Balloon Angioplasty

Natural History of the Pathophysiological Response to Injury in a Pig Model

Peter M. Steele, James H. Chesebro, Anthony W. Stanson, David R. Holmes, Jr., Mrinal K. Dewanjee, Lina Badimon, and Valentin Fuster

With the technical assistance of Holly B. Lamb, James M. Byrne, and Brenda I. Wendland

SUMMARY. The restenosis or occlusion that frequently follows balloon angioplasty is poorly understood. Thus, the pathophysiological response to angioplasty of the common carotid artery in 38 heparinized normal pigs was investigated by quantification of the radioisotopic labeled platelet deposition and histological and electron microscopic examination from 1 hour to 60 days after angioplasty. At 1 hour, the following findings were noted: complete endothelial denudation in all arteries, marked platelet deposition (44.7 ± 20.7 × 10⁶/cm²), mural thrombus in seven of 10 pigs, and a medial tear extending through the internal elastic lamina in nine of 18 arteries. All nine arteries with tears had associated mural thrombus and severe platelet deposition (76 × 10⁶/cm²); in contrast, the nine arteries without a tear had no mural thrombus and much lower platelet deposition (6 × 10⁶/cm²). Necrosis of medial smooth muscle cells was evident at 24 hours. Platelet deposition remained high at 24 hours (40.5 ± 20.6 × 10⁶/cm²), but was markedly reduced at 4 days (4.4 ± 1.5 × 10⁶/cm²), coincident with partial regrowth of endothelium or periluminal lining cells. No significant platelet deposition was noted at 7 days, when the endothelial cell type of regrowth was largely complete. Intimal proliferation of smooth muscle cells was mild and patchy at 7 days, significantly greater and more uniform at 14 days, and unchanged at 30 and 60 days after angioplasty. Complete thrombotic occlusion occurred in four (11%) of the 38 pigs. A significant stenosis present at 30 days after angioplasty was shown by histological examination to be due to organization of mural thrombus. Thus, balloon angioplasty produced extensive arterial damage and was a potent stimulus for acute platelet-thrombus deposition and subsequent intimal hyperplasia. These results may have important clinical implications in the prevention of restenosis and occlusion after angioplasty. (Circ Res 57: 105-112, 1985)
bolus of 100 USP units/kg given intravenously. The heparin was not reversed at the end of the procedure, and no further doses of heparin were administered.

Through a right femoral cutdown, the balloon catheter (Meditech 8 mm x 3 cm, polyethylene balloon) was advanced in the pig's right common carotid arteries under fluoroscopic visualization. The balloon was inflated to 6 atmospheres (Meditech pressure manometer) for 30 seconds (these balloons inflate to a maximal diameter of 8 mm). Five inflations at 60-second intervals were performed on both common carotid arteries (except for two pigs, killed at 1 hour, in which only one artery was dilated and the other served as a control). The average diameter of the common carotid artery was 5-6 mm. Selective carotid spot films were obtained before and immediately after the dilation procedure by the manual injection of 6 ml of diatrizoate meglumine and diatrizoate sodium (Renografin-76, Squibb), and plain spot films were obtained during dilation. Measurements taken from the spot films taken before, during, and after balloon inflation demonstrated that the diameter of the balloon inflated within the artery was only 9.1 ± 6.1% (mean ± SD) more than the diameter of the artery on the films obtained before dilation.

Angioplasty was performed on 38 pigs that were killed 1 hour, 24 hours, 4 days, 7 days, 14 days, 30 days, and 60 days after the procedure (Table 1). The arterial tissues then were removed, cleaned of all adventitia, and prepared for analysis.

Quantification of Platelet Deposition

Autologous platelets were labeled with \(^{111}\text{In}\) (tropolone) (Dewanjee et al., 1981) by a modification of our previously described method (Badimon et al., 1983), in which the platelets were labeled in plasma instead of acid citrate dextrose-saline. The platelets were injected 18-24 hours before sacrifice, in doses of 300-400 \(\mu\)Ci. The only exceptions were pigs that were killed 24 hours after angioplasty; in these cases, the platelets were labeled and injected 48 hours before sacrifice. The platelet deposition on each dilated artery (\(\times 10^7/cm^2\)) was calculated from platelet counts and \(^{111}\text{In}\) activity on the arterial wall and in blood by a method previously described by us (Dewanjee et al., 1984).

