HEALING CHARACTERISTICS OF ENDOVASCULAR STENT-GRAFT REPAIR OF EXPERIMENTAL AORTIC ANEURYSMS

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Communicated by Jānis Volokollākovs

The purpose of the study was to evaluate the healing response of endoluminal stent-graft repair of experimental aortic aneurysms. Abdominal aortic aneurysms (AAA) were created surgically in 30 sheep. Under fluoroscopic guidance an endoluminal nitinol/dacron stent-graft was inserted through the femoral artery. Two groups of animals were studied: group A (N=18)—straight stent-grafts and group B (N=12)—bilateral stent-grafts. Stent-graft prostheses were properly deployed and all aneurysms were excluded. All 18 straight stent-grafts and 11 of 12 bifurcated grafts were patent at the time of explant. Stent-grafts were well incorporated and were without mural thrombus. There was no stent-graft migration. One week after the procedure, scattered neutrophils, fibrin deposition and acute hemorrhage were seen within the Dacron mesh and aortic intima. At later times, the nature of the inflammatory component changed with loss of the neutrophils and the appearance of occasional lymphocytes and macrophages, including some multinuclear giant cells. Incorporation of the stent-graft by intimal fibrosis was well-advanced at 1 month, with increasing degrees of fibrosis observed at 3 and 6 months. There was no progression of fibrosis and no significant changes between 6 and 12 months.

We conclude that endoluminal stent-grafts can effectively treat experimental aortic aneurysms with consistent patency, secure fixation, and good incorporation into the aortic wall in this animal model.

Key words: aorta, aneurysm, stents, grafts, sheep model.

INTRODUCTION

Abdominal aortic aneurysms (AAA) are common in the infrarenal aorta and commonly involve the iliac arteries. Aneurysms may enlarge and rupture, and the only effective treatment is surgical repair (Johnston et al., 1991). Screening programs for the identification of AAA have suggested a prevalence of approximately 5% in patients aged 65–80 years (Collin, 1993; Scott et al., 1995). In general, approximately 20 patients per 100,000 population annually require AAA repair (Campbell et al., 1987; Roberts et al., 1990). This suggests that more than 500 patients require AAA repair in Latvia each year.

Recent advances in technology have resulted in the development of minimally invasive approaches to reduce the risk of major surgery. These have been applied to the treatment of AAA and they stimulated the investigation of transluminally placed endoluminal aortic stent-grafts.

The concept of transluminal placement of an endovascular prosthesis was first proposed by Charles Dotter in 1969 (Dotter, 1969). Successful endovascular repair of experimental aortic aneurysms using covered stents was first described by Balko in 1986 and Lawrence in 1987 (Balko et al., 1986; Lawrence et al., 1987). Although the healing of surgically implanted synthetic vascular grafts has been well described in animal models and man (Sauvage et al., 1974; Zacharias et al., 1987), the healing properties of intraluminal stent-grafts has not been well described.

This study was designed to evaluate the healing response of a self-expanding nitinol/dacron intraluminal stent-graft used to treat experimental aortic aneurysms in adult sheep.

MATERIALS AND METHODS

Thirty adult sheep weighing 70.9±5.2 kg were used in this study. All animals were treated and housed in an animal laboratory, and all care conformed to the Principles of Laboratory Animal Care (formulated by the National Society for Medical Research) and the Guide for the Care and Use of Laboratory Animals (prepared by the National Acad-
emy of Sciences and published by the NIH; publication No. 86-23, revised 1985). Each animal was fasted 36 hours prior to surgery.

Creation of aneurysm. All surgical procedures were performed using sterile technique. Before operation, the animals were sedated with intramuscular Diazepam (0.5 mg/kg) and Ketamine (10 mg/kg), then intubated, and anesthesia was induced and maintained with inhalation of a mixture of halothane and oxygen. Through a left flank and retroperitoneal approach, the infrarenal aorta was isolated. The infrarenal aorta was cross-clamped, and flow to the iliac vessels and spinal cord was maintained with a temporary indwelling intraaortic shunt. The aorta was opened longitudinally and a 4 cm x 6 cm knitted Dacron patch was sutured to the anterior aortotomy. This procedure using 5-0 polypropylene suture resulted in an aneurysm that was approximately 3.5–5.0 cm long. Each animal received Benzathine Penicillin-G (40,000 units per kg intramuscularly) for 5 days after the operation. No platelet drugs or anticoagulants were administered post-operatively.

