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Simulating the ideal geometrical and biomechanical parameters of the pulmonary autograft to prevent failure in the Ross operation

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Abstract

OBJECTIVES: Reinforcements for the pulmonary autograft (PA) in the Ross operation have been introduced to avoid the drawback of conduit expansion and failure. With the aid of an *in silico* simulation, the biomechanical boundaries applied to a healthy PA during the operation were studied to tailor the best implant technique to prevent reoperation.

METHODS: Follow-up echocardiograms of 66 Ross procedures were reviewed. Changes in the dimensions and geometry of reinforced and non-reinforced PAs were evaluated. Miniroot and subcoronary implantation techniques were used in this series. Mechanical stress tests were performed on 36 human pulmonary and aortic roots explanted from donor hearts. Finite element analysis was applied to obtain high-fidelity simulation under static and dynamic conditions of the biomechanical properties and applied stresses on the PA root and leaflet and the similar components of the native aorta.

RESULTS: The non-reinforced group showed increases in the percentages of the mean diameter that were significantly higher than those in the reinforced group at the level of the Valsalva sinuses (3.9%) and the annulus (12.1%). The mechanical simulation confirmed geometrical and dimensional changes detected by clinical imaging and demonstrated the non-linear biomechanical behaviour of the PA anastomosed to the aorta, a stiffer behaviour of the aortic root in relation to the PA and similar qualitative and quantitative behaviours of leaflets of the 2 tissues. The annulus was the most significant constraint to dilation and affected the distribution of stress and strain within the entire complex, with particular strain on the sutured regions. The PA was able to evenly absorb mechanical stresses but was less adaptable to circumferential stresses, potentially explaining its known dilatation tendency over time.

CONCLUSIONS: The absence of reinforcement leads to a more marked increase in the diameter of the PA. Preservation of the native geometry of the PA root is crucial; the miniroot technique with external reinforcement is the most suitable strategy in this context.

Keywords: Ross operation • Pulmonary autograft • Pulmonary autograft failure • Biomechanics and mathematical model • Finite element analysis

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INTRODUCTION

In newborns, children and young adults, diseases of the aortic valve can cause difficulties when one is seeking a suitable surgical therapeutic solution to match somatic growth. The pulmonary autograft (PA) has been proposed as an ideal substitute for the aortic root in cases of disease of the aortic valve or left ventricular tract obstruction [1–3]. Because of the contraindications for oral anticoagulants, practice guidelines recommend the Ross operation in paediatric patients and young adults [4–6]. Nevertheless, using the PA is hampered by conduit expansion and biomechanical failure, issues related to systemic regimens, somatic growth, tissue remodelling and stress distribution [7, 8]. Horer *et al.* [9] evaluated the role of an increase in the diameter of the neoaortic root and valve failure in the differential expansion of the annulus, Valsalva sinus and sinotubular junction (STJ) in children after the Ross operation. To circumvent this issue, Carrel *et al*. [10, 11] proposed external reinforcement to prevent the failure of the PA with excellent late durability of the PA root and leaflet. The clinical experience with echocardiographic follow-up measurements after the Ross operation with a reinforced or a non-reinforced PA demonstrated very different geometrical behaviours by the PA conduit implanted with 1 or the other technique. The reinforced Ross operation maintains the characteristics of a cylinder over time, whereas the non-reinforced operation acquires the shape of a truncated conus. On the basis of these clinical observations and of our previous investigations [12–14], we sought to investigate the biomechanics of root and leaflet stresses that determine PA expansion and valve dysfunction. We, therefore, first confirmed in a clinical series the different degrees of expansion of the aortic root in reinforced and non-reinforced PAs with echocardiography. Then, we compared with finite element analysis (FEA) the biomechanical properties and applied stresses of the PA root and leaflet to similar components of the native aorta root in a series of normal organ donors in order to simulate the biomechanical conditions experienced by the PA during the Ross operation. Unlike the study by Mookhoek *et al*., [8] which addressed the biomechanics of explanted failed PAs, we investigated regions prone to dilation and other factors involved in PA failure before its implant. For this reason, we performed this analysis on healthy PAs, thus simulating the actual conduits used in the operation. The final aim was to determine the ideal geometrical parameters of the PA and the best implant strategy to prevent failure and repeat surgery (Table 1).

