Endovascular stenting of juvenile vessels: consequence of surgical stent removal on vessel architecture

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Congenital heart disease;
Vessel architecture;
Stenosis

Introduction
Intravascular stents are an ideal adjunct for treatment of stenosis not responsive to balloon angioplasty and have been used successfully in pediatric patients with stenosis of the pulmonary artery, stenosis of the great veins, and post-operative stenosis of Fontan anastomosis.1 Re-expansion of stents has been shown to be feasible and safe even up to 3 years after implantation.2,3 However, placement of stents (e.g. in pulmonary arterial lesions and aortic arch stenosis) has limitations in infants and small children due to stent inflexibility, requirement for large sheaths, and concerns about creating fixed obstructions after the placement of small diameter stents in growing patients. Smaller stents with maximal achievable diameters of 9–10 mm therefore commit the patient to future surgery to enlarge the stented area once it has been dilated to its maximal diameter.4 The surgical removal of a stent is an aggressive procedure with possible destruction of the vessel wall.

This study originates from our clinical concern that stent removal could scar the vessel wall to the extent that further growth is limited. The objective of this experimental study was therefore to investigate the effect of stent implantation and later surgical removal on the architecture and therefore growth potential of juvenile vessels.

Methods

Experimental protocol
Institutional ethical committee (Catholic University of Leuven) approval was obtained to perform this study in sheep. Six weaned lambs (6 weeks old) were selected to undergo stent implantation in both the carotid artery and the jugular vein. A power calculation could not be performed as no information is available on incidences of the investigated subject. We therefore selected our sample size according to previous experience: a complete observation set of six animals was considered sufficient to correct for biological variability in a single endpoint, controlled prospective animal trial. The ethical restraints in the use of chronic animal experimentation had to be considered as well (each test takes 6 months).

The mean weight of the animals was 18 ± 2.2 kg. All procedures were performed under general anaesthesia. Anaesthesia was induced with ketamine hydrochloride (15 mg/kg) and maintained with fluanxane. We preferred the jugular vein and carotid artery because of the surgical accessibility and the fact that the untreated side could be used for comparison as control. Between procedures, the animals were returned to the farm and no drugs were administered. The stent implantations were performed through femoral
Access. An angiogram was taken in order to identify the required stent size. The arterial stents were implanted first and the side that was first entered with the catheter was used for stent implantation (therefore leading to a random allocation: four stents left and two stents right). For practical reasons, the same side was taken for the jugular vein to allow the surgeon to retrieve the stents through one surgical incision. A total of six venous and six arterial stents were implanted. Venous stents (6 zig CP stents, Numed, USA, manually cramped on balloon, length 28 mm) were expanded up to 12 mm (range 11–14 mm) and arterial stents (Multi-link premounted coronary stents, Guidant, Santa Clara, USA, length 15–20 mm) were expanded up to 4 or 5 mm. Stent diameter was estimated according to the vessel diameter (angiographically), therefore avoiding ‘oversizing’ of stents.

After 10 weeks (animal weight $43 \pm 6.9 \text{ kg}$), a surgical cut-down was performed at the level of the stent implantation. The animals were heparinized, the vessels clamped, and longitudinally opened. The stents were removed in toto. The longitudinal incisions were closed with a running polypropylene suture. No patch material was used: the vessel opening was closed primary leaving only a single longitudinal surgical scar. After another 10 weeks (animal weight $55 \pm 6.7 \text{ kg}$), angiography was performed and the affected and control sides compared with regard to vessel patency and diameter. Arterial access was obtained femorally and an aortogram performed for measurement of the carotid arteries. Venous angiography was performed via peripheral contrast injections from both ears comparing venous drainage to the treated and untreated jugular veins. Calibration for measurements was done using the angiographic catheter. The animals were subsequently terminated and the vessels dissected proximal and distal to the previously stented area. The complete segments were resected and submitted for histological analysis.

Histological analysis
The segments were transversally cut into 5 mm-thick tissue specimens and from each block a series of 4 $\mu$m sections were prepared in a standard way for histological examination. The samples were stained with haematoxylin–eosin and elastic stains to identify the integrity of the elastic lamina. The internal elastic lamina is generally more pronounced in arteries than in the corresponding veins; therefore, arterial injury was defined as destruction of the internal elastic lamina and venous injury was defined as a discontinuity of the media. The percentage of lumen patency was scored.

Data
Continuous data are presented with their mean value and standard deviation. The non-parametric Wilcoxon signed-rank test was performed (Statistica Software package, Tulsa, USA). A $P < 0.05$ was considered to indicate a significant difference.

Table 1
<table>
<thead>
<tr>
<th>Carotid artery</th>
<th>Control artery diameter (mm) (angiographically)</th>
<th>Treated artery diameter (mm) (angiographically)</th>
<th>Treated artery patency (%) (histologically)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>8</td>
<td>70</td>
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<tr>
<td>2</td>
<td>10</td>
<td>8</td>
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<td>3</td>
<td>11</td>
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<td>4</td>
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<td>6</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>11 (1)</td>
<td>9 (1)</td>
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</tbody>
</table>

Figure 1 (A) Overview of a carotid artery 10 weeks after removal of stent: partial disruption of the internal elastic lamina is observed. Neointima formation results in a reduction of the lumen to 70% of its original size. (Elastic Van Gieson stain ×25). (B) Detail of the same case. Between the media (right upper corner) and the neointima, residual parts of the internal elastic lamina is seen. (haematoxylin–eosin ×200).

