of neointimal cells PCNA-positive) with declining proliferation at 14 days (9.6 ± 1.3% PCNA-positive) and 28 days (1.1 ± 1.0% PCNA-positive). In human stented arteries, cellular proliferation has been evaluated in atherectomy specimens from patients with in-stent restenosis. In a study of 10 peripheral arterial lesions (6 femoral arteries, 3 iliac arteries, and 1 subclavian artery) with stents implanted 4 to 25 months, lesions from the stented segments were hypercellular with actin positive cells demonstrating high proliferative activity (24.6 ± 2.3% PCNA-positive). In contrast, another study of restenotic tissue obtained by coronary atherectomy from stents in place 2.5-23 months showed a relatively hypocellular extracellular matrix; cellular proliferation (determined by Ki-67 staining) was rare [10]. The reasons for the conflicting results among these atherectomy studies are uncertain and are probably due to variability and small size of the samples obtained by percutaneous atherectomy.

Stent Endothelialization

In a variety of experimental animals (rabbit, dog, pig), complete endothelialization of the stent surface may be seen as early as 7 days to approximately 4 weeks [28, 45, 56, 69]. Data from humans regarding stent endothelialization is limited. Anderson et al reported coronary stent endothelialization in a single stent 21 days post-implant [2]. Van Beusekom et al demonstrated complete endothelial stent coverage by 3 months in saphenous vein bypass grafts [67]. Repair on the luminal surface via reendothelialization may be a critical process in vascular healing via prevention or limitation of luminal thrombosis. Further, inhibition of continued neointimal growth has been felt to be a result of a restored endothelial surface. However, recent data demonstrate that the presence of an endothelial surface in and of itself is insufficient to inhibit the neointima; normal endothelial function and/or non-endothelium-dependent factors may be relatively more important than the presence or absence of an endothelial surface in suppressing neointimal expansion [68].

Neointimal Growth

The mature neointima consists of smooth muscle cells in a proteoglycan/collagen matrix. Experimental studies demonstrate organization of the intimal thrombus by 7-14 days with smooth muscle cell migration from the media and adventitia [61]. Cell proliferation within the maturing neointima is accompanied by matrix synthesis and the formation of a thick cellular neointima by 8 weeks [7, 56, 65]. In human atherosclerotic arteries, neointimal development is delayed compared with experimental animals, but is clearly present in all stents implanted ≥30 days (Figure 3) [2, 22, 30, 32]. Proteoglycans are macromolecules that

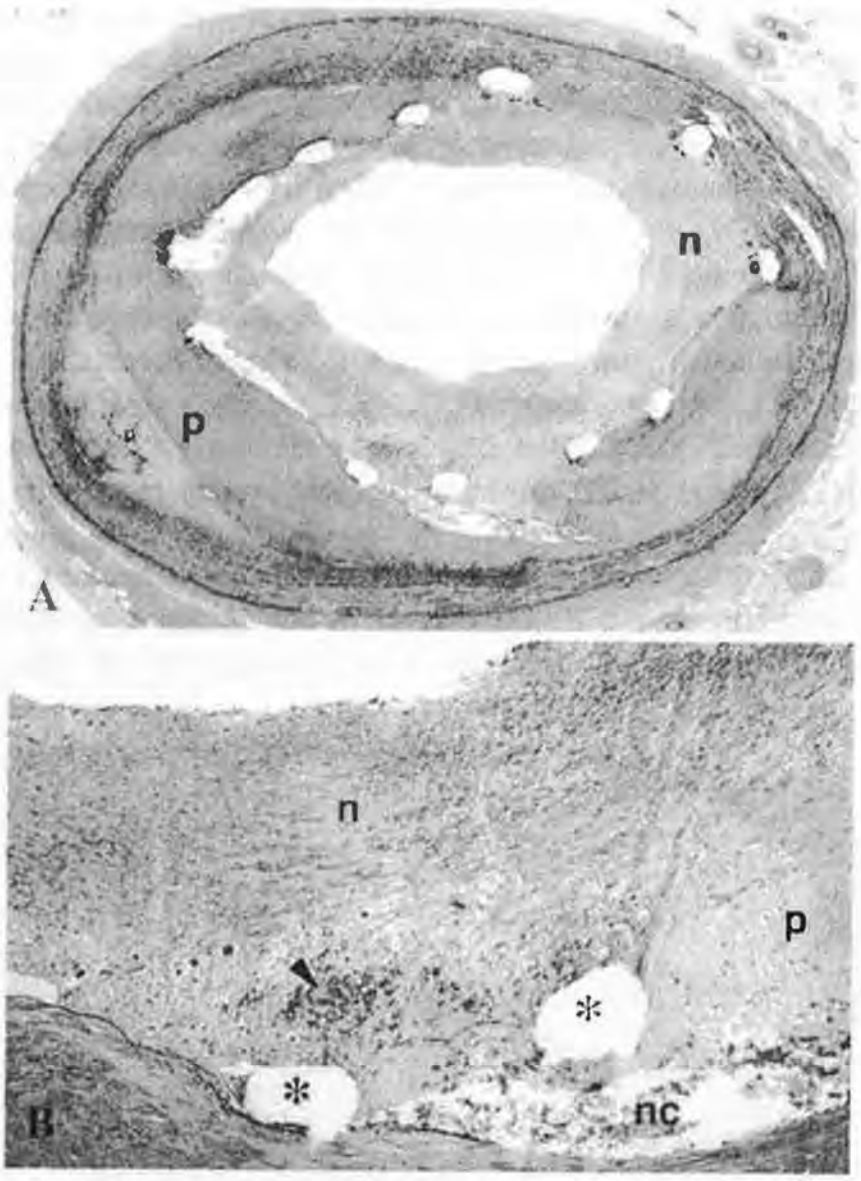

FIGURE 3

In-stent neointimal (n) growth 16 weeks after placement of a Palmaz-Schatz stent in the right coronary artery (panel A). Underlying fibrous plaque (p) is present. A higher power view of the neointima (panel B) demonstrates the proteoglycan-rich neointima (n) containing numerous smooth muscle cells. Near stent struts (*), an organizing thrombus (arrowhead) is seen. Fibrous plaque (p) and necrotic core (nc) are indicated. (Movat pentachrome stain)

are an important component of the extracellular matrix. They consist of specific glycosaminoglycans (chondroitin sulfate, dermatan sulfate, heparan sulfate, keratin sulfate) linked to a protein core via O-gylcosidic

linkages which are themselves bound to hyaluronic acid. Versican and hyaluronic acid have been identified in the neointima after stenting in human arteries [10]. Recently, we demonstrated that similar strong immunohistochemical staining for hyaluronic acid and chondroitin sulfate in the neointima of stented coronary arteries compared with PTCA-treated coronary arteries matched for the duration following stent deployment or PTCA (Figure 4). Neointimal smooth muscle cell density was also similar in matched stented and PTCA-treated coronary arteries [22]. The neointimal area was greater in the stented segments compared with PTCA arteries (3.06 ± 1.63 mm^2 versus 1.94 ± 1.20 mm^2, respectively, $p<0.05$). However, IEL area was larger (11.61 ± 2.14 mm^2) with stent placement compared with PTCA (7.88 ± 2.13 mm^2, $p=0.0001$) so that the neointima corrected for artery size (neointima/IEL) was similar in stents and PTCA.

Ultimate histologic success is dependent on lumen area and neointima growth within the stent [22]. In contrast to PTCA alone, stenting prevents negative remodeling of the artery as a component of the restenosis

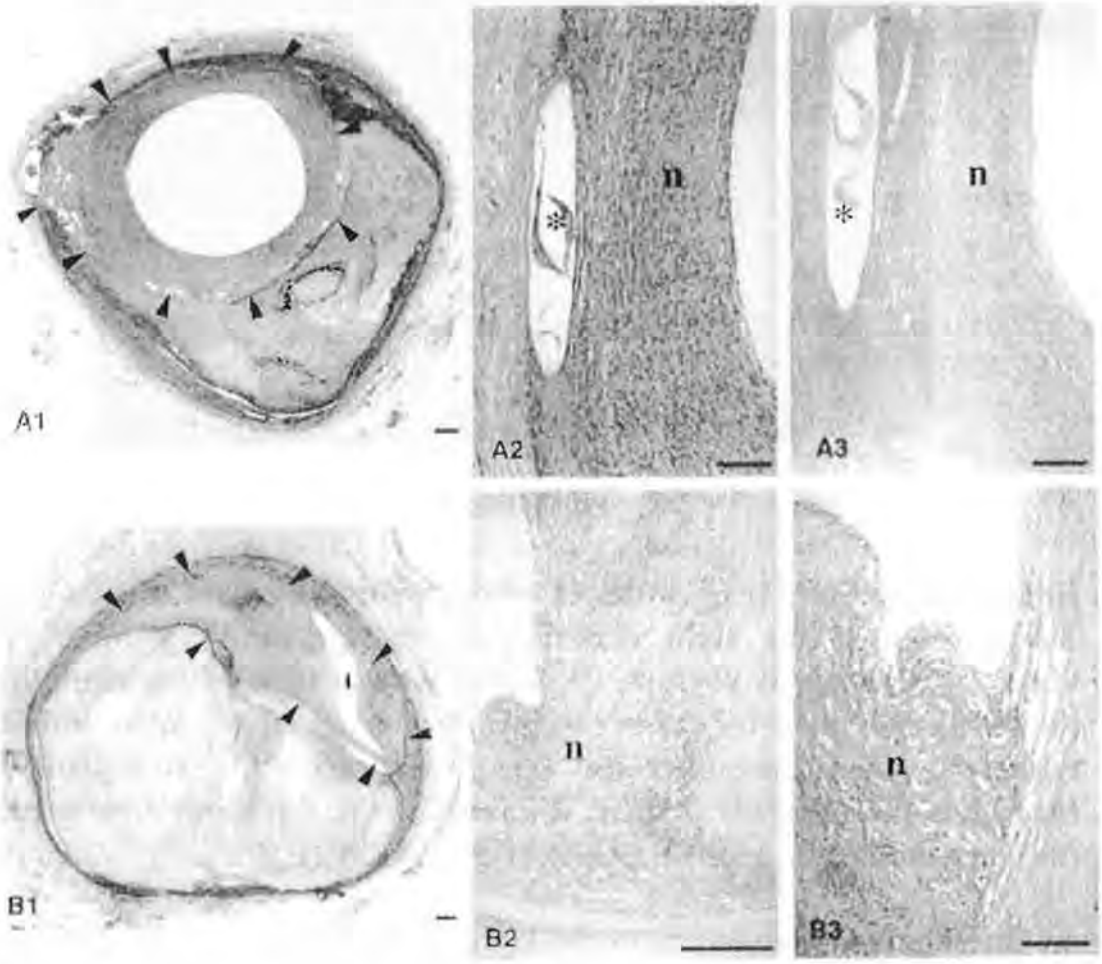

FIGURE 4 (Caption on page 149)

FIGURE 4 Caption (for Figure on page 148)

Neointimal cellularity and proteoglycans in chronic coronary stents compared with balloon angioplasty (PTCA).
A1: Low power micrograph of left circumflex coronary artery containing a Gianturco-Roubin stent placed 10 months antemortem. The neointima is outlined by arrowheads, and the stent strut is identified (*). The neointima is relatively thicker over the stent strut compared with the remainder of the arterial segment. Scale bar 0.20 mm.
A2: Alpha actin staining of neointima (n) identifying smooth muscle cells. Scale bar 0.12 mm.
A3: Strong alcian blue stain of the neointima (n) showing presence of proteoglycans, predominately of chondroitin sulfate and hyaluronic acid. Scale bar 0.12 mm.
B1: Low power micrograph of left anterior descending coronary artery treated with PTCA 13 months antemortem. The neointima is outlined by arrowheads, and the residual lumen (L) is indicated. Scale bar 0.16 mm.
B2: Alpha actin staining of neointima (n) identifying smooth muscle cells. The cell density is similar to the stented artery (A2). Scale bar 0.20 mm.
B3: Alcian blue stain of the neointima (n) showing strong staining for proteoglycans, similar in intensity to the stented artery (A3). Similar to stents, chondroitin sulfate and hyaluronic acid are the major constituents of the neointimal proteoglycans after PTCA. Scale bar 0.08 mm.
(Movat pentachrome: A1 and B1; smooth muscle actin immunostain: A2 and B2; alcian blue A3 and B3*). Modified with permission from reference 22.*

process. In our analysis of stented human coronary arteries, the mean neointimal area and neointima area/stent area in successes were 2.2 ± 1.1 mm^2 and 0.39 ± 0.12, respectively, versus 3.9 ± 1.9 mm^2 and 0.68 ± 0.15 in failures, respectively ($p<0.006$ and $p<0.0001$). There were no differences between successes and failures with respect to areas of the EEL, IEL, plaque, or stent [22]. There was a significant linear correlation ($p<0.0001$, $R^2=0.54$) between increased neointimal growth and increased stent size relative to the proximal reference coronary artery lumen [22]. Therefore, stent over-sizing relative to the reference lumen appears to be an undesirable goal in deployment.

Responses to Arterial Injury and Neointimal Growth

Placement of intra-arterial stents is always associated with vascular injury ranging from superficial damage to the endothelium and superficial layers of the media to full thickness medial rupture and adventitial stretch. Schwatz et al. showed the important positive correlation between the severity of arterial injury in stented porcine coronary arteries and subsequent neointimal growth [59]. Other experimental studies suggest important relationships among inflammation, vascular injury, and neointimal growth. In stented nonatherosclerotic balloon-injured rabbit iliac arteries, peak monocyte adherence was observed 3 days after stenting with maximal proliferation seen at 7 days [52]. There was a linear correlation (R^2=0.82-0.92) between monocyte adherence and neointima at 14 days [52]. Further, increased vascular injury correlated with increased neointimal growth, inflammation and thrombus formation [51].

The effect of the characteristics of the underlying vessel (morphologically normal media versus absent media due to medial tear) adjacent to the stent strut was addressed in a porcine double arterial injury model [8]. In areas where the arterial media was absent (damaged by balloon angioplasty 4 weeks prior to stent placement), neointimal thickness was greater than at strut sites that were adjacent to an intact internal elastic lamina and media [8]. In stented atherosclerotic human coronary arteries, increased arterial injury was associated with increased stent-associated inflammation [22]. Furthermore, in human coronary arteries containing stents for >30 days, neointimal thickness at stent strut sites was greater when medial damage (medial laceration or rupture) was present (0.69 ± 0.29 mm) compared with struts in contact with plaque (0.33 ± 0.26 mm, $p<0.0001$) or struts in contact with an intact media (0.29 ± 0.23 mm, $p<0.0001$) [22]. Taken together, the data from experimental work showing correlations among arterial injury, inflammation and neointima, and observations from human stents demonstrating increased inflammation and neointimal growth when medial damage is present suggest that a reduction of arterial injury during catheter-based interventions with stents may have a beneficial effect on late neointimal growth. Novel devices that do not require very high balloon inflations to accomplish close apposition of the stent to the arterial wall (*eg*, self-expanding bare stents) are currently in clinical trial [25].

STENT GRAFTS

Offering the potential advantages of endovascular stents and bypass grafts, and deliverable via a percutaneous approach, stent grafts have

been under active investigation for the treatment of cardiovascular disease. Previously, interpositional autologous or synthetic grafts have been the standard surgical approach for the management of peripheral arterial athero-occlusive and aneurysmal disease [1, 3, 54, 70]. However, long-term patency of synthetic grafts <6.0 mm in diameter have been complicated by thrombosis and intimal hyperplasia at the anastomotic sites [57]. The higher rate of graft thrombosis using synthetic material as compared with autologous veins may be secondary to incomplete endothelialization of the graft [57] as endothelialization >1.5 cm from the anastomosis of a synthetic interpositional grafts is rare. Additionally, smooth muscle cell proliferation and migration lead to neointimal hyperplasia secondary to medial injury to the host vessel during the creation of the anastomosis itself [60].

Building on the work on stents by Dotter, Cragg, Balko, and Paroldi pioneered the development of stent grafts for treatment of vascular disease and aneurysms [4, 15, 47]. Currently, intraluminally deployed endovascular stent grafts (tubular designs with or without bifurcated segments) are becoming an alternative for the management of iliofemoral occlusive disease [37-39, 48]. These grafts do not require the creation of a sutured anastomosis and thus do not cause anastomosis-associated vascular injury [72].

In patients and in experimental preparations, autologous veins or synthetic materials such as polyester (Dacron) or expanded polytetrafluoroethylene (ePTFE) have been used as graft material for covered stents [16, 46, 49]. Because it is dilatable, PTFE can be fashioned as a small profile stent graft system, delivered to the arterial treatment site via a percutaneous sheath, and balloon-dilated to the appropriate size [15]. However, because of a 30% elastic recoil, PTFE grafts must be over-dilated [15]. In contrast, Dacron is inelastic and is not dilatable in situ [15]. Therefore, precise sizing of Dacron stent grafts before deployment is necessary for optimal clinical outcome.

In "unsupported" stent grafts, the stents are located at the ends of the graft material and act as tethering points of the stent graft to the arterial wall. "Fully-supported" stent grafts, in which the stent is present for the entire length of the graft, provide greater longitudinal support and radial strength and are less prone to kinking [15]. The stent itself may be on the inside, the outside, or completely enveloped within the graft material. Stent placement inside of the graft allows for enhanced sealing of the interface of the graft material with the surrounding vessels [15]. However, this endoskeleton design provides for an uneven flow surface

and greater turbulence as stent struts protrude into the lumen. Protruding stent struts cause focal areas of low shear, which increase the likelihood of local thrombus deposition. Complete interweaving of the stent within the graft (*ie*, graft material on both sides of the stent) may be advantageous for long-term outcome as poor patency rates have been associated with endoprostheses in which the graft is unsupported and/or loosely attached to the stent [18, 73]. Further, completely enveloping the stent within the body of the ePTFE graft provides a more uniform luminal surface compared with a graft placed outside of the stent.

An advantage of covered stent grafts is prevention of embolization of friable atherosclerotic plaque material during device deployment. The ability for bare stents to penetrate the plaque necrotic core and potentially liberate atheroembolic material (Figure 5) was evident in our study of human coronary stent implants; the lipid core was focally penetrated by stent struts in 26% of arterial sections [22]. Plaque prolapse between stent struts, especially extrusion of the thrombogenic lipid core, are important events that may be effectively prevented via the placement of a stent graft.

Endothelialization

In interposition grafts, healing and endothelialization proceed from the anastomotic ends towards the center of the graft [12]. Endothelialization appears to be superior in endoluminally placed PTFE stent grafts compared to interpositional grafts [41]. The importance of graft proximity to endothelial cells was shown in a study by Bull et al in which interpositional ePTFE grafts implanted in canine carotid arteries showed endothelial cell migration from the native artery extending only 1.0 cm beyond the ends of the device [6]. In contrast, wrapping the external surface of the graft with a vein resulted in complete endothelialization of the ePTFE graft. Endoluminal deployment of a porous stent graft places the device in close proximity to a source of endothelial cells (vessel wall lining and vasa vasorum of the surrounding artery) along the entire length of the device and may be associated with exposure of the graft to physiologically important local concentrations of growth factors, cytokines, or other intercellular messengers, such as nitric oxide, which can diffuse through the porous graft [60]. These diffusable factors may further augment endothelialization in contrast to interposition grafts in which endothelialization proceeds from the ends of the graft only. The optimal pore size for graft endothelialization and healing is 60-90 μm [26].

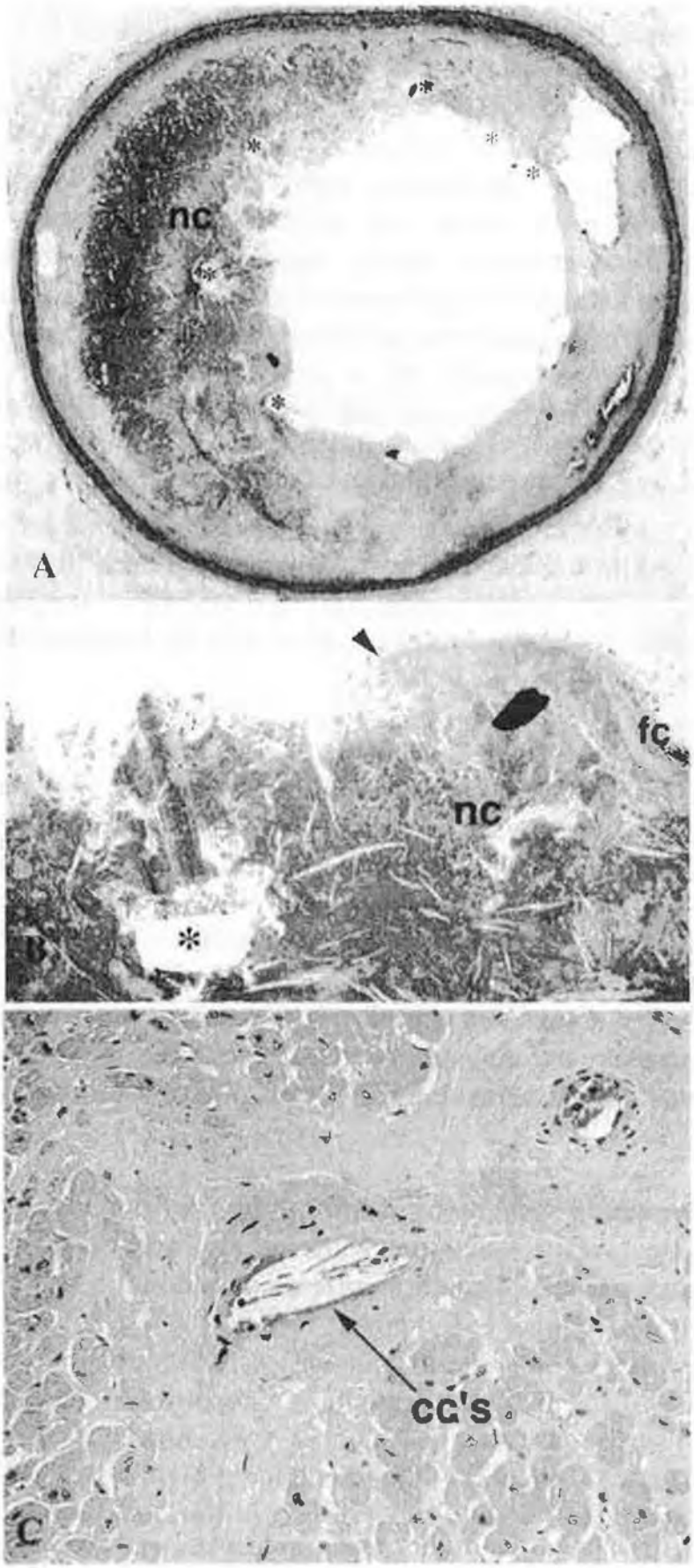

FIGURE 5. (Caption on page 154)

FIGURE 5 Caption (for Figure on page 153)

A 77 year old woman presented with an acute myocardial infarction and was treated with direct balloon angioplasty and stenting of the right coronary artery. Refractory myocardial no-reflow developed resulting in cardiogenic shock and cardiac arrest. In the stented portion of the right coronary artery, there was focal penetration by multiple stent struts into a large hemorrhagic necrotic core (nc, panel A). Several penetrating and non-penetrating stent struts are indicated (*). At higher power (panel B), a penetrating strut (*) is better visualized within the necrotic core (nc) that is rich in cholesterol clefts. The end (arrowhead) of the ruptured fibrous cap (fc) is present. Numerous small intramyocardial coronary arteries were occluded by atheroemboli containing cholesterol clefts (cc's, panel C) that were responsible for the myocardial no-reflow. A potential advantage of stent grafts over bare stents is a reduced frequency of atheroembolism. (Movat pentachrome: A and B; hematoxylin-eosin: C)

Inflammation

Dacron stent graft placement in experimental animals produces acute inflammation and a giant cell reaction associated with the graft and extending into the adjacent vessel wall [34]. Clinically, this inflammatory response has been postulated to correspond to the perivascular thickening observed by magnetic resonance imaging that lasts 4-6 weeks [35] and a "post-implantation" syndrome characterized by fever, leukocytosis, and elevation in serum C-reactive protein [5, 17]. In human endovascular stent graft explants, a foreign body type reaction was seen when the device had an external wrap on the PTFE or if placed within the adventitia [38].

Neointimal formation, endothelialization, and final healing

In interposition grafts, neointimal thickening occurs at the surgical anastomosis as a result of smooth muscle cell migration and proliferation secondary to medial injury in the host artery [11, 13, 23, 40]. Reduced neointimal growth is potential advantage of endoluminally placed grafts; Ombrellaro et al. found that intimal hyperplasia was greater in conventionally placed grafts as compared to endovascular grafts [42]. However, it must be recognized that neointimal growth along the length of a intraluminally placed stent graft will be proportional to the arterial injury associated with deployment. The use of self-expanding stent grafts, rather than balloon-expandable stents, may result in less arterial injury [9]. Marin described histopathologic findings from 7 stent grafts

explanted from humans from 2 weeks to 7 months post-deployment [38]. Organized thrombus within the graft was present at 3 weeks [38]. An endothelium was present in the perianastomotic region at 6 weeks and extended 1-3 cm from the ends of the graft at 3 months [38]. There was little neointimal development within the graft [38]. A subsequent angiographic study demonstrated less neointimal growth in the PTFE-covered portion of a Palmaz stent graft versus the uncovered portion of the device, suggesting that the presence of PTFE may inhibit smooth muscle cell migration into and proliferation within the graft neointima [37].

HEMOBAHN STENT GRAFT

We recently completed an evaluation of the long-term patency and healing characteristics of the HEMOBAHN™ stent graft in normal canine iliac and femoral arteries [71]. This device consists of a nitinol stent lined with an ultrathin ePTFE material. The thickness of the ePTFE used in this device (100-μm) is approximately five times thinner than the standard commercially available ePTFE used in surgically placed vascular grafts. The internodal distance (between two solid nodes of PTFE) is 30 μm, and a nonporous FEP/ePTFE laminate (1.0 mm width) bonds the graft to the stent along its entire length with 1.0 mm gaps so that half of the graft surface area remains porous. Further, unlike other endoprostheses in which the graft is sutured only to the ends of the stent [18], the ePTFE in this device is completely interweaved with the stent providing longitudinal support.

In this study, these stent grafts were placed with fluoroscopic and intravascular ultrasound guidance in canine iliofemoral arteries, and stent grafts were analyzed at two weeks, one month, three months, six months, and twelve months post-deployment. All stent graft implants were successfully deployed in the desired locations without foreshortening. All devices were widely patent at all time points. Two weeks after implantation, there was fibrin deposition covering 70-80% of the luminal surface and an inflammatory infiltrate near the graft material and the surrounding nitinol wires (Figure 6). At one month, there was increased fibrin deposition between the endoprostheses and the native artery, the inflammatory infiltrate was minimal, and no giant cell reaction was evident. Neointimal thickness in the mid-region of the device was less at 1 month (0.42 ± 0.02 mm) than at 2 weeks (0.65 ± 0.07 mm), most likely secondary to organization of mural thrombus. Three months after deployment, there was nearly complete healing of the space between the

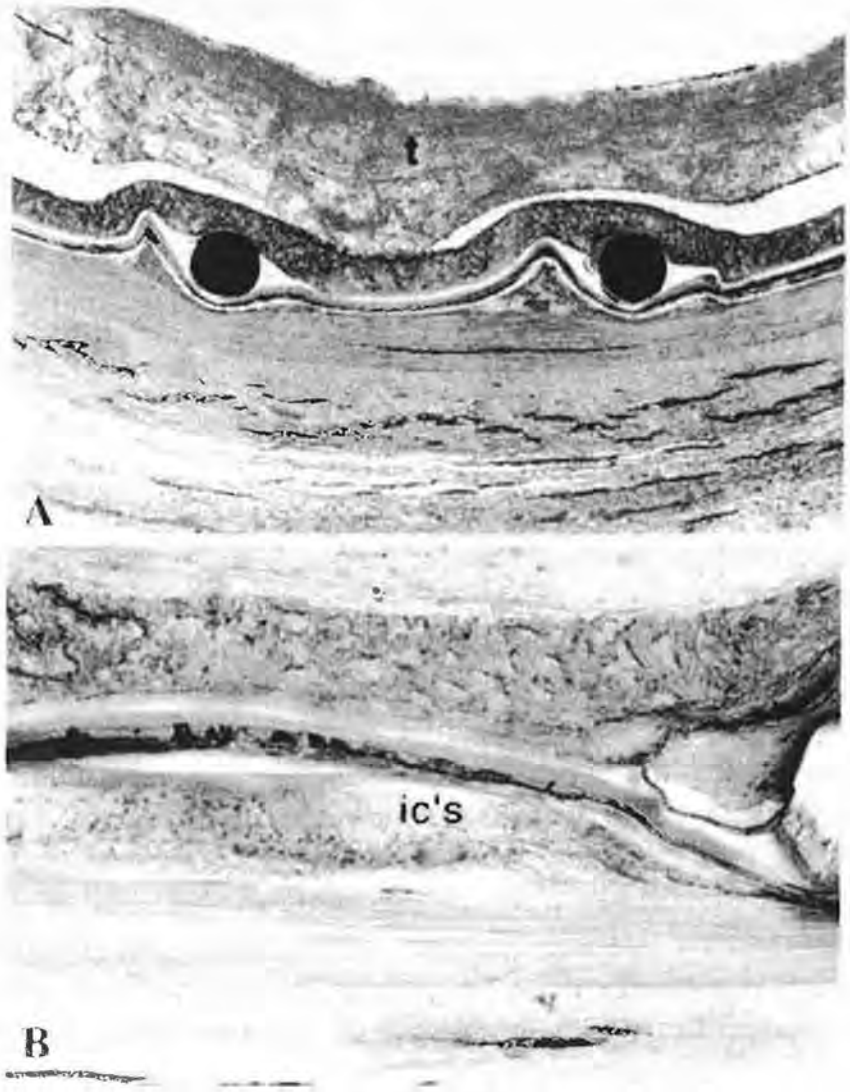

FIGURE 6

Hemobahn ePTFE-nitinol stent graft placed in canine iliofemoral arteries and evaluated 2 weeks post-deployment. The stent wires are enveloped with the ePTFE layers. A thin layer of thrombus (t) is seen (panel A) on the luminal surface of the stent graft. Between the stent graft and the media of the native artery, a thin layer of inflammatory cells (ic's) is present (panel B). (Hematoxylin-eosin stain)

ePTFE and the media with smooth muscle cells in a proteoglycan matrix. At three and six months after implantation, neointimal giant cells, thrombi, and calcification were observed in a few cases. At one year, macrophages were rare, and there were no giant cells. Neointimal growth (Figure 7) was observed in all grafts with a mean thickness of only 0.42 ± 0.03 mm at 12 months, determined by histomorphometry, resulting in only a 6% reduction in luminal area (measured by intravascular

ultrasound). There was minimal neointimal hyperplasia at the interface of the endoprosthesis and native arterial wall. Arterial injury, a determinant of late neointimal growth, was mild with this device; there was focal medial compression but no medial laceration or rupture. The self-expanding property of the nitinol stent used, in contrast to balloon-expanded stent grafts, may be an important feature in limiting damage to the underlying artery. Overall, the pattern of pathological responses--early mural thrombus associated with inflammation followed by neointimal growth--is similar to that observed in bare stenting in human atherosclerotic arteries.

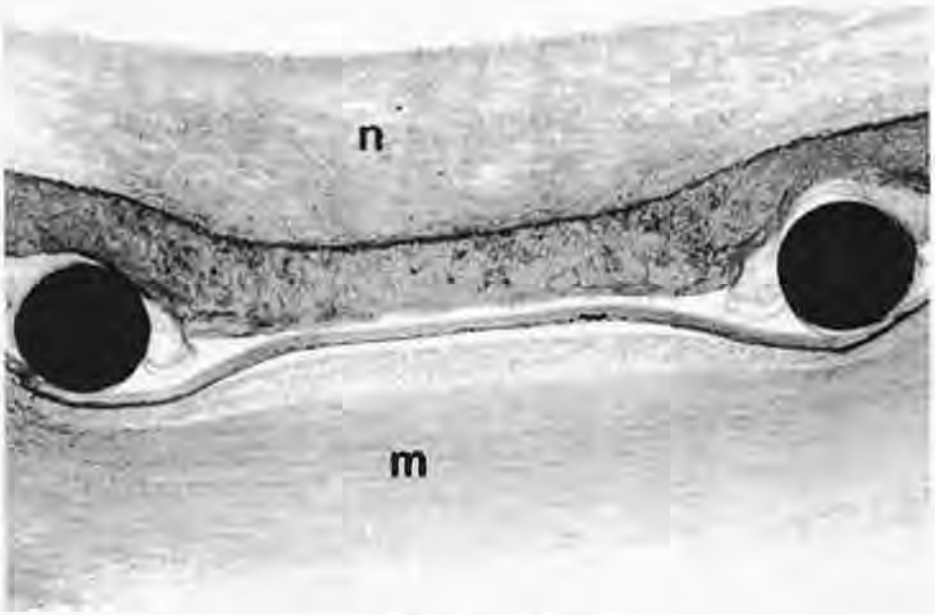

FIGURE 7

Hemobahn stent graft placed in canine iliofemoral arteries and evaluated 6 months post-deployment. The neointima (n) is fully organized consisting mostly of SMCs in a proteoglycan and collagen-rich matrix. A thin layer of neointima is also present between the outer layer of the graft and the media (m). (Hematoxylin-eosin stain)

Endothelialization was assessed by scanning electron microscopy. At 3 months, 75% of the surface of the graft was covered by endothelial cells, and at 6 and 12 months, there was 90-99% coverage (Figure 8). Endothelial cells were predominately spindle shaped and oriented in the direction of flow. There were no adherent platelets or inflammatory cells on the endothelial surface, suggestive of a functional endothelial lining. In previous studies, approximately two and a half times thicker ePTFE lined

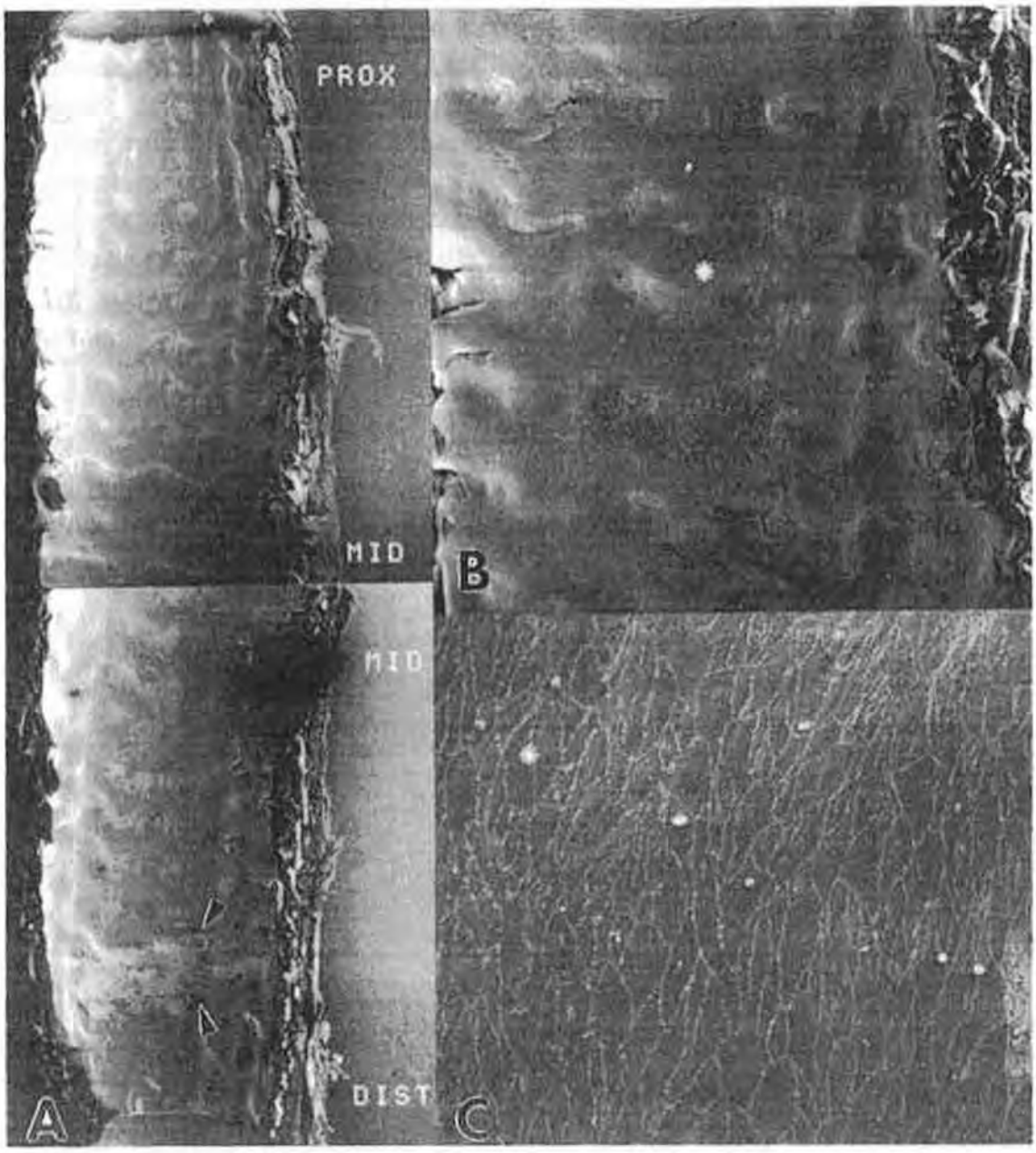

FIGURE 8

Scanning electron micrographs of an ePTFE-nitinol endoprosthesis explanted at 6 months; the device is opened longitudinally exposing the luminal surface (panels A-C). The device is 90% endothelialized (panel A). The distal end of the stent graft (bottom of panel A) shows a focal area of non-endothelialization (arrowheads). At high magnification in the mid-portion of the graft (panel B), there is near complete endothelialization. At higher magnification (panel C), longitudinally oriented endothelial cells with tight intercellular junctions are evident.

stent grafts were associated with incomplete endothelialization in the canine abdominal aortic aneurysm mode [44]. There was endothelialization only at the end stent grafts using approximately five times thicker ePTFE [42].

