Response of Normal Aorta to Endovascular Grafting

A Serial Histopathological Study

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Objective: To examine the histological changes caused by the presence of the endovascular stented graft in the native aorta.

Design and Intervention: Case series. Twenty Western crossbred adult male sheep underwent endovascular placement of an infrarenal aortic stented graft, using the Bard aortic aneurysm repair device catheter delivery system (Bard Vascular Systems, Dovermill, Mass). Six self-expanding wire hooks at the proximal anchor allow fixation to the aorta. After 1 month (n=6), 3 months (n=6), and 6 months (n=8), the animals underwent repeated angiography and intravascular ultrasonography to study the aorta and the graft. The aorta was explanted en bloc with the left renal artery, pressure perfused with a formalin gluteraldehyde solution, and then underwent histological examination with hematoxylin-eosin, trichrome, and elastic tissue staining.

Main Outcome Measures: Description of histological changes at various intervals after endovascular stented graft placement.

Results: Significant histological findings include (1) complete incorporation of the grafts into the aortic wall, with a pseudointima of smooth muscle cells and collagen; (2) a foreign-body reaction around the graft; (3) an organized blood clot noted between the graft and the aortic wall, without evidence of recent blood flow through the perigraft space or the lumbar vessels; and (4) focal replacement by collagen of the inner one third to one half of the media at the proximal anchor sites.

Conclusion: There was good incorporation of the graft without evidence of pressure necrosis, bleeding around the graft, or flow in the occluded lumbar vessels.

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ENDOVASCULAR repair of abdominal aortic aneurysms is a new, exciting, less invasive approach to the treatment of abdominal aortic aneurysms. Although the feasibility of this type of repair has been well documented,1,2 there is little information available regarding the long-term effect of the endoluminal stented grafts on the aortic wall. Questions regarding the pressure effects of the hooks, the incorporation of the graft, the lumbar vessel blood flow, and persistent aneurysmal blood flow still exist. The goals of this study were to examine the histological changes in the native aorta that were caused by the stented graft after 1, 3, and 6 months. We specifically chose not to use an aneurysm model for this study because issues related to the successful obliteration of the aneurysm with this device have already been reported.3,4

RESULTS

All implants were placed successfully. Angiography and intravascular ultrasonography confirmed placement and patency of the grafts in all cases. The mean±SD aortic diameter was 13.8±1.0 mm. Of the 20 grafts, 12 were 14 mm and 8 were 16 mm. The aortic grafts were oversized by 6.6%±4.7% of the cross-sectional area, as measured by intravascular ultrasonography. The lumbar vessels were occluded in all cases and no migration had occurred.

The 1-month specimens demonstrated complete coverage of the graft and anchor sites with an organizing pseudo-intima composed of smooth muscle cells

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MATERIALS AND METHODS

Twenty Western crossbred adult male sheep weighing 76.5 to 90 kg underwent endovascular placement of an infrarenal aortic stented graft. The studies had been approved by the Institutional Animal Care Committee at Boston University, Boston, Mass, and conformed to the principles outlined in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication N86-23).

The sheep were premedicated with xylazine hydrochloride (0.15 mg/kg) and glycopyrrolate (0.01 mg/kg) intramuscularly. After placement of an external jugular catheter, anesthesia was induced with an intravenous bolus of ketamine hydrochloride (1 mg/kg) and xylazine hydrochloride (0.075 mg/kg) and the sheep were intubated. Anesthesia was maintained with 1% to 2% halothane. The surgical site was prepared and draped by sterile technique.

The Bard aortic aneurysm repair device (Bard Vascular Systems, Dovermill, Mass) is a catheter delivery system with an endovascular implant with thin-walled woven polyester graft material reinforced by self-expanding wire anchors at each end. Six wire hooks are present at the proximal anchor to allow fixation to the aorta (Figure 1). The delivery system is a 16F sheath with a center tube that allows passage over a guidewire. The femoral artery was exposed. Using the Seldinger technique, the artery was cannulated and an introducer sheath was placed. Arteriography and intravascular ultrasonography were performed to measure the aorta for graft size. The animal was given heparin, 200 U/kg, and an activated clotting time was obtained. Once the clotting time was greater than 300 seconds, the 16F introducer was placed via a femoral arteriotomy. The aortic graft was delivered such that the proximal hooks were 0.9 to 2.1 cm distal to the left renal artery. The animals were allowed to recover.

After variable amounts of time (1 month [n=6], 3 months [n=6], and 6 months [n=8]), the animals were studied. The sheep were anesthetized as described above. Repeated angiography and intravascular ultrasonography were performed to study the aortas and grafts (Figure 2). Next, a laparotomy was performed and the aorta was explanted en bloc from just below the right renal artery to distal to the trifurcation, including the left kidney. At this point, the animal was humanely killed.

The specimen was pressure perfused with a formalin gluteraldehyde solution for 24 hours. The specimen then underwent macroscopic and microscopic evaluation. Histological examination was performed with hematoxylin-eosin, trichrome, and elastic tissue staining.

and collagen. There was a foreign-body reaction, including multinucleated giant cells, noted outside the graft and an organizing clot noted between the graft and the aortic wall. At the proximal anchor sites, there was focal replacement of the inner one third of the media with collagen. In 1 specimen, there was mild calcification noted at the proximal anchor site.

The 3-month specimens demonstrated complete coverage of the graft and anchor sites with an organized pseudointima composed of smooth muscle cells and collagen. The foreign-body reaction was still present outside the graft and there was an organized blood clot outside the graft. There was no evidence of recent blood flow in the peri-raft area. At the distal anchor site points, there was replacement of the medial smooth muscle with collagen, loss of elastic lamellae, and dystrophic calcification. In 3 of these specimens, there was intimal hyperplasia and replacement of the medial smooth muscle by collagen, the elastic lamellae were lost, and dystrophic calcification was noted focally at the proximal hook sites.

