Thoracic endovascular stent grafting inhibits aortic growth: an experimental study

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Abstract

Objective: Dilatation of the aorta at the landing zone site may be exaggerated by the radial force of stent grafts potentially limiting long-term results of endovascular therapy. We evaluated growth patterns and morphology of the thoracic aorta in young piglets after thoracic stent-graft placement. Methods: Eight domestic piglets (37 ± 2 kg) had an endovascular stent graft placed in the proximal descending thoracic aorta using retroperitoneal access. At implantation, the stent was oversized by 10%. Aortic size was documented after thoracotomy by intraoperative measurement and angiography. Subsequently the piglets were grown to adult size (181 ± 42 kg). At explantation 6–15 months later, CT scan and surgical evaluation for endoleaks, defined as perigraft flow, was performed. Histopathological assessment of the explanted aorta was performed in stented and non-stented segments and compared to five normal porcine aortas. Results: No endoleak (perigraft flow) or stent migration occurred even in 230 kg pigs. The stent grafts expanded to full size, but there was no further growth in the stented area. The aortic diameter increased significantly by 32 ± 9% 1 cm proximal to the stents (p = 0.0012) and by 45 ± 13% 1 cm distal to the stents (p = 0.0033). The stented area grew less than the proximal (p = 0.0011) and distal aorta (p < 0.0001). In all pigs, the distal aorta was larger than the proximal overstented segment. Histology of the stented aorta showed significant thickening of the intima (p = 0.018) and media (p = 0.006) with neointimal formation and segmental fibrosis of the inner 1/3 of the media with loss of smooth muscle cells and compression of the elastic fibers but normal architecture in the outer 2/3 of the media. Conclusions: Endovascular stent grafting may inhibit growth of the nonatherosclerotic normal aorta and lead to intimal hyperplasia and focal fibrosis in the inner media part adjacent to the stent. Stent-graft interaction with aortic tissue over time is important and should receive more detailed evaluation. Testing this interaction in an animal model of nonatherosclerotic dilative aortic disease could be of great interest.

Keywords: Descending thoracic aorta; Endovascular stent; Porcine aorta; Type 1 endoleak; Marfan syndrome

1. Introduction

The use of endovascular technologies to treat different areas of aortic disease is expanding rapidly and has proven to be effective in preventing aortic aneurysm rupture [1—4]. Early results of endovascular therapy for thoracic aortic disease with the current commercially available devices have been encouraging, but no long-term results are available yet. Results of thoracic endovascular therapy can be limited by late endoleaks due to progressive dilatation of the aorta at the fixation site. Dilatation of the stent landing zone has been shown to compromise late results after endovascular repair of the abdominal and thoracic aortic aneurysms. It carries a high risk of rupture and late endoleak has been shown to be an independent predictor of survival [4,5].

Indications for thoracic stent grafting are being expanded and more young patients with aortic trauma are treated with this modality. We were interested in the long-term interaction between stent grafts and aortic tissue in young developing aortas. Also, in stent grafting for aneurysmal disease the stent fixation zones are preferably in normal aortic segments.

We attempted to create an animal model with growing piglets for late enlargement of the thoracic aortic stent fixation zone leading to late perigraft flow, the equivalent of a type 1 endoleak in aneurysmal disease in our model. Even though experimental findings of healthy growing pig aortas can only be applied to stent fixation zones of patient aortas with great caution, we hypothesized that this could be a suitable animal model to evaluate the influence of stent graft design on the development of proximal perigraft flow, the equivalent of a proximal type 1 endoleak in aneurysmal disease. This...
animal model should allow for later systematic testing and proper selection of new and innovative endovascular and hybrid open surgical stent anchoring methods and could be of invaluable help in developing methods to prevent late endoleaks due to dilatation of the stent landing zone to improve long-term results. This series was therefore intended to serve as a control group using a standard covered stent for later testing of innovative stent-graft anchorage methods.

