JACC Vol. 22, No. 7
December 1993:2007–13

Re-expansion of Balloon-Expandable Stents After Growth

W. ROBERT MORROW, MD, FACC, JULIO C. PALMAZ, MD,* FERMIN O. TIO, MD,*
WILLIAM J. EHLER, DVM,† ADRIAN F. VANDELLEN, DVM,†
CHARLES E. MULLINS, MD, FACC‡

Detroit, Michigan and Lackland Air Force Base, San Antonio and Houston, Texas

Objectives. **The purpose of this study was to evaluate the feasibility of re-expansion of balloon expandable intravascular stents and to examine the gross and histologic effects of re-expansion on vascular integrity.**

Background. **Intravascular stents have been used successfully as an adjunct to balloon dilation of congenital pulmonary artery branch stenosis and postoperative stenosis of the pulmonary arteries in children. However, use of rigid stents in children could result in development of relative stenosis at the site of stent implantation with subsequent growth of the child.**

Methods. **Stainless steel "iliac" stents were placed in the thoracic aorta of 10 normal juvenile swine by a transcatheter technique. Angiography and re-expansion were performed at a mean of 11 weeks (n = 9) and again at 18 weeks (n = 5). After euthanasia, the aortic specimens were removed for gross and histologic examination.**

Results. **Stents were successfully implanted in 10 swine. Re-expansion was successfully performed in each animal at 11 weeks and at 18 weeks. Aortic growth produced a relative constriction of the aorta of 20% ± 10% (mean ± SD) at the site of stent implantation at both 11 and 18 weeks. Re-expansion produced a significant increase in mean stent diameter from 10.1 ± 1 mm to 12.3 ± 1.2 mm at 11 weeks and from 11.2 ± 0.7 to 13.5 ± 1.1 mm at 18 weeks after implantation ($p < 0.001$). Balloon dilation produced a relative increase in stent diameter of 21% ± 7% at 11 weeks and 18% ± 4% at 18 weeks. Stent re-expansion was accompanied by plastic deformation of the neointima without neointimal dissection. Where neointima was thick, there was no evidence of neointimal abrasion, but where neointima was thin, areas of localized neointimal abrasion were observed with focal fibrin and platelet adherence to the stent struts. There was no evidence of medial or adventitial hemorrhage or dissection produced by re-expansion.**

Conclusions. **Re-expansion of intravascular stents is feasible after growth in juvenile swine without significant injury to neointima, media or adventitia. The results of this study support careful and selective use of intravascular stents as an adjunct to balloon dilation of congenital stenoses in children.**

(J Am Coll Cardiol 1993;22:2007–13)

Balloon dilation has been shown to be an effective nonsurgical treatment of pulmonary artery stenosis and coarctation of the aorta in children and adults (1–5). However, long-term effectiveness of dilation of these nonatherosclerotic lesions has been limited by both immediate and late restenosis (2,3). Angioplasty with implantation of the Palmaz balloon-expandable stent (Johnson and Johnson Interventional Systems) is clearly superior to angioplasty alone in selected adult patients with iliofemoral stenosis due to atherosclerosis (6,7). Recently, angioplasty with implantation of balloon-expandable stents has been used successfully in children with pulmonary artery branch stenosis, stenosis of the great veins, ar d postoperative stenosis of Fontan anastomoses (8).

Despite successful use of stents for congenital and postoperative stenosis of the great vessels, the use of rigid stents in growing children has certain potential limitations. Growth of the child and the great vessel proximal and distal to the fixed diameter rigid stent will ultimately result in an acquired stenosis. Re-expansion of the stent that has become incorporated in the vessel wall may or may not be possible and, if possible, could result in tearing of neointima or media. The purpose of this study was to evaluate the feasibility of re-expansion of balloon-expandable stents after growth. In addition, we sought to describe both the gross and the histologic effects of re-expansion on the integrity of the neointima and the arterial media and adventitia.

Methods

Stent implantation. Experimental procedures performed in animals were in conformance with the guidelines of the American Heart Association on research animal use and

From the Division of Pediatric Cardiology, Department of Pediatrics, Wayne State University, Detroit, Michigan; †Clinical Investigation Directorate, Wilford Hall Medical Center, Lackland AFB, Texas; *Department of Radiology, The University of Texas Health Science Center, San Antonio, Texas, and ‡The Lillie Frank Abercrombie Section of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas. This study was supported in part by Air Force Surgeon General Grant 87-089.