### Table 1

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<thead>
<tr>
<th>Time of sacrifice</th>
<th>Pigs no.</th>
<th>Mural thrombus (no./total)</th>
<th>Platelets(^\ast) (no. (\times 10^7/cm^2))</th>
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<tr>
<td>1 hr</td>
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<td>24 hr</td>
<td>6</td>
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<tr>
<td>4 days</td>
<td>5</td>
<td>1/5 (1)(\ddagger)</td>
<td>4.4 ± 1.5</td>
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<tr>
<td>7 days</td>
<td>4</td>
<td>2/4</td>
<td>1.2 ± 0.6</td>
<td>+</td>
<td>62.4 ± 6.5</td>
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<tr>
<td>14 days</td>
<td>5</td>
<td>1/5 (1)(\ddagger)</td>
<td>0.2 ± 0.0</td>
<td>+</td>
<td>85.6 ± 15.9</td>
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<td>30 days</td>
<td>4</td>
<td>2/4 (1)(\ddagger)</td>
<td>0.2 ± 0.1</td>
<td>+</td>
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<td>60 days</td>
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<td>0.1 ± 0.0</td>
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\(\ast\) Mean ± se.

\(\dagger\) Endothelium or periluminal lining cells: -, absent; +, complete; ±, incomplete.

\(\ddagger\) Complete thrombotic occlusion.

### Tissue Analysis

The location of the dilated portion of the fixed artery was identified easily because of the in situ fixation that showed the almost invariable vasospasm proximal and distal to the involved area. This finding was confirmed in vivo by the films, as described previously. The dilated portion was divided into two segments (1-1.5 cm), and a segment of similar size was taken from the distal uninvolved artery. The tissue segments were examined under low-power magnification (x2 lens, Sunnex Laboratories) for the presence of mural thrombus formation.

From each arterial segment, 2- to 3-ring sections were removed and stained with hematoxylin and eosin and Lason's elastic-Van Gieson stain. The histological sections were examined by two investigators and a consensus evaluation was made. Histological sections were photographed. From these pictures, the thickness of the intima from the surface to the internal elastic lamina was measured in six equidistant sections that were again divided into 10 equal sections for a total of 60 measurements around the circumference of the intima.

Two longitudinal specimens were cut from each segment, coated with carbon and gold-palladium alloy, and examined with a scanning electron microscope (ETEC Autoscan). Representative areas were photographed and evaluated by at least two investigators, and a consensus reading was made.

Selected specimens were thin-sectioned (600-700 A), mounted on a 200-mesh copper grid, and stained with uranyl acetate and lead citrate. Sections were examined with a Philips 201 transmission electron microscope.

### Statistics

Student's t-test or the \(\chi^2\) test was used to determine statistical significance.

### Results

#### Arterial Injury and Repair

Balloon angioplasty produced complete endothelial denudation in the diluted area (Figs. 1B and 2A). Four days after the procedure, there was partial regrowth (Fig. 1C); by 7 days, the endothelium or periluminal lining cells had largely regrown (Fig.

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FIGURE 1. Scanning electron microscopic views of the luminal surface of the common carotid artery in the pig (original magnification, 1,000×). Panel A: normal endothelium. Panel B: completely denuded endothelium replaced by layer of adherent platelets 1 hour after angioplasty. Panel C: partial regrowth of endothelium or periluminal lining cells with a few platelets adhering to uncovered subintima 4 days after angioplasty. Panel D: endothelium or periluminal lining cells largely regrown with no adherent platelets 7 days after angioplasty.

Platelet-Thrombus Deposition

One hour after angioplasty, there was heavy platelet deposition on the subintima (Figs. 1B and 2B) that persisted to 24 hours (Table 1). The platelet deposition in an artery at an untouched site distal to the dilation was <0.5 x 10⁶/cm², which is the same value obtained from normal arteries in 10 control pigs (unpublished data). One hour after the angioplasty, 50% of the dilated arteries had a macroscopic mural thrombus (Table 2) in addition to the microscopic layer of platelets. A mural thrombus and marked platelet deposition was seen only in those arteries that had a medial tear (Figs. 2B and 4). Conversely, all arteries with tears had a mural thrombus (Table 2).

