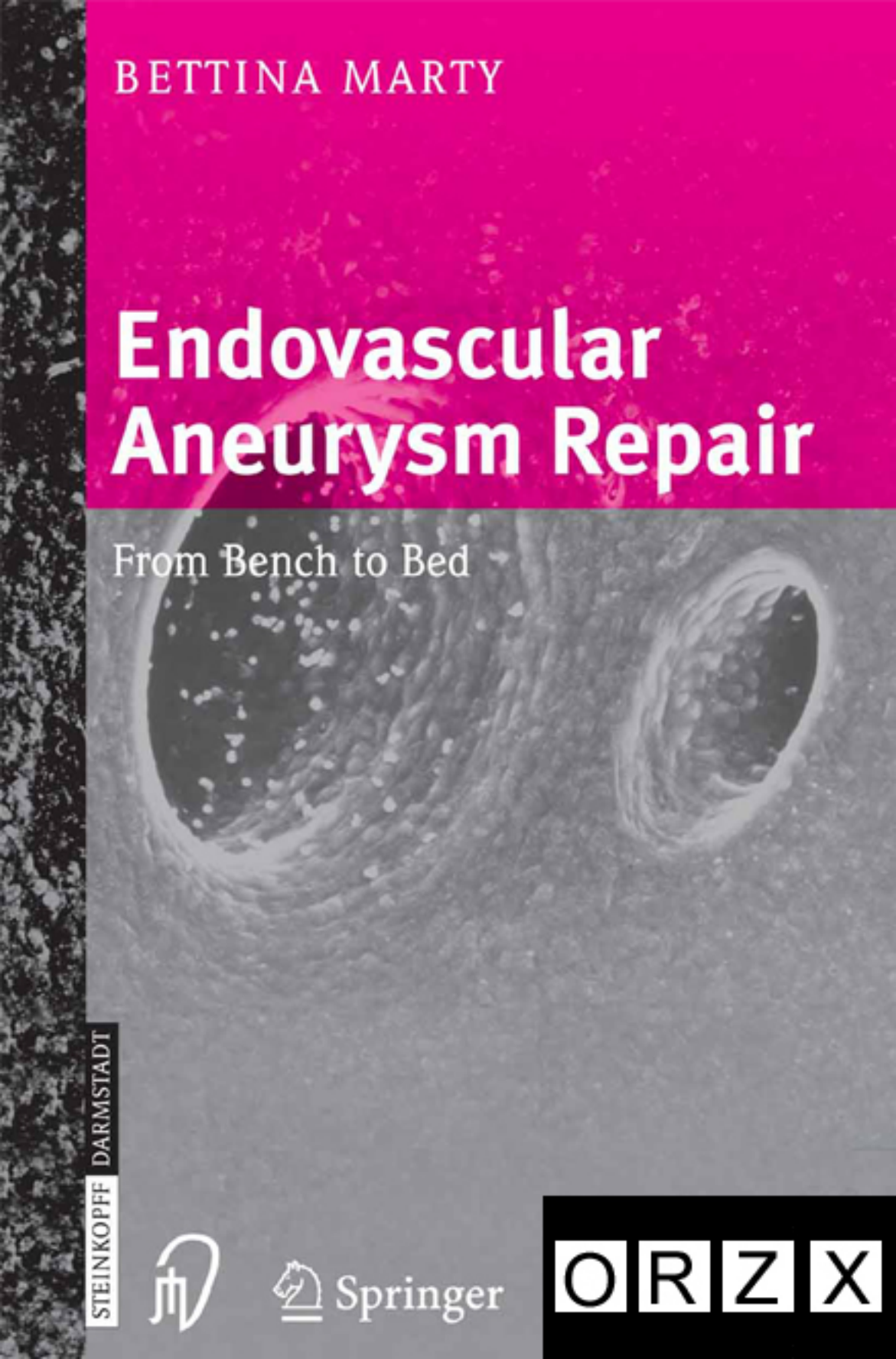
BETTINA MARTY

Endovascular Aneurysm Repair

From Bench to Bed



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From Bench to Bed

With 61 Figures (Some in Colour)
in 109 separate Illustrations and 13 Tables

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Foreword

In 1997, Dr. Marty visited Montefiore Medical Center in New York to pursue her research in endovascular aneurysm repair. During her 12 months stay, I had the pleasure to work closely with her. At Montefiore Medical Center, we have accepted over 20 researchers from around the World over the last 10 years. Among them, Bettina distinguished herself with her creativity, curiosity, and persistence, some of the most important abilities to be a successful surgeon scientist.

Dr. Marty is an established researcher in the field of vascular surgery and this book is a summary of her work in the field of aneurysm therapy. Some of her earlier investigations included basic research related to biological response to endoprostheses. When she proceeded to analyze the effect of endoleaks following endovascular repair in canines, many believed that the presence of an endoleak meant that the aneurysm was untreated and conversely, that absence of an endoleak guaranteed successful outcome. Dr. Marty challenged this conventional wisdom and conducted a study that is summarized in this book, while the second part of this book describes problems and solutions in the clinical setting. Dr. Marty has a very well balanced approach where she identifies problems in the clinical setting and takes them to the laboratory to solve them. I believe that this is an ideal approach and should be a role model for many surgeon scientists.

This book also provides a summary of the field of endovascular aneurysm repair and gives one a nice review of how this exciting field has evolved over the last ten years.

I recommend this book to be read by not only those clinicians taking care of patients with aneurysms but also young surgeon scientists who wish to understand some of the important issues in this field.

Takao Ohki

Acknowledgments

Si tu n'espère pas l'inespéré,
tu ne parviendra pas à le trouver.
Heraclit, 6th cent. B.C.

The advent of endovascular surgery represents a quantum leap in the evolution of vascular surgery. My professional career coincided with the exciting decade of endovascular surgery in the nineties. I had the opportunity to start first with experimental studies giving me insight into the biological response towards these new endoprosthetic devices and also the fate of the aneurysm left in situ. Later I performed endovascular aneurysm surgery in patients, and I encountered new and different challenges. The goal of this book was to summarize my own experience in endovascular surgery from the experimental beginning to clinical practice. It represents a document of our time illustrating a surgeon's growing personal experience on a small scale, while a dramatic upheaval in aneurysm surgery takes place worldwide.

I am very grateful to Karl Ludwig von Segesser whose leadership, knowledge and expertise have guided my vascular surgery career. I wish to thank Adam Fischer who taught me vascular surgery with responsibility, honesty and respect as the principles that guide all professional and personal relationships. I am deeply grateful to my father whose admirable standard and practice of surgery and patient care have earned my greatest respect.

The present work would have been impossible without the support from dedicated physicians, colleagues, friends, and family. I wish to thank Takao Ohki and Frank J. Veith, Montefiore Medical Center, New York, USA, who gave me unrestricted opportunity and support for experimental work. I would also like to recognize the encouragement and assistance of my teachers in general and vascular surgery which they have given me in my clinical work: R. Maurer (Zürich), H. Säuberli (Baden), U. Neff (Bülach), J. Largiadèr (Zürich) and P.L. Harris (Liverpool, UK). I am grateful to my brother Thomas Marty who assisted me accomplishing the benchwork models. Furthermore I appreciated the cheerful collaboration with Monique Augsburger and Sybille Egger-Rühle in performing the ex-

perimental studies, and the way they cared about the laboratory animals highly appealed to me. I should like to recognize the expert preparation of the histological slices Antonio Mucciolo provided me with, and the unflagging assistance of Mary Ellen Chatwin in editing my manuscripts. My thanks also go to the Institutes of Graphic Art of the University Hospitals in Zürich and Lausanne (P. Dutoit).

Contents

1 Introduction

Outstanding innovations in vascular surgery over the last fifty years suddenly made possible wholly new treatments. In 1949 Kunlin performed a femoro-popliteal bypass by a reversed saphenous vein for arterial occlusive disease of the lower limb [1]. In 1951 Dubost successfully performed definitive aortic aneurysm treatment by resection and implantation of a homograft [2]. In 1954 Eastcott reconstructed the carotid artery to avoid transient ischemic attacks [3]. In 1991 Parodi published the treatment of aortic aneurysms based on catheter technology. All these reference procedures became definitive and powerful therapies with a concept lasting for decades. Parodi's publication was accompanied by a far-sighted commentary of J. J. Bergan, anticipating the evolution of endovascular surgery [4]. He said, "…Dr. Juan Parodi and his colleagues have simplified aortic surgery…. There is no doubt that the procedure achieves its purpose. Predictably, it will be offered at first to patients who are at prohibitive risk for conventional aortic surgery. As experience grows, it will be offered to patients who are good surgical risks, even those with aneurysms smaller than the ones conventionally requiring surgical repair. During this time, complications will occur, some of which are cited in this initial clinical experience. As every interventional procedure has its own complications, new problems will arise. Opposition to the procedure will be mounted. In vascular surgery no change for the better has occurred that wise and good men have not opposed. Now that this initial barrier is broached, new applications …are predictable. Such change is inevitable…" The simplicity and minimal invasiveness of endovascular procedures incited worldwide enthusiasm for this technique. It was first used in high-risk patients who profit most from this treatment. Yet the aneurysm morphology in these patients is challenging with large aneurysms and tortuous iliac arteries of which only few are suitable for endovascular treatment. By contrast, in patients with favorable aneurysm morphology the benefits were indisputable, and younger and fitter patients requested endovascular surgery, too. Although the durability of endovascular aneurysm repair was not yet known, the treatment was applied to smaller aneurysms. In his initial report Parodi mentioned the specific complications of endovascular surgery, namely endoleakage, device misplacement, and occlusion of side branches due to overstenting. Indeed, incomplete aneurysm exclusion with or without endoleak owing to incom-

plete sealing at the fixation sites, retrograde aneurysm filling, fabric tears, device disintegration or migration remain the most frequent and most serious complications so far. They can result in aneurysm growth and even rupture. Controversy over credentialing and qualification in endovascular surgery arose right from the start. A claim for a new specialist was entered, the interventionist, based on the fact that these procedures require both surgical and interventional-radiological skills. Although the benefits of endovascular aneurysm surgery were obvious, famous vascular surgeons started to criticize it because of its presumed precocious application, the high rate of endoleaks, the need for long-term surveillance, and its questionable durability. Nevertheless, the indications were extended beyond aneurysm repair to include the treatment of traumatic lesions, arterio-venous fistulae, and ultimately carotid artery disease.

Endovascular surgery is part of a current wider cultural trend towards a gentler and more 'organic' co-operative relationship with nature. Open aneurysm repair is an aggressive approach consisting of replacement of the diseased aortic segment at the price of an abundant exposure, whereas endovascular surgery is minimally invasive, being performed through a remote access with catheter-based manipulations in the arterial system. This technique excludes the aneurysm that is left in situ. Today we know that aneurysms treated effectively by an endoprosthesis are likely to shrink as part of a healing process. Aneurysm regression is a new phenomenon associated with endovascular surgery, and one that acts counter to its natural history, which would strictly progress towards expansion and rupture.

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2 Historical background

The concept of endovascular grafting is almost one hundred years old and based on the idea of replacing the arterial wall by an internal tube reducing the lumen in case of an aneurysm or widening it in the presence of a stenosis. The first endovascular graft placement was performed by Alexis Carrel in a canine experiment in 1912 [1]. He entitled the study the 'permanent intubation of the thoracic aorta'. Rigid glass and aluminium tubes were inserted into the descending thoracic aorta through a direct small aortotomy following proximal and distal clamping. He proposed this technique for the repair of thoracic aneurysms. Carrel was, however, aware of the Achilles' heel of aneurysm repair by inlaid tubes, namely reliable fixation. Nevertheless, he considered this technique to be simple and superior to aortic resection and graft replacement. He was familiar with both implantation of inlaid tubes and aortic replacement by vein graft interposition, yet he considered the latter to be a dangerous procedure.

For the next forty years surgical attempts to treat abdominal aortic aneurysms met with little success. They consisted of electrothermically-induced thrombosis by placement of intraluminal wires, ligation of the aneurysm or endo-aneurysmorrhaphy. The surgical principles, namely excision of the diseased segment and restoration of the continuity were performed in a patient for the first time in 1951 by Dubost who interposed an aortic homograft following resection of an infrarenal aortic aneurysm [2]. This technique was used successfully in seven patients by DeBakey and Cooley who then standardized the treatment [3]. In 1952, Voorhees observed excellent biological compatibility of Vinyon-N, but it was not until 1957 when DeBakey introduced knitted Dacron tubes that were successfully used thereafter by every surgeon till these days [4]. An important technical modification was established in 1966 by Creech who proposed an intra-saccular anastomosis to reduce operating time and avoid damage to adjacent structures [5]. In 1974 Orr and Davies developed the graft inclusion technique into a straightforward procedure using exclusively tube grafts which were sewn to the aorta from inside and wrapped by the aneurysm sac without any attempts at resection [6]. Thereby a marked reduction in mortality was achieved particularly in ruptured aneurysms. Soon this technique became the golden standard for open aneurysm repair.

The idea of replacing the arterial wall by a tubular substitute from inside the artery remained an attractive idea throughout the century. In 1969 Dot-

ter inserted plastic tubes into the femoral canine arteries over a guide wire using a remote access [7]. The high thrombogenicity of the material and the small diameter of the tubes resulted, however, in occlusion prompting him to use open springs with better patency rates. Thereupon the potential of this technique using a remote access for catheter-based manipulations within the arterial system was recognized.

Tubular substitutes at the level of the aorta were less subjected to thrombosis owing to their large diameter and the high aortic flow. Yet direct access to the aorta for device insertion was still required to insert these tubes. In 1974 Dureau inserted Dacron tubes with a rigid Velour-covered Teflon ring directly into the ascending aorta in two patients with an acute dissection [8]. The prostheses were secured by tightening an external tape around the aorta at the level of the rings. However, this type of sutureless fixation carried an impending risk of tissue necrosis and did not gain widespread application.

It was not until the beginning of the eighties, when the concept of a transluminally inserted device was further developed. In 1982 Maass invented a self-expandable double helix spiral of stainless steel with a maximum expansion factor of five to one [9, 10]. For the first time remote access through a small peripheral artery with device deployment at the level of the large aorta was realized. The spirals were preloaded in a state of maximal tension on a small, 7 mm diameter introducer and inserted via iliac arteries. They were deployed by a remote torque release on the handle in the thoracic aorta using fluoroscopy. Maass demonstrated precise device deployment with circumferential alignment with the aortic wall, neointimal covering and absence of stenosis, thrombosis or perforation. He calculated the pressure transmitted to the aortic wall by the spirals in order to know its amount for reliable fixation without causing perforation. He recognized the significance of the spirals in aortic dissection by obliteration of the false lumen. At that time, Nitinol was discovered and considered the ideal material in these applications. The striking characteristic of Nitinol, a nickel titanium alloy, is thermal recovery. The spirals were designed by heating the wire over 525°C. Following cooling, the spirals were modified and constrained on a catheter. In body temperature, they transformed again into the original spiral shape. In 1983 Dotter implanted spirals into the femoral canine artery by use of a catheter and accomplished complete expansion by flushing the catheter with hot saline solution [11]. The same year, Cragg envisaged the application of a long spiral in the nonsurgical treatment of inoperable aortic aneurysms based on the observation of an excluded pseudoaneurysm [12, 13]. Maass was less enthusiastic because in his experiments he noted high-grade stenoses in tightly wound spirals. However, these experiments proved neointimal covering and patency of a metallic scaffold within the arterial system provided that its interstices were wide. Two problems remained to be addressed: First, the potential of the devices to expand, and second their equipment with sealing characteristics. In 1984 Lemole treated fifty-five patients with aortic aneurysms and dissections

by direct insertion of a straight Dacron prosthesis reinforced with metallic spools [14]. Fixation consisted in external tape ligatures as proposed by Carrel. Although they were carefully tightened to avoid tissue necrosis, in almost half of the cases the proximal spool had to be removed for technical reasons and the anastomosis sewn in the usual fashion. In 1985 Goddar presented a series of seven patients he was treating in a similar way [12]. He evaluated the diameter of the aortic neck by mitral valve sizers and used 24 or 26 mm internal diameter of the proximal prosthetic ring, a size well known today in endovascular aneurysm repair. However, the fixation of the prostheses remained a problem because the aorta had yet to be encircled by tapes, and additional stitches were necessary to ensure anchorage. In 1988 Matsumae used self-expandable springs to overcome this problem. He evaluated a Sutureless Intraluminal Graft with an Elastic Ring (SIGER) in the thoracic canine aorta [15]. Following direct device insertion a compressed metal adjusted spontaneously to the inner aortic diameter and held the position by friction force. He decreased aortic clamping time to less than three minutes because neither dissection nor tape ligation was necessary; however, the individual expansion force could not be controlled and was in some cases too high. Necrosis of the inner third of the media beneath the ring with an impending risk of rupture prevented their use in human beings.

Palmaz as the pioneer in stent development designed the fundamentals of a stent, analyzed the stent-tissue interaction and defined the optimal stent characteristics. A high expansion ratio will allow for a small introducer sheath. Stent expansion at the target site to a predictable diameter is necessary. A small stent surface combined with a high thromboresistance will enhance biocompatibility. Flexibility in length is required for device insertion, yet simultaneously radial stiffness has to be preserved attenuating intimal hyperplasia by the absence of micro-movements. Finally a good radiological visibility is important. In 1985 he designed a balloon-expandable stent mounted on a small 12 F angioplasty catheter and protected by a retractable sleeve [16, 17]. The stent consisted of a woven tubular wire mesh of stainless steel with soldered cross points to maintain expansion following balloon inflation. Redilation to a larger diameter was possible. Insertion without stent dislodgement, dilation of a stenosis by balloon inflation, and simultaneous stent placement was achieved all at once. Experimental evaluation in the canine aorta and visceral arteries showed a patency of 80% after four months. A functional neointima with areas of endothelium was demonstrated within the large interstices of the stent. The friction force of the stents was sufficient to prevent dislocation although the amount of pressure transmitted to the vessel wall remained unknown. In the following years various stent designs were developed, but besides the Palmaz stent successfully used in a clinical trial in 1988 [18, 19], only a few achieved clinical application, namely the Gianturco stent [20, 21], the Wallstent [22–24], and the Strecker stent [25, 26]. These stents represented a big step forward in endovascular technology and launched the evolution of stent supported prostheses, so-called endovascular grafts.

In the late eighties a few experimental studies demonstrated feasibility of endovascular aneurysm repair [27, 28]. Conventional fabric was attached to stents. These homemade endoprostheses were loaded on catheters and introduced via the femoral or carotid artery into the aorta in order to exclude experimentally created aneurysms. The fabric provided sealing and the stent anchorage. In 1991, Parodi and Palmaz demonstrated in a landmark publication the treatment of an infrarenal aortic aneurysm in six patients by means of a physician-fabricated endoprosthesis [29]. A large Palmaz stent was fixed by sutures to the proximal end of a straight polyester tube. This prototype endoprosthesis was mounted on a balloon catheter and covered by a retractable sheath. The assembly was introduced into the femoral artery, advanced into the aorta and positioned just beneath the renal arteries. Deployment was achieved by retraction of the sheath and stent expansion by inflation of the balloon. The stent provided anchorage of the tube graft from inside the aorta. For the first time, minimal invasive aneurysm repair in patients was achieved and initiated a decade of enthusiasm for a simplified yet demanding new technique.

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Experimental studies

1 Quantification of radial pressure caused by bare and covered Wallstents

Introduction

Anchorage of a stent within a vessel has to be reliable and durable in order to resist the shear forces of the blood flow. Initially when the stent is being deployed anchorage is exclusively determined by the radial force of the stent and the friction between the stent and the arterial wall. Later, biological fixation becomes additionally effective when the stent is progressively embedded into the underlying wall and covered by a neointimal layer. In clinical practice self-expandable stents are selected with a slightly larger diameter than the respective vessel diameter to provide reliable stent fixation, and balloon-expandable stents are expanded by a larger balloon than the corresponding vessel diameter, respectively. This empirical approach to stent fixation works very well. The mechanical properties of various stents, namely elasticity and compliance have been well investigated to predict the performance of a stent in vivo [1, 2]. However data regarding the radial pressure, once the stent is deployed, are rare. In the present study* [3] a physical model has been developed to calculate the radial pressure caused by self-expandable stents.

Material and methods

The mechanical characteristics of bare (n = 5) and covered (n = 5) Wallstents with a nominal diameter of 10 and a length of 60 mm were analyzed (Fig. 1). The Wallstent consisted of filaments of stainless steel (0.12 mm) woven in a criss-cross tubular pattern. Covered stents contained integrated porous polyurethane.

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* By kind permission of the Editor (*Swiss Surgery* 1996; Suppl. 1(3):4–7)

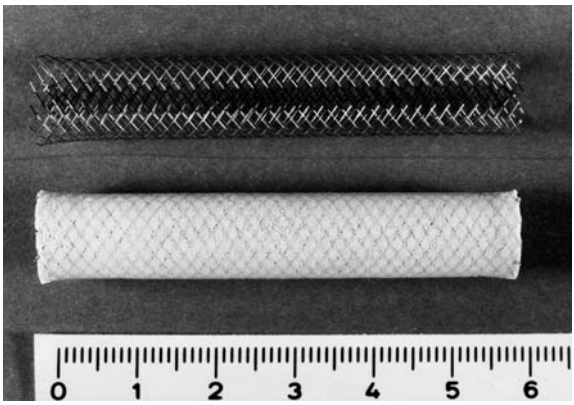


Fig. 1. Bare and polyurethane covered Wallstent

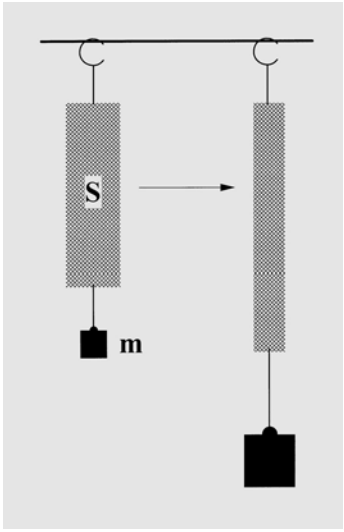


Fig. 2. Benchwork model to analyze the expansion of Wallstents. The stent becomes longer with increasing load and its diameter smaller. *m* mass; *S* stent

Measurements. Axial load was applied to the stents by weights at 0.02 kg increments to a total of 0.1 kg, followed by 0.05 kg increments to a total of 0.35 kg. Length and diameter of the stents were measured at each given load by sliding calipers. Load increased stent length, simultaneously diminishing stent diameter (Fig. 2). A plot of length versus diameter was created and described by a polynomial fit (Fig. 3). These measurements established the connection between the applied force and the corresponding change in length (Fig. 4). The resulting force was calculated. It is related to the applied weight or mass: Force = mass × gravity.

$$F = m \times g$$

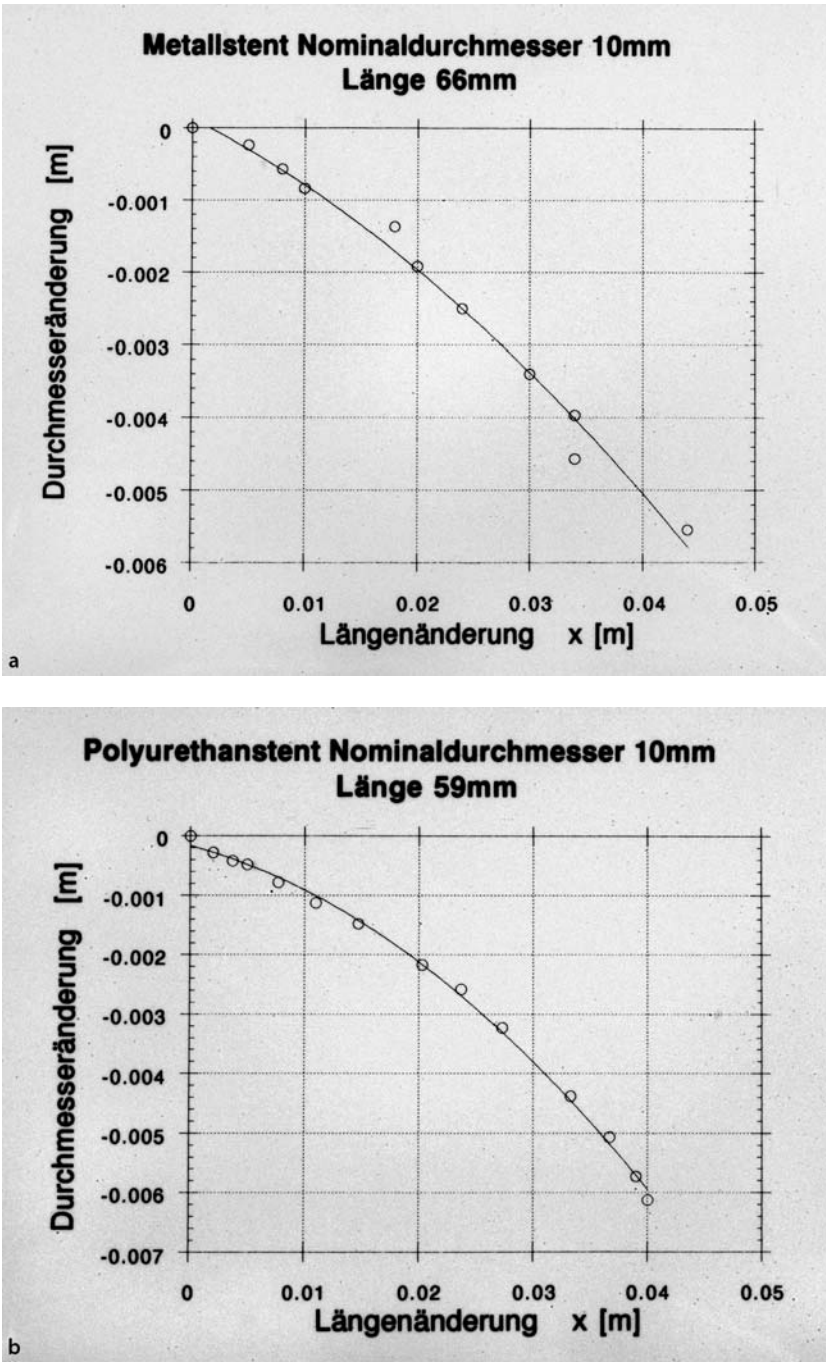


Fig. 3. A plot with a polynomial fit shows the relation between increase in length and corresponding decrease in diameter. **a,** for bare stents; **b,** for covered stents

Model. We used a simplified model to describe the elastic performance of the stents. The simultaneous longitudinal and radial deformation is described by a longitudinal and radial spring that is perpendicular to each other (Fig. 5). They have a constant (c_1 and c_2) and are connected by a coupling constant (κ).

Energy balance. A balance between the applied external energy and the deformation energy was performed to determine the constants c_1, c_2 and κ, using the formula: externally applied work = internally stored work.

$$W_{ext} = W_{int}$$

The energy balance was set equal over the whole range of stent deformation and allowed the calculation of the constants.

Calculation of radial pressure. The stent is considered an elastic cylindrical tube within another tube, namely the vessel. The stent surface is area = $2\pi \times$ radius $\times$ length.

$$A = 2\pi \times r \times l$$

The radial expansion force of the stent is calculated using the radial constant c_2: Radial force = constant$_2 \times \Delta$radius.

$$F_{rad} = c_2 \times (\Delta r)$$

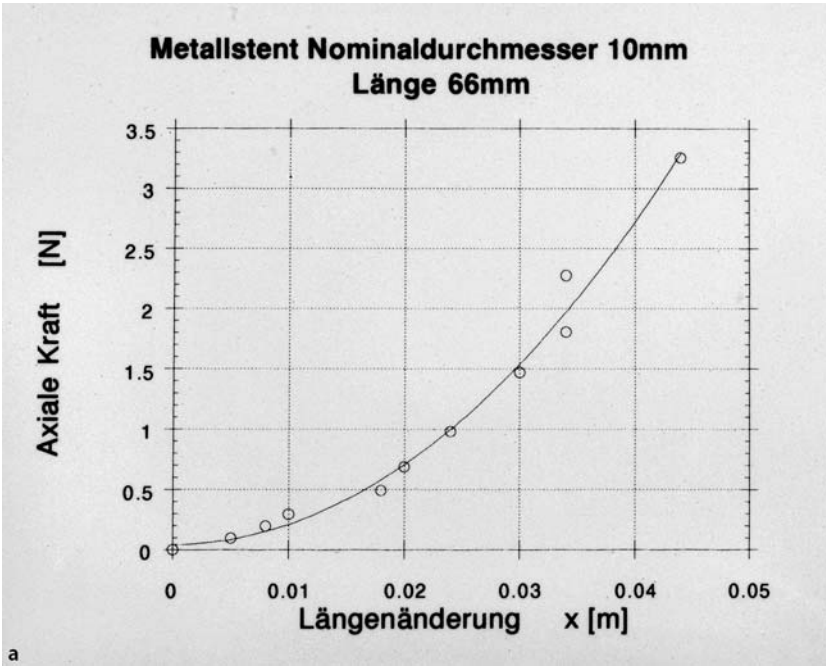
Finally the radial pressure is defined by the radial force divided by the outer surface of the stent (Fig. 6). Pressure = radial force $\times \Delta$radius divided by $2\pi \times$ radius $\times$ length.

$$p = \frac{F_{rad} \times (\Delta r)}{2\pi \times r \times l}$$

Results

Figure 3 demonstrates the relation between stent diameter and stent length. For example a 20 mm length increase of a bare stent is accompanied by a 2 mm diameter reduction. A further length increase of 20 mm results in a more pronounced diameter reduction of 3.2 mm. This non-proportional relation applies to the covered stent as well; however, the same increase in length corresponds to a smaller decrease in diameter.

The relation between force and length is shown in Figure 4. For example, an axial load of 1 N is required for a 24 mm length increase of a bare stent. An additional load of 1 N adds only 7 mm in length. This relation is valid for the covered stent too, yet the same axial load results in a smaller length increase. The area under the curve represents the energy required for stent deformation. A higher energy is necessary to achieve the same increase in length for the covered stent compared to the bare stent.