Manuscript received February 16, 1993; revised manuscript received June 21, 1993, accepted July 15, 1993.

Address for correspondence: Dr. W. Robert Morrow, Cardiology Division, Children's Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, Michigan 48201.

0735-1097/93/$6.00

JACC Vol. 22, No. 7
December 1993:2007–13

were approved by the Institutional Animal Use and Care Committee. We placed intravascular stents in the descending thoracic aorta of 10 juvenile swine (mean weight ± SD 18.6 ± 3.1 kg). The aorta was selected as the site of implantation because of its well developed media and elastic lamellae, intrinsic elastic recoil and resistance to dilation. Swine were premedicated with intramuscular ketamine hydrochloride (30 mg/kg body weight), underwent induction of anesthesia with intravenous sodium pentothal (10 mg/kg), and were maintained under general endotracheal anesthesia with a mixture of oxygen, nitrous oxide and Forane (0.5% to 1.5%). Both groins were sterilely prepared and draped and the femoral artery was entered by cutdown procedure or a percutaneous technique. A 10F or 12F 30-cm long Teflon sheath (Cook) was inserted and advanced to the abdominal aorta. Heparin, 100 U/kg, was then administered through the long sheath. Angiography of the descending thoracic aorta was performed in the lateral projection. The aorta immediately distal to the origin of the left subclavian artery was measured in systole after correction for magnification. A 0.038-in. (0.097-cm) guide wire was then advanced to the ascending aorta and a balloon catheter (Mansfield Scientific) with a balloon diameter 1 to 3 mm greater than the measured diameter of the aorta (8, 10 or 12 mm) was selected. A 30-mm long, 3.4-mm diameter stainless steel "iliac" stent (Johnson and Johnson Interventional Systems) was mounted coaxially over the unexpanded balloon and crimped manually using either the plastic balloon cover provided with the balloon (10- or 12-mm diameter balloons) or a specially constructed crimping tool (8-mm diameter balloons). Maximal theoretic diameter of the Palmaz stent occurs as slot diameter approaches slot length. The theoretic maximal expansion of this stent based on slot length and stent diameter is 12 mm. The balloon and stent assembly was then passed over the guide wire to the descending thoracic aorta and the balloon was rapidly inflated with diluted contrast medium. Balloon inflation was performed without the use of a manometric syringe. In two swine with initial stent expansion obtained with an 8-mm diameter balloon, the stent was immediately enlarged with a 10-mm balloon. After expansion of the stent, the balloon catheter was removed leaving the guide wire in place. An endhole angiographic catheter was advanced over the guide wire, and angiography was repeated.

Stent re-expansion. Stent re-expansion was performed at a mean of 11 ± 1.5 weeks (mean animal weight 65.5 ± 14.9 kg) in nine swine and repeated at a mean of 18 ± 2.1 weeks (mean animal weight 94.8 ± 1.2 kg) in five swine. The protocol for re-expansion was essentially the same as for initial implantation. Angiographic stent diameter, aortic diameter proximal to the stent, and aortic diameter distal to the stent were measured before and after re-expansion. Balloon diameter was selected to match aortic diameter proximal to the stent in eight swine. In one animal, the stent and proximal aorta were intentionally overexpanded with a 20-mm balloon.

Gross and histologic examination. Euthanasia was performed 24 h after the first re-expansion in four swine and after the second re-expansion in five. One animal died immediately after stent implantation because of inadvertent perforation of the abdominal aorta by the long sheath and dilator and therefore did not undergo re-expansion or histologic examination. In the remaining nine swine, the aorta with the stent was removed, flushed with normal saline solution, and fixed with 10% buffered glutaraldehyde under 100-mm Hg pressure. After fixation, the aortic specimen was cut longitudinally in two halves. One half was prepared for light microscopy and the other for scanning electron microscopic examination, as has been previously described (9). Fifty-five measurements of neointimal thickness overlying stents struts were obtained by light microscopy.

Statistical analysis. Stent and aortic diameters were compared by using analysis of variance for repeated measures. Significant differences between groups were assessed using the Scheffé test and Tukey test for multiple comparisons. Significance was set at a level of $p = 0.05$.

