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Support of the aortic wall: a histological study in sheep comparing a macroporous mesh with low-porosity vascular graft of the same polyethylene terephthalate material

Lucas Van Hoof[a,†], Peter Verbrugghe[a,†], Erik Verbeken[b], Tom Treasure[c,*], Nele Famaey[d], Bart Meuris[a], Paul Herijgers[a] and Filip Rega[a]

[a] Department of Cardiac Surgery, University Hospitals Leuven, Leuven, Belgium
[b] Translational Cell and Tissue Research, Department of Imaging & Pathology, University Hospitals Leuven, Leuven, Belgium
[c] Clinical Operational Research Unit, Department of Mathematics, University College London, London, UK
[d] Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Heverlee, Leuven, Belgium

* Corresponding author. Clinical Operational Research Unit, Department of Mathematics, University College London, London WC1H0BT, UK. Tel: +44-7957-168754; fax: +44-1233-740378;
e-mail: tom.treasure@gmail.com (T. Treasure).

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Abstract

OBJECTIVES: Wrapping with various materials was an early treatment for aortic aneurysms. Wrapping with low-porosity vascular grafts has been associated with graft migration and vascular erosion. An alternative is to use a macroporous mesh (MPM) made of the same polymer (polyethylene terephalate). We compared the histological outcome 1 year after wrapping sheep aortas with low-porosity grafts versus MPM fabrics.

METHODS: The 2 different fabrics were wrapped around the aorta of 3 sheep. After 1 year the aortas were excised. The 2 wrapped segments of aorta were compared with each other and control aorta. Histological examinations and measurements were made of the layers of the aortic wall in 36 prespecified locations in each of the 3 sheep.

RESULTS: Both fabrics were consistently surrounded by foreign body reaction and well-vascularized fibrosis. This was more pronounced with the low-porosity vascular graft material which was poorly incorporated and caused buckling at the transition between wrapped and unwrapped aorta. Conversely, the MPM was fully incorporated, resulting in a composite mesh/biological aortic wall. There was reduction of medial thickness with both materials but it was locally more extreme due to the corrugations in the vascular graft material. The findings were consistent between sampled locations and were similar in the 3 animals.

CONCLUSIONS: The different porosity and rigidity of the materials influences their incorporation into the aortic wall. The incorporation of the pliable MPM precludes the complications of migration and erosion which are seen after wrapping with low-porosity prosthetic vascular graft material.

Keywords: Aorta • Aortic root • Aneurysm • Marfan syndrome • Sheep

INTRODUCTION

When external support of aortic aneurysms is done in current practice it is usually by wrapping a vascular graft made of polyethylene terephthalate (PET), known generically as Dacron®. A tube graft is opened longitudinally and placed around the aorta with or without prior reduction aortoplasty [1]. When used as an interposition graft, the stiff corrugated wall of a low porosity graft allows it to curve without occluding but when used for external support, adverse consequences include migration, late rupture and erosion [2–6]. Tanabe *et al.* suggested 35 years ago that a macroporous mesh (MPM) might be superior because it allows an optimal fit, permits incorporation and presents little risk of damage to the aorta [7]. Laks' group used mesh to support the aorta in 102 patients over a 20-year period prior to 2007 [8, 9]. The aorta was not mobilized proximal to the left coronary artery. This provided a natural experiment. The aortic dimensions were stabilized where the aortic wall was covered with mesh but there was continued dilatation of the non-wrapped aorta. This led to reoperation in 2 cases and the opportunity for histological examination. The mesh had been incorporated and appeared to have stabilized the aorta, preventing further dilatation [9].

Wrapping was seen as a low risk procedure, at least in the short term, but as factory made composite grafts became

†The first two authors contributed equally to this study.

available, and surgical skills were refined, total root replacement could be done more consistently and safely [10]. Surgeons less often resorted to wrapping and were more ready to replace the aorta. The need for life-long anticoagulation made routine use of a mechanical valve unattractive for younger patients who wanted families and active life styles so valve sparing root replacement was developed but it increased the technical complexity of the surgery and the need for reoperation. The risks and benefits were balanced; neither was a perfect solution [11].