The ultrathin ePTFE used in this device may have augmented endothelialization via enhanced trans-graft cell migration. In an experiment designed to support the occurrence of trans-graft cell migration, four HEMOBAHN devices were wrapped with a nonporous material, poly (tetrafluoroethylene-co-hexafluoropropylene) [FEP], and implanted in canine iliofemoral arteries. FEP prevents endothelial migration to the luminal surface. In stent-grafts completely enveloped by FEP, only the proximal and distal ends of the device were endothelialized while non-occlusive mural thrombi were noted in the non-endothelialized mid-region of the endoprosthesis. In contrast, there was nearly complete endothelialization of devices wrapped with FEP only at the proximal and distal ends.

CONCLUSION

Vascular morphology after stenting in human atherosclerotic arteries demonstrates the following sequence: thrombus formation and acute inflammation early after deployment with subsequent neointimal growth. Increased inflammation early after stenting is associated with medial injury, and medial damage and oversizing relative to the proximal reference lumen correlate with increased neointimal thickening. Stent grafts are novel devices designed to treat athero-occlusive and aneurysmal diseases via a percutaneous approach. A reduced incidence of plaque embolization is likely with the use of a covered stent compared to a bare stent via avoidance of uncovered stent strut penetration into the necrotic core of atherosclerotic plaques. One may expect to encounter similar vascular responses to endoluminal stent grafts (thrombus, inflammation, and neointimal growth) as seen with bare stenting, and it is unknown whether the presence of graft material will provide a further stimulus for inflammation in an atherosclerotic substrate. The self-expanding HEMOBAHN stent graft, associated with nearly complete endothelialization, excellent luminal patency, and minimal neointimal growth, is a promising device for further study.

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Part IV

ANIMAL MODELING

Chapter 11

FROM CONCEPT TO OPERATING ROOM: ROLE OF THE FDA IN THE DEVELOPMENT OF STENT GRAFTS

John W Karanian, PhD

The Investigational Device Exemptions (IDE) regulation covers the clinical investigation of a medical device for the purpose of determining the safety and effectiveness of the device. The IDE regulation encourages the discovery and development of useful devices intended for human use. Optimum freedom of scientific investigators is maintained to the extent consistent with the protection of public health and safety and with ethical standards. The FDA encourages early interaction through the pre-IDE process during the development of a device or technology and during the preparation of an IDE application. This facilitates approval of the IDE application and progression into the clinical investigation.

The commercial distribution of medical devices is regulated by the Food and Drug Administration (FDA) under the authority of the Food, Drug and Cosmetic (FD & C) Act [4]. For example, manufacturers in the US commercially distributing or marketing medical devices must register their establishments with the FDA, list their devices, manufacturer their devices under an FDA mandated quality assurance

Keywords: *Investigational device exemption, medical device regulation, pre-clinical trial, clinical trial, regulation, stent graft, device evaluation*

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system, properly label their devices, obtain FDA clearance to market their devices, etc, in order to meet the regulatory requirements in the FD & C Act [2]. The presentation of adequate pre-clinical and, as appropriate, clinical data, provide safety and effectiveness information in support of marketing clearance for a device. During this evaluation process, the FDA performs its job which is to both protect and promote public health. The agency works to assure that patients and health care providers receive the benefit of high quality medical products and information on how to use them. This can be best accomplished through a cooperative effort with the regulated industry, investigators and health professionals. This paper reviews the pre-IDE process and the development of an IDE application for a significant risk study of a cardiovascular device such as a stent-graft. The facilitory role of the FDA in the regulation of clinical trials for medical devices will be discussed, and more specifically, the type of information required for pre-clinical stent-graft studies will be presented. The terminology and applicability of the IDE regulation and the type of study requiring an IDE application to the FDA are discussed.

The need for protection of public health became apparent when in 1937 an elixir was marketed which caused 107 deaths, mostly in children. This lead to the passage of the 1938 Food Drug and Cosmetic Act. Under this Act, the FDA had the authority to regulate quack devices or marketed devices which had problems. It was further determined that pre-market clearance requirements were needed after the widespread use of some dangerous devices, such as some intrauterine contraceptive devices, resulted in numerous serious injuries and deaths. Congress gave this authority to the Agency in 1976. Additional laws were passed in the 90's that provided greater enforcement authorities and tracking regulations, again in response to the public's perception that their interests were not adequately protected. The FDA therefore promotes and protects public health by keeping bad devices off the market, facilitating the introduction of good devices on the market, and monitoring marketed devices to make sure that they continue to be "good." In addition, there is a continuous effort to empower health care providers and patients with accurate information on devices.

Conducting a clinical investigation of a medical device requires approval under the IDE regulation prior to beginning the study, unless the study is one which is exempted from the regulation [1]. An "investigation" is a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. A clinical study is exempted from the IDE regulation if the device is used

or investigated in accordance with the indication in the approved labeling. For example, a comparative study of two endovascular stents for implantation in the common iliac artery for the treatment of stenosis due to atherosclerotic disease, where both devices are approved for that indication, would not require submission of an IDE application. The local institutional review board (IRB) may require approval of the study, at its own discretion. In contrast, if a study is designed to compare two stents for creation of an intrahepatic portosystemic shunt for prophylaxis of variceal bleeding and one stent is approved for that indication while the other is not, then an IDE application would be required. Both FDA and IRB approval would be required before the initiation of the study.

The degree of risk involved in the study determines the level of regulatory control required. A nonsignificant risk study may be approved by the IRB [3]. A significant risk study, one which presents a potential for serious risk to the health, safety or welfare of a study subject, requires explicit approval of an IDE application by the FDA and may not be conducted without the approval of both the IRB and the FDA [5]. In either case, the IDE regulation provides for the procedures for the conduct of clinical investigations of devices, including informed consent for all patients, adequate patient and data monitoring and maintenance of necessary records and reports. The investigations must meet the regulatory requirements regarding ethical conduct of human studies, requirements which adhere to the ethical guidelines of the World Medical Association Declaration of Helsinki on the protection of human subjects in biomedical research.

REGULATION OF CLINICAL TRIAL

In order to illuminate how to interact with the FDA it is important to understand some of the basic definitions and rules of device regulation in the United States. For example, understanding the difference between practice of medicine and clinical investigation is foremost in accepting the FDA's involvement in controlling the use of innovative devices such as endovascular grafts and stents. Historically, the FDA has purposefully avoided regulating the practice of medicine and has taken the position that physicians must have the latitude to do whatever is in the best interest of their patients. Use of a device as part of the "practice of medicine" does not require clearance through the FDA, and may not require review by an IRB, depending on the individual IRB's requirements. The investigational use of a device, even if it is legally marketed, is not the practice of medicine. "Investigational use" implies that the device is being used within a study protocol to collect

information about its safety and/or effectiveness. If the use of a device is determined to be investigational, a distinction is then made between a significant risk study and a nonsignificant risk study. This decision determines the level of regulatory control the study will be subject to. If the study is determined to be a nonsignificant risk study, approval of the study is given by the IRB without involvement of the FDA. If the study is a significant risk study, both the IRB and FDA must approve the study prior to its initiation. If a study involving the use of a device is determined to be a significant risk study, an Investigational Device Exemptions (IDE) application must be submitted to the Office of Device Evaluation in the FDA. What an approved IDE does is let investigators use uncleared devices in clinical studies of the safety and effectiveness of the devices. It exempts devices from marketing clearance and other regulatory requirements for the purpose of conducting such studies. An IDE may be submitted by the manufacturer of a device or by a responsible investigator who wishes to conduct a clinical investigation. The IDE may initially be submitted for a feasibility study, with expansion to larger, controlled studies as additional information becomes available [2].

The following briefly summarizes the proposed format for the content of the device description and report of prior investigations (I-III below) for an IDE submission. The Device Description should include a physical description of the device, intended use, the indicated use, its primary and secondary functions and the potential life of the device. The Report of Prior Investigations should include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation.

The Report of Prior Investigations should include:

I. Introduction (general summary; identification of potential safety and effectiveness issues through an analysis of potential failure modes; identification of design function and specifications; description of the design and design review process; and identification of tests that will demonstrate that the design requirements are met);
II. Test Reports (summary of methodology; detailed description (the test method or protocol; number of samples and observation per sample; test results; calculated statistical significance; acceptance criteria; and explanation of the clinical significance of the results);
III. Methodologies (pre-clinical *in vitro*, pre-clinical *in vivo* and clinical). The following general guidance on the level of clinical information expected may be applicable to the Report of Prior Investigations, and should also be utilized in the Investigational Plan for the proposed

clinical study: state purpose of study; identify endpoints; state study hypothesis; identify and justify devices to be evaluated; identify and justify study population; identify and justify assessment intervals; identify and justify assessment parameters and methods for assessment for each interval; describe procedure for managing potential variables; specify and justify number of each type of device to be evaluated; identify data to be collected; provide draft case report and informed consent forms; provide risk/benefit analysis; provide explant retrieval and analysis protocol; and discuss training program for investigators.

A similar level of information would be expected for the pre-clinical *in vitro* and *in vivo* sections, that is, adequate information to not only describe what was done, but also why. The communication of all data and experience in a concise and expedient manner is needed in order to optimize the review process. This can best be achieved by designing studies that support the intended use of the device and address the potential safety and effectiveness issues.

FACILITATING PROGRESSION TO CLINICAL TRIAL

Accurate anticipation of what the FDA expects may be problematic. Waiting to find out the answer may be both frustrating and costly. In recognition of these issues, we have implemented several initiatives in order to improve predictability and timeliness with regard to medical device reviews and approvals such as improving communication; accepting preliminary Investigational Device Exemptions (pre-IDE) applications; and encouraging feasibility studies.

Pre-clinical development and early clinical evaluation of new devices provide the database necessary for agency evaluation of clinical investigations to support marketing clearance for a device. The intent of the Pre-IDE document is to encourage a cooperative process which will facilitate progression into clinical studies. Pre-IDEs enable the sponsor of a study to submit protocols and preliminary data to the agency for informal review and comment via teleconferences, meetings and/or written correspondence. These documents are intended to be used to identify issues proactively and serve as a mode of communication between the agency and a sponsor before an official IDE is submitted and can be used to develop the Report of Prior Investigations sections for the official IDE. One should provide adequate device information in the form described in the Report of Prior Investigations as defined above, and should include: i) a rationale/justification for developmental strategy

based on anticipated safety and effectiveness issues, ii) basic descriptive information, iii) identification of safety and effectiveness issues (potential failure modes), iv) testing strategy and v) test methodology.

Once the appropriate test methodologies have been identified, it is necessary to develop the test methodologies, again based upon the intended use of the device and the anticipated safety and effectiveness issues. The justifications requested below should be based on statistical and/or clinical rationale with literature support when appropriate. The following is an example of the type of information required for pre-clinical and clinical studies:

A) Pre-Clinical *In Vitro*

1. state purpose of the test (*ie*, which S & E (Safety and Effectiveness) issue[s] is the test intended to address).
2. identify relevant parameters and variables
3. state study hypothesis (*ie*, specific objectives)
4. identify and justify devices to be tested (*eg*, controls, prototypes)
5. describe test apparatus, including accuracy, precision, and calibration information
6. describe test system (*eg*, pictures, block diagram, etc.)
7. explain how test system takes into account potential clinical conditions (*eg*, extreme operating conditions)
8. describe procedures for managing potential variables
9. specify and justify number of each type of device to be tested
10. specify and justify number of tests to be performed for each device
11. identify data to be collected, including frequency and documentation, for each parameter and variable

B) Pre-Clinical *In vivo*

1. state purpose of the study (*ie*, which S & E issue[s] are to be addressed)
2. identify endpoints (*ie*, safety, effectiveness, clinical utility), state study hypothesis (*ie*, specific objectives)
3. identify and justify devices to be evaluated (*eg*, controls, prototypes)
4. identify and justify animal model, including intended implant site, if appropriate
5. explain how appropriate animal care and welfare will be assured (*eg*, compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and/or the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences, approval of the Institutional Animal Care and Use Committee [IACUC])

6. identify and justify assessment intervals (*eg*, pre-procedure, procedure, follow-up intervals)
7. identify and justify assessment parameters and method of assessment for each interval
8. describe procedural methodology
9. explain how methodology takes into account potential clinical conditions (*eg*, extreme operation conditions)
10. describe procedures for managing potential variables, including bias reduction measures (*eg*, definitions [*eg*, success, failure, complications], management of protocols, data normalization, core review laboratories)
11. specify and justify number of each type of device to be evaluated, number of animals to be tested
12. identify data to be collected, including frequency and documentation, for each parameter and variable at each assessment interval
13. provide autopsy and explant retrieval and analysis protocol (*eg*, instructions for photographs,
14. storage, shipping gross observations, microscopic observations)

C) Clinical

1. state purpose of the study (*ie*, which S & E issue[s] are to be addressed)
2. identify endpoints (*ie*, safety, effectiveness, clinical utility, labeling claims)
3. state study hypothesis (*ie*, specific objectives)
4. identify and justify devices to be evaluated (*eg*, controls, prototypes)
5. identify and justify study population (*ie*, entrance criteria)
6. identify and justify assessment intervals (*eg*, pre-procedure, procedure, follow-up intervals)
7. identify and justify assessment parameters and methods of assessment for each interval
8. describe procedural methodology
9. identify and justify trial design (*eg*, randomized)
10. describe procedures for managing potential variables, including bias reduction easures (*eg*, definitions: success, failure, complications), data normalization, core review laboratories, randomization protocol)
11. specify and justify number of each type of device to be evaluated
12. identify data to be collected, including frequency and documentation, for each parameter and variable at each assessment interval
13. provide draft case report forms, including informed consent form
14. provide risk/benefit analysis

15. provide autopsy and explant retrieval and analysis protocol 16, discuss training program for investigators

As implemented by the office the pre-IDE allows for informal discussion, education, review and comment, as an alternative to the time-consuming, question-and-answer exchange of the IDE process. These efforts have resulted in open cooperation and communication with manufacturers, researchers, and the medical community during the early phase of development (and throughout the various R&D stages) of revolutionary technology. This is being accomplished through the use of interdisciplinary review teams, pre-IDE interactions, and unprecedented communication with device manufacturers and users. Implementation of this initiative has resulted in an improvement in the quality of IDE submissions and an increase in the first review cycle approval rate for IDEs [3].

SUMMARY AND CONCLUSION

The agency is continuously striving to streamline the review process and expedite the study of new medical devices which are important to the continued improvement of healthcare. An open environment is being encouraged between manufacturers, professionals, and the FDA. Since the FDA reviews data on a steep learning curve, the communication of all data and experience in a concise and expedient manner is needed to optimize the review process. It is important to interact with the agency early in the research and development process to assure that pre-clinical and clinical studies are designed to support the intended use of the device and to address the potential safety and effectiveness issues. Throughout the interactive process the agency will encourage the practice of evidence-based science. These initiatives allow for better and more efficient protection and promotion of public health.

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Chapter 12

A CRITICAL OVERVIEW OF ANIMAL MODELS FOR STENT-GRAFT RESEARCH

Michael J Hallisey, MD, Kenneth Wright, PhD

With the introduction of many new and unique endovascular stent-graft systems, there is a rapidly increasing need to validate the effectiveness of these devices prior to widespread clinical applications. Testing of these devices in bench or animal models will help to ensure patient safety and understand the potential benefits in human subjects; testing will also provide a better understanding of the strengths and weaknesses of individual devices. Standardization of these models may also allow a direct comparison of individual devices.

Although stent-grafts are made of many different materials, the goal of this therapy is rather singular: to provide a less invasive alternative to standard surgical therapies. The stent-graft device is delivered from an endovascular approach and should at least provide equal therapeutic benefit to the patient as the open surgical implantation for its counterpart applications. There are three main areas of application for these stent-grafts: 1. Exclusion of aneurysmal disease, 2. Bypass of atherosclerotic stenoses or occlusions, 3. Repair of injured or penetrated

Keywords: *Abdominal aortic aneurysm, endovascular therapy, angioplasty, stent, stent-graft, animal model*

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blood vessels. While there have been anecdotal reports of customized or home made stent-grafts for the latter two applications, the primary focus of stent-grafts to date has been for aneurysmal disease, particularly abdominal aortic aneurysms (AAA).

The ideal model for testing stent-grafts for AAA would have characteristics as similar to humans as possible. An exact model is not currently available in bench or animal form. However, if the goals of testing the stent-graft in an appropriately comparable model are met, then one can be satisfied that animal modeling for stent-graft testing has great potential.

GOALS OF ANIMAL AAA MODELS

The goals of AAA animal models are:

1. To mimic the size of human aortic and iliac vessels.
2. To mimic the elastin degradation seen in the media of the aorta containing an AAA.
3. To test the collateral lumbar or mesenteric vessels associated with the AAA sac.
4. To test the healing of the endothelium in the presence of a stent-graft.
5. To test the delivery of the new stent-graft device.
6. To mimic the human response to the stent-graft device (thrombogenicity, coagulation and fibrinolysis).

To achieve these goals, there are two factors that come into play: the choice of experimental animal species, and the type of experimental AAA created.

EXPERIMENTAL ANIMAL SPECIES

Many factors go into the choice of an appropriate animal species for testing. Although the most important factor may be a characteristic as close as possible to humans, no one animal can achieve all the necessary characteristics. For example, significant differences in the coagulation and fibrinolytic systems of an animal species and humans may bias the results of stent-graft placement. There are significant differences in cost, availability, ease of handling, and vessel size from species to species. Suffice it to say, there are four main species available for testing of stent-grafts: bovine, ovine, canine and porcine.

The canine species provides an easy to handle animal that is durable and has good vascular access sites. While the human aorta can average 24 mm in diameter, the canine aorta, however, can be on the smaller side, at approximately 9 mm diameter. Although a larger diameter canine aorta of approximately 12 mm can frequently be found in the greyhound species, some states with legalized dog racing have banned the use of greyhounds for animal research. An animal of 7 – 9 years of age and approximately 70 – 90 pounds is preferable because the aortic wall is thicker and more muscular. The canine is quite tolerant of prolonged anesthesia and is easy to penetrate with standard fluoroscopy. Another advantage is that in 1993, the Ad Hoc Committee of the Joint Councils of the Society for Vascular Surgery and International Society for Cardiovascular Surgery, North American Chapter recommended that the canine be used for pre-clinical testing of arterial grafts and prostheses [1]. The canine has two distinct characteristics that make it a good comparable model for AAA prostheses: 1. A lack of significant spontaneous endothelialization or prosthetic surfaces, which is similar to humans, and 2. A variable and relatively unpredictable tendency toward hypercoagulability, which provides an important test of device thrombogenicity. The canine also has an active fibrinolytic system. The disadvantage of this type of animal is that it can be expensive to purchase.

The swine species is relatively inexpensive and has an 8 – 9 mm aorta. The vascular morphology of the aortic wall is similar to humans, and the animals are relatively easy to handle. The swine is also difficult to paralyze which can be helpful if the collateral vessels on the aorta are covered by the prosthesis. However, the swine grow too fast for many prosthetic tests. A 6-month-old swine can be 90 pounds, but a 12-month-old swine can reach 250 pounds. Thus, long-term follow-up testing in the swine can be quite challenging. The aortic wall in the 90-pound swine can also be quite thin—this swine is of a young age and of relative inactivity compared to the canine. Other problems with swine are that they do not tolerate prolonged anesthesia, and the vascular access sites can be small relative to the aorta.

The ovine species possesses a larger aortic diameter in the 12 – 13 mm range. Aortic diameters as large as 16 mm can be found as well. This diameter can tolerate devices closer in size needed to treat humans. The ovine has good vascular access sites and is relatively tolerant of anesthesia. However, the ovine can be expensive to purchase as well as handle. The ovine possesses the zoonosis Q Fever, which is transmissible to humans, and requires preventive measures to avoid

infection. The ovine has an unpredictable fibrinolytic and coagulation system. Heparinization of the animal must be watched very closely with frequent evaluation of Activated Clotted Times (ACT).

The bovine species does provide vessel diameters as large as 18 mm and large enough to support stent-graft prostheses similar in size to humans. The clotting and fibrinolytic systems of the bovine are most likely closer to the human than the canine, ovine or swine [2]. However, the sizes of the animals make them difficult to handle and difficult to penetrate with fluoroscopy. The bovine can also be expensive to purchase and maintain.

AORTIC ANEURYSM MODELS

There have been many different models used for the testing of stent-graft prostheses; however, few of these models have been validated as viable models in isolated studies. Many of the models were introduced in collaboration with stent-graft testing.

Surgically-Created AAA Models

There are a few stent-graft reports using an acutely rupturing or dissecting aortic aneurysm. The most common method is the Blanton technique [3]; this involves surgical exposure of the aorta, cross clamping and a 120 degree transverse aortotomy incision. Dissecting a free edge and then suturing it back onto a proximal edge creates an intramural pocket. Williams, et al [4] described the use of a dissecting thoracic aortic aneurysm by intravascular perforation of the aortic wall followed by balloon dilatation. Unfortunately, this technique predisposes the animal model to considerable blood loss over a short period of time, and transfusions are necessary to avoid exsanguination.

The anterior patch model of AAA is one of the most commonly utilized techniques for AAA creation. The aorta is isolated under surgical exposure and cross-clamped below the renal arteries and above the iliac bifurcation. A longitudinal aortotomy is performed, and an elliptical patch is then sutured onto the aortotomy site. This creates a saccular type AAA. Many different materials have been utilized to produce an anterior patch AAA. These include Dacron [5, 6], rectus fascia without [6, 7] and with [8] peritoneum, jejunum [9, 10] and iliac vein [11].

Some of the anterior patch materials promote thrombus within the AAA sac, which closely mimics human AAAs. The anuerysms formed by jejunal patch have shown thrombus prior to stent-graft placement, but

none have been entirely thrombosed. However, no mural thrombus has been shown within the facial or iliac vein models. There is occasional thrombus in the Dacron patch models. The jejunal and fascial patch models have shown progressive enlargement leading to rupture. This can be an advantage in these models because it closely mimics human AAAs.

Collateral lumbar vessels within a human AAA are an important factor in sac blood pressure and potential endoleak after stent-graft placement. These collateral vessels remain patent within the aorta following patch placement and may be helpful in the evaluation of stent-grafts. For example, it has been shown that 80% of the lumbar arteries covered by the endograft are thrombosed 20 to 60 days following stent-graft placement. However, when the anterior patch model is created, the lumbar arteries are removed within the patched portion of the AAA sac. The patent collateral arteries are on the opposite wall of the AAA sac. Therefore, if this model is used for stent-graft placement, the collaterals are flush against the stent-graft and not within the AAA sac. Utilizing this model for stent-graft evaluation may give a false sense of exclusion of these collaterals.

The mural stripping model of AAA was described by Economou, et al [12]. This technique is used to create a saccular AAA in canines by surgically exposing the abdominal aorta and stripping the adventitia and 60 – 70 % of the media off the aortic wall. This was a technically difficult, time intensive and less predictable AAA because creation required gauging the depth of stripping. The aneurysm is more of a bulge, and the AAA does not enlarge.

The interposition AAA model involves replacement of the abdominal aorta with an interposition graft material [14]. The graft material can be pre-dilated into the shape of a fusiform AAA. This model can be created in just about any animal species, and the size of the artificial graft can be used to match the animal size. Several interposition materials have been used, including Dacron [14 – 18] Polyurethane [16] and bovine internal jugular vein [19].

This interposition model represents another open surgical technique within the chosen animal species. The aorta is again isolated and cross-clamped below the renal arteries. The infrarenal aorta is excised and replaced in an end-to-end fashion with the chosen graft material. These aneurysms have a high patency rate and some of the aneurysms may decrease in size, possibly due to surrounding or contracting fibrosis.

A very large AAA can be created in the animal model with this technique. In fact, aneurysms as large as those seen in humans have been created. This AAA model can be excellent for testing stent-graft delivery systems and deployment; however, it is not helpful for the study of the biologic response to the stent-graft or healing at the anastomotic surfaces.

A modification of this technique is the Faries pressure AAA model [20]. Surgically-replacing the aorta with a balloon-dilated graft of PTFE creates a fusiform AAA. A silicon strain-gauge pressure transducer is then secured within the aneurysm wall for continuous monitoring of the intra-arterial blood pressure.

Martin [21] and Boudghene [22] described the use of elastase to degrade the aortic wall and create an AAA. The goal of this technique is to create an AAA that has a similar morphology to human AAAs. This technique also involves open surgical techniques with exposure of the abdominal aorta. The lumbar arteries are ligated except for one, which is utilized for an infusion of elastase. Aneurysm development has been found to be dose-dependent. The aortic diameter can be as great as 2x the normal size with a decrease in aortic wall thickness by 50%. The histologic appearance of the AAA is similar to humans with degradation and degeneration of the medial layer of the arterial wall. Unfortunately, the technique is time-consuming, dose-dependent and involves ligation of the critical lumbar arteries.

Transluminally-Created AAA Models

Hallisey [23] described the first transluminal AAA model for the study of endovascular stent-grafts. This model does not require an open surgical exposure of the aorta. Only a unilateral femoral arteriotomy is required. A Palmaz™ stent (Cordis Endovascular, Johnson and Johnson, Warren, N.J.) is placed onto a balloon and introduced over a wire into the abdominal aorta using fluoroscopic guidance. The balloon is chosen to match a size twice the size of the animal species aorta. The stent is then inflated and over-dilated into the aortic wall. The technique preserves the lumbar arteries and collateral vessels. The AAA requires very little time to create, and as many as 3 can be placed per day. The aneurysm has also shown some degeneration of the elastin with the media of the aorta and has been shown to be stable in size at 30 days. This model leaves a normal section of aorta above and below the AAA, which can be utilized to evaluate stent-graft healing response.

RECOMMENDATIONS

In the testing of prostheses for the treatment of AAAs, the canine is the ideal species for the evaluation of graft healing, fibrinolysis, coagulation, cost and ease of handling. The best AAA model for the evaluation of a endovascular stent-graft would be a transluminally-created AAA utilizing a Palmaz™ stent in the canine species because of the predictable AAA size, the less-invasive technique and the preservation of collaterals. This model would also provide the necessary pre-clinical information for endograft development. However, the canine species does not provide large diameter aortas so that comparable-size delivery systems can be utilized. Therefore, additional short-term testing is also suggested utilizing larger ovine or bovine species in order to demonstrate graft deployment technique and to evaluate a human-size delivery system.

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Chapter 13

STENTS AND STENT GRAFT MODELING IN THE CANINE

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The development of stent graft technology has been achieved through a combination of efforts. Industrial experts have focused on areas such as metallurgic and fatigue testing of devices. Clinicians have focused on the applicability of such devices in their patients and participated in safety and efficacy trials. Investigations by basic scientists have focused on stent graft/arterial interactions and their biologic responses. Prior to the use of any new device or drug in humans, animal modeling is often used to test their safety and efficacy.

Early feasibility studies of endovascular stent graft technology used large animals with compatible size arteries, such as the cows or sheep [1, 15]. Hypercholesterol models such as the rabbit have been used to study arterial response to stents [43]. Porcine models have been used extensively, especially to model coronary restenosis. [16, 20, 39, 41].

Keywords: *Animal modeling, stents, stent-grafts, arterial*

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Primate models have been used to study the arterial healing after interposition grafting [7-9, 14]. Our group has chosen to use the canine model to study the histopathology of the arterial response to stents and stent grafts because of its similarities in biological healing to humans [37].

INTERPOSITION GRAFTING INVESTIGATION IN THE CANINE MODEL

Historically canines have played a significant role in medical research, especially in the areas of physiology, toxicology, immunology and vascular biology. Currently, over 180,000 canines are used for research in the US each year. Due to the sensitive nature of using companion animals in research, animal care committees have generally required a lengthy review process to justify their use. Canines possess an anatomy, physiology and disease response similar to man. Like many mammalian species, the canine has an aortic trifurcation; right common iliac, left common iliac and sciatic arteries. Their aorta measures roughly 10 mm in size with common iliacs of 5-8 mm depending on the weight of the animal. Histologically, the canine arterial wall is very similar to humans. It consists of 3 layers the tunica adventitia, tunica media and tunica intima. The size of canine arteries allows for use of human sized catheters and endovascular devices and potentially permits transfer of this technology directly to human trials.

Canines have a biologic response similar to humans when undergoing prosthetic arterial graft implantation. Sauvage, et al have reported a wide range of experience with several animal models of interposition prosthetic grafting to include canine, porcine, bovine, and simian [37]. In their review of over 1084 grafts implanted in humans and these four (4) species, they have found canines to be most similar to humans in biologic response to prosthetic grafting. Specifically, they have found both canines and humans show resistance to the development of pannus ingrowth from the anastomosis. They report man to have the slowest transinterstices ingrowth followed closely by canines. Porcine, bovine and simian models tend to show very rapid healing in contrast.

A review of the literature regarding the use of canines in vascular research shows that it is still used widely [2-4, 6, 10-12, 17-19, 21, 23, 26, 29-35, 38, 40, 42, 45, 46]. Critics, however, have pointed out that the

healing response in canines, although similar to humans, differs in several regards. Canine models of intravascular stenting tend to show more rapid endothelialization between 1-2 weeks [16]. Interposition vein grafts studied after a period of implantation show altered physiologic responses. These responses, however, do not seem to correlate with what is observed in human vein grafts and is therefore of questionable relevance [47].

MODELING ENDOVASCULAR AAA REPAIR IN THE CANINE

Probably the earliest report of using the canine to model the use of endovascular technology is by Dotter, who first introduced the concept [12]. In 1969, he experimented with the use of transluminally placed coilspring endarterial tube grafts in dogs. The dog model of endoluminal grafting has also been utilized extensively by Ombrellaro et al [29-34]. Over the past several years, this group from University of Tennessee has been reporting their experience with the use of canines to investigate stent graft technology. Using this model, they have found that placing stented grafts intra-arterially improves graft endothelialization and reduces intimal hyperplasia in the canine model. Furthermore, they have shown this seems to be associated with increased basement membrane deposition and decreased levels of platelet derived growth factor.

Several canine aortic aneurysm models have been reported in the literature. The canines native aorta has been used to test deployment of stent grafts by some investigators. [18, 29-34, 46]. Parodi, Laborde and others have reported their early endograft experience using a fusiform aneurysm Dacron graft interposition model [17, 35]. Other models used to investigate endograft treatment of aortic aneurysms include aortic patch angioplasty using jejunum [23] or Dacron [38, 43], and aortic balloon angioplasty after adventitia and media removal [26].

We investigated the technique of transfemoral aortic aneurysm grafting in 11 acute and 2 semi-chronic [6 week] animal experiments [13]. The endovascular stent graft and its delivery system underwent iterative revision using the data obtained from each successive experiment. Three different aortic confirmations were used to test deployment of these devices: native aorta, aortic patch angioplasty, and interposition of a graft in the shape of a fusiform aneurysm.

Aortic patch angioplasty is a relatively simple procedure to perform. It requires only partial aortic cross clamping and can be performed using expanded polytetrafluoroethylene [ePTFE] or woven polyester patches that are readily available. It does, however, still require general anesthesia to perform and does not make an aorta that is very aneurysmal.

The fusiform aneurysm graft has several advantages. Arteriographically, this model closely resembles the human situation [Figure 1].

The conformation challenges the delivery of the repair device across tortuous vessels. It also allows for evaluation of aneurysm exclusion. Furthermore, it may allow for the assessment of possible distal embolization of mural thrombus during trans aneurysmal catheterization and the fate of intra-aortic graft "pleating." The major problem with this model is that it is more expensive, labor intensive and involves survival animal surgery to prepare the animal model before each experiment. In addition, one can make the aneurysm too tortuous and be unable to cross with the repair device at all.

There are some benefits to simply using the animals, native aorta. This model requires no pre-experiment preparation and is very cost effective. It also allows for better assessment of the fate of lumbar arteries and determination of the interactions between the native aorta and the intraluminal graft in chronic experiments.

The method of graft fixation used in this endovascular grafting device combines the use of radial expansion forces by a polyalloy stent with anti-migration hooks. As has been shown in previous studies, flush seating of the endovascular graft against the aortic wall is imperative. Without total exclusion, the aneurysm may continue to be exposed to systolic arterial pressure and be at risk for rupture. The anchoring system used in this endovascular graft was successful in achieving a secure proximal anastomosis in all but one case.

The need for distal fixation of straight endovascular grafts is recognized. Without distal fixation, perigraft leak and continued perfusion of the aneurysm has been reported to occur [5, 38]. In this study, preliminary testing of the first endovascular graft prototypes

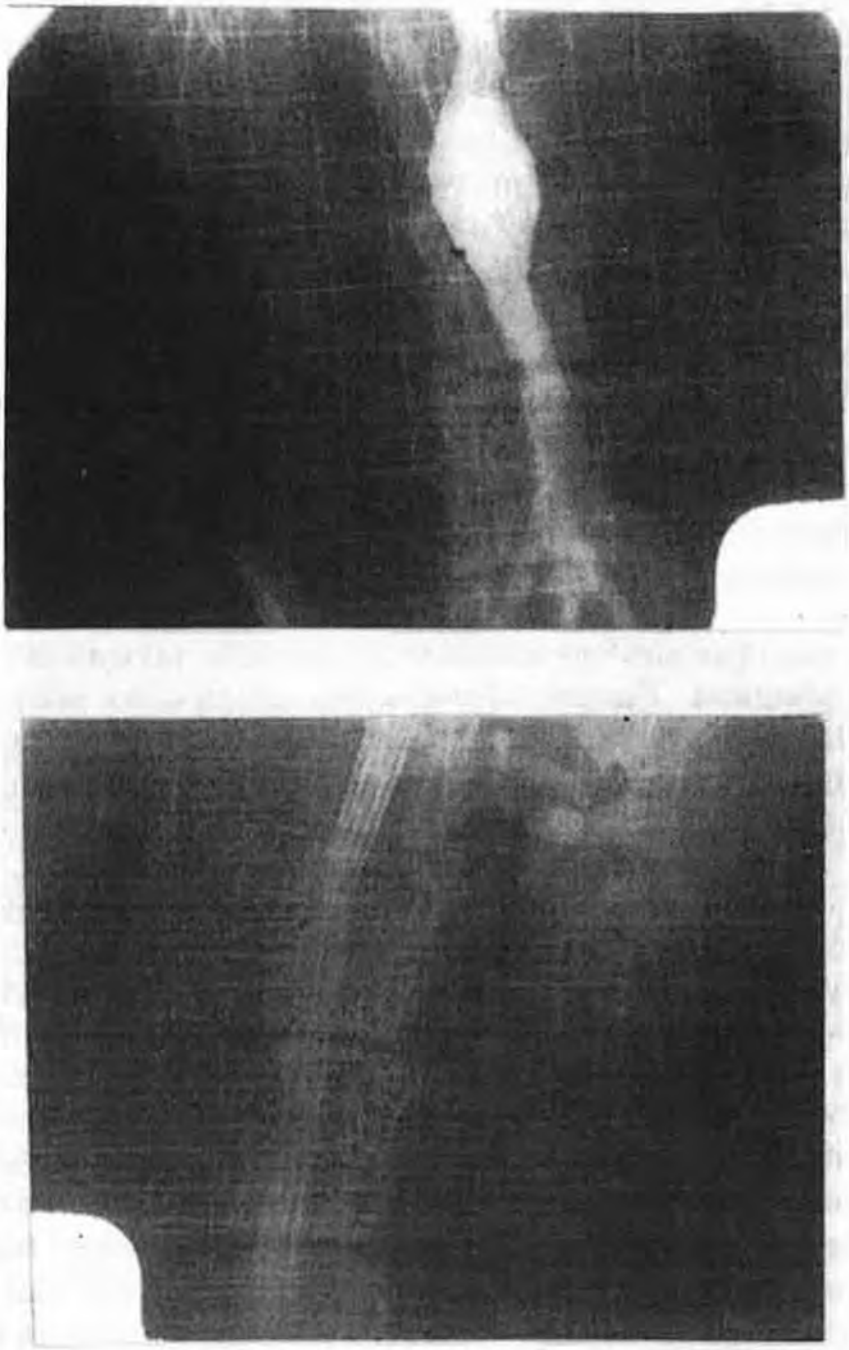

FIGURE 1

Fusiform aneurysm model in canine using interpositin of an aneurysmal aortic polyester graft. Before (top) and after (bottom) exclusion using an endovascular graft.

demonstrated graft twisting when no method of distal fixation was used. Interestingly, however, we did observe one case in this study where the lack of a distal anchor did not result in endovascular graft thrombosis. Despite this observation, we still feel distal graft fixation is important in endovascular aortic tube graft devices. This may not be the case in aortobifemoral endovascular grafts [5].