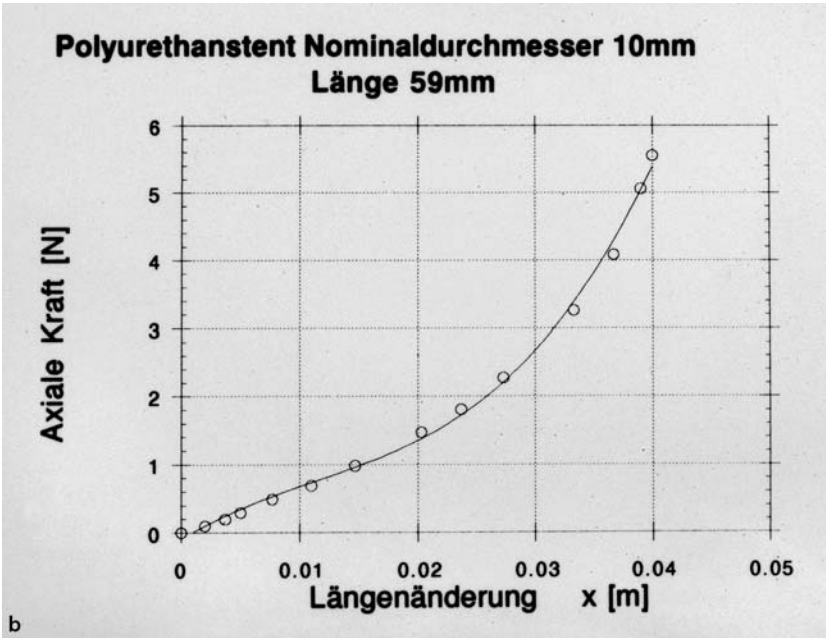


Fig. 4. A plot with a polynomial fit shows the relation between increase in length and applied force. **a** For bare stents; **b** for covered stents

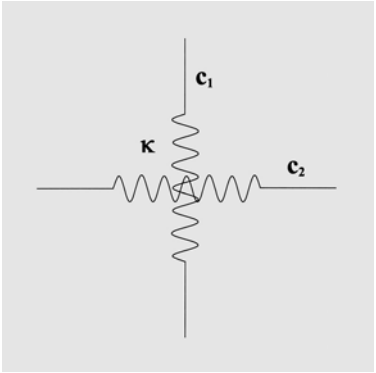


Fig. 5. The expansion of the Wallstent is considered as the expansion of two springs, which are perpendicular to each other. They have a longitudinal (c_1) and radial (c_2) constant and a coupling constant (κ)

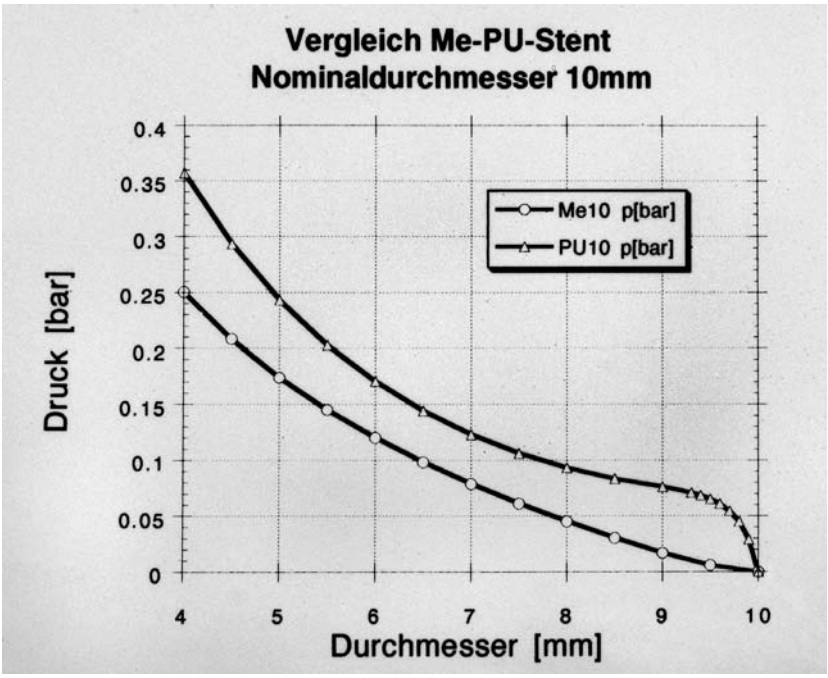


Fig. 6. The radial pressure of bare and covered Wallstents is shown as a function of the diameter. The pressure increases with decreasing stent diameter. The more constrained the stent is within a vessel, the stronger the radial pressure is on the vessel wall. Covered stents have a consistently higher pressure

Bare stents demonstrate a smooth increase in wall pressure with decreasing diameter (Fig. 6). The more constrained the stent is, related to its nominal diameter (10 mm in our study), the higher the radial pressure is. For example, a bare stent with a nominal diameter of 10 mm exerts a radial pressure of 0.02 bar on the inner surface of the surrounding wall of a

9 mm diameter vessel. The radial pressure increases considerably to 0.17 bar when the same stent is implanted in a vessel of 5 mm diameter. The radial pressure for the covered stent is consistently higher. For example, a covered stent with a nominal diameter of 10 mm exerts a radial pressure of 0.08 bar on a recipient vessel of 9 mm diameter.

Discussion

We focused for methodical reasons on a progressive change in stent length and measured the corresponding diameter in our benchwork model. However, the clinician is used to concentrate on the stent diameter, and thus he selects the appropriate stent with respect to the vessel diameter. In order to make the following text easier to understand, we will discuss the results in the way the clinician is used to look at the stent, and we will therefore focus on changes in the diameter.

Figure 6 gives the rationale for a moderate oversizing of stents corresponding to usual clinical practice. The radial pressure of a stent has to be just strong enough to provide sufficient friction for anchorage without damage to the vessel wall. Stents with an oversizing of 1 to 2 mm compared to the respective vessel diameter result in a low radial pressure as shown by Figure 6. Indeed, stents with a 10 to 15% oversizing are considered ideal enabling embedding of the metal frame into the subintimal layer. The indentations of the vessel wall caused by the metallic frame are instantaneously filled by thrombus and heal subsequently by endothelialization from the interstices [4, 5]. Contrarily, a large stent in a small vessel creates a high radial pressure on the surrounding vessel as demonstrated by Figure 6. The adverse effect of large stent oversizing has been experimentally demonstrated in coronary arteries. An extensive proliferative response was provoked by deep lesions of the vessel down to the adventitial layer with destruction of the wall structure [6, 7]. Therefore oversizing of more than 15% is considered a significant risk factor for instent restenosis due to intimal hyperplasia.

The polyurethane covered stent performed similarly as the bare stent, yet required a consistently higher deformation force. The polyurethane covering renders the stent slightly stiffer and enhances the friction at the crossing points of the tubular mesh-wire. Nevertheless, the excellent longitudinal and radial flexibility was not impaired. Figure 6 illustrates the higher radial pressure of a covered stent throughout the whole range of varying diameters with a sharp initial increase of radial pressure. This performance is likely to result in a more intense neointimal response besides the inflammatory reaction evoked by the polyurethane. Therefore covered stents should be more cautiously oversized and are probably at greater risk for instent restenosis.

This study illustrates also a characteristic feature inherent in the Wallstent, namely considerable stent shortening during expansion, as demonstrated by Figure 3. Every increase in stent diameter is accompanied by a corresponding decrease in length. Clinical experience showed that these stents, which are maximally constrained on a catheter at introduction into the vessel, undergo a 20 to 40% post-deployment reduction in length [8]. This has to be taken into account when treating a stenosis. Using the Wallstent requires technical skill. It is recommended to start progressively with stent deployment, first beyond the lesion. Then retraction of the semi-released stent towards the puncture site is proposed followed by centering of the stent across the lesion before complete deployment.

In conclusion, the process of stent expansion regarding bare and covered Wallstents was analyzed by measurements of change in stent length and diameter. A physical analysis of the expansion process enabled the calculation of the radial pressure to which the inner surface of the underlying vessel is subjected, for each corresponding stent diameter. The radial pressure of bare stents is small if they are minimally constrained, and increases progressively with larger stent diameters. Polyurethane covered stents cause consistently higher radial pressure. These data give rationale for a moderate oversizing using bare stents, and for a minimal oversizing of covered stents.

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2 Latex covering of Palmaz stents and its effect on stent expansion

Introduction

Bare stents are used in the endovascular treatment of stenotic lesions and occlusions. A covering makes them suitable for the exclusion of false aneurysms, arterio-venous fistulae and traumatic wall lesions [1–3]. In 1994, in the attempt to treat these lesions by stents, physicians covered Palmaz stents by a segment of thin-wall ePTFE that was predilated to a larger diameter. The prosthesis was secured to the metallic stent frame by sutures [1, 4]. The assemblage was mounted on a balloon angioplasty catheter and protected from dislodgement by a retractable sheath. The shortcomings of this construction are a relatively high profile and an inherent risk of suture breaks or fabric tears owing to the friction force during deployment. We covered Palmaz stents with a thin layer of natural rubber latex and investigated their mechanical characteristics by comparing the covered stents to the bare Palmaz stents* [5].

Material and methods

Latex coating. Six Palmaz stents with a length of 3 cm, an initial diameter of 3.4 mm and a wall thickness of 0.15 mm (P294; Johnson & Johnson Interventional Systems, Warren, NJ) were covered by latex. They were mounted on 4 mm glass rods, immersed into a bath of natural rubber latex and dried under room temperature (Fig. 1). Imperviousness and elasticity of the covering were evaluated by inflation of a latex tube of 4 mm diameter with a wall thickness of 0.2 mm, manufactured also by the author. Samples of latex were implanted in porcine subcutaneous tissue to evaluate the biological response.

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* By kind permission of the Editor (*Swiss Surg* 1996; 2:97–101)

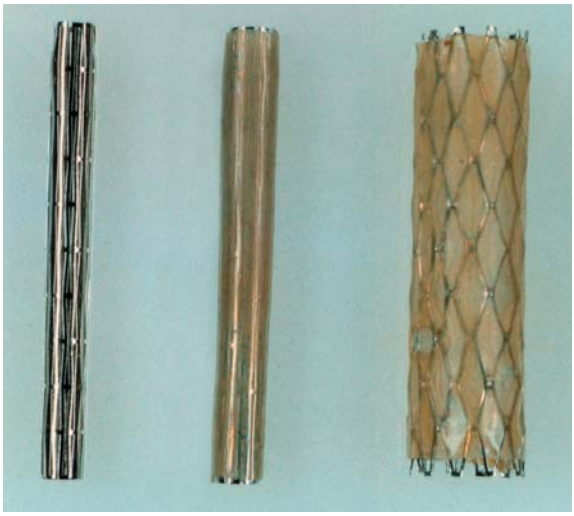

Fig. 1. Covering of Palmaz stents by a thin layer of natural rubber latex

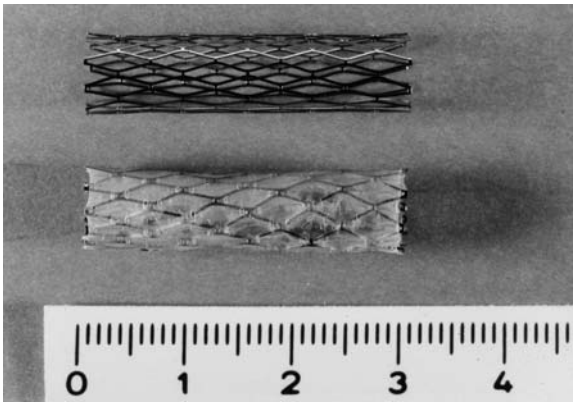

Fig. 2. Bare and latex covered Palmaz stents following expansion by an 8 mm balloon

Stent expansion. Six bare and six covered stents (Fig. 2) were expanded by angioplasty balloons with a nominal diameter of 6 and 10 mm and a length of 40 mm (Schneider{Europe} AG, Bülach, Switzerland) using inflation pressure with a stepwise increase from one to six bars. The diameter of the balloons and the external diameter of the stents mounted on the balloons were measured at their proximal, central, and distal level by sliding calipers at pressure increments of 0.5 bars (Fig. 3). A compressor with a manometer and a valve maintained a given pressure during the measurements (Fig. 4). The expansion of the balloon (E_B) was defined by the ratio of the balloon diameter (D_B) related to the nominal balloon diameter ($D_{B\ nom}$).

$$E_B = \frac{D_B}{D_{B\,nom}}$$

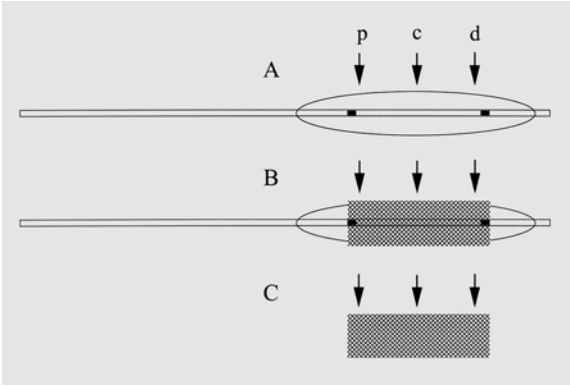

Fig. 3. Schematic drawing of the balloon (**A**), the stent mounted on the balloon (**B**), and the removed stent (**C**). The levels where the diameter has been measured are indicated. *p*, proximal; *c*, central; *d*, distal

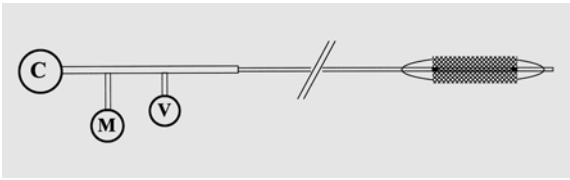

Fig. 4. Compressor to maintain a constant pressure during measurements. *C*, compressor; *M*, pressure gauge; *V*, valve

The expansion of the stents was defined by the ratio of the stent diameter ($D_{S\ mount}$) mounted on the balloon related to the nominal balloon diameter ($D_{B\ nom}$).

$$E_S = \frac{D_{S\ mount}}{D_{B\ nom}}$$

This allowed the comparison of the changing stent characteristics following expansion by balloons of different diameters.

Stent recoil. Following stent expansion, bare and covered stents were removed from the balloons and the central diameter of the removed stents was measured (Fig. 3 C). Stent recoil was defined by the ratio of the difference in diameter between the mounted stent ($D_{S\ mount}$) minus the removed stent ($D_{S\ remov}$) related to the diameter of the mounted stent ($D_{S\ mount}$).

$$R_S = \frac{D_{S\ mount} - D_{S\ remov}}{D_{S\ mount}}$$

Stent configuration. We defined the ideal stent configuration as a cylinder. In order to analyze the final configuration of the stents after removal from the balloons, we measured the diameter of the removed stents at their central and peripheral levels (Fig. 3 C). Stent deformation (DEF_S) was considered as a divergence from the ideal cylindrical stent configuration. It

was defined by the ratio of the difference of the central ($D_{S\ centr}$) minus the mean peripheral stent diameter ($D_{S\ periph}$) related to the central stent diameter ($D_{S\ centr}$).

$$DEF_S = \frac{D_{S\ centr} - D_{S\ periph}}{D_{S\ centr}}$$

All data are expressed as mean value ± SD. The non-paired t-test was used for comparison between bare and covered stents.

Results

The latex tube demonstrated imperviousness and elasticity at an inflation pressure of 180 mmHg (= 0.23 bar) and remained intact. All six stents could be successfully covered by a very thin membrane of latex. Expansion did not show any tears or defects of the covering. The histological analysis showed an impressive foreign body reaction with multinuclear giant cells at the implantation sites of latex (Fig. 5).

Figure 6 shows the expansion of the balloons, and the bare and covered stents as a function of a stepwise increase of the inflation pressure. In the low-pressure range smaller than 4 bars the curve of both types of stents steadily increased with augmentation of the pressure. The curve of the balloons is above the curves of the stents indicating that the balloons are inflated to 80%, whereas the stents are expanded only by 60 to 65%. Between 4 and 6 bars, the curves of the bare and covered stents are almost identical. In other words, the covered stents required approximately the same inflation pressure as the bare stents. The similarity of the stent curves demonstrates that stent expansion between 4 to 6 bars was mainly determined by the characteristics of the balloon. When the curve of the balloons is parallel to the curves of the stents, maximal inflation of the balloons is present.

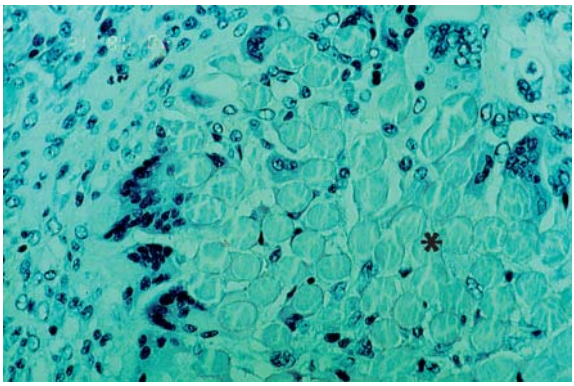

Fig. 5. Histological section of latex in subcutaneous tissue. Marked foreign body reaction with giant cells surrounding latex (asterisk)

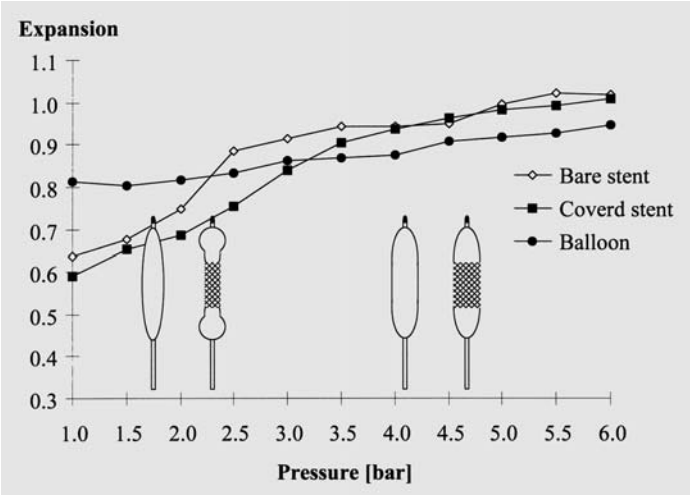

Fig. 6. The expansion of balloons, bare and covered stents that are mounted and expanded by the balloons is shown at different inflation pressures. The expansion of bare and covered stents is similar to each other within the pressure range of four to six bars

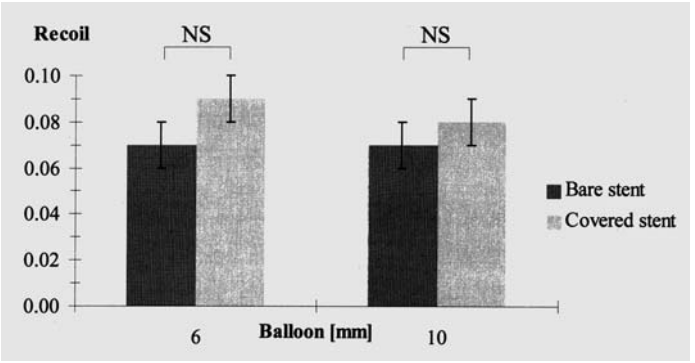

Fig. 7. Stent recoil is minimal for both bare and covered stents

The bare and covered stents showed a 7 to 9% stent recoil, that means they slightly collapsed following removal of the balloons (Fig. 7). Recoil was observed following stent expansion by both a six and a ten millimeter balloon.

Divergence from the ideal cylindrical form was observed in both types of stents following removal of the balloon (Fig. 8). The configuration of an ideal cylinder corresponds to 0 on the chart. The bare stents showed a minimal constriction of 3% in their central part, indicated by a negative value. Contrarily, the covered stents had a slight bulge of 3.5% in the central part with a corresponding positive value.

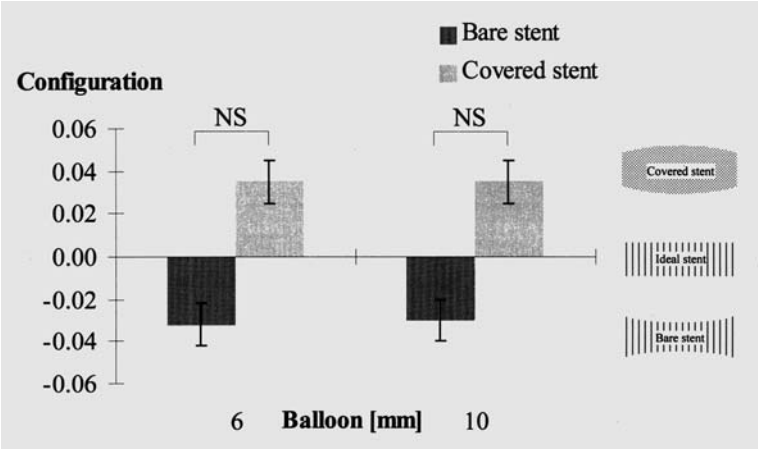

Fig. 8. Divergence from the cylindrical stent configuration was observed following removal of the balloons. Bare stents showed a slight central constriction and, contrarily, covered stents a central bulge

Discussion

The present experiment demonstrates that latex covering of stents is feasible and does not substantially alter the characteristics of the stents. We chose the Palmaz stent because of its rigidity probably resisting to the elastic recoil of a covering and the preservation of length during expansion. The final stent diameter is predictable because stent expansion is defined by the diameter of the balloon. For these reasons measurements are easy to perform. We selected latex for the production of covered stents because of its high elasticity and imperviousness. Yet the tissue reaction towards latex was inflammatory and extensive, jeopardizing probably the biocompatibility of latex covered stents and making them unsuitable for a long-term implant. The biocompatibility depends mainly on the accelerators as sulfur and zinc oxide, which are added for the vulcanization processing.

The latex covering was ultra-thin allowing stents to preserve their mechanical characteristics. Covered stents did not require a higher inflation pressure than bare stents between four to six bars. The covered stents did not collapse either after removal of the balloons. Their recoil was minimal and comparable to bare stents despite the propensity of latex to shrink. The plastic deformation of Palmaz stents is high, enabling maintenance of expansion without significant recoil. The stent is known for its rigidity and minimal elastic deformation [6, 7].

The rigid stent frame also prevents major deformation following expansion. Yet the rigidity is less strong at the ends of the stent, and this is the level where the elastic recoil of latex became effective by constricting the frame. The minimal bulge in the central part was a consequence of this ef-

fect. Contrarily, the bare stents showed flaring stent edges following expansion. This is also a consequence of the diminished rigidity of the terminal stent frame. The phenomenon is known in clinical use. It can become a problem if repositioning of an almost expanded stent is required, thereby causing a plaque disruption or a dissection.

The advantage of latex covering is its low profile. Latex fitted perfectly to both the expanded and the constrained stent. Thereby a low profile was maintained for stent insertion. A covering of PTFE lacks this advantage. PTFE has to be predilated and is therefore abundant. It has to be fixed and crimped on the constrained stent. PTFE has also an important recoil of 23% of the maximal balloon diameter to which it was predilated [8]. In case the PTFE covering is fixed to the internal surface of a Palmaz stent, the elastic recoil causes a significant luminal stenosis, as demonstrated in a canine experiment [9]. Therefore it was recommended to attach the PTFE covering to the external surface of the stent where it is buttressed against the vessel wall, following stent expansion.

In conclusion, latex covering of Palmaz stents is feasible. Stent expansion is not impaired, and stent recoil is minimal and comparable to bare stents. Latex has a slightly constrictive effect on the ends of the stent. Its advantage is a low profile, whereas its biocompatibility is problematical.

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3 The healing response towards polyurethane covered Wallstents – A histological investigation

Introduction

Device development and clinical application outpaces the experimental evaluation of endoprostheses including the healing response of the artery. Intraluminal prostheses may adversely affect the vessel by destruction of the endothelium, evocation of a proliferative response, and atrophy or laceration of the tunica media owing to isolation from oxygenated blood and compression by the radial force of the endoprostheses. Research focuses mainly on fabrics such as polyethylene terephthalate (PET) and polytetrafluoroethylene (PTFE) which were applied to endoprostheses because these materials have been used successfully for conventional bypass grafting for a long time [1–8]. Contrarily, polyurethane as an endovascular graft material is less investigated because of its inflammatory response and biodegradation [9–12]. In large vessels such as the aorta, granulation tissue is unlikely to cause an obstruction or major flow disturbance and can even be advantageous as it may enhance the fixation of the endoprosthesis. We evaluated the healing response of the porcine aorta towards a polyurethane covered Wallstent* [13].

Material and methods

Animals. Twelve adult minipigs (39 ± 4 kg) were used. Animal care and handling complied with 'Principles of laboratory animal care' and 'Guide for the care and use of laboratory animals' (NIH publication no 80-23, revised 1985). The protocol was approved by the institution's Animal Care Committee.

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Devices. Twelve covered Wallstents (Covered Vascular Wallstent™, Schneider {Europe} AG, Bülach, Switzerland) were used with a nominal length of 40 mm and a diameter between 7 and 10 mm. The distal end remained uncovered so as to provide perfusion of the iliac trifurcation. The stents were constrained by a retractable membrane on a 9.5 F introducer system (Fig. 1). The covering consisted of integrated microporous polyurethane with pores varying between 100–350 μm diameter (Fig. 2). The diameter of the wire filaments was 0.12 mm, and total the wall thickness amounted to 0.35 mm.

Implantation. The animals were sedated with thiopental sodium, intubated and ventilated with 1–1.5% halothane and nitrous oxide (Fig. 3). Each animal was administered 2 Mio. Units of penicillin. Arteriotomy of the right carotid was performed from a midline incision. 5000 U of heparin

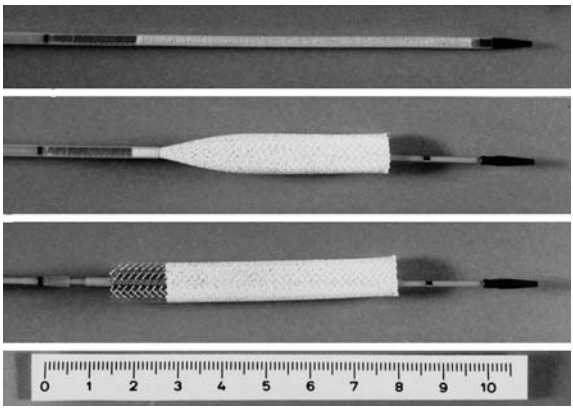


Fig. 1. Covered Vascular Wallstent™ mounted on an 11.5 F introducer. Note the 32% shortening of the endoprostheses from a length of 9.5 cm on the introducer to a length of 6.5 cm when the device is completely released and expanded to its nominal 9 mm diameter

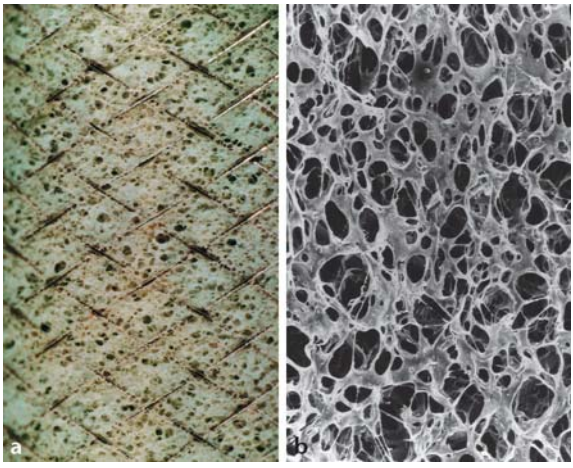


Fig. 2. Covering consisting of spongy polyurethane. **a**, luminal surface of endoprosthesis by magnifying glass (original magnification ×3) and **b** electron microscopy (original magnification ×45)

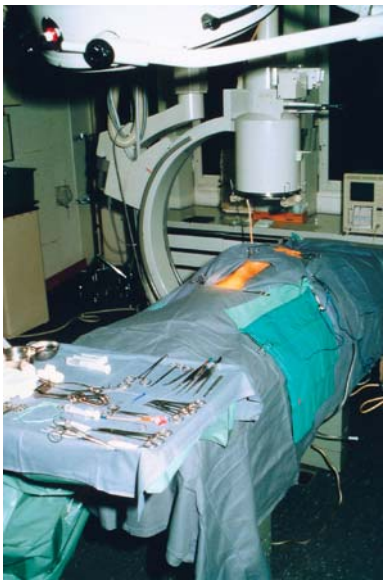


Fig. 3. Operating room in the laboratory: Equipment includes a set of vascular instruments, an angiographic table, and fluoroscopy

IV were given before a 10 F vascular sheath was inserted and advanced into the infrarenal aorta over a guide. A marker angiographic catheter (Sizing catheter, COOK, Queensland, Australia) was positioned above the renal arteries. Arteriograms were obtained by injection of 10 ml contrast dye (Iodamid, BRACCO, Milano, Italy). The images were recorded on a film cassette placed beneath the animal (one-shot arteriogram). The diameter of the infrarenal aorta was calculated by means of the marker catheter, and the appropriate stent size was selected. The introducer was inserted over the wire and the endoprosthesis deployed under fluoroscopic control. Carotid artery ligation was performed following completion arteriography. After the implantation, all animals were given morphine on the first postoperative day. No aspirin was given.

Explantation and specimen processing. The endoprostheses were reevaluated by arteriography at intervals of 37 ± 9 days ($n = 4$) and 199 ± 2 days ($n=4$). Before sacrifice, 10 000 U of heparin were administered to prevent clot formation on the luminal surface. The infrarenal aorta was excised, the specimens rinsed with phosphate-buffered saline, longitudinally bisected and photographed.

Light microscopy. One half of the specimen was processed for light microscopy and fixed with 10% neutral buffered formalin. It was transversely sectioned into 10 samples. Sample 1 and 10 represented the aorta proximally and distally to the endoprosthesis. The samples were processed through graded alcohol and embedded in paraffin. The wires were removed

from the blocks that were subsequently sectioned at 4 µm thickness. Slides were stained with hematoxyline + eosin and Elastica van Gieson. Cell types were analyzed by immunohistochemical staining, including smooth muscle cells (SMC) and endothelial cells (EC). SMC were identified with anti-smooth muscle actin (Progen, Readysystem Inc., Zurzach, Switzerland), and EC with anti-von Willebrand factor (BioGenex, San Ramon, California, USA). Measurements were performed by the use of a computerized image-analysis system (ImagePro, MediaCybernetics, Silver Spring, MD, USA) equipped with a conventional light microscope (Axioskope; Zeiss, Jena, Germany). The height of the respective layers was calculated by averaging three measurements of *minimal* thickness. Thereby erroneously high values owing to a section in a tangential plane were eliminated. The following layers defined the wall structures

- *Neointima [µm];* tissue between lumen and polyurethane covering.
- *Endoprosthetic wall [µm];* layer of polyurethane covering including voids owing to removed wires.
- *Interface [µm];* tissue layer between outer surface of polyurethane covering and tunica media.
- *Tunica media [µm];* measured beneath the voids, where compression is strongest.

Scanning electron microscopy. The other half of the specimen was processed for surface analysis by scanning electron microscopy. Samples were trimmed perpendicular to the long axis, fixed with 2% glutaraldehyde (cacodylate buffer 0.05 mol/L), and dried by the critical-point method. They were mounted on studs and sputter coated with gold-palladium. Photographs were taken from the luminal surface at 1000×magnification. Macro- and microphotographs of the luminal surface were scanned, and the area of thrombus and endothelium was measured by an image-analysis system.

Statistical analysis. Numeric values are reported as a mean value ± standard deviation (SD). Comparisons between early and late specimens were performed using a two-tailed Student's *t* test. A *P* value of < 0.05 was considered significant.

Results

The postoperative course and follow-up of all twelve animals was uneventful. The handling of the delivery system was easy and the deployment of the endoprostheses uncomplicated. All devices remained patent including perfusion of the renal and iliac arteries. The arteriograms revealed slight luminal narrowing owing to intimal hyperplasia at mid-term follow-up (diameter 8 ± 2 mm vs 6 ± 1 mm, NS, Fig. 4).

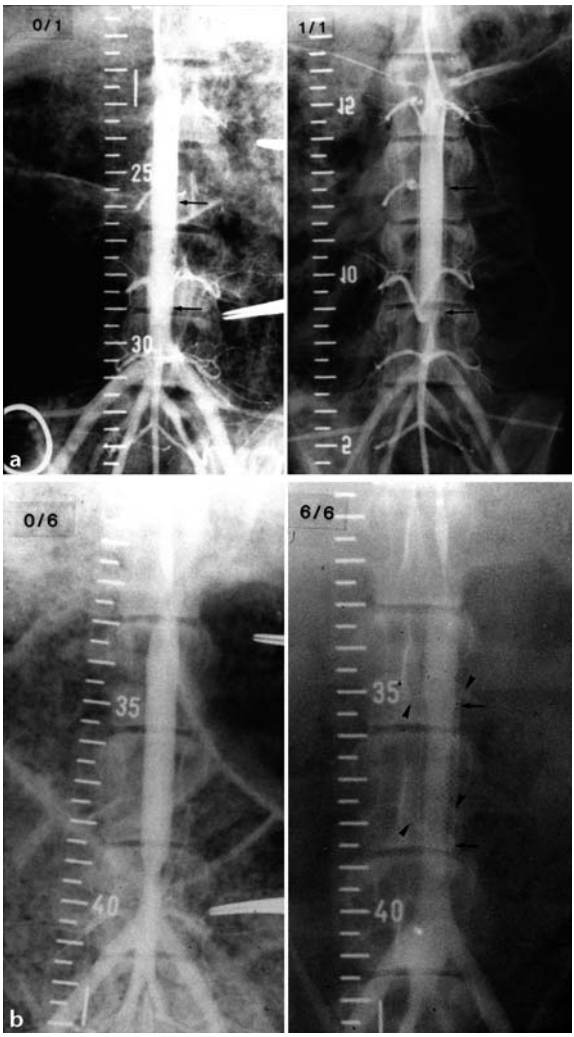


Fig. 4. Arteriogram following implantation of the endoprosthesis (left) and at follow-up (right): **a** after one month; **b** after six months. Intimal hyperplasia is present (*arrows*)

Gross examination. The endoprostheses were well incorporated into the aorta at autopsy. 15 ± 11% of the luminal surface of the endoprostheses were covered with thrombus after one month. A white glistening and thrombus-free neointima was present after six months (Figs. 5 and 6).

