Use of the Perforated Balloon Catheter to Infuse Marker Substances Into Diseased Coronary Artery Walls After Experimental Postmortem Angioplasty

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A perforated balloon catheter was used in human coronary arteries after postmortem angioplasty had been performed. The catheter used has a standard angioplasty balloon with a pattern of laser-produced holes, 25 μm in size, which generate streams of fluid under pressure. Studies of the routes by which marker substances enter diseased arterial tissue when infused by the perforated balloon after experimental angioplasty are described. A colored marker dye entered the new crevices and dissection planes created by the angioplasty, but did not extend >2 cm either proximal or distal to the perfused segment.

Horseradish peroxidase entered tissue not only from the lumen and adventitia as occurs with its infusion into normal tissue with the perforated balloon, but also extended from new crevices and dissection planes created by the angioplasty. Platelet aggregation, coagulation and cell proliferation, the likely causes of restenosis after angioplasty, originate in the sites of greatest tissue disruption and blood stasis. These postmortem studies suggest that active drugs are delivered to the arterial wall in a manner likely to be effective in preventing these events.

(J Am Coll Cardiol 1991;17:174B–8B)

Medications are usually administered by mouth or the parenteral route. In some instances (for example, skin disorders or certain gastrointestinal mucosal diseases), direct application of drug to the diseased site is possible. For vascular disorders, drug treatment is given indirectly (that is, systemically). For example, anticoagulant therapy is given systemically with intended benefit, but also with unintended complications and toxicity. In circumstances when the drug is expensive (for example, recombinant tissue-type plasminogen activator) considerable waste of valuable drug also results from its systemic use.

It has long been appreciated that the arterial wall is permeable to a variety of materials that are normally present in the circulation—albumin (1), fibrinogen (2) and cholesterol (3) to name a few—or that are introduced into the circulation for experimental reasons—for example, horseradish peroxidase (4,5) or radiolabeled liposomes (6). Furthermore, the rate and degree of penetration of arterial tissue depend on blood pressure (1,6). Hypertension accelerates penetration and even cells can be pushed into the wall if pressure elevation is extreme (7). Atherosclerotic disease itself increases permeability of a given site (5). Circulating materials

may be found in arterial tissue in a matter of minutes after their introduction (1,4,6).

In this era of new catheter techniques, we recently proposed (8–10) that the ready permeability of arterial tissue can be exploited to achieve local introduction of active drug at the disease site without exposing the entire circulation to that agent. It seems that in addition to considerations of toxicity, cost and efficacy of tolerable dosage, simple logic makes this approach attractive. Just as it makes no sense to cover one's entire body in a salve to treat a local skin lesion, so it would seem more desirable to direct therapy of vascular disease to the involved site rather than to the entire arterial surface. We (10) and others (11,12) have shown that drugs retain their desired activity in the microenvironment of a given vessel segment and, indeed, may even be more effective when administered locally (12).

We recently reported (9,10) studies of a perforated balloon catheter that allows local introduction of drug into the desired arterial segment. Conditions required for this have been described (9) for normal and diseased coronary arteries. Among many potential applications (10), one attractive use is pharmacologic prevention of restenosis after angioplasty. The present studies were designed to show the mechanism and degree of penetration of marker solutions into the diseased human coronary artery wall by use of the perforated balloon catheter after postmortem experimental angioplasty.

Methods

Hearts were obtained at autopsy performed within 24 h of death. The eight individuals (six men, two women) ranged in

age from 64 to 90 years. In each heart, the left anterior descending and right coronary arteries were studied. Studies were designed to track the routes of penetration of either green marker dye or horseradish peroxidase into the arterial wall when infused by the perforated balloon catheter.

Green marker dye. A standard angioplasty balloon (Miniprofile, USCI) was first passed into the left or right coronary artery until the catheter could be palpated in the appropriate vessel. The 2 cm balloon length was marked on the adventitia as well as 2 cm proximal and 2 cm distal to the balloon. In all studies, two inflations for 2 min each were made at 8 atm of balloon pressure. This pressure was designed to produce maximal disruption of the wall as a result of the angioplasty procedure. The balloon size chosen was either 2.5, 3 or 3.5 mm, depending on visual estimation of the arterial caliber from the adventitia for green marker and from the cut lumen for horseradish peroxidase.

After deflation and removal of the standard balloon catheter, a perforated balloon catheter of the same diameter (USCI) was inserted to the same distance in the relevant artery. Pressure inflation was then carried out for 1 min at 5 atm of pressure and either a 10% solution of green marker dye (Davidson Marking System, Bradley Products) or horseradish peroxidase (1 mg/ml type II peroxidase, Sigma) was infused. A volume of 0.5 to 3 ml was infused over 1 min. The infusate was seen to stream from the vessel lumen; the amount lost presumably reflected the degree of match of the infusion balloon to the inner diseased arterial wall. The perforated catheter was then deflated and removed.