Using this methodology, we found the concept of intra-aortic delivery of a self anchoring tube graft to be feasible. We were able to design a delivery system with a small enough outer diameter to allow a transfemoral approach in this canine model. The endovascular stent graft and delivery system were flexible enough to permit delivery across moderately tortuous iliac arteries. We found using both proximal and distal graft anchors necessary to ensure aneurysm exclusion and prevent graft twisting.

Several questions however remain to be answered prior to successful human applications. The fate of the aortic side branches such as the lumbar arteries and the inferior mesenteric artery. We are uncertain whether these arteries will remain patent, continuing to pressurize the aortic aneurysm and lead to eventual rupture. Recent reports from the literature have seen no significant increase in aneurysm size despite persistent collateral perfusion. [25, 36]. Another significant problem involves the development of "endoleaks." Preoperative graft sizing is crucial and usually involves not only circumference but also length. Endoleaks may originate from failure to exclude the inflow or outflow to the aneurysm or from device failure [22]. Continued enlargement of aneurysm necks over time has been reported to occur up to 2 years after endovascular grafting. [24]. This observation necessitates additional considerations for future graft design. These problems and others continue to challenge the development of endovascular methods of treating aneurysmal disease.

CANINE MODELING OF INTRAVASCULAR STENTING FOR PERIPHERAL VASCULAR DISEASE

Canines have also been used to study the effects of intravascular stenting on the treatment of arterial occlusive disease. One example of the

application of this model is in the investigation of NH development in either prosthetic grafts [21] or venous bypass grafts [27]. Neointimal hyperplasia is a major cause of late infrainguinal prosthetic graft failure. The arterial/graft anastomosis is an area where this is especially prevalent. There are multiple factors that are involved in the evolution of intimal hyperplasia at the anastomosis. Compliance differences between graft and artery, size mismatch and shear stress can increase smooth muscle cell proliferation and extracellular matrix production which are the components of neointima. Using a canine model, we designed a study to evaluate whether a new self-expanding Nitinol stent [Symphony™] placed across arterial/ePTFE graft anastomoses could reduce NH formation.

We used nine (9) purpose breed mongrel hounds weighing 25-35 kg; all were male. Through a midline abdominal incision the distal aorta and iliacs were exposed. End-to-end interposition grafts of 6 mm PTFE [Excel™] were sewn, replacing both iliacs (Figure 2). One iliac was used as the control and the other was stented. This was randomly assigned. The stented iliac artery had a 7.2 mm x 2 cm Nitinol hex stent placed across the proximal and distal anastomoses. The stents were placed through a separate carotid cutdown angiographically. A completion arteriogram performed at the conclusion of the procedure documented graft patency and accurate stent placement. Post-operatively, the dogs received aspirin every day and their femoral pulses were palpated to determine graft patency. Grafts were explanted at two time frames: 30 days [n=4] and 90 days [n=5]. Prior to explantation, arteriography was performed in all cases.

Using computer assisted quantitative analysis, both implant and pre-explant arteriograms were analyzed for change in lumen size. All grafted aortoiliac segments were harvested after pressure perfusion in situ. Histopathologic analysis was performed on transverse sections of the stented grafts at 5 points along the specimen of each limb. Sections were stained using Hematoxylin and Eosin stain or Masson's Trichrome for light microscopy. Smooth muscle cell proliferation was determined by using anti-Brdu antibody. Digital morphometry was performed to determine residual luminal area, lumen perimeter and internal elastic lamina area. The neointimal area was then calculated by subtracting luminal area from IEL area.

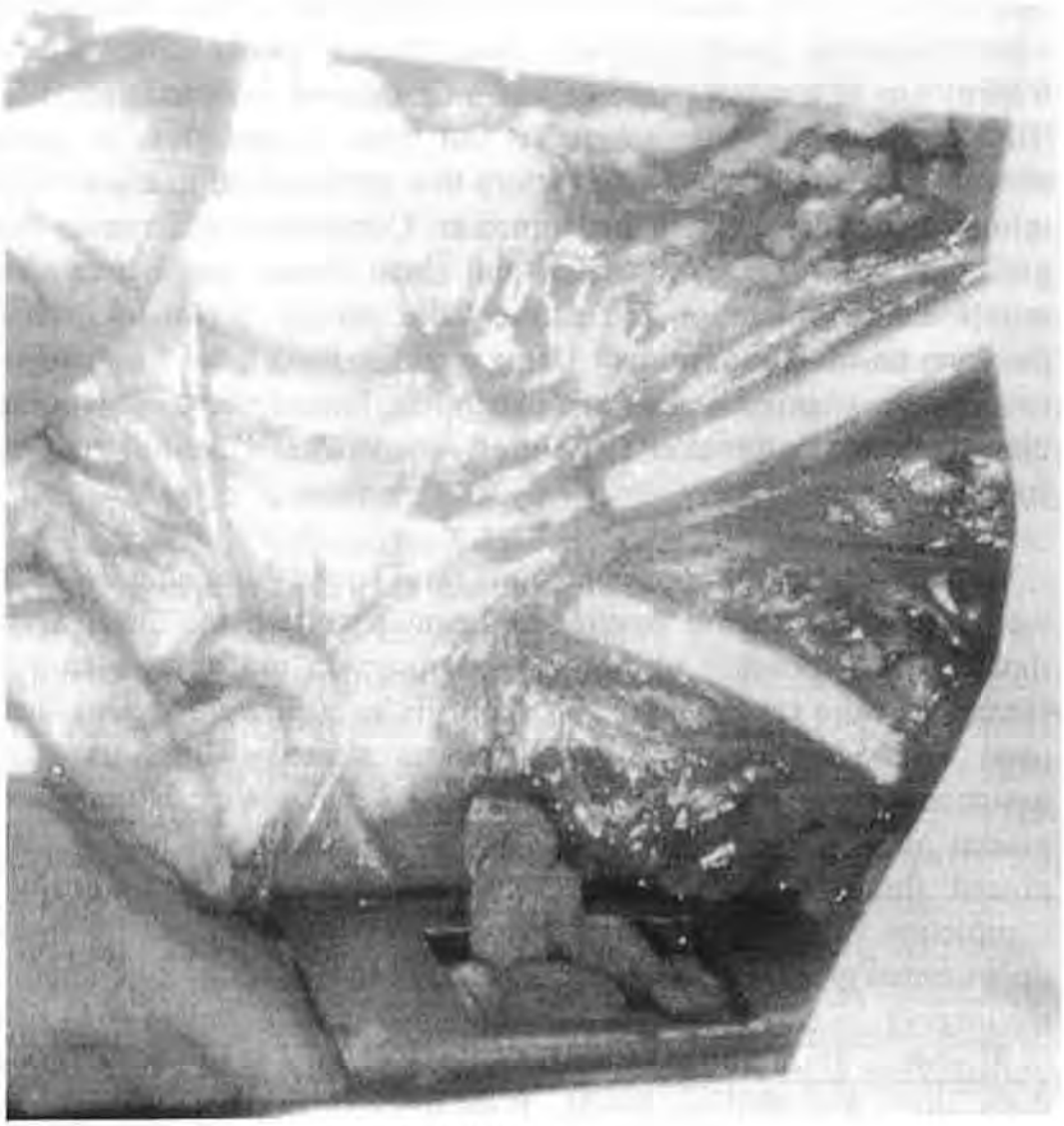

FIGURE 2

Canine model of end-to-end iliac interposition grafting. Six mm PTFE (Excel™) grafts placed to study effects of anastomosic stenting.

Nine dogs had 18 PTFE grafts implanted without complication. There were 9 hexstents placed at the proximal anastomosis and 9 at the distal anastomosis. All stents were deployed successfully. Grafts were explanted at 30 days and 90 days. On follow-up arteriograms, prior to sacrifice, all vessels were patent.

In this study, we found that stenting arterial ePTFE anastomoses resulted in significant gains in lumen area. These gains were maintained

over time despite the development of some NH. We found no difference in the development of neointima between 30 and 90 day specimens. We did find more neointima at stented anastomoses compared to controls, although this did not result in a significant loss of lumen area. In addition, we found smooth muscle cells in these stented areas continued to be in a proliferative state even at 90 days after stent implantation.

In a similar study, Chalmers found significantly less NH developed at the arterial/graft stented anastomosis than control. He did, however, demonstrate a significant increase in NH formation at the proximal stented anastomosis compared to the distal [3]. He also found that NH did not correlate with a change in mean luminal area. In summary, normal vascular healing, regardless of injury, results in NH. Formation of neointima may not however always mean restenosis or significant loss of luminal area. In the canine model, it appears that stenting does indeed alter the arterial-graft anastomosis by increasing and maintaining luminal area over time.

MODELING ENDOVASCULAR TREATMENTS OF AORTO-ILIAC OCCLUSIVE DISEASE USING THE CANINE

A third area of endovascular research using the canine model is the use of stent grafts for the treatment of aortoiliac or femoropopliteal occlusive disease. Several centers have used the canine model for investigation in this area [2, 28, 42]. Our group has studied the long term patency, healing and properties of endothelialization of a new ePTFE Nitinol stent for the treatment of aorto-iliac occlusive disease [44].

Thirty eight ePTFE-Nitinol covered stents [Hemobahn™] were placed in the ilio-femoral arteries of 18 adult greyhound dogs. The Hemobahn graft consists of a Nitinol stent lined with ultrathin ePTFE [Figure 3]. Devices were explanted at 2 weeks [n=4], 1 month [n=6], 3 months [n=6], six months [n=12] and twelve months [n=6]. Pre-explant arteriography was performed to confirm patency in all cases. Transverse sections were taken in the middle, and longitudinal sections were taken at the proximal and distal ends of the device [Figure 4]. The cross sectional area of each stent section was measured with digital morphometry. Scanning electron microscopy [SEM] was performed on selected specimens to evaluate the presence of thrombus, endothelial coverage, and

endothelial maturity. Immunohistochemistry using factor VIII was performed to identify the degree of graft endothelialization.

The patency rate for these devices was 100% (34/34) up to 12 months after implantation. The average rate of stenosis based on IVUS was 3% at 2 weeks and 8% at 12 months, with an overall rate of 5%. Neointima formation at midgraft cross sections was greatest at 3 months post implantation and decreased significantly at both 6 months and 1 year. The luminal surfaces of the devices were significantly endothelialized after three months and had 90-99% coverage by mature spindle shaped endothelial cells by 6 to 12 months. There was minimal inflammatory response to either the ePTFE graft material or to the Nitinol stent. Intimal hyperplasia at the proximal and distal ends of the device was minimal and not statistically significant between ends.

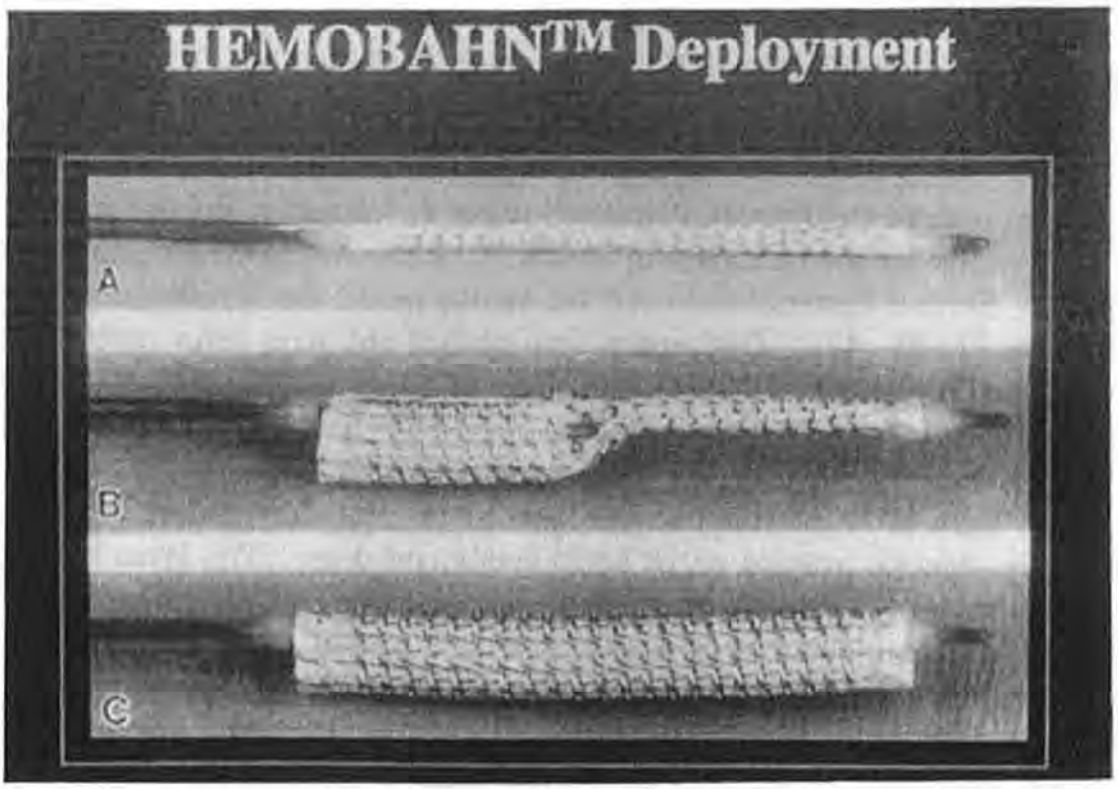

FIGURE 3

The Hemobahn endovascular graft consists of a Nitinol stent lined with ultrathin ePTFE. Deployment is as shown.

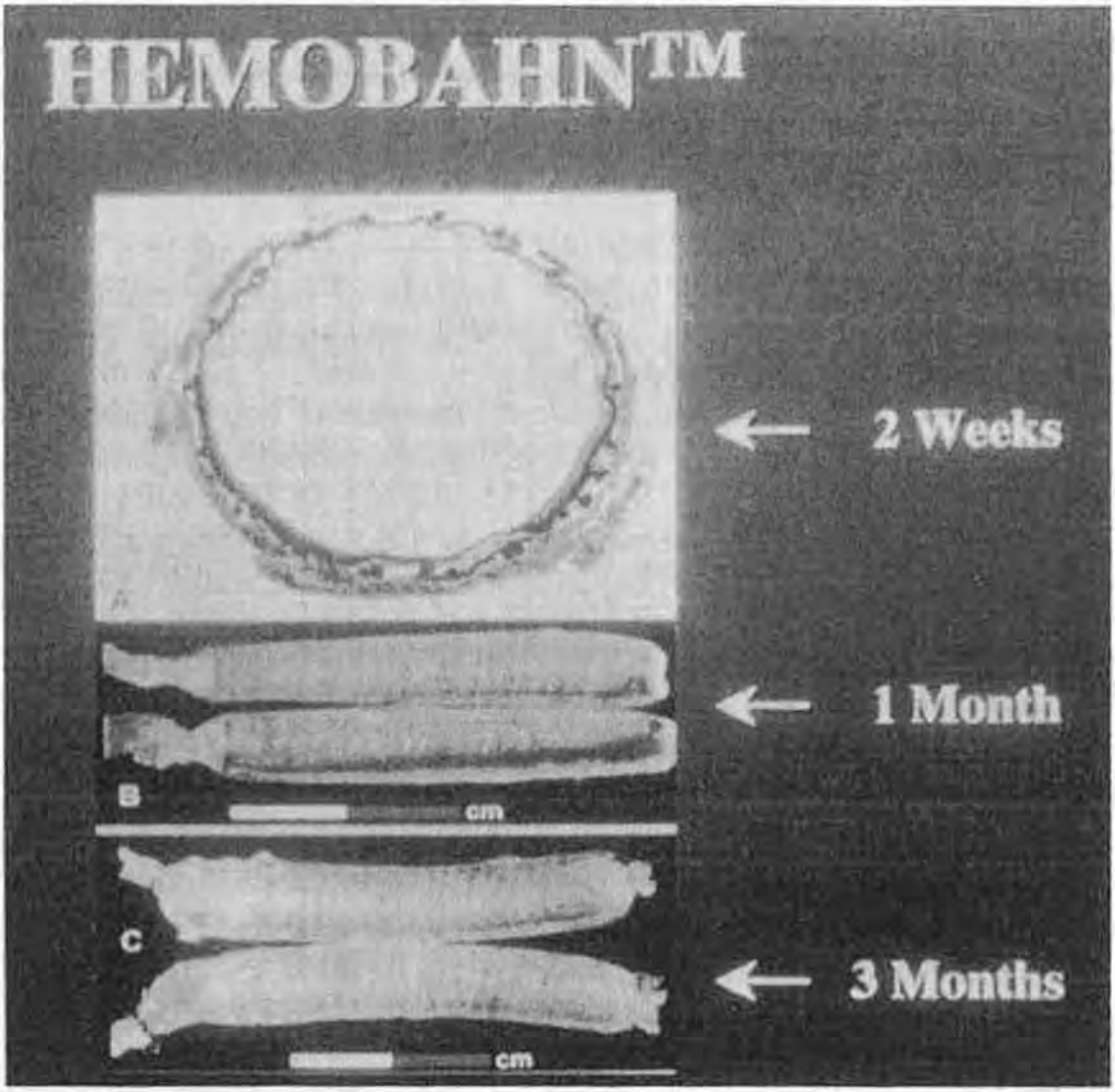

FIGURE 4

Mid graft transverse section shows minimal neointimal hyperplasia formation. Longitudinal of the device shows significant endothelialization after three months.

The source of endothelialization was investigated in 4 animals by implantation of a Hemobahn graft covered with polytetrafluoro-ethylene-co-hexafluoropropylene [FEP] in the center portion of the graft [n=2] and FEP covering the ends of the graft [n=2]. This FEP wrap is impenetrable by endothelial cells and, therefore, would control for any transgraft endothelial cell migration at these points. In the grafts with a central FEP

wrap, we found that endothelialization occurred only at each end of the graft and never completely covered the graft. In grafts with FEP wrap, at the ends we found nearly complete endothelialization at 6 weeks. This would indicate to us that transgraft migration of EC occurs significantly in the Hemobahn graft.

This new Nitinol/ePTFE covered stent had excellent patency in a canine model up to one year of implantation. Analysis of vascular remodeling reveals there to be early and near complete endothelialization of this covered stent with minimal NIH formation.

CONCLUSIONS

The canine model has been invaluable for the investigation and development of endovascular technology. The canine model excels in mirroring the human resistance to endothelialization and, therefore, serves as a useful model of stent and stent graft healing. This chapter attempts to characterize some of the uses of this model in the investigation of arterial stents and stent graft technology. Hopefully, this information will assist new investigators in reviewing the animal models available for use in vascular research and in considering their appropriateness before their use.

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Chapter 14

LARGE ANIMAL MODELS IN PRE-CLINICAL TRIALS

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Many animal species have served as models in pre-clinical trials. These animal models have greatly contributed to the better understanding of basic biology, as well as to the evaluation of medical device performance. Model choice is a critical decision for both basic and applied research. In pre-clinical trials, appropriate animal model selection should contribute to a reasonably accurate determination of the safety and efficacy of a potential therapy or medical device.

CRITERIA FOR MODEL SELECTION

The issues associated with the selection of an animal model for cardiovascular and other biomedical research have been debated from many different perspectives [4, 9, 16, 22, 31, 35]. Agreement over the most appropriate animal model for a pre-clinical trial may be difficult. However, consensus is possible for the basic factors, both experimental and practical, which one should consider in the selection of an animal

Keywords: *Large animal models, pre-clinical trials*

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model (see Table 1). Perhaps the most important question to address is whether an animal model is biologically appropriate for meeting the study objective(s). For instance, in a disease model, one should ask whether the model develops the disease spontaneously or if it is easily inducible. Is progress of the disease in the animal model like that normally observed in humans? For medical device evaluation, the animal model ideally should respond in the same manner as typically observed in humans for a similar device. The study should not be confounded by additional variables which are species-specific. The animal model should have relative genetic homogeneity in order to reduce the potential statistical error. Other things being equal, this will reduce the number of animals required for a study. In addition, one should have sufficient background knowledge of the model's biology in order to adequately assess the effects of the treatment or device on the animal. This background information can be obtained from three sources: 1) medical literature, 2) non-medical literature which reports on the biology of the animal (*eg*, agricultural and veterinary science), and 3) preliminary studies conducted with a new model to collect the necessary background information. The importance of background knowledge of a model is sometimes overstressed and may lead to the continued use of an inappropriate model chosen primarily because other researchers have reported its use in the literature. This type of reasoning may lead to potential oversights in medical research, such as the paucity of studies using women as biomedical research subjects [5], or moving prematurely on to clinical trials. It may be worth developing a new, more appropriate animal model even when there is a much studied, but less appropriate model available. One should weigh the amount of data already available on a given model against the appropriateness of an animal model and the study objective.

Although the experimental criteria for biological appropriateness are of primary importance, practical aspects of model selection are also important. The cost and availability matter, as does the ease of experimentally manipulating the animal. It is best if the animal is not extremely aggressive or fragile. Working with the animal should not pose a threat to the animal care staff or to the animal itself. The animal should also be sufficiently hardy to tolerate the experimental procedure with minimal procedural attrition.

TABLE 1
Criteria for Selection of an Animal Model

Experimental Criteria:
• Appropriateness of Animal Model for Satisfying Study Objective(s)
• Genetic Homogeneity of Animal/Species/Breed
• Background Knowledge of Biology of Animal
Practical Criteria:
• Cost and Availability
• Ease of Experimental Manipulation
• Ethical and Environmental Implications
• Societal Concerns

Naturally, one should take into account both the ethical and environmental implications of the use of an animal model. Moreover, the views society holds regarding the use of a particular animal for research should be seriously considered. An investigator should remain aware of and sensitive to both animal welfare and animal rights points of view [1]. These ethical considerations may weigh more strongly against the use of some animals (*eg* primates) than others.

For selection as a large animal model, the domestic pig (*Sus scrofa domestica*) fares well compared to other species in many respects, including those which are practical in nature. (Practical considerations in choosing a large animal model are compared in Table 2.) For example, domestic pigs and sheep cost less to purchase than dogs, minipigs, or nonhuman primates. Feeding and maintenance costs are usually lowest for the sheep, but pig costs are usually lower than the costs for dogs of a comparable size. Dogs and sheep are often favored because of their docile temperament, but unlike certain breeds of minipigs, the domestic pig is not usually aggressive. Proper handling techniques for pigs require relatively little training. Like sheep and cows, pigs have primarily been domesticated to serve as a food or fiber source for man, and therefore, have been bred to allow people to easily work with them. In general, pigs are not as cooperative as sheep, nor as willing to please as the dog. Pigs can be quite stubborn and it is important that animal handling staff understand how to work with, rather than against the pig [7, 14, 23].

Pigs are also relatively easy to feed and their diets can be easily formulated to accommodate a wide variety of ingredients, including those which can stimulate an elevation in blood cholesterol level and the development of atherosclerotic-like plaque. Although anatomical differences exist between the pig and human, the functional gastrointestinal physiology of the pig resembles the human's. The pig is therefore a useful model for dietary manipulations [23, 24, 25, 29]. Lastly, because pigs and sheep are meat producing animals, they (rightly or wrongly) stimulate fewer societal concerns regarding their use for animal experimentation.

TABLE 2[a]
Comparison of potential animal models

	Domestic Pig (6 mo./100 kg)	Adult Sheep	Dog	Nonhuman Primate	Minipig (6 mo./38 Kg)
Cost[b]	$	$	$$	$$$$	$$$
Nature	moderate	docile	docile	aggressive	aggressive
Staff Training	some	little	Little	yes	yes
Physiology	Monogastric/ omnivore	Ruminant/ herbivore	Monogastric/ carnivore	Monogastric/ omnivore	Monogastric/ omnivore
Adult Weight	>200 Kg	65 Kg	Varies[c]	Varies[c]	18-42 Kg
Societal Concerns	few	few	many	many	few

[a] Adapted from Thorndike and Turner [31].

[b] Approximate costs in 1998: $=$100-200; $$=$250-400; $$$=$600-700; $$$$>$2400

[c] Wide range, depends on breed/species.

When selecting an animal model, one should carefully weigh all of its advantages and disadvantages. A perfect model may not exist, but there may be an animal model which is clearly the best choice for a given study. There are additional factors which influence the selection of an animal model and while we may agree on these criteria, individuals will place different emphasis on each criterion. One additional factor which influences the choice of an animal model is previous use and experience with a particular species. An investigator's comfort level with a specific species is important. One may be uncomfortable using a particular species based on unfamiliarity and/or ethical concerns. How each factor

is weighted by an individual researcher will, of course, influence animal model selection. Another factor which may strongly influence or even determine the selection of an animal model is the facilities available to the researcher. However, animal facilities and cages can usually be adapted to accommodate a variety of species [27].

CARDIOVASCULAR SYSTEM MODELS

The characteristics of the cardiovascular system should influence selection of an appropriate animal model for cardiovascular research. For example, the size and anatomy of the target vessels should ideally be like that of the human. This is especially important for studies involving catheter-delivered medical device implants, such as stent grafts. In this context, it is advantageous if device-induced changes in vascular anatomy (*eg*, pathologic) are detectable by methods employed in human diagnosis. Given the role of lipids and of lipoprotein profile and metabolism in cardiovascular health, a model's lipid and lipoprotein metabolism should be considered when choosing an animal model. Ideally an animal model should mimic the human response with regard to the induction, progression and pathology of the atherosclerotic disease and the development of associated lesions.

The Pig as a Model

The pig is commonly used for pre-clinical research in a variety of biomedical research arenas. Use of the pig as a biomedical model has been covered at the International Symposia on Swine in Biomedical Research [32, 34]. Pigs are arguably the best model for many areas of investigation, including cardiovascular physiology, cardiovascular disease modeling (*eg* atherosclerosis), and evaluation of blood contacting medical devices. The pig has several advantages over other species with regards to cardiovascular research. The pig is capable of developing atherosclerotic-like disease [3, 9, 16, 19, 22, 35]. Unlike dogs, pigs are generally sedentary creatures, especially as they get older. This makes them a good model for the non-exercising human. Like the dog, the pig is intelligent and easily trained. For example, it can be trained for treadmill workouts to simulate exercise stress. Pigs can also be studied over a wide range of body weights, matching human body weights from a premature infant to an obese adult. It is therefore possible to evaluate full-size medical device configurations (*ie* no down-scaling is necessary) and the effects of growth in longer-term studies. Dietary manipulations

are also relatively easy in the pig [23, 24, 25, 30]. Furthermore, pigs (unlike the dog or sheep) can consume diets like those eaten by humans. In the pig, as in the human, blood metabolites such as cholesterol can be manipulated by diet [24]. In pigs, feeding a high cholesterol and fat diet can induce an atherosclerotic-like lesion [3, 6], especially when combined with arterial injury [6, 16, 22] and/or radiation [15]. In addition, pigs can also be bred to have genetically high levels of blood cholesterol [2, 24]. Other cardiovascular risk factors such as alcohol consumption and diabetes can be readily studied in the pig. One very important advantage to the pig model, especially for studies involving medical devices, is that pigs and humans are similar in vascular size and cardiovascular anatomy [19, 20, 22, 30]. Unlike the dog and minipig, the vasculature and heart of the domestic pig can accommodate full-size medical devices [36]. Additional similarities in cardiovascular anatomy are summarized in Table 3 which illustrates that the pig is very like the human in some important cardiovascular respects. For example, the pig and the human lack pre-existing collateral coronary arteries which are present in the dog [12]. Collateralization is also induced when a coronary artery is fully or partially blocked [8, 22, 28]. The pig and the human have a similar distribution of coronary arteries, as well as a similar pattern of growth for the heart and great blood vessels

TABLE 3

Comparison of cardiovascular anatomy.

	Pig	Human	Dog
Pre-existing Collateral Coronary Arteries	no	no	yes
Left Anterior Descending Artery (% supply to myocardium)	40%	40%	15%
Spontaneous Atherosclerosis-like Disease	yes	yes	no
Induced Lesions in Major Arteries	yes	yes	no

From [9, 16, 19, 22, 37].

from birth to puberty [30]. The distribution of blood flow through the coronary arteries is also similar between the pig and human [22]. The pig aorta has a true vasa vasorum like humans and therefore wound-healing characteristics are similar [20, 30]. Compared to the infectability of vascular grafts in the dog, the infectability in the pig is more similar to that of the human [26]. In addition, certain cardiovascular and hemodynamic measurements are also similar between the human and pig (Table 4)[33].

TABLE 4

Comparison of cardiovascular and hemodynamic measurements

	Pig	Human	Dog
Heart Rate (beats/min)	105 ± 10	70 ± 14	93 ± 18
Stroke Volume (ml/beat/min/Kg)	1.3 ± .3	1.1 ± .3	1.7 ± .4
Blood pressure	127/86	126/79	143/81
Blood volume (ml/Kg)	67 ± 4	69 ± 7	102 ± 12
O_2 Consumption (max/resting; ml/min/Kg)	56/7	57/4	82/17

Adapted from McKenzie [19], Gross [10] and Hannon et al [13].

Today most domestic pig breeds are relatively lean, despite the popular perception that these animals are obese. Today's lean pigs are similar to normal fit humans with regard to their body composition. However, pigs can be bred to a variety of fatnesses. Certain genetic strains are obese, while others are quite lean. The fat:lean ratio can be altered by diet. Given the availability of large numbers of genetically similar pigs, the experimental variation between these animals is much lower than that seen in mongrel dogs, thus yielding more consistent experimental results [28].

PRACTICAL CONSIDERATIONS

Despite their many advantages, some researchers are uncomfortable with the prospect of conducting research on pigs. Much of this apprehension may be due to unfamiliarity with the species and concern about its accessibility. Domestic pigs can grow to be quite large, and although they are relatively easy to handle, they should be treated with respect—especially intact boars. Pigs, by nature, are not aggressive and can be quite gentle when accustomed to human contact. However, the pig model does have some disadvantages. One major disadvantage for domestic pigs in cardiovascular research is their large body size at maturity and their rapid rate of growth. These two characteristics may limit the usefulness of domestic pigs for longer term studies of implants such as stent grafts (*eg* >60 days in 6 month-old growing pig). Mini-pigs grow at a slower rate and have a smaller weight at maturity. Alternatively, domestic pigs can be restrictively fed to limit their growth rate. Facilities requirements for the use of large domestic pigs may pose another potential disadvantage. However existing research facilities can often be adapted to accommodate pigs. For example, at the Food and Drug Administration's Laboratory of Cardiovascular Research and Biotechnology most of the facilities we use were designed for large animal use. However, we use a wide range of pigs (20 to 160 Kg) and have adopted facilities designed for large animal species other than pigs to meet our needs. We have also adopted equipment that was originally designed for humans for use with domestic pigs. Before surgery, test subjects are moved into a simple pre-operative animal holding area consisting of floor pens in an open room designed for cattle. Young growing pigs can also be kept in dog cages or crates [27].

Handling of Pigs

Special handling equipment is required for animal restraint for moving the untrained animal, and for the moving and lifting of larger anesthetized pigs. This equipment can be very basic and simple in design. Pigs can be restrained with hurdles or boards in order to give an intramuscular injection or to perform other simple, relatively painless procedures. Special restraint cages are useful, but it is our practice to confine pigs within their pens with a board in order to administer an intramuscular injection of drugs for anesthesia induction. Once a pig is anesthetized, it can be moved to the surgery room and onto the table. A winch (designed to remove an engine from an automobile) to lift and

suspend the pig in a canvas sling works well. (An adjustable table on wheels can also be used.) All metal parts of the sling (*ie* pipes and chains) are easily removed to avoid interference with fluoroscopy. We use a simple, inexpensive, easily adjustable device made of canvas, plastic pipe and Velcro to hold the animal supine on the surgery table and rope ties hold the legs in position for some procedures.

Vascular Access, Anesthesia, and Analgesia

Although the pig has few superficial blood vessels, the ear vein is readily accessible for placement of a simple butterfly catheter. Pigs can be maintained for long procedures with intravenous administration of an anesthetic cocktail or alternatively, anesthesia can be maintained with gas (*eg* isoflurane). We use an anesthesia cocktail (Appendix I) developed by V Pursel [11] to induce anesthesia. Anesthesia can be maintained with this cocktail, but for procedures requiring intubation, we use isoflurane to maintain anesthesia. Intubating a pig is challenging compared to other species, but with practice and familiarity the procedure becomes routine. Moon and Smith have written an excellent description of the proper intubation procedure in the pig [21]. Although isoflurane has minimal effects on cardiovascular function, other anesthetic regimes can be used. Swindle recently published a definitive description of anesthesia for pigs [29]. Halothane is not recommended for pigs since some animals carry a stress-susceptible gene which makes them very intolerant of this anesthesia gas [17, 18]. As mentioned, isoflurane, sometimes in combination with nitrous oxide, is the gas anesthetic of choice for pigs.

Sterile technique should be practiced because the pig, like the human, is susceptible to infection. If proper surgical techniques are used, the pig is very resilient and recovers rapidly from anesthesia and surgery. A clean recovery environment is important in order to avoid infection. The administration of penicillin prophylactically (im) prior to surgery is recommended as a precautionary measure. The pig's appetite returns quickly after surgery (unlike the ruminant), and depending on the severity and length of the procedure, can recover its full appetite within 12 hours; it may be advisable though, to restrict access to full feed for a day or two following surgery.

Although there are no large superficial arteries in the pig, both the carotid and the femoral are easily accessible and comparable in size to that of the human. A surgical cut-down procedure is standard in order to access either the carotid or femoral arteries. Both the carotid and femoral arteries cut-downs, although deep in the pig, are relatively quick (<15 minutes) and provide easy access to the heart, the coronary arteries, and the aorta. In our laboratory, we typically use femoral artery access for the placement of stents in the carotid arteries. The carotid artery is utilized for quicker and easier access to the coronary arteries. The pig's carotid and the femoral arteries are both about the same size as the adult human's and therefore, may receive full-sized catheters and devices. Fluoroscopy is typically used to visualize the delivery and placement of catheters and devices in pigs up to 140 Kg. Fluoroscopic visualization may be easier in some breeds of pigs than in others. For example, barrel-chested pigs such as the Poland China or Hampshire present more of a challenge in this regard compared to their thinner-chested cousins (*eg* Landrace, Large White).

CONCLUSION

In summary, the domestic pig has many advantages for use as an animal model in cardiovascular physiology and the study of interventional devices. The pig's coronary tree size and structure are similar to the human's, thus allowing for the use of full-sized medical devices. Well-defined genetic strains and large litters (averaging 10-14 pigs) reduce experimental variability and allow for the study of specific treatment permutations, such as obesity and high levels of cholesterol. The pig's lipid and lipoprotein profile and its digestive system are similar to the human's. As in the human, diet can be used to alter the pig's lipid and cholesterol profiles, as well as its body composition. Biological parameters are well-defined in the pig and provide the background knowledge necessary to evaluate treatment effects. Domestic pigs are readily available and relatively inexpensive to obtain and maintain. Experimental permutations are readily accomplished with pigs and most facilities can be modified to accommodate domestic pigs. Given that domestic pigs are meat animals and are normally reared in confinement, there are fewer societal concerns regarding their use in biomedical research. The pig may be the ideal model choice for pre-clinical trials investigating cardiovascular physiology and interventional therapeutics, satisfying both experimental and practical criteria for animal model selection.

