addition of 60 mM KCl resulted in significant vessel contraction (0.63 ± 0.11 mm), confirming the viability of the smooth muscle.

Role of the Endothelium

To examine the role of the endothelium in mediating angioplasty-induced vasoconstriction, rabbit
aortas (n = 6) with a control diameter of 3.65 ± 0.29 mm² were dilated with 5-mm balloons (average arterial stretch, 37%) after mechanical endothelial denudation. In contrast to the vessels with intact endothelium, there was a 4 ± 3% increase in cross-sectional area (9.65 ± 1.21 to 10.04 ± 1.13 mm²) of the balloon angioplasty segment after dilatation of the endothelially denuded aortas (p < 0.005 compared with endothelium-intact angioplasty segments). These data are illustrated in Figure 2D. The vasoconstrictor responses to increasing log-doses of phenylephrine in these endothelially denuded aortas were not significantly different from those of aortas with intact endothelium (p = NS, ANOVA), confirming that endothelial removal had not impaired the smooth muscle contractility. Scanning electron microscopy confirmed the effectiveness of the mechanical endothelial denudation (Figure 4D).

Cyclooxygenase Inhibition and Calcium Channel Blockade

Cyclooxygenase inhibition with indomethacin prevented vasoconstriction after 5-mm balloon angioplasty in rabbit aortas with a control vessel diameter of 3.62 ± 0.35 mm (average stretch, 38% beyond relaxed vessel diameter). In those aortas treated with 5.0 × 10⁻⁶ M indomethacin before angioplasty, there was a 3 ± 3% increase in vessel cross-sectional area after balloon dilatation (10.61 ± 0.79 to 10.94 ± 1.21 mm², p = NS) (see Figure 5A).

Pretreatment with ibuprofen also prevented vasoconstriction after 5-mm balloon angioplasty in rabbit aortas with a control vessel diameter of 3.53 ± 0.31 mm (average stretch, 42% beyond relaxed vessel diameter). In those aortas treated with 1.0 × 10⁻⁶ M indomethacin before angioplasty, there was 3 ± 3% decrease in vessel cross-sectional area after balloon dilatation (9.89 ± 0.77 to 9.55 ± 0.69 mm², p = NS) (see Figure 5B).

Calcium channel blockade with relatively high-dose verapamil partially inhibited angioplasty-induced vasoconstriction in rabbit aortas. After 5-mm balloon angioplasty in vessels pretreated with 1.0 × 10⁻⁵ M verapamil, there was an 11 ± 2% decrease in vessel cross-sectional area in the dilated segment (10.09 ± 0.59 to 9.01 ± 0.37 mm²), which was significantly less than the 31 ± 3% loss of cross-sectional area after balloon angioplasty in aortas not treated with verapamil (p < 0.01). However, the post-angioplasty vasoconstriction in aortas pretreated with verapamil was statistically significant (p < 0.05) (see Figure 5C).

Angioplasty-Induced Arterial Vasoconstriction in Pig Carotid Arteries

Arterial vasoconstriction was also observed after angioplasty in pig carotids with balloons that stretched the arteries by an average of 68% (range, 48–90%) beyond the relaxed, preangioplasty internal vessel diameters. The control diameter of the pig carotid arteries was 4.01 ± 0.73 mm. The maximal spontaneous vasoconstrictor responses of the balloon angioplasty and control segments after balloon angioplasty are illustrated in Figure 6. The average decrease in minimal vessel cross-sectional area after balloon angioplasty was 41 ± 5% for the balloon angioplasty segment (12.52 ± 1.33 to 7.34 ± 0.99 mm²) versus 2 ± 1% (12.10 ± 1.22 to 11.83 ± 1.01 mm²) for the control segment (p < 0.005). Marked focal arterial spasm, localized to the distal tapered end of the balloon, was observed in three of the four carotids after 8-mm balloon dilatation, whereas vasoconstriction throughout the dilated segment was observed in the three carotid arteries stretched more modestly with a 6-mm balloon. An example of this focal spasm after 8-mm balloon angioplasty is shown in Figure 7, with Panel A showing a long-axis ultrasonic image of the pig carotid artery before balloon angioplasty, Panel B showing the artery during balloon inflation, and Panel C demonstrating focal vasoconstriction in the segment.

Figure 6. Bar chart of immediate vasoconstrictor effects of balloon angioplasty in pig carotid arteries. Minimal segmental cross-sectional areas (mean ± SEM, n = 7, y axis) before (preangioplasty) and 5 minutes after (postangioplasty) balloon angioplasty (x axis) are shown for the nondilated (control segment) segments and the balloon injured segments (angioplasty segment).
underlying the distal tapered end of the balloon catheter 5 minutes after the final balloon inflation. The lack of arterial vasoconstriction in the most proximal (fully dilated) segment appeared to be the result of severe smooth muscle injury by a lack of normal vasoconstriction during dose-response testing with phenylephrine.

