BALLOON-EXPANDABLE intracoronary stents in the adult dog

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ABSTRACT We studied the acute and chronic biological reaction to balloon-expandable intracoronary stents in the adult dog. Twenty stainless steel stents were placed, by standard angioplasty techniques, into the left anterior descending, left main, or circumflex coronary arteries of 20 dogs. Angiography was performed at 1, 3, 6, and 12 months and animals were killed in groups of three at 1, 3, 8, and 32 weeks, for gross, light, and electronmicroscopic analysis. All dogs survived, all stents were patent, and there was no evidence of myocardial infarction, spasm, rupture, or aneurysm formation during follow-up (longest 18 months; average, 12 months). The stent was initially covered by a thin layer of thrombus that was replaced later by neointimal muscular proliferation that reached its maximal thickness by 8 weeks (p<.01). This neointima gradually thinned as it became more sclerotic and less cellular. The stents were covered completely by immature endothelium by 1 week without loss of side branches. We conclude that balloon-expandable intraluminal stents can be safely placed percutaneously into normal canine coronary arteries. Because of rapid endothelialization high patency rates can be expected, thus offering promise for clinical applications in man.


PERCUTANEOUS transluminal coronary angioplasty, or PTCA, stands as a milestone in the evolution of cardiology. When properly performed it offers a safe and effective alternative to coronary artery bypass surgery in certain patients. Primary success rates of 90% or greater can be expected in carefully selected patients. Optimism for long-term success, however, has been dampened by restenosis rates as high as 30%. Furthermore, despite remarkable progress in technology designed to enhance the safety of PTCA, 2% to 8% of all procedures result in urgent bypass surgery, usually as a direct result of abrupt closure from dissection, thrombosis, or spasm. 1, 2 Despite expeditious surgical reperfusion, the incidence of perioperative myocardial infarction has been reported to be as high as 58%. 3-5 Recent work with vascular stents by Palmaz et al. offers an alternative method for maintenance of patency of vessels subjected to balloon dilatation. Various peripheral applications of balloon-expandable intravascular stents in multiple animal preparations have demonstrated the ability of these stents to oppose elastic recoil and to potentially resist atherosclerotic restenosis due to rapid endothelialization. 6-11

The purpose of this study was to evaluate the early and late patency rates as well as the biologic reaction of normal adult dog coronary arteries to balloon-expandable intravascular stents as a prelude to human investigation.

Methods

Twenty adult dogs of both genders ranging in weights from 45 to 60 pounds were pretreated with 25 mg dipryidamole and 175 mg aspirin 1 day before the procedure. They were anesthetized with intravenous thiamylal and then intubated and ventilated with 1% to 2% halothane, nitrous oxide, and oxygen. A No. 9F introducer sheath was placed in the left carotid artery after limited surgical exposure of the vessel. One hundred IU/kg of intravenous heparin and 250 ml of intravenous LMW dextran 40 over 2 hr were given during the procedure. A No. 8.3F Stertzer (BARD, Billerica, MA) catheter with a small or medium curve was advanced to the aortic root through the sheath. With the dog in the left oblique position, left coronary arteriography was performed by hand injection of diatrizoate meglumine 76%.

After identifying the target vessel by ease of guiding catheter intubation, a standard balloon dilatation catheter was selected to match the radiographic diameter of the target vessel (3.0 or 3.5
mm). This way approximately 10% overexpansion was obtained, equal to the magnification factor of the system. A sterile stainless steel balloon-expandable intracoronary stent (15 mm length, 1.6 mm diameter) was slipped retrogradely over the collapsed balloon and crimped down manually between the platinum markers (figure 1). The balloon and stent assembly was passed through the guiding catheter over a standard PTCA guidewire down the target vessel. The stent was placed in proximal to mid segments of the target vessels, which included the left anterior descending artery (LAD) in 15, the circumflex artery in four, and the left main coronary artery in one animal without regard to proximity of side branches. A single dilatation to 6 atmospheres for 10 sec was performed, after which the balloon and guidewire were removed, leaving the expanded stent behind firmly impressed against the vessel wall. After delivery, repeat arteriography was performed to ensure patency, after which the dog was allowed to recover. Aspirin, 175 mg, and dipyridamole, 25 mg, were given daily for 3 months and then discontinued. No attempt to induce intimal disruption by predilating the arteries before stent delivery was made.

Follow-up angiography was performed at 1, 3, 6, and 12 months by a percutaneous femoral artery approach and with general anesthesia as before. Animals were killed in groups of three at 1, 3, 8, and 32 weeks, leaving eight animals available for long-term follow-up.