We implanted iliac limbs of the Anaconda® stent (Vascutek Ltd., Renfrewshire, Scotland), a polyester covered self-expanding nitinol stent, into the proximal descending aorta of young domestic piglets. Then the animals were allowed to grow to full adult size, before evaluation for perigraft flow (endoleaks) and stent migration was undertaken.

We report our findings and the influence of endovascular therapy on thoracic aortic growth patterns and morphology in domestic pigs after endovascular stent-graft placement.

2. Materials and methods

2.1. Study design

This study was approved by the review board for the care of animal subjects of the government executive (Regierungspräsidium, Freiburg, Germany) and was carried out in accordance with the national health guidelines for the use of experimental animals and in compliance with the European convention of animal care for the total duration of the study.

Eight domestic piglets (37 ± 2 kg) had an Anaconda® polyester covered self-expanding nitinol endovascular stent placed in the proximal descending thoracic aorta via retroperitoneal access to the abdominal aorta. The piglets were then allowed to grow to full adult size. Subsequent evaluation for stent migration and endoleaks by CT scanning and open surgery was performed under general anesthesia prior to explantation of the stented aorta for pathological analysis. Pig aortas of five pigs (average weight 100 kg) were collected fresh at the slaughterhouse for morphologic comparison with the eight experimental aortas.

2.2. Perioperative management and anesthesia

The pigs were premedicated with an intramuscular injection of midazolam and ketamine hydrochloride. Anesthesia was induced through an ear-vein with propofol. All piglets received 1 g intravenous (i.v.) cefazeline preoperatively. Pre-emptive analgesia was completed by i.v. injection carprofen prior to surgical intervention.

After endotracheal intubation of the young piglets and tracheostomy at the time of stent explantation in the large adult pigs, anesthesia was maintained using inhalative isoflurane and by an infusion of fentanyl and vecuronium bromide. Physiological respiratory parameters were maintained during mechanical ventilation and maintenance intravenous fluids were administered.

In piglets, the postoperative analgesia was accomplished by an intercostal block with 10 ml of 2% lidocaine at the end of the implant procedure and by a transdermal fentanyl patch applied between the shoulder blades after induction of anesthesia and by oral carprofen given daily for 3 postoperative days.

Starting on the first postoperative day, 100 mg of aspirin per day was given until the explantation of the stent. Close wound observation was performed. At the time of the second surgical procedure, after completion of CT scanning and the intraoperative measurements and testing for endoleaks of the aorta under general anesthesia, the adult pigs were euthanized by an intravenous injection of potassium chloride.

2.3. Intraoperative technique

For stent-graft implantation, the piglets were placed in a lateral position for a left thoracotomy. A strict sterile technique was utilized. A curvilinear retroperitoneal incision was made and the infrarenal aorta was exposed without entering the peritoneal cavity. Then a 6 Fr arterial sheath was placed in the infrarenal aorta using the Seldinger technique and a J-guidewire and a pigtail catheter were advanced into the aortic arch. The retroperitoneal access was selected due to the small femoral vessels in piglets. A lateral thoracotomy incision was carried out and the crossing vein below the aortic arch was ligated. The planned stent placement site was marked with multiple surgical clips and then the external diameter of the aorta was measured at the stent landing zone as well as at predetermined proximal and distal sites with a calliper. Each measurement was repeated five times.

The position of the pigtail catheter was verified with fluoroscopy and an aortography was performed. The diameter of the aortic lumen was determined with a reference needle placed directly next to the aorta in the

Fig. 1. Angiography at implantation of the Anaconda® stent graft. Note the injection needle next to the aorta with a known length used to determine the aortic size.
fluoroscopy field to avoid parallax error (Fig. 1). This allowed positioning of the stent in an aortic segment of an appropriate size. Then, the iliac limb stent graft (Vascutek Ltd., Renfrewshire, Scotland), sized 16 mm \( (n = 7) \) or 17 mm \( (n = 1) \) was advanced over a stiff Amplatz wire and released at the planned site. After a completion angiography, the endovascular instruments and wires were removed and the abdominal aortic stent insertion site was oversewn using a 5-0 prolene suture. The wounds were then closed using PDS and Vicryl sutures (Ethicon Inc., Somerville, NJ, USA), and the skin was closed in an intracutaneous fashion.