Tissue response. A prominent feature of healing characteristics was the integration of the devices and adherence to the aorta, particularly after six months. The endoprostheses were embedded into a chronic inflammatory tissue with infiltrates of lymphocytes, macrophages and multinuclear giant cells, and neocapillaries (Fig. 7). Inflammation was most extensive adjacent to the polyurethane layer and inside the pores. After six months, chronic inflamma-

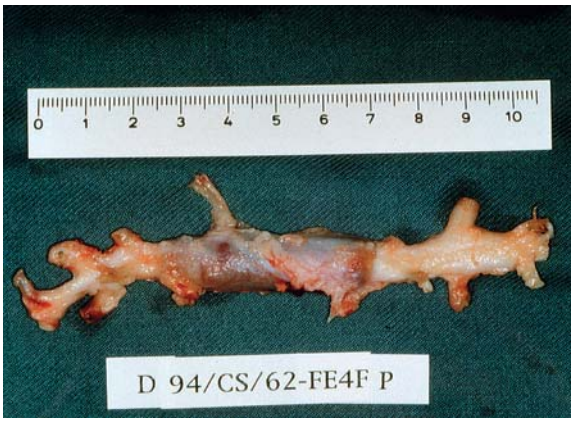


Fig. 5. Autopsy specimen after one month, showing aorta with renal and inferior mesenteric artery, and trifurcation. The infrarenal aortic segment containing the endoprosthesis is colored because of a thin layer of thrombus trapped between device and aorta

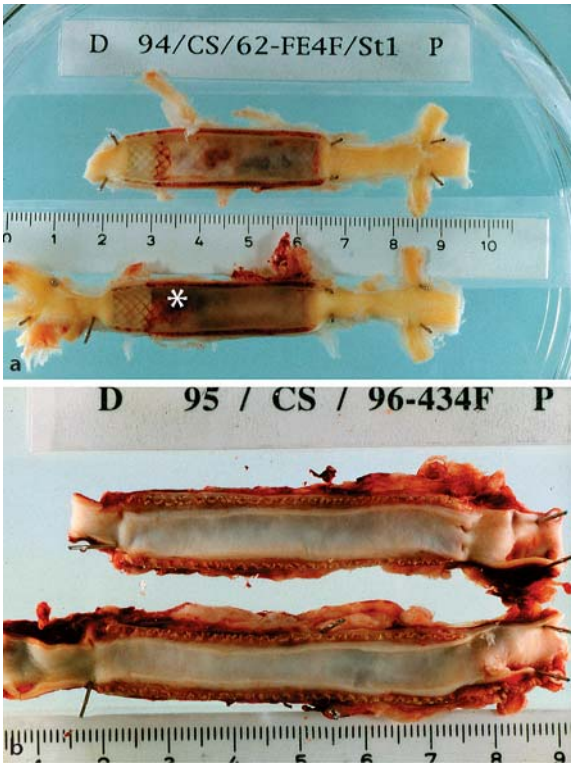
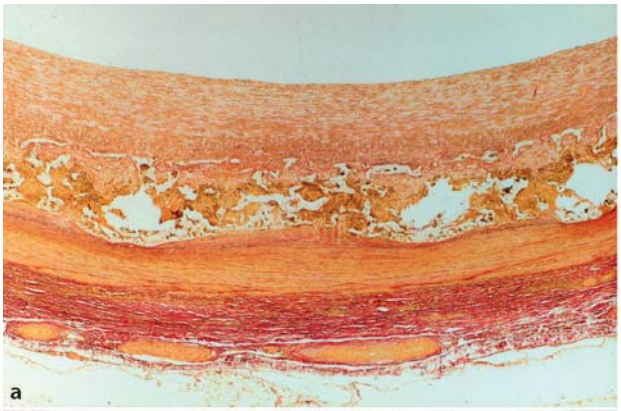


Fig. 6. Longitudinally opened autopsy specimen. **a** after one month. The luminal surface shows areas of thrombus (asterisk); **b** after six months. Complete integration of the endoprosthesis by a smooth thrombus-free neointima

tion was substantial. Intracellular polyurethane owing to phagocytosis was found in macrophages giving proof of biodegradation (Fig. 8). At that time, the polyurethane layer showed a uniform pattern of disruption. It was torn off in a wing-shaped form at one side of the wires and replaced by inflammatory tissue, whereas it remained attached to the contralateral wire side.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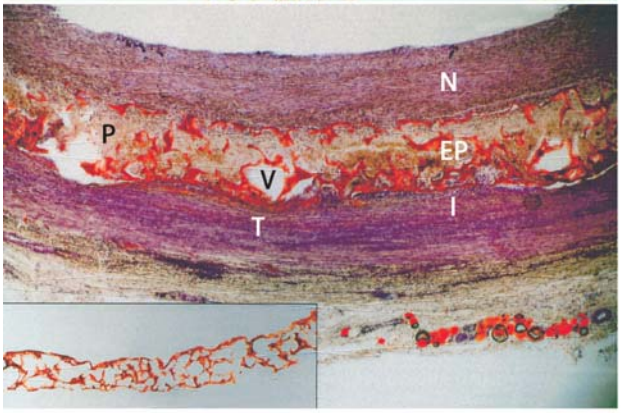
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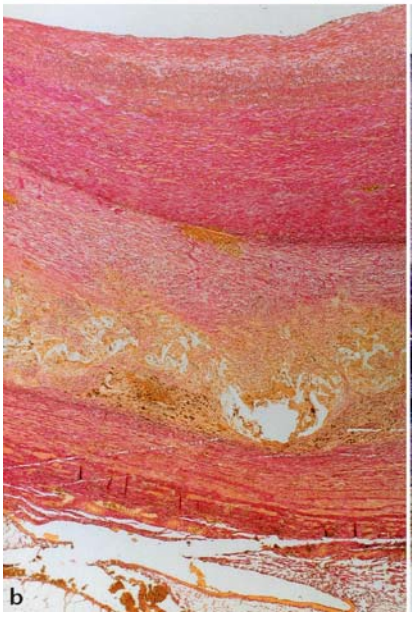
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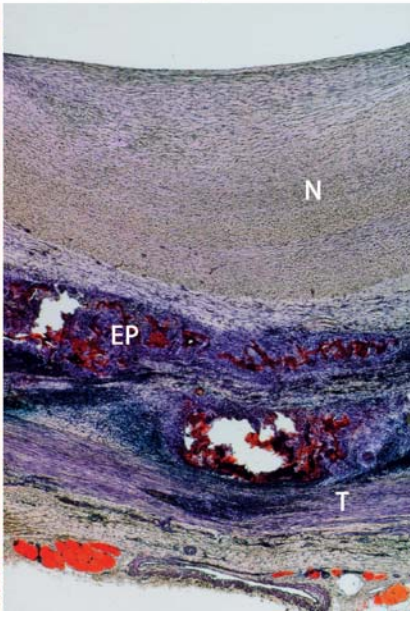
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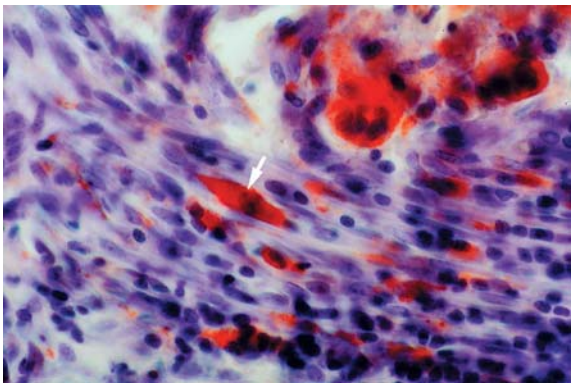

Fig. 8. Histiocytes with red-stained intracellular polyurethane (*arrow*)

Neointima: The neointima developed significantly from 154 ± 115 μm within one month to 1298 ± 85 μm within six months ($P < 0.001$) and was then about three times higher than the aortic wall (Fig. 9). Neointima consisted first of fibromyoblasts and became structured into three layers imitating an arterial wall. The medial layer was composed mainly of intercellular collagen (Fig. 7).

Endoprosthetic wall: The polyurethane layer was disrupted as mentioned above, and showed signs of biodegradation. It was completely integrated into a granulation tissue with the most extensive inflammation in contact to polyurethane.

Interface: The native endothelium of the aorta underlying the endoprosthesis was destroyed. After one month a thin interface of granulation tissue with disseminated spots of hemosiderin was present. After six months the wires compressed the tunica media to a greater extent and the interface was limited to the spaces between the wires.

Tunica media: It was compressed (261 ± 86 μm) beneath the stents to about half the thickness of the normal aorta within one month (Fig. 10) and remained stable with time (254 ± 57 μm). The indentations beneath the wires became considerable, yet without laceration of the tunica media. The amount of collagen increased with time.

Fig. 7. Representative histologic cross-sections of the endoprostheses with van Gieson elastin stain (top) and Sudan stain (bottom, original magnification ×31.5). **a** After one month, there is a thin neointimal layer consisting mainly of fibromyoblasts. The tissue within the pores of the covering is less cellular, but rich in intercellular matrix. Some deposits of collagen are visible in the tunica media. Inlay represents cross-section of non-implanted polyurethane covering which is stained red (original magnification ×31.5); **b** after six months, van Gieson elastin stain shows an important neointima with abundant collagen. The tunica media is altered and the collagen deposits have increased (top). Sudan stain demonstrates an inflammatory tissue rich in infiltrates adjacent to the covering and within the pores. The red-stained polyurethane is disrupted and disintegrated (bottom). *N*, neointima; *EP*, endoprosthesis; *I*, interface; *T*, tunica media; *V*, voids representing removed wires; *P*, pores within polyurethane covering

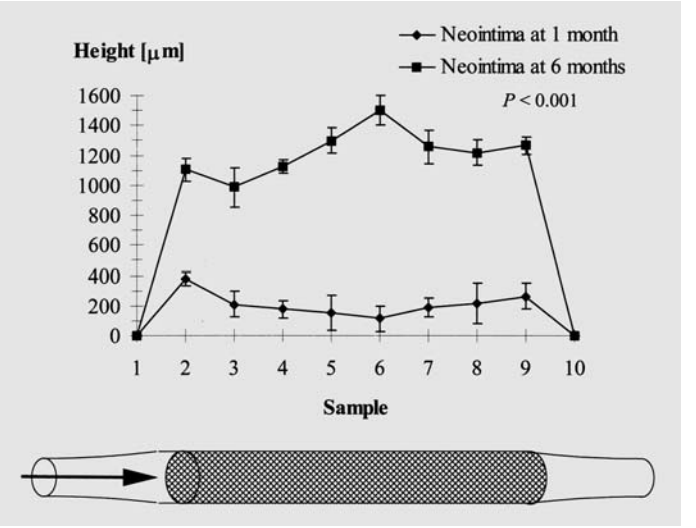

Fig. 9. Neointima thickness is minimal over the whole length of the endoprostheses after one month, yet has increased significantly within six months

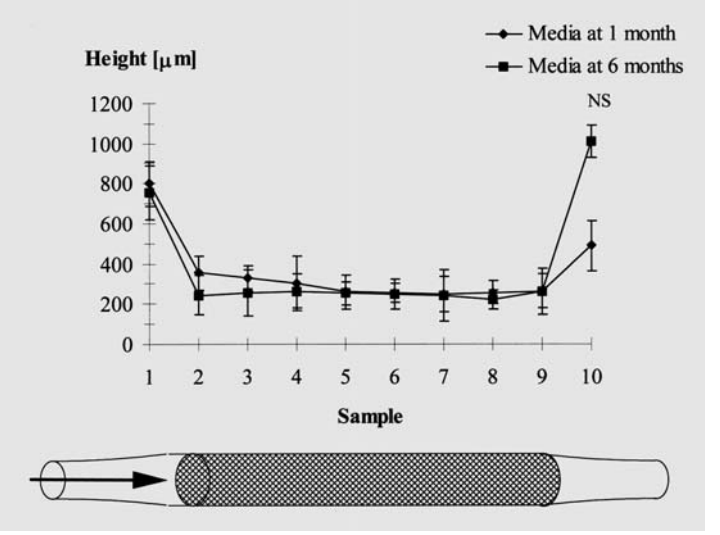

Fig. 10. Tunica media beneath the endoprostheses is compressed, compared to the adjacent native aorta

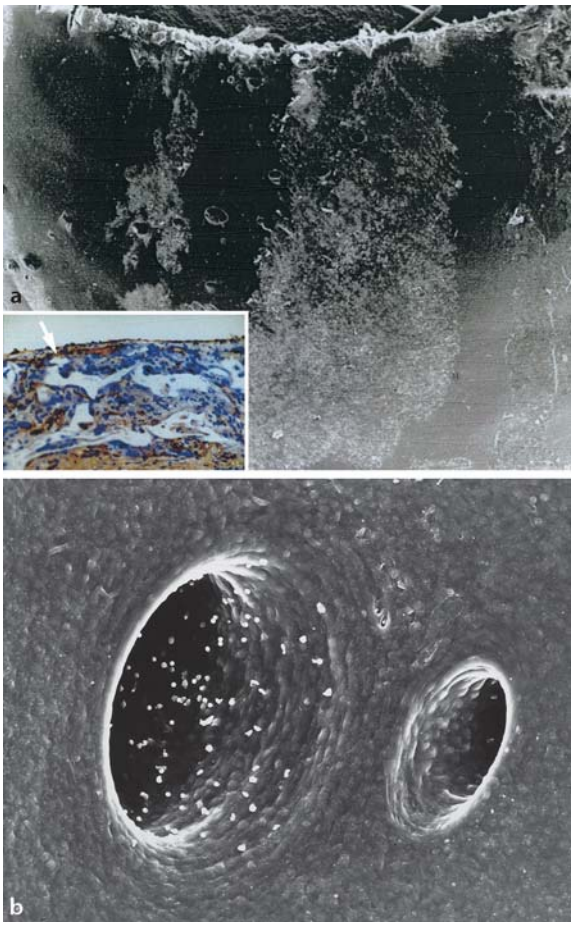

Fig. 11. a Electron micrograph of luminal surface. Dark areas are identified by high-power field and immunohistochemistry as endothelium (inlay shows neointima covered by a brown stained endothelium, *arrow*). Pores on the neointima are present (original magnification ×20, bar = 1 mm); **b** pores on luminal surface lined by endothelium (original magnification ×280, bar = 1 mm)

Endothelialization: Scanning electron microscopy showed areas of endothelial-like cells elongated in the direction of blood flow. Aggregates of fibrin, platelets and erythrocytes were also present. Immunohistochemistry identified these cells as endothelium. Pores located in endothelial areas were visible and lined by endothelium (Figs. 11, 12). Mean endothelial coverage was at 26 ± 19% and 36 ± 24% after one and six months (NS), respectively, with a high variation between specimens.

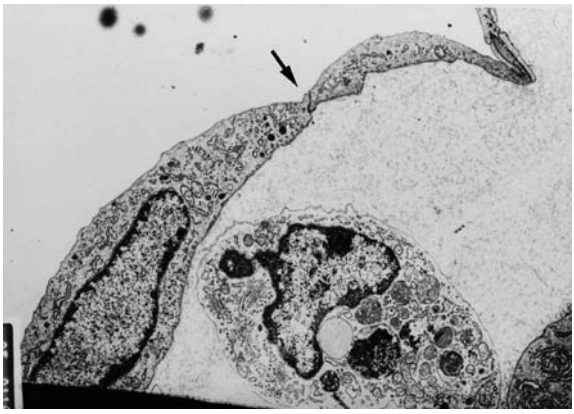

Fig. 12. Transmission electron microscopy identified endothelial cells by tight junctions (*arrow*). Intercellular matrix and myofibroblasts with endoplasmatic reticulum are underneath

Discussion

The polyurethane covered endoprostheses showed excellent performance including patency, a thrombus-free luminal surface, and integration into the aortic wall. Polyurethane is known to provoke a proliferative inflammatory response and a marked neointimal hyperplasia which is more conspicious than in the presence of polyester or PTFE [14, 15]. Experimental data regarding polyurethane in endovascular applications are sparse [9, 11, 12, 16]. Clinical evaluations of polyurethane covered stents confirmed a chronic inflammatory response composed of extensive lymphocytic infiltrates, macrophages, multinucleated giant cells, and neocapillaries [9, 11, 12, 16]. In the present study, we observed the inflammation to be restricted to the polyurethane layer without encroachment on the tunica media. The proliferative tissue is responsible for both, the integration of the devices into the aortic wall and their surprisingly marked adherence. A thick neointima covered the endoprostheses completely, without adversely affecting patency, thanks to the large diameter of the aorta. The combination of a proliferative interface and a spongy covering material enabling tissue ingrowth resulted in solid anchorage of the devices. This type of healing can be beneficial in endovascular grafting, where fixation of the endoprostheses in the undilated arterial segments is crucial.

The disruption of the polyurethane covering in our study is a matter of concern, although the interstices were filled by granulation tissue. We interpreted the regular pattern of disruption as a result of ongoing stent expansion while the covering is embedded into granulation tissue. Late expansion of Wallstents within the vessel following implantation has been clinically observed [17]. However, disruption of the covering does not make the evaluated device in its present design appropriate for aneurysm exclusion. In addition, we observed some degradation of polyurethane. It is known

that polyurethane is subjected to hydrolytic degradation [10], and replacement by a more stable polycarbonate polyurethane has been proposed [11].

Progressive compression of the tunica media without signs of laceration was noted in this study. It is a common, yet insignificant finding in arterial stenting [18, 19]. However, there was an increasing amount of collagen, representing scar tissue probably owing to the wall pressure of the devices. It is also worth mentioning that the tunica media of the aorta is predominantly elastic and does not have a lamina elastica interna. The latter is present in smaller muscular arteries such as the iliac, renal, and coronary arteries and, contrary to simple medial compression, laceration of this important structure by stent wires represents an important stimulus for neointimal proliferation [20, 21].

Endothelialization is important for a thrombus-free luminal surface and long-term patency, particularly in small vessels. Thrombus initially covering the luminal surface of the endoprostheses was subsequently replaced by a neointima with areas of endothelium. Animals have a higher potential for endothelialization than human beings [22]. Endothelium on the luminal surface of conventional and endovascular prostheses is experimentally proven by pannus ingrowth from the host intima across the anastomosis, yet is limited to a length of 10–15 mm [5]. Indeed, we observed endothelial covering of the anastomotic sites in all of the endoprostheses. Transmural ingrowth of microvessels from perigraft tissue towards the lumen is another mechanism discussed in the literature [23–25]. Finally fallout endothelialization of undifferentiated multipotential mononuclear cells from the blood can also occur [26, 27]. In human beings the capacity for endothelialization of vascular prostheses is very limited and restricted to anastomotic ingrowth [22, 28–30]. We used a spongy covering and observed pores on the luminal surface lined by endothelium. Although they were suggestive of sources of endothelialization, we did not detect any endothelialized channel through the endoprosthetic wall, and therefore we do not believe in endothelialization by graft porosity.

In conclusion, the present study demonstrated excellent performance of polyurethane covered Wallstents in the porcine aorta. Polyurethane evoked an extensive inflammatory response that finally incorporated the endoprostheses and enhanced fixation. Histology revealed a thick and thrombus-free neointima with areas of endothelium, and an interface of chronically inflamed tissue between the endoprosthetic wall and aorta, invading the pores of the covering. However, late disruption of the covering and signs of polyurethane degradation require device modifications before the endoprosthesis can be used in the endovascular treatment of leaking arteries.

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4 Biological fixation of polyester vs polyurethane covered stents in a porcine model

Introduction

Endovascular exclusion of aortic aneurysms is a valid treatment option today; however it requires suitable aneurysm morphology to introduce the device and to attach it in a non-dilated relatively healthy proximal and distal arterial segment. The securing sutures placed at open aneurysm repair have to be replaced by indirect means of fixation such as hooks and friction force in order to attach the endoprosthesis. Otherwise distal device migration can result in complications such as aneurysm reperfusion, rupture or occlusion of the prosthetic limbs owing to kinking. So far attachment depends exclusively on mechanical fixation. Hooks and barbs at the proximal level of the endoprosthesis engage the aortic neck with a tenfold increased fixation as compared to an unarmed endoprosthesis [1]. Large oversizing of the device diameter and a sufficient length of the aortic neck, free of calcification or thrombus, provide sufficient anchorage [2]. Biological fixation by incorporation of the proximal part of the endoprosthesis into the non-dilated aortic segment is likely to enhance adherence to the device. Data about the biological response of aortic endoprostheses are sparse owing to restricted retrieval of implanted devices. Loose contact of the endoprostheses within the aortic neck has been observed at explantation [3–6]. Poor graft incorporation was the consequence of lack of tissue ingrowth into the polyester covering [5, 6]. However, endoprostheses with a polycarbonate urethane covering proved to be firmly attached to the underlying artery at explantation [7]. Histology revealed an inflammatory tissue with collagen fibers throughout the covering, providing enhanced biological fixation.

Experimental data support these observations. Endoprostheses with a polyester or PTFE covering remained in loose contact to the underlying vessel wall [8–10]. On the contrary, a covering of polyurethane evoked a particularly intense inflammatory response [11]. This characteristic – formerly considered as a disadvantage in small vessels – can be beneficial in the aorta where a tight interface between the device and the aorta is required for adherence. The present study* [12] investigates the tissue re-

* By kind permission of the Editor (*Journal of Vascular and Interventional Radiology* 2002;13:601-607)

sponse of the underlying porcine aorta towards two different types of endoprostheses with tightly woven polyester versus porous polyurethane covering. Attention is particularly paid to the interface aorta-device representing the stratum of biological fixation.

Materials and methods

Animals. Eight minipigs weighing 40 ± 6 kg were used. All animals were treated in accordance with the "Principles of Laboratory Animal Care" (formulated by the National Society for Medical Research) and the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985). The protocol was approved by our institution's Animal Care Committee.

Endoprostheses. Two different types of devices were used. They were available with a nominal diameter of 8 and 10 mm and a length of 60 ± 2 mm. The first one (n = 4) consisted of a self-expandable stent with a porous polyurethane covering (Covered Vascular Wallstent™, Schneider Europe AG, Bülach, Switzerland, Fig. 1). The "Covered Vascular Wallstent" contains integrated polyurethane and differs from the commercially available "Wallgraft" which is covered with polyester. The stents were made of stainless steel wire (diameter 0.12 mm) woven in a tubular fashion. The covering consisted of integrated macroporous polyurethane representing the porous group (PUC stents). The diameter of the pores varied between 15 and 300 µm. The grafts were constrained on an unistep 11.5 F delivery system by a retractable Teflon sleeve. Complete expansion of the endoprosthesis was achieved by withdrawal of the sheath.

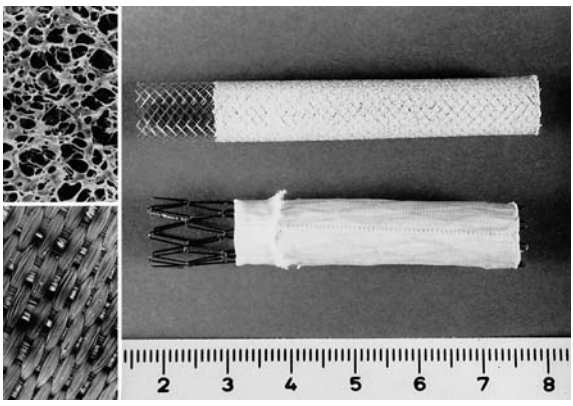

Fig. 1. Two types of endoprostheses with a distal end of bare wires (PUC, top) and covering partially removed (PEC, bottom) to disclose the metallic frame. Inlay with electron micrograph of the corresponding covering (original magnification ×340)

The second type (n = 4) consisted of a nitinol stent of longitudinal serpentines (diameter of the wire 0.28 mm) connected in series by ligatures of 7-0 polypropylene (EndoPro System 1^{TM}, Minimally Invasive Technology SARL, La Ciotat, France). They were covered by a thin woven polyester fabric (0.1 mm) representing the woven group (PEC stents, Fig. 1). The endoprostheses were inserted by a 10 F introducer and deployed by retraction of the Teflon sheath while the graft was held in position by the pusher. Additional balloon dilation was necessary to achieve complete expansion.

Procedure. General anesthesia was induced by an endotracheal canula and maintained with 1.5% halothane and nitrous oxide. Monitoring consisted of continuous electrocardiography, invasive blood pressure measurements and percutaneous record of oxygen saturation. The dimensions of the aorta and the device were measured after placement and at follow-up. For this purpose a calibrated angiographic catheter with 1 cm marker spacing (Sizing catheter, COOK, Queensland, Australia) was used. After heparinization an infrarenal aortogram in an anteroposterior view (cut film) through a carotid arteriotomy was obtained before graft placement. Following measurement of the aortic diameter, the respective endoprosthesis with an oversizing of one or two millimeter was selected. The endoprosthesis was inserted over a 0.038-inch guide wire under fluoroscopic control and deployed below the renal arteries. Measurements of the diameter and the length of the endoprosthesis were performed on plain X-rays immediately after deployment and before necropsy using the angiographic catheter as a reference.

Specimen retrieval and processing. Aortography was performed after a follow-up of six weeks. The animals were euthanized and the infrarenal aortic segment entirely removed. The specimens were divided longitudinally and cut into eight equal samples perpendicularly to the long axis. One half of the specimen was fixed in 2% buffered glutaraldehyde, dried and sputter coated with 20 nm gold for scanning electron microscopy (TEM 505; Philips, Eindhoven, The Netherlands). The other half was fixed with 4% paraformaldehyde, embedded in paraffin and stained with hematoxylin-eosin and van Gieson-Elastin for light microscopy. Immunohistochemical staining for endothelial factor VIII/von Willebrand factor (Accurate Chemical, Westbury, N.Y.) and smooth muscle cell α-actin (Dako Corp., Carpinteria, Calif.) was performed. Measurements were performed on histological cross sections, using a light microscope (Axioskop, Zeiss, Germany) with a direct image transferred to a personal computer running under an imaging program (ImagePro, MediaCybernetics, Silver Spring, MD, USA). The neointimal thickness of each sample was calculated by averaging three measurements taken from the area of maximal neointimal thickness. Medial thickness was calculated by averaging three representative measurements beneath the graft for each sample.

Statistical analysis. Data are expressed as mean ± SD. Comparisons of groups were performed using the Students unpaired t-test. Statistical significance was assumed at the 95% confidence interval ($P < 0.05$).

Results

The endoprosthesis deployment was successful without technical difficulty or complication. The animals showed an uneventful postoperative course. At follow-up all endoprostheses were angiographically patent. Some devices showed slight luminal narrowing.

Device characteristics. The infrarenal aorta demonstrated an average diameter of 8 ± 1 mm below the renal arteries and 7 ± 1 mm above the aortic bifurcation before implantation. During follow-up the PUC stents significantly increased 12.5% ($P = 0.009$) of their original diameter at implantation from 8 ± 1 to 10 ± 1 mm. They demonstrated simultaneously a subsequent 13% shortening in length from 62 ± 8 to 55 ± 10 mm. However, the PEC stents persisted in their original dimensions with an initial diameter of 8 ± 1 mm and a length of 59 ± 0 mm, and 8 ± 1 and 58 ± 0 mm at follow-up, respectively.

Macroscopic aspect of the endoprostheses. A thin white glistening neointima that merged smoothly at both ends of the devices with the native artery covered the endoprostheses completely in both groups. There was no thrombus formation on the luminal surface. Although both types of endoprostheses were covered by a neointima, their physical performance was different during preparation for histology. The PUC stents remained firmly attached to the underlying aorta without any disengagement. However, the PEC stents separated spontaneously from the aorta when cutting the samples during histological preparation.

Endothelial coverage. The perianastomotic regions were scantly covered by endothelium (Fig. 2) detected by scanning electron microscopy and identified by factor VIII staining (PUC stents 6 ± 6% proximally and 3 ± 3% distally versus PEC stents 7 ± 5% and 11 ± 9%, respectively). The central part of the endoprosthesis was endothelialized to a higher extent (PUC stents 11 ± 15% versus PEC stents 22 ± 18%, NS).

Characterization of graft incorporation. All of the endoprostheses were completely covered by a neointima (Fig. 3). Neointimal thickness was more pronounced in the PEC than in the PUC stents (average thickness 575 ± 113 μm versus 269 ± 51 μm, $p < 0.01$). The more extensively developed neointi-

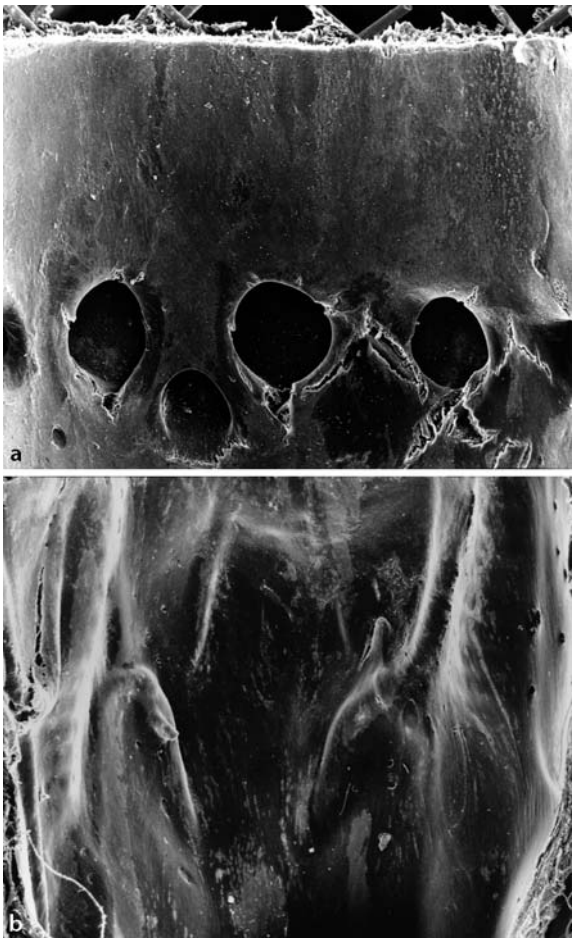

Fig. 2. a electron micrograph shows the distal transition zone of the PUC stent covered by neointima. The lacunae are the consequence of the transition between the covered part of the stent and the bare springs. **b** Proximal end of PEC stent. The metallic serpentines covered by neointima are distinguishable (original magnification ×20)

ma of the PEC stents showed a formation into two layers (Fig. 4). Fibroblasts, myoblasts and smooth muscle cells were predominantly present at the luminal site, whereas the more peripheral area of the neointima contained a substantial amount of collagen. There was absolutely no tissue ingrowth into the dense layer of the polyester covering. Infiltrates of lymphocytes and giant cells and even foci of calcification were present adjacent to the polyester. The neointimal structure of the PUC stents was more uniform, consisting mainly of fibroblasts, myoblasts, smooth muscle cells, and collagen (Fig. 5). Complete tissue ingrowth through the pores within the polyurethane was present, thereby firmly attaching the endoprosthesis to

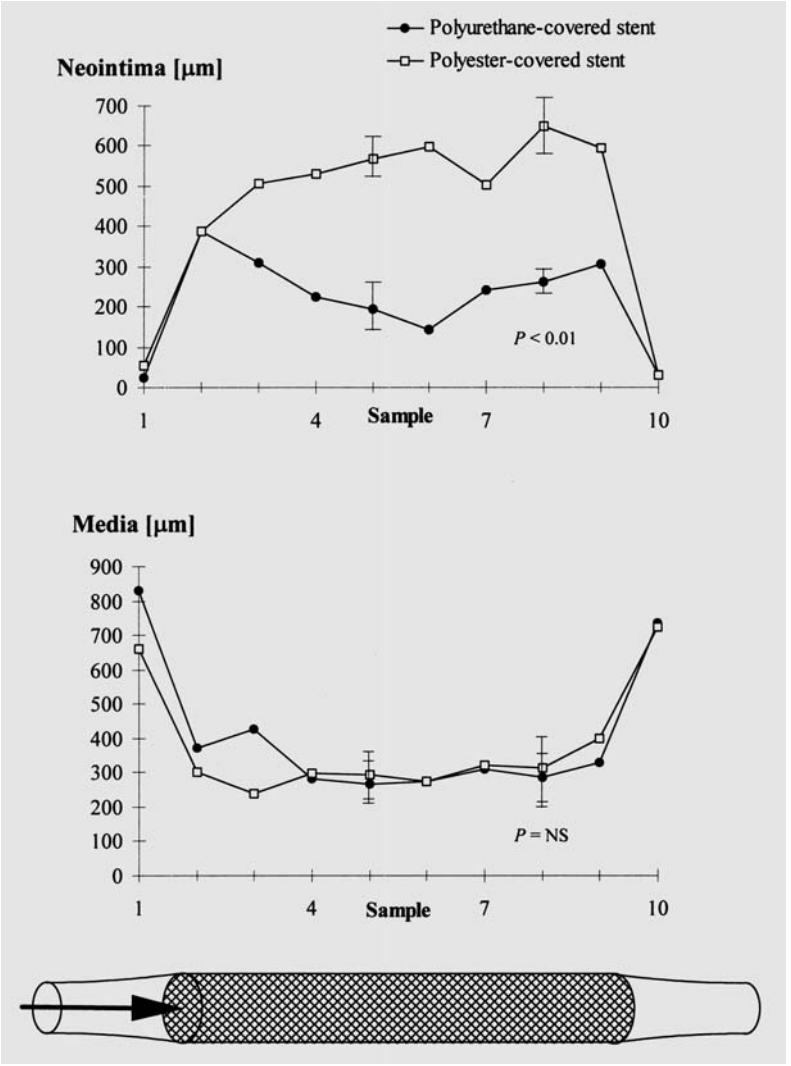

Fig. 3. Neointimal thickness of endoprosthesis (top) and medial thinning of native artery (bottom) over the whole length of the endoprostheses. The neointima is more prominent in the PEC stents. Both types of endoprostheses equally compress the tunica media of the underlying aorta. The histological cross sections of sample 1 and 10 represent the aorta proximally and distally to the devices

the native artery wall. Foreign body reaction of lymphocytic infiltrates with giant cells and a neovascularization were observed within the pores with disseminated spots of hemosiderin and fibrin deposits. This granulation tissue was present at the luminal site as well as in the perigraft space filling the pores from both sites.

