Restenosis After Balloon Angioplasty
A Practical Proliferative Model in Porcine Coronary Arteries

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A model of proliferative human restenosis was developed in domestic pigs by using deep injury to the coronary arterial media. Metal wire coils were delivered percutaneously to the coronary arteries of 11 pigs with an oversized, high-pressure \((14 \text{ atm})\) balloon and were left in place for times ranging from 28 to 70 days. During placement, the balloon expanded the coils and delivered them securely within the arterial lumen. Light microscopic examination of the vessels confirmed fracture of the internal elastic lamina by the coil. An extensive proliferative response occurred in 10 of the 11 pigs and was associated with a luminal area narrowing of at least 50% in all but one pig. The histopathologic features of the proliferative response were identical to those observed in human cases of restenosis after angioplasty. Immunohistochemical studies confirmed the prominence of smooth muscle cells in the proliferative tissue. A similar response was obtained in two of five porcine coronary arteries in which balloon inflation only was performed, without coil implant. This model is practical and inexpensive and closely mimics the proliferative portion of human restenosis both grossly and microscopically. Thus, it may be useful for understanding human restenosis and for testing therapies aimed at preventing restenosis after balloon angioplasty or other coronary interventional procedures. (Circulation 1990;82:2190–2200)

Despite the high initial success rate and widespread use of percutaneous transluminal coronary angioplasty (PTCA), restenosis appreciably limits the effectiveness of this valuable revascularization method.\(^1\) Restenosis occurs in 25–45%\(^6\)\(^7\) of all patients within 6 months, and attempts to pharmacologically prevent or reduce it using antiplatelet agents,\(^8\)\(^9\) anticoagulants,\(^9\) corticosteroids,\(^10\) and calcium channel blockers\(^11\)\(^12\) have been unsuccessful. Mixed results have been reported with oral fish oil therapy\(^13\)\(^14\) and aggressive lipid reduction.\(^15\)\(^16\)

Lack of a practical animal restenosis model has limited the ability to investigate potential therapies. If such a model were available, it might have the additional benefit of yielding insight into the mechanisms of the restenosis process itself. This report describes an experimental animal model of human coronary restenosis developed in domestic swine that accurately mimics the proliferative component of human restenosis and is practical as well as inexpensive.

Methods

Animals

All studies were carried out with the approval of and with adherence to the guidelines of the Mayo Clinic animal care committee.

The coronary arteries of domestic crossbred pigs (Sus scrofa) are comparable with those of humans in morphology and microscopic structure. This animal was thus chosen as one in which the coronary vessels might respond to injury similarly to the coronary vessels of humans. The carotid arteries of this animal have been studied previously\(^17\) as a model for the effects of balloon dilation.

Juvenile pigs (20–30 kg) were obtained from local farmers and fed a standard laboratory chow diet without lipid or cholesterol supplementation throughout the study.

Coil Configuration

The coil configuration that was used to produce vessel injury in this model was as follows. A length of wire (0.005-in. tantalum or stainless steel) was formed into a to-and-fro pattern so as to remain in a single plane. This structure was then wrapped about the surface of a cylinder-forming mandril either longitudinally or in a serially helical pattern. The diameter of the mandril was comparable with that of an expanded PTCA balloon (3.0 mm). The coil...
structure was then gradually compressed into smaller and smaller diameters and finally crimped on a fully deflated balloon (roughly 1.4 mm in diameter). The resulting three-dimensional configuration causes multiple wires to be present in a given section perpendicular to the vessel long axis.

Inflation of the balloon resulted in expansion of the coil to full balloon diameter. This configuration and expansion mechanism are similar to several balloon-expandable intracoronary stent designs, although use of the device to produce the model requires intentional arterial damage inflicted on the vessel wall through gross oversizing.