2.4. Evaluation of the endovascular stents

Stent explantation was initially performed at a weight of 150 ± 17 kg \( (n = 5) \). As no endoleak could be observed, the remaining pigs were allowed to grow even larger, and were explanted at 230 kg \( (n = 3) \).

At the time of explantation, all pigs were too large to obtain an interpretable angiography. Therefore, a CT scan (Sensation 16 FA, Siemens, Erlangen, Germany) with 170 ml i.v. contrast (Ultravist, Schering, Berlin, Germany) was performed under general anesthesia on all the pigs except the pigs that weighed 230 kg, which were too large for the CT scanning. Aortic dimensions were determined with CT and angiography using OsiriX software for Mac, version 2.7.5. 3D reconstructions were performed with an Aquarius workstation (TeraRecon Inc., San Mateo, California, USA). Surgical evaluation of the stented aorta, documentation of the stent location and size measurements of the external aortic diameter were performed. Then the stents were tested surgically for perigraft blood flow and stent migration (Fig. 2). After systemic heparinization the pigs were euthanized and subsequently the descending thoracic aorta was explanted with the adjacent aortic segments.

2.5. Histological analysis

Histopathological assessment of the explanted aorta was performed. Sections of aortic walls from all pigs were stained with hematoxylin–eosin (H&E), and Van Gieson elastica stains. As the nitinol cannot be cut with a regular microtome, the stent graft was very carefully peeled off the aortic wall prior to fixation. Slides were made from the cross section of the normal aortic wall and the stented aortic wall from all eight pigs. A set of four histologic slides per pig was prepared, two of which were for the normal aortic wall and the other two for the stented aortic wall. Morphometric data were gathered for all specimens. Medial and intimal thicknesses were measured using surface planimetry after obtaining digital images of histological specimens with a light microscope (mod. BX 45, Olympus Corp., Tokyo, Japan). In areas, where the intimal thickness showed a sinusoidal pattern, the thickness was measured at all peaks and valleys on the slide and the mean value was determined (Fig. 3). Intimal fibrosis and presence of granulation tissue were analyzed on H&E stains at original magnification \( \times 20 \) and both \( \times 200 \) and \( \times 400 \).

Medial thickness was measured as the distance between the innermost and outermost elastin layers. For stented tissue sections, the possible presence of media disruption and or compression of media layers were analyzed on Elastic stains both at original magnification \( \times 20 \) and \( \times 100 \).

2.6. Statistical methods

Specific comparisons of morphometric data were performed and aortic diameter and growth rates were compared. The continuous data from these measurements were analyzed using paired and unpaired t-tests and using the Mann–Whitney test for non-normal distributions, as appropriate. All significance tests were two-sided and a \( p \) value of less than 0.05 was considered to indicate statistical significance. Data analysis was performed using Instat 3 software for Mac (GraphPad Software, Inc., San Diego, CA, USA).

3. Results

3.1. Surgical results

All pigs survived the initial operation. Blood loss during the implant procedure was minimal except in one pig, where control of the stent insertion site in the abdominal aorta was associated with significant blood loss. All pigs were extubated...
and recovered well. Reintubation was required in one pig due to insufficient completion of general anesthesia; after 15 min of additional mechanical ventilation it could be extubated safely. There were two minor wound complications due to intense foreign body reaction to the Nr. 1 PDS suture, which was initially used to close the wound at the level of the fascia. Local wound care and removal of the suture fragments led to complete healing of these wounds. This problem was avoided later on by the use of Vicryl sutures.