METHODS

Study design

We retrospectively reviewed 66 patients from 1998 to 2002, aged 16 months to 62 years, with severe aortic valve disease who underwent a reinforced or a non-reinforced Ross operation either with the subcoronary or the miniroot technique in La Pitie Salpetriere Hospital (Paris, France) and in the Hospital of Bern (Switzerland). Morphological parameters were obtained for all patients with transthoracic echocardiography before hospital discharge and at a 15-year follow-up examination. This clinical information triggered the evaluation of the mechanical properties of pulmonary (3.5 cm in length) and aortic roots explanted from human organ donors compared with those of native valves by simulating the mechanical conditions of the operation. The lengths of the PA and the aorta were the same, corresponding to the average range of the miniroot inserted. The biomechanical test was integrated with the FEA evaluation, and the detailed geometry of the PA root was reproduced to tailor the best operative strategy. Survival, freedom from reoperation, thrombosis and reinfection were evaluated during the follow-up period, which ended September 2017. Clinical outcomes were evaluated via telephonic interviews with each patient or his general practitioner, and no patient was lost during the follow-up period.

Specimen collection and characteristics

All samples were retrieved from the heart under standard aseptic conditions at the Saint Louis Tissue Bank and processed 24 h after procurement. Tissues were prepared according to standard protocol (see Supplementary Material).

Constitutive model, material properties, finite element simulations

The samples were tested to evaluate the mechanical properties in the tension mode by a dynamic mechanical apparatus (Q-800 TA Instruments, New Castle, DE, USA). A mathematical description of a material's response to stress was performed using an Ogden-type hyperelastic material. FEA was performed using advanced commercial finite element method-based code and integrating the Ogden constitutive equation into the finite element library of the code ANSYS (ANSYS 13.0) (see Supplementary Materials for details).

Statistical analyses

Statistical analyses were performed with a commercially available software package [15]. Continuous data are summarized as mean ± standard deviation. A comparison of echocardiographic data over time was performed with the analysis of covariance, considering preoperative values as covariate and group (reinforced vs non-reinforced) as a fixed effect. Means between independent groups were compared using the unpaired Student's *t*-test. A comparison of categorical variables was performed with the χ^2 test. Survival analysis was performed with Kaplan–Meier methods; survival functions between reinforced and non-reinforced groups were compared with the log-rank test. A *P*-value <0.05 was accepted as statistically significant.

Table 1: Key points of the study

Question	Can an assessment of geometrical changes in the PA after the Ross operation contribute to safety and effectiveness outcomes with an established implant technique?
Findings	The first step was to test the differences in the stress responses of the native PA and the aorta before implantation using a predetermined length segment. The second step was to obtain a geometric model from the stress test results that showed the changes using the finite element analysis method. Finally, the geometric changes in the PA were compared with those from 66 reinforced and non-reinforced Ross procedures.
Meaning	The mechanically expanded and geometrical changes in the PA may be effectively prevented with external reinforcement of the PA for the Ross operation.

PA: pulmonary autograft.

RESULTS

Echocardiographic results

The target population included patients aged 16 months to 62 years with severe aortic valve disease, with a mean age of 29.4 ± 11.0 years. The mean age was 26.7 ± 8.5 years in the reinforced group and 30.9 ± 13.1 years in the non-reinforced group ($P = 0.126$). Baseline results and postoperative dimensions at the 15-year follow-up examination are shown in Table 2 and Fig. 1. The mean increase in diameters was 1.28 ± 0.38 mm (3.9%) in the non-reinforced group at the Valsalva level (compared with reinforced, $P = 0.001$) and 3.95 ± 0.64 mm (12.1%) in the non-reinforced group at the annulus level (compared with reinforced, $P = 0.001$). No statistically significant differences were found with regard to aortic valve disease (stenosis, regurgitation or mixed) at follow-up (Table 2). Results from the analysis of covariance are shown in Table 3, confirming that patients who received non-reinforced PA showed a trend towards more marked dilatation at the level of the Valsalva sinus and the STJ compared to the reinforced group, whose diameters remained stable over time.

Clinical results

Medium follow-up was 15.4 years, with a range of 15.0–18.7 years (15–18.7 years for the non-reinforced group and 15–16 years for the reinforced group). Overall survival is shown in Fig. 2A; freedom from reoperation is described in Fig. 2B (see Supplementary Material for details).

Biomechanics results

The stress–strain profiles indicate that the hyperelastic responses of the aorta and the PA roots are anisotropic, with a classical increasing slope as the stretch grows (Fig. 3A) (see Supplementary Materials for details). A biomechanically relevant result concerns the stress–strain response of the aorta and PA valve leaflets. In fact, similar qualitative and quantitative behaviours were exhibited by both tissues in relation to the applied forces and prescribed stretches (Fig. 3B). This result would explain the mechanical resistance and durability of pulmonary artery valves when transposed in the aortic position. After interpolation of the experimental stress–stretch curves (Fig. 3C), we uploaded the hyperelastic behaviour to the finite element model.