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APPENDIX I: ANESTHETICS AND ANALGESICS

Cocktail #1: for intramuscular injection

5 ml of xylazine (Large animal Rompun; 100mg/ml) is added to a bottle of lyophilized Telazol (500 mg/bottle).

Each ml contains:
100mg xylazine
100mg Telazol

Approximate dosage: 1 ml per 50 Kg BW

Cocktail #2: for intravenous injection

5 ml of xylazine (Large animal Rompun; 100mg/ml) is added to a bottle of lyophilized Telazol (500 mg/bottle).

Inject this into another sterile bottle and add:
20 ml Ketamine (100mg/ml)
2ml Atropine (15mg/ml)
2ml Torbugesic (10 mg butorphanol tartrate/ml)

Each ml contains:
17.2 mg xylazine
17.2 mg Telazol
69 mg Ketamine
1 mg Atropine
0.69 mg Torbugesic

Approximate dosage: 2 ml per 50 Kg BW to last for approximately one hour. More may be injected or infused to maintain anesthesia for longer.

Developed by VG Pursel [11]

Chapter 15

INDUSTRY PERSPECTIVES ON ANIMAL MODELING FOR STENT GRAFT EVALUATION

Thomas J McCarthy, DVM

This article represents industry's perspectives relative to animal modeling for stent graft evaluation. While preparing this talk I really had to consider how I could best communicate an industrial philosophy of device development without appearing minimalist or disregarding some very elegant and innovative animal models. We have heard about several such models today; all of which would likely serve as viable options for testing stent grafts.

I am also obligated to include a brief discussion of the corporate business decision making process as it relates to new device development. This will hopefully provide a sense of the environment in which our businesses operate.

Keywords: *Animal model, stent graft, FMEA, industry*

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This presentation will include what I would consider an ideal animal model as well brief comments on many areas of animal model as well brief comments on many areas of animal modeling including strengths and weaknesses of the process. Finally, I will briefly discuss safety testing and present an industry model of preclinical evaluation based on testing for failure modes. This presentation will be tailored primarily to evaluation of stent grafts for treatment of abdominal aortic aneurysms though the principles are applicable for the testing of any medical device.

INDUSTRIAL MEDICAL DEVICE DEVELOPMENT

Before a company decides to pursue development of a new product, it undertakes a thorough analysis of the short and long term monetary, technological, and legal aspects of this decision. The resultant business plan forecasts time to market entry, development costs, and return on investment and details how the product fits within the company's product portfolio, its manufacturability, marketing strategy, regulatory or competitive barriers to market entry, and key risks (patient safety, product complexity).

The key aspects of the business plan are time to market, return, and risk. If any of these appear unreasonable a company will refuse to develop this product even though it may have immense patient value.

THE FIRST SHALL BE FIRST

Being first to market is a very important aspect of the time/return/risk equation. In a market without competition a business can receive a premium for the product, establish a wide sales base, and rapidly recoup development costs. This assures the business of predictable revenue and cash flow.

Now, one may ask "What does this have to do with animal modeling for stent grafts?" Actually it has a great deal to do with animal testing. Once the commitment to move forward has been made, the timelines and deliverables are set. In today's highly competitive device industry these project timelines are incredibly aggressive, often based on best case scenarios.

This impacts the animal studies in that as soon as a device design is finalized, samples prepared according to the final manufacturing and sterilization process, must immediately enter into safety studies. Project delays due to creation of complex, unpredictable, or technically difficult animal models lead directly to delayed regulatory submissions, and, ultimately, to delays to market. This can have a significant effect on both the company's bottom line and the stock price, especially if a competing product hits the market first.

INDUSTRY'S IDEAL ANIMAL MODEL

Now that we have established the economic reality, let's examine some characteristics of the ideal model for stent graft testing from an industrial point-of-view. I believe it would have three significant characteristics and three ancillary characteristics [1].

SIGNIFICANT CHARACTERISTICS

- Vascular anatomy similar to man in size, structure, and distribution (no need for miniaturization of test stent grafts or delivery systems)
- Consistent, naturally-occurring AAA similar to man in geometry, rheology, and pathology (allows for safety and efficacy testing)
- Require little to no preparatory surgery (to minimize surgical mortality as well as use immediately)

ANCILLARY CHARACTERISTICS

- Inexpensive to purchase and house
- Readily available
- Easily and safely handled and sampled

ANIMAL MODELS: STATE OF THE ART?

We all know that no natural or created animal model truly reproduces the most significant aspects of the AAA syndrome in man [1]. Issues relating to vessel size and distribution, geometry of the aneurysm, local rheology, healing response, physiology, and pathology are significantly different

in even the most sophisticated animal models when compared to humans.

I am not advocating that industry's perspective is the elimination of animal models. I do feel, however, that it is important that we recognize that even the best animal models are fraught with limitations and questions of relevance. These limitations become most apparent when manufacturers must modify or downsize a device to accommodate an animal model. This practice, which is often extremely costly, is also very risky. The downsized device may result in new and unique modes of failure, which, due to species, size, and response differences, would be highly unlikely in the human clinical device [1]. The subsequent root cause analysis of these model-related failures impacts the project timelines as well as the project budget. An example of such a failure would be thrombosis of an iliac stent graft, which had to be downsized from 14 mm in the original design to 7 mm for the sheep model. We must stay focused on the goal, recognizing that we are not trying to make safe and effective stent grafts for animals.

THE ISSUE IS SAFETY

Given these business and model challenges, how should a manufacturer proceed when confronted with assessing the *SAFETY* of a new stent graft design. I have changed my focus from directly assessing a stent graft to assessing the safety of a stent graft. The reasons behind this change in focus are twofold. The first is that the patient's safety is of utmost importance to a device manufacturer. No company would knowingly allow its product to place a patient at greater risk than the current standard of therapy.

The second reason for this change in focus is based on the regulatory requirement that a new implantable device be demonstrated safe and have a reasonable probability of efficacy for use in clinical trials [1]. There is no specific regulatory requirement that a device necessarily be demonstrated efficacious in an animal model. This is an extremely important point when discussing animal modeling.

A manufacturer has much more latitude in demonstrating safety as opposed to efficacy. Efficacy implies a desired outcome or positive effect.

Safety implies that the device does no harm. Most of the time a manufacturer will conduct feasibility studies to infer efficacy or will attempt to show efficacy while concurrently demonstrating safety. However, the latter plan can be a very challenging or even impossible task due to the aforementioned challenges associated with animal modeling.

AN INDUSTRY MODEL

The recognition that animal models have limitations should not imply that *in vivo* safety evaluation of a new stent graft design cannot be accomplished. I do feel strongly that animal models are extremely important in providing relevant information on the safety of a stent graft design. The method I would advocate to complete the safety evaluation is to closely associate the animal testing to the Failure Modes and Effects Analysis (FMEA).

The Quality System Regulations [2] (QSR) clearly define a process for taking a prototypical product through the US regulatory approval process. One requirement of the QSR is a formal, detailed analysis of all possible device failure modes and the likely effects of each of these events on the patient. The FMEA is one tool for accomplishing this activity.

Every device design has a unique FMEA profile. Failures may be mechanical such as improper expansion of a self-expanding component, or physiologic as with occlusion due to intimal hyperplasia. In addition, the significance of the effect on the patient is ranked as to severity and likelihood.

At Baxter, we use the FMEA as a basis for designing the preclinical testing. The most likely and severe failures are prioritized for testing. We then use the most effective testing means available, be they *in vitro* or *in vivo* to demonstrate the absence of the failure modes in question.

The process begins by involvement, early in the design phase, of individuals who are knowledgeable of the physiologic failure modes of medical devices in humans and in most relevant species of animals. These

individuals are able to provide valuable input to the R&D engineers regarding the likely physiologic effects imparted by a particular design attribute.

After the FMEA has identified the potential failures for which evaluation must take place, animal models for the *in vivo* testing program are selected based on a specific model's ability to detect or predict the failure in question.

As an example, a physiologic failure mode of a stent graft may be emboli generation. This can be evaluated in a nonaneurysmal model in a sheep by placing a stent graft in the thoracic aorta and observing for an increased incidence of renal infarcts after some period of time. This model is simple yet very predictive since the kidneys are especially sensitive to ischemia secondary to thromboemboli.

In another example, a failure mode may be mechanical failure (collapse) due to fracture fatigue secondary to erosion in the wireforms. Due to the time required for the condition to develop and the low potential incidence, a relatively small study in animals is highly unlikely to detect this failure. An accelerated wear tester or other appropriately designed *in vitro* study would have a higher probability of detecting this failure.

USE OF MULTIPLE, APPROPRIATE ANIMAL MODELS

Since this industry model of testing is specific to failure modes, the use of several different models in different species with several different configurations of a stent graft may be necessary. The most important aspect is that the model be able to detect the failure in question [2].

In the safety evaluation of bifurcated stent graft designs we have used three different sheep models. A nonaneurysmal model using a tube stent graft with the significant design attributes of the bifurcated stent graft provided data on fixation, migration, biocompatibility, healing, vessel damage, thrombosis, and embolization. A simple patch aneurysmal model [1], again using a straight tube stent graft with the design attributes of the bifurcated stent graft, provided data on deployability, visualization, technical difficulty, exclusion, early thrombosis, and perigraft flow.

Finally, a bifurcated patch aneurysmal model provided data on deployment of the entire clinical system.

The protocols for each of these models were designed to collect data on specific failure modes. The use of the less sophisticated models for certain specific testing provided relevant safety data as well as financial and time benefits to the company. This program also reduced the surgical mortality associated with the creation of large numbers of bifurcated AAA in animals; some of which would have resulted in paralysis or rupture.

SUMMARY

Today we have discussed many aspects of industry's perspective on animal modeling. We touched on the fiscal reality of stent graft development, the importance of working within aggressive timelines, issues around safety and efficacy, and the many challenges associated with animal modeling. Finally, we have presented a model of preclinical testing which should address a business's concerns regarding timelines and cost, while incorporating the requirements of the QSR. A combined and specific *in vivo* and *in vitro* testing program, based on a detailed FMEA, should provide a manufacturer with a reasonable assurance of safety to proceed into early clinical trials. Because it is in the clinical trials that an innovative design can demonstrate its real value as a safe, effective, and lifesaving device.

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Chapter 16

STENT GRAFTS: FROM ANIMAL MODELS TO HUMAN CLINICAL APPLICATIONS

Anthony C Venbrux, MD

HISTORICAL PERSPECTIVE

Bare metal and covered stents have expanded minimally invasive, image-guided, therapeutic options for treatment of vascular disease. Charles Dotter first described transluminal application of a coiled spring in canine popliteal arteries in 1969 [11]. It was not until 1983 that Dotter and other investigators reported experimental results in animal models using different techniques for placement of bare metal vascular stents [5, 12, 21].

A significant expansion of stent technology involved the covering of bare metal stents with nonporous and porous materials. Investigators in 1986-97 used animal models to study the feasibility of transluminal placement and the vascular biological response to covered Stents [1, 4, 13, 15, 16, 18-20, 24, 27, 30, 31]. The endoluminal deployment of stent grafts for repair of aortic aneurysms in humans was first reported in 1991

Keywords: *Animal models, stent grafts, endovascular interventions, aneurysms, arteriovenous fistula, pseudoaneurysm*

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by Parodi, et al [25]. The development of improved endovascular techniques for treatment of vascular disease continues to progress largely due to the pioneering work of investigators using animal models. The purpose of this paper is to outline the important link of biomedical research using animal models. The purpose of this paper is to outline the important link of biomedical research using animal models to current human clinical trials involving the application of stent grafts.

HUMAN VASCULAR CONDITIONS POTENTIALLY TREATABLE WITH STENT GRAFTS AND THE ROLE OF ANIMAL MODELS

Traditional management of patients with disease has been surgical. The techniques, results and complications have been extensively reported in the medical literature. In contrast, the use of endovascular stent grafting is relatively new and continuously evolving. Vascular conditions in humans treated by conventional surgical approaches and recently by endovascular stent grafts include the following [2, 3, 6-10, 14, 17, 22, 23, 25, 26, 28, 29].

- True aneurysm in the abdominal aorta, thoracic aorta, subclavian, iliac and femoral arteries
- False or pseudo aneurysms in the same locations
- Arterial dissections
- Arteriovenous fistulas
- Femoral occlusive disease

Much of the work leading to human clinical applications of stent grafts is the result of feasibility trials in animal models. It is possible to create five conditions listed above in animals. The humane use of animals for evaluating stent grafts reduces the steep "learning curve" in the deployment of such devices in humans. Deployment feasibility, materials testing and histopathological effects on the vessel wall are but a few of the critically important data sets available as a result of feasibility trials in animal models.

The swine and canine models are primarily used for evaluating stent grafts. In our animal research facility at The Johns Hopkins Hospital, both have been used effectively for creating animal models of human disease. The Interventional Radiology Research Division has focused not only on the stent graft itself, but also on the technique of creating the model that attempts to mimic the disease process. The following research had been performed:

Swine Animal Model

- Deployment feasibility and histopathologic effect of a polyurethane-covered nitinol stent on the aorta and IVC (*ie*, in "normal," [nondiseased] growing farm swine).
- Use of a polyurethane-covered nitinol stent to occlude a surgically created iliac arteriovenous fistula.
- Deployment feasibility of a venous stent valve (*ie*, bioprothesis) in the inferior vena cava and iliac veins.

Canine Animal Model

- Percutaneous creation of iliac artery aneurysm for testing stent grafts.
- Feasibility studies of percutaneous deployment of polytetrafluoroethylene-covered (PTFE) nitinol stent in canine iliac artery aneurysms.

ANIMAL MODELS: TWO EXAMPLES FOR EVALUATING STENT GRAFTS

It is important, at first, to evaluate a stent graft in a biological system without the "variable" of disease present. In other words, an understanding of the impact of the device on "normal" vessels provides the investigator with initial data on deployment feasibility and device safety. Important questions are answered before the device is used in humans. A partial list of questions frequently answered during animals trials include:

1. Can stent grafts be safely deployed into the vascular system?
2. What vascular approach is best? For an aortic stent graft, should the device be placed via a femoral "cutdown," through a direct abdominal approach (surgical exposure), or through a prosthetic graft surgically affixed to the aorta (*ie*, vascular conduit, etc)?
3. Is the deployment system appropriate in terms of size, stiffness, etc?
4. Are the device and deployment systems radiopaque for image-guided procedures?
5. Is the device thrombogenic?
6. Is there a role for anticoagulation?
7. What about device durability in the long term? (*ie*, strut fracture, etc)

8. Does the device induce abundant intimal hyperplasia?
9. How does one address the problem of device malfunction?
10. Is there a nonsurgical means of correcting the problem without emergency surgery?

The animal feasibility studies and more pure rigorous trials for the Food and Drug Administration (FDA) data submission with invaluable information that cannot be acquired in pure "bench top" testing and flow models.

NONSURGICAL (PERCUTANEOUS) TECHNIQUE FOR THE CREATION OF AN ILIAC ARTERY ANEURYSM IN DOGS

Once studies have been completed in normal (nondiseased) animals, the next step is deployment in animal modes that mimic human pathology. Unfortunately, animal models of human disease have limitations. Nevertheless, the diseased state must be approximated in order to determine effectiveness of the stent graft. For example, one method described by our laboratory is the percutaneous creation of an iliac artery aneurysm in the canine animal model in order to "test" stent grafts. This model involves the use of bare metal, which is placed into the iliac artery and "over dilated" resulting in a fusiform, elongated, focal "true" aneurysm. A stent graft may then be deployed to determine the effectiveness of the device in terms of aneurysm exclusion. Should the device fail to properly exclude the aneurysm, minimally invasive image-guided techniques may be tried in an attempt to correct a problem (*ie*, a "leak"). Such image-guided techniques may include balloon dilation, over stenting, and transcatheter embolotherapy of the perigraft space to induce thrombosis outside the endovascular stent graft and embolization of problematic collaterals that might "repressurize" the aneurysms once excluded.

SURGICAL CREATION OF AN ARTERIOVENOUS FISTULA IN THE SWINE ANIMAL MODEL

In contrast to the percutaneous creation of iliac artery aneurysms in dogs described above, our animal research facility has also described a technique for surgical creation of an iliac-artery vein fistula in swine. This allows us to study the effectiveness of a polyurethane covered self expanding nitinol stent (or any stent graft) in sealing the high flow communication between the iliac artery and vein and mimics a post traumatic fistula (e.g., from a penetrating vascular injury).

The above are but two examples of animal models we have used to test stent grafts. Other investigators have described the application of stent grafts to treat experimental aortic dissection in the canine animal model [14-15].

Advantages of the animal models include the use of relatively few materials and the ability to study the impact of the device long term (*ie*, "survival" studies). Disadvantages include the inability to create a truly "diseased" condition. For example, the canine iliac artery aneurysm is created in a healthy animal, not an animal with atherosclerotic disease where the anatomy may be markedly distorted, the vessel wall irregular, the blood flow reduced and more turbulent. Another disadvantage includes the cost of animal maintenance (transport, feeding, etc); the relatively small size of the animal compared to humans and the sacrifice of the animal itself.

One costly and important lesson learned regarding the use of animal models: Avoid if possible, the evaluation of devices that are "custom made" for the specific anatomy of the animal species. A "smaller version" of a stent graft may deploy easily in a swine iliac artery but prove problematic when enlarged for human studies. Whenever possible, match the stent graft size in animals to that which will be used in humans.

CONCLUSION

Subject to the above outlined limitations, animal models provide the investigator with essential information regarding the expanding role of stents grafts in treating aneurysms, dissections, arteriovenous fistulas, and peripheral vascular disease in humans. Ongoing clinical trials in humans are largely the result of initial data acquired from animal studies. Improvements in stent graft design, reduction in the size of the deployment sheath, and a more thorough understanding of long term biological effects of stent grafts will be further defined through well designed animal studies. Regarding human application of stent grafts, patient selection, safety, efficacy issues, and long term effects of the device in disease vessels are but a few of the important issues currently being addressed in international human clinical trials.

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Part V

CLINICAL PERSPECTIVES

Chapter 17

MONTEFIORE EXPERIENCE WITH ENDOVASCULAR GRAFTS FOR THE TREATMENT OF ANEURYSMS AND OTHER ARTERIAL LESIONS: A FIVE YEAR EXPERIENCE

Takao Ohki, MD, Frank J Veith, MD

The operative mortality rate for elective repair of aortic aneurysms has decreased markedly, declining from 21% in early surgical series to under 5% reported in modern studies [1, 3, 4, 8, 30]. Lower extremity occlusive disease with ischemic tissue loss that once mandated major limb amputations can now be treated with either interventional techniques or bypass surgery resulting in favorable limb salvage rates [33]. Furthermore, despite advances in intensive care and resuscitation, major arterial injury from penetrating or blunt trauma has remained a challenging problem, especially when central arteries such as the aorta, the iliacs or the subclavian arteries are involved [9, 19, 29].

Keywords: *Abdominal aortic aneurysms, endovascular, stent-graft, vascular*

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Significant perioperative morbidity and mortality still occur despite improvements in the management of these vascular lesions, particularly in those cases with severe comorbid medical illnesses, scarring from previous operations, or multiorgan trauma [5, 6, 22, 32]. In addition, even in good risk patients, standard vascular repairs have associated morbidity, and the quality of life following such treatment may be impaired by incisional pain, sexual dysfunction and other problems. Furthermore, lengthy hospital stays contribute to rising health care costs. All these negative effects are related to the large incision and extensive tissue dissection required for access to the arterial pathology or adjacent vessels.

Stented graft is an alternative treatment to standard open vascular surgical repairs. These grafts may be inserted through remote arterial access sites to treat vascular lesions without the need to directly expose the diseased artery through an extensive incision or dissection. At Montefiore Medical Center in New York, 234 stented grafts have been used in 174 patients over the last 5 years, to treat aortic and other arterial aneurysms or pseudoaneurysms, long segment arterial occlusive disease, or traumatic arterial lesions. This article will review this stented graft experience.

STENTED GRAFT FOR THE TREATMENT OF ABDOMINAL AORTIC ANEURYSMS (AAAs)

We performed the first stent-graft repair of an AAA in North America in November, 1992 [26]. Since then, we have treated 60 AAAs using endovascular grafts. Several different endovascular grafts are currently undergoing clinical trials for the treatment of AAAs at Montefiore Medical Center. These devices include the Vanguard graft, the Talent graft, the EVT graft, the Parodi type graft and the Montefiore graft (Figure 1). Each graft has its own inclusion and exclusion criteria based on the health status of the patient and the anatomy of the aneurysm. During the past year, a patient who is a good surgical risk (without significant comorbidities) has been evaluated for the Vanguard or the EVT graft. If the patient is of high surgical risk, he or she has been evaluated for the Talent graft. If the patient does not match the inclusion criteria for any of these grafts, then the patient has been evaluated for the Montefiore graft. In brief, patients with complex AAAs, such as those with marked angulation of the proximal neck (>60 degrees), extensive

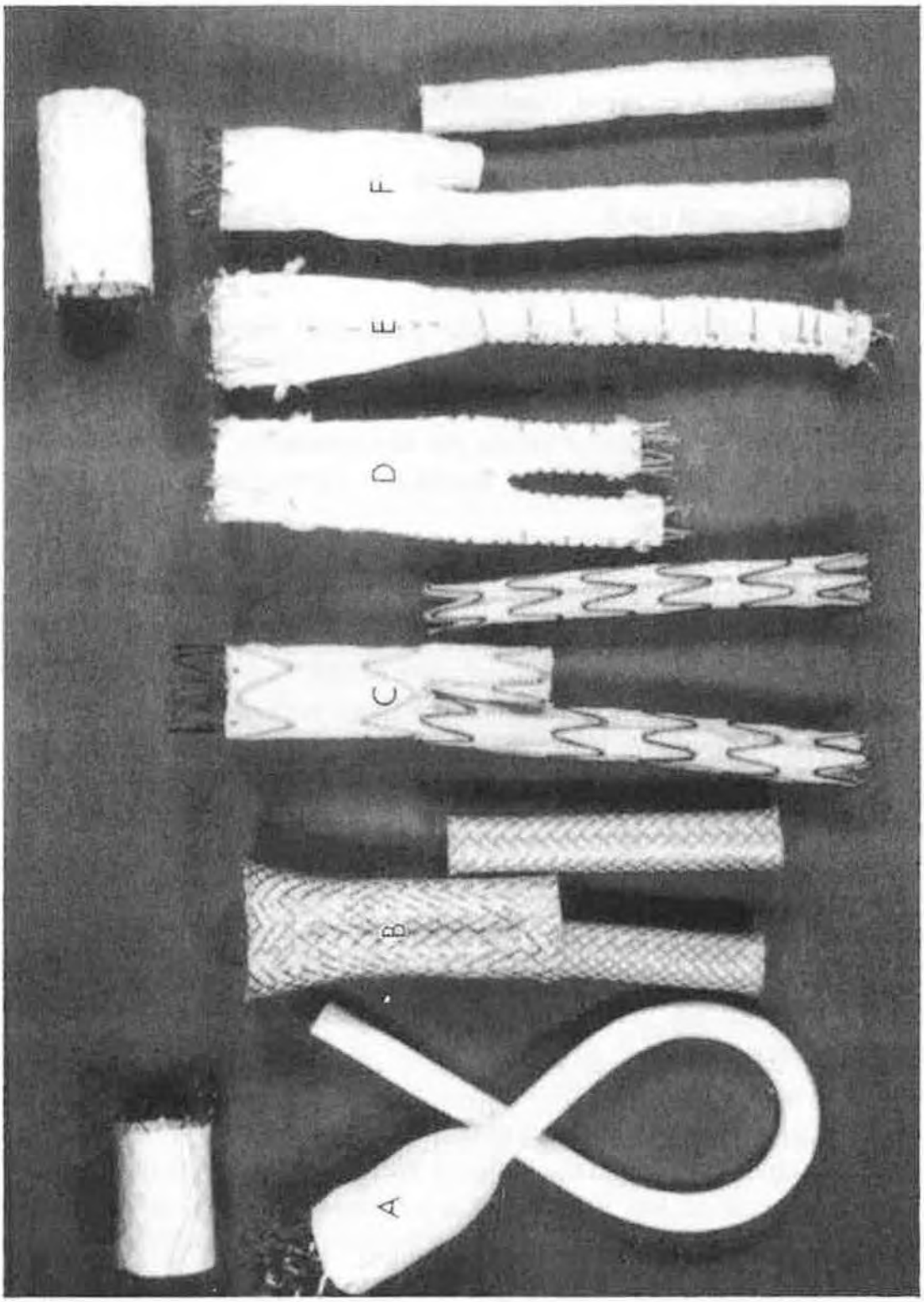

FIGURE 1 (caption on page 236)

FIGURE 1 Caption (for Figure on page 235)

Various types of endovascular grafts used for the treatment of AAA

A. Montefiore graft constructed from a large Palmaz stent and an ePTFE graft. A covered stent made in a similar manner which is used for rescue procedures is above.
B. Corvita bifurcated endoluminal graft.
C. Talent bifurcated graft.
D. EVT bifurcated graft.
E. EVT aortoiliac graft.
F. Vanguard bifurcated graft. (A proximal extender is shown above.)

(Reprinted with permission from T Ohki, and FJ Veith. Five year experience with endovascular grafts for the treatment of aneurysmal, occlusive and traumatic arterial lesions. Cardiovasc Surg, 1998; 6:552-565)

common iliac artery aneurysmal involvement, or a short neck (<1.5 cm) are excluded from the industry made devices. However, many of these have been successfully treated with our own Montefiore graft (Figure 2A, B). Currently, open repair is reserved for those patients who cannot be treated by any of these protocols. Since most of the industry made devices have not been available until mid 1997, a majority of the AAAs treated to date at our institution have been treated with one of the "surgeon made" devices including the Parodi graft and the Montefiore graft.

Improvements made on the "surgeon made graft"

Initially, we used the Parodi type aortoaortic or aortoiliac grafts for AAAs. However, as we gained experience, we modified it into the Montefiore aortofemoral graft because of some difficulties we encountered with the original Parodi type graft (Figure 3A, B). The first difficulty was calculating the exact measurement of the length of the graft. Since the original Parodi device required placement of a second stent to fix the distal end of the graft, it was crucial to obtain an accurate measurement of the graft. In complex AAAs, we found this difficult to do despite the use of all the recommended imaging methods. The Montefiore graft employs a graft that is long enough so that the distal end of the graft emerges from the arteriotomy site used for insertion. Thus, the surgeon can tailor the length of the graft by cutting the excess graft at the arteriotomy site and fixing the distal end of the graft within the artery by a

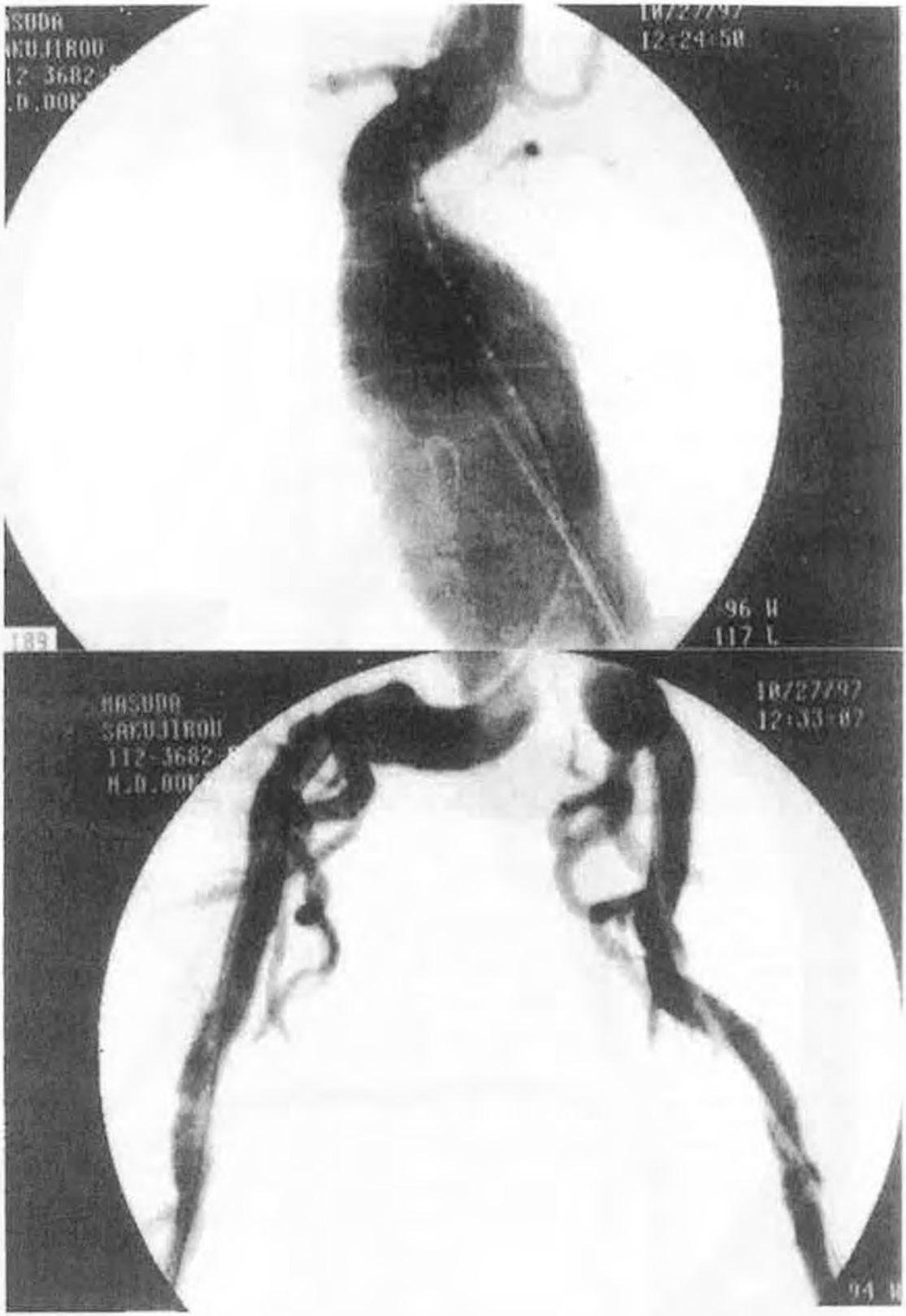

FIGURE 2A (Caption on page 239)

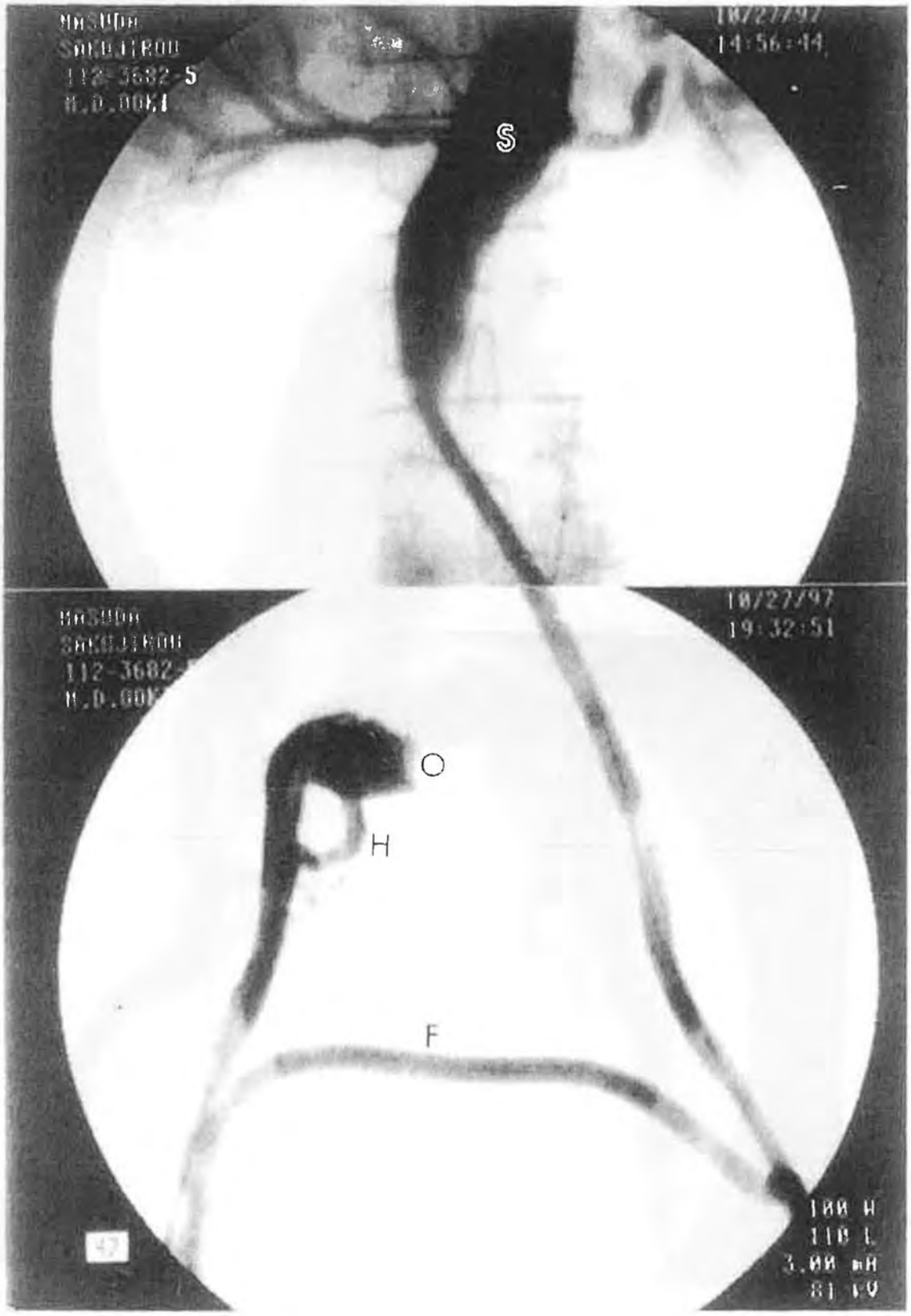

FIGURE 2B (Caption on page 239)

FIGURE 2A Caption (for Figure on page 237)

Intraoperative angiogram of a complex AAA. Due to the versatility of the Montefiore graft, preoperative angiogram is not mandatory and an intraoperative angiogram was obtained to confirm the CT findings. This case was excluded from other industry made devices due to 1) aortic angulation of 80 degrees, 2) large bilateral common iliac arteries (>16mm).

FIGURE 2B Caption (for Figure on page 238)

Completion angiogram reveals complete exclusion of the aneurysm. Note that the aortic angulation has decreased due to the strong radial force of the large Palmaz stent (S) which is placed across the renal arteries. A femorofemoral bypass (F) and the placement of an occluder (O) In the right common iliac artery completes the procedure. H: hypogastric artery. *(Reprinted with permission from Ohki T, Veith FJ. Five year experience with endovascular grafts for the treatment of aneurysmal, occlusive and traumatic arterial lesions. Cardiovasc Surg 1998; 6:552-565).*

hand-sewn endoluminal anastomosis. This modification obviated the need for the precise, and often difficult, preoperative assessment of graft length. In addition, this feature permitted the treatment of an aneurysm with extensive external iliac artery disease. Other limitations of the original Parodi graft were its inability to treat AAAs with short, proximal necks (< 1.5 cm) and the frequent occurrence of proximal endoleaks. To overcome this problem, the cephalad end of the graft material in the Montefiore graft was marked with a metallic marker that could be seen fluoroscopically, and the bare portion of the proximal stent was deployed across the orifices of the renal arteries. This technique offered maximum contact between the proximal attachment device and the proximal aortic neck (Figure 3B). As noted by Parodi and others, we have found the value of aorto-aortic tube grafts to be limited by a high incidence of distal attachment site endoleak and have largely abandoned this procedure except in unusual circumstances (Figure 4).