3.2. Endovascular results and aortic growth

No perigraft flow (endoleak) or stent migration was noted on open surgical evaluation and by the available imaging methods even in the 230 kg pigs. Fig. 2 depicts a typical finding after surgical testing for endoleak. The stents expanded to full size, but surprisingly there was no further aortic growth in the stented area. As determined by direct intraoperative measurement, the aortic diameter increased significantly by 32 ± 9% 1 cm proximal to the stents (p = 0.0012) and by 45 ± 13% 1 cm distal to the stents (p = 0.0033). The aortas had a taper zone of about 2 cm proximal and distal to the stent before they reached full size, which was a 48–68% increase in diameter depending on the animal’s weight, compared to the size at implantation.

Direct surgical measurements and the CT scan dimensions correlated highly with each other. The stented area grew less than the aorta 1 cm proximal (p = 0.0011) and 1 cm distal to the stented area (p < 0.0001). In all pigs, the distal aorta was larger than the proximal overstented segment, as can be seen in Fig. 3.

3.3. Histopathology

There was no morphological difference in the five healthy control aortas compared to the nonstented aortic wall segments in the eight experimental pigs. Histology in the non-stented segment shows that the intimal surface consists of a single layer of flattened endothelial cells and fine elastic laminae, similar to human anatomy [6]. The media, which is relatively thick, consists mainly of elastic tissue and collagen fibers (Fig. 5A and B). The thin layer of the adventitia contains connective tissue with both collagen and elastic fibers. It carries the vasa vasorum, which supply the arterial wall. These findings were identical in the five aortas from the slaughterhouse and in the experimental non-stented aortic segments.

Aortic wall thickness data obtained by histopathological assessment of the stented and non-stented aortic wall of the pigs revealed significant difference in the stented segment of the medial, intimal and total wall thickness, shown in Table 2.

In the stented segments, intimal fibrosis is visible on the external aspects of the stent-graft device and shows a sinusoidal undulating pattern in thickness (Fig. 4). This corresponds to the distance to the nitinol metal stent-struts causing periodic compression of the intima leading to a typical sinusoidal shape of the intimal fibrosis. This neointimal reaction is composed of granulation tissue in the inner layers, foreign body giant cells reaction and neovascularization (Fig. 5C and D).

In the stented segments, medial thickness also increased significantly compared to the non-stented segments. Moreover, in a total of six of the eight pigs, compression of the media in the inner 1/3 is found (Fig. 6A and B), and in four of these there is disruption in the inner 1/3 of the media with loss of smooth muscle cells, fragmentation of elastic fibers, medial and neointima.

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**Table 1**

Comparison of aortic diameters at implantation and explantation

<table>
<thead>
<tr>
<th>Location of measurement</th>
<th>Aortic diameter, implantation</th>
<th>Aortic diameter, explantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Open surgical</td>
<td>Angiographic</td>
</tr>
<tr>
<td>1 cm proximal to landing zone</td>
<td>19.9 ± 0.7</td>
<td>16.7 ± 1.3</td>
</tr>
<tr>
<td>Proximal stent landing zone</td>
<td>18.8 ± 0.7</td>
<td>16.0 ± 0.8</td>
</tr>
<tr>
<td>Distal stent landing zone</td>
<td>18.0 ± 0.5</td>
<td>14.4 ± 1.0</td>
</tr>
<tr>
<td>1 cm distal to the stent</td>
<td>16.4 ± 0.3</td>
<td>13.6 ± 0.9</td>
</tr>
</tbody>
</table>

* Denotes a significant change (p < 0.05) compared to the corresponding implantation value.

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**Table 2**

Aortic wall dimensions

<table>
<thead>
<tr>
<th></th>
<th>Non-stented aorta</th>
<th>Stented aorta</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal architecture</td>
<td>Normal</td>
<td>Intimal fibrosis</td>
<td></td>
</tr>
<tr>
<td>Intimal thickness (μm)</td>
<td>314.29 ± 332.56</td>
<td>1142.86 ± 634.05</td>
<td>0.018</td>
</tr>
<tr>
<td>Medial thickness (μm)</td>
<td>1615.17 ± 167.52</td>
<td>2007.14 ± 151.19</td>
<td>0.006</td>
</tr>
<tr>
<td>Total wall thickness (μm)*</td>
<td>1930 ± 370</td>
<td>3150 ± 660</td>
<td>0.0105</td>
</tr>
<tr>
<td>Adventitia architecture</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

Continuous data are given as mean ± SD.