At 4 days after angioplasty, the platelet deposition was significantly reduced (P < 0.05); this decrease coincided with the partial regrowth of an endothelial cell type (Fig. 1C; Table 1). No significant platelet deposition (Fig. 1D) was noted at 7 days, at which time the endothelial cell type of regrowth (periluminal lining cells) was largely complete, as seen by

1D), except in focal areas overlying mural thrombus. The nuclei of the smooth muscle cells in the media frequently adopted a corkscrew shape (Castaneda-Zuniga et al., 1980) 1 hour after angioplasty (Fig. 3). By 24 hours, there often was necrosis of the smooth muscle cells and damage to the normal architecture of the elastic fibers.

Of the 18 arteries examined at 1 hour after angioplasty, nine (50%) showed a tear that extended through the internal elastic lamina and into the media to a variable depth (Fig. 4). The dilated arteries without a tear were thinned and showed less of a corkscrew pattern and less necrosis of the smooth muscle cells than did the arteries with tears.

The reparative process in the media of the dilated arteries was evident at 14 days after angioplasty with connective tissue remodeling in an attempt to restore the luminal contour to normal. Elastic stains of histological sections showed loss or distortion of normal elastic fibers with fibrocellular ingrowth into areas of necrosis and into defects devoid of elastic fibers that were probably created by a previous acute tear.
FIGURE 2. Transmission electron micrographs from site of dilation 1 hour after angioplasty. Panel A: monolayer of degranulated platelets spread across subintima adjacent to internal elastic lamina (I) (original magnification, 10,500x). Panel B: thrombus (T) composed mainly of aggregated and degranulated platelets attached to underlying medial connective tissue and smooth muscle cells within a tear. Internal elastic lamina is absent (original magnification, 3,000x).

both scanning and transmission electron microscopy. Whether smooth muscle cells contribute in part to this endothelial cell type of layer is uncertain.

In four (11%) of the 38 pigs, the mural thrombus progressed to complete thrombotic occlusion, the earliest of which was evident at 24 hours after the procedure (Table 1).

The mural thrombi that were detected at 7 days or later showed evidence of organization and even simulated a significant stenosis by a fibrous plaque (Fig. 5, A and B).

Intimal Proliferation of Smooth Muscle Cells (Table 1)

At 7 days after angioplasty, intimal proliferation of smooth muscle cells was seen, but it was patchy, and the thickness of the intima (62.4 ± 6.5 mm × 10⁻³) was significantly more (P < 0.05) than in undamaged control arteries (31.0 ± 1.0 mm × 10⁻³). By 14 days, intimal proliferation was significantly more (P < 0.05) than at 7 days, and was more uniform around the circumference of the artery. At 30 and 60 days, the thickness of intimal proliferation was not significantly greater than at 14 days.

Discussion

PTCA, particularly of the coronary arteries, has made a significant impact in a short time on the
treatment of stenotic arterial disease (Grunzig et al., 1979; Kent et al., 1982; Vlietstra et al., 1983; Hartzler, 1983). Despite this development, many basic questions concerning the pathophysiological events after balloon injury remain unanswered. This study addressed some of these questions.

**Animal Model**

It is extremely difficult to find an appropriate animal model for experimental angioplasty. Rabbits (Faxon DP et al., 1982; Sanborn et al., 1983) or dogs (Castaneda-Zuniga et al., 1980; Pasternak et al., 1980) have been used in previous studies. Neither animal develops atherosclerosis naturally, although a high-cholesterol diet (2%) after endothelial denudation in the rabbit produces intimal thickening with a large number of foam cells (Faxon et al., 1982; Sanborn et al., 1982). The diet also induces very high serum levels of cholesterol (1,476 ± 467 mg/dl) (Sanborn et al., 1982). Thus, although a stenotic lesion is produced by this model, there could be major limitations in relating this pathophysiological response to angioplasty to man because of the unnatural situation of an excessive amount of lipid in the arterial wall. Our study used pigs, animals that spontaneously develop atherosclerosis without cholesterol feeding (French et al., 1965; Fuster et al., 1982b) and whose platelet-coagulation system is more closely related to humans’ (Folts and Rowe, 1983; Leach and Thorburn, 1982). Because they were young, the pigs in this study did not have atherosclerotic lesions, nor were they given a high-cholesterol diet. The normal lipid levels may have reduced the platelet-vessel wall interaction and degree of smooth muscle cell proliferation. Pigs of this age have a serum cholesterol of 101 ± 13 (sd) mg/dl and triglycerides of 53 ± 19 mg/dl (Fuster et al., 1982). The disadvantage of this model is the lack of an atherosclerotic lesion to dilate. However, because of the lack of lesion bulk, it might be expected to result in a lesser expansion of the external diameter (<10% average increase in diameter compared with predilation) and lesser degree or frequency of deep arterial wall damage [tears into media in approximately 50% of normal arteries (Lam et al., 1985)] compared with nearly inevitable splitting of the atherosclerotic plaque in a successful angioplasty (Castaneda-Zuniga et al., 1980; Block et al., 1981)]. This decreased damage could decrease the stimulus for and the amount of platelet-thrombus deposition. Thus, this model probably underestimates the response to angioplasty compared to the clinical situation. In addition, although continuous heparin infusion in rats after air injury to the endothelium has inhibited smooth muscle cell proliferation (Guyton et al., 1980), the single dose of heparin used in this study would not be expected to affect the smooth muscle cell proliferation in these pigs.