Operative and Adjunctive Techniques

All endovascular graft procedure was performed in an operating room with the patient prepared for conversion to a standard open vascular

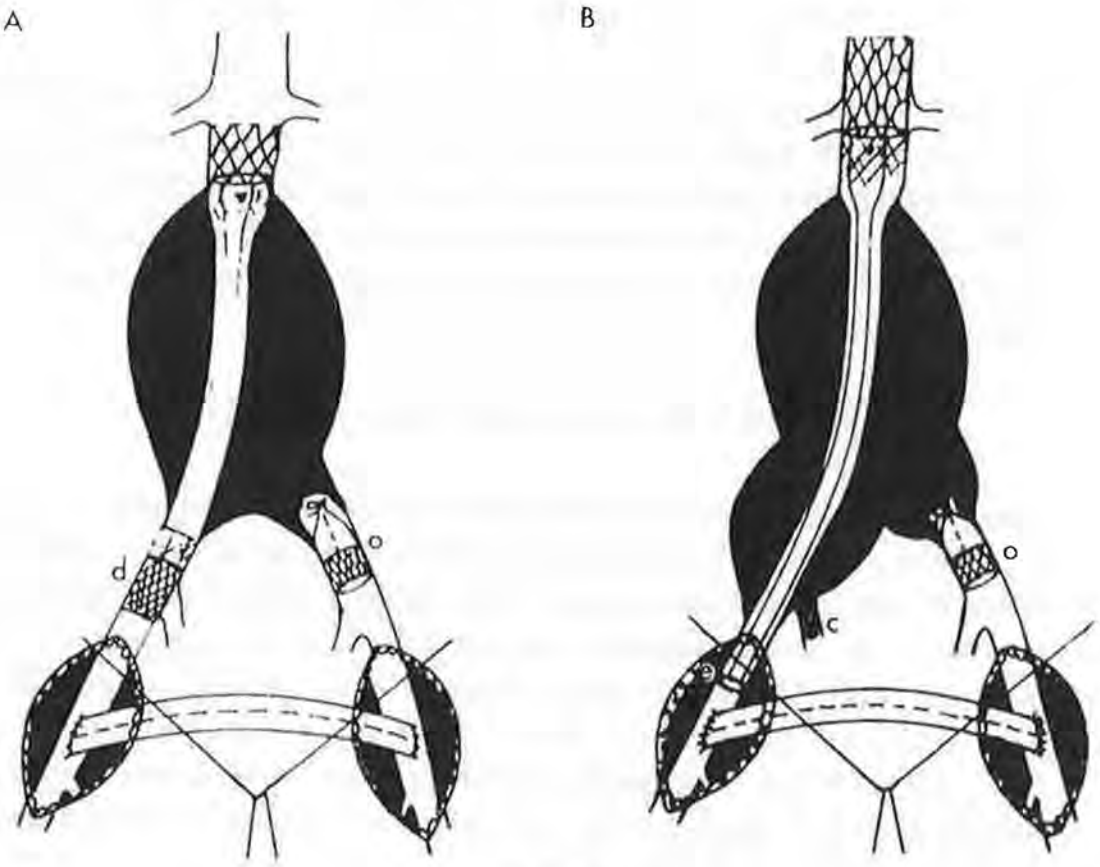

FIGURE 3

A. Parodi type graft. The proximal stent is placed below the renal arteries and the distal end of the graft is fixed with a second stent (d) in the iliac artery. A standard femorofemoral bypass and placement of a occluder device (o) in the contralateral iliac artery completes the procedure.

B. The Montefiore graft. The bare portion of the proximal stent is placed above the renal arteries in order to maximize the fixation within the aorta. The graft covered portion of the stent marked by the radiopaque bead is placed just below the renal arteries. The distal end of the graft is brought out of the insertion arteriotomy site where it is cut to the appropriate length and fixed with a hand-sewn endoluminal anastomosis (e). (c: embolization coils, o: occluder device) *(Reprinted with permission from T Ohki , FJ Veith, LA Sanchez, JC Parodi. Varying strategies and devices for endovascular repair of abdominal aortic aneurysms. Seminars in Vascular Surgery 1997; 10: 242-256).*

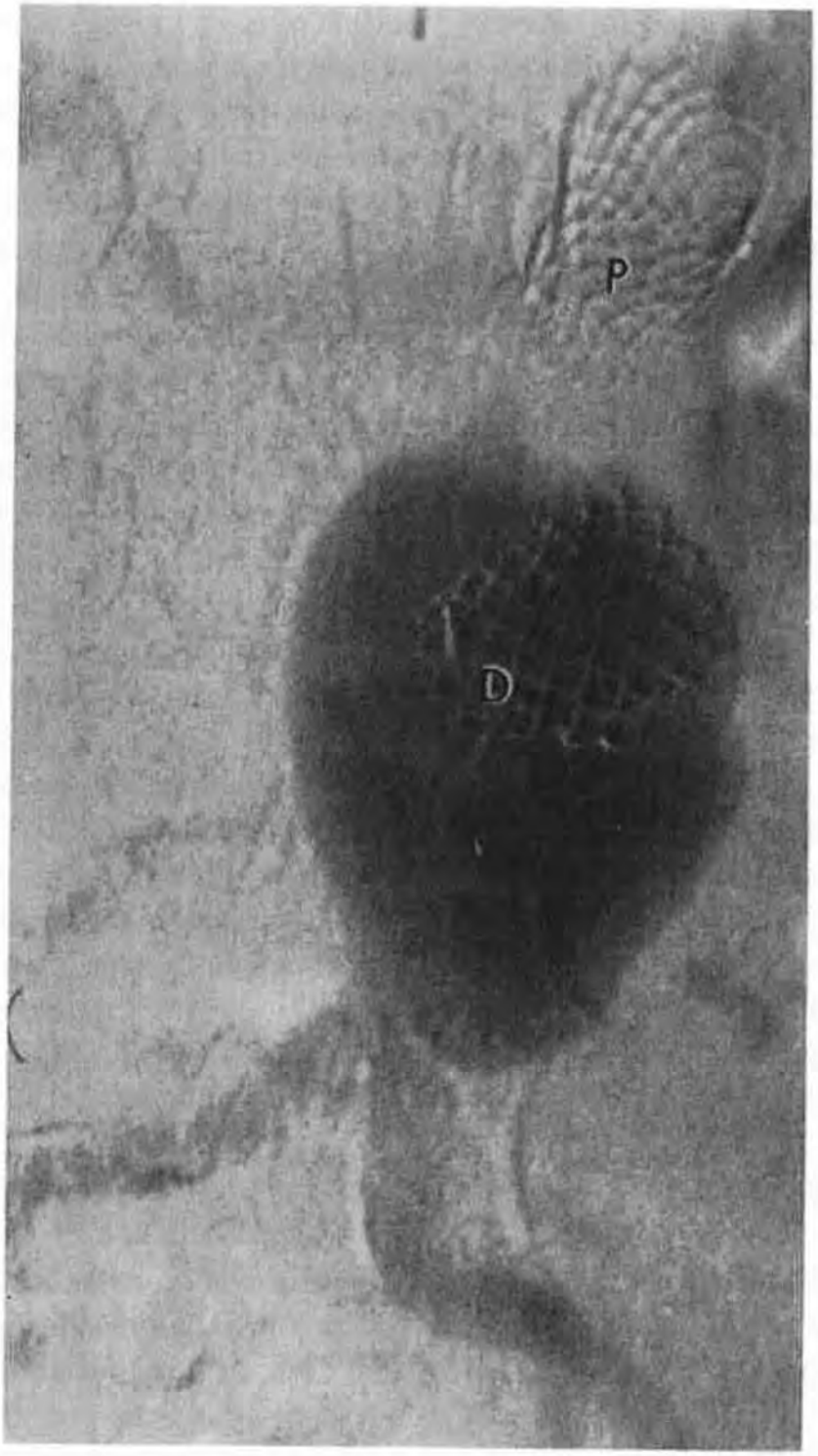

FIGURE 4

Angiogram taken one year after endovascular aortic aneurysm repair with Parodi type aortoaortic graft. The distal fixation stent (d) has been dislodged into the aneurysm and a large endoleak is apparent. This patient subsequently underwent surgical repair of the aneurysm. P: Proximal stent.

surgical repair if required. Bilateral surgical exposure of the common femoral arteries was followed by insertion of a diagnostic catheter into the aorta via the side contralateral to that used for insertion of the aortic graft. The location of the renal artery, aortoiliac bifurcation, and hypogastric arteries as well as the site for proximal graft implantation was identified arteriographically. A delivery catheter containing the endovascular graft was then advanced over a super stiff wire. If difficulty was encountered advancing the device through a diseased, tortuous iliac artery, one of the following techniques were used. First, pressurization of the delivery catheter was performed, which in many cases is sufficient to insert the device. If this failed, additional proximal dissection of the external iliac artery from the surrounding tissue through a groin incision was carried out. This maneuver will usually straighten any tortuosity in the external iliac artery. Finally, a snare was introduced from a left brachial artery puncture site to capture the guide wire introduced from the groin. By applying tension on both ends of the "through and through" guidewire, most of the tortuosity of the aortoiliac system was significantly reduced, and the introduction of the delivery system was usually successful (Figure 5A, B). In addition, if there was stenosis in the iliac system, balloon dilatation prior to insertion of the device was undertaken. Following confirmation of the location of the lowest renal artery, the proximal stent was deployed by inflating the deployment balloon under fluoroscopic guidance. During balloon inflation, the patient's blood pressure was lowered to a mean of 60-70 mm Hg, or asystole was temporarily induced by means of an intravenous bolus of adenosine (20-30 mg) to help stabilize the stent during balloon inflation and deployment.

After the main aortofemoral endovascular graft had been deployed, an occluder device was placed in the contralateral common or external iliac artery, depending on the absence or presence of a common iliac artery aneurysm. In the latter circumstance, coil embolization of the hypogastric artery would also have been performed. This has only been done in our highest risk cases in whom no other alternative has been possible. Finally, a standard femorofemoral crossover graft was constructed (Figure 3).

Completion arteriograms and intravascular ultrasound (IVUS) were performed to assure adequate flow thorough the grafts and the absence of an "endoleak." IVUS can identify many abnormalities, such as graft compression or stenosis which are not always apparent on angiography [15]. In addition, when the graft does not extend to the femoral artery,

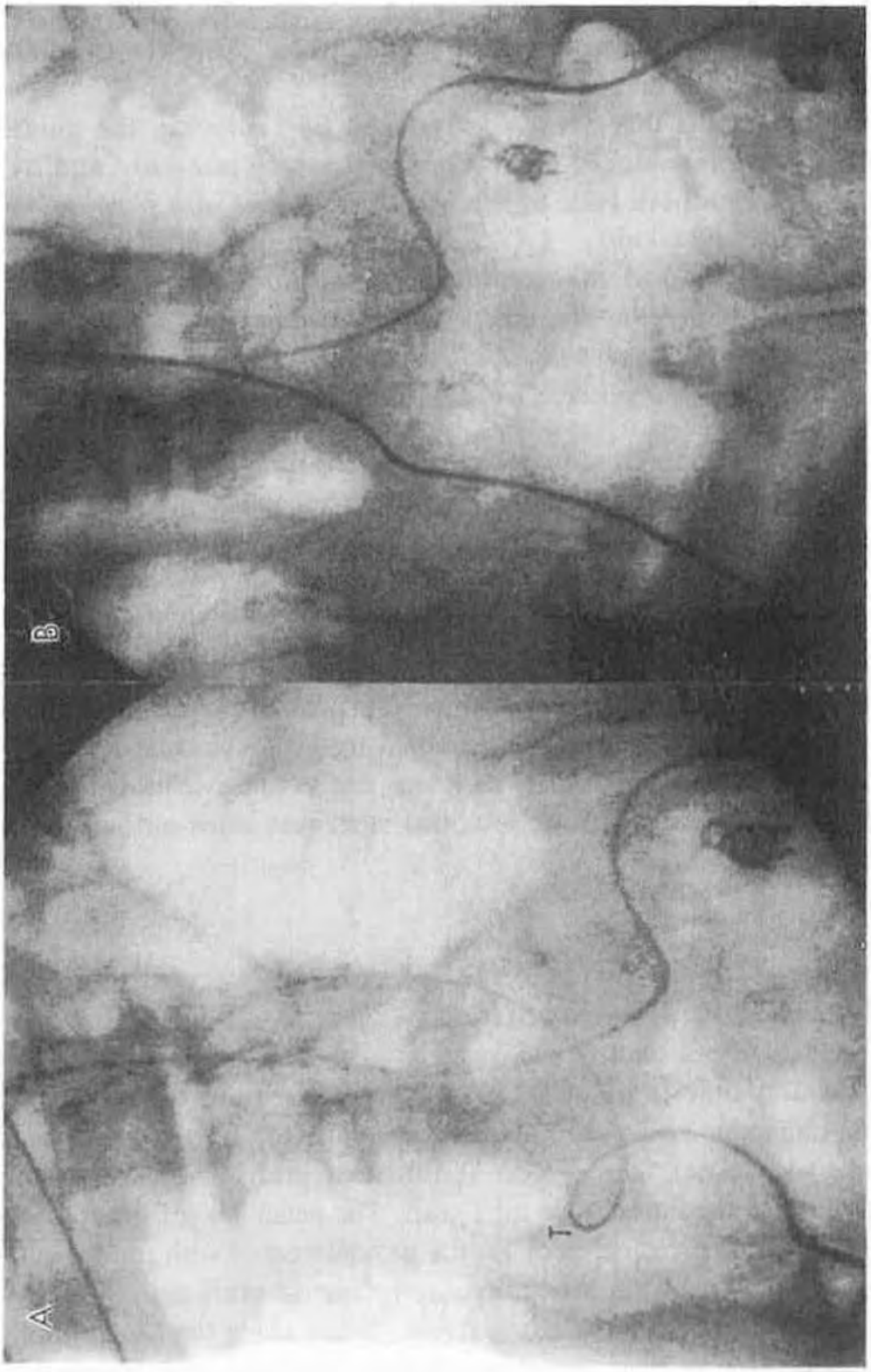

FIGURE 5 (Caption on page 244)

FIGURE 5 Caption (for Figure on page 243)

Fluoroscopic image after insertion of a guidewire. Note the marked tortuosity of the right iliac vessels (T).
The tortuosity of the iliac vessels is reduced by capturing the guide wire with a snare introduced from a brachial artery puncture and by applying tension on both ends of the wire. (*Reprinted with permission from T Ohki, FJ Veith, LA Sanchez. Transluminally placed endovascular grafts for the treatment of aortic and iliac artery aneurysms. In: Current diagnosis and treatment of aortic and peripheral arterial aneurysms. Calligaro KD, MJ Dougherty, L Hollier, (Editors), WB Saunders Co, Ltd, London, 1997).*

IVUS can detect iliac artery dissections which, if unrecognized, can produce outflow obstructions. When such lesions were detected, they could easily treated by additional balloon dilatation or placement of a Palmaz stent or Wallstent (Figure 6A, B).

Endoleaks were treated by one of the following techniques. If an endoleak was due to low deployment of the proximal stent, a PTFE covered Palmaz stent was deployed proximal to the previously deployed graft to seal the leakage (Figure 1). If it was due to under-deployment of the stent, further dilatation of the proximal stent was often sufficient to seal the leakage.

RESULTS

Parodi Type Graft Vs. Montefiore Graft

In our first 41 AAAs treated endovascularly, 8 were treated with the Parodi type aortoiliac graft and 13 with the Montefiore aortofemoral graft. The remaining cases were treated with either the EVT graft (tube, bifurcated, aorto-iliac), the Talent bifurcated graft, the Vanguard bifurcated graft or the Parodi type tube graft. The mean size of the AAAs and the length of the proximal neck for the groups treated with the Parodi type aortoiliac graft and the Montefiore aortofemoral graft were 6.8 cm and 18 mm, 6.8 cm and 21 mm, respectively. When using the Montefiore graft, we were able to treat aneurysms with a proximal neck length of shorter than 10 mm. The rate of endoleaks appeared to be lower with the Montefiore graft (50% vs 31%). There was one mortality in each group.

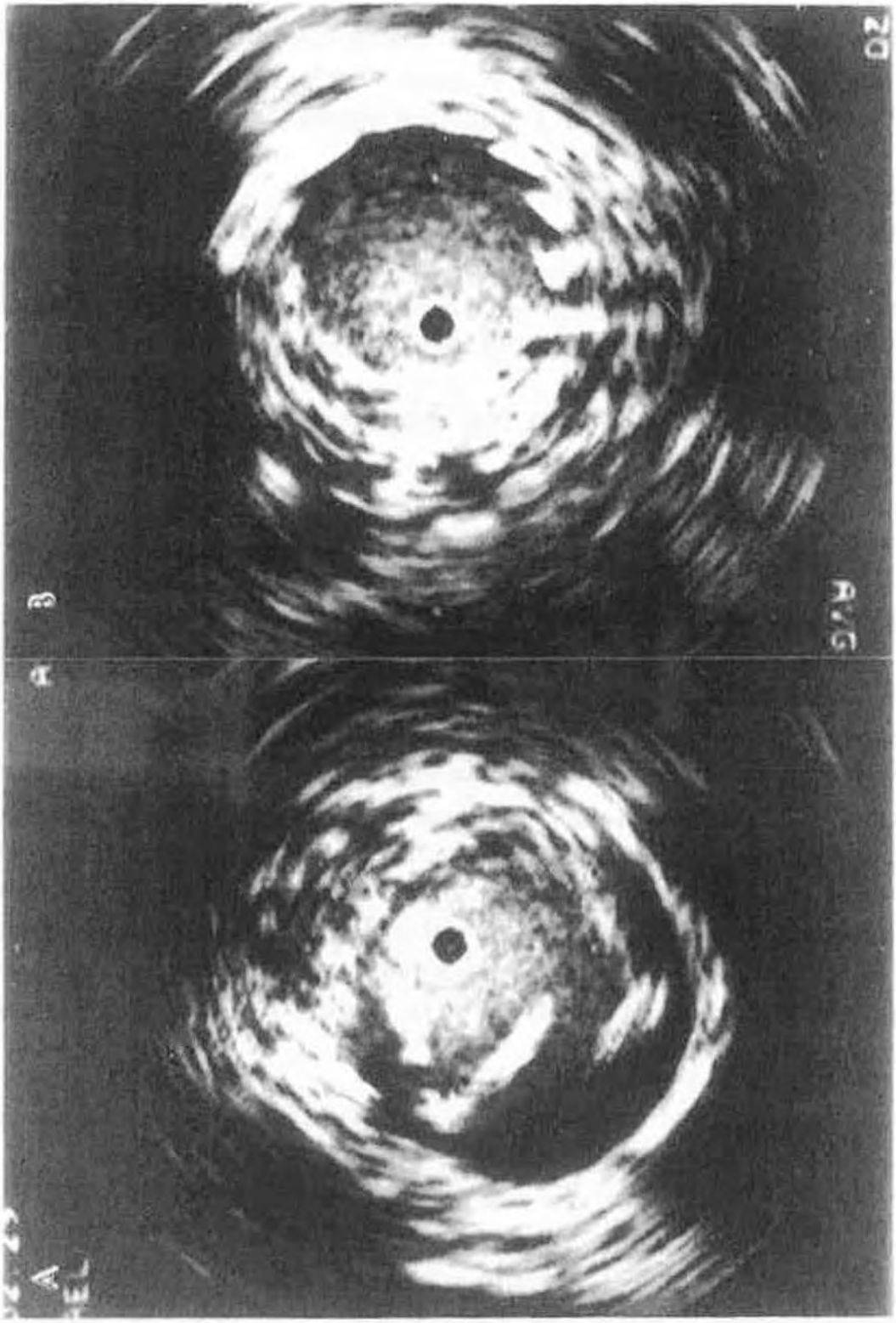

FIGURE 6 (Caption on page 246)

FIGURE 6 Caption (for Figure on page 245)

A) Intravascular ultrasound image showing dissection of the external iliac artery secondary to the passage of a large introducer device. This was not apparent on completion angiogram.

B) Intravascular ultrasound image following placement of a Wallstent to fix the dissection. *(Reprinted with permission from T Ohki, FJ Veith. Five year experience with endovascular grafts for the treatment of aneurysmal, occlusive and traumatic arterial lesions. Cardiovasc Surg 1998; 6:552-565).*

STENTED GRAFT REPAIR OF ISOLATED ILIAC ARTERY ANEURYSMS

Surgeon-made endovascular grafts similar to those devices described previously have been used to treat 20 patients with isolated common and/or internal iliac artery aneurysms. In all of these patients, the devices have been inserted successfully and have remained patent, except for one, for the period of follow-up (mean 33 months, range 6-60 months). One patient, whose iliac graft thrombosed, required a femorofemoral bypass and has continued to remain asymptomatic and the aneurysm remains excluded. One additional patient, whose original endovascular graft was fixed proximally in a clot-filled segment of common iliac artery, presented with enlargement and rupture of his iliac artery aneurysm. He has done well following standard repair. In retrospect, this patient should have been treated primarily with an aorto-femoral endovascular graft so that the proximal stent would be fixed in a portion of the artery without thrombus.

STENTED GRAFT REPAIR OF AORTOILIAC OCCLUSIVE DISEASE

Construction of the Stented Graft

Surgeon-made endovascular grafts which is composed of a Palmaz balloon-expandable stents (P-294, Cordis, Johnson & Johnson Interventional Systems, Warren, NJ) and 5 or 6 mm thin walled polytetrafluoroethylene (PTFE) grafts (WL Gore and Associates, Flagstaff, AZ; and IMPRA, Inc, Tempe, AZ) (Figure 7A). The stent is

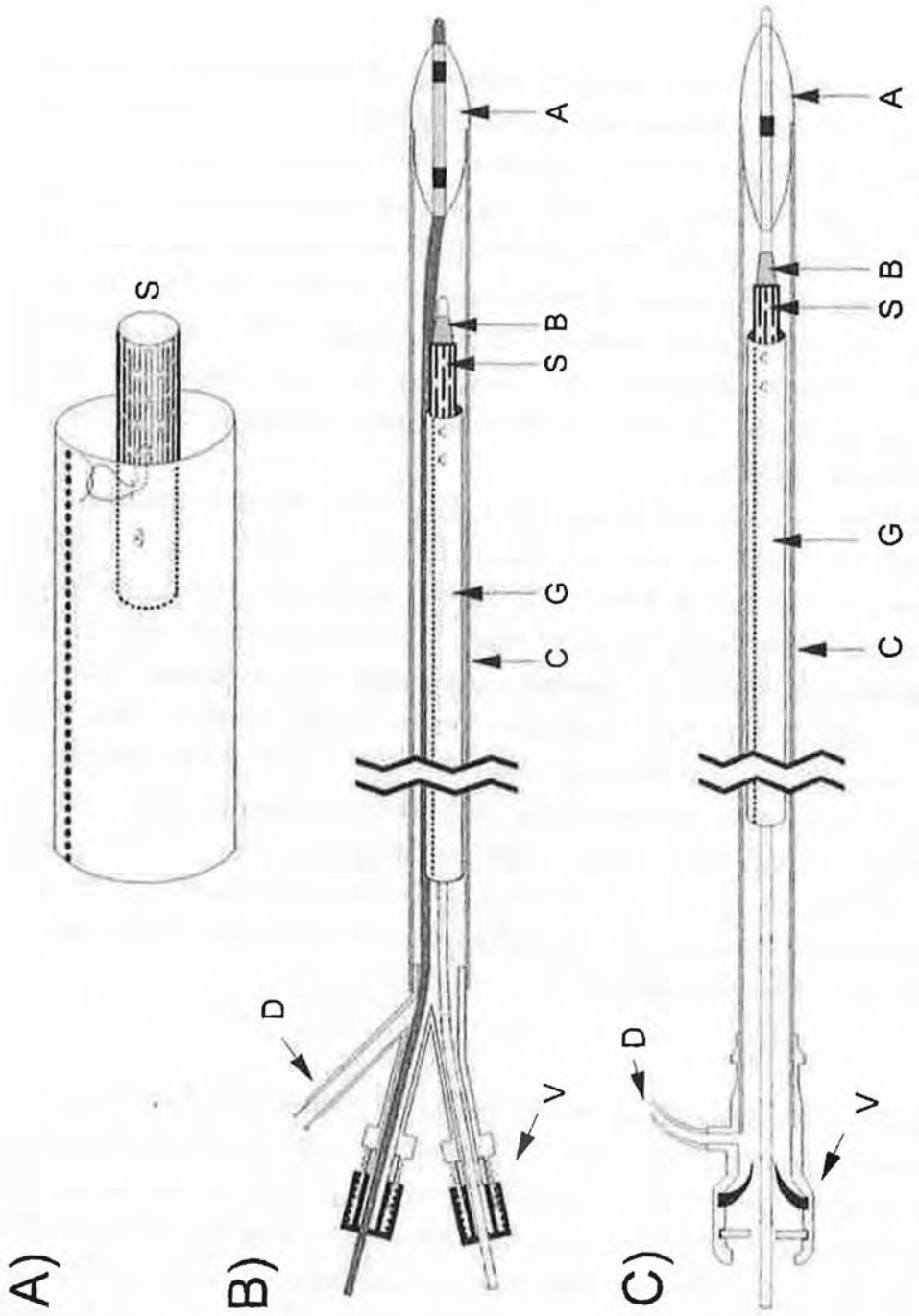

FIGURE 7 (Caption on page 248)

FIGURE 7 Caption (for Figure on page 247)

Schematic Drawings of an Endovascular Graft and the Delivery Systems

A) An endovascular thin walled polytetrafluoroethylene (PTFE) graft. A Palmaz balloon expandable stent (S) is sutured to the graft using 4 diametrically opposed "U" sutures (two on each side) which permit one-half of the stent to protrude from the graft.

B) Double balloon catheter introducer/delivery system used for the delivery and deployment of endovascular stented grafts. In this system, the introducer catheter is equipped with two separate balloon catheters. Balloon "A" functions as a mechanism to form a tapered tip to the catheter system and also allows pressurization of the flexible sheath.

C)* After saline is injected from port D. The second balloon (B) functions to deploy the overlying Palmaz stent (S). With expansion of balloon B, the endovascular graft (G) becomes firmly fixed to the underlying arterial wall. (V = hemostatic valve) C) An alternative delivery system consisting of a single balloon catheter which has two balloons on a single shaft. The first balloon serves as a tip balloon (A), while the stent graft complex is mounted onto the independent deploying balloon (B). (V = hemostatic valve) *(Reprinted with permission from T Ohki, ML Marin, FJ Veith, et al. Endovascular aortounifemoral grafts and femorofemoral bypass for bilateral limb-threatening ischemia J Vasc Surg, 1996; 24: 984-997).

attached to the proximal end of the PTFE graft by 4 CV-6 PTFE sutures (WL Gore and Associates) so that one-half of the stent protrudes from the end of the graft (Figure 7A). After suturing the graft to the stent, the stent-graft complex is mounted onto an angioplasty balloon by manually crimping the stent over the 6-8 mm x 4 cm angioplasty balloon (OPTA, Cordis, Johnson & Johnson Interventional entire stent, graft, and balloon complex is then inserted into a delivery sheath Systems, Warren, NJ; Diamond, Medi-tech, Inc, Watertown, MA). The (Figure 7B). A smooth transition zone at the end of the sheath is created by using a 6 mm x 4 cm tip balloon. The tip balloon is adjusted so that one-half of the tapered portion of the balloon protrudes from the distal portion of the delivery

sheath. A modified form of this delivery system consists of a dual balloon catheter (tip balloon and stent-deploying balloon) on a single shaft (Figure 7C). In both delivery system configurations, the tip balloon functions to create a smooth transition zone at the distal end of the delivery sheath as well as to occlude the sheath which permits pressurization of the sheath when saline is injected from the flush port. The pressurization provides variable pushability and flexibility of the sheath, depending on the amount of pressure applied. This feature facilitates the insertion of the delivery sheath through diseased and tortuous iliac arteries.

Issues Related to Bilateral Iliac Disease

In cases in which the iliac artery is occluded or diffusely stenosed bilaterally, a bilateral stent-graft repair can be performed (Figure 8A). We initially performed this procedure. However, since bilateral reconstructions were technically more difficult and often resulted in compromised outcomes, we now prefer to perform a unilateral repair followed by a femorofemoral bypass (Figures 8B, 9) [23]. The iliac artery in which the endovascular graft is deployed and the positioning of the proximal stent are determined by preoperative angiographic findings. Deployment of the endovascular graft will likely result in occlusion of the internal iliac artery and all the small branches along the vessel that are covered by the graft. The presence and quality of the internal iliac artery will, therefore, influence the side of endovascular graft access and deployment. Similarly, the length and degree of disease of the common or external iliac artery will often determine the technical difficulty associated with vessel recanalization. Generally, it is easier and safer to recanalize through a stenotic rather than an occluded lesion. In addition, shorter lesions are easier to recanalize. The classification of disease patterns, the side to be used for endovascular graft insertion, and the location of the proximal stent can be determined using the algorithm outlined in Figure 10.

Operative Technique

Following sheath placement in the femoral artery, either a Benson wire (Cook, Inc., Bloomington, IN) or a Glidewire (Terumo, Tokyo, Japan) is used for recanalizing the occluded iliac artery. Under fluoroscopic control, a directional catheter is used to direct and control the guidewire through the occluded or stenosed iliac artery [23]. It is of paramount importance to return to the true lumen at the proximal end of the occluded segment, since the guidewire has a tendency to traverse the dissection

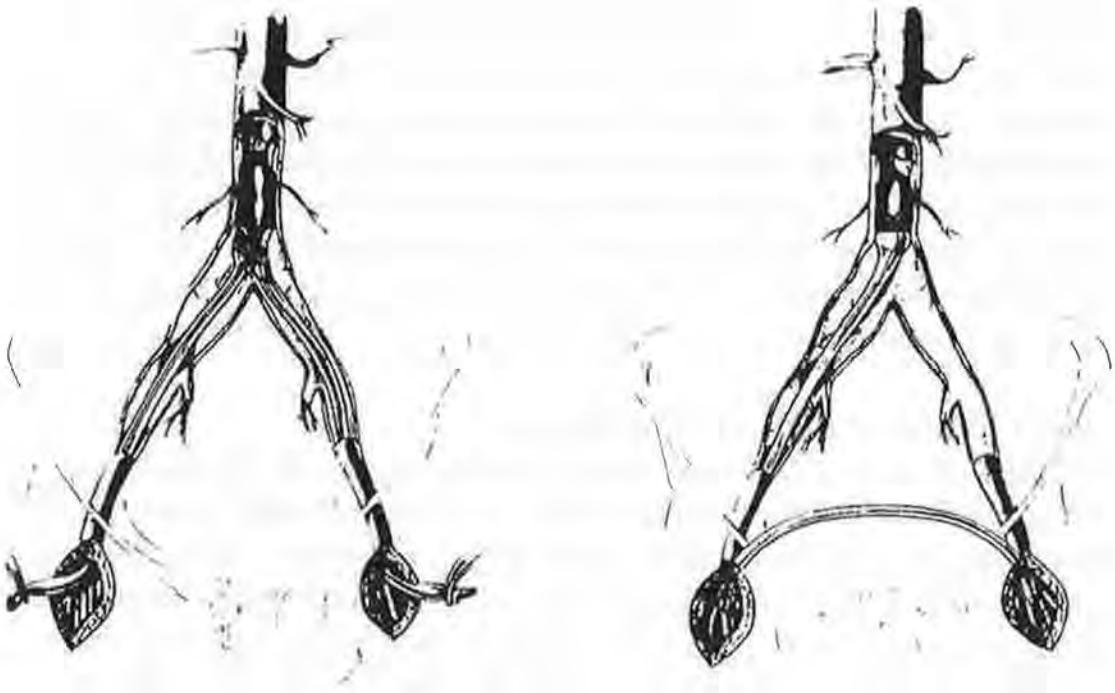

FIGURE 8

A) Drawing of bilateral endovascular aortofemoral graft insertion. Two stents are squeezed into a small, diseased distal aorta. ***(Reprinted with permission from T Ohki, FJ Veith, RA Wain, LA Sanchez. In Current Review of Minimally Invasive Surgery, 3rd edition, DC Brooks, Editor, Philadelphia: Current Medicine, 1998)***

C) Drawing depicting the completion of an endovascular aortoiliac bypass and a standard femorofemoral bypass.

plane (between the adventitia and the media) through the occluded segment. In cases in which the contralateral iliac artery is patent, recanalization may be performed with a catheter placed through a percutaneous puncture of the contralateral femoral artery. This technique has the advantage of assuring that the recanalized lumen will always join the true lumen at the proximal site.