* Measurement of total wall thickness excludes adventitia but includes neointima.
fibrosis but normal architecture in the outer 2/3 of the media (Fig. 6C and D). All the compression and local disruption observed in the media was limited to localized areas spaced 4—5 mm apart, corresponding to the distance to the nitinol metal stent-struts causing periodic disruption due to local compression of the arterial wall (Fig. 4). No difference in adventitial layer was noted between the two groups.

4. Discussion

4.1. Endoleaks in endovascular therapy

Endovascular stent-graft repair of thoracic aortic disease has emerged as a viable alternative to surgical repair and is now viewed as an innovative, safe treatment method with less morbidity and a shorter hospital stay than open surgery [7]. The incidence of endoleaks for stent grafts in the abdominal aortic position of 15—52% has been significant [8,9], and even though the incidence in the thoracic stent grafts has not been well defined, endoleaks do occur and patients require frequent imaging follow-up.

This experimental study was particularly designed to study the long-term interaction between stent grafts and aortic tissue in young developing aortas and to create an animal model for growth of the thoracic stent landing zone with the anticipation that perigraft flow would result from the growth of the stented aortic wall of normal growing piglets. Such a model would allow in the future to evaluate various stent designs that could prevent landing zone dilatation and late type 1 proximal endoleaks. We did not create an experimental aneurysm at the time of implantation, as we did not intend to study type 2—5 endoleaks, but the development of proximal perigraft flow due to growth of the aorta, the equivalent of a type 1 endoleak at the proximal stent landing zone in a normal sized aorta. However, no endoleaks or stent migration could be observed with this model after full growth of the pigs up to 230 kg. Due to the lack of growth beyond the full stent size of the overstented aortic segment, this animal model is not suited to study growth or dilatation of the stent fixation zone leading to perigraft flow, the equivalent of endoleaks, as it was intended.

4.2. Influence of stent grafts on vascular growth

We made an unique observation, which appears to contradict conventional wisdom, that covered endovascular stents placed inside the aortic lumen of young growing aortas actually inhibit aortic growth. Even after detailed analysis of our data this unexpected finding cannot be fully explained. Little is understood on regulation and physiology of normal large vessel growth. From congenital cardiac experience it appears that augmenting flow in a hypoplastic vessel, such as with a Blalock—Taussig (BT) shunt to a hypoplastic pulmonary artery (PA), can lead to growth of the pulmonary artery to normal dimensions. In addition to flow, a BT shunt also increases the pressure exposure to the vessel wall. It has been suggested, that the presence of pulsatility might have an additional growth effect on normal pulmonary artery development, as the creation of a right-ventricle to PA conduit appears to lead to better PA growth than a conventional, less pulsatile BT shunt [10]. The observed inhibited aortic growth in the stented area could be due to vascular hemodynamics and the change in pressure profile on the arterial wall due to the polyester covered endovascular stent. With placement of a covered endovascular stent and full expansion of the stent, most mechanical forces of the arterial lumen get absorbed by the stent, leading to lower wall stress, less pressure exposure and reduced pulsatility exposure of the aortic wall. Each one of these factors could explain the lack of normal vascular growth observed in this study.

Also, the observed fibrous reaction and scarring of the aortic wall might interfere with normal aortic growth and potentially could play an additive role in the observed blunting of aortic growth.
4.3. Histopathology

Experimental studies have demonstrated that the arterial wall presents with a multifactorial response to mechanical lesions, dominated by intimal hyperplasia [11]. The arterial response occurs mainly in the intimal layer and is characterized by cellular proliferation leading to intimal thickening [12,13]. The morphological characteristics of this neo-formed tissue are consistent with intimal fibrosis. This process has been felt to be more important in small coronary vessels, as it can limit patency rates, than in large arteries.