Results

Stent implantation and re-expansion. Implantation of stents was performed successfully in 10 swine. Final balloon diameter at *initial* implantation was 10 mm in four swine and 12 mm in the remaining six. One animal died immediately after stent implantation because of inadvertent perforation of the abdominal aorta by the long sheath and dilator. In one animal with initial stent expansion to 8 mm, the stent embolized to the descending abdominal aorta. This stent was then expanded to a diameter of 10 mm. At follow-up angiography a small aneurysm was noted at the distal end of the stent. This stent was re-expanded at follow-up without aortic rupture.

Re-expansion was successful in each study animal at both 11 and 18 weeks. The angiogram in Figure 1 illustrates the typical appearance of stenosis that developed after growth and the increase in stent diameter with re-expansion. Aortic growth produced a relative stenosis of the aorta of 20% ± 10% at both 11 and 18 weeks. At the first re-expansion, mean stent diameter increased from 10.1 ± 1 mm to 12.3 ± 1.2 mm and from 11.2 ± 0.7 mm to 13.5 ± 1.1 mm at the second re-expansion (Fig. 2). The effect of repeat expansion of stents on aortic diameter was highly significant ($p < 0.001$). Range testing using Scheffé and Tukey tests revealed significant differences between initial stent diameter and stent diameter after both the first and the second re-expansion, and between stent diameter after the first and after the second re-expansion. Balloon dilation produced an increase stent diameter of 21% ± 7% at 11 weeks and 18% ± 4% at 18 weeks. Ultimate stent diameter after re-expansion was greater than 12 mm in seven of nine swine. Balloon diameter at the first re-expansion ranged from 12 to 20 mm and at the second re-expansion from 15 to 18 mm. Although re-

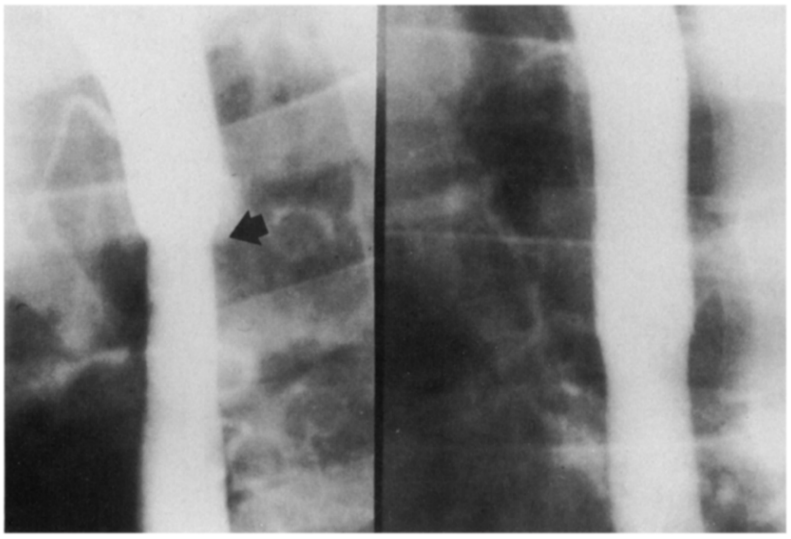


Figure 1. Angiogram of the descending aorta before (left) and after stent re-expansion (right) in one swine. Acquired stenosis that has occurred with growth can be seen at the site of stent implantation (arrow). Stent diameter increased with re-expansion, leading to relief of stenosis and slight expansion or the aorta.

expansion was successful in each case, ultimate stent diameter was less than balloon diameter in most animals.

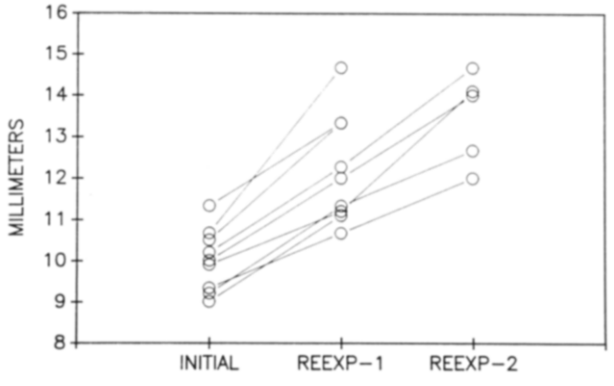
One swine that underwent intentional overexpansion of the stent and aorta with a 20-mm diameter balloon was found at necropsy to have aortic rupture with a localized periaortic hemorrhage. There was a longitudinal tear in the stent with an associated longitudinal tear in the aortic wall.