To evaluate penetration of green marker dye, 2 cm of artery corresponding to balloon length as well as the proximal and distal 2 cm segments were quickly removed and placed in buffered formalin at room temperature. Decalcification in 20% formic acid was done overnight and processing into paraffin blocks carried out. Histologic sections, 6 μm thick, were cut and stained with hematoxylin-eosin. Generally, three arterial rings were taken from the center ballooned segment and two rings each, proximal and distal, from the proximal and distal 2 cm segments. Green marker dye retained its characteristic bright green color on the pale background of stained arterial tissue in tissue sections.

Horseradish peroxidase. For studies of horseradish peroxidase penetration, the artery was sectioned approximately 6 cm from the orgin. Depending on the caliber of the vessel, a standard angioplasty balloon (Miniprofile, USCI) was passed into the proximal or distal end for a distance just adequate to cover the entire balloon. The angioplasty procedure and subsequent perforated balloon infusion sequence were done with horseradish peroxidase as described for the green dye. After removal of the perforated balloon, three arterial rings were quickly taken from the ballooned arterial segment and placed in 3% cold buffered glutaraldehyde (0.2 M, pH 7.4) for 2 h. The tissue was then transferred to 7.5% sucrose-cacodylate solution (0.2 M, pH 7.4) for 18 h at 4°C. Rings were then placed in a small amount of embedding medium (Tissue-tek II, Lab-tek Products) and snap frozen in

isopentane for storage. Two or 3 days later, 6 μm sections were cut on the freezing microtome and placed on gelatin-coated slides. Although tearing of some sections did occur, even calcium-rich lesion could be cut.

Incubation of the slides with 3,3' diaminobenzidine was carried out soon after sectioning. In most cases, a segment of nondistended artery had been removed and was used as control segment for the 3,3' diaminobenzidine reaction. Briefly, the incubation was carried out for 15 to 30 min at room temperature as described previously (8,13). Slides with attached tissue were then passed through dehydration solutions to xylene, coverslipped and allowed to dry. Reaction product was appreciated as a dense brown precipitate on a colorless background of tissue.

Results

Postmortem angioplasty resulted in many characteristic findings seen with coronary angioplasty in humans (14,15). Flaps of atherosclerotic plaque were split from the media, tears in the calcified plaque and media occurred and dissection planes between diseased media and surrounding adventitia were common.

Marker dye studies. A total of eight arteries in four hearts were studied. In two cases, dissection planes were seen to extend to the distal adjacent nonballooned segment, but in no case did they extend beyond the 2 cm length of the distal segment that was adjacent to the ballooned 2 cm segment. The dye was never seen in the proximal 2 cm adjacent segment.

Dense green dye not only entered dissection planes, but accumulated in splits between plaque and media (Fig. 1A). The infusion catheter also forced perfusion fluid into the microcirculation of the ballooned segment, whether in adventitial vessels or microvessels in the plaque itself (Fig. 1B).

Horseradish peroxidase studies. Eight arteries in four hearts were studied. Whereas green dye only delineated tissue planes created by the angioplasty (and infusion) catheters, horseradish peroxidase entered the arterial tissue itself when it was delivered by the infusion catheter. Penetration of horseradish peroxidase occurred in the expected intima to media direction, as well as from the adventitia (Fig. 2A). (This had also been previously seen in the normal dog brachial artery and diseased human coronary arteries not previously subjected to angioplasty [8].) A control artery is shown for comparison (Fig. 2B).

In the present study, horseradish peroxidase also entered wall substance through splits in tissue created by the prior angioplasty procedure (Fig. 2A). The depth of penetration was variable, at some times not extending through the entire arterial wall and at other times clearly present to a depth of several hundred microns (Fig. 3).

We could not detect any preferential uptake into the arterial wall that correlated with the amount of disease present. In addition, it was not possible to accurately assess
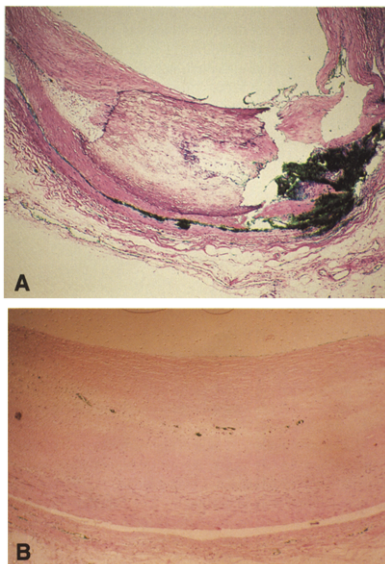
Figure 1. Green dye infusion. A, Cross section of artery subjected to postmortem angioplasty. Note dye in recesses of intimal plaque and outer dissection plane (magnification ×20). B, Presence of marker dye in microvessels of atherosclerotic plaque and adventitia. Lumen is at the top (hematoxylin-eosin; original magnification ×25).

relative penetration of horseradish peroxidase into different components of the plaque (for example, lipid versus fibrotic) because development of 3-3' diaminobenzidine reaction product requires an aqueous environment. Therefore, lipid-rich areas generally show a fainter (or even nonexistent) reaction product than that of more fibrotic zones.