We found an increase in wall thickness in the intima as well as in the media. Alteration of medial and intimal cell population and inflammation found in this study are comparable with other previous studies and confirm that endovascular stent grafting in a normal aorta leads to fibrosis in the intimal layers and segmental alterations on the inner third of the media. In our study, the implantation of stents in a normal aorta identified significant intimal fibrosis limited to the region where the stent was placed, characterized by presence of granulation tissue in the inner layers, foreign body giant cell reaction and neovascularization, indicating a local inflammatory reaction. This type of tissue reaction is normal to foreign materials with a chronic inflammatory response composed of fibrous scarring and foreign body giant cells.

Most likely, the observed fibrous reaction is a response to a stretch injury at the time of stent implantation by the 10% oversized stent as well as a reaction to chronic mechanical trauma due to the transmission of intravascular pressure of the initially oversized stent graft to the arterial wall in addition to a foreign body reaction. Even if caution must be exercised in interpreting our experimental findings towards human clinical use, the elastic and intimal layer changes observed could contribute to the knowledge of aortic histology after stent-graft deployment procedures in the nonatherosclerotic aorta, i.e. after stent-graft therapy for thoracic aortic rupture. There are few descriptions of aortic morphology after stent-graft therapy [14]. The lack of neointima found in this study was felt to be caused by a sampling error or inadequate preservation of the explanted human specimens.

Other groups made similar experimental findings. Formichi et al. [15] placed stents in the canine thoracic aorta. After 3 months in situ, they found similar findings with some remodeling of the aortic wall with rearrangement of the elastic lamellae adjacent to the nitinol wires, intimal thickening and inflammatory reaction with polymorphonuclear cell invasion. Marin et al. [16] studied 26 polytetrafluoroethylene-based endovascular grafts that had been implanted for 2 weeks to 7 months. In the 3-month-old specimens, they found neointimal formation and a foreign body reaction characterized by the presence of multinucleated giant cells.

In contrast to these findings, Castaneda et al. [17] evaluated morphological changes in atherosclerotic pig aortas implanted with nitinol stents covered with polyester. They did not find significant differences in the thicknesses of the intima and media layers of the proximal and distal segments of the aorta and iliac arteries. It appears, that their observed morphological reaction to the implantation of stents in middle caliber atherosclerotic vessels in a more short term model does not reflect changes observed in a our long-term study in large normal vessels.

4.4. Traumatic aortic rupture

Several small series report a lower mortality in patients treated with stent-graft repair than with conventional surgery, even though the long-term durability of this treatment is unknown [18,19]. We were unable to find any reports describing the morphologic changes of the aortic wall after stent-graft treatment for traumatic rupture. As several reports describe late stent-graft failure after endovascular treatment for aortic rupture necessitating open surgical repair, it would be of great interest to analyze the aortic wall at the time of stent-graft explantation to determine the reaction of the young human aorta to the currently available thoracic aortic stent grafts.

4.5. Nonatherosclerotic dilatation of the aorta

Open surgical management is favored to endovascular repair in nonatherosclerotic aortic aneurysms. In these patients, the long-term complication rate of open surgical interventions is high [20]. Marfan syndrome (MFS) and related connective tissue disorders have been a contraindication for stent-graft repair in all investigational device exemption protocols to date. The use of endovascular stent grafts in MFS patients is limited. It is advised that the stent grafts should be primarily used for preventing focal pseudoaneurysms in patients with an existing aortic graft which can be used for proximal and distal loading zones. Without the existing graft, it is thought that the fixation zones will be prone to dilatation and endoleaks because of an inherited fragility of the aortic wall [21,22]. However there have been reports on small numbers of Marfan patients with aortic dissection where endovascular stent-graft placement has been found to be feasible and technically successful [23,24].