Gross and histologic effects of stent re-expansion. Figure 3 shows the gross appearance of aortic stents after implantation and re-expansion. The stent occupied a subintimal position with a nearly continuous layer of neointima covering the stent struts. The neointima extended over the struts wherever the struts were in contact with the aortic intima. With re-expansion, the stent struts appeared to have moved beneath the neointima without dissection or the development of a neointimal flap. Small areas of hemorrhage with corresponding hemosiderin staining marked the original position of stent struts before re-expansion. In some areas, there was localized abrasion of the neointimal layer exposing bare struts. In two specimens, small nonobstructing intraluminal thrombi were seen. There was no obstruction of small intercostal or spinal arteries originating from the aorta in the area of stent implantation.

The light microscopic appearance of the neointima and aortic wall corresponded to the gross appearance of the fixed specimens. The neointima was thin with a mean neointimal thickness of 35 ± 36 μm and a corresponding mean thickness of the aortic wall underlying the stent of 1,210 ± 270 μm (Fig. 4). In 72% of samples neointimal thickness was <35 μm. With exception of the one case noted above, there was no evidence of medial or adventitial hemorrhage or dissection. Where the neointima was abraded, a localized reaction could be seen with focal fibrin and platelet deposition over the stent strut (Fig. 5). Leukocyte and giant cell infiltration was noted adjacent to struts in the subendothelial collagenous layer. Aortic implantation was associated with variable degrees of medial compression (Fig. 6) but no evidence of medial or adventitial hemorrhage or dissection. Focal areas of mild atrophy of medial elastic lamellae were seen in some specimens.

Scanning electron microscopy demonstrated a smooth layer of neointima covering stent struts (Fig. 7). Leukocytes and platelets were seen adhering to stent struts in areas where neointima was abraded by re-expansion.

Figure 2. Change in stent diameter in millimeters in nine swine at 11 weeks (REEXP-1) and in five swine at 18 weeks (REEXP-2). Re-expansion was successfully accomplished in all animals at both 11 and 18 weeks. The increase in mean stent diameter with re-expansion was significant ($p < 0.001$), with significant changes in stent diameter at both 11 and 18 weeks.



Discussion

Balloon angioplasty of coarctation of the aorta and pulmonary artery branch stenosis are effective in relieving stenosis in many cases (1–5). Failure of balloon angioplasty may be due to resistance of the stenotic lesion to balloon dilation or to immediate elastic restenosis. Late restenosis is commonly observed after dilation of pulmonary artery branch stenosis (3) and can also occur after angioplasty of