Discussion

Angioplasty-induced arterial vasoconstriction has been well described both clinically\(^1\)-\(^3,15\) and in animal models,\(^8,16,17\) yet the exact mechanism(s) of this phenomenon have not been fully defined. This vasoconstriction may be a contributing factor in abrupt vessel closure after percutaneous translumini-
Arterial Vasoconstriction

the potential mechanism(s) of angioplasty-induced vasoconstriction. Various studies have demonstrated that angioplasty-induced endothelial injury may promote vasoconstriction by the loss of EDRF, impaired ability to degrade vasoactive substances such as serotonin, adrenergic nerve dysfunction, alterations in vessel wall arachidonate metabolism, or a combination. Many of these animal studies have proposed that angioplasty-induced arterial vasoconstriction is due primarily to the effects of vasoactive substances released by aggregating platelets (e.g., thromboxane and serotonin) at the site of endothelial injury. In a rabbit iliac artery model of angioplasty-induced arterial vasoconstriction (in vivo), LeVeen et al observed severe arterial spasm, localized to the distal end of the balloon catheter, which was resistant to premedication with verapamil. Similarly, it has recently been observed that calcium channel blockade does not prevent spontaneous coronary artery vasoconstriction after PTCA in humans. The observations that verapamil and diltiazem are not completely effective in preventing angioplasty-induced vasoconstriction in vivo and that relatively high dose verapamil only partially inhibited vasoconstriction in our in vitro model are compatible with the hypothesis that this vasoconstriction is receptor-mediated, "myogenic," or both and not mediated by voltage-dependent calcium channels.

In a pig carotid artery model (in vivo), Lam et al found a significant correlation between the degree of platelet deposition and localized vasoconstriction at the site of angioplasty-induced arterial injury and suggested that postangioplasty vasoconstriction is primarily due to platelet aggregation. Arterial spasm was again localized to the site of the distal tapered end of the balloon catheter, with presumed smooth muscle injury ("paralysis") in the more proximal arterial segment. This spasm was only modestly inhibited by antiplatelet agents. It is interesting to note that the localization of the spasm seen in this in vivo model (attributed to platelet aggregation) is virtually identical to that seen in vitro studies in the absence of platelets. The observation that the severity of the arterial spasm observed in both the rabbit iliac and pig carotid artery in vivo models was greater than that observed in vitro suggests, however, that both platelet aggregation (with release of vasoactive substances in the balloon injured segment) and "stretch-pressure-dependent" mechanisms play a role in angioplasty-induced vasoconstriction.

Pressure-Induced, Endothelially Mediated Arterial Vasoconstriction

There has been a tremendous interest in recent years in the role of endothelium in regulating arterial motor tone. Endothelium derived vasoactive substances have traditionally been associated with vasodilatory responses but may, under certain conditions, produce vasoconstriction. Myogenic (stretch-dependent) tone has been considered to be endothelium independent. However, recent studies by Harder, Vanhoutte, and Oso et al suggest that some forms of stretch- or pressure-induced "myogenic" tone are endothelium dependent. In a number of mammalian species (dogs, cats, and rats), vascular endothelial cells appear to serve "a transducer function" in that a mechanical force (e.g., increased intraluminal pressure or stretch or both) may stimulate the release of an endothelium derived vasoactive substance (capable of activating calcium-dependent, smooth muscle cell contraction. This vasoconstriction is blocked by cyclooxygenase inhibition and, therefore, appears to be mediated by an endothelium derived cyclooxygenase product (endothelium-derived contractile factor 2 [EDCF]).

These data presented from our series of experiments suggest that stretch-pressure--induced, endothelium-dependent, myogenic activation is one cause of arterial vasoconstriction after balloon angioplasty. We have found that this vasoconstriction was 1) stretch-pressure--dependent (i.e., seen primarily with \( \geq 30\% \) stretch beyond relaxed vessel diameter), 2) did not occur in the absence of endothelium or extracellular calcium, 3) was only partially inhibited by verapamil, and 4) reversed spontaneously with a time course consistent with postangioplasty endothelial cell loss. Our findings that indomethacin and ibuprofen inhibited this stretch-pressure--induced endothelium-dependent arterial vasoconstriction suggest that a prostanoid endothelial cell product (possibly EDCF 2) is responsible for this contractile response. We cannot exclude the possibility that a nonprostanoid cyclooxygenase product (e.g., superoxide radical) could be this putative EDCF. It seems unlikely that the inhibition of angioplasty-induced vasoconstriction by indomethacin is due to its effects on calcium movement across cell membranes because indomethacin, at the dose used in our preparation, does not affect potassium chloride--induced smooth muscle contraction (Katusic et al and unpublished data).