It would be highly interesting to evaluate the influence of endovascular stenting as described in our current study on aortic growth in a previously described bovine model of Marfan syndrome [25,26]. If inhibition of growth should be observed due to fibrosis of the aortic wall, the concept of prophylactic endovascular therapy as a treatment for early stages of aortic dilatation in connective tissue disease could be reassessed. However, the reaction of growing bovine aortas with Marfan syndrome to stent-graft therapy cannot be predicted based on our data.

In summary, we found a profound inhibition of aortic growth in healthy piglets in the stented segment of the descending thoracic aorta with histopathological evidence of fibrosis of the intima and focal scarring of the inner media, which prevented perigraft blood flow and stent migration. Stent-graft interaction with aortic tissue over time is important and should receive more detailed evaluation. Testing this interaction in an animal model of nonatherosclerotic dilative aortic disease could be of great interest.

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References


Appendix A. Conference discussion

Dr M. Turina (Zurich, Switzerland): In my opinion, the results confirm the expectations; that the stent-induced fibrosis limits the growth of the aorta to the diameter of the stent.

Your second observation, the increase of aortic diameter distal to the stent, warrants closer scrutiny. This observation is especially important in the recent era where a large number of patients and even children with coarctation are treated with endovascular stent grafts.

I have three questions for you. First, you might address the problem of stenting in growing children. With the aortic growth being limited to the stent diameter, there should be an age or size limit where the stenting should not be used as it will create an hourglass narrowing of the aorta with proximal and distal dilatation and proximal hypertension.

Second, the author might explain why they did not use the control group of the nonstented healthy animals to observe the aortic dimensions. Is the aortic segment distal to the stent larger than expected, or is it just the normal size of the aorta in this position?

And third, your narrowing in the area of stent causes disturbances in blood flow with some loss of pulsatility and possible endothelial lesions. Did you perform any special histological analysis to detect possible functional changes in the aortic endothelium distal to the stent?

Dr Siegenthaler: In stent grafting for coarctation there are different stents that are being used than in our experiment. In this experiment we used self-expandable covered nitinol stents. The pediatric cardiologists usually use balloon-expandable steel stents that are not covered to treat coarctations.

The advantage of these steel stents is that they are very rigid and they have a wide range of diameters for each stent to which they can be dilated with a balloon. So what the pediatric cardiologists often do, they put in a balloon-expandable stent in a small child, then they wait for some fibrous reaction, and then later they go back and further dilate that same stent.

In terms of the minimum size for a child, when stents should be applied or not, I don’t think I can give you a good answer based on this study.

To your second question, why we had no control group. This experiment was actually set up that the eight pigs were our control group, and we wanted to use different stent designs later on to compare their results to this control group, which was supposed to develop type 1 proximal endoleaks. We used five healthy aortas from the slaughter house for the histological controls.

In terms of aortic size, those aortas did not look aneurysmal like a post-stenotic dilatation at explantation and also in the CAT scans,
there was a nice continuous distal aortic taper. But purely scientifically speaking, we have no control group and we can’t prove for sure that there was no unusual growth of the distal aortic segment based on our study alone.

In terms of functional physiologic endothelial function proximal and distal to the stent, we did not perform any physiologic analysis. We did a very detailed histologic inspection of all specimens, and we compared the slaughter house healthy aortas to the segments that were taken from the aortic wall proximal and distal to the stent, and there really was no difference in wall thickness or architecture. But we don’t know if there could have been a difference in endothelial function.

Dr. A. Haverich (Hannover, Germany): The diameter of the aorta between 37 kg piglets to 230 kg at the end of the experiment was less than 30% in growth. Wouldn’t you think that if you would have started the experiment at the size of 20 kg that would have been the better idea? You could see the changes over time much easier, and you also would have been able to do both angiography and CT scan. I don’t think the weight in kilogram is a good parameter for the size of the aorta.

Dr Siegenthaler: I think that is a very good idea. The problem with the piglets is that their aortas and peripheral vessels are extremely small compared to the total body size. I mean, it’s very unexpected to have a 20 mm aorta for a 230 kg pig.

We have a size limitation in terms of how small we can go because the abdominal aorta in some of those piglets really just barely could fit the endovascular stent introduction system.