Sacrifice was performed in accordance with Animal Welfare Regulations outlined by the local Animal Investigation Review Board and the American Physiologic Society. The animals were given enough intravenous thiopental to induce respiratory coma. Then, after 5000 units of intravenous heparin, each heart was removed intact through a right thoracotomy incision. The left main coronary artery was cannulated and 5% dextrose, and water, silver nitrate, and 10% buffered formalin were injected sequentially.6 Coronary arteriography of the explanted, intact heart was then performed, after hand injection of contrast, to examine target vessel patency in two orthogonal projections, with the use of 100% air-gap magnification.

The left main coronary artery was perfused at 100 mm Hg pressure with formalin solution overnight and then prepared the following morning for gross pathologic, light, and electron microscopic examination. The specimens with the metal stent were sectioned by a procedure reported previously.6 The percent stenosis was measured off the angiographic cut film with calipers and compared with the degree of stenosis observed by light microscopy.

Factor VIII–related antigen was investigated on the endothelial surface of the stents by an immunoperoxidase method.12

Angiographic lumen diameter changes and implantation-induced intimal thickening were assessed by analysis of variance.

Results

All stents were successfully delivered to the target vessels without spasm, migration, rupture, or abrupt thrombosis. Recovery was uneventful in all 20 dogs, except for occasional mild hematomas at the cutdown site. The eight dogs available for follow-up were followed angiographically for an average of 12 months (range 10 to 18). Angiography demonstrated vessel patency in all the animals. There was no case of late perforation, aneurysm formation, or migration. Furthermore, all branching vessels were spared regardless of their size. Figure 2 shows the angiographic appearance of the LAD after stent placement and at follow-up of 1, 6, and 12 months. Systematic radiographic measurement of the stent lumen showed that the immediate postimplantation diameter was slightly larger than the target vessel diameter before stent implantation (figure 3). This was due to purposeful overdilatation (by approximately 10%, as explained in the Methods section) to accommodate the stent wall thickness of 0.003 inch and the anticipated intimal growth. Mild luminal encroachment occurred at 1 month, but luminal diameter did not fall below preimplantation levels except in one case. At 6 months follow-up, the diameter was not significantly different from the target site diameter before stent placement.

The histopathologic findings in the specimens explanted at 1, 3, 8, and 32 weeks correlated with the radiographic examinations and provided an explanation for the observed changes in luminal diameter. At 1 week, grossly the stent was easily seen through a glinting layer of neointima in the longitudinal section, as illustrated in figure 4 A. There was little change in the gross specimen after 3 weeks except for more prominent hemosiderin deposits (figure 4, B). At 8 weeks the stent was obscured by thick neointima (figure 4, C). By 32 weeks the stent was easily seen through a thin layer of sclerotic intima (figure 4, D). Histopathologic
FIGURE 2. Angiographic appearance of a stent (arrows) in the LAD immediately after placement (a) and at 1, 6, and 12 months of follow-up (b, c, and d, respectively). Note that there is no spasm acutely or compromise of the luminal diameter over time and that side branches are spared.

FIGURE 3. Luminal diameter immediately before and after stenting and at 1, 3, and 6 months. Due to deliberate over dilation to accommodate stent wall thickness and expected intimal hyperplasia the luminal diameter is greater immediately after stenting (p<.01). Although at 1 month there is some minimal luminal obstruction due to thrombosis, by 3 and 6 months there is progressive enlargement of the lumen to a dimension that tends to exceed somewhat the original diameter (NS). One standard deviation is represented by vertical bars.

analysis revealed the pathophysiologic basis for these gross observations. At 1 week the struts of the stent locally depressed the arterial wall, and the indentations were filled with thrombus material largely composed of red cells and fibrin covered by immature endothelium (figure 5, A). In the 3 week specimen, the neointima covering the stent was more cellular and hemosiderin-laden macrophages partially replaced the underlying thrombus (figure 5, B). At 8 weeks the degree of intimal hyperplasia peaked due to fibroblast proliferation so that intimal thickness was greatest (p<.01): the amount of underlying residual thrombus was minimal (figure 5, C). By 32 weeks the neointima was thinner than previously and appeared less cellular with more intercellular ground substance present. Hemosiderin pigments consisting of intercellular hematoidin deposits were occasionally seen. The arterial media appeared thinned, particularly at the points of
FIGURE 4. Gross specimens, longitudinal sections. A. One week. The stent is easily seen through a translucent layer of neointima. B. Three weeks. Hemosiderin deposits are evident, but otherwise there is little change from 1 week. C. Eight weeks. Thick neointima totally covers the stent. Side branch ostia are patent. D. Thirty-two weeks. The stent is easily seen through neointima. There is a smooth transition from stented to adjacent nonstented arterial segments. Side branch ostia remain patent.

