REINFORCING THE PULMONARY ARTERY AUTOGRAPH IN AORTIC POSITION
THE ROSS PROCEDURE WITH A TEXTILE MESH SLEEVE:
A HISTOLOGICAL EVALUATION
Emma Vanderveken¹; Julie Vastmans²; Tom Verbelen, MD, PhD¹,³; Peter Verbrugghe, MD¹,³;
Nele Famaey, PhD²; Eric Verbeken, MD, PhD⁴; Tom Treasure, MS, MD, FRCS, FRCP⁵; Filip
Rega, MD, PhD¹,³

¹ Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium
² Department of Mechanical Engineering, KU Leuven, Leuven, Belgium
³ Department of Cardiac Surgery, University Hospitals Leuven
⁴ Department of Imaging and Pathology, KU Leuven, Leuven, Belgium
⁵ Clinical Operational Research Unit, UCL, London, UK

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Correspondence: Emma Vanderveken
Department of Cardiac Surgery
University Hospitals Leuven
Herestraat 49, 3000 Leuven, Belgium
Tel: +32 16 34 42 60
Fax: +32 16 34 46 16
E-mail: emma.vanderveken@kuleuven.be
**ABSTRACT**

**Objectives:** The Ross procedure involves replacing a patient’s diseased aortic valve with their own pulmonary valve. The most common failure mode is dilatation of the autograft. Various strategies to reinforce the autograft have been proposed. Personalized external aortic root support (PEARS) has been shown to be effective in stabilizing the aortic root in Marfan patients. In this study, the use of a similar external mesh to support in the context of a Ross procedure a pulmonary artery autograft was evaluated.

**Methods:** The pulmonary artery was translocated as an interposition autograft in the descending thoracic aortas of ten sheep. The autograft was reinforced with a polyethylene terephthalate mesh (n=7) or left unreinforced (n=3). After six months, a CT-scan was taken and the descending aorta was excised and histologically examined using Hematoxylin-eosin and Elastica van Gieson stains.

**Results:** The autograft/aortic diameter ratio was 1.59 in the unreinforced group, but much less in the reinforced group (1.11) (p<0.05). A fibrotic sheet, variable in thickness and containing fibroblasts, neovessels and foreign body giant cells, was incorporated in the mesh. Histological examination of the reinforced autograft and the adjacent aorta revealed thinning of the vessel wall due to atrophy of the smooth muscle cells (SMC). Potential spaces between the vessel wall and the mesh were filled with edema.

**Conclusions:** Reinforcing a pulmonary interposition autograft in the descending aorta with a macroporous mesh showed promising results in limiting autograft dilatation in this sheep model. Histological evaluation revealed atrophy of the SMC, and consequently thinning of the vessel wall within the mesh support.

**Keywords:** Ross procedure; Reinforcement; Pulmonary autograft; PEARS; Histology; Marfan.
INRODUCTION

In the Ross procedure, the healthy pulmonary artery root is used as an autograft to replace the diseased aortic valve (1,2). Compared to replacement with an animal tissue valve, the living valve tissue is less prone to failure and compared with a mechanical valve, the patient is spared mandatory lifelong anticoagulation (2-4). Published by Ross in 1967, it was an early innovation in the history of aortic valve replacement (5). It remains an attractive solution for young patients with aortic valve disease, but has only been adopted sporadically because of anxiety about surgical complexity, the compromise of a healthy pulmonary valve and later deterioration of either or both the autograft and the replacement pulmonary valve (3,5,6). Autograft dilatation of the pulmonary artery root in aortic position is the most important failure mode after Ross surgery, occurring in 17% to 55% of patients at 5 to 10 years follow-up. Up to 12% of patients ultimately require autograft replacement due to substantial dilatation (2-4,7,8). Clinical experience is that the the autograft increases in diameter on exposure to systemic pressure. This is not detrimental to autograft valve function. It is not predictive of later dysfunction. there may be further dilation during the first year and beyond. (9,10). To tackle the drawback of autograft dilatation, various reinforcement techniques have been developed but none has been consistently successful (11-15).