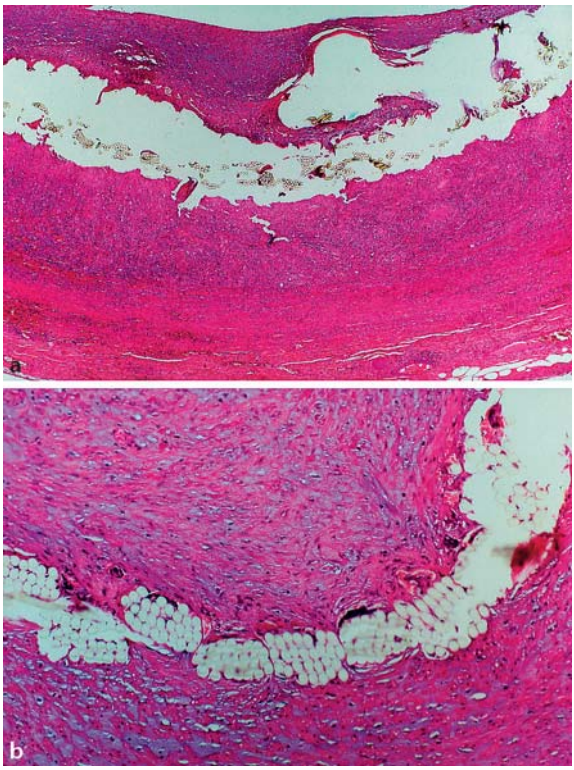

Fig. 4. a Histological cross section, PEC. Separation of neointima and underlying aorta from the tightly woven polyester covering (original magnification ×31.5). **b** Limited tissue ingrowth into the fabric (original magnification ×125)

A compression of the tunica media with distension of elastic fibers to a near linear shape was present in both types of stents. The average thickness of the tunica media was 741 ± 73 µm at the level of the intact aorta. It markedly decreased beneath the level of the polyurethane and the polyester covering (321 ± 58 µm versus 301 ± 53 µm, respectively, NS) (Fig. 3). The lamina elastica interna was preserved and appeared only slightly indented by the wires.

Discussion

Two observations are interesting in this comparative study, both associated with the polyurethane-covered stent: The firm attachment of the device to the underlying aorta and its late expansion after implantation. Experimental studies evaluating the tissue response towards endoprostheses demonstrated a mature thrombus-free neointima with an inner cellular layer composed of fibroblasts and smooth muscle cells, and an outer collagen-rich

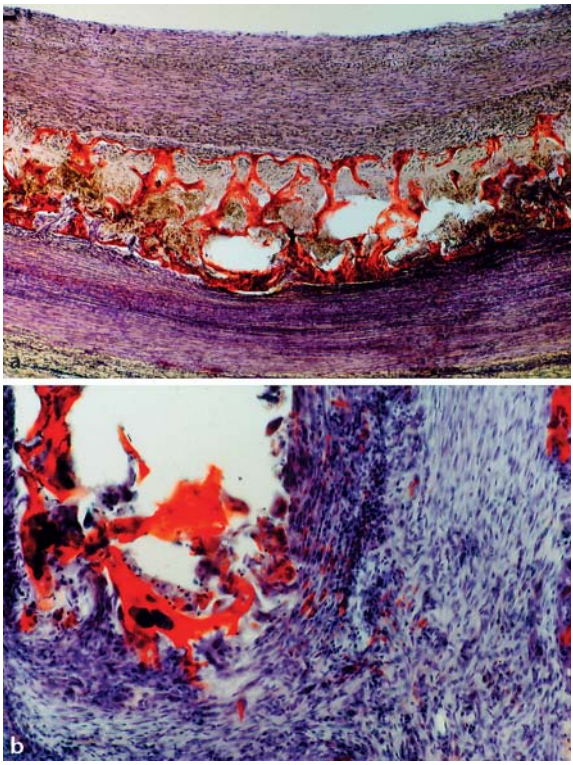

Fig. 5. a Histological cross section, PUC. Integration of the spongy, red-stained polyurethane into a chronically inflamed tissue (original magnification ×50). **b** Infiltrates around stent wires (removed) and within pores (original magnification ×125)

and elastin-poor layer [8, 10, 11, 13–17]. The average neointimal thickness was 390 μm in endoprostheses with a polyester [15] and 460–490 μm in those with a thin-walled PTFE covering [10, 18]. These findings are consistent with our data. The covering used was predominantly thin woven polyester [8, 13–15] and PTFE [10, 17, 18], but polyurethane was evaluated as well [11, 16]. Endothelium covered the luminal surface partially [9, 11, 14, 17, 18] or as a complete lining [8, 15] and was noted at the anastomotic sites and the central part of the endoprostheses in the present study. In most of the reports, complete neointimal covering was considered equal to device incorporation, yet not much attention was paid to the tissue beneath the endoprosthesis and its adherence to the aortic wall. Though some investigators mentioned adherence [11, 14, 15], others observed splitting of the excised specimen into three distinct layers during preparation: the neointima, the polyester covered stent and the aortic wall [8]. Spontaneous separation of PEC stent as a consequence of the loose interface between covering and aorta was also noted by us. Histologically, the perigraft space was filled with organized thrombus without any tissue ingrowth into the covering, a finding observed by other investigators, too [8, 13, 14]. Thin polyester fabric woven tightly to provide low porosity and high strength is

the preferred material in endovascular applications in order to enable low profile [19]. These characteristics do not favor tissue ingrowth and, in addition, the polyester itself appears to inhibit maturation of the surrounding tissue [20]. Therefore the term 'graft incorporation' used for endoprostheses with a complete neointimal covering might be misleading considering the poor adherence of the device.

Clinical reports using the same type of endoprostheses with a polyester covering noticed a systemic inflammatory response with intraoperative blood pressure drop, postoperative fever and an important release of TNF-α following implantation [21, 22]. These reactions were attributed to device manipulation within aneurysmal thrombus releasing cytokines. We did not observe hypotension during graft placement since we did not use an aneurysm model. Local inflammatory signs after graft placement in stenosed arteries have been observed in clinical settings consisting of pain, swelling and an erythema at the implantation site [23, 24]. Histological examinations of human arteries responding towards these endoprostheses showed infiltrates of multinuclear giant cells and mononuclear cells consistent with our findings [25].

The PUC stents remained adherent to the aorta during histologic workup as expected for incorporated grafts. An extensive granulation tissue invaded the porous covering from both the luminal and the perigraft sites, providing adherence to the aorta. This was also observed by other investigators [11, 26]. The importance of graft porosity for healing of vascular substitutes was demonstrated experimentally by a vascularized tissue invading the pores and ultimately providing an endothelial lining of the luminal surface [27, 28].

The biological response in animals differs considerably from that in human beings [20, 29]. The failure of human grafts to heal may be due to differences in species, age, and biological quality of the surrounding tissue. However, we noted some similarities of the tissue response in the experimental setting compared to findings following explantation of endoprostheses in human beings. These human endoprostheses equipped with a polyester covering disclosed poor endovascular healing [5, 6, 25]. The perigraft space responsible for anchorage was filled with partially organized thrombus not adherent to the external polyester covering, resulting in easy detachment from the aortic wall during preparation [6, 30]. However, one report investigating endoprostheses with a polyurethane covering noted adherence to the aortic wall owing to ingrowth of an inflammatory tissue into the polyurethane fibers from the luminal and the perigraft space [7]. This is consistent with our findings in PUC stents. The spongy polyurethane provides an excellent matrix for an inflammatory tissue and the extent of proliferation may be programmed by the size of the pores. One may speculate that biodegradable polyurethane will be subsequently replaced by the granulation tissue, thereby incorporating the metallic frame of the device. Future endoprostheses could be equipped with a short segment of polyurethane covering at the ends, providing improved anchorage at the proximal and distal fixation sites.

The second important observation in our study was the late expansion of the PUC stents. The tubular self-expandable mesh-wire has a high radial and longitudinal flexibility resulting in an excellent circumferential alignment. The lamina elastica interna was not disrupted as a consequence of the relatively moderate radial expansion force exerted by the stents. There was thinning of the media with rarefaction and stretching of the elastic lamellae and an increased amount of collagen. A relatively unaffected aorta underlying the endoprosthesis was also noted by other investigators [13, 14, 31]. An extensive dilation of the vessel by the stent itself is in fact undesirable, yet a certain potential for late expansion may be advantageous in cases where dilation is expected. A significant dilation of the proximal aortic neck of about 1 mm per year is known following endovascular [32] and open standard aneurysm repair [33]. This increase can be well compensated by the late expansion of the self-expandable tubular mesh-wire used in our study. Future endoprostheses could be equipped with a proximal segment of this tubular mesh-wire to achieve optimal circumferential alignment and to compensate for late neck expansion.

In conclusion, enhanced biological fixation was achieved by an extensive granulation tissue invading the porous polyurethane covering of the endoprosthesis, whereas the smooth polyester covering remained in loose contact with the aorta in the absence of any tissue ingrowth. These findings can have an impact on the development of future endoprostheses. Conventional designs might be modified and equipped with a short segment of porous polyurethane covering at both ends to provide biological fixation. The tubular self-expandable mesh-wire seems appropriate to compensate for late neck dilation.

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5 Animal models for endovascular graft application

Introduction

Endovascular aneurysm repair is nowadays an established treatment with its own complications, including persistent aneurysm perfusion, loosening of the fixation at the attachment sites, device migration, and kinking, and device failure in the mid- and long-term. The outcome of endovascular aneurysm repair and the design and material of the endoprostheses that are in clinical use are continuously reviewed by physicians and manufacturers. Experimental models are suitable to evaluate devices that have been improved or modified, and to address some of the complications associated with endovascular surgery. An ideal animal model does not exist and the present models vastly lack the pathophysiological characteristics of aneurysms observed in human beings: atherosclerosis, intraluminal thrombus, disruption of the elastic lamellae, inflammatory infiltrates in the tunica adventitia and media and increased proteolytic activity in the aneurysm wall. Aneurysmal disease does not exist in animals, with some exceptions. Spontaneous dissecting aneurysms occur in some strains of turkeys which have high blood pressure and early atheroma formation [1]. Aneurysms have been genetically induced in the "Blotchy mouse" based on a deficiency in collagen and elastin cross-linking [2]. These aneurysms are confined to the thoracic aorta with rupture at points of greatest stress. Histopathology is comparable to humans with fragmentation of elastic fibers and marked inflammatory cell infiltrates in the adventitial and medial layer. Pseudomicroaneurysms were produced in gene knockout mice which have a homozygous gene deletion for apolipoprotein E resulting in formation of atherosclerotic plaques including fragmentation of the elastic lamellae [3]. Most of these animals are far too small and not suitable for the evaluation of endovascular devices. However, there is still a demand for aneurysm models despite considerable progresses in endovascular surgery. A systematic review gives useful information for further experiments in this domain. The respective literature is sparse [4–6]. We made a detailed review of experimental models that have been used in the context of endovascular graft applications.

Animal models

The most frequently used animals for aneurysms are pigs and dogs and rarely sheep. Dogs allow for repeated non-invasive follow-up examinations such as pressure measurements by sphygmomanometer and duplex sonography, yet their availability is restricted by animal right societies. Accordingly costs for dog keeping are high. Pigs and sheep are not suitable for repeated physical examinations, but they are less expensive. Sheep are rarely used, although their vessels are large and their coagulation system is close to human beings. The canine and porcine vascular system has an appropriate size for introduction and implantation of endovascular devices with common femoral arteries varying from 3 to 5 mm in diameter and an infrarenal aorta from 6 to 12 mm (Fig. 1). In general, porcine arteries are slightly smaller and more delicate with regard to vascular manipulations, and their femoral arteries are deep in the groin and less suitable as access vessels. The porcine aorta is preferably approached by a left retroperitoneal exposure because of the voluminous intestines, whereas the canine aorta can be easily accessed by a midline incision because of lack of intra-abdominal fat tissue. There are interspecies differences in terms of coagulation system, neointimal hyperplasia and endothelialization.

Neointimal structure is strikingly similar in human beings, dogs, and pigs. The number of cells, their composition and the proteoglycan matrices are essentially the same, yet their intimal response to injury is dramatically

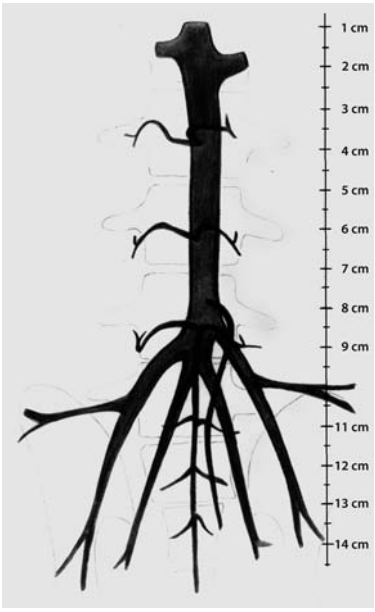

Fig. 1. Anatomy of porcine aorto-iliac vascularity including aortic trifurcation, inferior mesenteric artery originating distally, prominent arteria sacralis mediana, and three pairs of lumbar arteries

different [7, 8]. The neointimal proliferation in dogs is minimal even after substantial injury to the medial and adventitial layer. Their fibrinolytic system is highly efficient, favoring graft patency [9]. It might be worth mentioning that the early experiments with endovascular devices were performed in the canine model as the standard surrogate. In 1969, Dotter implanted the first metallic coil springs in canine femoral arteries [10]. Maass placed his specially designed metallic "Double-Helix" in the thoracic and abdominal canine aorta in 1982 [11, 12], and in the following years Dotter and Cragg evaluated the first nitinol coil springs in their vascular system [13–15]. The first tubular wire-mesh stents were implanted in 1985 in the canine aorta by Palmaz [16]. These results were probably also encouraging thanks to the propitious vascular and coagulation system of the dog with a discrete neointimal response and an active fibrinolysis. The first clinical trials of stent implantation in the iliac and coronary arteries in 1987/88 ensued directly from these experiments [17, 18]. The evaluation of endovascular devices in the porcine model produces less favorable results because the healing response is stronger with important hyperplasia and, additionally, the pig has a very reactive coagulation system with fast clotting and slow lysis [9]. Instead, their ability for endothelialization of a prosthetic luminal surface is high, whereas dogs have a limited capability for endothelialization, similar to human beings. The endothelialization in human beings is minimal and restricted to the anastomotic sites, with an endothelial layer of about 5 to 10 mm length, both in conventional and intraluminally placed prostheses [19–23]. The decision about the most appropriate animal model has to be made based on the aggregated knowledge of the different animal species including their advantages and shortcomings, regarding both the study goal and the laboratory facilities.

Aneurysm models

Various models have been used to evaluate the technical aspects, efficacy, and biocompatibility of endoprostheses within the thoracic and abdominal aorta. The most popular one is the aneurysm patch model. Research focused first on the feasibility of endovascular aneurysm repair with relatively simple models. Later more complex models investigated complications specifically related to endovascular surgery, such as endoleak and pressure transmission to the aneurysm sac. Some clinical issues, such as aortic neck dilation and distal device migration owing to poor neck quality, are still difficult to address by experimental models. Many useful models have been developed, among them the canine and porcine models were most frequently used. Paraparesis as a consequence of prolonged aortic cross clamping and fatal hemorrhage, anastomotic bleeding or aneurysm rupture, are the most important perioperative risk factors for the animal.

Aneurysm patch model. This was the most frequently used model because the operation is simple and safe, resulting in a sufficiently large aneurysm. The aorta was preferably exposed by a laparotomy. Following aortic cross clamping and control of the lumbar arteries by loops, a long aortotomy was made and subsequently closed by a large patch (Fig. 2). A period of eight to twelve weeks allowed the animals to recover until the endovascular intervention was performed. Advantages of this model include a large aneurysm suitable to evaluate kink resistance of the endoprosthesis, the preservation of lumbar arteries enabling retrograde aneurysm perfusion, and the potential of aneurysm shrinkage following endovascular exclusion in case an autologous patch is used. Thrombosis of untreated aneurysms did not occur and thrombus formation has been rarely observed (Fig. 3). Aneurysms with an artificial patch measured 22 mm in diameter, whereas larger aneurysms with a diameter of 30 to 35 mm were obtained by autologous material. Polyester was the patch of choice for most authors [24–29]. The operative mortality, 7%, was relatively low. Nevertheless polyester can induce a periprosthetic fibrosis in dogs, resulting in a considerable morbidity including hydronephrosis, renal failure, or bowel obstruction [24]. Incomplete endovascular exclusion and patency of lumbar arteries entailed few and liquid thrombus, whereas successful exclusion resulted in complete thrombosis of the aneurysm sac (Fig. 4). Shrinkage of the aneurysm as a biological indicator for aneurysm healing following treatment was not observed in the presence of an artificial patch.

Aneurysm creation by a patch of rectus abdominis fascia was associated with an important morbidity and mortality of 11 to 33% [24, 30–32]. The main reasons were paraplegia, probably due to prolonged aortic cross

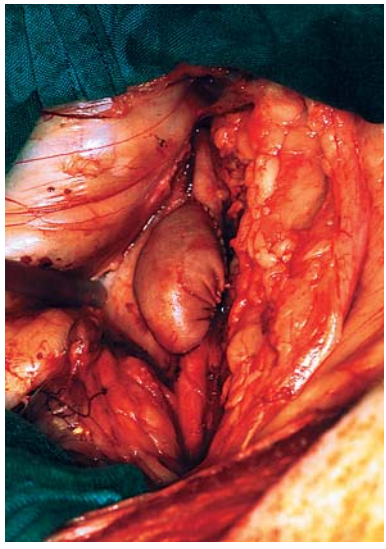

Fig. 2. Aneurysm made by a xenograft patch (equine pericardial patch) through a left retroperitoneal approach. The kidney is left in situ and the peritoneal content rotated to the right

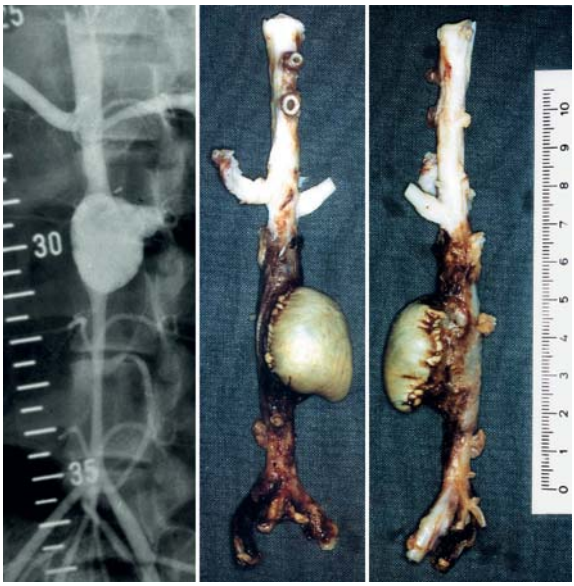

Fig. 3. Arteriography of infrarenal aorta in a-p view. The aorta distally to the aneurysm is spastic (left). Autopsy specimen of the aneurysm that was excluded by a polyurethane covered Wallstent, front view (center) and profile (right)

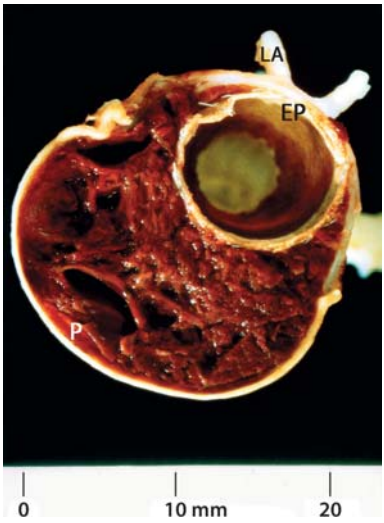

Fig. 4. Transverse section through the excluded aneurysm containing fresh thrombus, and the endoprostheses (polyurethane covered Wallstent). *EP:* endoprosthesis; *LA:* pair of lumbar arteries; *P:* xenograft patch

clamping, fatal hemorrhage secondary to anastomotic bleeding or aneurysm rupture, and hematoma of the patch harvesting site. Aneurysm rupture occurred in up to 33% within the first three weeks [24, 30, 32]. Aneurysms made of fascia enlarged by 60 to 90% during the follow-up period [30–32]. Thrombus within the aneurysms was absent, yet aneurysm shrinkage and healing was observed following treatment. Fascia is certainly not the best material for a patch because of its reduced resistance to shear

stress. Fascia consists of fibers that are orientated in mainly one direction, and therefore the patch tends to ravel out at the suture line. Presumably for these reasons aortic cross-clamp time was prolonged, and hemostasis was difficult to obtain, resulting in a higher mortality. These complications were not reported when using vein as a patch material [33, 34]. The vein is an appropriate substitute for the arterial system; nevertheless these aneurysms enlarged themselves by 19% during follow-up. They had no thrombus and the lumbar arteries remained patent. A 10% diameter reduction and thrombosis were noted following exclusion [33].

Jejunum as a patch material was selected in order to create a model with an inherent risk of rupture [35, 36]. 88% of these aneurysms ruptured rapidly within eighteen hours to eleven days post creation. Following endovascular treatment, they remained subjected to a high risk of rupture in the presence of attachment site endoleaks. The operative trauma associated with the creation of this model was important and, accordingly, the morbidity was as high as 45% including rupture and paraplegia despite immediate aneurysm exclusion. Aneurysms that were successfully excluded healed and the aneurysm sac even disappeared [35].

Aneurysm interposition model. These aneurysms are entirely artificial, pre-fabricated and usually standardized to one size. Fusiform aneurysms consisting of polyester [27, 37–39] or polyurethane [38] were produced by the manufacturers, and aneurysms made by balloon dilation of a PTFE tube graft [40–42] were physician-fabricated. At operation, a segment of the infrarenal aorta precisely fitting the length of the artificial aneurysm was excised following ligation of lumbar arteries, and the aneurysm was interposed by end-to-end anastomoses. The creation of this model was, however, associated with some technical problems. A short aortic defect entailed kinking and thrombosis of the aneurysm, and excision of a long aortic segment resulted in anastomotic bleeding. These technical difficulties were probably responsible for a mortality of 12 to 60%, including infection, hemorrhage, and paraparesis owing to ligation of lumbar arteries and prolonged aortic cross-clamping [27, 38, 41–43]. Another complication was periprosthetic fibrosis around the anterior and lateral surface of the prosthetic aneurysms, resulting in post-renal failure and bowel obstruction. Aneurysm rupture occurred only in a physician-made xenograft of bovine jugular vein three weeks after implantation [43]. Artificial aneurysms had a diameter of 25 to 35 mm and remained stable over a follow-up of four to eight weeks. Surprisingly, they did not show thrombus formation. Following aneurysm exclusion, kinking of the endovascular grafts was observed in 75% in a study performed in 1992, and subsequent graft thrombosis with paraplegia occurred in 25% [37]. In the mid-nineties the pre-fabricated aneurysms became more complex in order to investigate endoleaks and endotension. They were equipped by a pressure transducer. An endoleak was created by an endovascular graft with a fabric defect [42], or a segment of a coaxially placed Argyle shunt at the proximal fixation site

[29], or an endoleak channel connected to the aneurysm [44]. The shortcoming of the interposition model is the artificial aneurysm sac that impairs thrombus maturation and organization, thereby preventing the aneurysm from shrinkage following exclusion. Accordingly, reduction in aneurysm diameter has only been rarely observed because of the prosthetic material the aneurysms are made of [37, 39, 43].

Elastase-induced aneurysm model. This model is particularly attractive because it has similarities to aneurysms in human beings where large numbers of inflammatory cells in the adventitia and media and an increased cytokine and matrix-degrading protease activity were demonstrated [45]. In this model the use of elastase, either by an infusion in an isolated aortic segment or by topical application on the aortic adventitia, prompted the progressive development of fusiform aneurysms secondary to an immune-mediated elastin failure [46–49]. Destruction or disappearance of the elastic lamellae and inflammatory cell infiltrates of the tunica media was observed. The model was first developed by Martins in 1962, but aneurysms were created in only 50% [50]. Anidjar established it in rodents and produced infrarenal aortic aneurysms with a diameter of 100 to 420% of the proximal aorta [48, 51]. However, the model did not achieve popularity in large animals. It was successfully created only once in dogs under the assistance of Anidjar two years later [46]. The canine infrarenal aorta was surgically exposed, the side branches ligated and the aortic segment was pressure perfused with a solution of porcine elastase during one hour following aortic cross-clamping [52]. Evaluation of the appropriate amount of elastase prior to the experiment in vivo was crucial. It was calculated to 2800 U on the assumption that 35% of abdominal aorta constitutes of elastin and 1 U elastase degrades 1 mg of elastin. 1500 U were ineffective for aneurysm creation, whereas more than 3000 U resulted in aneurysm rupture and death of two dogs within 24 to 72 hours [52]. Perfusion of the exposed aortic segment was technically not easy and leakage was present in five of eight dogs, yet morbidity was low. In addition, the aorta enlarged only 50% to a maximal diameter of 12 mm. Histology showed moderate parietal thrombosis, decreased medial thickness with fragmented elastic lamellae, and an intense inflammatory reaction. The elastase-induced aneurysm model seems to be tricky and, indeed, four years later another research group failed to reproduce a single aneurysm [53]. Thrombotic aortic occlusion was observed in 67% of the animals, with severe deterioration of their condition. Necrotic lesions and inflammation of the aortic wall were present in all cases.

Transluminally created aneurysm model. The creation of an experimental aneurysm by endovascular means has the advantage of minimal invasiveness and small operative trauma. The very first experimental aneurysm for subsequent endovascular exclusion was incidentally produced in 1984 by Cragg et al. when they evaluated the transluminal placement of coils in the

arterial system [15]. A false aneurysm developed over a six-week-period owing to a long mural dehiscence by a catheter lesion of the canine aorta. The aneurysm was successfully excluded by a tightly wound nitinol coil and healed completely restoring the original aortic diameter. Subsequent attempts of transluminally created aneurysms were based on overdilation of the aorta by large balloons. However, the healthy aorta of laboratory animals showed amazing recoil and did not respond to angioplasty. In 1987 Zollikofer et al. investigated the effect of massive balloon dilation on the aortic wall [54]. Overdilation of 90% of the thoracic aorta and of 110% of the abdominal aorta resulted in only 15% and 40% luminal increase, respectively. At dilation, segmental rupture of the tunica intima and media occurred whereas the adventitial layer, although damaged by focal hemorrhage of the vasa vasorum, remained intact. Complete healing of these lesions by neointimal hyperplasia prevented further aortic dilation. Marty et al. showed that the elasticity of the porcine aorta is exceeded at an overdilation of 300% resulting in complete rupture with a long transmural tear corresponding to the length of the balloon (Figs. 5, 6, 7) [55]. Hallisey resolved this dilemma of insufficient aortic dilation and impending rupture by simultaneous stent implantation and overdilation of 200% of both, the aorta and the stent [56]. The angiographic appearance of these aneurysms was attractive, yet the frame of the stent makes the aneurysm wall stiff, preventing healing or shrinkage of the aneurysm sac following endovascular exclusion. The rigid stent edges at the end of the aneurysm can probably damage the fabric of a subsequently implanted endoprosthesis. Never-

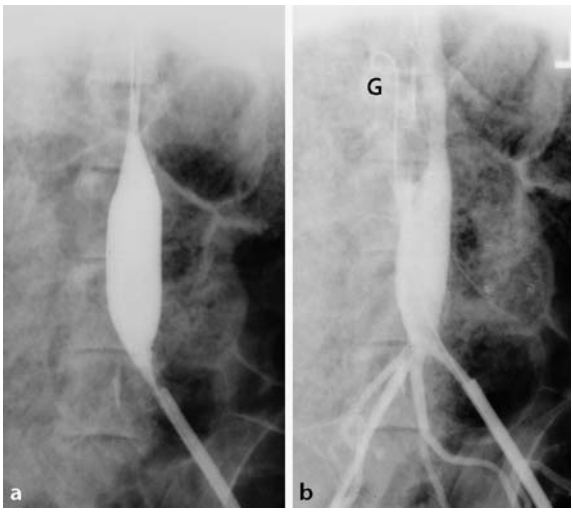

Fig. 5. a 300% overdilation of the aorta (6 mm diameter) by a 19 mm trifold angioplasty balloon (left). **b** Subsequent arteriography shows dilation and rupture of the infrarenal aorta (right). Contrast extravasation into retroperitoneum. *G,* tip of guide wire in retroperitoneum

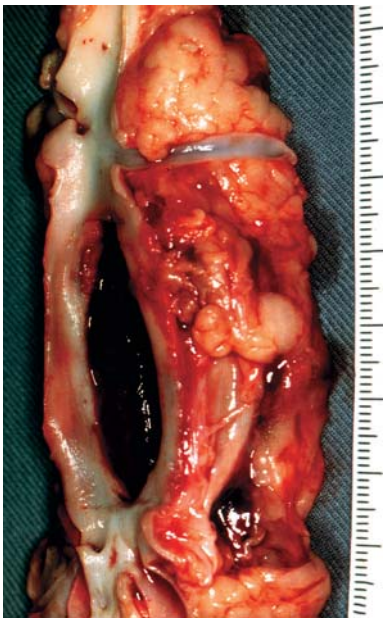

Fig. 6. Autopsy specimen of infrarenal aorta containing a long tear corresponding to the balloon length

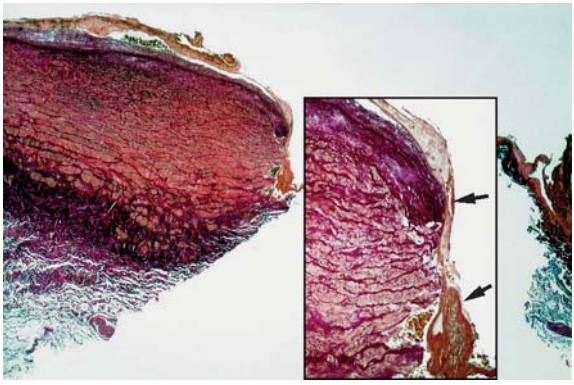

Fig. 7. Histology of transmural aortic rupture. Inlay shows fibrin apposition (*arrows*) on intimal and medial layer with focal hemorrhage at the site of rupture

theless, transluminal creation of aneurysms or pseudoaneurysms is a promising method.