Wrapping, however, was not completely set aside [1, 12–14]. The material placed around the aorta has been referred to as 'external grafting' [15], 'wrapping' [1], and 'girdling' [9] providing a 'jacket' [16] 'sleeve' [17] or 'corset' [12]. None of these garment analogies and least of all 'a wrap' adequately conveys the made-to-measure snug fit of personalized external aortic root support [18]. The proposal to use computer aided design to make a personalized mesh came from an engineer patient [16]. The favourable characteristics of pliability and porosity proposed by Tanabe 35 years ago were implemented [7] but a missing piece of research evidence was a systematic histological evaluation of the tissue response to PET mesh. The only patient death, more than 4 years after personalized external aortic root support revealed full incorporation of the PET mesh [19] as had been seen at reoperation following *ad hoc* wrapping [8, 9]. In an experimental study by our group, PET mesh placed around the carotid artery in growing sheep [20] became embedded in the vascular wall, increasing the aortic tensile strength 5-fold from a mean value of 189 N/cm^2 to 856 N/cm^2 [20]. The findings were consistent in the small number of sheep ($n = 5$). This was a reminder that in the laboratory we could study genetically similar healthy sheep of the same age, under controlled laboratory conditions, in great detail. The large 'N' required for research in patients is due to the wide variability in the nature of the disease itself and the biology of the patients. Furthermore, we only have sporadic opportunities to study the histology on biopsy or autopsy tissue. The present report compares the histological features of material derived from a low-porosity prosthetic vascular tube graft versus MPM as used in personalized external aortic root support in just 3 sheep but is a planned systematic experiment.

MATERIALS AND METHODS

Fabrics used

Two fabrics used for aortic support were evaluated. Chemically, both are made of PET microfibers, combined into multifilament threads and woven or knitted to form a fabric. Gelweave® is an off-the-shelf woven low-porosity graft (LPG) used as a relatively stiff vascular graft with a corrugated aspect, allowing it to bend without occluding. The MPM is knitted, pliant, flat and has interstices of about 0.7 mm [9, 21]. The material used in these studies is that used in the ExoVasc® PEARS support, provided by Exstent Limited, Tewkesbury UK.

Operation and sample acquisition

Approval for the project was obtained through the Ethical Commission at the KULeuven (number: P144-2010). Sheep ($n = 3$) were anaesthetized using intravenous ketamine 10 mg/kg followed by isoflurane inhalation. The aorta was exposed. One piece of each of the test materials was wrapped around the aorta in a single layer and sutured to make a sleeve, varying which material was proximal or distal. Twelve months after implantation the animals were killed with high-dose pentobarbital and potassium according to institutional guidelines. The wrapped aorta and surrounding tissues were removed along with non-wrapped aorta to serve as control tissue. The aortic wall thickness was measured with calipers before fixing with 6% formaldehyde.

Histological evaluation

Samples were embedded in paraffin wax and longitudinal slices were taken through 4 quadrants of the aortic wall to assess variability. Microscopy slides were stained with haematoxylin and eosin, Verhoeff's elastic stain and Picrosirius Red collagen staining.

For each fabric, 3 slides per sheep, each containing a longitudinal slice through all quadrants, stained with haematoxylin and eosin, were photographed at 10x magnification. These were submitted to histological assessment using a semi-quantitative scale.

The media and adventitia underneath both fabrics was compared with non-wrapped aorta with regards to thickness, amount of vascular smooth muscle cells and continuity versus fraying of elastin fibres in both media and adventitia and collagen fibres in the adventitia. The fibrotic reaction underneath, within and outside of the fabric was described using the following parameters: cellular infiltration, foreign body giant cell reaction, neovascularization and density of collagen. Good incorporation was defined as high cellular and collagenous infiltration into the fabric, surrounding the microfibers, with fibrosis reaching from the outside of the fabric to the adventitia. An in-depth histological evaluation was performed of the transition zone, the area between wrapped and unwrapped aorta, with regards to buckling and tearing of structural fibres.