It is 14 years since Personalized External Aortic Root Support (PEARS) was used for the first time to halt aortic root expansion in Marfan patients. PEARS is a procedure in which a soft macroporous mesh sleeve is custom made based on the patient's CT and/or MRI images and surgically placed around the dilated area (16). Note that PEARS has only been used when the aorta has reached a diameter sufficient for adult hemodynamic function because it fixes the aortic shape and size. By the end of 2017, 117 patients with aortic root aneurysms, predominately due to genetically determined aortopathy, have had an operation to place an
ExoVasc mesh support in 14 centers (17,18). A modification of this technique might be a promising new option for autograft reinforcement during the Ross procedure.

It has been found that the external mesh, closely fitting the aorta, becomes fully incorporated in the adventitia and preserves the vascular architecture, in contrast to wrapping with low porosity and poorly fitting Dacron grafts (17,18). A clinical case report confirmed these findings and showed that the supported aneurysm had the histological appearance of a normal aorta as opposed to Marfan related degeneration (19). Verbrugghe et al. investigated the histological characteristics more thoroughly in sheep (20). They reported full incorporation of the exostent in the outer layer of the carotid artery and minimal structural changes in the wrapped arterial wall. Recently, the principle has been applied to the Ross pulmonary autograft in seven patients. No follow-up data on these patients is yet published.

Currently, there is very limited data concerning the incorporation of the ExoVasc mesh support and its influence on the histological properties of the aorta. Concerns about thinning of the media of the aorta within the ExoVasc mesh support, and the potential for aortic dissection within and beyond the exostent support have been raised by critics. The neo-aorta no longer relies on the media for its strength and relative thinning can reasonably be reviewed as an adaptive change and to date, dissection within or beyond the support has never been seen in 470 patient years of follow up. If the technique is to have a place in the clinical use of the Ross procedure, further investigation of the impact of ExoVasc mesh implantation around the pulmonary artery could bring further insights. Our goal was to assess in a large animal model whether the macroporous mesh can be used to protect pulmonary artery tissue in aortic position from dilatation. We wanted to study the effect of the mesh on the histological features of the arterial wall.

MATERIALS AND METHODS
**Surgical procedure**

The animal experiments were approved by the Animal Ethics Committee of the KU Leuven (P053/2013). In thirteen Lovenaar sheep, a pulmonary artery interposition graft was placed in aortic position. Three of them died during surgery and were excluded from further analysis. Only female sheep were used to avoid inter-gender differences. The sheep were sedated with an intramuscular injection of ketamine (15 mg/kg). Subsequently, anesthesia was induced and maintained with isoflurane (5% and 2-3% respectively). Through a left thoracotomy, the pulmonary artery was carefully exposed. During cardiopulmonary bypass, ± 15 mm of pulmonary artery was resected and relocated as an interposition graft in the descending aorta.

In seven sheep (age 40.1 ± 7.3 weeks), the pulmonary autograft was reinforced with a polyethylene terephthalate mesh with a pore size of 0.7 mm (Exstent Ltd., Tewkesbury, UK). The amount of overlap of the mesh on the aorta was about 1 cm on both sides. By contrast, the autograft was left without reinforcement in three control sheep (age 37.2 ± 5.8 weeks). Six to eight months later, a CT-scan was taken and the sheep were euthanized with euthasol (120 mg/kg). After sacrifice, cylindrical samples of both pulmonary artery and descending aorta were excised in all sheep. Additionally, unreinforced pulmonary artery tissue in aortic position of one control sheep was collected. A diagram of the surgical procedures and the tissues collected is shown in Figure 1.

**Aortic diameter**

The diameter of the pulmonary artery and the pulmonary autograft was measured on the CT-images. In addition, the diameter of the descending thoracic aorta about 1.5 cm proximal and distal to the pulmonary autograft was measured.

**Histological analysis**
The obtained samples were fixed in paraformaldehyde (6%) and dehydrated (Medite TES 99), before being embedded in paraffin. 5-μm-thick serial cross-sections were created (Microm HM360) and stained with Hematoxylin and eosin and Elastica van Gieson stains using standard laboratory protocols. All specimens were examined with the use of a Zeiss Imager M2 microscope and pictures were taken with an Axiocam MRc5 camera. Measurements of the wall thickness and the smooth muscle cell and elastin content were performed with AxioVision software (carl Zeiss AG, Oberkochen, Germany).

Statistics

Data was analyzed with Matlab R2016b (MathWorks Inc., Natick, Massachusetts, USA) and with Microsoft Office Excel (Microsoft Corp., Redmond, Washington, USA). Results are displayed as mean ± standard deviation (SD). A p-value less than 0.05 was considered significant. Variables were compared using the unpaired t-test.