JACC Vol. 22, No. 7
December 1993:2007–13

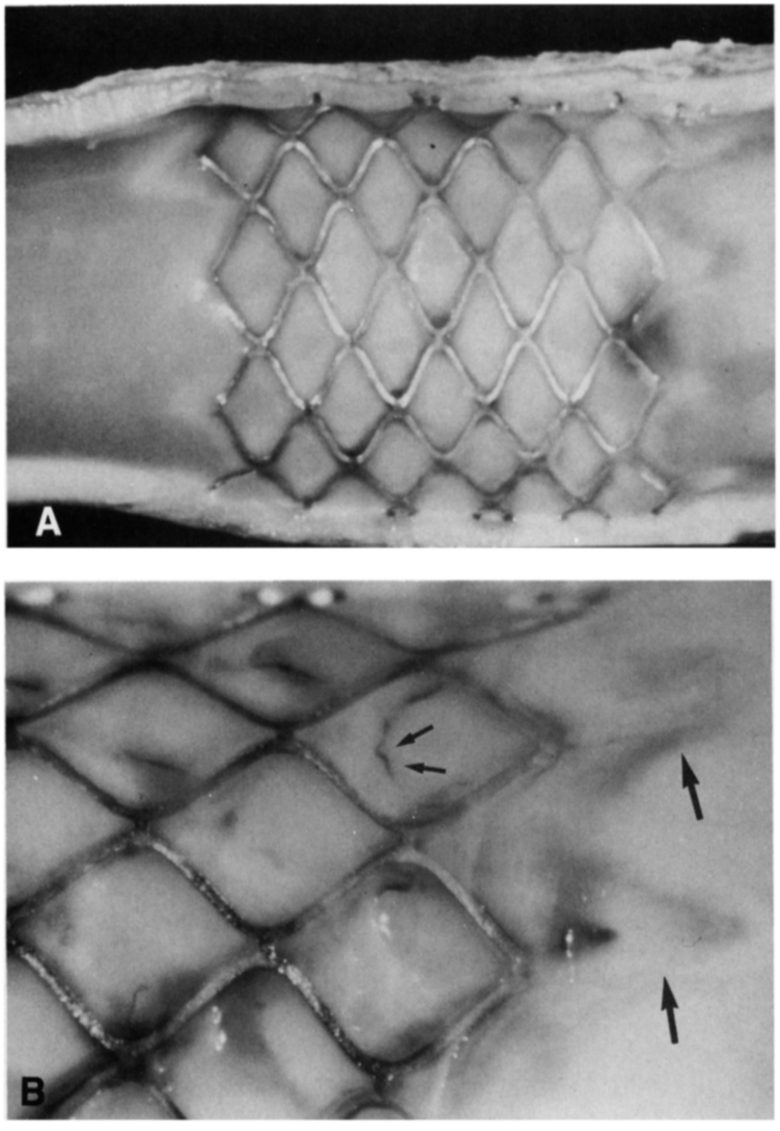


Figure 3. Gross inspection of stents after re-expansion demonstrated a nearly continuous layer of neointima covering the stent struts. The stent occupied a subintimal position with minimal compression of the aortic media (A). Overexpansion is evident with slot diameter being much greater than slot length in most areas. B, The original position of struts before re-expansion is marked by areas of intimal thickening (large arrows) and neointimal vasculature (small arrows). With re-expansion, the stent struts appeared to have moved beneath the neointima. Re-expansion resulted in small areas of intimal abrasion over some struts.

coarctation (1,2). Placement of intravascular stents could prevent immediate and late restenosis after angioplasty of pulmonary artery branch stenosis and coarctation. Stent placement could also reapply the intima after intimal tears in angioplasty of coarctation or pulmonary branch stenosis allowing healing without aneurysm formation.

Figure 4. The neointima was intact over most stent struts despite re-expansion. Light microscopic examination of specimens demonstrated a characteristically thin layer of neointima (arrow) with minimal subendothelial stroma that extended over the surface of the space occupied by struts. There was minimal subendothelial collagenous stroma with an average neointimal thickness of 35 ± 36 μm over struts.

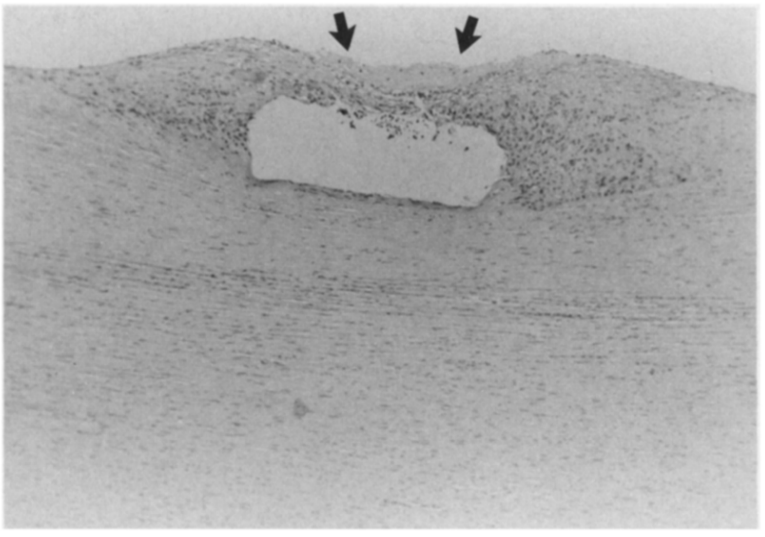


Figure 5. In some areas thrombi were seen adherent over the surface of struts (arrows) where abrasion had occurred with re-expansion. In addition to the surface fibrin and platelet thrombi there was a mild inflammatory infiltrate consisting primarily of multinucleated giant cells and mononuclear cells seen in the neointima immediately adjacent to stent struts.