Measurements

Twelve separate measurements were made on each of the 3 slides per aorta providing a total of 36 measurements for each dimension. For non-wrapped aorta the measured layers were media, adventitia and total wall thickness. For MPM, the fabric with the fibrosis within and outside of the mesh was also measured. For the corrugated LPG material, the thickness of fibrosis varies related to the peaks and troughs of the crimping. The same pattern of measurements was performed in both locations and averages calculated.

Statistics

For each dimension, for the full set of the 36 measurements, the mean and standard deviation were calculated. For the dimensions applicable to all 3 conditions, paired *t*-tests were performed on the mean of the measurements for each comparison within each aorta/sheep dyad (control versus LPG; control versus MPM; MPM versus LPG). Statistical analysis of the measurements was conducted with SPSS (IBM SPSS statistics, Sun Microsystems, US).

RESULTS

Macroscopic evaluation

Upon inspection, a thick fibrotic peel was observed extending just past the limit of the fabrics (Fig. 1A). On manipulating

segments of wrapped aorta, they were less compliant than control aorta. The sectioned portions show that for LPG, the native aorta was relatively free within a fibrotic shell (Fig. 1B). On the contrary, the native wall within MPM was attached to the fabric (Fig. 1C). The LPG ridges can be seen through the endothelium (Fig. 1B). There were no signs of dissection, thrombus formation or intraluminal migration of either fabric.

Histological examination

Aortic architecture. Deep to both fabrics there was a decrease in vascular smooth muscle cells with approximation of elastic fibres and thinning of the media, on the whole more pronounced for LPG (Fig. 2B). MPM produces uniform thinning of the media while the LPG fabric causes variable thinning. In some locations there is disappearance of nearly all vascular smooth muscle cells, most frequently with LPG, leaving only elastic fibres in the media. Elastic fibres are mostly structurally conserved yet appear fragmented or frayed in some areas, more so with the LPG fabric. No damage to the endothelium, hyalinization of the media, oedema or calcification was noted with either fabric.

The collagen and elastin bundles in the adventitia underneath both fabrics appeared compressed, frayed and sometimes torn. The adventitia was evenly thinned underneath the MPM fabric (Fig. 2C). This is in contrast to LPG, where there was an alternation of heavily compressed adventitia, underneath the ridges (Figs. 2B, 6B), with less compressed adventitia in between.

Fibrotic and cellular reaction. The fabric fibres (that is their constituent threads) are surrounded by a cellular reaction

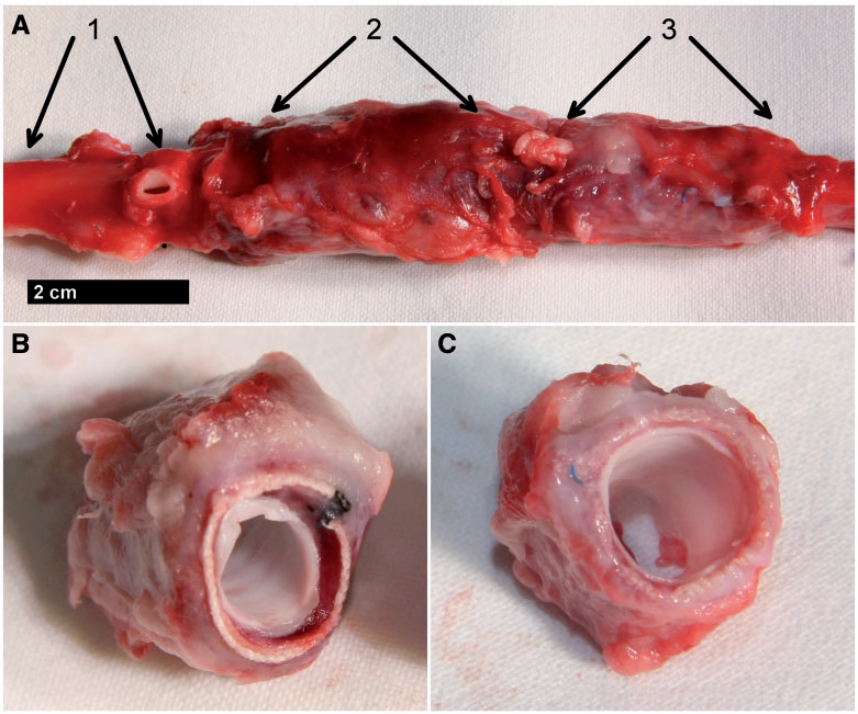

Figure 1: Excised descending aorta. (**A**) The unwrapped aorta (1) appears normal. Low-porosity graft (LPG) (2) with a thicker fibrotic sheath than macroporous mesh (MPM) (3). (**B**) LPG-wrapped aorta. (**C**) MPM-wrapped aorta.