The simulation outcomes are reported synoptically in Fig. 4A–C. In particular, Fig. 4B shows the sequence of the overall deformation of the system with increasing applied pressure. The contour plots show how the radial displacements grow non-linearly with the exerted pressures, generating significant strain gradients along the vessel axis, which are considered primarily responsible for the aneurysmal deformations. The bulging shape of the deformed autograft determines the radial displacement gradients associated with the migration of the suture section upwards because of the competition with the adjacent aorta. This finding confirms the expected inelastic, irreversible deformation processes prodromal to tissue damage and failure in the absence of any PA reinforcement.

Table 2: Baseline and 15-year follow-up echocardiographic data

	Reinforced (n = 30)	Non-reinforced (n = 36)	P-value
Baseline, annulus (mm), mean ± SD	24.9 ± 3.2	26.0 ± 2.1	0.098
Baseline, Valsalva (mm), mean ± SD	30.1 ± 1.8	32.6 ± 2.5	0.001
Baseline, STJ (mm), mean ± SD	29.1 ± 2.1	28.9 ± 2.3	0.715
Follow-up, annulus (mm), mean ± SD	24.8 ± 3.2	27.3 ± 2.0	0.001
Follow-up, Valsalva (mm), mean ± SD	30.2 ± 1.9	36.6 ± 2.1	0.001
Follow-up, STJ (mm), mean ± SD	29.3 ± 2.0	36.3 ± 2.3	0.001
AVR grade at follow-up			0.474
0	17	18	
1	6	5	
2	4	3	
3	2	7	
4	1	3	
Severe AVR (Grade 3+) at follow-up	3	10	0.071
Moderate-to-severe AVS at follow-up	1	1	0.896
Mixed AVS and AVR disease at follow-up	2	3	0.799

AVR: aortic valve regurgitation; AVS: aortic valve stenosis; SD: standard deviation; STJ: sinotubular junction.

DISCUSSION

Prompted by our clinical experience [15, 16], this study provides new biomechanical observations on the properties of leaflets and the root of the PA in comparison to the native aorta. PA valve regurgitation has been reported to reach an incidence of about 40% at 20 years after a Ross operation with a freedom from pulmonary valve dysfunction of 53.5% [17]. Many studies support the benefits of adding external reinforcement to the PA [10, 12, 14, 16, 18–21], whereas other studies report negative or neutral findings [22, 23].

Better long-term results are closely related to a deeper understanding of the biomechanical effect of the Ross operation. Our findings are in agreement with previous studies of Carr-White *et al.* [22] and Horer *et al.* [9], who described the non-linear

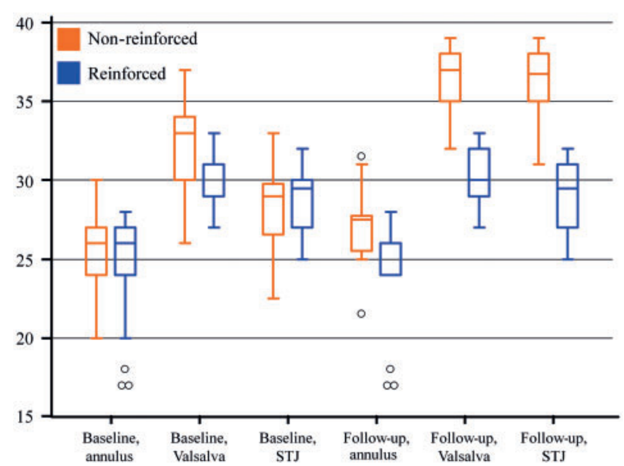

Figure 1: Box plots: aortic root dimensions obtained at baseline and at 15 years of follow-up in the reinforced and the non-reinforced groups. Results are expressed in millimetres. STJ: sinotubular junction.

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Table 3: Analysis of covariance: echocardiographic data

Follow-up variables	Tests of between-subject effects			Estimated marginal mean at follow-up	Mean difference[a]	Mean difference: *P*-value	95% CI for mean difference
	Sum of squares	*F*-test	*P*-value				
Annulus	33.4	27.6	<0.001	R: 25.3 NR: 26.8	1.46	<0.001	0.91–2.02
Valsalva	316.6	130.7	<0.001	R: 30.9 NR: 35.9	5.05	<0.001	4.17–5.93
STJ	816.0	243.3	<0.001	R: 29.2 NR: 36.3	7.07	<0.001	6.16–7.97

[a]Based on estimated marginal means.
CI: confidence interval; NR: non-reinforced group; R: reinforced group; STJ: sinotubular junction.