Discussion

The present studies extend our understanding of the effects of local infusion on diseased arterial tissue subjected to a prior simulation of balloon angioplasty. Characteristic tears in the tissue were induced by the latter procedure (14,15). However, many physiologic conditions present during actual angioplasty were obviously not reproduced (namely, temperature, blood pressure and blood flow).

What is accomplished by the perforated coronary infusion catheter. Insights into what is and is not accomplished by the perforated infusion catheter were gained. Specifically,
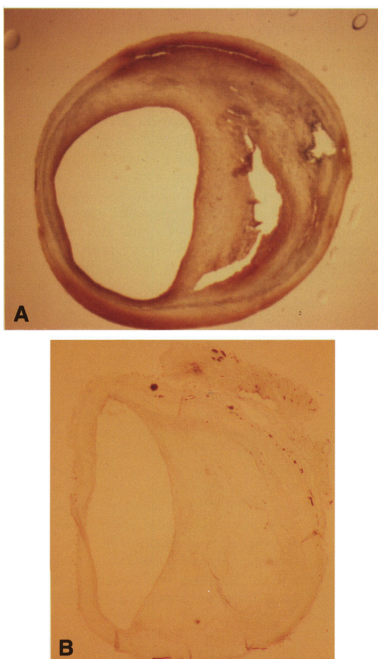

Figure 2. Horseradish peroxidase infusion. A, Cross section of artery with brown reaction product throughout, but concentrated near splits in outer media and plaque (original magnification ×6). B, Cross section of control artery reacted with 3-3' diaminobenzidine, but not infused with horseradish peroxidase. Only red blood cells with inherent peroxidase activity show reaction product (original magnification ×7).

infused material enters the cracks and crevices induced by angioplasty, and wave fronts of perfusate extend into the tissue itself from the intima and adventitia as well as from the new splits created. Whereas full penetration of the diseased wall was not achieved in every instance, 1 min of infusion at 5 atm of pressure seemed adequate.

Potential role in preventing restenosis. The presence of the horseradish peroxidase marker in the dissection planes and extension into the wall tissue itself are reassuring with respect to the specific problem of restenosis after coronary angioplasty. Local thrombosis and platelet aggregation con-
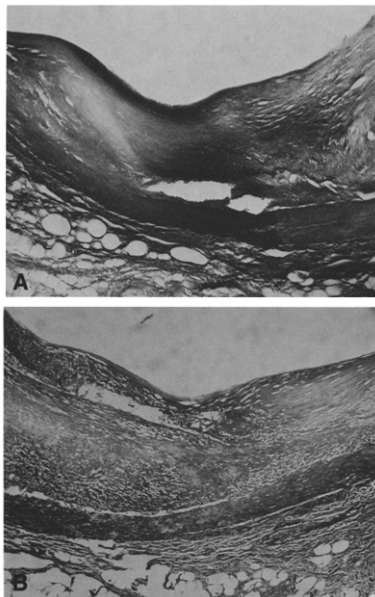
Figure 3. Horseradish peroxidase infusion. **A,** Cross section of plaque showing dense (**black**) reaction product throughout the wall (original magnification ×70). **B,** Cross section of plaque showing reaction product throughout the media and adventitia. The greatest amount is seen on the inner and outer aspects of the plaque (original magnification ×55). Lumen is at the top.

tribute to restenosis (14–16), but increasing clinical (16,17) and experimental (16,18) evidence implicates cell proliferation from the injured wall site as a major factor. The patterns of local clot development and cell proliferation that lead to progressive narrowing of the lumen can be seen to extend from the clefts and dissection planes created by the angioplasty procedure (14–16). If pharmacologic control of these events is the goal of local infusion with the perforated catheter, it is crucial to concentrate active drug at the wall sites where cell proliferation seems to be triggered and blood flow stasis is greatest. Such localization seemed to be the case in the present postmortem study.

The duration of drug presence and the concentration of effective drug needed locally can only be determined in a more physiologic model. Indeed, such studies are now underway by us and others (11). The ineffectiveness of many

parenteral or oral drugs (19–25) and the limits on dose or convenience, or both, of seemingly active agents imposed by the intravenous route (26–28) (or need to pretreat for many days by the oral route [29,30]) make local administration a very attractive option. Alternatives to the infusion catheter that concentrate local drug at the angioplasty site include incorporation of immobilized drug into stent material and the use of periadventitial drug delivery (12); both methods seem to raise formidable technical problems.

Conclusions. Whatever the ultimate approach to successful prevention of restenosis, methods of local administration of materials into the blood vessel wall can prove useful in understanding and perhaps treating a variety of vascular diseases (10). The infusion catheter method (called percutaneous drug angiotherapy) is but one approach. Conceptually, we need no longer be restrained by the requirement that drug treatment of discrete vascular disease be systemically administered.

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