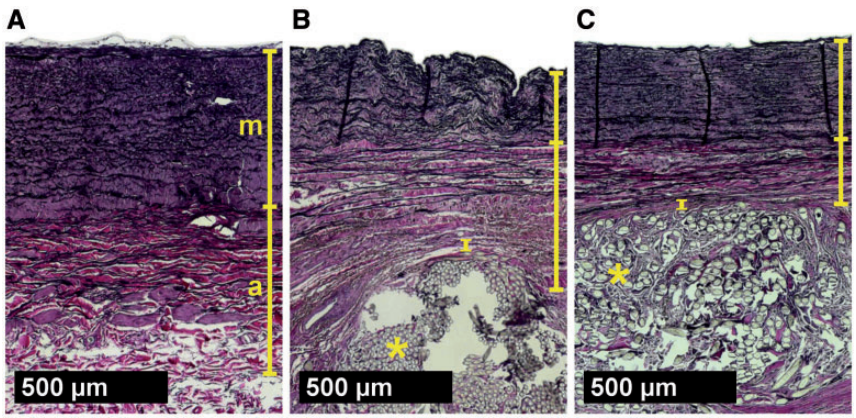

Figure 2: Media (m) and adventitia (a) with demarcation lines used in measurements and the thin fibrotic reaction directly under the fabrics (short lines). Verhoeff's elastic stain, 10x magnification, longitudinal slices. (**A**) Unwrapped aorta. (**B**) Low-porosity graft (*) with uneven thinning of media and adventitia. (**C**) Macroporous mesh fabric (*) with even thinning.

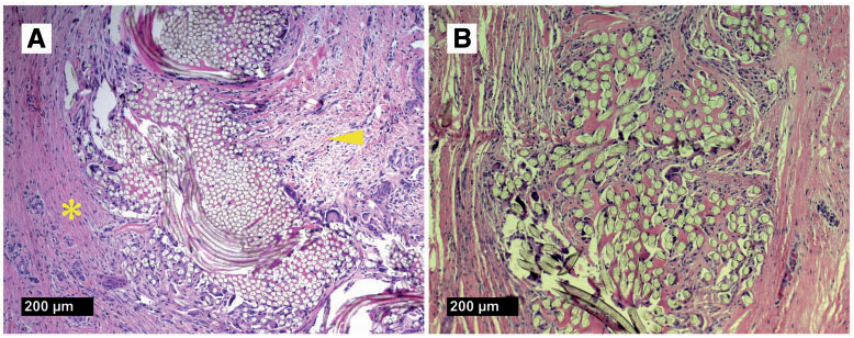

Figure 3: Fabric and surrounding reaction, haematoxylin and eosin, 10x magnification, longitudinal slices. (**A**) Low-porosity graft with surrounding cellular reaction, dense fibrosis outside of the fabric (*) and vascular and loose fibrotic reaction underneath (arrowhead). (**B**) Macroporous mesh with surrounding cellular reaction. Dense fibrosis within and on both sides of the fabric.