Procedure

All pigs underwent intramuscular injection of 12 mg/kg ketamine and 8 mg/kg xylazine for anesthesia. They were placed supine, and the ventral neck region was infiltrated with 1% xylocaine (total dose, 10 ml) for local anesthesia. Continuous electrocardiographic monitoring was performed. The right external carotid artery was exposed, and an 8F arterial sheath was placed. Heparin (5,000 units) was administered intravenously as a bolus.

The PTCA balloons (3.0 mm) and metallic wire wrap were inflated such that the balloon would deposit the coil securely in place within a coronary artery. The balloon size (3.0 mm) was substantially larger than these pig coronary arteries, which are typically 1.5–2.5 mm in diameter.

The left main or right coronary artery was engaged using standard techniques with an 8F PTCA guide catheter under fluoroscopic visualization. To engage the left main coronary artery from either carotid artery, a standard right Judkins JR4 curve was used. Conversely, to engage the right coronary artery, a standard left JL4 curve was used. Thus, the left/right engagement methods are reversed from those used in the human femoral artery approach. The balloon/metallic coil device was advanced into either the left anterior descending, circumflex, or right coronary artery over a 0.014-in. PTCA guide wire. The balloon was inflated once to high pressure (14 atm), deflated, and removed. Another bolus of heparin (5,000 units) was then administered. Fluoroscopy and selective contrast injection confirmed both vessel patency and coil location. Repeat angiography was performed within 15 minutes to confirm vessel patency. The carotid vessel was repaired, using standard techniques, or ligated, and the neck wound was closed with interrupted sutures. The pigs were returned to quarters and closely observed. No antiplatelet agent was used at any time, and no additional heparin was given.

To determine the response of the coronary vessels to oversized, hyperbaric balloon inflation only (without coil implant), the procedure was performed identically except that a PTCA balloon was used without a metallic coil mounted on it. This latter procedure was performed in five pigs. An additional three pigs underwent coil implantation in which the coil was matched more closely to the vessel diameter, in an effort to establish the fact that oversizing the coil is an essential part in the production of medial injury and vessel response.

Histopathology

Pigs were killed at times from 28 to 70 days by using intravenous barbiturate and KCl. Two pigs died spontaneously at 9 and 11 days after coil implant. All hearts were removed immediately after death and perfusion-fixed at 100 mm Hg for 24 hours with 10% neutral buffered formalin. Those coronary artery segments containing the metal coils were easily identified externally.

These segments were carefully removed from the heart with at least 1 cm of normal vessel proximal and distal to the coil. Gross sectioning of the fixed vessels was performed at 2-mm increments perpendicular to the vessel axis. Coils were left in place, and cutting was done with sharp, hardened scissors. Individual coil wires were cut first, followed by the arterial tissue. This method resulted in minimal vessel size and shape distortion before embedding in standard paraffin block.

Each embedded arterial segment was cut and stained with hematoxylin-eosin and Lawson’s elastica-van Gieson stains. Immunohistochemical stains including actin, desmin, and vimentin were performed on a subset of three pigs.

Each 2-mm histological section was examined to determine the site of maximal luminal narrowing for a given artery. The section with the most severe stenosis was used to measure the following parameters: major and minor axes of the native vessel lumen (measured from internal elastic lamina to internal elastic lamina across the largest and smallest diameters) and major and minor axes of the stenotic lumen (residual lumen diameters). Percent area stenosis was calculated assuming the lumen to be an ellipse (area = \( \pi \times \text{major axis} \times \text{minor axis} / 2 \)). Measurements were made microscopically using a calibrated eyepiece reticle.

All sections were examined by an experienced cardiac pathologist (W.D.E.) for comparison with human restenosis tissue in regard to cell type, architecture, and amount of ground substance. The human tissue for comparison was obtained previously from patients undergoing directional coronary athectomy for the treatment of restenosis.