Initial experience with placement of the Palmaz stent in children with pulmonary artery stenosis has been encouraging (8). Dilation with concomitant stent implantation was effective in relieving stenosis in all cases without the need for overdilation and with few complications. However, pulmonary artery stenosis and coarctation usually present in young children and produce serious abnormalities of hemodynamics that are often progressive. Therefore, it is not desirable nor often possible to delay angioplasty and stent implantation until children have grown to near adult size. Despite successful use of stents for congenital and postoperative stenosis of the great vessels, the use of rigid stents in the great vessels of growing children has potential limitations. With growth of the child and lack of growth of the stented vessel, a relative stenosis develops. Re-expansion of the stent which has become incorporated into the vessel may be impossible and, if possible, may produce significant vessel injury.

Stent re-expansion. We designed this study to examine the feasibility of stent re-expansion after growth and after adequate time for neointimal development. We selected the thoracic aorta as the site of implantation because of its well developed media and elastic lamellae, resistance to dilation and intrinsic elastic recoil. In this study, stents were successfully implanted in all animals and, at follow-up angiography, remained patent without change in stent diameter. However, as expected, a relative stenosis developed with growth in all animals.

Re-expansion was successful in all cases with a significant change in vessel diameter at both 11 and 18 weeks after implantation. Moreover, ultimate stent diameter was greater than the theoretic maximal stent diameter of 12 mm in seven of nine swine. Re-expansion was accomplished with low pressure valvuloplasty balloons. However, balloon size exceeded ultimate stent diameter by 2 to 4 mm in some animals. Greater re-expansion could potentially be accom-

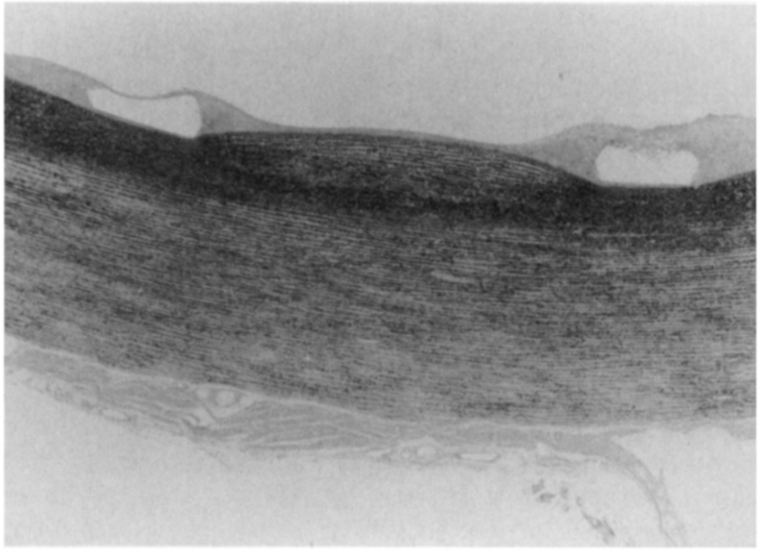


Figure 6. Compression of the media was demonstrated to varying degrees. The compression of elastin fibers illustrated in this specimen is most pronounced in the inner zone of the media immediately underlying the stent. Variations in staining of elastic fibers in the outer zone may represent mild atrophy of the medial elastic lamellae. There was no medial hemorrhage or tearing noted after re-expansion.