Failed attempts of aneurysm creation. Simple dilation of the aorta by very large balloons results either in aortic dilation or in fatal rupture [54, 55]. Surgical exposure of the aorta in order to apply mechanical damage to the vessel is also an intricate and unreliable technique. In 1960 Economou et al. evaluated intramural injection of toxic agents or transmural freezing with liquid CO_2 for the production of aneurysms, yet these methods were ineffective and the lesions healed promptly by intimal hyperplasia [57].

Although an 'exarterectomy' including removal of the adventitial and 70% of the outer medial layer was effective to cause persistent aneurysms [57], other authors failed to reproduce this cumbersome technique and were obligated to perform additional balloon dilation of the weakened aortic segment [58].

In vitro aneurysm models. These benchwork models are excellent to investigate a particular aspect of endovascular aneurysm exclusion, e.g. aneurysm sac pressure in function of a varying parameter, such as an endoleak of different sizes or an aneurysm content of varied consistency. The model was composed of an artificial aneurysm connected to a tubing system, a pulsatile pump, and a collecting system [59–62]. A rubber tubing was used to make the system compliant. A pressure and flow transducer were integrated in the circuit. Pulsatile flow of 2 to 5 l/min and systolic pressure from 100 to 200 mmHg was generated at a pulse rate of 80 beats/min, and resistance was adjusted by varying the diameter of the outflow tube. The aneurysms were made of latex tubing [59, 62] or PTFE [60], and a pressure transducer was implanted into the aneurysm sac (Fig. 8). A solution of glycerol similar to plasma, or heparinized blood was used as perfusion fluid. The models investigated mainly transmission of systemic pressure to the aneurysm sac in the presence of complete and incomplete aneurysm exclusion. Various endoleaks were created consisting of fabric defects in the endovascular graft [59], or endoleak channels of PTFE tubes were attached to the aneurysm sac [60, 61]. Fresh blood as aneurysm content was replaced by thrombus [60] or gelfoam [44] to investigate the effect of pressure attenuation. This aneurysm model is excellent to obtain more insight into physical processes regarding the aneurysm and its separation from the hemodynamic system.

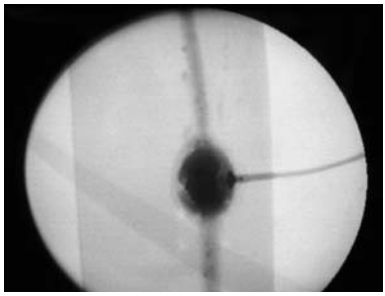

Fig. 8. Contrast enhanced radiograph of an aneurysm made of PTFE and interposed in an artificial circuit. A pressure transducer is fixed to the aneurysm wall

Conclusions

There is no 'best aneurysm model' to evaluate the performance of endovascular grafts and, simultaneously, to give insight into the fate of the aneurysm left in situ. Atherosclerosis, thrombosis, and ultrastructural and inflammatory changes in the aneurysm wall as the three key characteristics of human aneurysms are only approximately reproduced in experimental models. However, there are various excellent in vivo and in vitro aneurysm models that are highly suitable for the investigation of a particular aspect of endovascular treatment. The aggregated knowledge of all aneurysm models should be carefully studied and integrated in order to design effective models.

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6 Endoleaks following endovascular repair of experimental aneurysms: Does coil embolization with angiographic 'seal' lower intraaneurysmal pressure?

Introduction

Endoprostheses are an attractive alternative to open aneurysm repair. One of the major concerns regarding endovascular aneurysm treatment is the presence of flow outside the graft, the so-called 'endoleak' [1]. Endoleaks have been reported in 7–37% of endovascular aortic aneurysm repair [2–9]. They are caused by incomplete sealing between the endovascular prosthesis and the aneurysm necks, defects within the prosthesis itself, or patent branches arising from the aneurysm. There is uniform agreement that major endoleaks which lead to aneurysm enlargement require treatment. Endoleaks with aneurysm enlargement have been observed when the proximal or distal seal of the endovascular graft is imperfect. Fabric tears, particularly in bifurcated endovascular prostheses, have been reported following difficulties to deploy the graft or after guide wire manipulations to insert the second limb [10, 11]. On the other hand minor endoleaks associated with patent branches often do not produce aneurysm enlargement, and they are sometimes observed without interventional treatment [4, 5, 11]. However, the exact fate of an endoleak and its significance on pressure transmission remain to be clarified. There are a variety of options for the treatment of an endoleak, ranging from endovascular repair to conversion into open surgery. Recently, coil embolization has been attempted to treat persistent endoleaks [12]. However, efficacy of this approach has not yet been determined. The purpose of this study* [13] was to evaluate the effect of major endoleaks, caused by defects in the graft on intra-aneurysmal pressure (IAP), and to determine the efficacy of coil embolization for the treatment of these endoleaks with regard to reduction of IAP.

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Materials and methods

Preparation of aneurysm models

Aneurysm. An experimental fusiform aneurysm was created by balloon dilation of an 8 mm PTFE graft (WL Gore and Associates, Flagstaff, AZ) with a 30 mm modified prostate balloon (Dowd II PET, Medi-tech, Inc., Watertown, MA) resulting in a final aneurysm diameter of 23 mm. An implantable silicon strain-gauge pressure transducer (P 6.5-x6, Königsberg Instruments, Pasadena, CA) was then fixed within the aneurysmal wall for chronic pressure measurements (Fig. 1, group I). The metallic portion of the transducer was positioned on the inner surface of the aneurysm wall, thereby measuring the pressure within the aneurysm sac.

Endovascular graft without endoleak. The grafts were constructed by dilating 4 mm PTFE grafts with 10 mm balloon catheters (Blue Max, Medi-tech, Inc.). A balloon expandable Palmaz stent (P 104, Johnson & Johnson Interventional Systems, Warren, NJ) was secured to the proximal end of the graft with 2 sutures. These endovascular grafts were mounted on 10 mm×60 mm balloon catheters (Blue Max, Medi-tech, Inc., Watertown, MA) and backloaded into an 11 Fr introducer sheath (Fig. 1, group II).

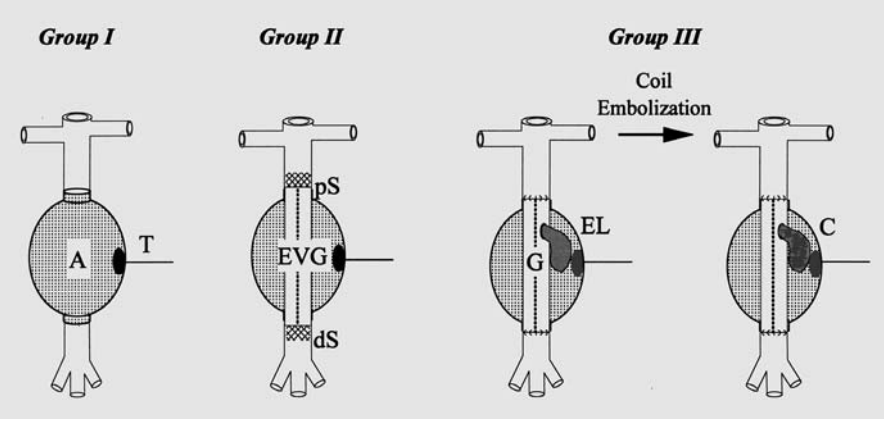

Fig. 1. The various types of models used in this study. *Group I:* Untreated PTFE aneurysms. *Group II:* Aneurysms excluded by an EVG without an endoleak. *Group III:* Aneurysms containing an EVG with an endoleak. These EVGs had a 4 mm diameter hole in the graft representing the endoleak. Subsequently the endoleak was treated by coil embolization. *A:* aneurysm; *T:* pressure transducer; *EVG:* endovascular graft; *pS:* proximal stent; *dS:* distal stent; *G:* graft; *EL:* endoleak; *C:* coils

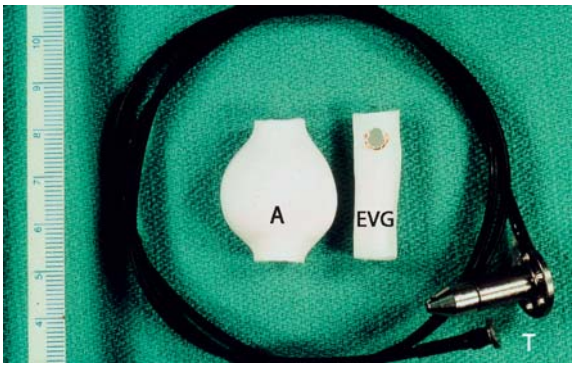

Fig. 2. Artificial aneurysm made of PTFE with an EVG containing a punched hole with a radiopaque marker. The EVG is placed inside the aneurysm and sutured to it at both ends. A pressure transducer tip is sutured to the aneurysm wall. The transducer has a cable and a connector that is placed in a subcutaneous tunnel and guided out at the neck of the animal. *A:* aneurysm; *T:* pressure transducer tip; *EVG:* endovascular graft

Endovascular graft with endoleak. The endovascular grafts for these models were constructed with 4 mm PTFE tube grafts that were dilated with 10 mm balloon catheters to a final graft diameter of 9 mm. Afterwards each graft was perforated proximally with a 4 mm aortic punch (Medtronic, Minneapolis, MN) that created a graft defect causing an endoleak. The site of the defect was marked with radio opaque wire for subsequent fluoroscopic detection. The EVGs were then coaxially placed within the aneurysms created in the above fashion and secured with sutures to the proximal and distal ends of the aneurysms for subsequent implantation (Fig. 1, group III and Fig. 2).

Operative procedures

Aneurysm implantation. Fifteen female mongrel dogs weighing 25–30 kg underwent operative procedures. They were divided into three groups. Group I (n = 4) included animals with untreated aneurysms. The animals in group II (n = 4) had EVGs without an endoleak, while those in group III (n = 7) had a hole within the EVGs causing an endoleak. The animals were anaesthetized with intravenous sodium pentobarbital (18–20 mg/kg body weight), intubated and placed in a supine position. They received one gram of cefazolin intravenously. After administration of heparin (50 U/kg body weight), the aorta was cross-clamped and a 30 mm segment of the aorta was resected. Untreated aneurysms (group I and II) and aneurysms containing an EVG with an endoleak (group III) were sutured to the aorta in an end-to-end fashion, using a running suture. The pressure transducer cable and the connecting skin appliance were passed through a subcuta-

neous tunnel and guided out at the neck of the animals. All animals were treated in accordance with the "Principles of Laboratory Animal Care" (formulated by the National Society for Medical Research) and the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, revised 1985).

Additional procedures. *Endovascular exclusion*: The aneurysms in group II were excluded from the circulation by the insertion of an EVG through a carotid arteriotomy 14 days after aneurysm implantation, as described previously [14]. After an initial aortogram the EVG was positioned in the infrarenal aorta and the proximal stent was deployed at the proximal neck of the aneurysm. The distal end of the EVG was secured by a second Palmaz stent (P 104) that was inserted separately, mounted on a 10 mm×2 cm balloon catheter. *Coil embolization*: Four weeks after implantation of the EVG in group III, the endoleaks were embolized with multiple curled metallic coils (diameter 3 and 4 mm, length 20 and 30 mm [Embolization Coil, Cook, Bloomington, IN]). An aortogram was obtained via carotid arteriotomy to demonstrate the endoleak. A 5 Fr torque catheter (Bern Berenstein, Meditech, Inc.) was advanced so that the tip canulated the site of the endoleak origin which was visualized by the previously placed wire. Three to four coils per animal were delivered to pack the endoleaks tightly (Fig. 1, group III).

Measurement of intra-aneurysmal pressure

IAP was measured by the pressure transducer in conjunction with an analogue-digital board (Metrabyte DAS-1402, Triton Technologies, San Diego, CA). The accuracy of these devices in aneurysmal pressure measurements has been reported previously [15]. Pressure measurements were performed daily for four weeks following aneurysm implantation (group I), exclusion by an EVG (group II) and exclusion by an EVG with an endoleak (group III). Group III was followed during an additional four weeks after coil embolization. Measurements were obtained of both systolic IAP by the pressure transducer and systolic blood pressure (SBP) from a pressure cuff on the animals' forelimb. To eliminate the effect of differences in SBP within each animal, IAP was expressed as a ratio.

$$IAP = IAP_{syst}/SBP$$

The aneurysmal pulse pressure (APP) was defined as the difference between systolic and diastolic intra-aneurysmal pressure.

$$APP = IAP_{syst} - IAP_{diast}$$

Assessment of endoleak

Aortography was performed through a carotid arteriotomy in each animal immediately after implantation of the artificial aneurysms and the EVGs. Color duplex studies (Sonolayer 140, Toshiba America Medical Systems, Inc., Yonkers, NY) were obtained after two and four weeks in all groups. A spiral contrast CT scan (High speed Advantage scanner, General Electric Medical Systems, Milwaukee, WI) was performed after two weeks in group II and after two and six weeks in group III. All studies were performed with the animal under general anesthesia (pentobarbital 18–20 mg/kg). We defined the endoleak in accordance with White et al. [10] as contrast extravasation outside the EVG, but within the aneurysm sac. The size of the endoleaks was assessed by measuring the maximal diameter of contrast extravasation on transverse sections of CT image studies.

Statistical analysis

Data are expressed as mean ± SD. Comparisons of treatment groups were performed, using two-tailed student t-test analysis. Statistical significance was assumed at the 95% confidence interval ($p < 0.05$).

Results

Two animals were sacrificed prior to completion of the study. One animal in group III was sacrificed 21 days after the operation, owing to a suspected graft infection that was, however, not confirmed later. The aneurysm in this animal was filled with semi-solid thrombus, except for a blood filled cavity located at the level of the graft hole (Fig. 3). This area represented persistent perigraft flow and correlated with the CT scan. Graft thrombosis causing paraplegia four weeks after implantation of the endovascular graft with an endoleak required sacrifice of another animal in group III.

Pressure measurements

Group I. Untreated aneurysms demonstrated an average value for systolic IAP-ratio of 0.96 ± 0.06 (Fig. 4). The mean APP was 62 ± 15 mmHg (Table 1).

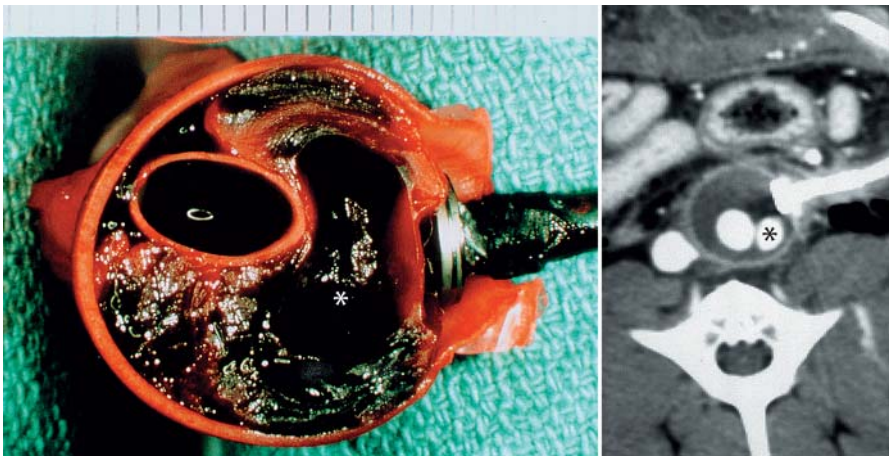

Fig. 3. Morphological appearance of an endoleak: Macroscopic view of the transverse section of an aneurysm (group III). A blood-filled cavity representing the endoleak (asterisk) is located adjacent to the EVG at the level of the graft defect. Corresponding transverse section on contrast enhanced CT scan (*right*)

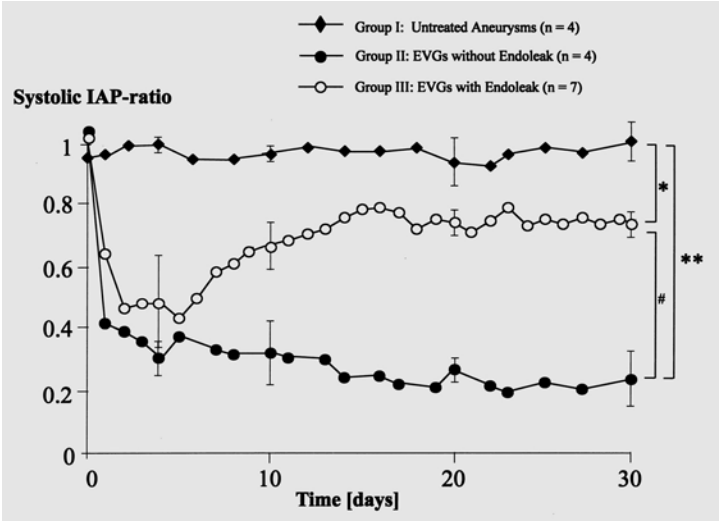

Fig. 4. IAP measurements. Mean values for the systolic IAP-ratio in group III decreased on the first postoperative day and re-increased and stabilized at a high level. IAP-ratios remained high in untreated aneurysms (group I) and low in animals of which an aneurysm had been excluded by an EVG without an endoleak (group II). At day 30: * $P = 0.025$, ** $P = 0.0009$, # $P = 0.003$

Group II. The average value for the systolic IAP-ratio decreased and stabilized at 0.34 ± 0.16 where it remained throughout the period of observation (Fig. 4, group I vs II, $P < 0.001$). The mean APP also decreased to 12 ± 11 mmHg (Table 1, group I vs II, $P < 0.001$).

Table 1. Mean aneurysm pulse pressure (±SD) in group I–III

Group	Aneurysm pulse pressure (mmHg)
I Untreated aneurysm	62 ± 15
II Endovascular graft without endoleak	12 ± 11
III Endovascular graft with endoleak	30 ± 16
III Endoleak after coil embolization	26 ± 13

At day 30: $P < 0.001$ (group I vs group II and III); $P = 0.013$ (group II vs III) not significant (group III before and after embolization)

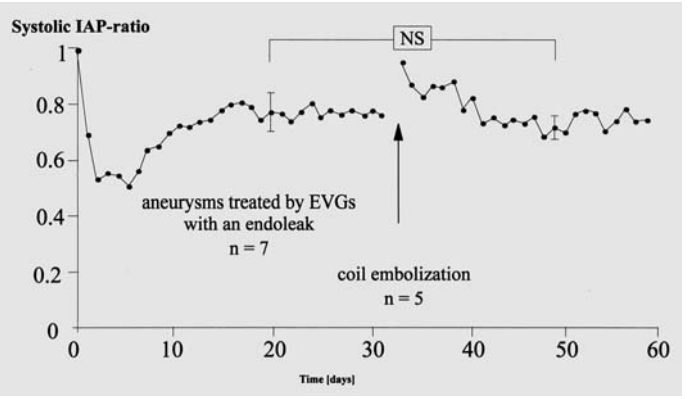

Fig. 5. Mean values for systolic IAP-ratio before and after coil embolization of the endoleaks in group III. Immediately after embolization the IAP-ratio increased, possibly owing to thrombus destruction following the placement of coils. Coil embolization failed to decrease IAP-ratio during the period of one month

Group III. In animals with aneurysms and EVGs with an endoleak, the mean systolic IAP decreased during the first 7 days and then re-increased and stabilized at 0.75 ± 0.18 (Fig. 4, group III vs II, $P = 0.003$). The endoleaks resulted in a high mean APP of 30 ± 16 mmHg (Table 1, group III vs II, $P = 0.013$). Immediately after coil embolization, the average value for systolic IAP increased somewhat (to 0.88 ± 0.12 during the first 6 days and then stabilized at 0.76 ± 0.14 for the remaining observation period (Fig. 5, pre vs post embolization at day 20 and 50, *NS*). Coil embolization did not affect APP which remained at 26 ± 13 mmHg compared to 30 ± 16 mmHg before embolization (Table 1, *NS*).

Imaging

Group I. The aneurysms showed minimal mural thrombus formation on arteriographic examinations, as described and illustrated previously [14, 15].

Group II. None of the completely excluded aneurysms demonstrated an endoleak on arteriography, duplex or CT scanning.

Group III. All endoleaks were clearly demonstrated by color duplex (Fig. 6 c). Duplex measurements revealed the hole of the graft wall to be 20 ± 5% of the graft circumference. Only a small amount of contrast extravasation was visualized on angiograms (Fig. 6 a). On CT image, an oval extravasation of contrast that was confined to an area adjacent to the hole in the EVG was visualized (Fig. 6 b). There was a wide variability in the maximal diameter of the endoleaks measured on CT image (range 3.8–14.9 mm) with a mean diameter of 7.2 ± 3.7 mm. The diameter of the endoleaks measured on CT did not correlate with the systolic IAP-ratio.

After coil embolization, all endoleaks were 'sealed' angiographically (Fig. 7 a). Furthermore, neither CT scan nor color duplex could demonstrate contrast or flow within the aneurysm at the site of the previously visualized endoleak, thereby confirming 'sealing' of the endoleaks (Fig. 7 b, c).

Discussion

The main goal of aneurysm treatment is complete exclusion of the aneurysm from blood flow. However, endovascular grafting for abdominal aortic aneurysms is not always successful, and incomplete exclusion has been reported in 7–32% [2–9]. There is some confusion regarding the treatment of endoleaks because the significance of endoleaks on pressure transmission is unknown. The size and source of an endoleak have been considered to be important factors in determining its outcome. Minimal contrast extravasation may resolve itself within days or weeks following endovascular aneurysm exclusion [2, 4, 11, 16], whereas other endoleaks may persist, resulting in aneurysm rupture. In our experiment the size of the original hole in the graft wall was consistent. Nevertheless, the size of the endoleaks showed a high variability on arteriography, CT scans, and duplex imaging. The different sizes of the endoleaks might be secondary to differences of the coagulation system and hemodynamic status in each animal. Although the size of the endoleaks varied extensively, a consistently high systolic pressure as well as a high pulse pressure were transmitted to the aneurys-

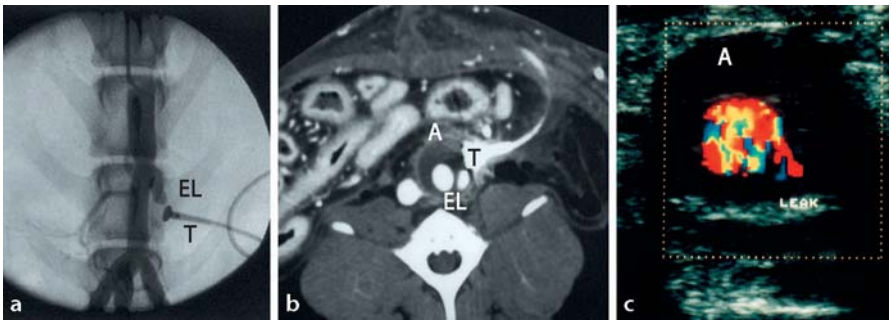

Fig. 6. Aneurysm with an endoleak following endovascular repair. **a** Arteriogram (left); **b** contrast enhanced CT scan (center) and **c** colored flow duplex (right) visualizing the endoleak. *EL:* endoleak; *A:* aneurysm; *T:* pressure transducer

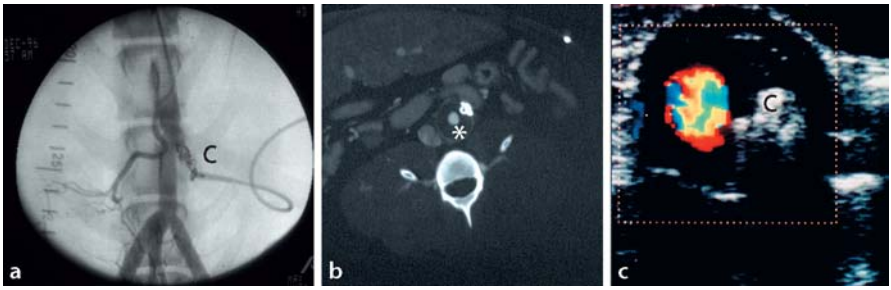

Fig. 7. a Coil embolization of an endoleak following endovascular aneurysm repair. Arteriogram (left); **b** contrast enhanced CT scan allowing differentiation between contrast dye and coils (center), and colored flow duplex (right). Arteriography and CT demonstrate 'sealing' of the endoleak, without contrast outside the EVG (star). There was no flow around the coils on color duplex. *C:* coils

mal wall. The size of the endoleak does not seem to be a relevant factor for pressure transmission. Since both the systolic and the pulse pressure are considered to be important factors for further aneurysm expansion and rupture [17], we recommend an aggressive treatment strategy for endoleaks, regardless of their size. Our findings also confirm some of the clinical experience where rupture of aortic aneurysms following endovascular repair has been reported, with small endoleaks or even in the absence of a demonstrable endoleak [4, 7, 9, 11].

The transmitted pressure in the presence of an endoleak showed an initial decrease, followed by an increase and stabilization at a high value after one week. The initial drop within the first postoperative day may be secondary to initial thrombus formation. Fibrin linking the cellular elements might give the thrombus more stiffness, thereby reducing pressure transmission. After one week, fibrinolysis may have contributed to thrombus liquefaction, causing a new increase in the systolic IAP-ratio [18].

In the present study, incomplete endovascular aneurysm exclusion owing to an endoleak resulted in a high pulse pressure of the aneurysms, whereas complete exclusion led to cessation of the aneurysmal pulse pressure. We consider the aneurysmal pulse pressure to be representative of demonstrating aneurysmal wall movement between peak systolic pressure and minimum diastolic pressure. These results confirm the clinical findings when the wall movement of the endovascularly excluded aneurysms was measured with ultrasonic echo-tracking scans [19]. In this study, in andcomplete aneurysm exclusion with an endoleak led to high aneurysmal pulsatility. But complete aneurysm exclusion minimized pulsatile wall movement.

There are different options to treat an endoleak. Conversion to open repair is envisaged if the endoleak is not amenable to an endovascular approach, for example if the aneurysm neck enlarges itself with subsequent migration of the prosthesis. Incomplete exclusion owing to an incorrectly sized device, misplacement of the stent or a gap between modules of an endoprosthesis might be treated by the placement of an additional covered stent. Coil embolization is a further option for treatment, but its true efficacy is not yet proved [12]. Tight packing of the endoleaks by coils has been considered to be important to achieve solid thrombus formation. In our experiment, despite tight packing and complete thrombosis with an angiographic and CT 'sealing' of the endoleaks, the pressure did not significantly decrease. Aortic blood pressure was transmitted through the thrombus, thereby exposing the aneurysm wall to nearly unimpeded pressurization. Coil embolization failed to interrupt pressure transmission to the aneurysmal wall and therefore may not be a reliable option for the treatment of this type of endoleak. According to the law of Laplace a reduction of the IAP by closure of the endoleaks (e.g. coil embolization) will only be an amelioration regarding the risk of rupture. Elimination of the risk of rupture might be achieved if the IAP decreases to the level of 0.34. This value was obtained after complete aneurysm exclusion in group II. Furthermore an initial increase in IAP was noted after coil embolization. This increase was probably due to the destruction of thrombus by the placement of coils. But these manipulations may subject the aneurysm to an increased risk of rupture. However, the findings of our study do not indicate that coil embolization of endoleaks will always be ineffective. There may be endoleak morphology with a narrow communication between the aorta and the aneurysm sac or with lower pressurization of the aneurysm sac, favorable for successful coil embolization. This may certainly be the case if the endoleak is due to residual patent branches that open into the lumen of the aneurysm. Coil embolization of these branches or of collaterals feeding them may provide effective treatment of endoleaks [20]. However, our study does not elucidate the effect of retrograde endoleaks due to residual patent branches. We consider some of these endoleaks benign although the observation by Resnikoff et al. [21] showed that this will not always be the case. The authors treated aortic aneurysms by open surgery, including proximal

and distal ligation. In 2% the aneurysm sac remained patent and, if there was pulsatile flow, they ligated the lumbar arteries.

In conclusion we developed an animal model to study the chronic effect of endoleaks on aneurysmal pressure. The consequence of an endoleak in terms of pressure transmission is not easy to address by clinical studies. Incompletely excluded aneurysms with a large endoleak transmit significant pressure to the aneurysmal wall, subjecting the aneurysm to the persistent risk of rupture. On the contrary, completely excluded aneurysms showed low aneurysmal pressure. The treatment of endoleaks by coil embolization may initially cause an increase in aneurysmal pressure. Coil embolization is not a reliable treatment for endoleaks with a large communication between the aorta and the aneurysm, resulting in high-pressure transmission to the aneurysm sac. In this situation coil embolization fails to reduce intra-aneurysmal pressure.

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7 Does large oversizing of self-expandable endoprostheses compensate for aortic growth?

Introduction

Self-expandable stents remain attached to the aortic wall during the phase of growth, whereas rigid stents loose partially contact with the underlying vessel owing to their fixed initial dimensions [1]. The problematic relationship between intraluminal device and growing aorta is relevant in the endovascular treatment of coarctation of the juvenile aorta (CoA) and is investigated on an experimental and clinical base [2–10]. Preferential use is given to balloon-expandable stents with high radial force, preventing recoil of the diseased aortic segment following dilation. Secondary to growth of the aorta, stent redilation at the level of CoA is sometimes required because of a relative stenosis [6, 9, 11]. Careful imaging studies revealed partial detachment of the stent ends from the enlarging aortic wall beyond the level of CoA, yet consequences such as thrombosis or embolization had not been observed [11, 12].

Endoprostheses (EPs) consisting of a metallic frame and a fabric covering, are constantly evolving and may open new perspectives in endovascular CoA treatment, enabling more assertive dilation through the implanted EP, without risk of aortic rupture or pseudoaneurysm formation [11]. Oversizing of self-expandable EPs probably allows for compensation of growth without separation from the aortic wall. At follow-up, an eventual restenosis at the level of the CoA could be securely redilated thanks to the endoprosthetic covering which seals an aortic tear immediately. The interaction between oversized EPs and a growing aorta is, however, poorly investigated. Most of the experimental studies focus on the performance of rigid, balloon-expandable stents in the context of CoA and the feasibility of redilation at termination of growth [2–5]. A single study only addresses the performance of oversized, self-expandable Gianturco stents in an enlarging aorta [1]. So far no data are available investigating the response of a growing aorta towards oversized EPs with a covering. But the previously mentioned studies have a shortcoming, in as much they use the diameter in order to demonstrate enlargement of the devices instead of referring to the cross sectional area. The area is the crucial parameter for analysis of the lumen for two reasons: First the prosthetic lumen of a recently im-

planted EP can be considerably irregular, and therefore it is impossible to define the representative diameter. Second, area times velocity defines the blood flow in a linear approximation, and therefore the area (not the diameter) is determining the hemodynamic significance. This study* [13] evaluates the performance of different types of oversized covered EPs in a normal juvenile porcine aorta by analyzing the lumen area over time, and assesses the healing response of the underlying vessel.