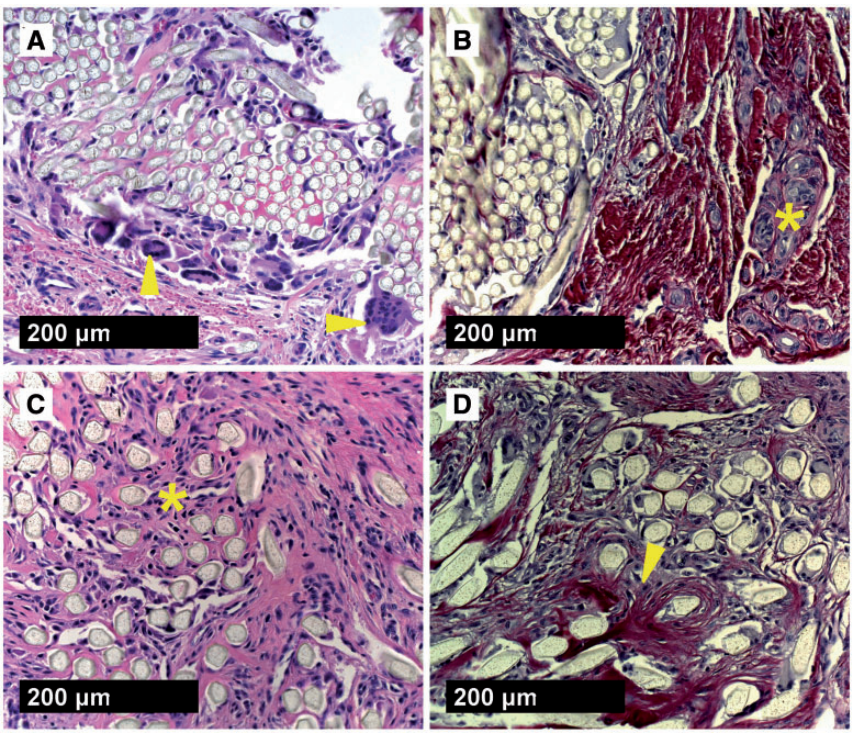

Figure 4: Detail of cellular reaction surrounding fabrics, 20x magnification. (**A**) Low-porosity graft (LPG), haematoxylin and eosin. Moderate collagenous infiltration and many foreigh body giant cells (arrowheads). (**B**) LPG. There is little collagneous infiltration of the low porosity material. The asterisk (*) marks a neovessel. (**C**) Macroporous mesh (MPM) haematoxylin and eosin. Good microscopic incorporation (*) with fibroblasts, extracellular matrix and neovessels. (**D**) MPM, Picrosirius red. Excellent collagenous infiltration within fabric (arrow).

embedded in collagen, consisting of fibroblasts, neovessels and typical foreign body giant cells (FBGC) yet no lymphocytes or granulocytes (Fig. 3). MPM appeared well incorporated as the cellular and fibrotic reaction permeates into the fabric, surrounding nearly all of the fabrics' loosely packed microfibrils (Fig. 4C and D). The LPG was associated with a denser cellular infiltrate with more and larger FBGC than the MPM (Fig. 4A and B). The degree of cellular and especially collagenous infiltration within the densely packed microfibrils was limited.

Beyond the cellular infiltrate around the fabric, fibrosis became predominant with denser and more organized collagen containing more, larger neovessels and no FBGC, only fibroblasts. The fibrosis outside of LPG was not continuous with the fibrosis under the fabric as the fibrotic reaction did not extend uniformly through the material, as shown in Fig. 5A. The LPG fabric itself appears as one continuous sheet without discernable pores. The MPM fabric (Fig. 5B) appears entirely incorporated in a fibrotic sheath with fibrosis bridging and filling up the spaces between the macrofibres. The dense fibrosis outside of the fabric is continuous with the thin layer of fibrosis underneath it.

Transition zone. For both fabrics, thinning of the native arterial wall extends approximately to the edge of the perifabric reaction, at most 1.5 mm past the fabric's edge. Beyond this point, the arterial wall appears normal (Fig. 6A and C). The MPM fabric is characterized by a gradual transition of architectural changes and limited tearing of fibres in the adventitia (Fig. 6D). Underneath the LPG fabric, a gradual transition is observed yet with folding of the media and transection of elastin fibres (Fig. 6B). In the