JACC Vol. 22, No. 7
December 1993:2007–13

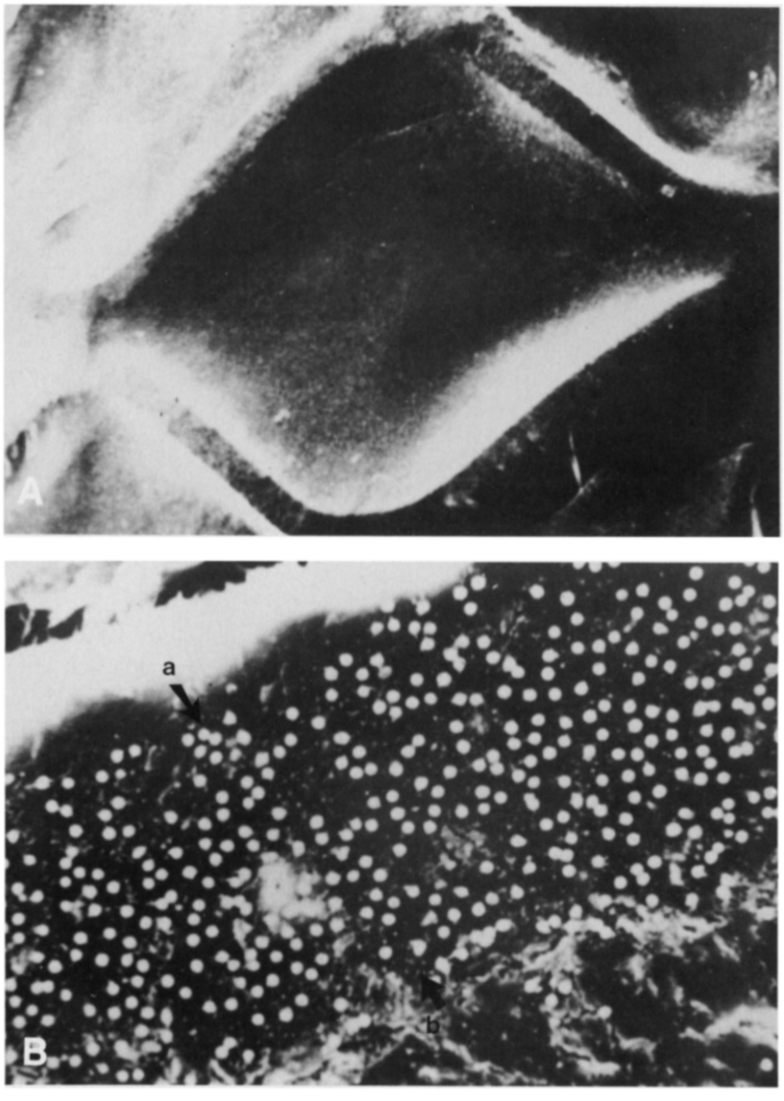


Figure 7. Scanning electron microscopy demonstrated a smooth neointimal layer over the stent (A) where the neointima was intact. However, in areas where neointimal abrasion had occurred, leukocytes (a) and platelets (b) could be seen adherent to the stent struts (B).

plished with the use of high pressure balloons, although high pressure balloons are presently not available in diameters greater than 12 mm. Intentional overexpansion with a 20-mm diameter balloon was associated with stent fracture and aortic rupture in one case. We believe that stent rupture in this animal was due to a defective stent that was rejected for human use but thought to be suitable for this study. Subsequently, use of 20-mm diameter balloons for expansion of the Palmaz stent has not resulted in stent rupture (8). Resistance to re-expansion in this study may also have been due to the inherent elastic recoil of the normal aorta. The elastic recoil of naturally occurring stenosis of the pulmonary arteries or aorta may be greater or less than that observed in this model. Final stent diameters of 14 to 15 mm achieved in some animals in this study after re-expansion with 18-mm diameter balloons would provide adequate vessel diameter to relieve stenosis and prevent restenosis with growth in most patients with pulmonary artery branch stenosis and coarctation (11–13).

Vascular effects of re-expansion. Because re-expansion could potentially result in injury to the neointima or media, we examined both the gross and histologic effects on vessel wall integrity. Medial and adventitial integrity were preserved with stent re-expansion. *Re-expansion was also accomplished with minimal effects on the arterial neointima.* Neointimal abrasion was apparent overlying some struts by both gross and microscopic examination. Gross inspection of specimens revealed evidence that the stent struts moved beneath the neointima as the stent shortened with re-expansion. However, this strut movement did not result in dissection of the neointima or development of neointimal flaps. Moreover, by both light microscopy and scanning electron microscopy, platelet and fibrin aggregates were seen at the site of denuded neointima representing the early stages of repair. The adherence of platelets and fibrin to stent struts is part of a thrombotic process that ultimately leads to development of a new layer of neointima (14). Platelet activation and fibrin deposition initiated by re-expansion could also result in an on-going process of thrombosis resulting in development of intraluminal thrombi. Nonobstructing thrombi adherent to stents were found in two swine in this study. Subsequent studies in animals and

children treated with antiplatelet agents after implantation have shown no evidence of thrombosis (8,15–17). Swine in this study did not receive antithrombotic agents after implantation or re-expansion. Use of antiplatelet agents such as salicylates could have prevented the development of intraluminal thrombi. However, because neointima formation may be closely related to a limited process of thrombosis, lysis of thrombi and rapid endothelialization, antiplatelet agents and other anticoagulant agents could interfere with development of a uniform neointima. Studies are underway to examine the effect of antiplatelet agents in the healing of neointimal abrasions and development of intraluminal thrombi after re-expansion of stents in the great vessels.