Material and methods

Endoprostheses

Four different types of oversized, self-expandable EPs were evaluated (Fig. 1). Manufacturers indicated a standard nominal diameter of 20 mm and a length varying between 40 to 60 mm when the EPs are fully expanded ex vivo. We calculated their nominal area to 314 mm^2 using the formula

$$\text{area} = \pi \times r^2$$

Four EPs of each type were implanted. They were supplied sterile and by courtesy of the manufacturers (WORLD MEDICAL manufacturing corp., Sunrise, Florida USA; Stenford Groupe Valendons S.A., Nanterre, France; Schneider Europe AG, Bülach, Switzerland). The four types of EPs were:

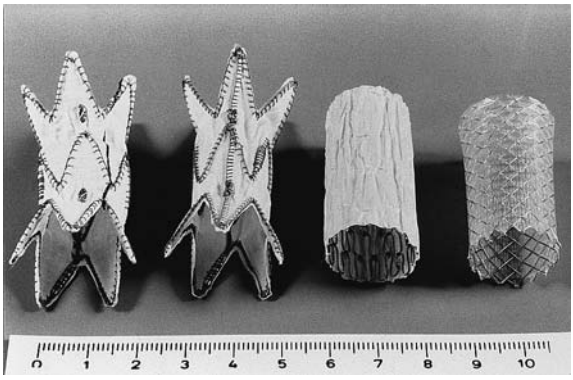

Fig. 1. Four types of endoprostheses used in this study: Talent, TalentLoPro, Stenway, and Wallstent (*left to right*)

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- *Talent™-EPs* made of three monofilament (0.55 mm) nitinol serpentines in series connected with a single monofilament. The outer covering was a fabric of woven low permeability polyester (0.18 mm). The total length was 50 mm, including the zigzag-shaped open web that had no fabric between the triangles. The EPs were mounted on a 20 F delivery catheter with a central balloon and were constrained by a retractable sheath.
- *Talent™LoPro™-EPs* contained the same metallic frame as mentioned above, yet the covering was made of ultra-thin (0.06 mm), ultra-high-strength woven polyester. The low profile allowed for an 18 F delivery system.
- *Stenway®-EPs* consisted of thin (0.45 mm) and small nitinol serpentines connected in series by 6-0 polypropylene sutures, with a total device length of 40 mm. The outer covering was woven ultra-thin polyester (0.05 mm). The EPs were constrained by a retractable sheath on a 20 F delivery catheter with a tip balloon.
- Oesophageal *Wallstent™-EPs* consisted of stainless steel wires (0.12 mm) woven in a tubular fashion with a length of 50 mm. The frame was covered by ultra-thin sealing polyurethane. The EPs were mounted on an 18 F Telestep Delivery System.
- *Non-oversized EPs* were Talent™LoPro™ devices with a nominal area of 154 mm^2 (diameter 14 mm) and a length of 60 mm.

Implantation and evaluation by IVUS

Experimental procedures conformed to the *Guide for the Care and Use of Laboratory Animals* (National Academy Press 1996) and were approved by the institutional animal use and care committee. Twenty EPs were implanted in the descending thoracic aorta of twenty juvenile pigs. Animals were premedicated with xylazine (0.1 mg/kg) and atropine 2 mg IM, and underwent induction of anesthesia with halothane and oxygen. They were maintained under general endotracheal anesthesia with a mixture of oxygen, and halothane (0.5% to 1.5%) and were placed in a slightly right-lateral position. They were given 2 400 000 IU penicillin IM. The left thoracoabdominal side was sterilely draped. Cardiac rate and rhythm and transcutaneous oxygen saturation were monitored throughout the procedure.

The infrarenal aorta was exposed through a left retroperitoneal approach. A 9 F introducer was placed in the aorta following administration of heparin (100 U/kg IV). In order to measure the area of the descending thoracic aorta and the EP, intravascular ultrasound (IVUS) with a 12.5 MHz probe (Sonicath Ultra 6, Boston Scientific Corp., Watertown, MA USA) and a motorized pullback (Clear View Ultra™, Boston Scientific Corp.) were performed to measure the cross-sectional area of the aorta (aortic lumen) and the implanted EP. The latter had a prosthetic lumen defined by the area within the prosthesis, and a perfused lumen given by the area perfused by the blood stream. We focused exclusively on the area, not the diameter, for

the reasons mentioned above. Mean diameters are selectively indicated in brackets to give an idea for comparison with the literature, and we are fully conscious about the fact that the area, although the correct parameter, is an unusual dimension for clinicians. We defined the proximal landing zone 10 cm distally to the left subclavian artery, irrespective of intercostal arteries which are here of minor relevance for the spinal perfusion. The descending thoracic aorta was measured by IVUS at several levels. The proximal landing zone was identified by IVUS and fluoroscopy. The EP was inserted over a 0.038-in guide wire through a small aortotomy and deployed under fluoroscopy. A balloon was used to open the self-expandable EP when it was included in the introducer system. The EP and the aorta were visualized by IVUS with motorized pullback, and measurements of representative cross sections were taken. The area of the aorta 5 cm distant to the proximal and distal end of the implanted EP was determined in order to obtain valuable data of aortic growth. Following closure of the wound, all animals were given 500 mg paracetamol IM every 4 to 6 hours for postoperative analgesia and thereafter 100 mg aspirin daily.

The data acquired by IVUS were analyzed by an imaging software (EchoQuant V. 3.36, INDEC Systems, Inc., Mt. View, California, USA). The area of three representative cross-sections, namely the midportion of the EP, and the aorta were measured (Fig. 1). An eventual stenosis within the EP was related to the proximal aorta in order to normalize the differences in aortic size and calculated using the formula

$$\%\ \text{stenosis} = [1 - (\text{true lumen}/\text{aortic lumen})] \times 100\,.$$

Follow-up catheterization and histologic examination

At follow-up, the aorta was catheterized in a manner similar to the method described for the implantation procedure. The cross-sectional area was measured by IVUS as previously mentioned. After a follow-up period of 117 ± 18 days the animals were euthanized, the thoracic aorta excised and perfusion fixated with 100 mmHg pressure with 10% buffered glutaraldehyde. The excised aortic specimen was cut longitudinally into two halves and the luminal surface photographed. The specimens were processed by dehydration, then defatted and embedded in methyl methacrylate at 4 °C. After tempering the blocks were cut with a diamond circular saw (EXAKT 300CP, Norderstedt, Germany). Sections with a thickness of 500 µm were taken of the representative levels. They were glued on Plexiglas and polished to a final thickness of 5–8 µm. Two slides per level were prepared and stained with Giemsa (G) and Van Gieson-elastin (VE) for light microscopic examination. G was used to evaluate the cell morphology and the inflammatory response. Inflammation was assessed semiquantitatively as absent, minimal (one to three nodular infiltrates), moderate (three to six infiltrates), and extensive (more than six infiltrates per visual field at 40× magnification).

Statistical analysis

All data are presented as mean ± SD. Comparisons within one type of EPs and between the TalentLoPro-EPs and the non-oversized-EPs used the two-tailed *t* test. Probability values less than 0.05 were considered significant.

Results

Implantation and deployment at the target site were successfully performed in each animal. Two animals developed an abscess and one animal a lymphocele at the incision site. This was successfully treated by debridement and antibiotics. Mean animal weight at implantation and autopsy was 43 ± 11 kg and 99 ± 16 kg, respectively.

Intravascular ultrasound

The descending thoracic aorta was curved and conical. The increase of the aortic lumen indicating growth was 60 ± 50% in the proximal and 77 ± 95% in the distal thoracic aorta ($P < 0.001$, Fig. 2). The lumen of the central part

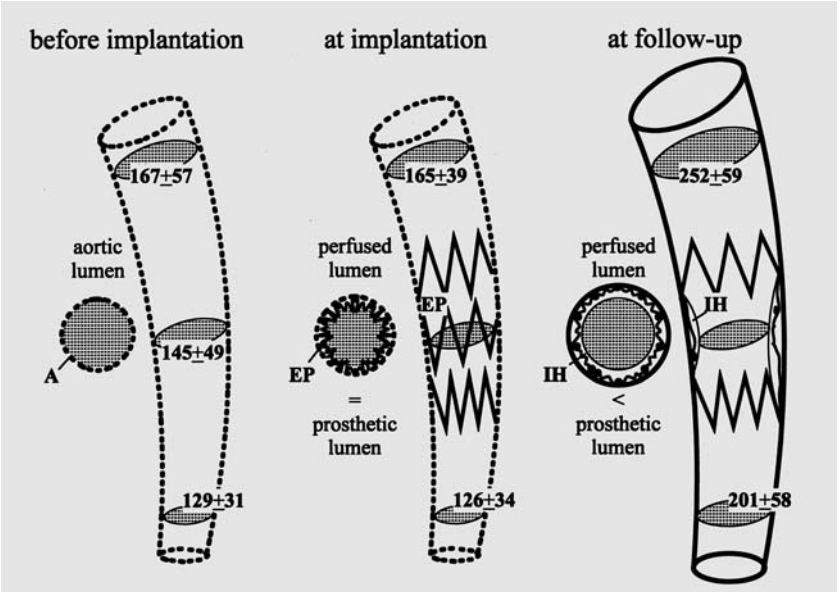

Fig. 2. Schematic drawing of the descending thoracic aorta containing an EP. The three representative cross-sections [mm^2] are shown measured at different times. *A:* aorta; *EP:* endoprosthesis; *IH:* intimal hyperplasia

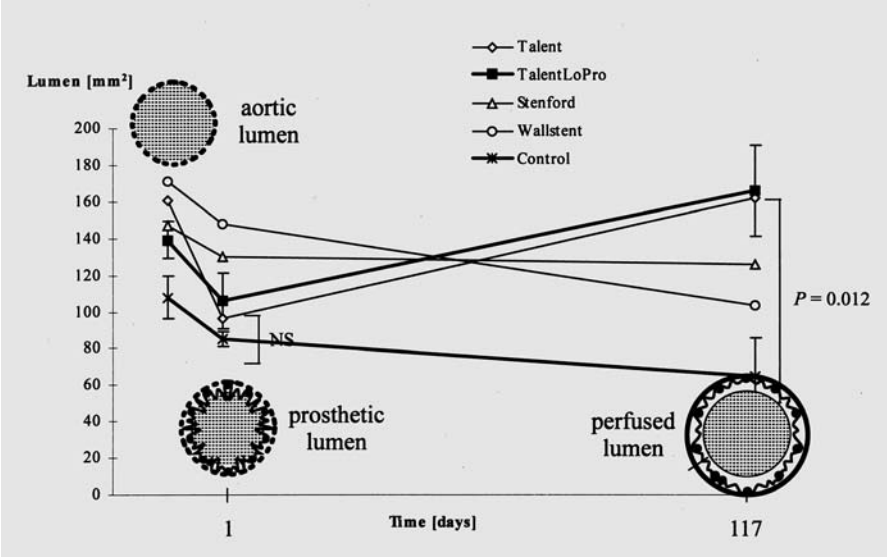

Fig. 3. The change of the lumen over time is shown for each type of EP including the non-oversized EPs before and at implantation, and at follow-up

of the EP was subjected to a changing morphology over time. At implantation, the perfused lumen was identical with the prosthetic lumen. At follow-up, intimal hyperplasia rendered the luminal surface smooth, yet narrowed the prosthetic lumen. The perfused lumen became therefore smaller. Mean oversizing of the EPs (nominal prosthetic area 314 mm^2) related to the aortic area before implantation was 99 ± 41% (48 ± 22% in diameter). The non-oversized EPs (nominal prosthetic area 154 mm^2) were minimally larger than the aorta with 11 ± 2% (14 ± 9% in diameter) in order to prevent distal dislocation.

The prosthetic lumen. At implantation, the EPs were incompletely expanded and did not substantially dilate the adjacent aorta. The prosthetic lumen corresponded to the perfused lumen immediately after implantation (Fig. 2). The Wallstent- and Stenway-EPs initially achieved the largest lumen thanks to a circumferential alignment and minimal folding. In particular, the Wallstent-EPs were perfectly aligned with a smooth and circular contour. All EPs of the type Talent showed irregular lumina with folds of the unsupported covering. Among them the non-oversized EPs had the smallest lumen (Figs. 3, 4 and Table 1, p. 85).

At follow-up, the Stenway-EPs demonstrated the largest prosthetic lumen with significant expansion and partially stretched folds. The non-oversized EPs showed the smallest prosthetic lumen in consequence of their limited nominal area. Thanks to their small dimensions, they achieved the highest percentage of expansion (Table 1, Fig. 4).

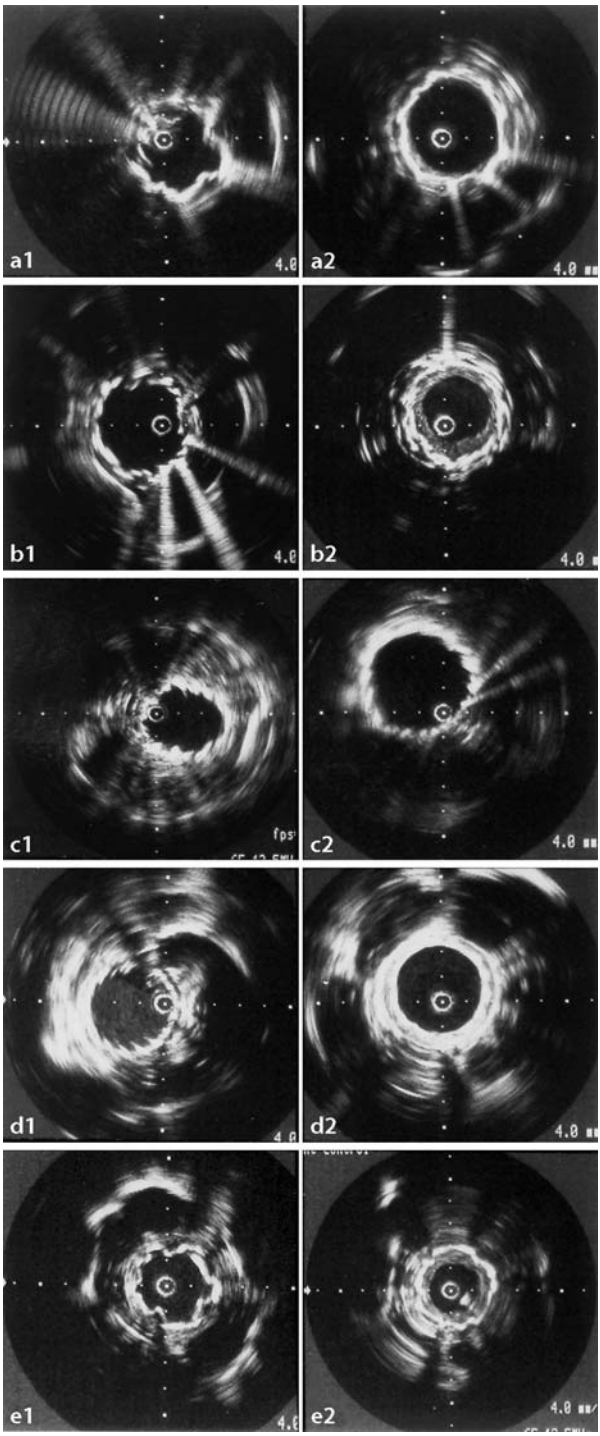

Fig. 4. IVUS imaging of the four types of EPs and the non-oversized EPs at implantation (left) and follow-up (right). **a** Talent; **b** TalentLoPro; **c** Stenway; **d** Wallstent; **e** Non-oversized. Scale is 4.0 mm/div

Table 1. Expansion of the EPs and size of the perfused lumina after termination of growth

EPs	Implantation		Follow-up						
	Nominal area [mm^2]	Prosthetic lumen [mm^2]	Prosthetic lumen [mm^2]	Expansion of prosthesis [% nom. area]	P [a]	Perfused lumen [mm^2]	Prox. aortic lumen [mm^2]	Relative stenosis [b] [%]	P [c]
Talent	314	96 ± 62	202 ± 61	64 ± 19	*NS*	162 ± 53	232 ± 16	31 ± 20	*0.043* [d]
TalentLoPro	314	106 ± 20	228 ± 67	73 ± 21	*0.048* [d]	166 ± 52	283 ± 59	39 ± 25	*NS*
Stenway	314	130 ± 27	250 ± 32	80 ± 10	*0.001*	126 ± 63	267 ± 72	47 ± 31	*NS*
Wallstent	314	148 ± 33	186 ± 39	59 ± 13	*NS*	104 ± 30	265 ± 29	60 ± 14	*0.006*
Non-oversized	154	85 ± 4	129 ± 13	84 ± 8	*0.012*	65 ± 21	213 ± 90	65 ± 19	*0.053* [d]

[a] prosthetic lumen at implantation vs prosthetic lumen at follow-up
[b] related to the proximal aortic lumen
[c] perfused lumen vs proximal aortic lumen
[d] these values are considered not significant because of the high standard deviation

Table 2. Significance of oversizing in lumen gain during growth. Comparison between oversized and non-oversized TalentLoPro-EPs

EPs	Implantation	Follow-up	
	Prosthetic lumen [mm^2]	Prosthetic lumen [mm^2]	Perfused lumen [mm^2]
TalentLoPro	106 ± 20	228 ± 67	166 ± 52
Non-oversized	85 ± 4	129 ± 13	65 ± 21
Unpaired *t* test	NS	$P = 0.027$	$P = 0.012$

The perfused lumen. At follow-up the TalentLoPro- and Talent-EPs had the largest perfused lumina despite marked IH in the TalentLoPro-EPs (Fig. 3). The perfused lumina of the Stenway- and in particular of the Wallstent-EPs were smaller. Yet the smallest perfused lumina were present in the non-oversized EPs. The comparison between the TalentLoPro- and the non-oversized EPs showed a significantly larger prosthetic and perfused lumen at follow-up in favor of the oversized TalentLoPro-EPs (Table 2). IH narrowed the prosthetic lumen to some extent in all of the EPs, but it also simultaneously smoothened luminal irregularities, enabling an almost circular contour of the perfused lumen (Fig. 4).

Relative stenosis. A moderate stenosis of 60 ± 14% was present only in the Wallstent-EPs (Table 1).

Autopsy findings and histology

Distal spikes in five of the twelve Talent-like EPs penetrated but did not perforate the aortic wall, without formation of a pseudoaneurysm. On histologic sections the spikes penetrated the tunica media, but the adventitial layer remained intact. All EPs were patent and covered by a glistening neointima of variable thickness (Fig. 5).

The Talent-, TalentLoPro- and non-oversized EPs demonstrated a moderate inflammation of the neointima and interface adjacent to the covering. It consisted of nodular and diffuse histiolymphocytic infiltrates with neovessels, hemosiderin and a few giant cells. The same inflammatory pattern was present in the Stenway-EPs, yet less pronounced. On the contrary, the Wallstent-EPs evoked a marked foreign-body type reaction with giant cells of the neointima and the interface focally encroaching on the inner media. The infiltrates were denser with numerous giant cells. Multiple foreign bodies were present, probably consistent with degraded polyurethane. In all of the EPs IH was developed to a different extent. It filled out the grooves of the covering and thereby created a circular lumen contour. The tunica media was compressed and partially lacerated beneath the wires of

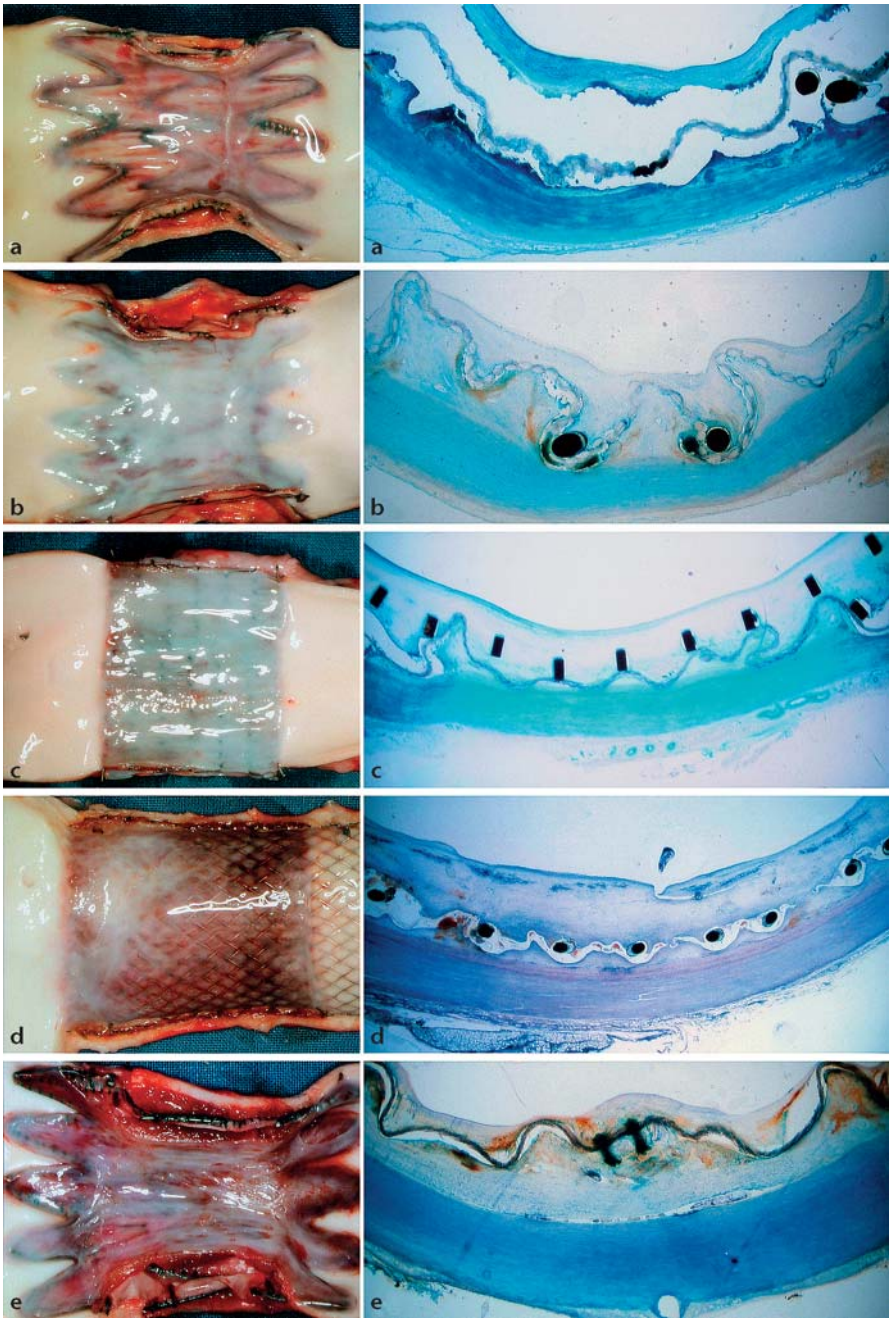

Fig. 5. Autopsy specimen (*left*) and histologic cross-section (*right*) of the four types of EPs and the Non-oversized EPs. **a** Talent; **b** TalentLoPro; **c** Stenway; **d** Wallstent; **e** Non-oversized. Original magnification ×10

the Talent-, TalentLoPro- and non-oversized EPs. Medial lesions were less pronounced beneath the Stenway-EPs and absent in the presence of the Wallstent-EPs.

Discussion

Significance of oversizing and implications for future graft design. The present study demonstrates that in the phase of growth oversized EPs will finally result in a significantly larger perfused lumen than non-oversized EPs. Oversizing is important for two reasons. First, the high radial force of oversized EPs probably distends the aorta at implantation thereby maintaining a large lumen. On the contrary, the expansion force of non-oversized EP is weaker and unable to distend the aorta, and therefore the thickness of the endoprosthetic wall causes a marked reduction of the perfused lumen. Second, self-expandable EPs are capable of keeping pace with aortic growth by progressive expansion. Because the prosthetic lumina of oversized EPs are initially larger than those of non-oversized EPs, a 70 to 85% increase of lumen area during growth ultimately becomes more impressive in oversized EPs.

The design of the EP influences the area of the prosthetic lumen, following deployment of the device. At implantation, the Wallstent-EPs achieved a perfect alignment without folds owing to a narrow-meshed metallic frame. On the contrary, the TalentLoPro-EPs showed an irregular prosthetic lumen owing to protruding folds of the unsupported covering between the metallic zigzags. In the growing phase, the Wallstent-EPs lacked further expansion because of their weak radial force. On the other hand, the TalentLoPro-EPs followed aortic enlargement thanks to their strong expansion force. A more ideal design would preferentially consist of a modified Talent-like metallic frame, yet with closely arranged zigzags and a covering with elastic properties.

The larger the prosthetic lumen, the lower the effect of IH: The rationale for oversizing. After termination of growth, the TalentLoPro- and Talent-EPs showed the largest perfused lumen and absence of stenosis thanks to their wide prosthetic lumen. The impact of IH is best demonstrated comparing the largely oversized versus the non-oversized EPs of the same type. IH in the TalentLoPro-EPs was irrelevant thanks to their wide prosthetic lumen. Intimal thickness was comparable in the TalentLoPro- and non-oversized EPs, and therefore it reduced the small prosthetic lumen of the non-oversized EPs to a much greater extent. The Wallstent-EPs, although oversized, finally also showed small perfused lumina that resulted in a moderate 60% stenosis compared to the proximal aortic lumina. We would like to remind that all our data are related to the lumen area, not to the di-

ameter. A 75% cross-sectional *area* stenosis corresponds with a 50% *diameter* reduction and is considered a moderate stenosis [14]. The relative stenosis was the consequence of a combination of minimal device expansion and IH in the Wallstent-EPs.

Covering material, neointimal hyperplasia and vessel injury. The covering material consisted mainly of woven polyester well known in endovascular aneurysm exclusion [15, 16]. The hyperplastic response towards thin woven polyester in the present study was important in the EPs of the type TalentLoPro. Neointimal thickness showed to be influenced by residual folds of the covering. A neointimal buildup smoothed folds and produced a regular luminal contour, recreating the base for laminar flow characteristics. The composition of the neointima was a moderate foreign-body type inflammatory reaction consistent with findings in prosthetic graft application [17, 18].

The proliferative response towards polyurethane showed a more extensive inflammation and signs of degradation of polyurethane. Although the present Wallstent-EPs are specifically used for oesophageal stenting in order to occlude fistula [19], other polyurethane covered Wallstents have been evaluated in the vascular system [20, 21]. We were interested in investigating various types of EPs in order to obtain as much information as possible.

In the present study the injury to the underlying aorta consisted of a compression of the tunica media with discrete splitting at the wire site owing to the expansion force. It was present in the EPs of the type Talent and in the Stenway-EPs, whereas it was absent in the flexible Wallstent-EPs because of their weak radial force. The penetrations of some of the distal spikes through the aortic wall, exclusively seen in EPs of the type Talent, were probably a consequence of the conical shape of the aorta and its curved course, conflicting with the cylindrical configuration of the devices.

Possible clinical applications of oversized covered EPs. Endovascular treatment of CoA with bare stents carries the risk of pseudoaneurysm formation, aortic dissection, or disruption during dilation. Pseudoaneurysms have been reported in the few series of CoA stenting in 6–17%, namely in six patients [7, 10, 12]. The treatment by implantation of a second bare stent does not seem appropriate since some aneurysms remained perfused through the stent frame [10]. Three reports in the recent literature describe successful exclusion of a pseudoaneurysm in the adult by a covered EP [7, 11, 22].

CoA treatment by covered EPs in older children or adults could be advantageous because of the sealing effect of the covering, rendering intimal-medial tears innocuous. The dilation of the CoA through the EP could be performed more assertively. Oversized EPs could probably make subsequent redilations safe up to the nominal area of the device and provide proximal and distal alignment with the aortic wall owing to their progressive expansion, compensating for aortic growth.

In conclusion, large oversizing of self-expandable EPs compensates for aortic growth, maintaining a large perfused lumen following the phase of growth. Progressive expansion of the device minimizes the effect of IH. The TalentLoPro-EPs showed the best performance. Lack of oversizing results in a significantly smaller perfused lumen. Today, clinical applications for covered EPs are pseudoaneurysms following treatment of CoA. A wider application of EPs that are oversized and implanted in a growing organism seems promising, yet remains to be determined.

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Clinical applications

1 Classification of infrarenal aortic aneurysms with respect to endovascular suitability

Introduction

Endovascular technique relies entirely on pre-interventional imaging with few possibilities for intra-procedural adjustment, unlike open surgery where unexpected findings are recognized under direct vision and problems are solved by straightforward manipulations. The morphology of aortic aneurysms is crucial for the suitability of an endovascular repair [1–3] and also important for its outcome [3]. In particular, a segment of relatively normal aorta between the renal arteries and the beginning of the aneurysm, namely a proximal neck, is a prerequisite for fixation of the endoprosthesis. The first endovascular treatment was performed in 1991 for an infrarenal aortic aneurysm with a proximal and distal neck reliably anchoring a straight endovascular tube graft [4]. In fact, tube grafts are easier to implant and require fewer manipulations than bifurcated endoprostheses. We were interested to know how many infrarenal aortic aneurysms are suitable for an endovascular tube graft repair. The aim of the study* [5] was to analyze the morphology of infrarenal aneurysms based on preoperative imaging.

Methods

The operating charts of a consecutive series of patients were reviewed who underwent open surgical repair of an infrarenal aortic aneurysm between 1. 1. 1988 and 31. 12. 1993 at the Department of Cardiovascular Surgery, University Hospital, Zürich. A total of 576 patients were given elective or urgent aortic replacement. 298 patients (52%) were treated by bifurcated prostheses and 278 patients (48%) by tube grafts. The present study focuses on the latter group of patients. Inclusion criterion was a set of hard

* By kind permission of the Editor (*Swiss Surgery* 1996; 2:219–222)

copies of a contrast enhanced computer tomography (CT) scan with a slice thickness of 5 or 8 mm within the last two months before the operation. Measurements were taken of the diameter and length of the proximal and distal neck, and the distance between the lowermost renal artery and the aortic bifurcation. The largest transverse diameter of the aneurysm and the smallest transverse diameter of the perfused lumen were considered representative. Eight measurements per patient were performed. The length of an aortic segment was calculated by multiplying the number of slices with the slice thickness. The presence of a neck was assumed if the segment was cylindrical with a minimal length of 15 mm or slightly conical with a diameter increase of less than 5 mm. The 'saccular index' was calculated by the ratio of the aneurysm diameter divided by the aneurysm length [6]. Rupture of the aneurysm was recorded. Data are expressed as mean ± SD.

All data are presented as mean ± SD. Comparisons between groups were made by means oneway ANOVA and posthoc analysis. Probability values less than 0.05 were considered significant.