It is recognized that balloon angioplasty causes complete endothelial denudation (i.e., 100% loss of endothelial cells in the dilated segment), given sufficient washout time. However, this endothelial loss does not occur instantaneously after bal-
loon angioplasty without intentional intimal rubbing (see Figure 4). It is speculated that the endothelium (compressed during balloon inflation) "interprets" the balloon-induced increase in intraluminal pressure as an inappropriate increase in arterial blood pressure, thus stimulating the release of an endo-
thelial derived contractile factor(s) before endo-
thelial cell denudation. Although one cannot exclude the possibility that the release of an endothelially derived contractile factor(s) is the nonspecific result of a loss of endothelial cell membrane integrity after balloon-induced injury, one might argue that this mechanism would just as likely result in vasodilata-
tion (e.g., from prostacyclin or EDRF release or both) as vasoconstriction. The fact that there was no impairment of vasoconstrictor responses to phenyl-
ephrine after endothelial denudation reasonably excludes the possibility that the inhibition of angioplasty-induced vasoconstriction after endo-
thelial denudation was due to smooth muscle injury.

Role of "Arterial Paralysis" in the Localization of Vasoconstriction

Angioplasty-induced smooth muscle injury ("arterial paralysis") appears to play an important role in determining the localization of angioplasty-
duced vasoconstriction. Some animal studies have suggested that balloon angioplasty routinely causes immediate and severe smooth muscle injury and arterial paralysis.8,42 We have found that only extreme degrees of arterial stretching (inflated bal-
loon diameters 70% or more beyond the relaxed vessel internal diameter) will injure arterial smooth muscle sufficiently to impair vasoconstriction responses in a perfused whole-vessel model (unpublished data on rabbit aortae, T.A. Fischell, U. Nellessen, D.A. Johnson, and R. Ginsburg). This degree of arterial stretching was achieved in three of the four pig carotid experiments using 8-mm balloons. In these pig carotid artery experiments (e.g., Figure 7), there appear to be three pathophys-
ologically distinct vessel segments: 1) proximal segment, severely stretched (>70% beyond relaxed vessel diameter) by the fully inflated body of the balloon and thereby paralyzed and incapable of constricting to a stretch-pressure stimulus; 2) focally contracted segment underlying the distal tapered end of the balloon (stretched ~30–50% beyond relaxed vessel diameter), which is adequately dis-
tended to provoke a stretch-pressure–dependent response but not stretched sufficiently to impair smooth muscle contractility; and 3) distal segment, without significant stretch-pressure stimulus, and thus no vasoconstriction despite preserved smooth muscle integrity. In the 5-mm balloon, rabbit aorta experiments and the other pig carotid artery ex-
periments balloon angioplasty resulted in vasocon-
striction throughout the dilated segment (e.g., Figure 3) because these segments were not stretched adequately to paralyze the smooth mus-
cle but were distended sufficiently to provoke stretch-pressure–dependent vasoconstriction.

Limitations of Study

Although these studies clearly demonstrate that balloon angioplasty in nondisease rabbit and pig arteries can provoke vasoconstriction independent of platelet aggregation and neurogenic input, it cannot necessarily be implied that these mecha-
nisms play a role in the vasoconstriction observed after balloon angioplasty in diseased human coro-
ary arteries. Certainly, other mechanisms, such as platelet induced vasoconstriction4,8 or loss of EDRF9 may also play a role in promoting this angioplasty-
duced vasoconstriction. In addition, it is unclear whether the atherosclerosis present in human arter-
ies subjected to balloon angioplasty may alter endo-
thelial cell function, prostaglandin production, and other mediator pathways and thereby alter the pathophysi-
ology of angioplasty-induced vasoconstriction. Another potential limitation of this study was that there were no direct measurements of arterial distention pressures during balloon infla-
tions. Despite this, it is reasonable to assume that these distention pressures were significantly higher during 5-mm balloon inflations (average stretch, 39% beyond relaxed vessel diameter) than during 4-mm balloon inflations (average stretch, 12%), suggesting that this angioplasty-induced vasocon-
striction was pressure dependent. One cannot exclude the possibility that mechanical stimuli, other than increased transmural pressure (e.g., stretching of the endothelial cell surface, or shear stress) were the provocative stimuli leading to vasoconstriction.

The spontaneous relaxation of the arteries observed during the first 15–45 minutes after balloon angi-
oplasty has been interpreted as being the result of endothelial cell loss after initial injury. Alternatively, it could be argued that the spontaneous reversal of the vasoconstriction was due to the withdrawal of the stretch-pressure stimulus and washout of EDCF.

Summary

These studies demonstrate that balloon angioplasty-
induced arterial spasm may be caused, at least in part, by stretch- or pressure-induced endothelium-
dependent vasoconstriction, independent of platelet aggre-
gation and autonomic influences. The observation that calcium channel blockers, antiplatelet agents, heparin, or a combination have demonstrated only limited efficacy in preventing angioplasty-induced vasoconstriction6,15,17,21 is consistent with the hypo-
thesis that a stretch-pressure–dependent mechanism contributes to this form of traumatic arterial spasm, in vivo. The findings suggest that this angioplasty-
duced vasoconstriction is mediated by an endothelium-derived cyclooxygenase product(s).

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References


Key Words • spasm • endothelium • indomethacin • calcium • ibuprofen • calcium channel blockade
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