RESULTS

Macroscopic evaluation

During the initial surgery, as in clinical experience with the Ross procedure, immediate dilatation of the autograft in both the control and reinforcement group was visible. After six to eight months, macroscopic examination showed that the ExoVasc mesh was entirely surrounded by an inhomogeneous fibrotic sheet, extending to either end of the material. The lumen was well preserved and showed no erosions or obstructions. Finally, the aorta proximal and distal to the autograft appeared normal in both groups (Figure 2).

Aneurysmatic dimensions

The diameter of the thoracic aorta proximal and distal to the pulmonary autograft served as a reference to indicate the amount of dilatation. In the control group, the autograft/aortic diameter
ratio was 1.59 ± 0.40 at sacrifice. A significant smaller ratio of 1.11 ± 0.06 was measured in the reinforced group (p < 0.05) (Table 1).

**Histological evaluation**

The mean native aortic and pulmonary arterial wall thicknesses of the reinforced group were 2.86 ± 0.47 mm and 1.61 ± 0.59 mm respectively. After reinforcing the pulmonary autograft and the adjacent aorta, the mean wall thicknesses, measured from the tunica intima to the tunica adventitia, significantly decreased to 1.36 ± 0.63 mm (53% decrease) and 0.84 ± 0.22 mm (42% decrease), six to eight months after surgery (p < 0.05 and p < 0.05). In contrast, if the mesh and fibrotic sheet are included in the wall thicknesses, they increase with 3% and 57% respectively (Table 2). However, there is a large variation in increase, ranging from -27% to 37% for the aorta and from -12% to 132% for the pulmonary artery, due to the variable thickness of the fibrotic sheet.

Atrophy of the vascular smooth muscle cells (SMC) was present in all the samples of both the wrapped pulmonary autograft (Figure 3) and the surrounding wrapped aorta (Figure 4), causing the uniform thinning. An average decrease of 34% ± 21% and 36% ± 27% in SMC concentration was measured in the wrapped pulmonary autograft and wrapped aorta respectively. Overall, the elastin fibers appeared intact, although in some areas, fragmented elastin fibers were seen. As a consequence of vessel wall thinning, the density of the elastin fibers increased by 28% ± 36% for the pulmonary autograft and 25% ± 21% for the aorta. The SMC/elastin ratio in the pulmonary artery and aorta decreased from 3.00 ± 0.62 to 1.12 ± 0.54 and from 0.81 ± 0.40 to 0.39 ± 0.19 respectively, again illustrating the atrophy of the SMC after wrapping. The evolution in SMC and elastin fiber content per sheep is given in Table 3.

In this experiment, the macroporous mesh was not custom made to fit as it has been in clinical use. After six to eight months, the gap between the vessel wall and the mesh was mainly filled.
with fluid and a limited amount of fibroblasts. Additionally, edema between the elastin fibers in the media of the vessel wall was sometimes present (Figure 4B). The mesh itself was entirely covered by a fibrotic sheet, consisting of collagen fibers, fibroblasts, neovessels and foreign body giant cells.

In one control sheep, samples of aorta, pulmonary artery and pulmonary artery in aortic position were collected. The initial thicknesses of the aortic and pulmonary arterial wall were 1.07 mm ± 0.05 mm and 1.90 mm ± 0.11 mm respectively. Overall, after placing the pulmonary artery in aortic position, the wall thickness stayed the same. However, more variability in wall thickness was present (1.06 mm ± 0.18 mm). Concerning the SMC and elastin amount, no conclusion can be drawn since samples of only one sheep were available and these samples show a large variability.

**DISCUSSION**

*Effect of external wrapping on autograft dilatation*

In theory the Ross procedure is an attractive alternative to the standard aortic valve replacement for young patients allowing the potential of many years free from anticoagulation and re-operation. This has been achieved for many patients but it has not been widely adopted due to major concerns about technical difficulty, trading ‘single valve disease for the double valve disease’ and the long term failure due to autograft dilatation and consequent aortic regurgitation. (6) In order to avoid the deterioration of the autograft, several reinforcement techniques and materials have been developed (11-13,15). In our sheep study reported here, a macroporous ExoVasc mesh was used to successfully limit autograft dilatation of the pulmonary interposition graft. Nappi et al. used a similar approach to reinforce the pulmonary interposition autograft in growing sheep. Their semi-resorbable macroporous mesh prevented pulmonary autograft dilatation while allowing the natural process of growth (21-23). Overall, studies
investigating pulmonary autograft dilatation after wrapping with different materials came to the same conclusion, namely reduction or complete prevention of dilatation (11-15). However, the experiences with a low porosity Dacron and Gore-Tex graft were unsatisfactory (2).