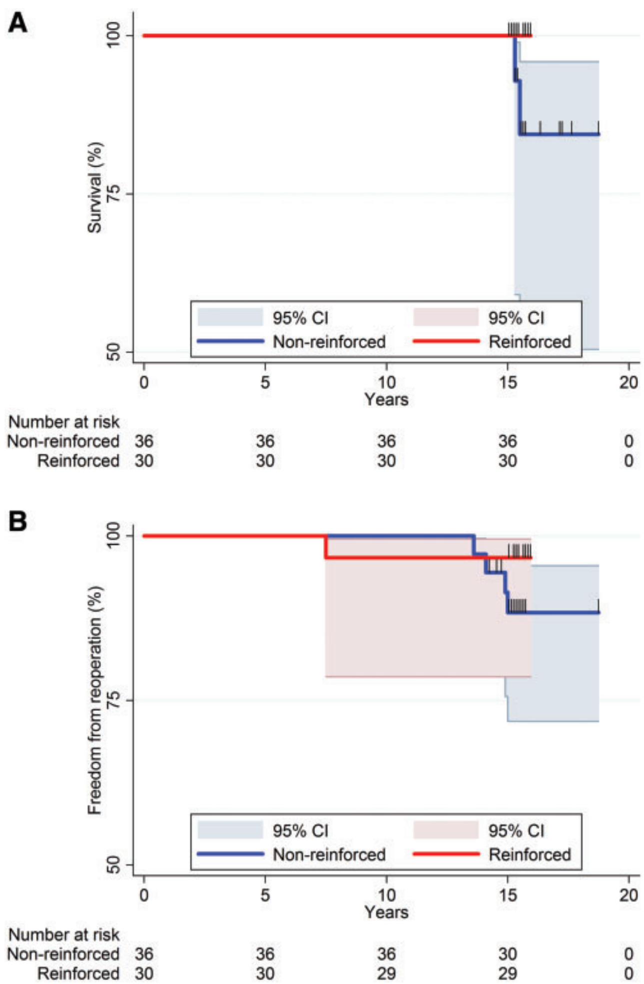


Figure 2: Follow-up results: survival (**A**) and freedom from reoperation (**B**) in reinforced and non-reinforced groups. Please note that the vertical axis is truncated. CI: confidence interval.

behaviour between growth, remodelling and stress shielding of PA transposed in a systemic pressure regimen. The increased compliance and reduced wall stiffness of the PA compared to the native pulmonary artery and of the failed PA compared to the native aorta might explain dilation of the PA.

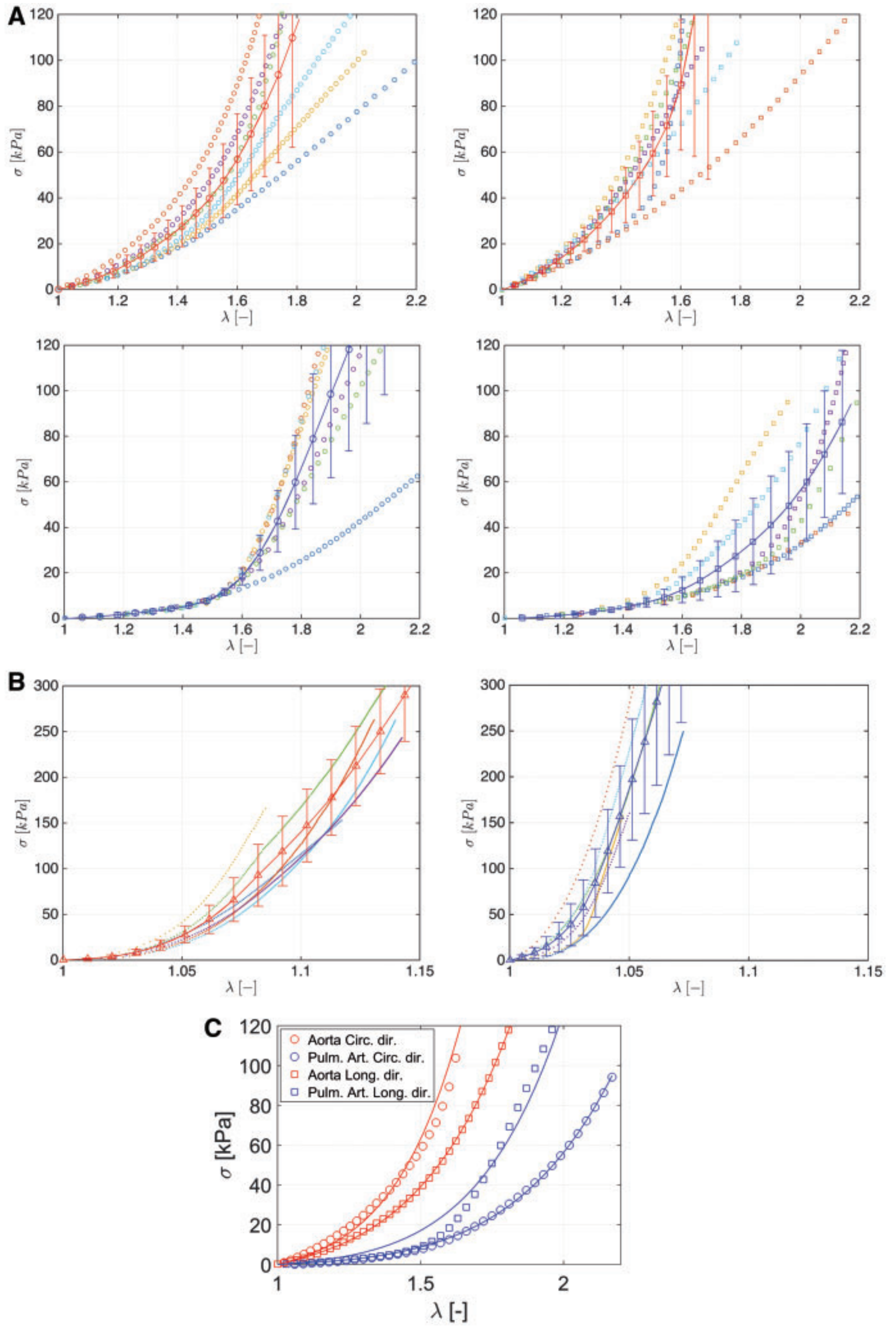
Biomechanics and finite element analysis of the pulmonary autograft leaflet and root