Contact with the struts (figure 5, D). Scanning electron microscopy of the stent lumen at 1 week demonstrated incomplete endothelialization and immature endothelial cells, as indicated by their bulging nuclei (figure 6, A). The 3 week specimen showed a mosaic type of endothelial cover with interdigitating cell junctions highlighted by the silver chloride deposits (figure 6, B). Mature endothelium with the elongated cell axes oriented in the direction of flow characterized the 32 week specimens (figure 6, C). The endothelialization process coated the metal struts completely, but did not compromise side branch orifices in any case (figure 6, D). The luminal surface of the stents tested positive for factor VIII-related antigen, thus validating its endothelial origin.

The thickness of intimal hyperplasia as measured from the luminal surface of the struts to the new lumen was maximal in the 8 week specimens and minimal by 32 weeks (figure 7). Allowing for somewhat different observation periods, these findings correlate well with the radiologic measurements and explain the minimal early narrowing and the late tendency toward widening of the lumen.

Discussion
PTCA has become the standard of therapy for carefully selected individuals with atherosclerotic heart disease who otherwise would require coronary artery bypass grafting. It is estimated that over 100,000 coronary angioplasty procedures were performed in 1985 in the United States alone. Unfortunately, a small percentage of patients who undergo PTCA are at risk for abrupt closure due to spasm, thrombosis, or acute dissection, and these patients usually require urgent bypass surgery. Under these circumstances, even with the most rapid reperfusion techniques, the myocardial infarction rate is as high as 58%. A larger percentage of patients (30%) return with recurrent stenosis of the original lesion within 6 months.

Challenged with these problems of abrupt closure and gradual restenosis in both coronary arteries and the peripheral circulation, Palmaz et al. developed a proto-
FIGURE 5. Light microscopic specimens. A, One week. Thrombus (T) and fibrin deposition predominates. Immature endothelial cells separate the thrombus from the lumen (L). B, Three weeks. Thrombus is replaced with myofibroblastic cells. The media (M) appears compressed beneath the strut. C, Eight weeks. Intense fibroblast proliferation dominates and neointimal thickness is greatest. Endothelium is highlighted with silver stain. The media is thinner than after 3 weeks. D, Thirty-two weeks. Mature endothelial cells cover thin sclerotic ground substance that has replaced the thick cellular response seen at eight weeks. The media continues to atrophy. *Stent.

type expandable intravascular stent made of stainless steel that could be mounted snuggly over standard balloon dilatation catheters in the collapsed state, thus allowing easy percutaneous delivery to the target site."

Preliminary work in the peripheral vessels was encouraging, demonstrating total early endothelialization of the stent in 1 to 3 weeks, depending on the animal preparation. Excessive intimal hyperplasia was a rare finding, but predictably occurred when vessel outflow distal to the stent was restricted.

A more streamlined version of the stent has now replaced the early cumbersome prototype and the experience with this design has been reported in the literature. Its mechanism of expansion is based on plastic deformation of a stainless steel tube with staggered, parallel, rectangular slots beyond its elastic limit, thus preventing recoil. Each rectangular slot is deformed to a diamond configuration, thus maximizing the exposure of viable endothelium and minimizing the total area of the metal-blood interface, as seen in figure 1.

Other investigators have published their experience with intravascular stents and report good results in experimental animals. However, these stents all have in common a predetermined expanded size. Therefore, a mismatch between stent and vessel diameter may result in thrombosis, perforation, or dislodgement and migration. The advantages of the Palmaz stent are that (1) it fits conveniently on most standard commercially available balloon catheters with a very streamlined low profile, (2) it has a diameter expansion ratio of up to 6:1, (3) it expands only to the limit of expansion of the preselected balloon, and (4) it does not migrate due to its secure impression into the vascular intima at the time of delivery. Moreover, since the percentage of the stent area that is free space is approximately 70% in the collapsed state and 85% in the fully expanded state,
thrombogenicity is low. Finally, the stent does not continue to expand over time, a feature common to spring-loaded stents.