The 6-month specimens demonstrated complete incorporation of the graft into the aortic wall, an organized pseudointima, a foreign-body reaction, and an organized blood clot outside the graft, all similar to the 3-month specimens (Figure 3). The changes in the aortic wall at the distal anchor sites were unchanged from the 3-month specimens. There were some changes at the proximal hook sites that were similar to the 3-month specimens. One aorta had intimal hyperplasia only; 1 aorta had replacement of the smooth muscle by collagen only; and 6 aortas had intimal hyperplasia and significant disruption of media with replacement of the medial smooth muscle by collagen and disruption of elastic lamellae.

There is little information available regarding the pathological changes that occur in the arterial wall after an endovascular stented graft is placed. Several reports exam-
of endothelial cells in grafts is species-specific and the formation of endothelial cells lining the graft in our sheep model may not be relevant to humans, we did not investigate the presence of endothelial cells.

Although previous reports have not demonstrated any inflammatory reaction around a prosthesis, in our study, a foreign-body reaction was noted in all specimens and did not change significantly between 1 and 6 months. There was no evidence of infection. Also noted in the perigraft area was an organized blood clot. The blood clot was noted in the 1-month specimens and was completely organized by 3 months. There was no evidence of blood flow or recent nonorganized blood between the graft and the aortic wall or in the occluded lumbar vessels in any of the specimens, demonstrating effective obliteration of the lumen of the native aorta with this particular device.

The question of pressure necrosis is an important one. If an endovascular stented graft is placed to prevent rupture of an abdominal aortic aneurysm, one must be sure the graft will not weaken or erode through the wall at the stent site. Rousseau et al9 have previously described localized cellular necrosis in the layer beneath the stent due to a high mural pressure. The structure of the Bard aortic aneurysm repair device graft creates 3 areas where there is pressure on the aortic wall: the proximal anchor site, the distal anchor site, and the proximal hook sites. There were histological changes noted at all 3 sites; however, no necrosis was noted. The proximal and distal anchor sites had focal changes, including partial replacement of the smooth muscle of the media with collagen. In a few instances calcification was noted and, occasionally, disruption of the elastic lamellae. These changes were completed by 3 months and there was no further progression in the 6-month specimen.

Reidy10 has previously described smooth muscle cell response to stimulus. Smooth muscle cells have the ability to express various phenotypes under different stimuli. Mechanical stretching, endothelial injury, and pressure may cause the smooth muscle cell to divide or migrate. An abnormal matrix, which may be fibrillar or collagenous,11 is found around these activated smooth muscle cells. Collagen formation is a normal healing response to injury. The focal changes of collagen replacement in the media are a healing response to the pressure on the aorta from the self-expanding wire stents used as anchors. There was no evidence of necrosis and no evidence of progression of these changes beyond 3 months. Further long-term studies are necessary to determine if disruption of this layer could lead to progressive dilation of the neck of an aneurysm.

There are a few reports describing stenosis and occlusion of intravascular stents and grafts secondary to intimal hyperplasia.12,13 Although the only histological change noted between 3 and 6 months was intimal hyperplasia at the hook sites, there was only a small amount noted in each specimen. The distal anchor sites did not display any intimal hyperplasia, and this was probably related to the lack of endothelial cell injury at this site. There was no evidence of stenosis or occlusion of this stented graft.

In conclusion, the histological changes seen after successful placement of an endovascular aortic stented graft in a sheep model are encouraging. There was good in-
Endovascular repair of aortic abdominal aneurysms is a promising new technique rapidly emerging on the horizon. The graft is inserted through a femoral cutdown and placed under fluoroscopic control, thus obviating an abdominal incision. Technical advances are being announced in increasingly shorter intervals. Although the devices are not yet approved for general use, it is clear that some, if not most, of our patients with aortic abdominal aneurysms will be treated by this method in the future.

Technically, a graft can be successfully inserted in almost all properly selected patients. The reluctance to embrace this technique is because of our lack of long-term follow-up and thus the long-term fate of these endografts. The grafts are held in place by a stent expanded against the wall of the aorta. Therefore, the material presented in this article is of extreme relevance.

White and her associates have demonstrated that these grafts cause relatively little damage to a normal sheep's aorta. The authors rightfully point out that there are limits in extrapolating animal data to humans and I would like to underscore that comment.

Patients with aortic abdominal aneurysms tend to have large arteries; ie, they are aneurysm prone. Furthermore, the aortas continue to enlarge even after open infrarenal abdominal aortic aneurysmectomy. In a recent review, 18 (55%) of 33 such patients had a measured enlargement of 2 to 24 mm of the proximal aortic cuff during a mean of 89 months. The iliac arteries also were dilated on follow-up computed tomographic scans. The smaller aortas tended to enlarge to a lesser degree and larger aortas to a greater degree. Interestingly, some large endografts are no longer being manufactured.

The animal model is a nonatherosclerotic model. One can only speculate if the findings would be different in a hypertensive, hypercholesterolemic subject with overt atherosclerosis. We have all seen that the human aorta at the neck of an aneurysm is far from a normal healthy artery. The relatively mild collagen deposition and calcification might become much more exaggerated and the intimal hyperplasia likewise could be more impressive. In my opinion, this is the most disturbing criticism of the information presented in this article.

Articles such as this are needed so we may understand the events that are associated with endovascular grafting. Similar studies in atherosclerotic preparations would be a logical next step. Long-term follow-up of grafts placed in humans will be necessary before the ultimate fate of these grafts is known.

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References


Invited Commentary