Results

Coil Implantation

Eleven pigs underwent successful coil implantation and survived chronically. During this same time period of successful implants, coil implantation attempts were made in an additional eight pigs, all of which died acutely (within 6 hours of implantation) for the following reasons: there were four anesthetic and procedural deaths and four deaths related to
severe coronary artery injury by the coil itself. Overall survival was thus 11 of 19, or 58%.

All pigs had patent vessels, determined angiographically within 15 minutes of coil implantation. Two pigs died at 9 and 11 days, respectively, after coil implantation. At autopsy both of these pigs showed extensive proliferative neointimal tissue with severe stenosis of the vessel lumen. No acute thrombus was observed in either pig at the site of the coil-induced stenosis. Thus, it was assumed that these severe stenoses rendered each heart ischemic during normal activity and caused a fatal arrhythmia. In the pig heart, vulnerability to ischemic ventricular fibrillation is well known and presumably relates to a lack of collateral circulation.

The remaining nine pigs survived without complications or clinically apparent problems until death by euthanasia (Table 1). Light microscopy in all pigs revealed a proliferative neointimal response of varying magnitude. Figure 1 demonstrates gross stenosis caused by the proliferative neointima.

In all pigs, rupture of the internal elastic lamina by at least some of the metallic coil wires was evident, and the coil usually resided in the vessel media. Figure 2 shows a low-power photomicrograph of another stenotic segment. Rupture of the internal elastic lamina is evident, and the coil wires have been driven entirely through the vessel media. A thick neointima is present, causing significant luminal stenosis. Mild chronic inflammation was usually evident around each coil wire. No qualitative histopathologic differences were noted between the tantalum-implanted versus the stainless steel–implanted vessels.

A normal vessel just proximal to coil placement is shown for reference in Figure 3. Figure 4 is of particular interest because not all wires ruptured the internal elastic lamina. The greatest degree of proliferation resulted from the two coil wires that ruptured the internal elastic lamina, with neointima growing to confluence between them in the vessel lumen. On the contralateral side of the vessel, however, the lamina remained intact, media was not entered, and substantially less smooth muscle cell proliferation is seen. At the bottom portion of this section, normal media without any proliferation is seen. This is the segment with the greatest distance between coil wires.

Table 2 shows the stenotic and native lumen sizes and the resulting percent area stenosis. When examined under higher power, the histological characteristics of this proliferation are identical to those of tissue obtained from 38 humans who had angiographic restenosis after PTCA and underwent directional atherectomy with the Simpson atherectomy catheter. Figure 5 is a side-by-side high-power microscopic comparison of the pig proliferative tissue and a representative sample of human restenosis tissue. That these proliferative tissues (human and porcine) are virtually identical is evident in terms of cellular appearance, cell density, and amount of intercellular ground substance. Immunohistochemical stains (actin, desmin, and vimentin) in the porcine tissue showed that these proliferative

<table>
<thead>
<tr>
<th>Animal number</th>
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<th>Coil material</th>
<th>Coil location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>Tantalum</td>
<td>RCA</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>Stainless</td>
<td>LAD</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Tantalum</td>
<td>RCA</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>Stainless</td>
<td>LAD</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>Stainless</td>
<td>LAD</td>
</tr>
<tr>
<td>6</td>
<td>11*</td>
<td>Stainless</td>
<td>LAD</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>Tantalum</td>
<td>CX</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
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<td>CX</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
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<td>LAD</td>
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<td>CX</td>
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<tr>
<td>11</td>
<td>9*</td>
<td>Tantalum</td>
<td>LAD</td>
</tr>
</tbody>
</table>

RCA, right coronary artery; Stainless, stainless steel; LAD, left anterior descending coronary artery; CX, circumflex coronary artery.

*Spontaneous death; remaining animals were euthanized.