After successful wire passage, a 6-8 mm in diameter angioplasty balloon is passed over the wire and the iliac artery is dilated along its entire length. The previously prepared endovascular graft device is then

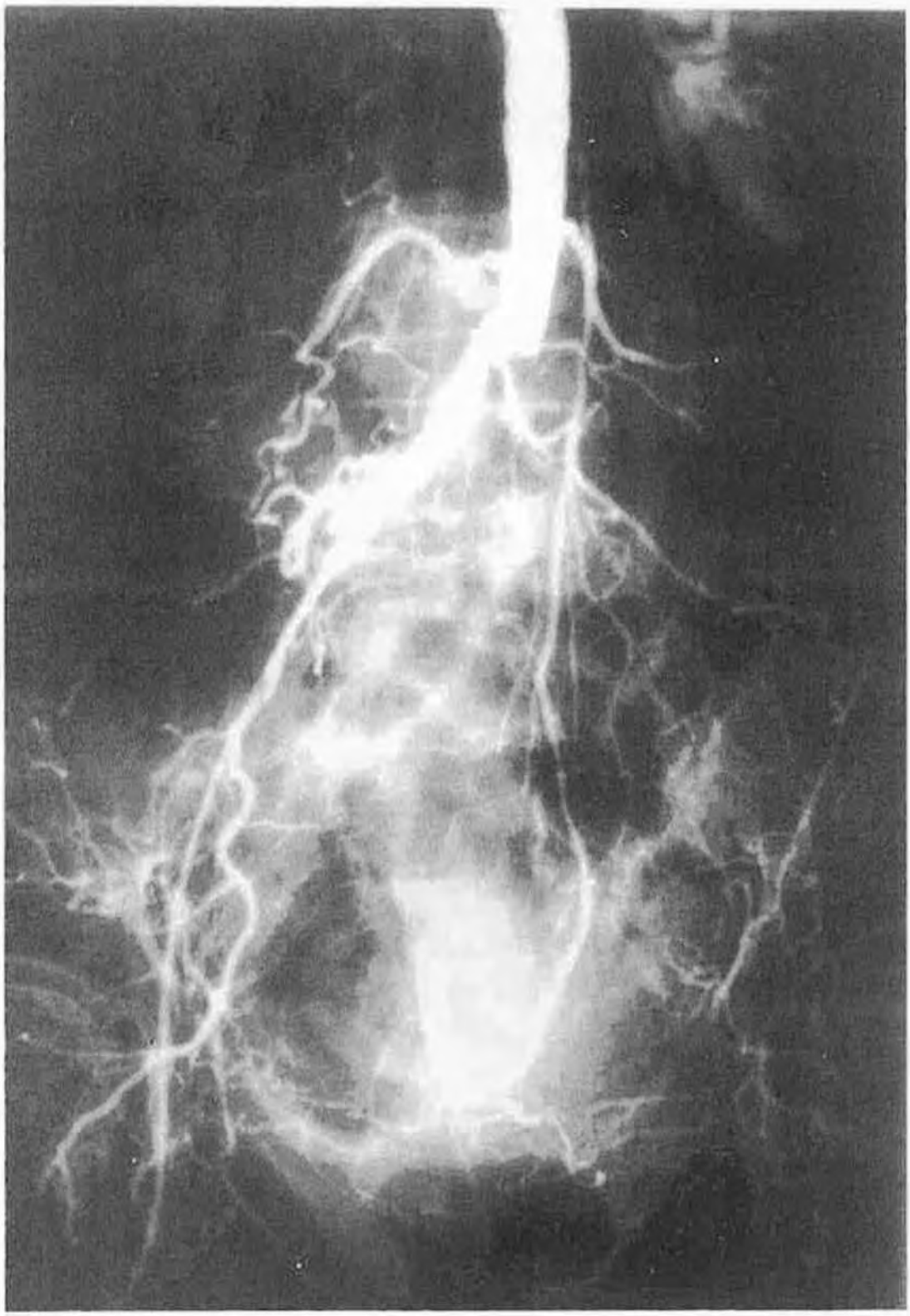

FIGURE 9A (Caption on page 253)

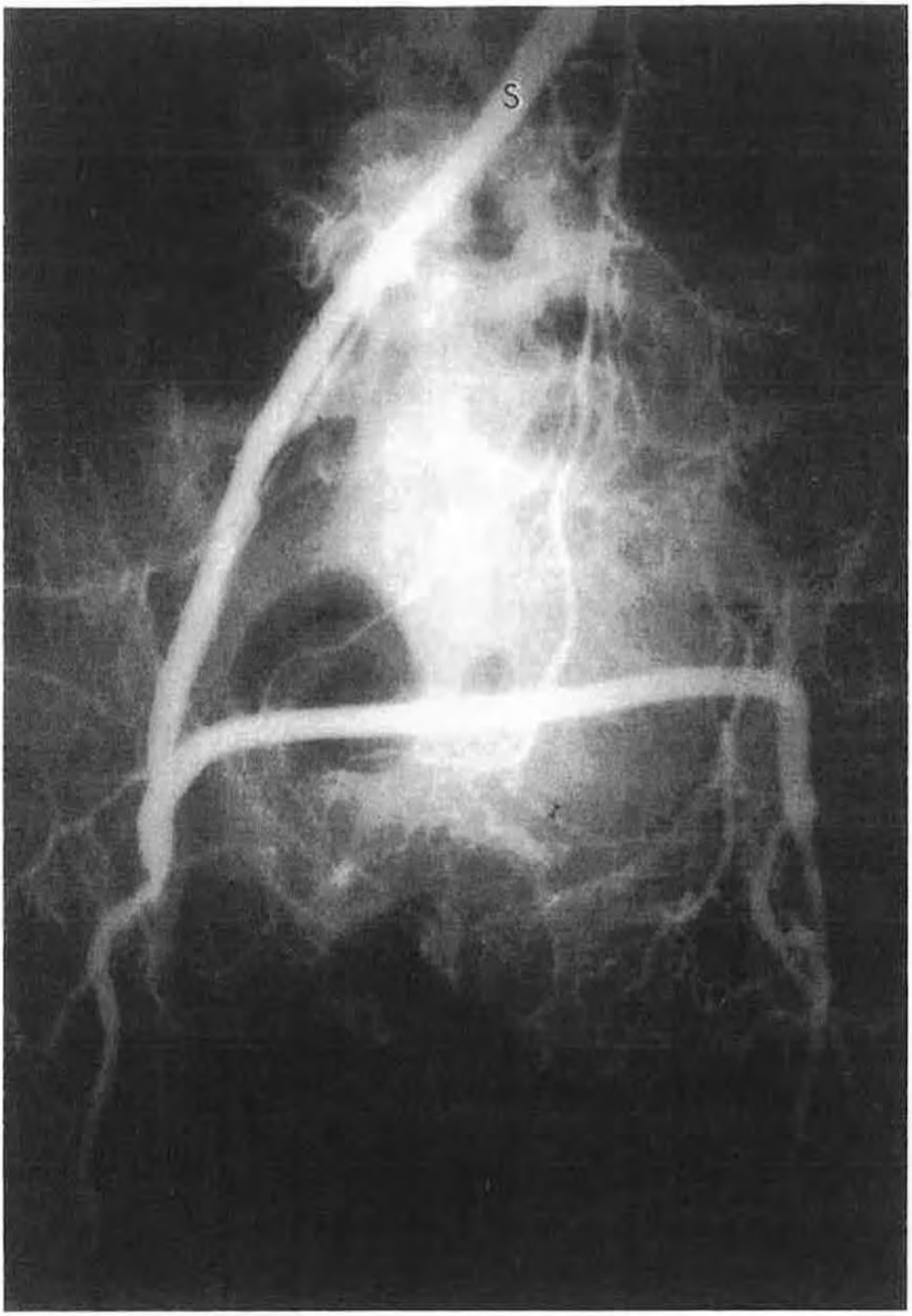

FIGURE 9B (Caption on page 253)

FIGURE 9 Caption (for Figures on pages 251 and 252)

A) **Preoperative arteriogram of a patient who presented with bilateral foot gangrene. The right external iliac artery is occluded, and the iliac system is occluded from its origin on the left side. Due to the ease of recanalization, the right side was chosen for recanalization and graft insertion.**

B) **Completion arteriogram. By placing the stent (S) above the lesion (within the distal aorta), and performing the endoluminal anastomosis in the femoral artery, a good angiographic result was obtained. However, this has also resulted in the sacrifice of the existing hypogastric, epigastric and superficial circumflex iliac arteries, suggesting that the patient may end up requiring a higher level of amputation when the graft fails compared to what he might need otherwise.**

inserted into the newly created tract within the arterial wall over the same guidewire. Once the fixation stent is fluoroscopically located at the appropriate predetermined site, the tip balloon is deflated and the sheath is partially retracted while holding the balloon catheter in place. The exposed proximal stent can now be deployed. The introducer sheath is then completely withdrawn, permitting the redundant portion of the distal end of the endovascular graft to emerge from the arteriotomy in the access vessel. The distal, redundant portion of the graft is then cut to an appropriate length and endoluminally hand-sewn into the patent, distal runoff vessel (Figure 11).

For bilateral occlusions, a 6 mm, externally supported, thin walled PTFE graft is used for the femorofemoral bypass. The arteriotomy site used for insertion of the endovascular graft serves as the proximal anastomotic site of the femorofemoral bypass (Figure 11). The graft is then subcutaneously tunneled to the contralateral side, and the recipient anastomosis is performed in a standard fashion to the patent distal runoff vessel.

RESULTS

During the five year period, endovascular graft repair for aortoiliac disease was performed in 55 patients. The vast majority of these patients had major contraindications to standard treatment. The mean age of the

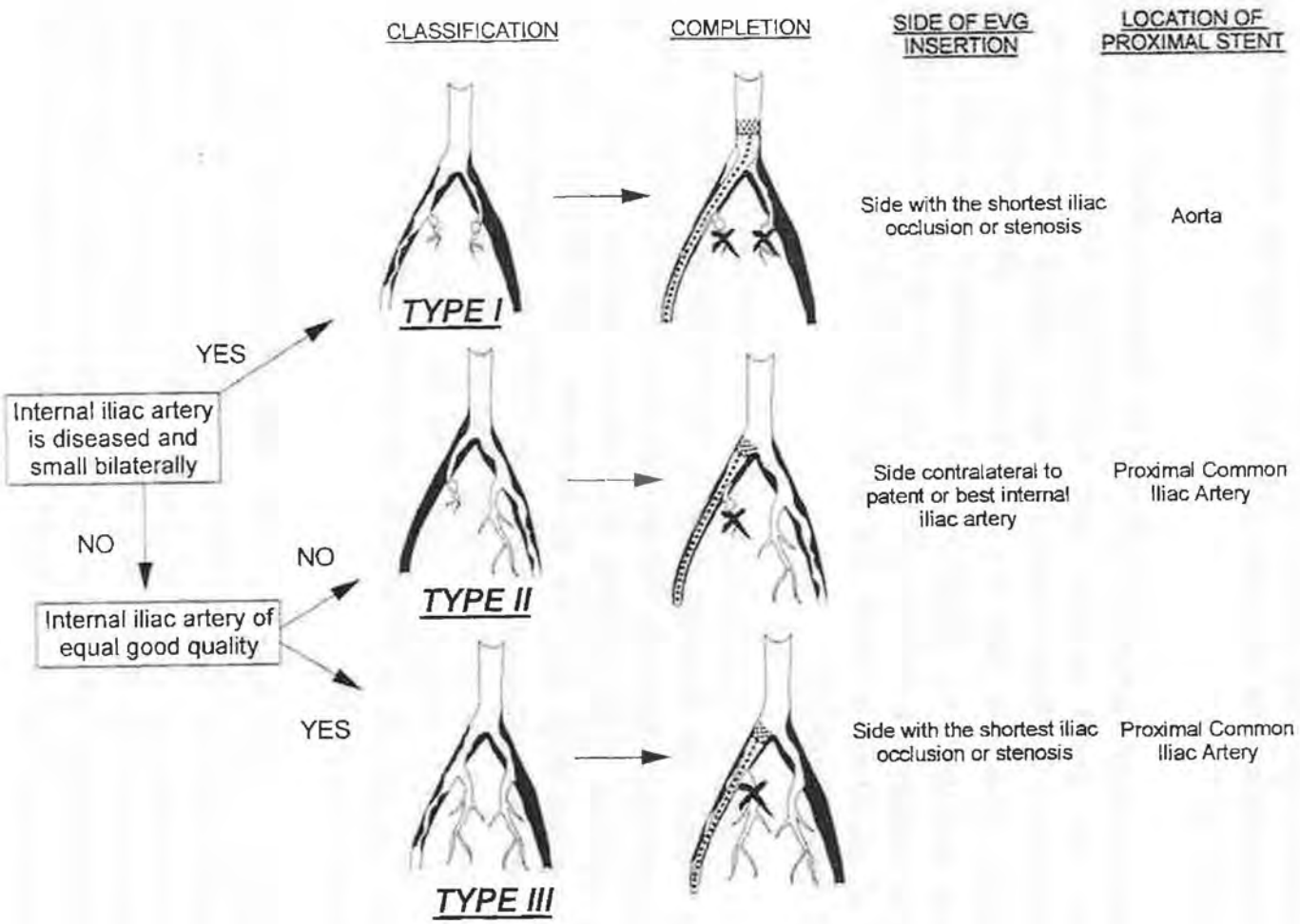

FIGURE 10 (Caption on page 255)

FIGURE 10 Caption (for Figure on page 254)

Algorithm and classification of endovascular grafting for bilateral aortoiliac occlusive disease.

The classification of the distribution of disease, the determination of the appropriate side for graft insertion, and the identification of the location for proximal stent deployment may be approached using this algorithmic outline. *(Reprinted with permission from T Ohki, ML Marin, FJ Veith, et al. Endovascular aortounifemoral grafts and femorofemoral bypass for bilateral limb-threatening ischemia J Vasc Surg, 1996; 24: 984-97).*

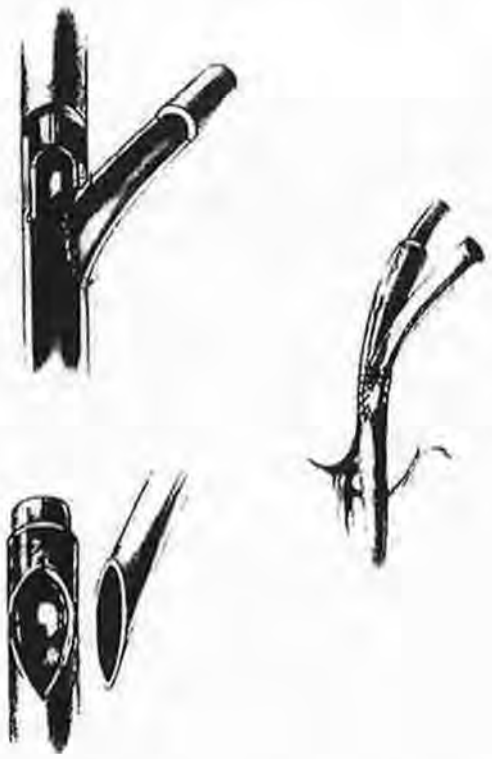

FIGURE 11

The distal end of the endovascular graft will emerge from the arteriotomy site and then be cut to the appropriate length. The endovascular graft is then endoluminally hand-sewn to the interior of the femoral artery (A). The proximal anastomosis of a femorofemoral bypass is then performed over the arteriotomy site (B, C).

patients was 67 and there were 28 males and 27 females. Forty-six percent of the patients had diabetes, 81% had coronary artery disease and 19% had COPD. Of note is that 60% of the patients had a history of myocardial infarction. Technical success was achieved in 94% of the patients. The cases that failed were due to inability to recanalize the occluded segment. The mean graft length was 23 cm, and simultaneous infrainguinal bypass was performed in 47% of the cases. The complication rate was 10%, and 30 day mortality was 4%. Using life table analysis employing the intention-to-treat principle, primary (78 ± 7%) and secondary (86 ± 6%) rates were achieved at 3 years. The graft failures were attributed to the endograft in 2 patients (4%) and progression of inflow, outflow, or an undefined cause in 4%, 12%, and 2%, respectively. Limb salvage and patient survival rates at 3 years were 93 ± 4% and 71 ± 7%, respectively.

STENTED GRAFT REPAIR OF ARTERIAL TRAUMA

Devices and Technique

We have predominantly used a surgeon made graft with a Palmaz stent in combination with a thin walled PTFE graft covering to perform arterial repairs of pseudoaneurysms and arteriovenous fistulas. The stents varied between 2 - 3 cm in length (Palmaz P-204, 294, 308) and were fixed inside 5 or 6 mm Gore-Tex grafts by 4 "U" stitches (Figure 12). The stented graft was then mounted on a balloon angioplasty catheter which had a tapered dilator tip firmly attached to its end. The entire device was contained within a 10-12 Fr delivery system for over-the-wire insertion either percutaneously or through an open arteriotomy.

We have also utilized for traumatic arterial lesions an alternative device, the Corvita endoluminal graft (Corvita Corporation, Miami, FL), which is fabricated from a self-expanding stent of braided wire. The stent is covered with polycarbonate elastomer fibers (Figure 13). This stent-graft may be cut to the desired length in the operating room using wire cutting scissors and then loaded into a specially designed delivery sheath. This sheath has a central "pusher" catheter which is used for maintaining the graft in position while the outer sheath is withdrawn, releasing the self expanding stent-graft.

RESULTS

All procedures but one were performed in the operating room under fluoroscopic (Philips, BV 212, Netherlands) and intravascular

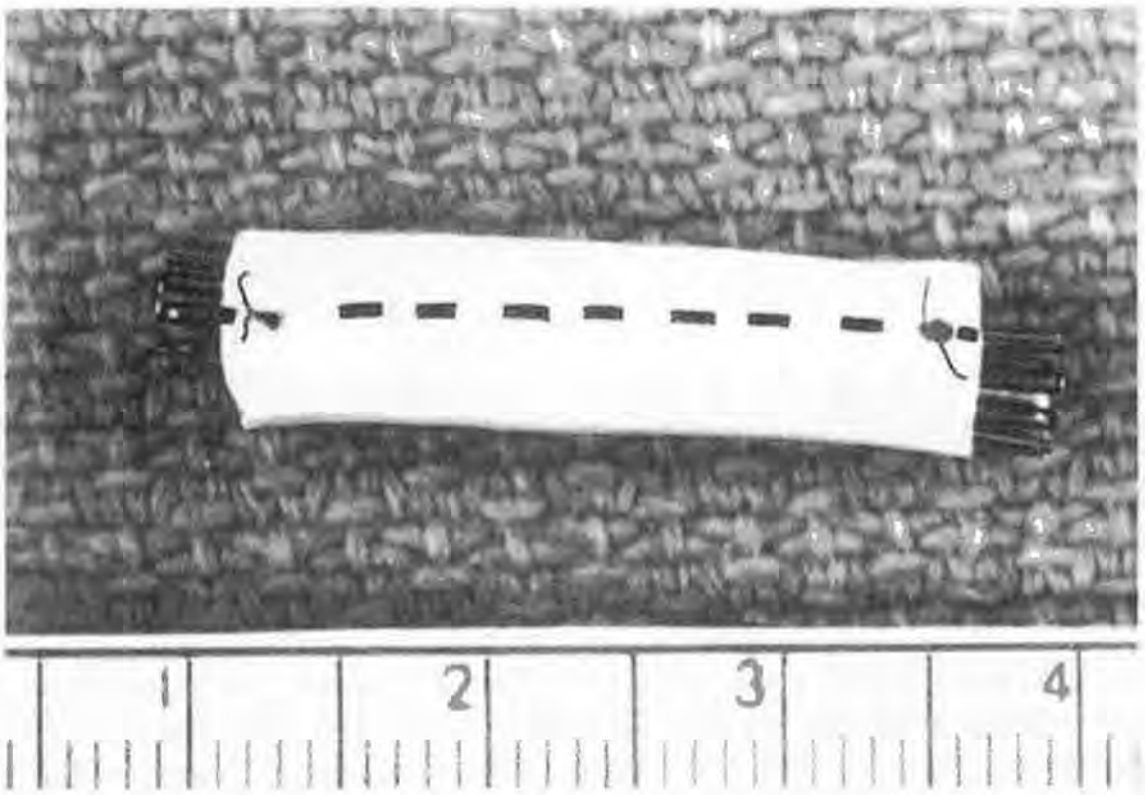

FIGURE 12

Endovascular graft used for traumatic arterial lesions.

ultrasonographic control (Hewlett Packard Company, Paramus, NJ). One Corvita graft was inserted in the angiography suite. A total of 17 stented grafts or covered stents have been used to treat 17 patients with traumatic arterial lesions. Seven injuries occurred as a result of gunshot wounds (Figure 14A, B, C); 1) as a result of a knife wound; there were 4 iatrogenic catheterization injuries; 2) iatrogenic arterial traumas (gynecological surgery or lumbar disk surgery); and 3) occurred as a result of arterial graft disruptions possibly associated with infection.

All injuries except for one were associated with an adjacent pseudoaneurysm. In five instances, the arterial injury formed a fistula to an injured adjacent vein. Associated injuries were present in 8 patients with arterial trauma. The majority of the cases were performed under either local or epidural anesthesia. One patient, who had an axillary pseudoaneurysm repaired with a stented graft, required a vein patch to close a small brachial artery insertion site. Procedural complications were limited to one distal embolus which was removed by suction embolectomy

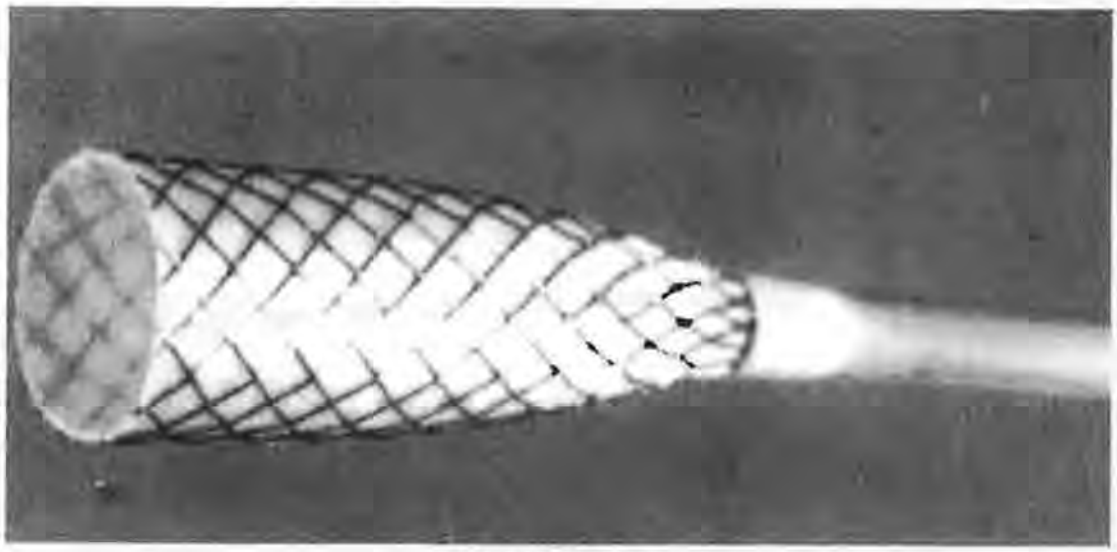

FIGURE 13

Corvita endoluminal graft used for arterial trauma. This graft is manually crimped into a 9 or 10 Fr delivery sheath. (*Reprinted with permission from T Ohki, FJ Veith, WR Bertucci, B Marsan, LA Sanchez. New technologies for vascular injury. Curr Opin Crit Care, 1997; 3: 456-469).*

and one wound hematoma which resolved without further intervention. intervention. Graft patency was 100% with no early or late graft occlusions (mean follow-up 30 months [range 6-56 months]). One patient with a left axillary-subclavian stent-graft developed compression of the stent at 12 months and was treated with balloon angioplasty. This device has not thrombosed with follow-up over 3 years. Another patient who received a Corvita graft required a balloon angioplasty and stent placement for intimal hyperplasia (Figure 14D).

DISCUSSION

After the first successful repair of endovascular grafting for the treatment of AAAs was reported by Parodi [25], the indications for endovascular grafting were expanded to include arterial occlusive disease [16, 18], occluded grafts [19], peripheral aneurysms [20, 21], paraanastomotic aneurysms [22], and traumatic arterial lesions [23, 34]. Based on the currently available reported results, endovascular grafting for traumatic central arterial lesions and isolated iliac artery aneurysms in high surgical risk patients seem to be already justified. Although the endovascular graft

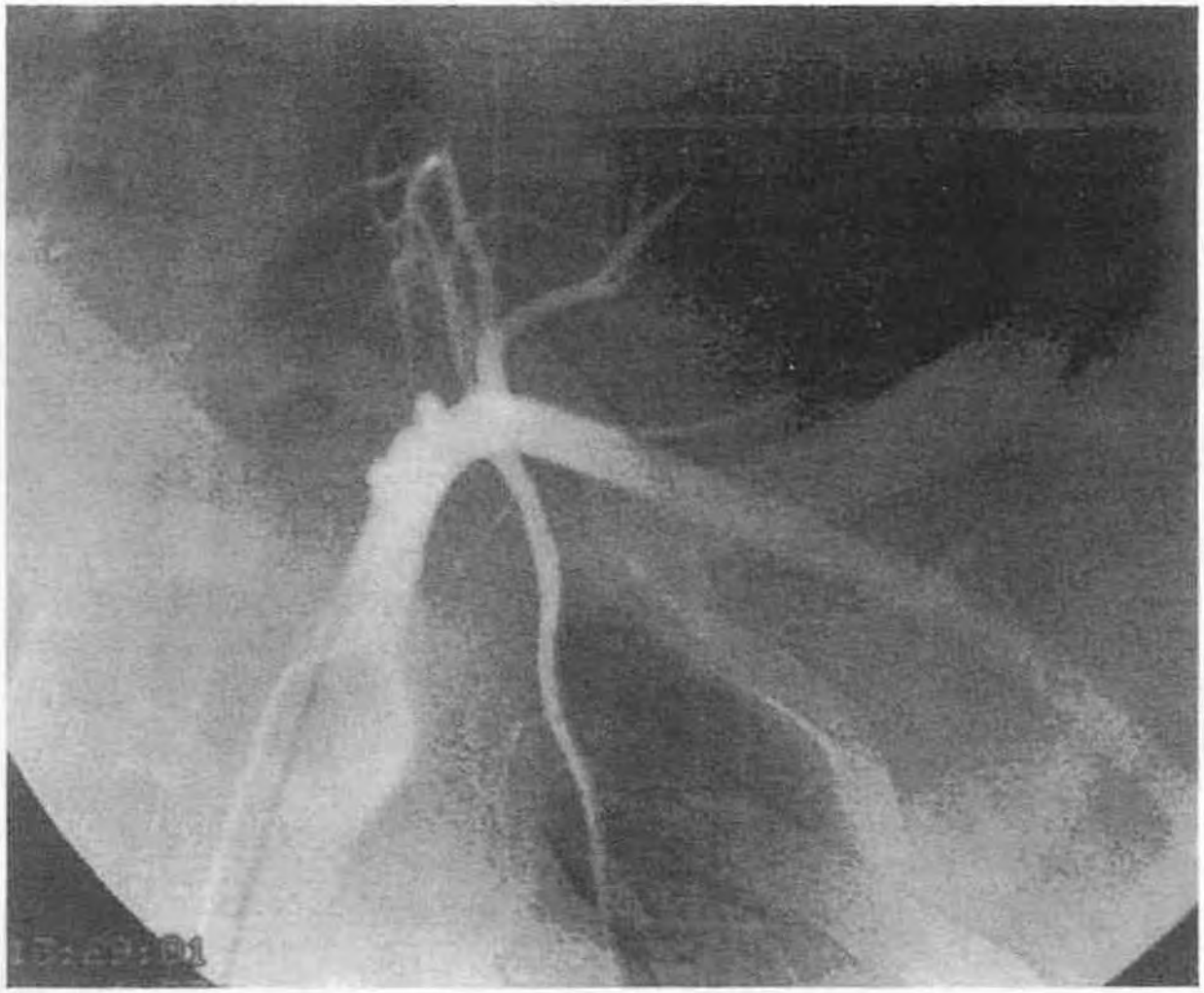

FIGURE 14A (Caption on page 263)

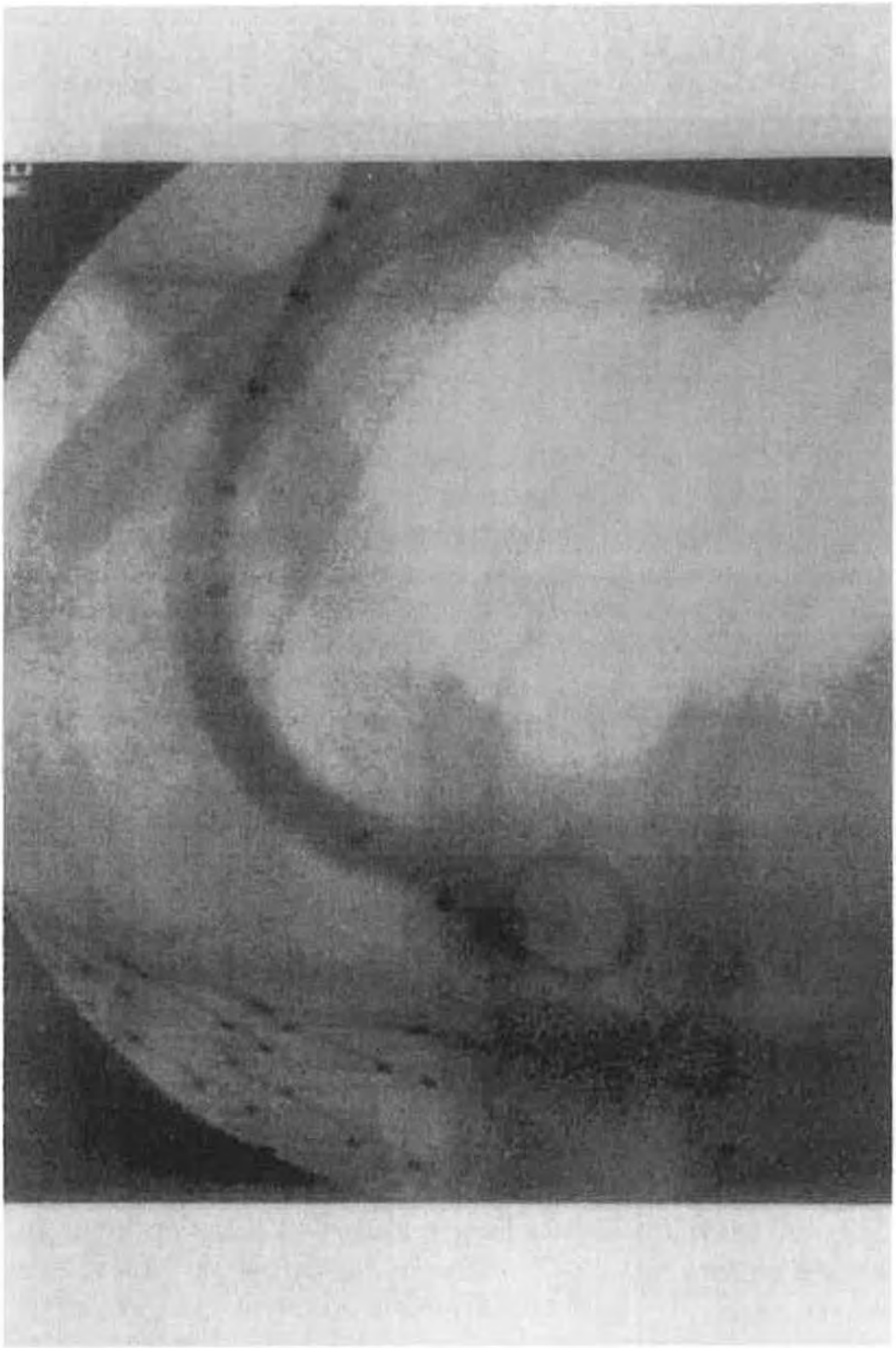

FIGURE 14B (Caption on page 263)

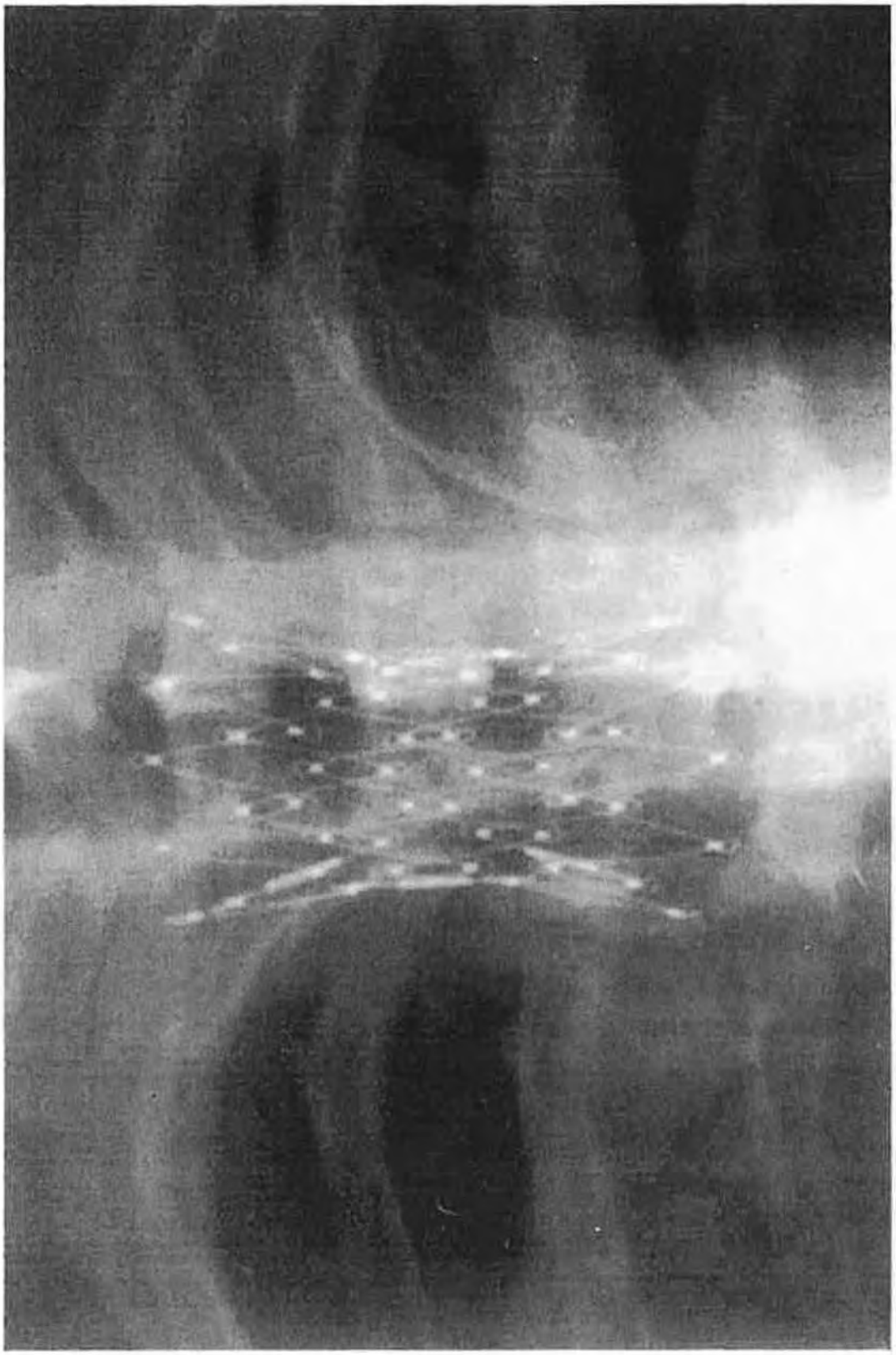

FIGURE 14C (Caption on page 263)

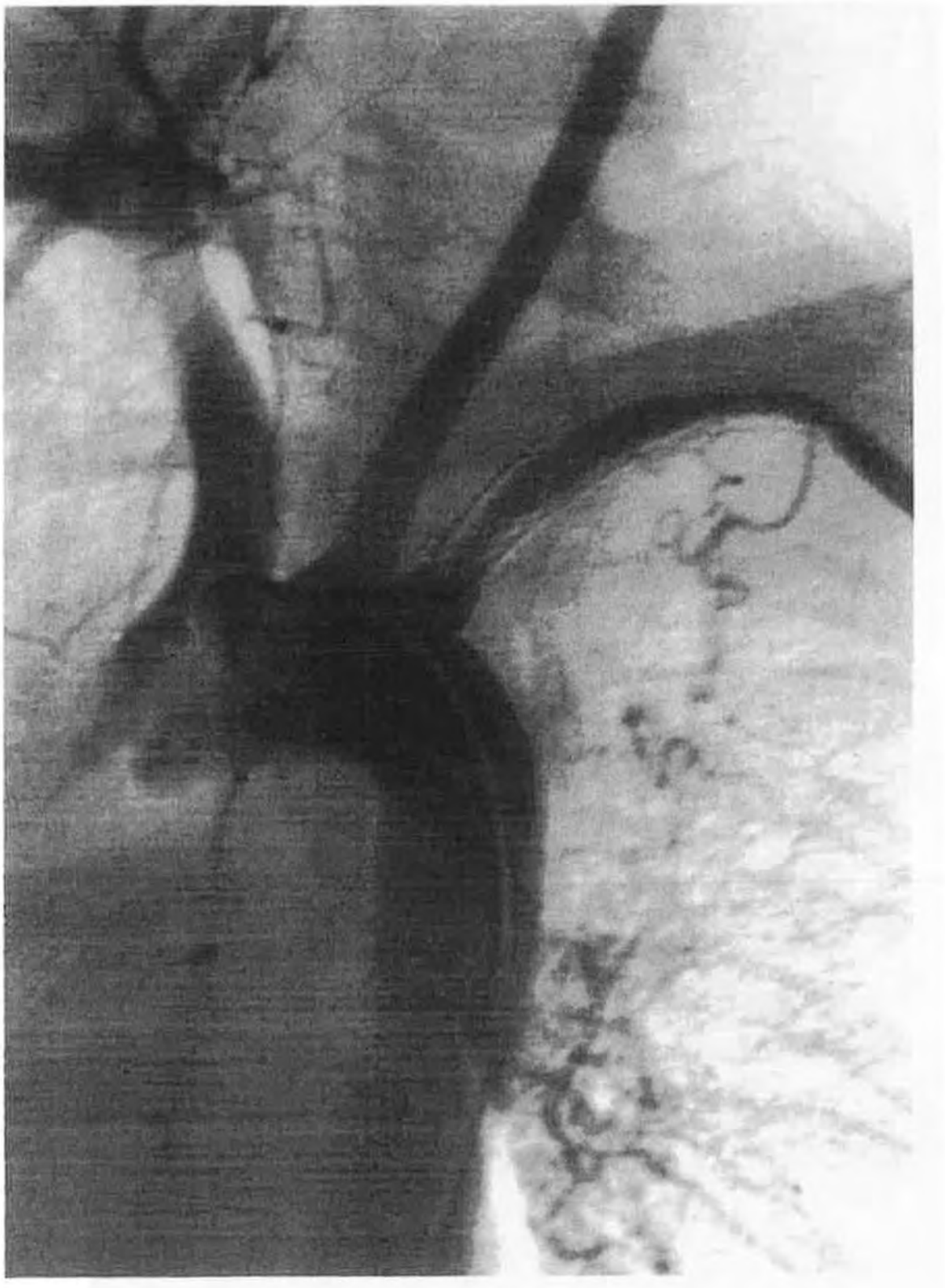

FIGURE 14 D (Caption on page 263)

FIGURE 14 Caption (for Figures on pages 259-262)

This 19 year old male had a gunshot wound to the chest that traversed the mediastinum from right to left injuring his esophagus, trachea, and left subclavian artery.

A) The initial arteriogram shows occlusion of the left vertebral artery and a small pseudoaneurysm at that site. He was transferred to our institution following placement of a covered esophageal stent to repair his tracheo-esophageal fistula.
B) A Corvita endoluminal graft was placed across the lesion and the pseudoaneurysm was excluded from the circulation.
C) A plain x-ray film demonstrates the esophageal stent and the Corvita graft in the left subclavian artery.
D) Four months after graft insertion, his left radial pulse was diminished, although he remained asymptomatic. An angiogram reveals intimal hyperplasia throughout the graft although it is more prominent at either ends of the graft. The lesions were treated by balloon angioplasty and a Palmaz stent. *(Reprinted with permission from T Ohki, FJ Veith, LA Sanchez. Endovascular treatment of upper extremity injury. Seminars in Vascular Surgery, 1998).*

treatment of AAAs in good risk patients appears to hold a major interest for both physicians and manufacturers, the safety and long-term efficacy of this treatment remain to be proven. This is due to the significant rate of complications, including "endoleaks" and distal embolization, as well as to the availability of standard aneurysm repair techniques which have been proven safe and durable.