Results

Based on the data of 89 aneurysms, a classification into three distinct types of aneurysms has been created (Fig. 1 and Table 1). Type I aneurysms have a sufficiently long proximal and distal aortic neck and are rather spherical. They are present in only 11%. Type II aneurysms still have a proximal neck, yet lack a sufficiently long distal neck. Aneurysm diameter and per-

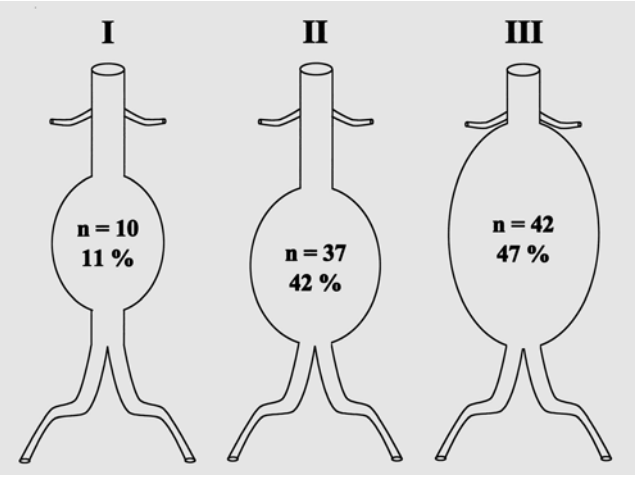

Fig. 1. Morphological classification of 89 aneurysms into three distinct types

Table 1. Three different types of aneurysms: Their morphological characteristics and rate of rupture

Relevant characteristics	Unit	Type of aneurysm			
		I	II	III	*P* [a]
Patient's age	[y]	65 ± 9	67 ± 10	72 ± 7	*0.02* [b]
Prox. neck D	[mm]	24 ± 4	25 ± 4	na	0.48
Prox. neck L	[mm]	30 ± 19	36 ± 16	na	0.32
Dist. neck L	[mm]	18 ± 5	na	na	
Infrarenal aortic L	[mm]	116 ± 23	116 ± 19	117 ± 21	0.97
Aneurysm D	[mm]	53 ± 13	60 ± 15	70 ± 18	*0.003* [b]
D of perfused lumen	[mm]	34 ± 9	38 ± 13	41 ± 19	0.38
Saccular index	ratio	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	*0.05* [c]
Rupture	[%]	0	5	19	*0.048* [d]

na: not available; *D,* diameter; *L,* length
[a] group I vs III; [b] group III vs I and II; [c] group III vs II; [d] group III vs I

fused lumen are slightly larger. The configuration is less spherical. They are present in 42%. Type III aneurysms have both the significantly largest diameter and the largest perfused lumen involving the entire infrarenal aorta. They are fusiform. This morphology is distinctly different from the one in type I aneurysms. Type III aneurysms are most frequent in 47%. They are significantly associated with advanced age.

None of the type I aneurysms and only two of the type II aneurysms (5%) that have a mean aneurysm diameter of 53 ± 13 mm ruptured. However, the risk of rupture is significant in fusiform aneurysms of type III. Rupture occurred in eight patients (19%) with type III aneurysms of which the mean aneurysm diameter was 70 ± 18 mm.

Discussion

A classification into three types of aneurysms was made based on the presence or absence of an undilated segment adjacent to the aneurysm. A proximal neck is an important prerequisite for an endovascular treatment, enabling fixation of the device. It was present in 53% of the aneurysms in this study. It is estimated that about 50% of infrarenal aortic aneurysms are suitable for an endovascular repair because of a proximal neck [1, 7]. This percentage is probably smaller owing to other important factors, such

as quality and angulation of the neck and tortuosity and size of the iliac and femoral arteries. Type I aneurysms including a proximal and distal neck are present in only 11%, and this finding is coincident with other studies [1, 7]. Although, at first sight, these aneurysms seem to be ideal for a tube graft repair, they are associated with a high rate of leakage at the fixation sites [8–10]. The placement of a tube graft the length of which corresponds to the length of the infrarenal aorta is technically demanding and carries a risk of renal artery occlusion owing to covering of their orifice, whereas the implantation of a slightly shorter tube graft runs the risk of poor anchorage within either the proximal or distal neck. In addition, progressive dilation of the distal aortic neck with loosening fixation and leakage has been observed [8, 11, 12]. Therefore these aneurysms are better treated with bifurcated endoprostheses [8, 13].

Type III aneurysms progressed beyond the feasibility of an endovascular repair because of involvement of the entire infrarenal aorta, therefore lacking a proximal neck. These aneurysms had the largest mean diameter of 70 mm and were fusiform. Indeed, the aneurysm diameter correlates with aneurysm length, and large aneurysms are also long [13]. The rate of rupture was important at 19%. Our data corroborate a previous study which noted longer and more fusiform aneurysms to be at a significantly higher risk of rupture than spherical aneurysms, less frequently predisposed to rupture [6]. In fact, we did not observe rupture either in type I aneurysms. The present classification seems to characterize the progressive evolution from small spherical aneurysms of the central or distal infrarenal aorta towards large fusiform aneurysms encroaching on the entire infrarenal aorta. These large aneurysms were the most frequent ones. Unfortunately they cannot be treated by endovascular means at present, although patients with ruptured aortic aneurysms will probably profit most from an endovascular approach.

The study has some limitations. The length of aortic segments is probably underestimated because the transverse sections of the CT scan were not perpendicular to the longitudinal axis of the aorta. For the same reason, the maximal diameter is likely to be overestimated in tortuous or bulging aneurysms though we referred to the transverse diameter. Only spiral CT scan with imaging processing and central lumen line measurements is accurate for both dimensions [14].

In conclusion, based on the present classification of infrarenal aneurysms the feasibility of an endovascular repair was calculated at about 50% including type I and II aneurysms including a proximal neck. Type I aneurysms mostly suitable for endovascular surgery are rather small and rare, with a minimal risk of rupture. Type III aneurysms are large and characterized by absence of a proximal neck and an important risk of rupture, and are best treated by open surgery.

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2 Systematic and exclusive use of intravascular ultrasound for endovascular aneurysm repair – The Lausanne experience

Introduction

The interventionist is used to rely on arteriography and fluoroscopy for endovascular aneurysm repair. He is particularly familiar with the angiographic appearance of the aorta and the plain view of the device as it appears on the fluoroscopic image. Intravascular ultrasound (IVUS) creates high-quality cross-sectional views and might therefore be equally important for an endovascular repair. IVUS interrogation of aortic aneurysms allows for precise measurements and quality assessment of the aortic neck [1, 2]. The target site of device deployment, namely the lowermost renal artery, is reliably identified [2, 3]. In a previous study, we showed that IVUS was efficacious for the precise positioning of endoprostheses, replacing completion arteriography [4]. Post-deployment quality control by IVUS includes expansion of the device and its apposition to the aorta and patency of major branches [3]. Therefore IVUS is considered an important adjunct to endovascular interventions [5–8]; however, only few physicians use it as the principal navigation tool for device implantation [4, 9]. The purpose of the present study* was to analyze our five years' experience in infrarenal aortic aneurysm treatment, based on a systematic and exclusive use of IVUS for the endoprosthetic repair.

Patients and methods

Database and patient demographics. From February 1998 to August 2002, a consecutive series of 88 patients with an infrarenal aortic aneurysm were treated by our institution. All data regarding each patient, procedure, and follow-up were entered in a computerized vascular registry. Endovascular repair was offered the patients liberally, provided their aneurysm

* By kind permission of the Editor (European Journal of Cardio-thoracic Surgery & Interactive Cardio Vascular and Thoracic Surgery 2005; in press)

Table 1. Patient characteristics

	Number (n = 88)	Percentage [%]
Demographics		
Male gender	82	93
Average age [years]	70 ± 7	
Comorbidities		
Hypertension	48	55
COPD	45	51
Previous PTCA or CABG	35	40
Peripheral vascular disease	21	24
Renal insufficiency[a]	15	17
Diabetes	11	13
Stroke or TIA	9	10
Multiple abdominal surgery	8	9
Coronary artery disease	7	8
End stage renal disease	6	7
Liver cirrhosis/polycystosis	5	6
Previous lung resection	3	3

COPD, chronic obstructive pulmonary disease; *PTCA,* percutaneous transluminal angioplasty; *CABG,* coronary artery bypass grafting; *TIA,* transient ischemic attack.
[a] renal insufficiency defined as creatinine > 105 mmol/l

morphology was suitable. Therefore both low and high-risk patients were included. Many of them had concomitant medical conditions that rendered conventional open surgical repair most riskful (Table 1).

Endoprostheses. Early (first and second) and late-generation devices of the Talent (Medtronic World Medical, Sunrise, Fla) and Excluder (Excluder™, WL Gore and Associates, Flagstaff, Ariz) endoprostheses were used according to their availability and the morphological characteristics of the aneurysm. In the beginning the Zenith (Cook, Inc., Bloomington, Ind), Vanguard (Boston Scientific, Oakland, NJ) and Stenway (Stenford Groupe Valendos S.A., Nanterre, France) endoprostheses were occasionally used, but the latter have meanwhile been taken off the market.

Preoperative investigation. Preoperative assessment included standard contrast arteriography with a calibrated catheter and a helical-computed tomographic scan, with intravenous contrast and images acquired at 3-mm intervals. Coil embolization of an internal iliac artery in the presence of an aortoiliac aneurysm or dilation of a stenotic iliac artery were preferentially performed at the time of calibrated arteriography, prior to aneurysm exclusion.

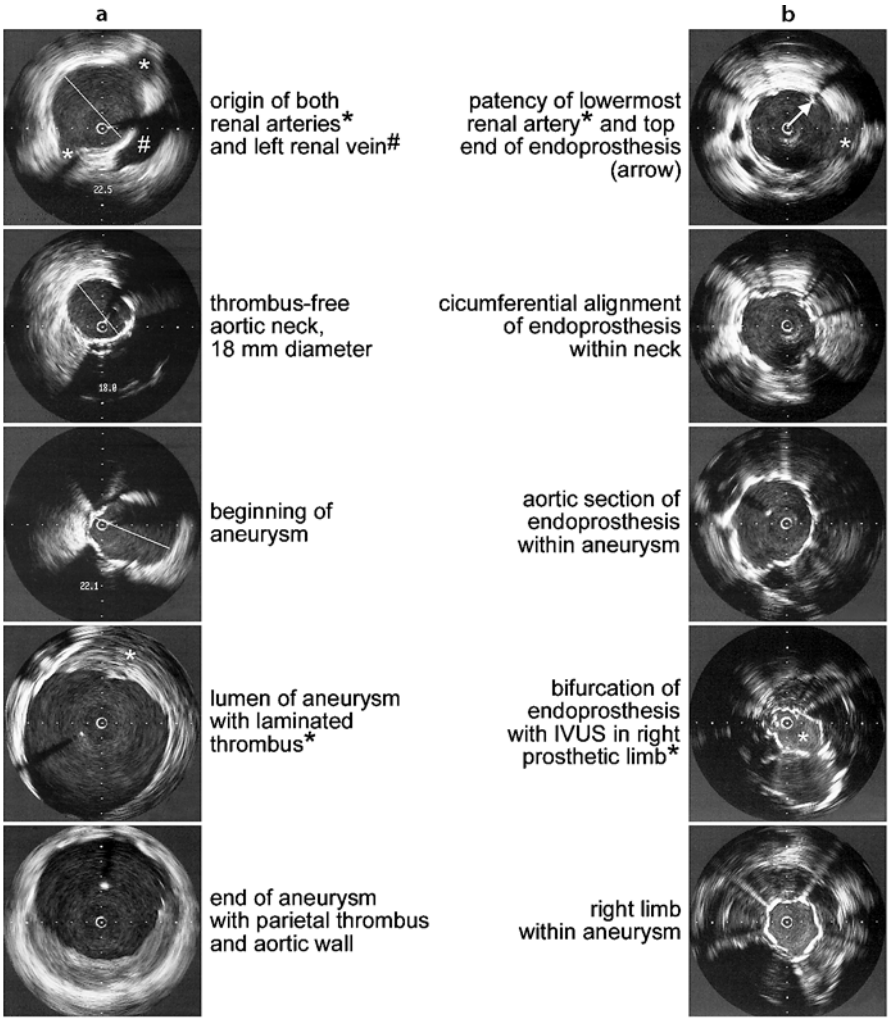

Fig. 1. a Manual pullback by IVUS starting with the left renal vein. **b** Quality control demonstrating device expansion, alignment and patency of major branches

IVUS-based aneurysm repair. Basically our team consisted basically of a surgeon performing the intervention and operating also the IVUS machine and the fluoroscopy, an assisting surgeon, and a technical nurse. All procedures were carried out in the operating room under general anesthesia in most of the patients, and local or epidural anesthesia in high-risk patients. They were prepared as for open surgery. The repair was routinely performed by two surgeons, one of them operating also the IVUS machine. Both common femoral arteries were exposed, and an 8 F introducer (Introducerkit, Boston Scientific, Meditech, Watertown, MA) was inserted. A 6 F,

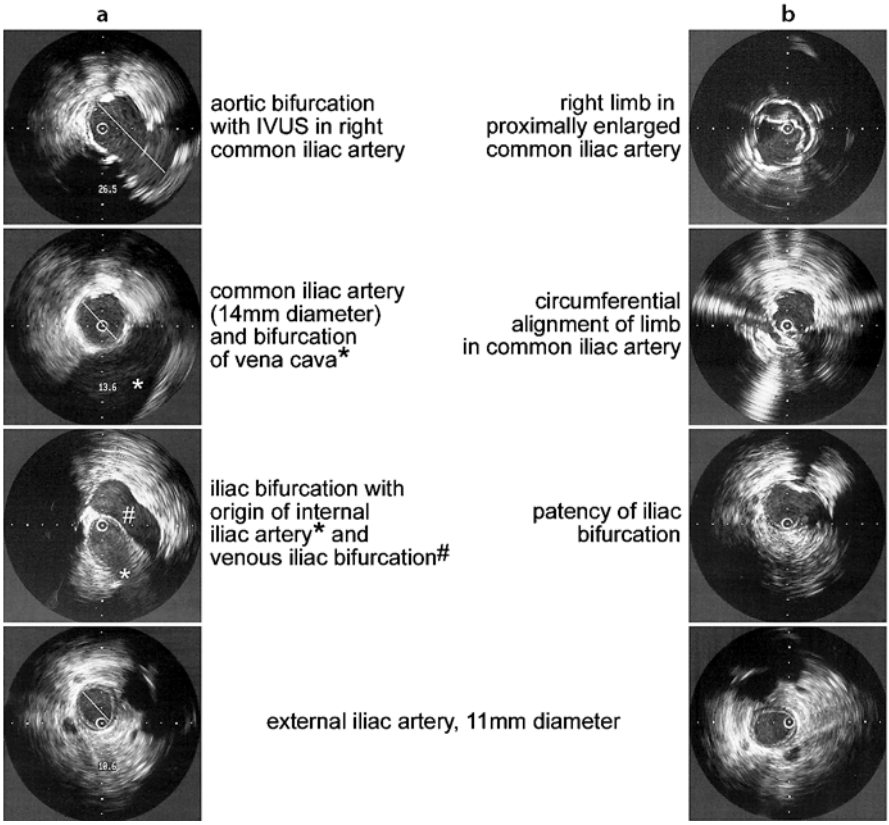

Fig. 1 (continued)

12.5 MHz probe of an intravascular ultrasound (Sonicath Ultra 6, 12.5 MHz Imaging catheter, Boston Scientific) was advanced in a monorail fashion over a 0.035″ guide wire. The target site identification process was standardized by a manual pullback of the IVUS probe, starting with the left renal vein (Fig. 1). The renal arteries are expected close and often slightly above the renal vein. The celiac trunk, the superior mesenteric artery, and the most caudal renal artery were identified and the latter was marked by a radiopaque marker on the patient's abdomen under fluoroscopy (Fig. 2). Pullback and fluoroscopy enabled the positioning of a second marker at the distal end of the proximal neck and a third marker at the aortic bifurcation within the fluoroscopic field. This "one fluoro position" was used as the standard technique. In 2001, we started to center the renal arteries in the fluoroscopic field of view in order to minimize parallax error. Following guide wire exchange the endoprosthesis was inserted and systolic blood pressure lowered to 80 mmHg. The device was deployed at the predetermined level under fluoroscopic control (Fig. 2). IVUS was

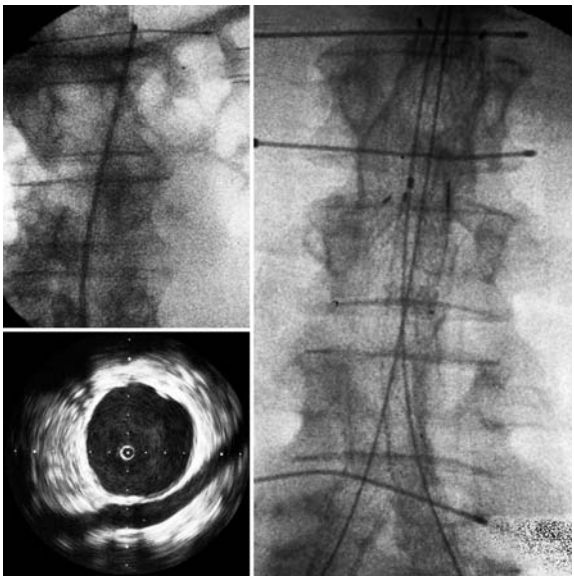

Fig. 2. Identification of left renal vein (*left:* by IVUS and scopy), length of aortic neck, and aortic bifurcation by IVUS and fluoroscopy in a single field of view. Endoprosthesis deployed at the predetermined marker (*right*)

also used to identify the position of the guide wire within the contralateral limb, prior to unloading the prosthetic leg. Finally, complete expansion of the endoprosthesis and patency of the renal and internal iliac arteries were verified by IVUS.

Postoperative monitoring and follow-up examination. The patients were entered into a standard follow-up protocol that included office visits within 1 month of surgery and duplex sonography of the aneurysm during the hospital stay and after 3, 6, and 12 months. Plane radiographs of the abdomen and a contrast enhanced helical CT scan were obtained after twelve months and then yearly. Arteriography was performed selectively on the basis of a persistent endoleak or aneurysm expansion.

Statistical analysis. All data are presented as mean ± SED. Differences between groups were evaluated with a χ^2 test and reported as significant if the p value was less than 0.05.

Results

Patient demographics. There was an average of 2.4 comorbidities per patient that made conventional surgery riskful. Hypertension, coronary artery bypass grafting, or angioplasty, and an obstructive lung disease were the

most common comorbidities (Table 1). Follow-up ranged from 7 to 43 months (34 ± 16 months).

IVUS. All interventions were promptly performed by the surgical team, and the operation of the IVUS machine did not cause any problem. IVUS reliably assessed the length and quality of the aortic neck and visualized clearly the renal arteries, the aneurysm, and the aortic and iliac bifurcation in all cases. Arteriography was not necessary. Technical difficulties with device deployment were noted in 13 cases, including high friction force during retraction of the sheath. As a consequence, a device position, lower than intended, was observed in 12 cases, in one of them the endoprosthesis was anchored within thrombus. One position was too proximal, and IVUS revealed an occlusion of one renal artery orifice. Patency was restored by distal displacing of the device with the help of an inflated balloon. Incomplete aneurysm exclusion owing to a short iliac limb in an aortoiliac aneurysm was detected once by IVUS and subsequently treated with an extension. In five cases IVUS detected incomplete alignment of a prosthetic limb requiring additional balloon dilation. There were no technical difficulties related to the use of IVUS. However, sometimes the delicate probe had to be replaced by a new one.

Mortality and morbidity. 30-day perioperative mortality was at 2% (2/88). Causes of death included congestive heart failure and consumptive coagulopathy. Four perioperative conversions (5%) were necessary owing to an important endoleak that was not amenable to endovascular means. Three tube grafts were associated with a major attachment site endoleak. An

Table 2. In-hospital morbidity

	Complication	No.
Systemic	Congestive heart failure	5
	Renal insufficiency [a]	5
	Arrhythmia	1
	Consumptive coagulopathy	1
	Paraparesis	1
Procedure related	Acute conversion	4
	Limb occlusion	4
	Renal artery occlusion	2
	Graft infection [b]	1
	Atheroembolization	2
Total complications (% of patients with one or more compl.)		26 (22)

[a] dialysis was not required
[b] healed with antibiotics

Table 3. Death, conversion and type I endoleaks in early vs late generation devices

Complication	Early devices	Late devices	*P*
	Patients with endoprosthesis (n = 88)		
Death	2/53	0/35	0.51
Acute conversion	4/53	0/35	0.15
Type I endoleak	22*/53	0/35	< 0.001

* three of twenty two were *distal* attachment site endoleaks related to the use of tube grafts

Table 4. Type and configuration of endoprostheses

	Talent	Excluder	Zenith	Stenway	Vanguard	Total
Bifurcation	40	21	2	7	2	72
Aorto-monoiliac	3					3
Tube	8	3		2		13
Total	51	24	2	9	2	88

endovascular repair with a bifurcated graft failed because of a transgraft (type III) endoleak. The orifice of the contralateral limb was located too close to the aneurysmal wall, thus preventing canulation. Nineteen patients suffered major complications including conversion, with a total 30-day major morbidity of 22% (Table 2). All acute conversions and deaths occurred in the first 53 patients who received early generation devices (NS, Table 3). Minor morbidities consisted of a hematoma, two lymphocele and two groin infections accounting for 6%. Late death unrelated to the aneurysm or its repair occurred in 8 patients (9%) during the follow-up period.

Aneurysm morphology and types of endoprostheses. Maximum aortic diameter ranged from 40 to 83 mm (55 ± 12 mm). The average of the proximal aortic neck was 22 ± 3 mm with a range of 18 to 34 mm and a length of 21 ± 13 mm. 20% (18/88) of the patients had a conical neck with an average increase of 5 ± 2 mm of the distal diameter. Angulation was not systematically measured, but obvious angulation > 60° was considered unfit for endovascular repair. Types and configurations of the endoprostheses are detailed in Table 4.

Endoleaks. Early endoleaks were present in 36% (32/88), including conversions. Duplex sonography, obtained prior to discharge, revealed 18 proximal or distal attachment site endoleaks (type I; 20%), 5 retrograde side-branches (type II; 6%), and 4 graft defects (type III; 5%). *Type I endoleaks:* Tube grafts showed a poor performance with 54% proximal or distal endoleaks (7/13). Endoleaks were significantly associated with early gen-

Table 5. Fate of attachment site endoleaks

	Type I endoleaks		
	proximal	distal	total
Acute conversion	3	1	4
Sealing	1	0	1
Persistence + stable AAA	3	0	3
Rupture	1	0	1
Extension/embolization	7	2	9
Late conversion	4	0	4
Total	**19**	**3**	**22**

eration devices used for the first 53 patients (Table 5). Regarding the fate of these attachment site endoleaks, three persisted in size, with a stable aneurysm diameter. They were not treated by secondary procedures because of their inadequate length or a tortuous configuration of the proximal neck, a stable aneurysm diameter, and major comorbidities. Nine patients required secondary endovascular interventions, including a proximal or distal extension (Fig. 3), or coil embolization in case the endoleak was small. In one of them, a proximal attachment site endoleak persisted de-

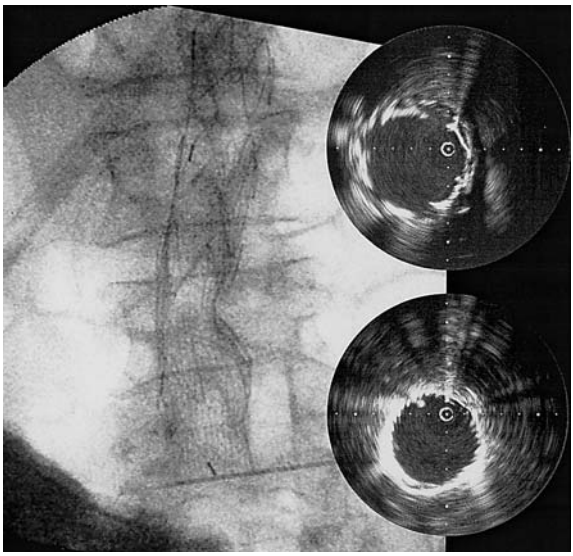

Fig. 3. Treatment of a distal endoleak by an extension. The procedure is performed based on IVUS. After the identification of the aortic bifurcation, an extension is placed as distal as possible and precisely positioned on the bifurcation

spite an extension. One small attachment site endoleak sealed. An increase in aneurysm size or distal migration of the endoprosthesis with subsequent limb occlusion was observed in four patients, requiring late conversion after 24 months. One patient with a proximal endoleak probably died of an aneurysm rupture three months after the procedure. ***Type II endoleaks:*** They showed spontaneous sealing in three of five patients after 12 months, in one of them with aneurysm shrinkage. Coil embolization of a lumbar and inferior mesenteric artery was performed in one of the two remaining patients. In the other patient a small endoleak persisted, associated with a stable diameter of the aneurysm. ***Type III endoleaks:*** One of the four type III endoleaks was due to an incomplete sealing between the contralateral limb and aortic section, and was sealed during follow-up. Three type III endoleaks were a consequence of the impossibility to deliver the contralateral limb. During the procedure or shortly afterwards the respective iliac artery occluded probably owing to damage to the arterial wall following endovascular maneuvers, and these patients received a femoro-femoral bypass. One endoleak was treated by the placement of an occluder device into the prosthetic segment via the left subclavian artery. In the remaining two patients who were exposed to a high risk, the endoleaks persisted with a stable aneurysm diameter.

After one year the total percentage of endoleaks decreased to 10% (9/88) thanks to secondary interventions and spontaneous sealing.

Secondary procedures. Twenty-one out of 88 patients (24%) underwent secondary procedures. Coil embolization or extension for the treatment of endoleaks was performed in nine patients during follow-up. Late conversion was necessary in six patients (7%). Three suffered an enlargement of the aneurysm that became symptomatic. One patient showed distal migration of the endoprosthesis that was proximally anchored within thrombus, however, there was no evolution towards a detectable endoleak or enlarging aneurysm. Migration resulted in occlusion of one prosthetic limb. Two patients with first-generation devices had claudication owing to a kinking of both limbs and disintegration of the prosthetic limbs from the main body part. All patients tolerated surgery well. Four patients (5%) suffered occlusion of one limb during the initial 30 days and 2 patients (2%) during follow-up. Limb occlusion was treated by thrombolysis, stent placement, or thrombectomy in 3 patients, with femoro-femoral bypass in 3 patients, and late conversion in one patient.

Aneurysm size. Aneurysm size was calculated for patients with a follow-up of 12 months or more. A CT scan was available in 51 patients. Maximum aortic diameter decreased by 5 mm or more in 15 patients (29%). Maximum aortic diameter remained unchanged (change < 5 mm) in 33 out of 51 patients (65%). Maximum aneurysm size increased by 5 mm or more in 3 out of 51 patients (6%). Two patients with an aneurysm increase had an endoleak on CT scan. The third patient who was on dialysis showed no

endoleak on CT scan, but the entire thoraco-abdominal aorta which was extensively calcified increased in diameter, and the patient was therefore unfit to undergo any further interventional procedure.

Discussion

The rationale to rely entirely on IVUS for the implantation procedure was the reduction of technical equipment and personnel in order to achieve an easy and quick setup with around-the-clock availability. In a former study we demonstrated the equivalence of IVUS to arteriography in endovascular aneurysm repair [4], and this study supports the feasibility of an exclusively IVUS-based repair without confirmatory or completion arteriography. Based on IVUS, the target site of deployment, including the left renal vein and the adjacent renal artery orifices, was identified in all cases without any difficulties. We also consider IVUS useful in verifying the proper position of the guide wire in the main graft body after canulation of the contralateral limb, as experienced by others [9]. Regarding quality control, IVUS was effective in visualizing incomplete expansion in some endoprostheses due to a 360° cross-sectional view. Arteriography alone, or indirect evaluation of graft stenosis, such as pullback pressure gradient measurements [10], would probably have missed it. In addition, we appreciated the fact as it enabled us to renounce completely contrast dye for the implantation procedure in patients with a known prevalence of 13 to 21% renal failure [11, 12].

A drawback of this IVUS-based strategy is the risk of missing endoleaks and thus their prompt treatment. Indeed, we noted a high rate of early endoleaks, particularly attachment site endoleaks. Although the complication of endoleaks is nowadays reduced to 2–3% in centers of excellence, a meta-analysis of clinical studies demonstrated endovascular aneurysm repair still to be associated with 24% endoleaks, mainly owing to an ineffective proximal or distal fixation [13, 14]. We identified several factors that are responsible for this complication. We noted a significant relation between early generation devices and type I endoleaks. The high friction force during the initial step of deployment in some of these devices resulted in an accidentally low placement in twelve cases predisposing insufficient sealing. Ease in device delivering is a prerequisite to precise positioning and is nowadays granted by the manufacturers. The literature demonstrated better performance of improved devices [14, 15] with a decrease of endoleaks from up to 30% [16] to under 13% [11, 17]. Another reason for type I endoleaks in our study is the “one fluoro position” technique we used in the beginning. The divergence of the X-ray beams is highest at the outskirts of the fluoroscopic screen, resulting in parallax error. Using this technique, the more angulated and rotated the aortic neck is, the lower the endoprosthesis is placed related to the renal arteries. The most accurate device position is

achieved by the technique used by Broeders et al. [18]. They propose centering of the target site of deployment in the fluoroscopic field, and adjusting the C-arm to the angulation of the aortic neck by proximal tilting and left-right rotation. This technique is equally important using aortography as well as IVUS for identification of the target site. IVUS generates cross-section views perpendicular to its probe. In angulated necks the probe often takes an eccentric position, and therefore the C-arm has to be adjusted in order to localize the probe precisely at the level of the renal artery orifices. A further reason for type I endoleaks was our liberal policy regarding endovascular repair during the first years, including high-risk patients with challenging neck configuration. As endovascular surgery was evolving worldwide, hostile neck anatomy was identified as an important risk factor to proximal endoleaks. Short, wide, and markedly angulated necks are burdened with this complication in 36%, and neck angulation exceeding 60° is associated with a 70% risk of adverse events including leakage, acute conversion, and death [19]. One more reason for the endoleak rate in our study was the use of tube grafts in fusiform aneurysms. 54% of aorto-aortic tube grafts were associated with this complication. Endovascular tube grafts were first developed before bifurcated endoprostheses became available. They were given preference because of their ease in handling and implantation. Today they are, however, no longer recommended because of an inherent 26 to 57% risk of attachment site endoleaks [20]. The type III endoleaks in our study deserve a special comment. They were mainly due to the impossibility of implanting the contralateral leg. Although it is not specifically mentioned in the literature, we often experienced the introduction of a guide wire into the second limb as the most demanding and time-consuming step of the intervention.

We noted a low mortality of 2% in our study comparable to other recent studies [11, 15, 21, 22]. The relatively high total morbidity is explained by the presence of various preexistent comorbidities in our patient group and the inclusion of technical complications. Acute lower limb ischemia owing to graft limb occlusion was present in 5%, consistent with the literature [11, 23, 24]. This complication was, however, successfully resolved by lysis and stenting or a femoral crossover bypass. Acute conversions were necessary only in patients receiving early generation devices. Nowadays the risk of acute conversion is indicated with less than 2% in the literature thanks to improved graft designs and a large endovascular experience [11, 21, 22]. Secondary interventions to maintain aneurysm exclusion or graft patency were necessary in one fourth of our patients. Endovascular aneurysm treatment is not considered as durable as standard surgical repair [15], and the literature indicates a need for secondary procedures in 10 to 27%, yet most of these interventions can be performed with a high success rate by endovascular means [15, 25]. Late conversion is kept in reserve for complex graft failure and required only in 2 to 4% [16, 21, 22]. We noted 7% in our study, mostly owing to insufficient proximal fixation with endoleakage and kinking of prosthetic limbs in devices that are no longer on the market.

In conclusion, systematic and exclusive use of IVUS for implantation of endoprostheses is a valid alternative technique, and complications related to the use of IVUS seem to be very rare. The identification of the target site by IVUS is easily made and reliable. Centering and adjusting the fluoroscopic view when localizing the IVUS probe and selection of straight aortic necks with little angulation enhance precise deployment. Early generation devices and tube grafts were mainly responsible for a high rate of attachment site endoleaks in this study.

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3 Endoprosthesis and intravascular ultrasound: The tools for straightforward repair of traumatic aortic rupture

Introduction

Since Klassen's first successful repair of a traumatic rupture of the aorta (TRA) in 1959 [1], a prompt diagnosis and aggressive management by immediate surgical repair is standard practice. Mortality remains high at 12 to 21%, yet paraplegia has been diminished from 19 to 2% thanks to the use of active distal perfusion with partial cardiopulmonary bypass [2–4]. The advent of endovascular technology, however, changed this concept. An endoprosthetic repair with sealing of the aortic disruption is considered more and more a safe, effective and timely treatment option, resulting in a reduction of mortality and morbidity [5–10]. Implantation of the endoprosthesis is preferentially performed by a multidisciplinary team in an angiographic suite, yet with standby of complete cardiopulmonary bypass equipment [7, 9, 11]. The exclusive use of intravascular ultrasound (IVUS) for the endovascular repair, without using arteriography, is a promising tool to simplify the procedure, provide around-the-clock availability, and reduce personnel. We report our experience in the management of TRA with endoprostheses and intravascular ultrasound (IVUS) during the last six years as powerful means for ease and speed in the treatment of this life-threatening condition.