Figure 1. Gross photograph of luminal compromise resulting from the metallic coil placement. These cut sections were taken from the same left anterior descending coronary artery, within 3 mm of each other. The implantation of coil wires is shown in the proliferative section (arrows, right), while a normal appearing vessel is seen where there were no coil wires (left). The proliferation induced by the injury nearly obliterated the lumen of this vessel, resulting in a severe stenosis.
cells were of smooth muscle origin, evidenced by the strong presence of actin and vimentin and significantly less desmin.

**Balloon Inflation Only**

Five additional pigs underwent oversized, overpressured balloon inflation only, without coil implantation. Table 3 shows results from this series. Three of these five pigs had a proliferative response to deep medial injury although the percent stenosis was somewhat less in two. In one pig, there was complete occlusion as from acute thrombosis and, in retrospect, represented excessively severe oversizing of the balloon to the vessel (a small diagonal artery). The remaining two pigs had little or no proliferation seen. Figure 6 depicts one of the two vessels that underwent proliferation and moderate luminal obstruction.

**Coil Implantation, Not Oversized**

The three pigs with coil implantation in which coil size was closely matched to vessel size did not exhibit appreciable proliferation. Figure 7 shows the minimal amount of neointimal proliferation in a representative animal from this group.

**Discussion**

Efforts to reduce or eliminate restenosis after PTCA have largely been unsuccessful. These efforts have been hampered by a lack of knowledge regarding the pathophysiological mechanisms of human restenosis and the lack of an accurate animal restenosis model with substantial proliferation. Histopathologic observation of restenotic tissue from living patients has become readily available with the advent of directional atherectomy.\(^{18}\) Given this information, there is considerable interest in identification of an animal model similar to human restenosis.

**Other Animal Models**

Previous angioplasty animal models have not addressed the proliferative aspects of restenosis directly, concentrating instead on the atheromatous nature of the lesions.\(^{19,20}\) The model described by Sanborn et al\(^ {21}\) has been frequently used. In this model, rabbits fed atherogenic diets have serum cholesterol levels frequently exceeding 1,000 mg%. The resulting atheromatous lesions of the aorta, iliac, and femoral vessels contain many foam cells in addition to intimal thickening. Although balloon denudation of endothelium increases proliferation,
many foam cells are present in contrast to those found in human restenosis. Another model of restenosis in pig carotid arteries involves endothelial denudation with neointimal proliferation. In this model, however, significant proliferative stenoses are not produced unless caused by an occluding, organized thrombus. The carotid or iliac arteries of these models are elastic vessels, as opposed to the coronary arteries (muscular arteries), which contain proportionally more smooth muscle. These noncoronary vessels may thus be less suitable for a coronary artery restenosis model since smooth muscle proliferation is likely a major factor in the genesis of restenosis. The current model results in obstructive lesions histopathologically identical to the proliferative component of human restenosis, in contrast to prior models.

Medial Injury and Restenosis

This model mimics the injury induced by PTCA by causing extensive deep medial injury. Oversizing the balloon for the target vessel results in severe elevations of vessel wall tension. This is followed by chronic tension in the medial smooth muscle due to the presence of the wire coil. Some degree of foreign body irritation also likely results from the wire coil itself. The small diameter wire on the surface of the balloon results in extreme shear stresses from the small radius of curvature of the wire. Many wires thus penetrate the internal elastic lamina into media rather than simply circumferentially distending the vessel.

Figure 4 strongly suggests that extensive smooth muscle proliferation is a response to rupture of the internal elastic lamina and consequent medial injury. Rupture of the internal elastic lamina during PTCA, medial laceration, and subsequent restenosis have been documented in humans. Mechanical medial injury is a known factor in generating a proliferative response. It is evident that simple overdistension of the vessel wall alone, without medial injury, does not produce the intense proliferation in this model, since portions of the vessel media that were stretched but not penetrated by wire exhibit mild or no proliferation whatsoever. This model suggests that lacerations or splits of normal media may contribute substantially to the genesis of restenosis.