Stent-graft implantation. After full recovery, 10–20 days after creation of the aneurysm, the animals were again sedated with Diazepam and Ketamine and anesthetised with endotracheal halothane. Both common femoral arteries were exposed and intravascular sheaths were introduced over a guide wire under fluoroscopic control. Aortography and intravascular ultrasound (IVUS) was performed to define aneurysm size and morphology and aortic dimensions.

Eighteen straight (group A) and 12 bifurcated (group B) stent-grafts (Medtronic / AneuRx, Cupertino, California) composed of a thin-wall polyester graft supported externally by self-expanding nitinol cylindrical stents were used to exclude the AAA (Fig. 1.). The prosthesis had radiopaque markers to aid orientation of the endoluminal stent-graft. The straight prosthesis diameters chosen (11–14 mm) were slightly larger in diameter than the aortic diameters previously defined, and the length of the stent-graft was 7.5 cm. The bifurcated stent-graft consisted of two to four pieces. The main segment of the bifurcation was 11–14 mm in diameter and had an aortic length of 5–13 cm. The iliac segments were 6–8 mm in diameter, and were sufficient in length to overlap into the bifurcation segment by 1 cm to 2 cm and reach into the external iliac artery.

After systemic heparinisation was initiated (200 U/kg) intravenously, a 18Fr introducer sheath (Medtronic / AneuRx, Cupertino, California) was advanced into the aorta under fluoroscopic guidance. The stent-graft delivery system was advanced through the sheath to the appropriate position. The straight stent-graft (group A) or main segment of the bifurcated stent-graft (group B) was deployed under fluoroscopic guidance and the catheter was withdrawn. For the bifurcated stent-graft, the iliac stent-graft segment was advanced and deployed through the contralateral femoral artery immediately after stent-graft deployment. Angiography and IVUS were performed to confirm proper positioning of the graft.

Explantation. At the time of sacrifice, 1 week to 12 months after stent-graft placement, the animals were again anaesthetized and angiography and IVUS were performed through the femoral artery to evaluate the stent-graft. The aortic specimens containing the stent-graft, with at least 5 cm native aorta distally and proximally, were explanted at the predetermined time intervals. Selected follow-up intervals were 1 week (N = 3, N = 2), 1 month (N = 3, N = 2), 3 months (N = 3, N = 2), 6 months (N = 6, N = 3), and 12 months (N = 3, N = 3). The abdominal aorta (and iliac arteries for the bifurcated model) were isolated and visualised in situ. The animal was then euthanised with a lethal dose of euthanasia solution, and the stent-graft with native aorta were excised as one specimen. The entire specimen was fixed in 10% neutral buffered formaldehyde solution for a minimum of 24 h at 100 to 150 mm Hg.

Morphologic evaluation. Following fixation, each specimen was examined grossly to evaluate endothelial ingrowth, neo-intima, and the presence of adherent thrombi within the lumen of prosthesis. Specimens from each animal at each time point were then sectioned for histologic evaluation. Tissue sections were taken from the proximal and distal stent-graft interfaces with the native aorta, and from the proximal, middle and distal portions of the stent-graft. The tissue sections from the native vessel, 5 cm proximal and distal to the stent-graft, served as controls.
Sections were stained with hematoxylin and eosin for general histologic evaluation, with EVG to illustrate elastin and the internal and external elastic laminae, and with trichrome to demonstrate collagen deposition.

Scanning electron microscopy was performed on specimens taken from the interior of the native vessel, proximal and distal to the stent-graft.

RESULTS

The endoluminal stent-graft was successfully deployed and the aneurysm was completely excluded from the circulation in all 30 animals (Fig. 2.). There was no peri-operative mortality. All 18 straight, and 11 of 12 bifurcated stent-grafts remained patent throughout the study. One bifurcated stent-graft was trombosed at the time of explant without any clinical signs.

Based on angiographic, IVUS and gross examination, there was no evidence of stent-graft migration or compression, no pseudoaneurysm formation, and aneurysm was completely excluded at the time of sacrifice.

A variety of morphological changes involving the endovascular prosthesis and the underlying aortic walls were observed, the nature of which changed over time.

One week after the procedure, scattered neutrophils, fibrin deposition and acute hemorrhage were seen within the Dacron mesh and aortic intima. At later times, the nature of the inflammatory component changed with loss of the neutrophils and the appearance of occasional lymphocytes and macrophages, including some multinuclear giant cells. Incorporation of the stent-graft by intimal fibrosis was well-advanced at 1 month, with increasing degrees of fibrosis observed at 3 and 6 months. There was no progression of fibrosis and no significant changes between 6 and 12 months. There was evidence of increased reaction in the arterial wall around the smaller bifurcated stent-graft legs with a proportionally greater degree of intimal fibrosis observed in the iliac arteries compared to the infrarenal portion of the stent-graft. Due to the smaller luminal size of the iliac arteries, the intimal proliferation was associated with fairly significant luminal constriction, with occluding thrombus observed in the right and left stent-graft legs of one group B animal at 3 month follow-up.