So probably we could have gone for five or maybe even 10 kg smaller animals, but at this point, the minimal possible size with a pig model will be reached.

Dr. J. Bachet (Paris, France): A stupid question from the moderator. You wanted to have endoleaks and you didn’t. Couldn’t you make a small hole in some grafts, in a few animals to be sure to get an endoleak and to survey it for 4 months?

Dr Siegenthaler: I am sure you could do something like that, but our goal was really to create a model for a type I endoleak and find methods of how to prevent aortic wall dilatation. That was the goal of the whole study. And interestingly enough, a conventional iliac covered stent already did the trick in preventing aortic growth, which we never expected.

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**Editorial comment**

**Performance of stentgrafts in growing arteries: there is demand for super-adaptable devices**

The long-term impact of implanting stentgrafts on the behavior of growing arteries is still not fully understood. The ability of the aorta in its growing phase to react to and repair injuries induced by an implanted stentgraft makes this a unique and special area of research. Typically, a stented aortic segment containing either a bare stent or a stentgraft will develop stenosis, while the adjacent non-stented aortic segments grow and increase to their normal size and function as demonstrated by Siegenthaler et al. [1]. In clinical settings, stenting of aortic coarctation in adolescents usually requires redilation compensating for growth to avoid stenosis. Currently, the challenge facing stent and stentgraft design is the ability to adapt their geometries to the potentially large increase in the aortic dimensions over time.

In analyzing stentgraft performance in growing arteries, two key factors have to be considered: luminal area and wall thickness. First, the luminal area, and indeed not the diameter itself, is crucial for the aortic function in directly determining flow and should be used as the reference metric. The luminal area in a growing aorta is ultimately determined by the nominal area of the stentgraft minus the area of intimal hyperplasia. Stentgrafts have to be oversized by 10–20% to give sufficient frictional force to prevent migration at implantation. However, moderate oversizing might not be enough to match the ultimate adult aortic dimensions. By studying the performance of highly oversized self-expandable stentgrafts we noticed them compensating for some aortic luminal narrowing, thereby minimizing the effect of intimal hyperplasia [2]. Yet a moderate stenosis of 30–60% of the aortic area persisted. While high oversizing seems beneficial for the long-term performance of stentgrafts, they should have a minimal profile at implantation when constrained in a relatively small aorta. Highly oversized stentgrafts in a growing aorta can have folds of the fabric resulting in a large profile. We noticed that intimal hyperplasia optimizes flow characteristics by filling up folds creating a smooth circular lumen, yet the luminal area becomes smaller increasing the degree of stenosis. We do not yet know if these stentgrafts can fully expand to their nominal area by repeated dilations.

The second factor in the analysis of stentgraft incorporation in the context of growth is aortic wall thickness. While deploying a stentgraft, blood is trapped between the device and the aorta, and the resulting clot becomes embedded with fibroblasts. This layer is commonly referred to as the interface, and can be substantial in the folds of the stentgraft fabric, while practically absent underlying the stent struts, which become embedded into the tunica media by the radial force of the stent itself and pulsation pressure. Within the stented area the thickness of the aortic wall is mainly composed of intimal hyperplasia including the protruding folds of the fabric with consecutive luminal narrowing. This underlines the importance of low profile devices. The fate of the tunica media underlying the device is currently unclear, yet medial thinning has been observed. Since the medial layer varies considerably, only measurements of its area are reliable. However, as long as the stentgraft remains implanted, the thickness of the media may well be irrelevant.

The experimental setting of aortic growth with its high reparative potential towards injury is not comparable to the clinical setting of dilative arteriopathy in adult or elderly individuals, with their minimal capacity for integration of a stentgraft into the aortic wall. In the growing aorta, the interface itself, fixes and seals the device to the aortic wall, and in this context, the term endoleak should be avoided.

The study by Siegenthaler et al. supports the view that as endovascular surgery evolves, the interaction between relatively rigid stentgrafts and growing arteries should be a topic of further research in order to develop highly...