Effect of external wrapping on histological features

One of the most frequently voiced concerns associated with historical ‘wrapping’ of the aorta is thinning of the arterial wall. This concern arose mainly from two case reports describing an extremely thin aortic wall several years after Dacron graft-supported aortoplasty (24). Robicsek et al. coined the term under-the-wrap atrophy (25). These observations may be inherent to the use of a low porosity vascular graft material, which was not designed for this purpose but to be a prosthetic replacement for the aorta. In a previous experiment of our research group, a low porosity Dacron vascular tube graft and macroporous ExoVasc mesh material were implanted around the abdominal aorta of the same three sheep for twelve months. Atrophy of the vascular SMC in the tunica media was present with a Dacron wrap while changes were much less pronounced in the aortic wall sleeved with the macroporous mesh (26). In the current study, depletion of the SMC in the mesh supported pulmonary arterial and aortic wall, and the corresponding thinning of those vessel walls, was also seen. An overall increase in wall thicknesses was seen due to the fibrotic sheet covering the mesh.

In contrast to our results, Nappi et al. reported thinning of the media in their control group and an intact media in the reinforced group (22,23). Also Verbrugghe et al. reported minimal structural changes in the tunica media of carotid arteries of growing sheep after implantation of a macroporous mesh for four to six months (20). Similar observations were mentioned in two follow-up studies of patients with aortic wall reinforcement with a highly porous mesh. The aortic wall architecture was well preserved after wrapping and no erosion of the mesh through the aortic wall was observed (27,28). A more recent patient report confirmed these findings, additionally mentioning that the supported aortic root had the histological appearance of a
normal aorta. Also, the fact that the unsupported aortic arch showed medial degeneration raises
the possibility of microstructural recovery of the damaged aorta after wrapping (19).

As stated above, our results are in line with the previously mentioned concern of thinning.
However, in this context thinning of the media does not result in loss of strength (30) or an
increased propensity for dissection.

*Mechanical analysis*

Mechanical testing of similar samples is reported by Vastmans et al. (30). The difference in
behavior of aortic and pulmonary arterial tissue was clearly visible. The stress-strain curves
indicated that the pulmonary artery is ‘stiffer’ than the aorta. After mesh support, the difference
in stiffness was less evident. In addition, exposed to aortic pressure, no difference between the
arterial tissues with or without mesh was visible, since at low pressures, the macroporous mesh
nicely fits around the artery and does not contribute significantly to the mechanical stiffness.
Only at higher pressures, the textile fibers of the mesh are put under tension and start to
contribute mechanically. These results indicate the importance of a personalized mesh. The
mesh should have no influence at physiological stresses and only restrict motion at higher
pressures, which is only possible if the mesh encloses the vessel precisely.

*Experimental sheep model*

Sheep are widely used for testing cardiovascular surgical devices because of the cardiovascular
similarities between sheep and humans (30). Therefore, we developed an experimental model
of a pulmonary artery interposition graft in sheep. Performing an actual Ross procedure from
our perspective is not feasible in sheep due to anatomic differences (21,30). Firstly, the
ascending aorta is too short and immobile. Secondly, re-implantation of the coronary ostia on
the pulmonary autograft is challenging since they are positioned very low. Third, and most
important, the failure mode of the human Ross operation takes place over decades. This is not
evaluable in animal experiments. In our model the behavior of the pulmonary artery under systemic pressure was examined, avoiding the complexities of the valve leaflets, coronary ostia and the sinuses of Valsalva. The one centimeter overlap of the mesh of onto the aorta protects the anastomosis. Despite these limitations we consider re-implanting the pulmonary artery in the descending aorta to be a clinically relevant model. This experimental approach is lower risk for the survival of the animal, reproducible and allowed us to assess the histological and structural effects of mesh reinforcement on the pulmonary artery under systemic hemodynamic conditions.