The long term behavior of the grafts and the arteries in which they are placed, and the consequences of small or minor (branch) endoleaks and hypogastric occlusion are some additional issues that are of concern regarding the endovascular repair of aortic aneurysms. It has generally been thought that occlusion of the hypogastric artery may be harmful and lethal, particularly if this is carried out bilaterally. Iliopoulos, et al described their experience with surgical hypogastric occlusion which led to lethal complications such as lower extremity paralysis, buttock necrosis, anal and bladder sphincteric dysfunction and colorectal ischemia [25]. However, our experience to date has failed to confirm this [26]. We have intentionally occluded 48 hypogastric arteries to facilitate the

endovascular repair of abdominal aortic and iliac artery aneurysms, and only 9% resulted in non-lethal consequences. These complications included 3 cases of buttock claudication and 1 case of colonic mucosal ischemia. None required additional intervention, and all resolved with conservative therapy. Therefore, we currently believe that unilateral coil embolization of hypogastric artery occlusion can be safely performed. Bilateral hypogastric artery occlusion may be required in cases in which bilateral common iliac arteries are aneurysmal. However, the safety of this procedure has yet to be proven.

As far as the management of endoleaks, there seems to be uniform agreement that large endoleaks should be aggressively treated. In fact, rupture of AAAs following endovascular repair with large endoleaks have been reported [27, 28]. However, the appropriate treatment of minor (branch) endoleaks or those that have spontaneously sealed remains a matter of considerable debate.

Placement of the uncovered portion of the stent above the renal artery resulted in a reduction of endoleak incidence; however, the consequences of this on the renal function remain a concern. Malina et al. reported that in 18 cases in which the renal arteries were covered by stents, all renal arteries remained patent [29]. This study also showed no changes in serum creatinine levels before and after stent placement. We have placed the bare portion of the stent across the renal artery in 15 patients and also did not encounter any renal artery occlusions or renal dysfunction as measured by serum creatinine levels. However, suprarenal stent placement also has the potential to complicate open repair if it is required. Therefore, in cases with sufficient neck length (>2.0 cm), we still believe that the uncovered portion of the stent should not be placed above the renal arteries.

Although there are several concerns regarding the efficacy and safety of endovascular graft in the treatment of AAA, encouraging mid-term results has also been reported [30]. In addition, Matsumura et al and others have reported shrinkage of the AAA following successful endovascular graft repair [31-34].

Our mid term patency rates following endovascular graft repair for aortoiliac occlusive disease appear to be encouraging especially when one considers that the majority of the patients had long iliac occlusions, critical limb ischemia, and contraindications to standard treatment.

However, the value of the endovascular graft treatment was limited by the sacrifice of patent collateral branches such as the hypogastric artery and the superficial circumflex iliac artery (Figure 9A, B). In standard surgical bypass operations, it is unlikely that these collaterals would be sacrificed. These collaterals may become important if the graft fails. In that case, the patient will be more ischemic than he originally was and might require a higher level of amputation. This is one reason we have not been using this technique to treat patients without a threatened limb. Further modification in device design and operative technique is required to overcome this problem. With such modifications, we believe endovascular graft will play an important role in the future treatment of patients with extensive iliac occlusive disease.

The current experience with endovascular graft for the treatment of isolated iliac aneurysms and of central artery traumatic lesions has been encouraging. Because standard surgical treatment of these lesions can be difficult and morbid, particularly in patients with serious comorbidities and surgical contraindications, we believe that endovascular grafting should presently be considered a viable therapeutic option. Moreover, it is likely that this form of less invasive repair will become the future treatment of choice for these lesions.

ACKNOWLEDGEMENTS

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Chapter 18

EXPERIMENTAL AND CLINICAL DEVELOPMENT OF AORTIC STENT GRAFTS AND REVIEW OF CONTEMPOTARY TYPES OF DEVICES

Nicholas Kipshidze, MD, PhD
Harry Sahota, MD, Ivan Bakhutashvili MD, PhD

Surgical intervention with graft interposition is the traditional treatment strategy for the patients with aortic aneurysms. Substantial clinical advances in the surgical management of these patients have led to a decline in the operative mortality risk to the range of 5% to 20% [4, 25, 36]. But for an elderly population with other serious medical problems open surgical graft replacement of aneurysms is still associated with substantial morbidity and mortality. Moreover, in patients requiring emergency intervention, operative mortality rate is nearly 50% [1-3].

Keywords: *Aneurysm, stent, endovascular graft*

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Stent Graft Update, Edited by J Vossoughi, N Kipshidze, JW Karanian

Endoluminal stent-graft placement, a new, less invasive alternative technique for repair of aortic aneurysms, has been clinically investigated in a number of centers [7, 8, 23, 32, 40], and initial results from these early feasibility studies indicated that this approach is an attractive alternative to open surgical repair and may potentially reduce the operative risk, hospital stay, and procedural cost in selected patients.

The purpose of this review is to discuss the most frequently used endoluminal stent-grafts.

HISTORICAL BACKGROUND

The era of percutaneous and transluminal interventions began in mid 1960's with the pioneering work of Charles Dotter who dilated peripheral arterial stenosis with graded Bougie catheter. Doctor Dotter [10] was perhaps the first to introduce an arterial stent through a remote artery, but like many ideas of this brilliant scientist, this work was not well understood by the medical community at that time. Further developments on endoluminal arterial stenting has led to improvement in both material and configurations used to construct the device so that it will fulfill the requirements of remote insertion and expansion at the site of deployment. A variety of endoluminal grafts has been developed. Stainless steel and nitinol provided the framework for early devices and the first experiments were performed.

However, there are unknown chapters in this history of development of intervascular grafts. Soon after the pioneering work of Charles Dotter and his collaborators, there was another development on the other side of the Atlantic behind the Iron Curtain. A vascular surgeon, Anatoly Kononov, in the small town of Kharkov (Ukraine, USSR), dreamed of the possibility of treating aortic aneurysm and atherosclerotic stenosis by intravascular techniques. The first experiments with stent-grafts were done in the early 1970's (Figures 1 and 2). In 1973, a series of experiments were performed on dogs in which Dr Kononov implanted balloon expandable stent grafts in aorta (Figures 2 and 3). All experiments were successful, and he applied for a patent with the USSR patent office on April 16, 1974. In the original patent application for his prosthetic device, Kononov described all features of the current stent-grafts: 1) Sizing, 2) Balloon expandable stent-grafts, 3) Pins for fixation. However, the patent experts refused to grant him a patent. Recall, this

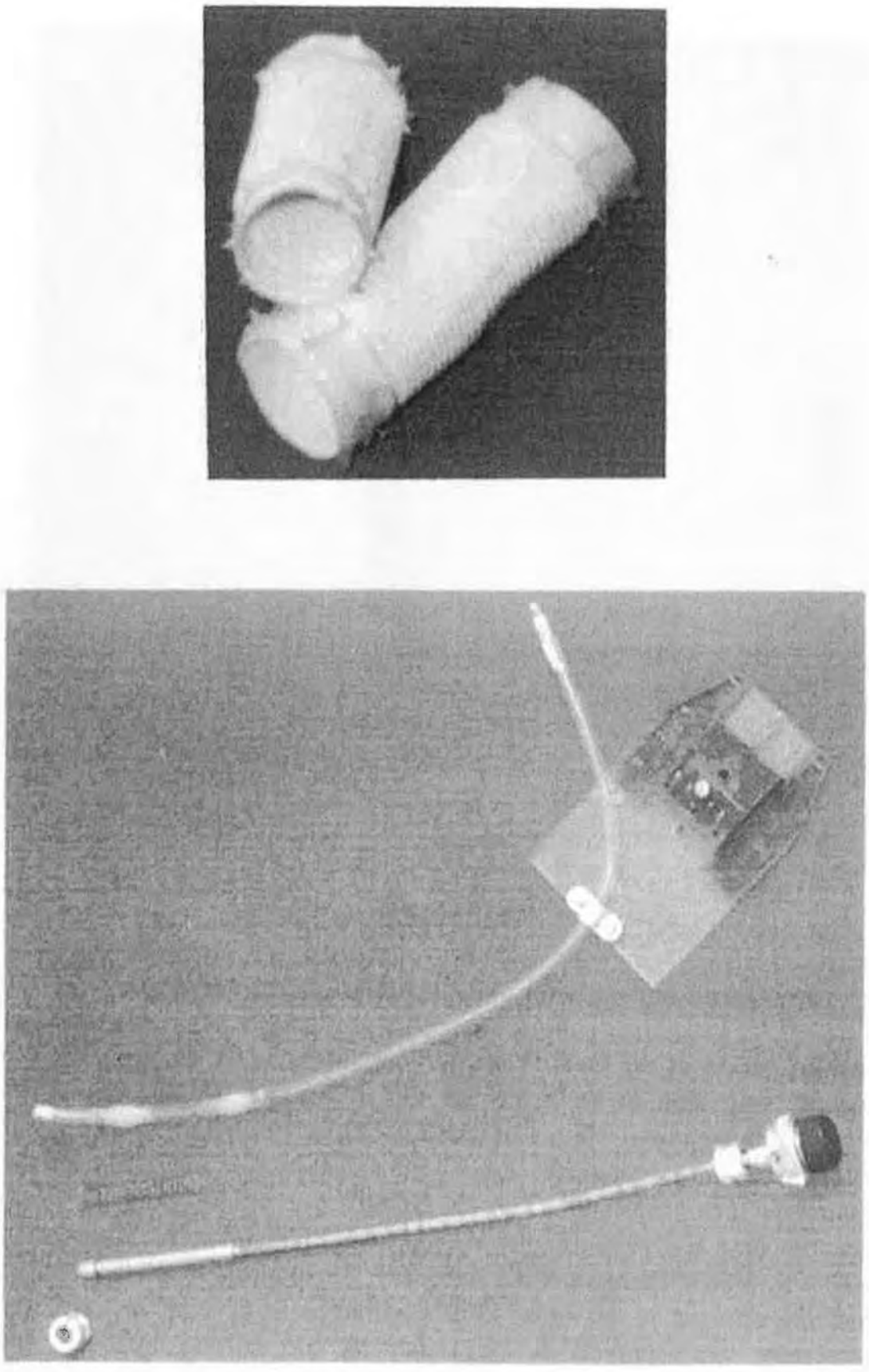


FIGURE 1: Kononov's stent-graft (top) and delivery device (bottom)

FIGURE 2

Stent-graft and catheter delivery device in the aorta of a dog

was the period of the Cold War. No one in the West, or even Eastern Europe, was able to be aware of this research. Dr Kononov was persistent in his ideas. He performed more experiments and somehow was able to reapply for the patent. Finally the patent by Kononov, "Device for Implanting a Prosthesis in a Tubular Organ", was granted with a priority date of May 5th, 1979 (Figure 4), date of Publication of Description 5/8/1979, USSR Patent # YDK 615. 477. 85 (088.8). It is also of note that this scientist in the early 1970's managed to develop several very interesting interventional devices such as the cutting balloon, and artherectomy catheter. The patent numbers and names for both of these devices have been issued. However, this story didn't have a happy

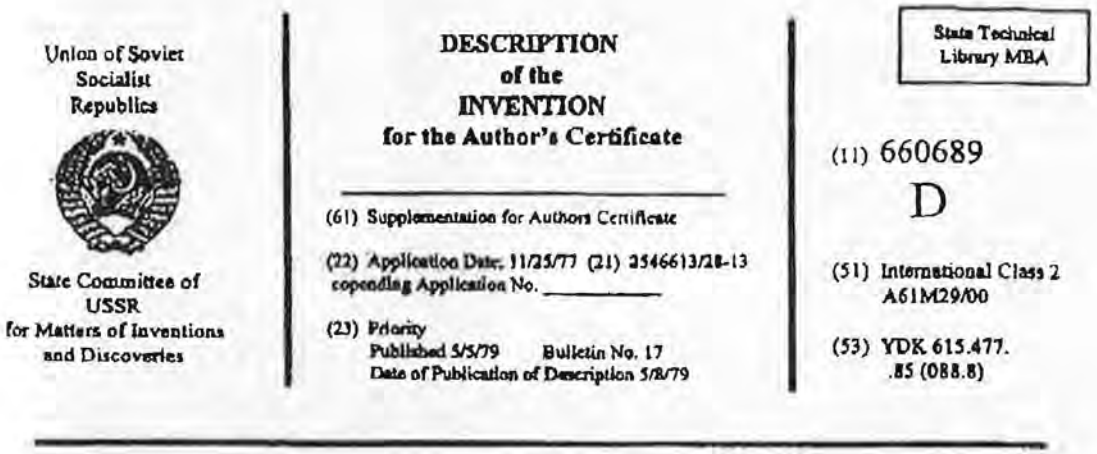
FIGURE 3

Successful deployment of the stent-graft in the aorta

ending, and instead of recognition of Dr Kononov's (Figure 5) experimental work in development of stent-graft device, he was criticized in his institute by his peers and also by his colleagues in Moscow. He was

limited to the practice of medicine, and he also did not have the freedom to perform any more experimental studies.

However, in late 1985, a Ukrainian surgeon, Nicholas Volodos, from the same institution modified this device and was the first to place an endovascular graft transluminally to treat a patient with iliac artery occlusive disease [37]. A self-expanding stent device covered with a Dacron graft material was used to treat a long-segment aortoiliac obstruction.



Union of Soviet Socialist Republics

State Committee of USSR for Matters of Inventions and Discoveries

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(53) YDK 615.477.
.85 (088.8)

(72) Author of Invention (Inventor): A. Ya Kononov

(71) Applicant: Kharkov Scientific - Research Institute Of General and Emergency Surgery

(54) **"A. Ya Kononov's Device for Implanting a Prosthesis in a Tubular Organ"**

FIGURE 4

USSR patent granted to Dr Kononov on "Device for Implanting a Prosthesis in a Tubular Organ"

To complete the historical perspective, the contribution of another Russian physician, a pioneer of soviet endovascular surgery, Professor

Joseph Rabkin, who first performed human iliac stent implantation in March 1984 needs to be recalled [31]. He developed a nitinol self-expandable stent and conducted experiments in canine models in 1982-1983. Doctor Rabkin was also the first to use a balloon catheter to expand the stent in humans.

Despite the fact that Dr Rabkin reported his clinical experience with the use of the stents in November of 1984 at North American Radiology meeting in Chicago, he is not recognized as a pioneer of stent implantation. Later, Dr Rabkin immigrated to the United States of America in early 90's, retired and currently resides in Boston, Massachusetts.

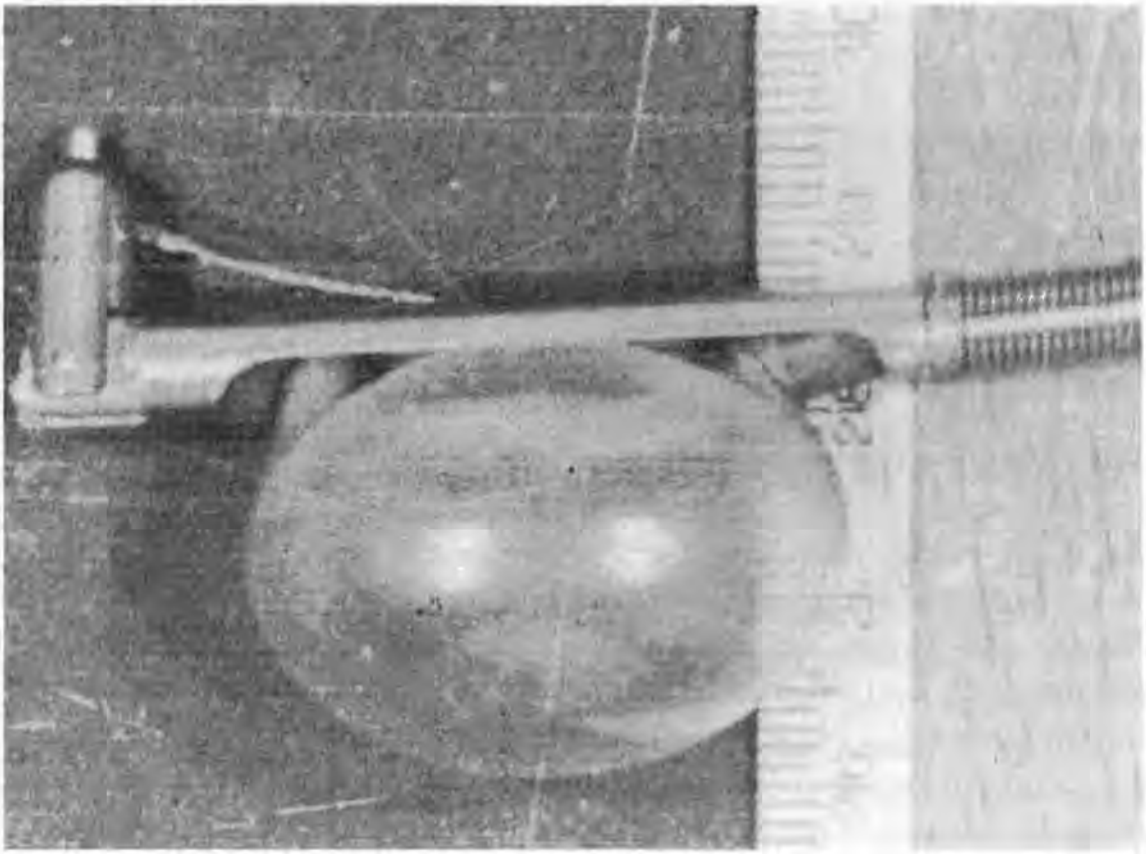

FIGURE 5

Atherectomy Catheter

Several authors studied the use of these devices in the treatment of experimental aneurysms [1, 2, 3, 8, 21, 36].

In 1990, Huan Parodi and his colleagues inserted such a graft to treat an abdominal aortic aneurysm in a high-risk patient, whereupon these devices

began to attract the widespread interest of vascular surgeons, interventional radiologists and others [27]. Since 1991, Parodi et al reported to have placed transluminally endovascular grafts in more than 50 aortic aneurysm patients along with 7 patients with a variety of other vascular entities [2, 28].

Multiple reports have now confirmed the clinical applications of endovascular stent grafts for a variety of vascular lesions [14, 20, 21, 24, 39].

Clinical observations of aortic aneurysms and traumatic lesions by Parodi [2, 28], of femoropoliteal occlusive disease by Cragg and Dake [16], of abdominal aortic and other aneurysms by May, White et al, [20, 21, 39], of infrarenal aortic aneurysms with long well-defined proximal and distal necks by Moore and Viscera [24], of thoracic aortic aneurysms by Dake, Miller et al, [14], of abdominal aortic aneurysms requiring treatment with a bifurcated transluminaly placed endovascular graft by Chuter et al, [5], all reported about less invasive and possibly superior treatment.

This chapter will survey the types of devices for AAA, thoracic aorta and peripheral arteries.

SURVEY OF THE TYPES OF DEVICES

The EVT aortic tube graft and bifurcation graft. (Endovascular Technologies, Menlo Park, California)

Endovascular Technology currently has three ELG devices under study: the tube graft, the bifurcation graft and the aortoiliac graft. Aortoiliac graft was developed because the tube and bifurcation grafts were suitable only in approximately 13% and 25% of patients respectively [24]. The tube graft consists of the EVT expandable sheath and a catheter delivery system that contains the prosthesis. A hemostatic means of vascular access for passage of the catheter delivery system and subsequent manipulations are provided by the EVT expandable sheath, which is an over-the-wire system. The leading edge is collapsed to provide ease of passage. The over-the-wire system is 27 French in diameter when fully expanded and contains a double-valve system that minimizes blood loss. A lightweight woven Dacron fabric constitutes the graft and has an attachment device comprising the series of hooks that engage the aortic wall as the balloon catheter expands.

Similarly, the bifurcation graft consists of two parts: an expandable sheath, and a catheter delivery system.

A lightweight woven Dacron with a self-expanding attachment system constitutes the graft. A balloon catheter system is present in the body of the graft and in the ipsilateral limb; the contralateral limb contains a deployment system attached to a pull wire.

Moore summarized the clinical results in December of 1997 [24]. Out of a total of 106 EVT tube grafts placed, 96 insertions (91%) were technically successful. In Phase II trials of the tube graft, 88 insertions were compared with 90 surgical controls: 30 day mortality in EVT tube graft patients was 0, and in surgical controls, it was 3.3%; serious complications were 0 and 3.3; mean hospital stay (days) was 2.4 and 8.2 respectively; in EVT tube graft patients mitral endoleak was 23% and back-bleeding 20%. EVT bifurcation graft Phase II results compared to surgical results were as follows: 30 day mortality 1.9% and 3.9%; serious complications 1.9% and 2.9%; mean hospital stay (days) 3.9 and 7.6 respectively.

The United States experience with EVT grafts alone indicates that out of a total of 35 tube graft insertions, 32 were successful; 27 of 31 bifurcation grafts were placed successfully, as were 8 of 9 aortoiliac grafts [24]. No deaths were registered in the United States series, but one case of paraplegia was seen in the aortoiliac group. Patients receiving grafts were lower in morbidity and mortality than in surgical controls and hospital stays were shorter in patients receiving endovascular treatment. Endoleaks resulting from an incomplete seal at the proximal or distal attachment site or from branch back bleeding of lumbar or inferior mesenteric arteries were the primary technical complications seen with EVT devices. Enlargement of the aneurismal sac was the result of persistent endoleaks and may necessitate additional endovascular or surgical repair. Fractures in the hooks on some grafts were reported in early clinical testing, and it caused temporary halting of trials until the manufacturer resolved the problem.

Medtronic-AneuRx modular bifurcated graft (Medtronic, Inc Minneapolis, Minnesota)

A main bifurcation segment and a contralateral iliac limb are the primary components of this graft system, and aortic and iliac extender cuffs as

additional modular components are also available, which are designed to maximize versatility at the time of insertion and then maintain structural integrity. A thin-walled, noncrimped, woven polyester serves as a graft material and allows introduction in a low profile delivery catheter and, via tissue ingrowth, facilitates a healing response. Nitinol, a self-expanding nickel-type titanium alloy, which serves as an exoskeleton to provide column and hoop strength, is included in the components comprising the device. The delivery system uses orientation markers for proper stent-graft positioning at the time of procedure. The self-expanding device is introduced using low-profile 21-F and 16-F delivery catheters. The device is secured by the proximal sealing cuff of the main bifurcation segment and uses a frictional seal. The radiopaque system is compression- and kink-resistant and guidewire- and ultrasound-compatible. The modular system allows the adaptation of a variety of abnormal conditions and requires only a 1.5-cm cephalad neck for fixation. Adequate sealing at its proximal and distal ends is possible due to dimensional variability of the graft.

In December of 1997, Fogarty [11] summarized the clinical results on the insertion of the Medtronic-AneuRX Modular Bifurcated Graft. No conversions to an open procedure were required in the first 75 patients, and no device migration was revealed. The study showed limited operation time and blood loss. Patients were extubated rapidly and required an average stay of 0.7 days in the intensive care unit. Follow-up in 16 months but the size of AAA decreased revealed one endoleak and patient has been simply reevaluated every 3 months. Investigators reported one death related to gangrene and cholecystitis. Six patients had complications: transient ischemia of the colon (n=1), respiratory insufficiency (n=1), ischemia of the limbs (n=2), and emboli (n=2).

Diethrich [9], on routine follow-up discovered one endoleak in 25 devices deployed at the Arizona Heart Institute AneuRx trial. The endoleak was discovered at the junction of the right limb and has subsequently been sealed with an endocuff; there have been no conversions and no deaths. This study revealed the only complications related to difficulty in delivering the device through small iliac arteries.

Corvita endoluminal graft. (Corvita Corporation, Miami, Florida)
This prosthesis consists of a tubular, self-expanding, multiwire, Elgiloy® braid that is coated with a Corethane® (Polymer Technology Group,

Berkley, California), a porous polycarbonate elastomer isolating the metallic surface of the graft from the bloodstream.

The Corethane coating presents as a nonwoven structure, which is integrally bonded to the braided wire structure and pitch angle of its fibers is matched to that of the wire braid. Corethane maintains hemostasis and facilitates tissue ingrowth, while the wire braid is the load bearing part of the device.

These devices may be compressed up to one-sixth of their original diameter and are manufactured in diameters of 5 to 45 mm. The new designs include tube, bifurcated, and aortoiliac grafts that use a 21-F delivery catheter (or a 13-F catheter in the iliac limb).

Panetta [26] reviewed European and US clinical results. But sixty percent of reviewed cases were acceptable for use of bifurcated prosthesis as it required a less than 30% angle of the aorta at the cephalad end. The endoleak rate in early European trials with the tube graft was 38%, and 30% of cases required application of additional limbs in the iliac arteries as well as the use of stents for stabilization. The FDA now prohibits early on preclotting of the prosthesis.

After the insertion of 41 bifurcated devices in the United States, 2 required conversions, and 2 iliac limb occlusions were reported. The worldwide experience showed 72 of the bifurcated devices has been placed with 3 early endoleaks not persisting at three months. According to Dr Panetta, the Corethane coating of these devices brought very little "healing."

Meadox Vanguard endovascular graft (Boston Scientific Corporation, Natick, Massachusetts)

This graft was used extensively in Europe from 1993 to 1996 and is comprised of a redesigned device based on the Mintec Stentor endograft system. This device represents about 50% of the entire experience as it has been used in the largest number of implants worldwide. This flexible, self-expanding, tubular prosthesis consists of a nitinol wire tube covered with woven polyester. The device consists of 3 separate sections formed from a nitinol wire of the same length in a repeating geometric pattern. Three sections of the device are held together by sutures to form the framework.

The endograft is available in straight tubular or bifurcated configurations of a variety of diameter and length specifications to accommodate most vascular morphology of aortoiliac segments in patients with aneurysm.

A delivery system of concentric sheaths includes compressed and positioned endograft, which is advanced within the arterial lumen over a 0.035-inch guidewire to the point of proximal aortic deployment just distal to the lowermost renal artery.

Two separate delivery catheters are used for the insertion of bifurcation the endograft. The primary aortic trunk of the bifurcation endograft is inserted by a 21 French sheath. It consists of one complete iliac limb for the ipsilateral iliac artery, and the proximal stump of the contralateral iliac limb, which is constructed as a single unit of fabric covering the nitinol segmental rings. A smaller delivery sheath is 12 French in outer diameter and may be inserted percutaneously or by direct surgical access and within the opposite femoral artery and adds the contralateral iliac limb of the endograft to the primary. Despite the observations of suture breakage, Eurostar trial evidence suggests that the clinical risk to patients from this breakage is extremely low [12].

A single delivery sheath contains a compressed Vanguard tube graft, while 2 separate delivery catheters are required for the use of the bifurcated graft. The primary introducer is 21 French and the secondary catheter that delivers the contralateral iliac limb is 12 F.

The Eurostar trial Vanguard device was reviewed by Beebe [2] in December 1997 and included 290 cases with a technical success rate of 88.7%, conversion rate 2.4% with primary endoleak in 14 patients (4.8%) and secondary leak was seen in 16 (5.5%), where 2 were closed with surgery, 2 closed spontaneously, and 1 ruptured. The mortality rate in this series was 4.1%.

In the United States, the protocol in this series excluded non surgical candidates and the aneurysm was required to be 4 cm or larger. Proximal device sizes were 22 to 26 mm, iliac limb device sizes were 10 to 14 mm, and the straight -tube grafts were 22, 24, and 26 mm. Eight-six bifurcated and 9 straight-tube grafts were placed. The author reports that there were 2 conversions related to iliac access problems. No endoleak had been discovered, and there were no death [2]. Blum, et al [3] reported

a clinical success rate of 96% in a total of 116 cases in Europe. There were 2 (1.7%) endoleaks (1 persistent).

TALENT endoluminal graft placement system (World Medical Manufacturing Corporation; Sunrise, Florida)

This graft system is comprised of four components: placement catheter, nitinol spring stent, hollow introducer sheath and push rod with plunger. Dacron lined self-expanding nitinol spring stent is compressed over a polyurethane placement catheter with multiple lumens. The hollow introducer sheath of the system includes a hemostasis valve and a side port with a stopcock that may be used to inject or withdraw solution and control the stiffness of the sheath. Deployment of the nitinol spring allows outward expansion of the device for fixation to the vessel wall above and below the aneurysm. A straight-tube graft and bifurcated designs of this prosthesis are commercially available.

Taheri and colleagues [34] summarized the results of multicenter trials. The device has been placed in more than 100 patients. Of the first 100 patients, 63 received the bifurcated graft, and the remaining 37 received straight-tube grafts. Four endoleaks were reported initially (3 proximal, one distal), and all sealed spontaneously within 3 weeks of the procedure. There was no report of distal embolization in this series. The conversion rate with this device was 4% [35]. More than 800 of these devices were deployed, and it represents nearly a quarter of the market.

White-Yu endovascular GAD graft (Baxter Healthcare Corporation; Irvine, California)

This device is comprised of a woven polyester prosthesis with an intrinsic Elgiloy wire graft attachment system along the body of the graft. A straight tube graft and tube graft variations for use in thoracic aortic, iliac, or peripheral aneurysms are available. The systems can be delivered through 18-FTO and 24-F sheaths.

Clinical results of 79 aortic procedures were reported by White et al [38]. Out of a total of 79, 76 were abdominal aortic, and 3 thoracic aortic; 39 used the straight-tube graft, 20 use the tapered aortoiliac grafts, and 20 used the bifurcated grafts. The technical success rate was 81% in patients receiving abdominal aortic grafts and 100% for the thoracic grafts. There were five (14%) primary endoleaks and two (5, 6%) conversions to surgery with the tube grafts; two primary and two secondary endoleaks were treated by four additional endografts. The aortoiliac grafts reached

95% of technical success, with one case (5%) of thrombosis requiring conversion to open surgery. The bifurcated graft reached almost 75 % of technical success with one case (5%) of thrombosis requiring conversion and four (20%) technical failures. No endoleaks were detected in the aorthoiliac or bifurcated grafts. There was one case of embolus to the distal femoral artery without microembolisation. Over a mean of 18 months there was no late graft thrombosis, stenosis, or graft migration. In successfully treated cases the size of aneurysm has diminished.

Perth HLB Endograft (COOK Incorporated; Bloomington, Indiana)
This is a self-expanding modular, bifurcated system made of a barbed Gianturco Z-stent frame with multiple stents throughout the length of the graft. The graft material is woven, noncrimped Dacron that is sewn over the suture. Small gaps between the stents allow some flexibility, and hooks attached to the top stent embed in the aorta and help stabilize the top end of the graft in the neck of the aneurysm.

Sieunarine summarized clinical experience of the Perth endograft with 140 insertions [33]. Two proximal endoleaks were associated with distal migration of the graft into the aneurysm sac. Three graft limb occlusions occurred in early series with the bifurcated system because it was not stented along the entire length of the graft.

CONCLUSIONS

On the basis of initial clinical experience, it can be assumed that endoluminal stent-grafting to repair a large variety of arterial aneurysms is feasible in a large population of patients and also can be performed in high-risk, otherwise inoperable patients, with acceptable mortality. The incidence of endoleaks is acceptable, many of which are treated by subsequent endovascular procedures. These procedures are well accepted by patients because of the decrease in recovery time and short initial hospitalization. Cost of the current procedure remains high because of the high price of the devices and diagnostic and follow-up studies. Endoleaks leading to aneurysm rupture are attentively to be discovered and careful follow-up is required following endovascular graft repair. Hopefully, continued improvement in the device will occur in the future and provide reducing of its cost with mass production, which in turn will decrease the cost of procedure.

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Chapter 19

ENDOVASCULAR AORTIC GRAFTING-INVESTIGATOR'S EXPERIENCE FROM LABORATORY CONCEPT TO CLINICAL TRIAL

Rodney A White, MD, Carlos Donayre, MD, Irwin Walot, MD, George E Kopchok, BS

The concept of deploying a vascular graft to treat lesions by passing the prosthesis through the lumen of the vessel has been considered for many years. Inadequate methods of intraluminal fixation delayed development. The invention of intravascular stents provided the first secure method to attach a vascular prosthesis to the endoluminal surface of a blood vessel. Early experiences and pioneering clinical work with these methods were reported by Volodos and Parodi and began the rapid evolution that has occurred in the development and clinical assessment of these devices [1, 2].

INITIAL HARBOR-UCLA EXPERIENCE

Our experience with endovascular prostheses began in 1992 with a series of animal experiments that observed the healing of various types of

Keywords: *Endovascular prostheses, stents, aneurysms, intravascular ultrasound*

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Stent Graft Update, Edited by J Vossoughi, N Kipshidze, JW Karanian

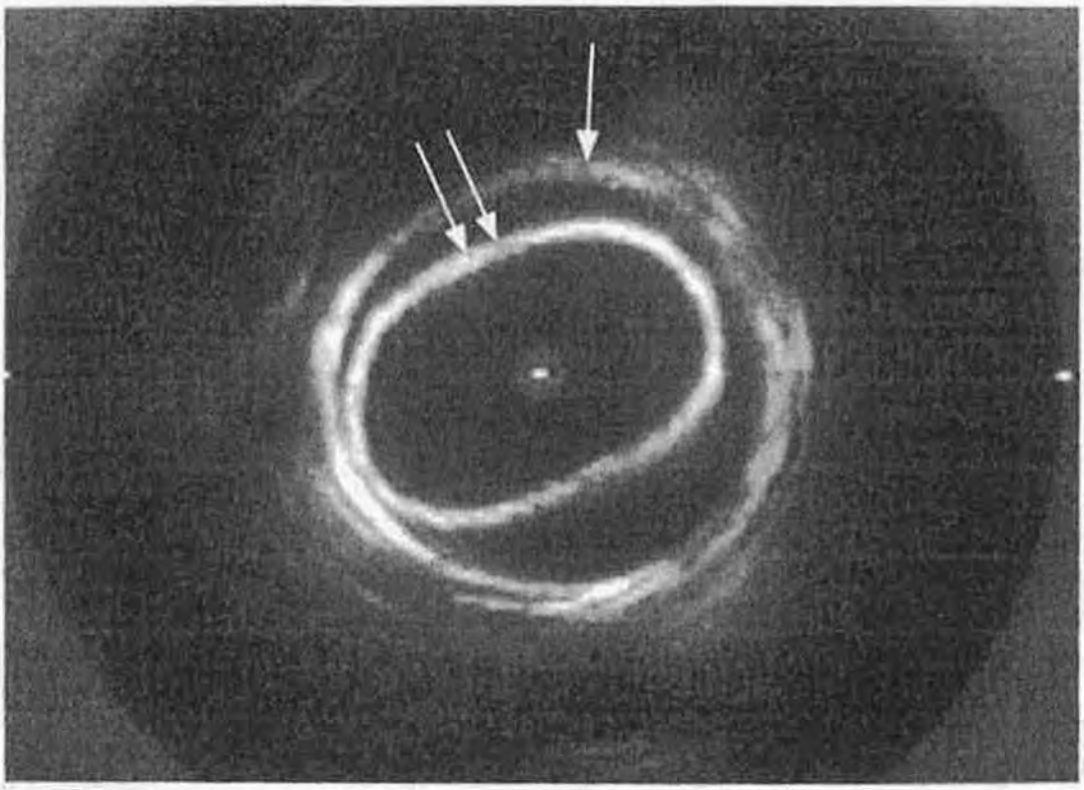
Dacron and PTFE stent-grafts deployed as aortoiliac prostheses [3]. For obvious reasons, the trend has been towards using thin-walled fabrics so that deployment can be accomplished through low profile delivery systems. In this regard, thinner wall materials were easy to deploy but lacked adequate circumferential luminal force to prevent partial collapse of unsupported fabric tubes during pulsatile arterial flow. With arterial pulsations, unsupported thin-walled vascular grafts collapsed during systole, while thicker crimped fabrics or fabrics supported along the length with stents remained opposed to the vessel wall (Figure 1 & 2). The animal experiments demonstrated that healing of endoluminal grafts occurred quite rapidly if the prosthesis remained in apposition to a normal arterial segment, while healing was delayed and the lumens were narrowed if thrombus accumulated between the graft and the arterial wall. Healing of the fabric was also delayed or did not occur if the grafts were apposed to thrombus in experimental aneurysms.