**Relation of Injury to Mechanism of Angioplasty**

Balloon angioplasty produced endothelial denudation in all arteries examined acutely, and major mechanical damage to the arterial wall. The most impressive feature was that a medial tear (Fig. 4) was noted in 50% of arteries. These tears appeared similar to the disruptive lesions of the media and to atherosclerotic plaque reported in patients and in atherosclerotic rabbits after angioplasty (Block et al., 1981; Sanborn et al., 1983; Essed et al., 1983). As previously suggested (Castaneda-Zuniga et al., 1980; Block et al., 1981; Sanborn et al., 1983), such a tear or fracture of the intimal plaque and adjoining media is usually necessary for a successful procedure.

The frequent finding of smooth muscle necrosis in the media at 24 hours after angioplasty is of interest. This effect may be very desirable, essentially making the artery an inert conduit (incapable of vasospasm). In none of the arteries in these animals did spasm occur in the dilated segment. However, coronary spasm is usually multifocal; thus, angioplasty would not be an appropriate treatment, even in certain resistant patients with angiographically documented coronary artery spasm.

**Platelet-Thrombus Deposition**

There is little information and no quantitative data about platelet deposition after angioplasty. The scanning electron microscopic appearance soon after the procedure in a small number of dogs has been described (Pasternak et al., 1980), but there is no reported data about the natural history or determinants of platelet-thrombus deposition.

This study confirmed the suspicion that angioplasty was a potent thrombogenic stimulus (Table 1). Endothelial regrowth seemed to protect against de novo platelet deposition both quantitatively (Table 1) and qualitatively (Fig. 1). Therefore, in this model, the critical period for platelet-thrombus deposition would include at least the first 4 days after the procedure. This finding suggests that future intervention studies should particularly involve therapy that is started before the procedure in order to achieve adequate blood levels of antithrombotic therapy to prevent platelet-thrombus deposition that begins during the procedure. In this model, therapy should be most potent for the first 4–7 days after the procedure, but this duration may differ in humans with atherosclerotic disease.
As has been observed in other models of endothelial injury (Fishman et al., 1975; Groves et al., 1979; Fuster et al., 1983), the platelets were deposited on the subintima as a thin layer (usually a monolayer). In addition, a mural thrombus was noted in half of the arteries from pigs killed within an hour, was related to the presence of a medial tear, and contributed greatly to the measured platelet deposition (Fig. 2B; Table 2). The exposed media seemed to be an overwhelming stimulus for platelet deposition and thrombus formation, even in fully heparinized animals. We would expect that the tear or fracture of a plaque produced by angioplasty in humans (Block et al., 1981) would be no less thrombogenic.

The reasons that deeper arterial injury caused a greater thrombotic stimulus are not clear but may in part be related to both the enhancement of thrombosis with the exposure of fibrillar collagen found predominantly in the media and adventitia (Baumgartner and Haudenschild, 1972) and the destruction of two natural antithrombotic systems present in intact endothelial and subendothelial arterial layers, namely, the prostaglandin system with prostacyclin production and the fibrinolytic system (Kwaan and Astrup, 1967; Moncada et al., 1977; Cragg et al., 1983). Prostacyclin production varies by the site in the arterial wall; as the arterial wall layers approach the luminal surface, the prostacyclin production increases (Moncada et al., 1977). Loss of the antithrombotic mechanisms noted above is also accompanied by a greater thrombotic stimulus from the exposure of collagen to circulating blood. Exposure of platelets to the basement membrane alone may result in platelet spreading without release (Baumgartner et al., 1976), whereas platelet adherence to fibrillar collagen results in both spreading and release of proaggregating substances from within the platelet granules (Baumgartner et al., 1976; Kinlough-Rathbone et al., 1980). In addition, thrombin generation via the intrinsic or extrinsic coagulation pathways promotes both platelet aggregation and the production of fibrin which stabilizes platelet thrombi (Nemerson and Nossel, 1982). The exposure of collagen to circulating factor XII or factor XI can activate the intrinsic pathway (Wilner et al., 1968; Walsh, 1972) and, thus, stimulate thrombin generation. Likewise, the acutely damaged area of the arterial wall can generate tissue thromboplastin, which activates the extrinsic pathway and thus promotes thrombin generation and further thrombosis (Nemerson and Pitlick, 1972). Cells from the deeper layers of the arterial wall, fibroblasts and smooth muscle cells, generate greater peak thromboplastic activity than the cells at the luminal surface, the endothelial cells (Maynard et al., 1977). All of these factors may contribute to the greater frequency and severity of platelet-thrombus deposition with deeper arterial wall injury.