Limitations and further research

We acknowledge the fact that only one CT-scan per sheep makes it hard to evaluate autograft dilatation. The baseline diameter of the pulmonary interposition graft was not measured by CT, the 6-months/postoperative pulmonary autograft diameter ratio describes the differential effect. In addition, no knowledge on the cardiac phase during which the CT-scan was taken is available. As a final remark, the lack of sufficient control sheep is one of the limitations of this study, leaving uncertainty as to the reproducibility of the changes in wall thicknesses and composition. In any further studies, more imaging and more control sheep can be considered.

Conclusion

To evaluate the effect of exostent reinforcement on dilatation of the pulmonary artery interposition graft and on the histological features of the arterial wall, we developed a reproducible and clinically relevant sheep model. Reinforcing the pulmonary autograft with a macroporous mesh, currently used to halt aortic root expansion in Marfan patients, successfully limited autograft dilatation. Thinning of the media, due to atrophy of the vascular SMC, was present in all of the samples. However, the mesh supported pulmonary arterial wall was stronger when tested mechanically. We propose for discussion that a macroporous mesh is
likely to be applicable to circumvent the major drawback of the Ross procedure. This is being considered for clinical use and the first clinical uses will be reported soon.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.
FIGURES

Figure 1. The surgical procedure with a list of the collected tissues. The removed portion of the main trunk of the pulmonary artery has been replaced with standard low-porosity vascular interposition tube graft (white). The colour key identifies the aorta and pulmonary artery and where they have been reinforced. For ease of interpretation the illustrations are based on human anatomy. PA: Pulmonary artery.

Figure 2. (A) Surgical view of the pulmonary artery in aortic position. An instantaneous dilatation of the autograft was noticed. (B,D) Macroscopic analysis of the reinforced pulmonary autograft after six to eight
months, revealing a fibrotic sheet covering the mesh and a preserved lumen. (C) Macroscopic analysis of the pulmonary autograft of a control sheep after six to eight months.

Figure 3. Transverse microscopic sections of native pulmonary artery and wrapped pulmonary autograft of sheep 0091, Elastica van Gieson stain, magnification x25. The lumen is marked with *. (A) Native pulmonary artery. (B) Wrapped pulmonary autograft with increased density of the elastin fibers due to atrophy of the vascular smooth muscle cells.

Figure 4: Transverse microscopic sections of native and wrapped aorta of sheep 0091, Elastica van Gieson stain, magnification x25. The lumen is marked with *. (A) Native aorta. (B) Wrapped aorta with uniform thinning of the media. Fluid accumulation between the vessel wall and the mesh (arrowhead) and peripheral within the media of the vessel wall (Δ) is clearly visible.
Figure 5: Transverse microscopic sections of aorta, pulmonary artery and pulmonary artery in aortic position of control sheep 0321, Elastica van Gieson stain, magnification x25. The lumen is marked with *.

(A) Pulmonary artery. (B) Aorta. (C,D) Pulmonary artery in aortic position. Both pictures are taken from the same transverse microscopic section, showing the large variability in wall thickness and composition.¹

### Table 1: Diameter data of the reinforced group (top) and control group (bottom) at sacrifice

<table>
<thead>
<tr>
<th>Sheep</th>
<th>Diameter aorta (mm)</th>
<th>Diameter autograft (mm)</th>
<th>Autograft/aortic diameter ratio</th>
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<td>21.64 ± 0.76</td>
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<td>Mean ± SD</td>
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<td>33.26 ± 10.01</td>
<td>1.59 ± 0.40</td>
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SD: Standard deviation. The diameter aorta is the average of the aortic diameter about 1.5 cm proximal and distal to the interposition graft.

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<table>
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<th>Sheep</th>
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<th>After reinforcement</th>
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Mean ± SD 2.86 ± 0.48 1.61 ± 0.59 1.36 ± 0.47 0.84 ± 0.22 2.93 ± 0.66 2.39 ± 0.62

PA: Pulmonary artery; SD: Standard deviation. The wall thickness includes the tunica intima, tunica media and tunica adventitia. The total wall thickness includes the three layers of the vascular wall as well as the mesh and the fibrotic sheet.
**Table 3:** Data on the impact of mesh implantation on the vascular smooth muscle cell and elastin amount

<table>
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<tr>
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<td>25.09 ± 20.93</td>
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SMC: Smooth muscle cells; PA: Pulmonary artery; SD: Standard deviation.
REFERENCES


Reference List