The animal endoluminal graft experiments demonstrated that successful deployment, secure fixation and long-term healing could be accomplished by combining certain conventional vascular prostheses with available stents to secure the ends of the graft. In particular, infrarenal aortic canine implantation, which classically has been used to evaluate the healing, tensile strength and long-term patency of vascular prostheses suggested that the endoluminal grafts would function in humans.

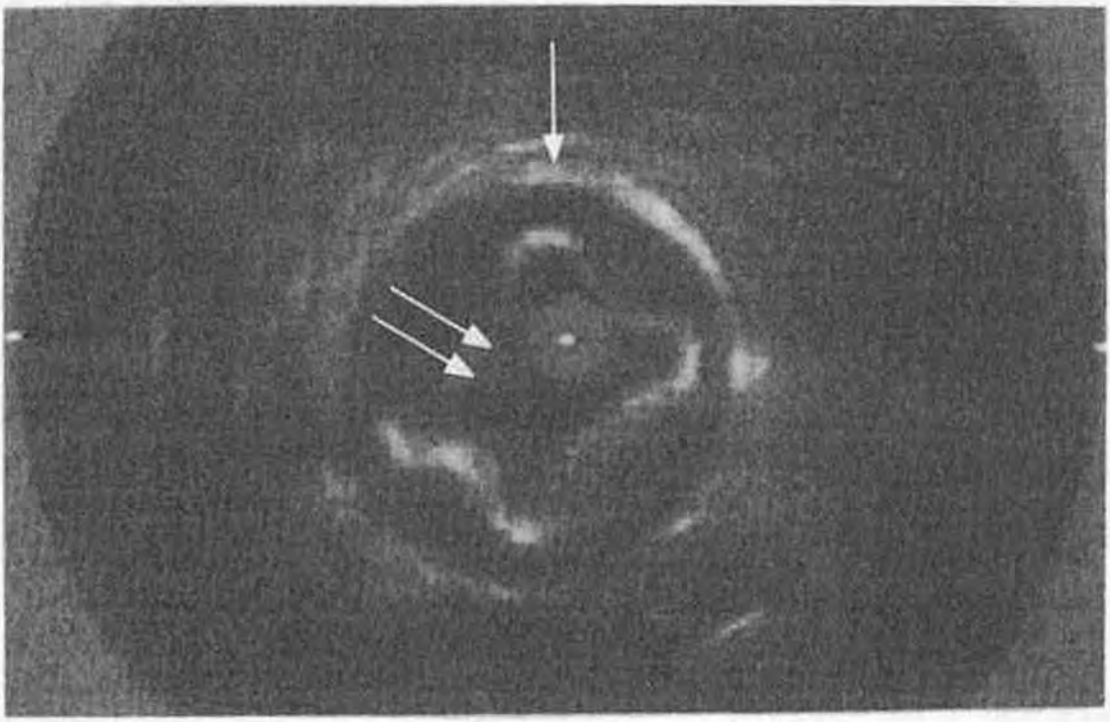
HUMAN CLINICAL TRIAL

Based on more than two years of animal experimentation, we filed an Investigator Sponsored Investigational Device Exemption (IDE) with the Food and Drug Administration for the endovascular deployment of conventional Dacron fabrics secured within the lumen by available vascular stents. This application was approved in 1994 for clinical investigation and was the first sponsor initiated IDE approved in the US for evaluation of investigator assembled devices to treat aortoiliac and traumatic aneurysms.

Fourteen aortoiliac devices combined with femorofemoral bypasses were used to treat abdominal aortic aneurysms, 3 iliac endoluminal prostheses were deployed to treat iliac artery aneurysms, and 3 stent grafts were used to treat subclavian artery traumatic injuries (Figure 3). The preliminary success of these initial investigations was reported following significant follow-up with several important observations being made [4, 5]. Aside from demonstrating the ability to treat severely

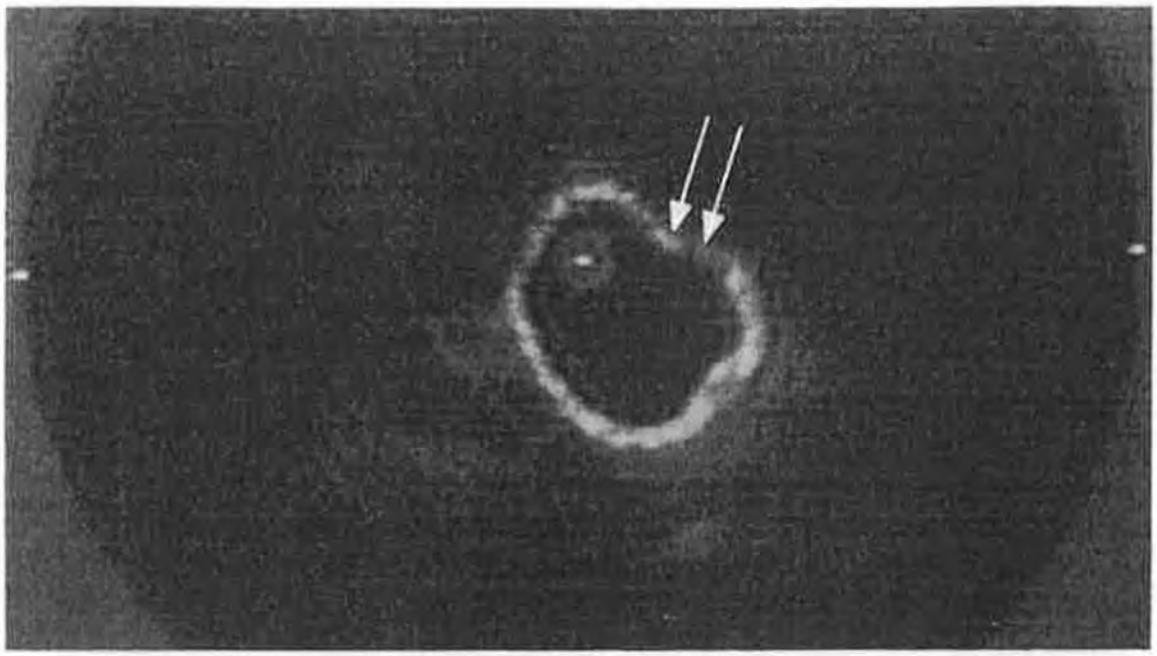


(A)



(B)

FIGURE 1 (Caption on page 291)



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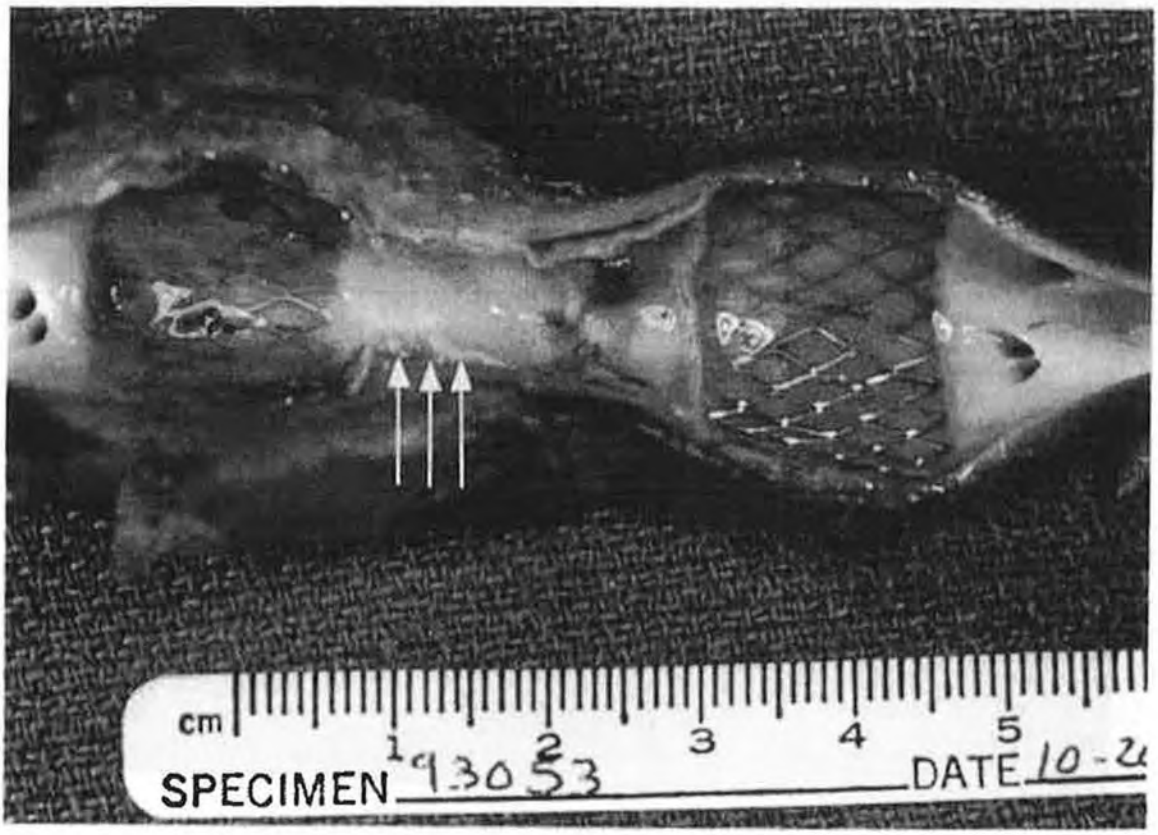

(D)

FIGURE 1 continued (Caption on page 291)

FIGURE 1 Caption (for Figures on pages289 and 290)

IVUS images of motion of an uncrimped vascular prosthesis (double arrows) relative to the vessel wall (single arrow) during arterial pulsation at implant. (A) Maximal expansion, and (B) maximal collapse of graft. (C) IVUS image, and (D) gross inspection of same segment of prosthesis at 30 days demonstrates narrowing of graft (triple arrows) that occurred in areas of wall motion. All IVUS figures are of comparable magnification to permit comparison of luminal dimensions at time of implantation and 30-day interval. ***Reproduced with permission of White RA, et al: The role of cinefluoroscopy and intravascular ultrasound ultrasonography in evaluating the deployment of experimental endovascular prostheses. J Vasc Surg 21:365-74, 1995***

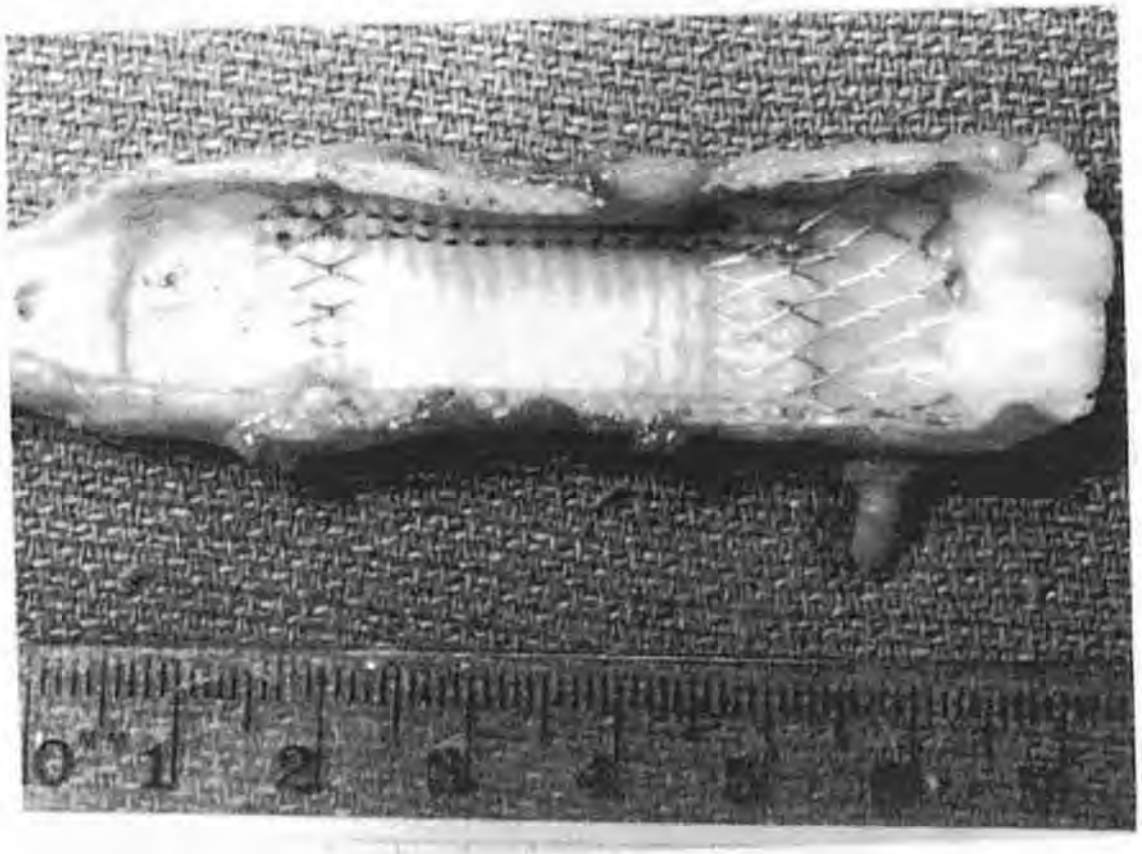

FIGURE 2

Woven Dacron velour graft at 60 days with thicker-crimped wall demonstrating the healing compared to thinner fabric in Figure 1. ***Reproduced with permission of White RA, et al: The role of cinefluoroscopy and intravascular ultrasound ultrasonography in evaluating the deployment of experimental endovascular prostheses. J Vasc Surg 21:365-74, 1995***

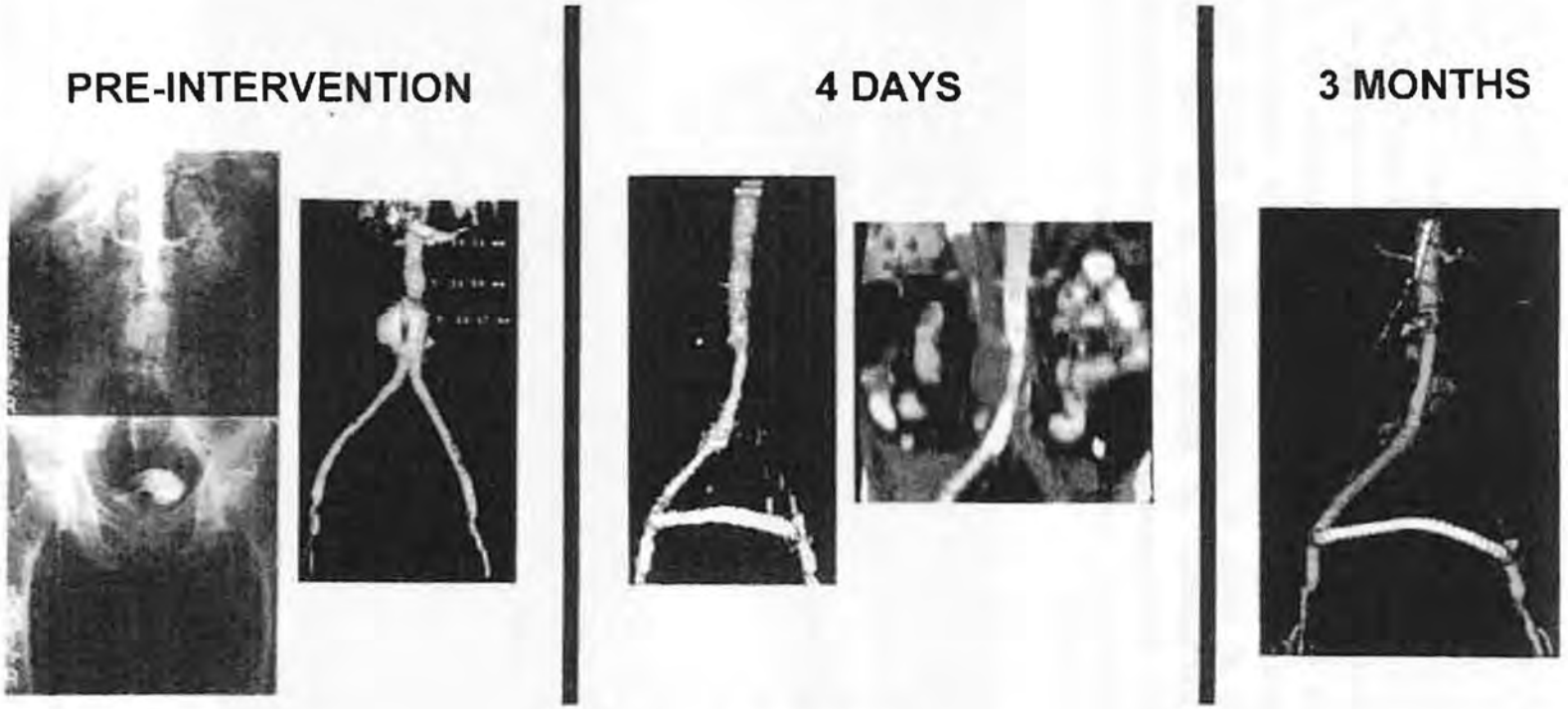

FIGURE 3

Composite of spiral CT scans of an aortic pseudoaneurysm pre-intervention, at 4 days, and at 3 months following treatment with an aortic endograft. ***Reproduced with permission of White RA, et al: Endoluminal graft exclusion of a proximal para-anastomotic pseudoaneurysm following aortobifemo-ral bypass. J Endovasc Surg 4:88-94, 1997***

ill patients successfully using endoluminal bypass, the preliminary potential for regression in size of aneurysms with time and the recognition of morphology changes in the aneurysm as regression occurs became apparent (Figure 4) [6]. These remodeling changes have been demonstrated to have significant impact on the long-term conformity of the endoluminal graft and are addressed by various means in more advance commercial devices. Although we have continued to follow patients enrolled in the investigator IDE, the need for custom made devices has dramatically decreased with the increased availability of commercial protheses.

ADVANCED COMMERCIAL DEVICE EXPERIMENTAL ANIMAL EVALUATIONS

As commercial interest inendovascular prostheses developed, we performed several pre-clinical animal studies that supported clinical investigation of the bifurcated Medtronic Aneurx device, and the Boston-Scientific passenger and Schneider Wallgraft endografts (Figure 5) [7, 9]. They were performed in both aortoiliac and canine iliac artery models. Additional prototype studies have examined the healing and performance of various forms of balloon expandable and self-expanding PTFE endoluminal prostheses primarily in the canine aortoiliac position [10, 11]. Several of these animal evaluations have supported current manufacturer IDEs to assess the safety and efficacy of these devices in patients.

CURRENT CLINICAL STUDIES

Our most extensive clinical studies for treating abdominal aortic aneurysms have been done using the Aneurx bifurcated device [12, 13]. Our current clinical experience with this device includes 160 patients with infrarenal abdominal aortic aneurysms, and several patients with custom devices for treatment of aortic pseudoaneurysms. Over the 36 months we have been using this device, we have evaluated 230 patients who were candidates for the study. The 70% inclusion rate for patients entering the study highlights the current potential of the technology. Fifteen additional patients who were not candidates for the Aneurx device were treated with larger diameter Talent™ devices (World Medical Manufacturing, Sunrise, Florida), raising the entry rate of patients presenting with aneurysms to approximately 75%. We anticipate that the percentage of patients who are candidates will increase with advances in the technology and as methods to choose patients for various procedures improve.

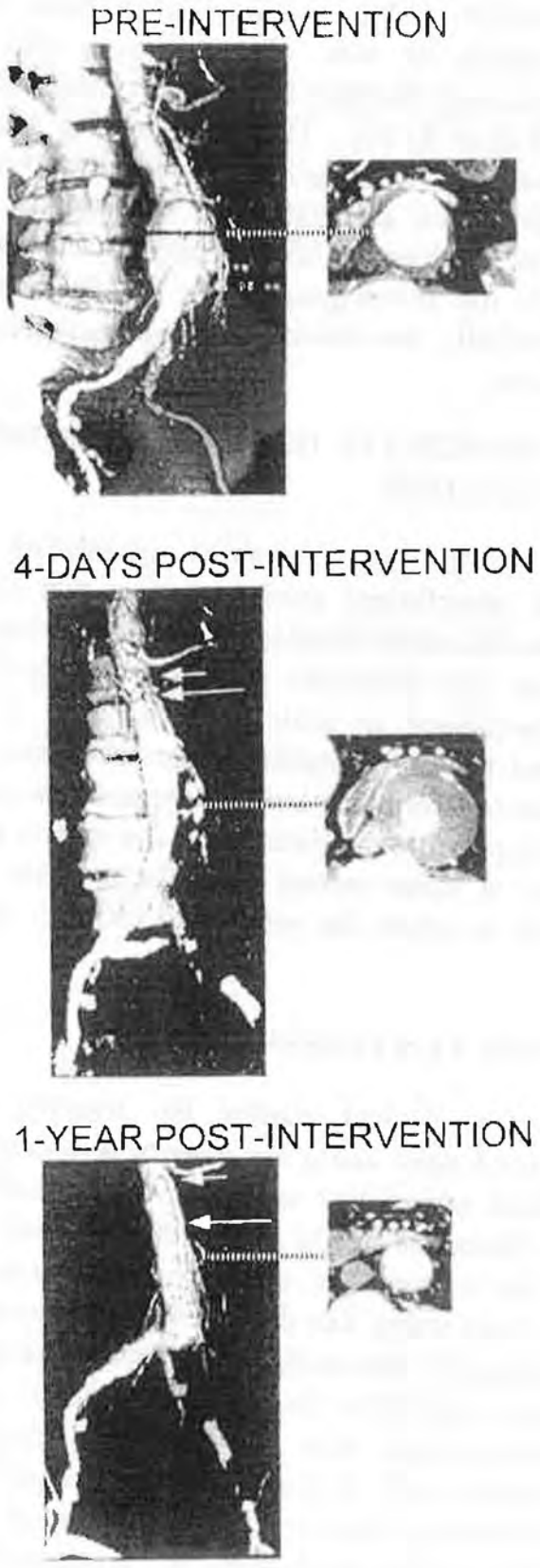

FIGURE 4 (Caption on page 295)

FIGURE 4 Caption (for Figure on page 294)

Spiral and axial CT images of an aneurysm acquired from the same level in aortoiliac vessels before intervention, 4 days after intervention, and 1 year after the procedure. Note location of superior mesenteric artery (short arrow) compared with cephalad end of proximal stent (long arrow) in 4-day and 1-year reconstructions. In some areas, false appearance of mild residual dilation of aortic and iliac segments is a result of calcification in the wall of vessels being indistinguishable from contrast within the arterial lumen on the shaded surface-rendered reconstructions. ***Reproduced with permission of White RA, et al. Regression of an abdominal aortic aneurysm after endograft exclusion. J Vasc Surg 26:133-7, 1997***

We feel that the percentage of patients we have been able to successfully treat has been increased by the imaging protocol we use to assess patient candidacy. This includes the CT and angiographic methods required by the FDA approved experimental protocols. In addition, we have relied heavily on intravascular ultrasound (IVUS) to screen questionable patients where the size of access vessels or the availability of secure fixation sites for iliac limbs is in question. In approximately half of the patients we have screened with IVUS prior to intervention who might otherwise be eliminated as candidates for endoluminal repair, we have been able to identify fixation sites with the intravascular ultrasound that were not determined by the CT scan or angiography. In this way, we feel that IVUS has enhanced our ability to identify secure fixation sites and increase the number of patients who can be enrolled in studies. In addition, we feel that IVUS is particularly important for identifying appropriate sites and dimensions for device fixation and for exclusion of significant lesions such as small areas of aneurysmal dilatation in the vessels (*ie*, "blisters") that are otherwise not apparent by CT or angiographic exam (Figure 6). We also feel that the IVUS examination has enabled initial secure fixation in many patients who otherwise might have had potential for early or late endoleaks if the IVUS interrogation were not performed. Although we have no data beyond our own bias to support this opinion, we have noted significant variation in the dimensions that are obtained from angiographic and CT determinations compared to IVUS, with the accuracy of CT and angiography being limited by the technique and expertise of the investigators performing the interrogations. Although 3-dimensional (helical) CT scans with axial surface rendered 3-D and maximal intensity

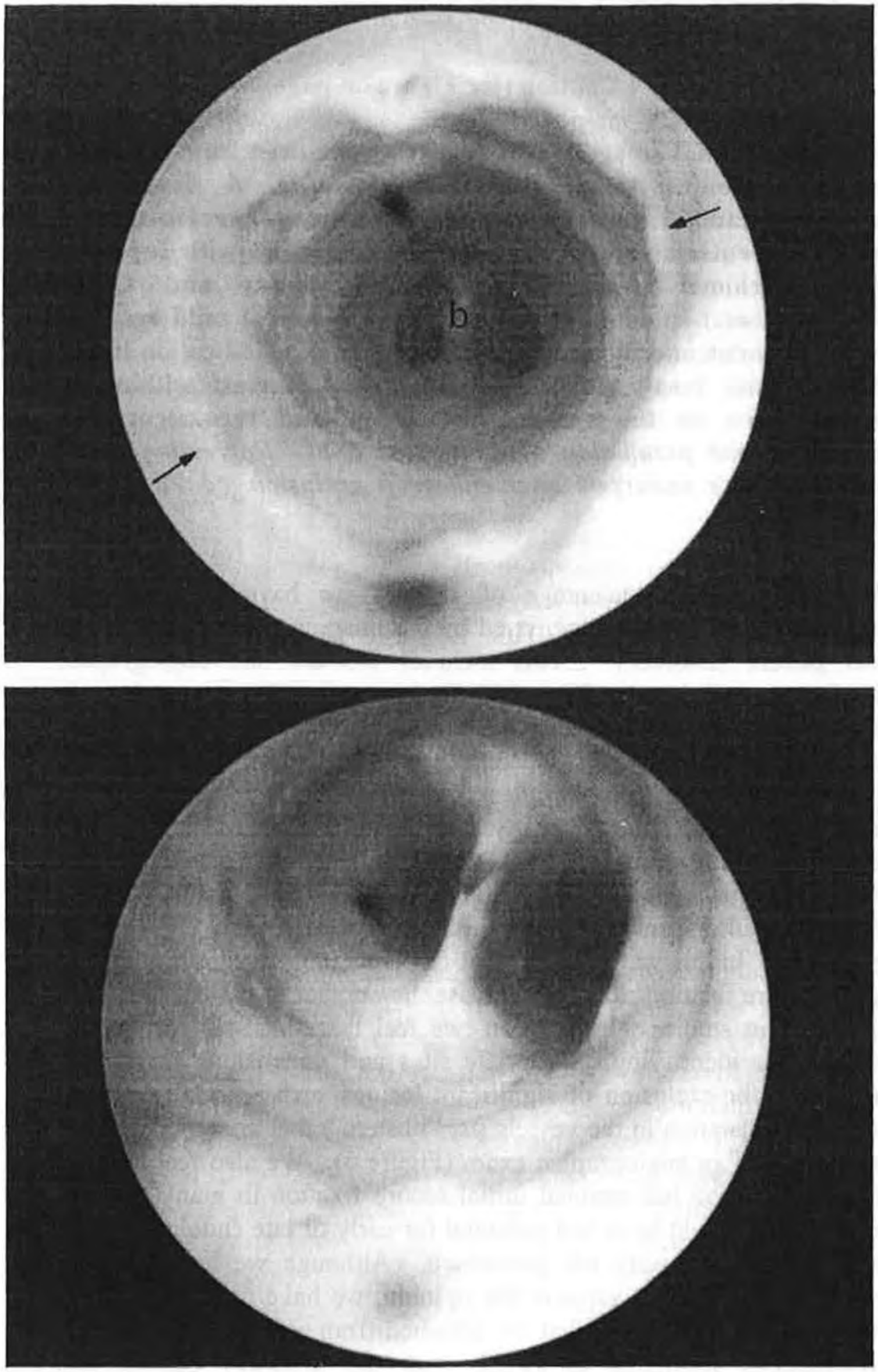

FIGURE 5 (Caption on Page 297)

FIGURE 5 Caption (for Figure on page 296)

Angioscopy of luminal surface of bifurcated endovascular prosthesis at 6 mo implantantion in the canine aorta. A, View of the the entire length of bifurcated body from infrarenal end of prosthesis (arrows) to bifurcation. B, View of aortic bifurcation and both iliac limbs. ***Reproduced with permission of White RA, et al. Evaluation of a modular endovascular bifurcation prosthesis in a canine aneurysm model. J Vasc Surg 24:1034-42, 1996***

projections (MIPS) have been used to select approximately 70-80% of patients for the procedure, we have performed IVUS examinations in 20-30% of patients to determine final candidacy. Using this approach, we have been able to limit unsuccessful technical deployment to 1 of 180 total aortoiliac procedures (<1%) due to inadequate access through the iliac arteries.

Although technical performance of aneurysm exclusion has been demonstrated with many devices, the current phase of investigation focuses on the long-term healing of devices and associated morphologic changes in aneurysm volume following successful exclusion [14]. The incidence and significance of early and late endoleaks is also a priority investigation. Our current evaluations are focusing on the evolution and importance of these factors using conventional axial and 3-D CT angiogram reconstruction. We are also examining the morphologic and volumentic changes that occur with time using an interactive computer analysis of CT data manufactured by Medical Media Systems (MMS, West Lebanon, NH). We feel confident that careful patient selection criteria and long-term follow-up will enable expedient future development of endograft technologies.

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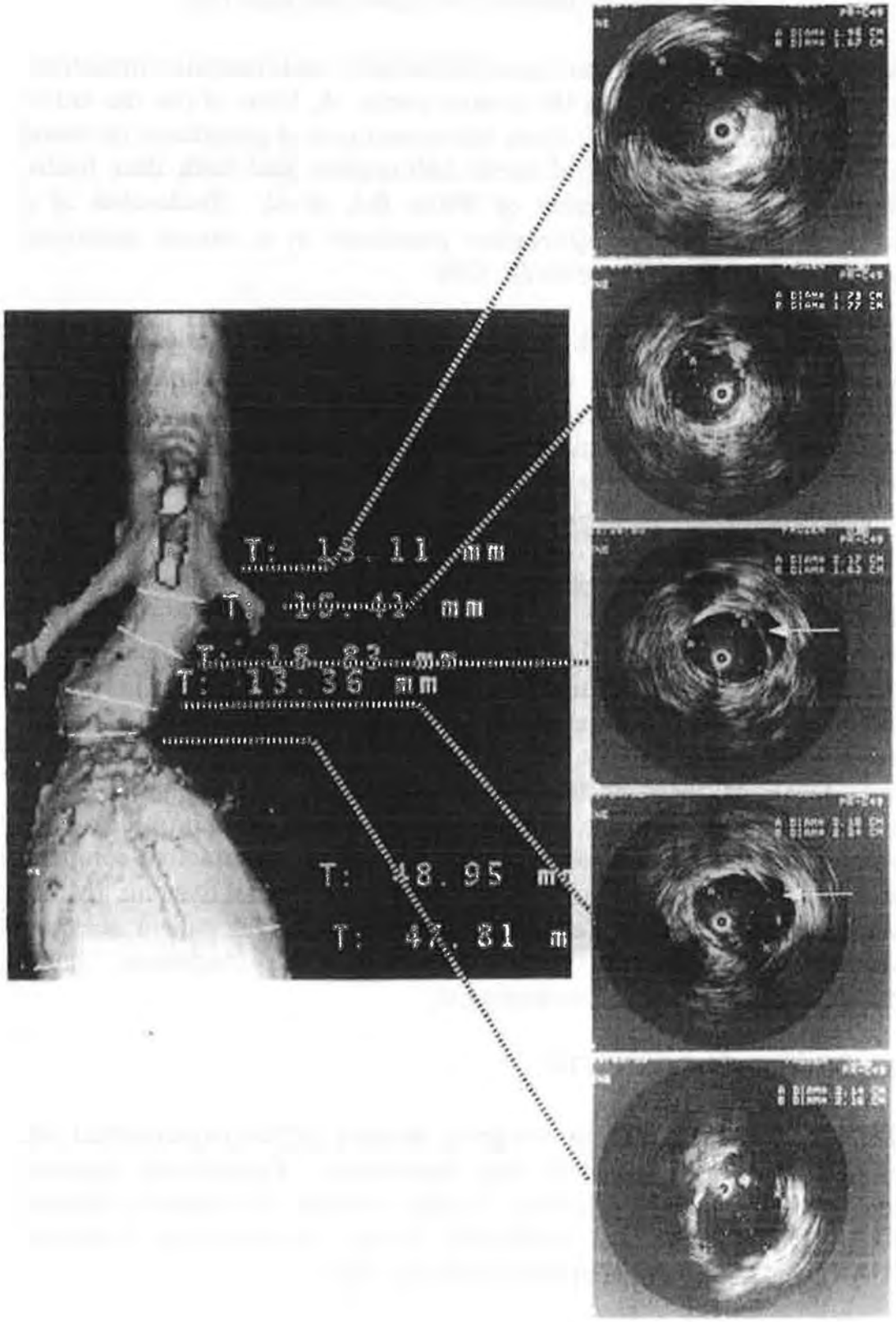

FIGURE 6 (Caption on page 299)

FIGURE 6 Caption (for Figure on page 298)

Spiral computed tomographic images of the proximal neck of an abdominal aortic aneurysm (left) with the corresponding intravascular ultrasound axial images obtained along the length of the neck at the designated levels. Note the break in the intimal surface (arrows) where an independent pulsatile segment of the aortic wall was apparent on the real-time images. ***Reproduced with permission of White RA, et al: Aortic aneurysm morphology for planning endovascular procedures. Texas Heart J 24:160-6, 1997***

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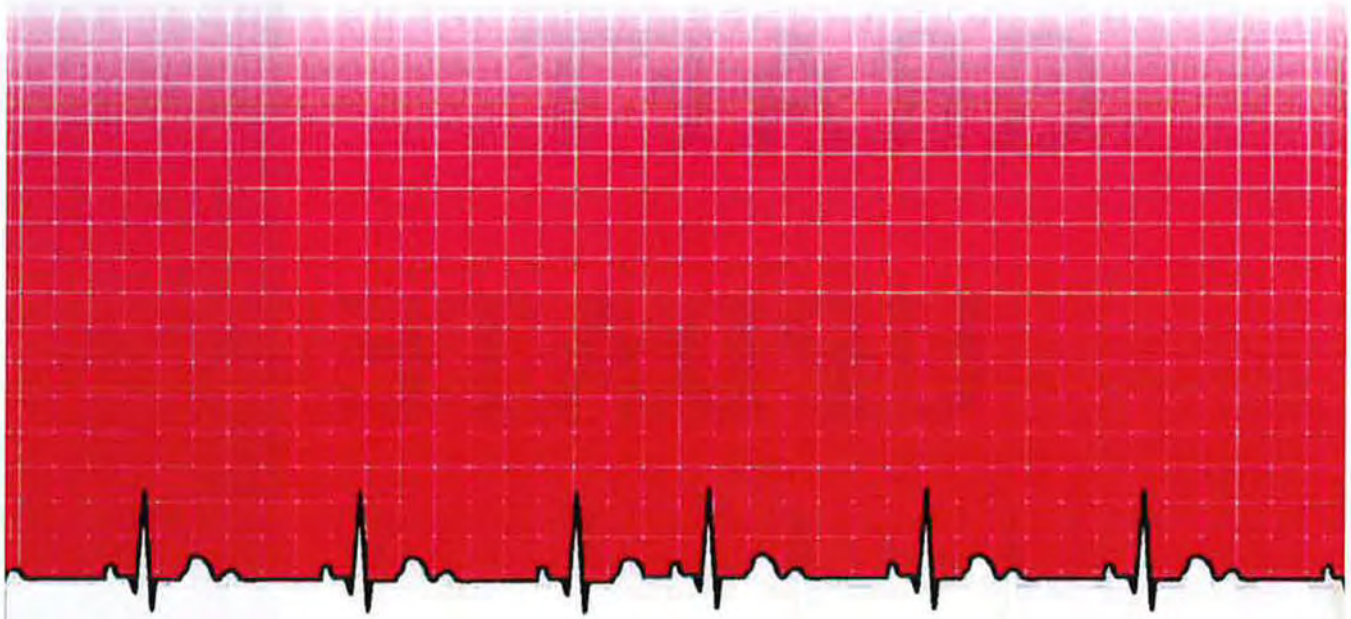

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Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on April 26, 2017, a complete and entire copy of **EXHIBIT 1041, STENT GRAFT UPDATE TEXTBOOK** has been served in its entirety by e-mail on the following addresses of record for Patent Owner:

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