Results
Arteries
Table 1 summarizes the vessel diameter (evaluated angiographically) and vessel patency (scored histologically) in comparison with the control side 10 weeks after surgical stent removal. The vessel diameter is slightly smaller than the control side. There is only mild stenosis in two cases (up to 30%). Histological analysis (Figure 1A) illustrates preserved arterial wall architecture. There is no specific injury. The two cases with mild stenosis are due to moderate intima hyperplasia at the level of local injury of the elastic lamina (Figure 1B).

Veins
Table 2 summarizes the vessel diameter (evaluated angiographically) and vessel patency (scored histologically) in comparison with the control side 10 weeks after surgical stent removal. Two veins proved to be completely occluded and two severely stenosed. The overall size of the veins was significantly smaller when compared with the control side ($P = 0.02$). Histological analysis shows a preserved media of the
vein wall in the four non-occluded vessels (Figure 2A). The two occluded vessels proved to contain thrombus. Amazingly, their vessel wall architecture was as well preserved (Figure 2B) as the non-occluded vessels. The lumens of the two severely stenosed vessels were filled with thrombus, but recanalization had occurred, as histologically documented by the presence of newly formed vessel lumens within the occluding thrombus.

### Table 2

<table>
<thead>
<tr>
<th>Jugular Vein</th>
<th>Control vein diameter (mm) (angiographically)</th>
<th>Treated vein diameter (mm) (angiographically)</th>
<th>Treated vein patency (%) (histologically)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2</td>
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<tr>
<td>6</td>
<td>10</td>
<td>8</td>
<td>20</td>
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<tr>
<td>Mean (SD)</td>
<td>14 (5)</td>
<td>8 (8)</td>
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#### Discussion

In the management of congenital heart disease, balloon-expandable stents have been used with success for obstructive vascular lesions that tend to recoil or collapse after dilatation. However, stent implantation in stenotic vessels of infants and small children can be problematic because there is no ideal stent model that is small enough to be easily introduced into the infant femoral vein or artery and, at the same time, large enough to be re-dilated during growth to adult vessel diameters. Such implants can be life saving, though in the immediate post-operative period and in some instances the interventional cardiologist has no other option but to commit the patient to later surgical removal of a stent. In patients with univentricular hearts, for example, a combined surgical and interventional strategy is often needed to optimize the growth of structures. Stent implantation in hypoplastic pulmonary arteries after a bidirectional cavopulmonary connection is sometimes necessary in order to address clinical problems such as venous congestion and severe cyanosis. These stents usually have to be excised during completion of the Fontan operation.

Surgical removal of a stent is an aggressive procedure with possible destruction of the vessel wall to such an extent that the further growth potential is limited. In this experimental study, it is shown that vessel wall architecture remains remarkably well preserved on histopathological examination. All arteries were patent, but four out of six veins were thrombosed. We hypothesize that the surgical trauma caused by the endarterectomy results in a higher risk for thrombosis in a non-pulsatile, low blood velocity and low-pressure environment. The pulmonary artery has a high blood velocity in the normal circulation. After a bidirectional or total cavopulmonary connection, a non-pulsatile, low flow, and low pressure circulation is created, possibly simulating venous type flow. These findings suggest that anti-aggregate treatment and/or anticoagulation might be indicated in this clinical setting. It cannot be excluded though that the morphology of the vessel wall itself may also play a role in the increased venous thrombosis risk after stent removal.

#### Limitations of the study

Stents were implanted in non-stenosed vessels. Stent expansion with mild stretch of vessel (as in this series) will therefore not disrupt vessel architecture; however, such disruption may be the case when stents are expanded in stenosed vessels.

A comparison is made between the jugular vein and the carotid artery and the response of growth of the vessel after stenting. There are no stents available that are suitable for use in both small arteries and large veins and therefore stents of different designs had to be used (CP stents in the jugular veins and multi-link pre-mounted coronary stents in the carotid arteries). The difference in stent design and stent material introduces a variable which is difficult to evaluate, as it is theoretically possible that different metallic properties of stents may induce a different type of response in a vessel. It is our experience from clinical practice though that intimal proliferation (with in-stent stenosis) tends to develop more in smaller stents, than in larger...
stents. CP stents (used in the jugular veins in this study) are often used for stenting coarctation of the aorta in adult patients and has never caused any in-stent thrombosis or significant in-stent stenosis due to intimal proliferation. However, when coronary stents are used in smaller arteries, i.e. aorto-pulmonary collaterals, in-stent stenosis due to intimal proliferation is often seen.

**Conclusion**

Vessel wall architecture remains well preserved after surgical removal of stents implanted in juvenile arteries and veins. However, stenting and subsequent surgical removal results in a high risk of venous thrombosis. Anti-aggregate treatment and/or anticoagulation might therefore be indicated after stent removal in the low flow and low-pressure environment (bidirectional/total cavopulmonary connections).

**Future perspectives**

Surgery because of mismatch of stent size and vessel growth during development may hopefully be avoided in future with the use of biodegradable stents and the development of the so-called breakable stents in infants and children. These stents are still experimental and the biodegradable stents are currently only available up to a maximum diameter of 3.5 mm, which limits the use in older infants and children.

**Acknowledgements**

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**References**