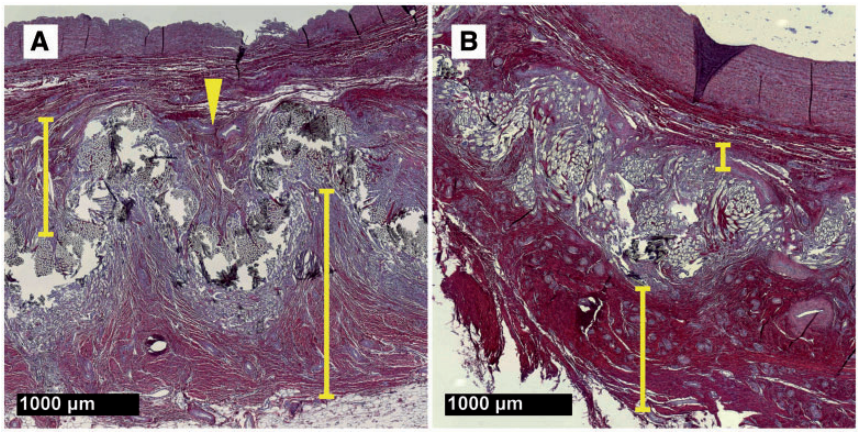

Figure 5: Overview of fabric and fibrotic sheath, Picrosirius red staining, reconstruction of 10x magnification images, longitudinal slices. The lines indicate the limits to the thinner fibrotic reaction underneath and the thicker fibrosis outside of the fabric. (**A**) Low-porosity graft fabric. Large neovessels within loose fibrosis between the fabric and adventitia (arrowhead). Outside of the fabric, a dense sheet of fibrosis containing smaller vessels. (**B**) The macroporous mesh fabric is well-incorporated in the homogeneous perifabric fibrotic reaction. Small neovessels within layer of dense fibrosis outside of the fabric, marked by the longer bar.

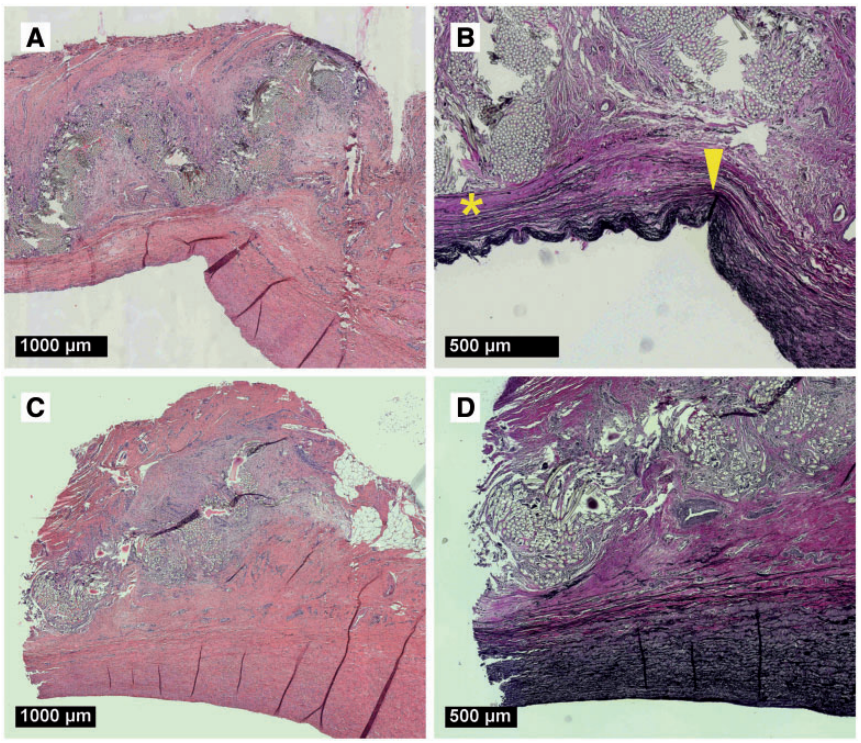

Figure 6: Transition zone, reconstructions of images taken at 10x magnification, longitudinal slices. (**A**) Low-porosity graft (LPG), overview, haematoxylin and eosin. Buckling of the aortic wall. (**B**) LPG, detail, Verhoeff's elastic stain. Buckling of highly atrophic tunica media (arrowhead) and compression of adventitia underneath ridges with severed structural fibres (*). (**C**) Macroporous mesh (MPM), overviews, haematoxylin and eosin. Gradual transition of architectural changes. (**D**) MPM, detail, Verhoeff's elastic stain. Gradual compression with well-preserved architecture.

transition zone of this fabric, tearing of adventitial structural fibres is pronounced.