That a proliferative response was elicited by inflating an oversized balloon suggests that the method of medial injury may not be as important as the injury itself. In the pigs that underwent balloon inflation only, the proliferation was produced less reliably. This reliability factor might be improved with further study, but at present the coil injury method appears preferable.
Closely matching the coil/balloon size to vessel size resulted in minimal proliferation, consistent with the concept that proliferation is proportional to degree of injury. Furthermore, it suggests that the vessel injury resulting from the coil rather than the coil itself is responsible for the proliferation. This obser-

TABLE 2. Laminal Compromise Data in Coil-Implanted Pigs

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Area stenosis (%)</th>
<th>Native lumen</th>
<th>Stenotic lumen</th>
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<tr>
<td>11</td>
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<td>2.40</td>
<td>2.13</td>
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</table>

Percent area stenosis = 100 × [1.00 - (stenotic area / native vessel area)] = 100 × [1.00 - ((π × stenotic major axis × stenotic minor axis) / (π × native major axis × native minor axis + 4))].

Vessel area = π × major axis + 2 × minor axis / 2.
vation implies that the invasive cardiologist should strive to minimize vessel injury when performing PTCA or other interventional procedures.

**Role of Lipids in Restenosis**

In contrast to primary atheromatous lesions, the human restenotic lesion consists of a vigorous proliferation of smooth muscle cells that have likely migrated from damaged media into the lumen as part of the reparative process. The proliferative nature of the restenotic lesion thus differs distinctly from the original atherosclerotic disease. The time course of restenosis is appreciably shorter, also suggesting a different mechanism.

No atherogenic diet was fed to the pigs in the present study. The production of histology resembling proliferative restenotic morphology without hyperlipidemia also supports the concept that restenosis is a process independent from atherosclerosis. Hyperlipidemia might intensify the observed proliferative response, a possibility not tested in this study. Although the proliferative effects might have been promoted further with a high cholesterol diet, hyperlipidemia is clearly not a necessary condition for production of the proliferative response in this model.

**Foreign Body Response**

Stainless steel and tantalum are relatively biologically inert materials. However, both materials stimulated restenoticlike neointima in this model. This may be from the chronic, severe mechanical tension placed on the vessel due to the oversized coil expansion, from a foreign body reaction, or from both. Since only a minimal amount of chronic inflammation was observed in this model, it is likely that inflammation was a lesser factor in stimulating proliferation. This is consistent with the fact that a proliferative response was also produced in pigs that underwent balloon inflation only, with no coil present. That there were no apparent histopathologic differences between the tantalum and stainless-steel coils supports the concept that injury from the coils, and not the coil material itself, caused the proliferation.

**Platelets and Thrombus**

The role of platelets and thrombus is not well defined in the current model. In the hyperlipidemic rabbit iliac artery, a statistically significant reduction in restenosis was found when antiplatelet agents were used after balloon dilation of a stenotic segment. Platelet deposition and release of growth

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**Figure 5.** High power side-by-side comparison of a representative sample of human restenosis (left panel) and tissue from the porcine restenosis model (right panel). The character of cells and proportion of ground substance is identical. Hematoxylin-eosin stain was used. Magnification, ×300.
FIGURE 6. Representative section from one pig that underwent inflation only, without coil implant. Note the proliferative neointima, not as obstructive as in those vessels injured by the coil method. Elastic–van Gieson stain was used. L, lumen; NI, neointima; M, media. Magnification, ×30.

Factors may play a role in the genesis of this model; it was for this reason that no antiplatelet agents were used at any time in this study. Platelet deposition and thrombus at the site of medial injury and on the coil itself would be expected in this model. This deposition could be a factor responsible for the proliferation of smooth muscle cells.\textsuperscript{28,29} Prior reports\textsuperscript{17} suggest that endothelial regrowth protects against platelet-thrombus deposition. Therefore, it is possible that the initial days after angioplasty when endothelium and neointima are forming may be critical in the genesis of the proliferative response. Aspirin pretreatment of these pigs before and after coil implant might have diminished the proliferative response.