Patients and methods

Between September 1998 and March 2004, a consecutive series of seventeen patients underwent repair of TRA. Data were collected prospectively and analyzed retrospectively. TRA was diagnosed, whenever possible, in the emergency room, using spiral computed tomography (CT). All patients received general anesthesia in the operating room. The cardiovascular surgeon on call performed the procedure. Standard equipment included an IVUS machine (Clearview, Boston Scientific Corp, USA) operated by the

surgeon and a simple image intensifier (Siremobil compact, Siemens, GE). Endoprostheses with a range of sizes were available 'off the shelf' in the operating room. Repair of TRA was given preference, with the exception of other non-aortic life threatening lesions that were treated first during the same anesthesia. With the patient in a supine position, one femoral artery was canulated in a standard fashion following low-dose heparinization (100 U/kg body weight). A left anterior oblique view was used to expose the aortic arch. The IVUS probe was inserted over a guide wire and a manual pullback was performed. The origin of the left subclavian artery and the proximal and distal extent of the aortic disruption were marked on the patient's thorax by a radio opaque marker (Fig. 1). The endoprosthesis was inserted over a superstiff guide wire and positioned at the appropriate level. Just before deployment hypotension was induced (systolic arterial pressure approximately 50 mmHg) either by an inflow occlusion maneuver as previously published [12], or vasodilative drugs. The origin of the left subclavian artery was routinely overstented by the non-covered part of the endoprosthesis. Subsequently, expansion and correct position of the endoprosthesis was confirmed by IVUS. During hospital stay a contrast enhanced computed tomography (CT) was performed to prove sealing of the aortic tear (Fig. 2).

Results

All patients suffered a rapid deceleration trauma. Two patients were paraplegic on arrival in the emergency room (Table 1). In three patients immediate laparotomy was required because of abdominal bleeding. Emergent endovascular repair was performed in ten patients, followed immediately by another operation in eight of them. In the first six patients of this series, the diagnosis of TRA was made during hospital stay (Table 2).

Duration of endovascular repair was 98 ± 35 min and fluoroscopy 7.7 ± 5.6 min. Blood loss accounted for 467 ± 452 ml. IVUS visualized the lesion and the origin of the left subclavian artery in all patients. The aortic tear was often extensive, with a contained pseudoaneurysm. One patient had a circumferential wall disruption causing pseudocoarctation with absence of femoral pulses. The mean distance between the ostium of the left subclavian artery and the aortic disruption was short at 13 mm, this segment of preserved aorta was, however, sufficient to provide anchorage of the device and sealing of the tear. One third of the patients had an associated short dissection towards distal starting from the lesion (Table 3). One early generation endoprosthesis could not be deployed, requiring reloading within a larger sheath. Discrete device misplacement occurred in three cases. In two of them IVUS visualized partial occlusion of the left common carotid artery by the endoprosthesis that could be successfully

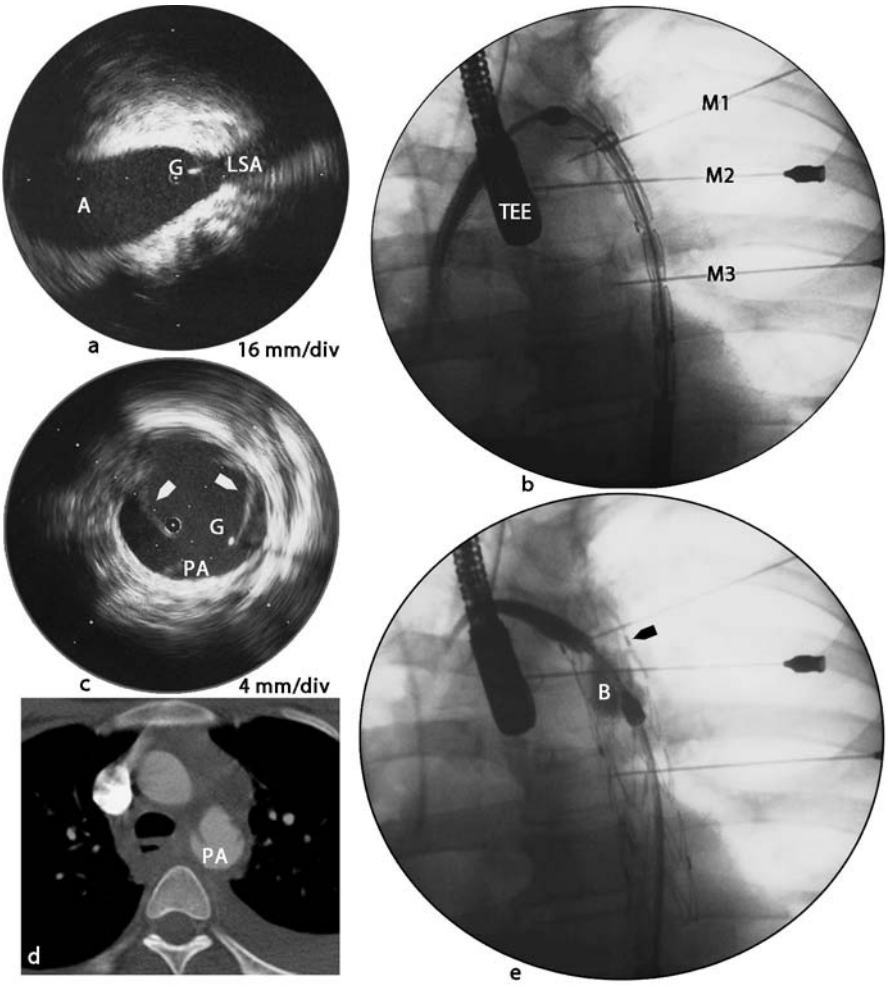

Fig. 1. Technique of endovascular repair. **a** IVUS is within the aortic arch (A). The ostium of the left subclavian artery (LSA) is identified. **b** The ostium is localized by a marker (M1) under fluoroscopy. **c** Manual pullback of IVUS visualizes the aortic disruption (*arrows*) and the pseudoaneurysm (PA). **d** The image of IVUS corresponds to the preoperative CT scan. **b** The proximal (M2) and distal (M3) extent of the aortic disruption is marked under fluoroscopy. The endoprosthesis is positioned with the proximal covering at the level of the subclavian artery. The bare springs are released by retraction of the sheath. **d** The endoprosthesis is deployed with the marker (arrow) just beneath the subclavian ostium. Inflation of the balloon (B) further expands the endoprosthesis. TEE, transoesophageal echographic probe; G guide wire

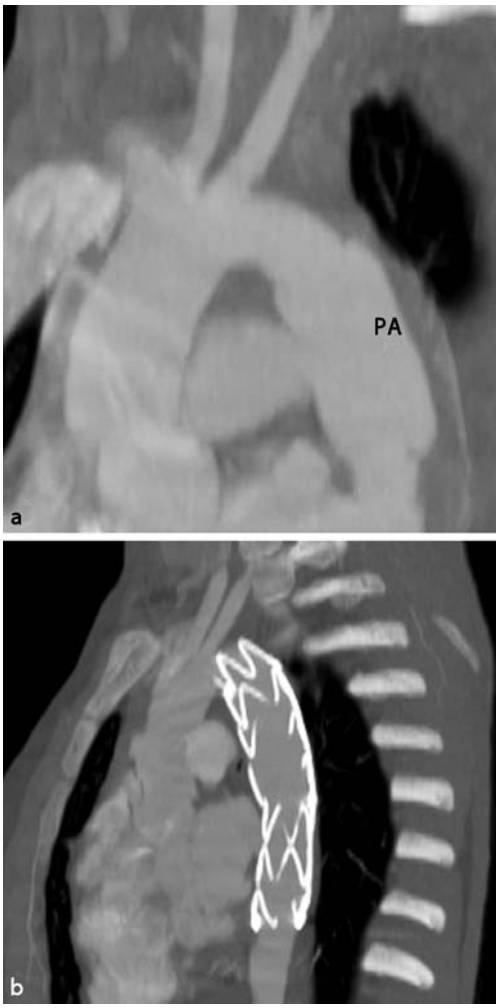

Fig. 2. Reconstruction by CT angiography demonstrates an aortic disruption with a pseudoaneurysm (PA) and **b** sealing of the lesion by an endoprosthesis. There is no contrast extravasation

displaced by an inflated balloon. Incomplete covering of an aortic tear required a proximal extension in the third patient. Accurate placement was achieved by the covering located just beneath the subclavian ostium. A small caliber femoral artery was reconstructed in two patients, in one of them the device had to be inserted via external iliac artery (Table 4).

Postoperatively there was no new onset of paraplegia. One serious complication related to the endovascular repair was noted. A patient, in whom the endoprosthesis required distal displacement, suffered a right-sided hemiparesis probably owing to manipulations within the aortic arch with subsequent embolization into the left carotid artery. She recovered with minimal sequels during hospital stay. There were no complications related

Table 1. Patient characteristics

	Number (n = 17)	percentage [%]
Male gender	10	59
Age [years]	38±20	
ASA [a]		
-II	5	30
-III	6	35
-IV	6	35
Cause of injury		
– motor vehicle accident	13	76
– fall from height	4	24
Paraplegia at admission [b]	2	12
Intraabdominal bleeding	4	24

[a] ASA, American Society of Anesthesiologists; [b] associated with spine injury

Table 2. Priority of operations

	Emergent	Delayed 11 ± 14 days (range 1–42)
Repair of TRA (n = 17)	*10*	*7*
– exclusive	2	7
– plus fracture stabilization	5	
– plus embolization [a]	3	
Surgery for bleeding of spleen/liver/lung	*3*	*1*

[a] of spleen/liver/kidney

Table 3. Aortic dimensions and lesion characteristics

Aorta	Dimension [mm]
proximal diameter	24±5
distal diameter	23±4
distance LSA – lesion	13±8
Disruption	**Number [%]**
circumference $< 180^\circ$	6 (35)
circumference $\geq 180^\circ$	11 (65)
associated dissection [a]	5 (29)

Values are mean ± SD. *LSA*, left subclavian artery; [a] distal to disruption, length 27±11 mm

Table 4. Procedural details

Endoprosthesis		Dimension [mm]
proximal diameter		27 ± 3
distal diameter		27 ± 3
total length		117 ± 19
Technical complications	**Number**	**Treatment**
laceration of CFA	2	vein patch
iliac artery stenosis	1	balloon dilation
sheath not retractable	1	reloading in larger sheath
deployment to proximal	2	displacement by balloon
deployment to distal	1	proximal extension

CFA, common femoral artery

to the access site. All patients had well palpable and symmetrical radial pulses. Enhanced CT confirmed sealing of the aortic disruption in all cases. At discharge or transfer the condition of some patients was impaired by the sequels of their serious non-aortic lesions.

Discussion

Endovascular repair of TRA promises to be straightforward, effective, and safe, and some of its aspects compare distinctly favorably to open aortic surgery, contributing probably to a reduced mortality. Endovascular repair is performed in a supine position. This is advantageous for patients with instable spine fractures, whereas in open surgery the patient has to be turned to the right side to perform a left thoracotomy. Vascular exposure is limited to the femoral vessels, resulting in a short operating time. Thoracotomy and single-lung ventilation are avoided in patients frequently presenting pulmonary contusions. Minimal doses of heparin are sufficient, whereas in open aortic repair high-dose heparinization is required for partial cardiopulmonary bypass and aortic cross clamping, although heparin-coated circuits can be used. Full systemic heparinization in these multiple-injured patients was associated with a mortality of 18%, probably secondary to impairment of cerebral injuries and pulmonary hemorrhage [4], whereas mortality was 12% in patients without or low heparinization [2, 4]. Actually the endovascular series of TRA are small, consisting of nine to twelve patients [6, 7, 9, 10] or representing case reports [5, 13–15]. However, there were only two deaths (4%) in a total of 48 patients.

The risk of paraplegia in open surgery of TRA is related directly to both the duration of aortic cross-clamping, in particular when exceeding 30 minutes, and the surgical technique used [4]. Excellent results with only 2% paraplegia have been achieved by the use of a partial cardiopulmonary bypass [3, 4]. So far, no incidence of paraplegia has been reported with the limited endovascular experience in the repair of TRA [5–7, 9, 10, 13–15]. There is no need for cross clamping with this technique. Aortic flow is interrupted only during deployment when the endoprosthesis is partially expanded following a period of induced systemic hypotension. Other drawbacks of aortic cross-clamping are equally avoided in endovascular surgery, namely decreased end-organ perfusion to the spinal cord, abdominal organs, and lower extremities, proximal hypertension with increased intracranial pressure, and the physiologic derangement associated with the use of a cardiopulmonary bypass, as well as minor complications such as Horner syndrome and left vocal cord paralysis related to the site of clamping.

7 to 21% of patients with TRA arriving at the hospital die from aortic exsanguinations or other serious lesions before reaching the operating room [4, 16]. However, the majority of the initial survivors are unlikely to develop free rupture secondary to preservation of the pseudoaneurysm by the parietal pleura and structures of the mediastinum. Therefore the concept of prioritizing injuries and managing the immediately life-threatening ones followed by a delayed, elective repair of TRA, has been proposed [16–18]. Controlled normotension by the use of β-blockers until aortic repair is essential to reduce aortic wall stress, thereby minimizing the risk of free rupture [16]. Endovascular surgery attenuates the issue of the optimal timing because of its minimal invasiveness and short operating time. Nevertheless, it was our policy to perform the procedure on an emergency base (including aortic repair immediately before or after another major operation) or as soon as the diagnosis was established.

The use of IVUS in endovascular repair of TRA has distinct advantages. Most of these multiple-injured patients arrive after regular office hours when it becomes increasingly difficult to organize a joint intervention of different specialists promptly. Delay is minimal with a competent endovascular surgeon on call providing the technical equipment and a range of endoprostheses. The IVUS machine is mobile, readily transferable to the operation room where the patient is being prepared, has a sterile handle, and is operated by the surgeon. Based on precise instant measurements of the aortic dimensions [19], the appropriate endoprosthesis is selected. Characterization of the lesion by IVUS is accurate and includes both the transverse and longitudinal extension of the aortic tear. IVUS identified an associated longitudinal dissection in one third of our patients, probably escaping from standard intraoperative arteriography. The extent of the dissection has an effect on the selection of the device length. Therefore repair by short aortic cuffs [5] (35 mm) without IVUS interrogation of the lesion is probably not always appropriate. IVUS as a tool for quality control reveals incompletely covered tears that can be instantaneously treated by an

extension. We did not experience difficulties in identifying the ostium of the left subclavian artery by IVUS as the proximal target of deployment. The aortic segment between left subclavian ostium and aortic lesion is usually short at 10 to 15 mm [20, 21], and sometimes even less than 10 mm. This aortic neck is crucial with regard to anchorage of the endoprosthesis and sealing of the disruption. In order to improve fixation, endoprostheses are equipped with bare springs proximally (uncovered metallic struts) which are placed over the subclavian orifice. IVUS eliminates the need for left brachial artery catheterization recommended for marking off the left subclavian artery ostium [10, 11, 22] and also reduces the consecutive risk of brachial artery thrombosis [7, 9].

Three major complications specific to the endovascular treatment have been reported. Incomplete sealing can be fatal if it remains unrecognized during the procedure, and was responsible for one death in the reported series [10]. Cerebral embolization secondary to manipulations within the aortic arch was the cause of a stroke in our series, and has been reported in the literature, too [7]. Patients with TRA are mostly quite younger and their arterial system is healthy with a lower risk of embolization than in elderly patients. Compression of the left mainstem bronchus with subsequent atelectasis owing to expansion of the pseudoaneurysm has been reported in three cases [6, 9, 13]. This complication has been successfully resolved by transient bronchial stenting. It is not clear why these pseudoaneurysms rapidly grew after exclusion without a visible endoleak. Occlusion of the left subclavian artery, either accidentally or intentionally by covering the subclavian ostium, required for a very short aortic neck, is well tolerated in 79% [23]. Exceptionally transposition of the subclavian artery is necessary later for left arm claudication [23].

Postoperative control by CT was encouraging and demonstrated sealing of the aortic disruption in all patients with partial resolution of the pseudoaneurysm. Reliable anchorage and durable mid-term results can be expected since the endoprosthesis is anchored in healthy aorta; however, this remains to be determined.

This study supports the impression that excellent initial results are obtained by an endovascular repair of TRA. It is probably justified to consider it as a treatment of choice. IVUS is a useful tool to accomplish the procedure quickly and safely. It provides the surgeon with a precise morphology of the aortic disruption.

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4 Partial inflow occlusion facilitates accurate deployment of thoracic aortic endografts

Introduction

Endovascular treatment of thoracic aortic lesions showed to be beneficial for patients thanks to its minimal invasiveness and low morbidity [1–3]. Though the procedure is straightforward and promptly accomplished, there are some technical challenges. The strong propulsive forces of aortic flow at the thoracic level can interfere with the deployment of the device. In particular, distal displacement is imminent in the presence of a windsock phenomenon created by delayed retraction of the sheath, or by inflation of a large occluding balloon to achieve complete device expansion. Improvement in endoprosthetic equipment and creation of a period of controlled hypotension address this problem. Nowadays hypotension is mainly accomplished pharmacologically; however, the required dose of drug varies considerably, and the duration of hypotension is limited and cannot immediately be prolonged in case of a technical problem. Cardiac preload reduction by balloon occlusion of the vena cava has been proposed as an effective means to lower blood pressure [4, 5]. In the present study* [6] partial inflow occlusion by interruption of the venous return through the inferior vena cava (IVC) was used as an adjunct to enhance precision in the placement of thoracic endoprostheses.

Patients and methods

From April 1998 to February 2002, twenty-one endovascular procedures in twenty patients (15 men; mean age 60 ± 18 years) were performed. All endoprostheses were deployed using partial inflow occlusion. Written informed consent was obtained from the patients.

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Two different first- and second-generation endoprostheses were used. Fourteen patients were treated with eighteen Talent stent-graft systems (Medtronic AVE, Sunrise, Fla), a self-expandable device with a retractable sheath. A balloon catheter can be used to complete graft apposition to the aortic neck. Six patients were treated with six Excluder tubular aortic graft systems (Gore, Flagstaff, Ariz). Deployment is accomplished by a pull-wire releasing a sleeve, and graft expansion starts in the middle and extends quickly towards both ends. A trilobed aortic balloon expands the graft without occluding the aorta completely.

The procedure was carried out in the operating room with the patient in general anesthesia and in dorsal position on an angiographic table. Systemic pressure was monitored by a right radial catheter. The common femoral artery and the ipsilateral vein were exposed for introduction of the endoprosthesis and the venous occlusion balloon catheter, respectively. Intravascular ultrasound scanning (IVUS), transoesophageal echocardiography (TEE), and fluoroscopy were used to determine the extent of the diseased aorta and the proximal landing zone accurately.

A purse string suture was placed onto the femoral vein surface. After heparinization, a large 8 F Fogarty occlusion catheter (balloon 43 ml [Edwards, Irvine, CA, USA]) was inserted into the vein through a small incision, slightly inflated and advanced into the right atrium under TEE guidance. Then the endovascular graft was inserted into the femoral artery and positioned at the level of the aortic lesion (Fig. 1). The balloon of the occlusion catheter was fully inflated with 50 ml diluted contrast dye under

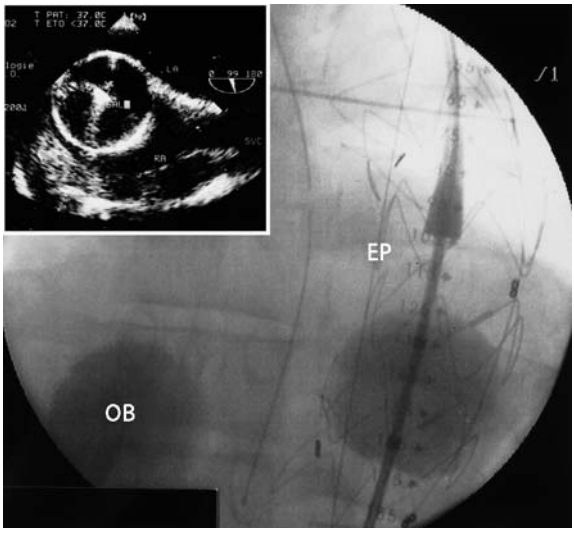

Fig. 1. Fluoroscopic image with the occlusion balloon (OB) in atrial position and the endoprosthesis (*EP*) expanded by the balloon of the stent-graft system. Inset shows the echocardiographic image of the occlusion balloon in the right atrium (RA) and the superior vena cava

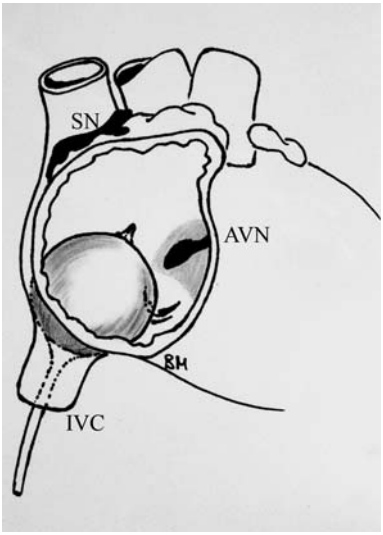

Fig. 2. Schematic drawing showing the position of the balloon in the right atrium. Traction on the catheter completely blocks the venous return through the inferior vena cava (IVC). The sinus (SN) and atrioventricular node (AVN) are distant to the balloon, and therefore the risk of arrhythmia becomes unlikely

TEE control, and the orifice of the IVC was occluded by applying traction on the catheter (Fig. 2). Release or increase of traction adjusted systolic blood pressure promptly between 40 to 50 mmHg while the endoprosthesis was deployed. Then the balloon was progressively deflated to avoid an abrupt increase in cardiac preload. The endoprosthesis was interrogated with IVUS to verify complete expansion. Thereafter the balloon was removed and the venous incision closed by tightening the purse string suture. Alignment of the proximal end of the endoprosthesis with the radiopaque marker on the fluoroscopic image confirmed precise device position at the target site. TEE was used to demonstrate the absence of aneurysm pulsatility and flow within the aneurysm.

Results

Twenty-one interventions were performed for thoracic aortic lesions, including nine aneurysms and pseudoaneurysms, six isthmic ruptures, three dissections, two fistulas and an endoleak after aneurysm exclusion. A total of nine patients (45%) had a cardiac history including atrial fibrillation (two patients) and coronary artery disease (five patients), three of whom having previous aorto-coronary bypass grafting. Two patients had a myocardial contusion with a moderately reduced ejection fraction following traumatic rupture of the aortic isthmus. The mean ejection fraction measured during preoperative work-up was $54 \pm 13\%$.

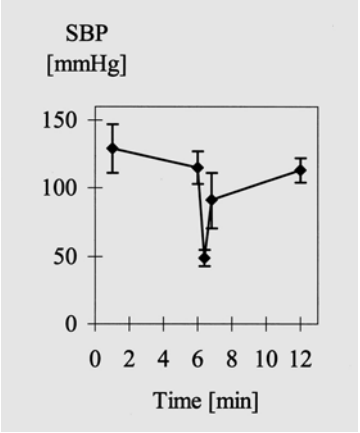

Fig. 3. Mean systolic pressure during partial inflow occlusion in twenty-one procedures. Partial inflow occlusion establishes a short period of hypotension ($p<0.001$), followed by a return to almost normal blood pressure

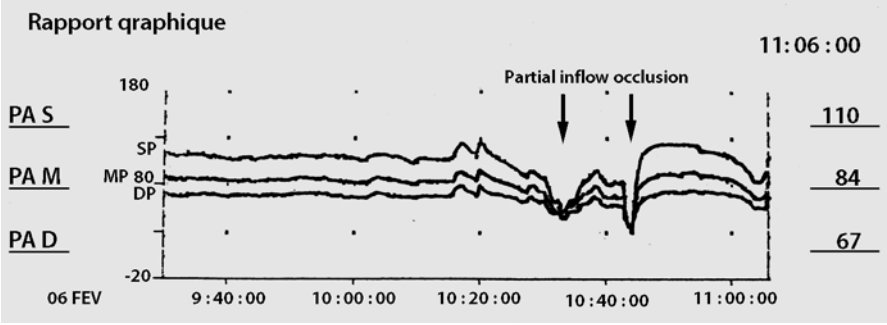

Fig. 4. Pressure wave forms including systolic (SP), mean (MP), and diastolic pressure (DP), recorded during anesthesia for repair of a thoracic aneurysm by two endoprostheses. Partial inflow occlusion (*arrows*) reduces the systolic pressure and, more importantly, the pulse pressure as a consequence of transient low ejection fraction

Partial inflow occlusion was effective to reduce systolic blood pressure from 129 ± 18 to 49 ± 6 mmHg in all procedures ($p < 0.001$, Fig. 3). The decline in pulse pressure (difference between systolic and diastolic pressure) with subsequent reduction in aortic flow during partial inflow occlusion is well demonstrated by the pressure wave form recordings during an endovascular repair (Fig. 4). The maneuver of partial inflow occlusion usually took less than one minute (52 ± 14 s). Seven patients required moderate doses of dopamine (100–200/µg/min) or ephedrine ($1–2 \times 5$ mg) post-deployment. One balloon ruptured within the atrium, yet the device was already deployed. Post-deployment cardiac evaluation by TEE revealed a function comparable to pre-occlusion state. No arrhythmias or ST-segment depressions were encountered. There were no complications related to the venous access site.

In all patients the endoprostheses were precisely deployed at the target site and no dislocation occurred. However, in one patient with an aneurysm, the device was too short, covering the aortic lesion incompletely, and a proximal and distal endoleak were present. These were successfully treated by two extensions during a second intervention. Postoperative complications related to the endovascular repair were as following: One patient who received an endoprosthesis for a suture aneurysm of the distal thoracic aorta showed a transient paraparesis. He also had a deep venous thrombosis in the leg opposite to the venous access site and subsequently suffered from pulmonary embolism. Another patient with an acute type B dissection had a stroke following a parieto-occipital infarction.

Discussion

Controlled hypotension during deployment of thoracic endoprostheses is most commonly achieved by pharmacological means including adenosine [7–9], nitroprusside, and β-blockers [10, 11], or nitroglycerin [8], with good results. However, the drawbacks of drug-induced hypotension are a wide variability of the required dose, tolerance, and inability to prolong the hypotensive period immediately in case of any technical difficulties in the deployment of the device. These shortcomings force the surgeon to wait initially and haste during the most critical moment of the procedure.

In search of a better control over the hypotensive period, cardiac preload reduction has been proposed [4, 5]. Partial blockage of the venous return was achieved by the positioning of a balloon within the IVC near the right atrium [4]. We positioned an occlusion balloon in the right atrium. TEE localizes the balloon easily and reliably in the atrium adjacent to the coronary sinus. Following complete inflation of the balloon in its atrial position, slight traction on the catheter is applied to occlude the orifice of the IVC completely, including blockage of the entire venous return through the hepatic veins. Partial inflow occlusion with a balloon in the right atrium is superior to cava occlusion, whereas it is never clear how many hepatic veins are blocked. Complete venous blockage has been proposed, too, and was accomplished by two balloons, one in the inferior and another in the superior vena cava [5]. We consider interruption of flow through the superior vena cava unnecessary because IVC interruption alone accounts for approximately two thirds of the total venous return to the heart. In addition, occlusion of the superior vena cava reduces the cerebral arterio-venous pressure gradient, resulting in diminished perfusion of the brain.

The major advantage of partial inflow occlusion is the precise control over the duration and extent of the hypotensive period, literally enabling the use of “controlled hypotension”. Endoprostheses are usually deployed within 30 seconds [7]. We demonstrated that partial inflow occlusion pro-

vided a sufficient duration of hypotension. The maneuverability of this technique is helpful in avoiding haste during device deployment, and hypotension can be prolonged if required in order to overcome technical problems. On the contrary, this option is not possible with adenosine, the most widely used drug to achieve temporary asystole for deployment. Adenosine which induces an atrioventricular block has a maximal duration of 20 to 30 seconds until breakthrough ventricular escape beats start to re-establish aortic flow, eventually hampering deployment. The maneuverability of partial inflow occlusion based on its mechanical manner of working allows for quick establishment of hypotension and prompt restoration of normotension. Sometimes, vasodilators might be necessary to intensify hypotension and moderate doses of inotropes or vasoconstrictors might be helpful to re-establish normal blood pressure. The extent of controlled hypotension achieved in this study is considerable at a mean systolic pressure of 50 mmHg. Yet the decrease in stroke volume is the cornerstone for precise device positioning. The direct consequence of a diminished stroke volume is a reduction of aortic flow and its propulsive forces. On the contrary, controlled hypotension induced by vasodilators usually provides a moderate systolic pressure between 60 and 80 mmHg [1, 2, 12], and the cardiac output can even be augmented. We are therefore convinced that partial inflow occlusion with concomitant flow reduction is superior to drug-induced pressure reduction.

Partial inflow occlusion can be safely applied to patients with ischemic heart disease because myocardial oxygen demand is not increased during a short period of hypotension, thanks to an important preload reduction. Accordingly, we did not observe ST-segment depressions or T-alterations. The balloon in the right atrium is unlikely to induce arrhythmias because its position at the orifice of the IVC is distant from the sinus or AV node and, indeed, we did not observe this complication. Nevertheless, it is advisable to have defibrillation pads and transthoracic pacing ready which makes part of the standard equipment in a cardiovascular unit. The risk of cardiac complications is present through the use of adenosine, too. Although adenosine is considered safe, it can precipitate atrial fibrillation in 12% [13]. The systematic use of adenosine in endovascular aneurysm repair carries a 9% risk of cardiac events, requiring activation of a temporary pacemaker in 4% in order to treat a prolonged asystolic response [7].

There is a growing tendency for aortic endoprostheses to be used in the repair of the aortic arch [14] or ascending aorta [15] where a precise and effective control of hypotension is indispensable to avoid the potentially fatal consequences of a misplacement. The relevance of the partial inflow occlusion technique is related to the fact that the closer the proximal landing zone of the device is located to the heart, the more important it becomes to reduce aortic flow.

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Future perspectives

Vascular surgery will change dramatically over the next decades. New technology will revolutionize the way we visualize the blood vessels. Diagnostic methods will be noninvasive with three-dimensional imaging of the entire vascular system, replacing conventional arteriography, as patients will demand less invasive methods for both diagnostic evaluation and therapy.

Today endovascular aneurysm repair is a valuable and highly beneficial treatment in the presence of a suitable morphology. Yet anchorage of the device within the aorta has to be extended beyond a friction force-based concept and include also a biological component beside a more sophisticated mechanical fixation. A better and more durable anchorage will allow the repair of aneurysms with a short or even absent neck.

The ultimate goal of endovascular aneurysm treatment is its application in ruptured aneurysms. Patients in hemorrhagic shock will profit tremendously from a straightforward procedure with a minimal trauma load. Thus the mortality may be dramatically reduced. However, for the time being endovascular repair requires precise knowledge of the aneurysm morphology, and even a spiral CT scan is too time-consuming under these circumstances. Intravascular ultrasound for intraoperative seizing and device navigation is probably the ideal tool. Further requirements for the emergency repair are endoprostheses that can adapt themselves to a wide range of neck diameters and aneurysm lengths. There is no doubt that this goal will one day be achieved.

The treatment of both abdominal aortic aneurysms, including visceral branches and aortic arch aneurysms including supraaortic branches, is another future application to endoprostheses. Extensive thoraco-abdominal exposure or deep hypothermia with the use of a cardiopulmonary bypass could be avoided. Branched or fenestrated grafts have already been in use, but their application is extremely time-consuming, complicated, and tricky, and therefore still on an investigational base.

Vascular surgery is developing towards a demanding, highly technology-based specialty offering patients with an aortic pathology a tremendous benefit.

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