Measurements. The most relevant dimensions, the total thickness of the aortic wall, the support material together with its fibrotic reaction, the media, and the adventitia, are shown in Fig. 7. The overall aortic thickness differed by 45% from smallest to largest aortic thickness making pooling the data from the 3 sheep unwise. For each of the 3 vertical sets of data (control, LPG and MPM) the individual sheep are set out from left to right according to size. A fuller set of measurements (mean and SD) are set out in Table 1. The measurements from the 3 sheep are proportionally similar, giving a coherent and consistent result.

DISCUSSION

The obvious limitation of the study is that only 3 sheep experiments were done. To compensate, we have taken multiple measurements in each part of each aorta in each sheep. In this study 3 x 24 x 36 = 2592 measurements were made alongside a similar

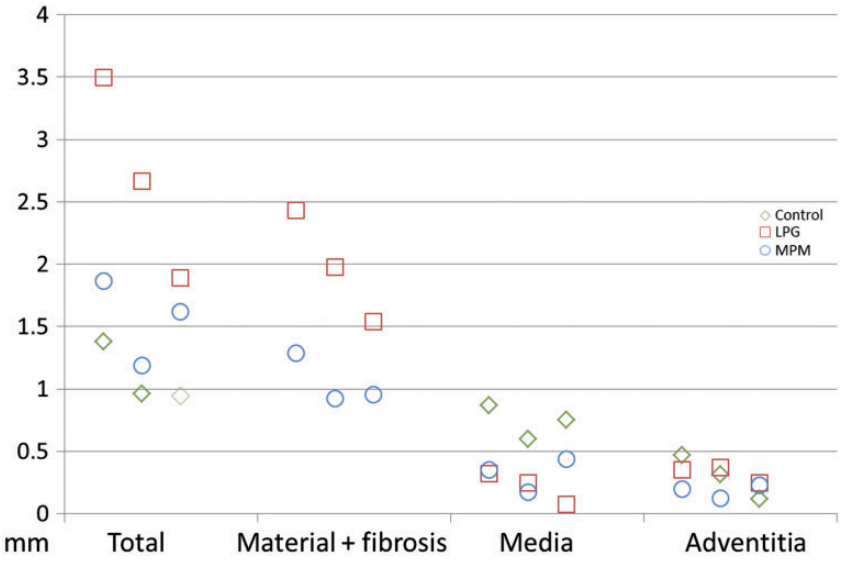

Figure 7: Each data point is the average of 36 measurements spaced around the aorta's circumference in each of the 3 excised aortas. The figure illustrates the total thickness of the wall for each sheep/aorta dyad. The measurements have a high degree of consistency within each aorta, and the relative differences are consistent from one sheep/aorta to another so the 3 are shown separately. For each measurement (Total, M + F, Media, Adventitia) each of the 3 vertical sets of data (control, low-porosity graft (LPG) and macroporous mesh (MPM) are set out from left to right so that the sheep overall size ranks from left to right and is consistently so. The overall thickness is increased in the wrapped segments, significantly for LPG versus control ($P = 0.05$) but less so for MPM versus control ($P = 0.09$). The thickness of the fibrotic sheath including the material is greater for LPG versus MPM ($P = 0.03$). The thickness of the media is reduced in both supported segments: LPG versus control ($P = 0.03$), MPM versus control ($P = 0.02$). There were no significant differences in the thickness of the adventitia.

Table 1: The means of 36 measurements (mm) for each of the 3 sheep. The individual sheep are ranked left to right by overall thickness of the total aortic wall as in Figure 7.