The proximal and distal native aorta sections (control) were normal in all cases with no evidence of inflammation or reaction.

We conclude that this endoluminal self-expanding stent-graft can successfully treat experimentally created aneurysm. There was consistent patency, secure fixation, and incorporation within the aortic wall in sheep model. The healing response was similar to that previously described for surgically implanted aortic prosthetic grafts.

There was evidence of smooth muscle cell injury in the aortic media one week and one month after the procedure, most often at or near the proximal graft-aorta interface. Smooth muscle cell necrosis was localised in the inner one-third of the aortic media in 1-week and 1-month animals. At later times there was no evidence of aortic smooth muscle cell injury. There was no substantial increase in the severity of degenerative changes, including elastin loss and smooth muscle vacuolation after 3 months. Patchy areas of mild

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Fig. 2. Transfemoral endoluminal repair of an experimental AAA in adult sheep with Medtronic / AneuRx stent-graft. a, Preoperative angiogram demonstrates an AAA; b, after transfemoral insertion of the stent-graft, the aneurysm lumen is excluded from the circulation.
medial scarring were found at 3 to 12 months, representing areas of healing. There was no significant difference between straight and bifurcated stent grafts.

Significant ingrowth of fibrous tissue into and along the luminal borders of the Dacron mesh, which increased with time, was observed in all cases. This growth occurred throughout the length of the prosthesis lumen, and was not isolated to the ends of the prosthesis. Small blood vascular channels were often observed within fibrous tissue growth, providing evidence of neovascularization. Neovascularization increased in degree and frequency over time, with changes at 6 months, and 12 month being substantially equivalent. (Fig. 3).

Fig. 3. a, Electron micrograph demonstrating a smooth hole near the junction between the dacron mesh and the natural lumen in a 3 month animal; b, electron micrograph of dacron mesh encased in fibrous tissue sheets-collagen in a 6-month animal.
DISCUSSION

The main characteristics of an “ideal vascular graft”, defined by Weselowski (Weselowski et al., 1961) are: ease of mechanical handling, durability, nontoxicity, maximal tissue permeability, and minimal implantation porosity. Despite the surrounding stent, the woven Dacron portion of the prosthesis behaved as previously described (Sauvage et al., 1974; Haverich et al., 1984). From previous animal studies in which healing of synthetic arterial grafts has been evaluated, it is apparent that Dacron grafts heal through an early fibrinous incorporation which is gradually organised. This initial fibrous capsule is relatively stable and can remain essentially unchanged for weeks or even months (Pasquinelli et al., 1990; Weselow, 1982). The stent-graft showed definitive evidence of this healing process after one month follow-up. There was observed early organisation of the pannus along the luminal surface of the graft. In the comparison of 3-, 6-, and 12-month specimens, there were minimal qualitative differences in the maturity of the collagen tissue in the pannus, suggesting advanced healing already by 3 months post-implantation. Overall, the morphologic changes found in our study were typical of the cellular response to prosthetic graft materials placed in the vasculature.

Different types of animal models have been used to evaluate stent-grafts. Yoshioka (Yoshioka et al., 1988) placed self-expanding stents covered with expandable nylon in normal dog aorta without creation of an experimental aneurysm. Mirich (Mirich et al., 1989) used a dog model in which he created an aneurysm by removing the aortic media. We used a knitted Dacron patch to create an aneurysm. This produced a large size aneurysm in all animals. To prevent spinal cord ischemia observed by other colleges using large animals, we used a tubular shunt in the aorta for maintenance of blood flow during aneurysm creation. Unfortunately, there is no ideal animal model for such experiments, and surgically created aneurysms in the animal model are not necessarily comparable in configuration to the most common AAA’s in humans. Therefore, the clinical use of this procedure in humans in the diseased and anatomically more difficult cases requires further study.

REFERENCES


Received February 13, 1998

DZĪŠANAS PROCESS, EKSPERIMENTĀLI IZVEIDOTAS AORTAS ANEIRISMAS ĀRSTĒJOT AR ENDOVAZĀLI IEVIETO TAM STENTA PROŢĒZEM