Conclusions. Although growth of juvenile animals results in relative stenosis at the site of stent implantation, re-expansion is feasible and is effective in relieving stenosis. Re-expansion which is performed after adequate time for formation of a complete neointima is accompanied by plastic deformation of the neointima with stents sliding beneath the neointima as shortening occurs. This change in stent position occurs without producing intimal flaps or dissection. With the exception of one stent that ruptured with intentional overexpansion, re-expansion does not produce medial or adventitial injury. Questions remain regarding the optimal use of antithrombotic agents to prevent thrombosis after re-expansion of stents. The results of this study support careful and selective use of intravascular stents as an adjunct to balloon dilation of congenital stenoses in children.

References

1. Morrow WR, Vick GW, Nihill MR, et al. Balloon dilation of unoperated coarctation of the aorta: short and intermediate-term results. J Am Coll Cardiol 1988;11:133–8.
2. Beekman RH, Rocchini AP, Dick M, et al. Percutaneous balloon angioplasty for native coarctation of the aorta. J Am Coll Cardiol 1987;10:1078–84.
3. Rothman A, Perry SB, Keane JF, et al. Early results and follow-up of balloon angioplasty for branch pulmonary artery stenoses. J Am Coll Cardiol 1990;15:1109–17.
4. Lock JE, Castaneda-Zuniga W, Fuhrman BP, Bass JL. Balloon dilation angioplasty of hypoplastic and stenotic pulmonary arteries. Circulation 1983;67:962–7.
5. Ring JC, Bass JL, Marvin W, et al. Management of congenital stenosis of a branch pulmonary artery with balloon dilation angioplasty. J Thorac Cardiovasc Surg 1985;90:35–44.
6. Palmaz JC, Gardia OJ, Schatz RA, et al. Placement of balloon-expandable intraluminal stents in iliac arteries: first 171 procedures. Radiology 1990;174:969–75.
7. Richter GM, Noeldge G, Roeren T, et al. First long-term results of a randomized multicenter trial: iliac balloon expandable stent placement versus transluminal angioplasty. Radiology 1990[abstract];177(Suppl P): 152.
8. O'Laughlin MP, Perry SB, Lock JE, et al. Use of endovascular stents in congenital heart disease. Circulation 1991;83:1923–39.
9. Palmaz JC, Sibbitt RR, Reuter SR, et al. Expandable intraluminal graft: a preliminary study. Radiology 1985;156:73–7.
10. Mullins CE, O'Laughlin MP, Vick GW, et al. Implantation of balloon-expandable intravascular grafts by catheterization in pulmonary arteries and systemic veins. Circulation 1988;77:188–99.
11. Clarkson PM, Brandt PWT. Aortic diameters in infants and young children: normative angiographic data. Pediatr Cardiol 1986;6:3–6.
12. Fitzgerald SW, Donaldson JS, Poznanaski AK. Pediatric thoracic aorta: normal measurements determined with CT. Radiology 1987;165:667–9.
13. Sievers H, Onnasch DGW, Lange PE, et al. Dimensions of the great arteries, semilunar valve roots, and right ventricular outflow tract during growth: normative angiocardiographic data. Pediatr Cardiol 1983;4:189–96.
14. VanBeusekom HMM, Van der Giessen WJ, Suylen RJ, et al. Histology after stenting of human saphenous vein bypass grafts: observations from surgically excised grafts 3 to 320 days after stent implantation. J Am Coll Cardiol 1993;21:45–54.
15. Morrow WR, Smith VC, VanDellen AF, Ehler WJ, Mullins CE. Placement of balloon-expandable stents in surgically created pulmonary artery stenosis: gross and histologic observations [abstract]. Circulation 1990;82 Suppl III:III-582.
16. Benson LN, Hamilton R, Dasmahapatra H, et al. Percutaneous implantation of a balloon-expandable endoprosthesis for pulmonary artery stenosis: an experimental study. J Am Coll Cardiol 1991;18:1303–8.
17. Rocchini AP, Meliones JN, Beekman RH, et al. Use of balloon-expandable stents to treat experimental peripheral pulmonary artery and superior vena caval stenosis: preliminary experience. Pediatr Cardiol 1992;13:92–6.