Control	Mean	SD	Mean	SD	Mean	SD
Media	0.87	0.10	0.60	0.06	0.75	0.12
Adventitia	0.47	0.13	0.32	0.11	0.12	0.03
Total	1.38	0.16	0.96	0.11	0.95	0.09
Macro	0.89	0.18	1.30	0.57	0.61	0.10
Low porosity graft (LPG)						
Media	0.32	0.11	0.25	0.09	0.07	0.03
Adventitia	0.35	0.13	0.37	0.16	0.25	0.14
Adventitia under ridge	0.27	0.09	0.23	0.07	0.08	0.03
Adventitia under wave	0.30	0.08	0.26	0.08	0.14	0.03
Total wall microscopic	3.49	0.47	2.66	0.34	1.89	0.41
Total wall macro	2.66	0.38	2.57	0.34	2.35	0.30
Total fibrosis and graft	2.43	0.37	1.97	0.24	1.54	0.39
Fibrosis under ridge	0.09	0.07	0.05	0.02	0.04	0.01
Fibrosis under wave	0.67	0.24	0.51	0.18	0.62	0.14
Fibrosis outside	1.21	0.43	1.05	0.54	0.73	0.35
Graft material	0.48	0.11	0.37	0.08	0.44	0.12
Graft	1.53	0.14	1.34	0.11	1.33	0.15
Macroporous mesh (MPM)						
Media	0.35	0.10	0.17	0.08	0.44	0.11
Adventitia	0.20	0.08	0.13	0.05	0.23	0.09
Total fibrosis and graft	1.29	0.39	0.92	0.18	0.95	0.12
Fibrosis under	0.12	0.06	0.08	0.02	0.11	0.04
Fibrosis outside	0.46	0.27	0.30	0.13	0.28	0.12
Total wall microscopic	1.87	0.55	1.19	0.22	1.62	0.20
Total wall macro	1.30	0.35	1.81	0.58	1.66	0.73
Graft	0.70	0.16	0.53	0.11	0.56	0.10

number of systematic, qualitative evaluations. The findings were consistent within and between the sheep. Variable and incomplete data acquisition of observational data is inescapable in observational clinical research even if we seek to overcome it by large numbers in meta-analysis [1, 11] On the positive side, by taking our specific research question to the laboratory, we were able to observe the response to the 2 different materials in animal of the same genetic stock, complete the experiment in a predictable time frame, and make comparable measurements in experimental and control tissue. This does not negate the general

limitation of extrapolating results in normal animals to what might happen clinically in the lifetime of humans with Marfan syndrome; all of our conclusions must be viewed in that light. *Caveat emptor!*

The tissues response of the aorta to support material has been observed some years after implantation but it has inevitably been sporadic and anecdotal [3, 6, 9, 19]. Previous studies have given only brief accounts of the histological findings which suggest that there had been relatively cursory examination as part of clinical pathological inspection which focusses on attributing the cause of death rather than scientific enquiry. Our histological examinations have been systematic and thorough. The findings are consistent with scientific accounts of biological reaction to foreign materials. After acute and chronic inflammation, there is granuloma formation and initiation of fibrous capsule proliferation by fibroblasts as well as neovascularization. Initially, polymorphonuclear cells colonize a polymer graft after implantation, followed by a shift towards lymphocytes, macrophages, epitheloid cells and finally, foreign body giant cells [22, 23]. This is the final and persistent stage of tissue healing surrounding a biomaterial [24]. The 0.7 mm of MPM ensures tissue ingrowth, anchoring the fabric to the tissues [25–28]. In our experiments, MPM is well-incorporated at a microfibril level as the cellular reaction permeates the mesh entirely between its constituent threads (Fig. 4C and D). Additionally, the mesh is entwined with a collagenous periadventitia and therefore forms a stable composite with the aorta (Fig. 5B). These observations are consistent with human post-mortem findings [9, 19].

The important outcome was that closely applied MPM is consistently well incorporated in marked contrast to low porosity vascular graft LPG. We believe we have obtained a coherent and trustworthy answer to the primary question asked of this experiment and that it is likely to be applicable in human biology. We conclude that the legitimate clinical concern about migration and vascular erosion resulting from the use of corrugated vascular tube grafts LPG as wraps in patients, does not apply to MPM. The mesh is fully and intimately incorporated due to its macroporous and pliant nature. The appearances seen with low porosity vascular grafts on CT imaging [14] are not seen with the clinical use of the mesh as has been shown on repeated imaging for what is now 333 patient years of follow-up.

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Conflict of interest: none declared.

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