In the current model, the foreign body coil may have slowed endothelial regrowth. Thus, there might have been longer exposure of media to blood elements that increased the amount of platelet deposition, thrombus, and consequent cellular proliferation. Acute studies in this model should be examined to establish the degree of thrombus and platelet deposition at the site of vessel injury.

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Area stenosis (%)</th>
<th>Diameter (mm) Native lumen</th>
<th>Diameter (mm) Stenotic lumen</th>
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<td></td>
<td>Major</td>
<td>Minor</td>
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</tr>
<tr>
<td>5</td>
<td>0</td>
<td>2.94</td>
<td>2.19</td>
</tr>
</tbody>
</table>

Percent area stenosis = 100 × [1.00 − (stenotic area ÷ native vessel area)] = 100 × [1.00 − (\(\pi\) × stenotic major axis × stenotic minor axis ÷ 4) ÷ (\(\pi\) × native major axis × native minor axis ÷ 4)].

Vessel area = \(\pi\) × major axis ÷ 2 × minor axis ÷ 2.

*Thrombotic occlusion.
Implications for Coronary Artery Stents

The analogy between the metallic coil implanted in this model to generate restenosis and the current generation of self-expanding or balloon-expandable metallic stents intended to prevent restenosis is obvious. The proliferative response in this pig model resulted from intentional, severe oversizing and overinflating the balloon on which the coil was mounted. The intent in this model was to injure media to stimulate a vigorous healing response. Neointimal tissue covering stents in experimental animal stent placement is likely a mild foreign body response but has never been shown to proliferate as severely as noted in this model. Experimental stents have been placed in normal animal vessels, quite different from freshly dilated atherosclerotic human vessels. Restenosis data from human studies with stents are inconclusive, although restenosis despite stenting has been documented with varying incidence.

Nevertheless, there may be important clinical lessons from the induction of substantial proliferation with this coil-injury model. Vessels to be stented should be dilated first by a balloon alone, rather than by using the stent/balloon combination as a primary dilation device. This should be done to minimize damage to the vessel from the extreme shear forces generated at stent wire sites that occur with the stent/balloon catheter combination. If perforation of the internal elastic lamina is indeed responsible for increasing the proliferative response, predilation using a balloon alone should help eliminate further damage to the lamina at stent wire sites.

Although there has been recent speculation that different stent designs might result in lower restenosis rates, this principle has never been scientifically tested either in animal models or in human clinical trials. The current study did not address this principle. The coil configuration was flexible, and a wire size was used similar to that in clinically implanted stents. It is safe to assume that vessel damage from deep medial injury after rupture of the internal elastic lamina resulted in the majority of proliferations in this model since proliferation from nonpenetrating wires was not as severe as when media was injured. Thus, sizing and deployment may be as important as specific stent design and configuration. Designs that are stiff, significantly altering the three-dimensional vessel course, might result in chronic forces that could result in increased vessel damage.

These considerations are appreciably altered in the case of stent placement in an atherosclerotic lesion that has undergone dilation. The primary
reason for stenting is optimizing and maintaining vessel lumen, in opposition to smooth muscle proliferation induced by the stent. These are opposing forces for which an optimum balance must be sought. Extremes on either end may result in less favorable luminal results. It is possible that this model could be used to study some of these factors, especially with regard to optimal stent sizing. Different coil designs might also be tested for relative efficacy at maintaining lumen as a tradeoff against smooth muscle cell stretch and damage.

Conclusion

This porcine model for the proliferative component of human restenosis is accurate and simple and develops in a short period of time. Whereas the model may differ from human restenosis in its mechanism of production, the gross and histopathologic results appear identical to those found in human restenosis. Therapies aimed at reducing the occurrence of restenosis might thus be easily evaluated using this model.

Acknowledgments

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