In 11% of the pigs, the mural thrombus progressed to complete thrombotic occlusion (Table 1). Although the timing of this occlusion is uncertain, since no observation was possible before the time of sacrifice, the histological appearance was that of old and organizing thrombus, suggesting that this started during the acute phase. In a larger series of control pigs, we observed acute occlusion within 1 hour of angioplasty in two of 48 (4%) arteries (Lam et al., 1985). It is uncertain whether continuation of heparin beyond the acute period would have influenced this development. No thrombi were apparent on the monoplane angiograms obtained soon after the angioplasty; however, angiography is not sensitive for the detection of mural thrombi. Our preliminary studies with in vivo imaging using In-labeled platelets suggest that this is a much more sensitive method of detecting mural thrombi in arteries (Steele et al., 1984a). Thus, the process of mural thrombus formation probably starts during the procedure, and may be present immediately after PTCA in man (similar to observations in iliofemoral angioplasty (Ezekowitiz et al., 1983)) but may not be evident angiographically.

Possible Mechanisms of Restenosis

Restenosis remains a challenging clinical problem that affects 25%–35% of patients within 6 months after PTCA (Dangoisse et al., 1982; Holmes et al., 1984). Although some clinical features are associated with an increased risk of restenosis (Holmes et al., 1984), the cause is unknown. The data from this study suggest that restenosis may occur via two mechanisms, both of which are instrumental in the development and progression of atherosclerosis (Ross and Glomset, 1976; Fuster and Chesebro, 1982).

First, platelet deposition on the damaged arterial wall can form a mural thrombus, which may undergo organization and cause restenosis. In this study, we have shown that a medial tear is a very potent stimulus for thrombus formation. Mural thrombi can organize over a period of weeks and result in an obstructive lesion (Fig. 5) that eventually in indistinguishable from a fibrous plaque (Jorgensen et al., 1967). In our study, the frequency of mural thrombi immediately after angioplasty despite full heparinization suggests that these thrombi may be a very important mechanism for restenosis in man.

Second, the platelets deposited early after angioplasty may, by the release of platelet-derived growth factor, induce the smooth muscle cells in the media to migrate to the intima and proliferate. This intimal proliferation of smooth muscle cells may contribute to restenosis. This mechanism is essentially the response to injury hypothesis of atherogenesis (Ross and Glomset, 1976). We observed this intimal proliferation in pigs, and it also has been reported recently in a patient who died 5 months after angioplasty (Waller et al., 1983).

The contribution of these mechanisms to restenosis may vary, depending on a number of features: composition and distribution of the atherosclerotic plaque, blood lipid levels, balloon size, and pressure.
and duration of inflation, presence and degree of exposed media, degree of smooth muscle cell necrosis, platelet deposition and thrombus formation, recoil and degree of fibrous tissue ingrowth in the arterial wall, and vasospasm. Despite the multiplicity of possible contributing factors, this study strongly suggests that the early platelet-thrombus deposition after angioplasty plays a pivotal role in the pathophysiological response to balloon injury and may be closely involved with the process of restenosis (Fig. 5). Thus, although this model does not reproduce the human situation of dilating a high-grade lesion and probably underestimates the clinical response to angioplasty, it may provide a basis for screening potential antithrombotic and platelet-inhibitor agents for use in future drug trials for the prevention of acute occlusion and restenosis after arterial angioplasty (Steele et al., 1984b, 1984c), as suggested by the negative response to low molecular weight dextran in our animal model and the negative response in patients (Steele et al., 1984b, 1984c).

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