The present study was a natural extension of the previous experience with peripheral small vessel implantation. Several new problems were addressed because of the peculiarities of the coronary circulation. In particular, the coronary arteries move in synchrony with an actively beating organ, creating a potential for stress and strain concentration areas at the interface of the stent edges and adjacent intima. This could have resulted in a disruption of the healing process and perhaps have led to local aneurysm formation from gradual mural weakening. Furthermore, it was anticipated that spasm might be particularly exaggerated in the coronaries by the presence of a foreign body. However, neither of these potential problems was encountered in this animal preparation.

Our results indicated that the healing pattern and endothelialization process in response to implantation of the stent are no different in dog coronary arteries than in other organs. The early appearance of thrombus and cellular infiltrate gradually resolves, giving rise ultimately to a thin layer of neointima that is grossly indistinguishable from that of adjacent nonstented ar-

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**FIGURE 6.** Scanning electronmicroscopic specimens. A, One week. Raised immature amorphous endothelial cells are seen. B, Three weeks. The cells are flat and mosaic in appearance, an indication of their immaturity. C, Thirty-two weeks. The endothelium is fully mature and is characterized by well-defined elongated cells aligned in the direction of flow. D, Scan of a metallic strut of an expanded stent spanning a side branch at eight weeks. There is thorough coating of the metal with viable endothelium without compromise of the lumen ostium.

**FIGURE 7.** Neointimal thickness during follow-up. Intimal thickness peaks at 8 weeks (p<.01) but regresses considerably by 32 weeks. One standard deviation is represented as vertical bars.
tery. The media thins as the distending wall stress to which it is exposed is borne in part by the stent. Follow-up as long as 3 years in peripheral arterial stents in our laboratory has not revealed aneurysmal dilation associated with this medial thinning. As noticed in prior studies, branching side vessels in the region of the stent remain patent since the ostia are invariably spared.

It should be noted that previous investigators have concluded that the dog is a stringent preparation for testing the biocompatibility of prosthetic materials in vascular spaces and therefore can be used for preclinical testing of prosthetic devices. This is due to the aggressive intimalization process that quickly covers prosthetic material and eventually overcompensates with intimal hyperplasia, which is even more exaggerated in smaller vessels such as the coronary arteries. This observation enhances the significance of our high patency rates in this particular preparation since most surgical prosthetic materials thrombose in experimental animals at a diameter less than 4 mm. Our excellent success rate in such a stringent preparation is attributable primarily to the streamlined profile of the stent in the collapsed state. When expanded, the device is pressed flush into the endothelium, offering no obstruction to laminar flow. The high ratio of open space to metal at expansion results in preservation of viable patches of endothelium between struts, thus giving the best chance for rapid multicentric endothelialization over the stent. This is a critical design feature for patency of any vascular stent and preservation of side branches.

The applicability of these findings to use of the stent in diseased human coronary arteries must remain speculative. The endothelialization process in man may be quite different than in the dog, as may be the biologic reactivity to stainless steel. It is encouraging, however, that data from atherosclerotic rabbit aorta preparations studied by Palmaz et al. indicate that compressed plaque continues to expand outside of the stent while never compromising the lumen in animals fed a high-cholesterol diet. Thus, restenosis did not occur in any of 24 animals. Whether the same observation will be seen in man is unknown. However, Sigwart et al. reported their experience with self-expanding stainless steel vascular stents in 24 diseased human coronary and 10 peripheral arteries and in their study, with the longest follow-up of approximately 9 months on warfarin therapy, patency was 100%. One coronary stent thrombosed acutely but was treated successfully with urokinase and in follow-up remains patent. Another thrombosed without symptoms. Using the same stent, Joffre et al. reported on 10 coronary implants, four of which thrombosed. These preliminary results must be viewed cautiously until more data become available.

Whether warfarin therapy is necessary over the long term will depend on how quickly endothelialization in man takes place, if at all. Since most experimental animals endothelialize rapidly it is not surprising that antiplatelet therapy can be discontinued in 90 days without adverse effects. The appropriate antithrombotic regimen for humans remains unknown and must be tested in the future by carefully controlled randomized trials.

In conclusion, we have studied the feasibility of delivering balloon-expandable intravascular stents into normal dog coronary arteries. We have confirmed that the biologic reactivity to such permanently implantable devices is favorable in long-term follow-up and that high patency rates can be expected. The potential problems of migration, spasm, rupture, aneurysm formation, and excessive intimal hyperplasia or thrombosis did not occur, offering a promising outlook for application of the technique in man as a possible solution to abrupt closure and restenosis after PTCA.

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