Finite element analyses show that the realistic response of the aorta–autograft ensemble cannot be captured by modelling simplifications such as numerical simulations performed by taking into account the 2 vessels separately [8]. In fact, the interplay among the material properties of the autograft and the aorta, suture regions, geometry and dilation constraints imposed by the annulus is crucial for determining the effects that actual stress concentrations, strain localization onsets and deformation gradients have on the success of the Ross operation. Proper descriptions of both boundary conditions (the presence of the suture region and the constraint given by the annulus) and the non-linear response of the vessels are crucial for determining actual stresses and the dimensional expansion of the PA structures and how this dilatation phenomena relates to the age of implant of the PA.

Whereas the aorta revealed a consensual increase in stress and deformation in circumferential and longitudinal directions, the pulmonary artery showed a better adaptability in the longitudinal direction and a steeper curve in the circumferential response, suggesting the ability of the PA to evenly absorb mechanical stresses and potentially explaining its known tendency towards dilatation over time. Secondly, a higher degree of resistance to deformation of the valve leaflets with a stiffer behaviour in respect to the aorta for applied loads of about 240 kPa (1800 mmHg) was demonstrated. Based on the simulations, it is thus expected that substituting the native aorta with the PA root induces an instantaneous elastic increase of the vessel diameter of about 32–33%, which is associated with a corresponding decrease in thickness of about 23–24%. The biomechanical simulation and the FEA algorithm demonstrated in the non-reinforced PA a significant change in geometry with loss of cylindrical configuration and achievement of a truncated conus shape with an enlarged base in the expanded region of the STJ.

Clinical application

Length of conduit and technique of implantation. The length of the conduit to be implanted and the technique of implantation need to be specifically tailored to the patient. Apart from the annulus, which proved to be the less deformable structure in the root, in this study, we observed a consensual increase



	μ_1	α_1	μ_2	α_2	μ_3	α_3
Aorta Long. dir.	3.86	5.78	18.2	-0.028	1.06	0.579
Aorta Circ. dir.	3.51	7.15	18.6	0.0023	0.651	0.238
Pulm. Artery Long. dir.	1.04	6.93	58.0	-0.017	-0.42	0.762
Pulm. Artery Circ. dir.	0.662	6.41	85.0	-0.022	1.62	0.910

Figure 3: (**A**) Stress–stretch curves for the aorta: longitudinal (top left) and circumferential (top right) direction; stress–stretch curves for the pulmonary artery: longitudinal (bottom left) and circumferential (bottom right) directions. (**B**) Stress–stretch curves for pulmonary (left) and aorta (right) leaflet. (**C**) A synopsis of the (top) average stress–stretch curves for both the aorta and the pulmonary artery along the 2 mechanically relevant directions and (bottom) a table with the relevant parameters. art: artery; circ: circumferential; dir: direction; long: longitudinal; pulm: pulmonary.

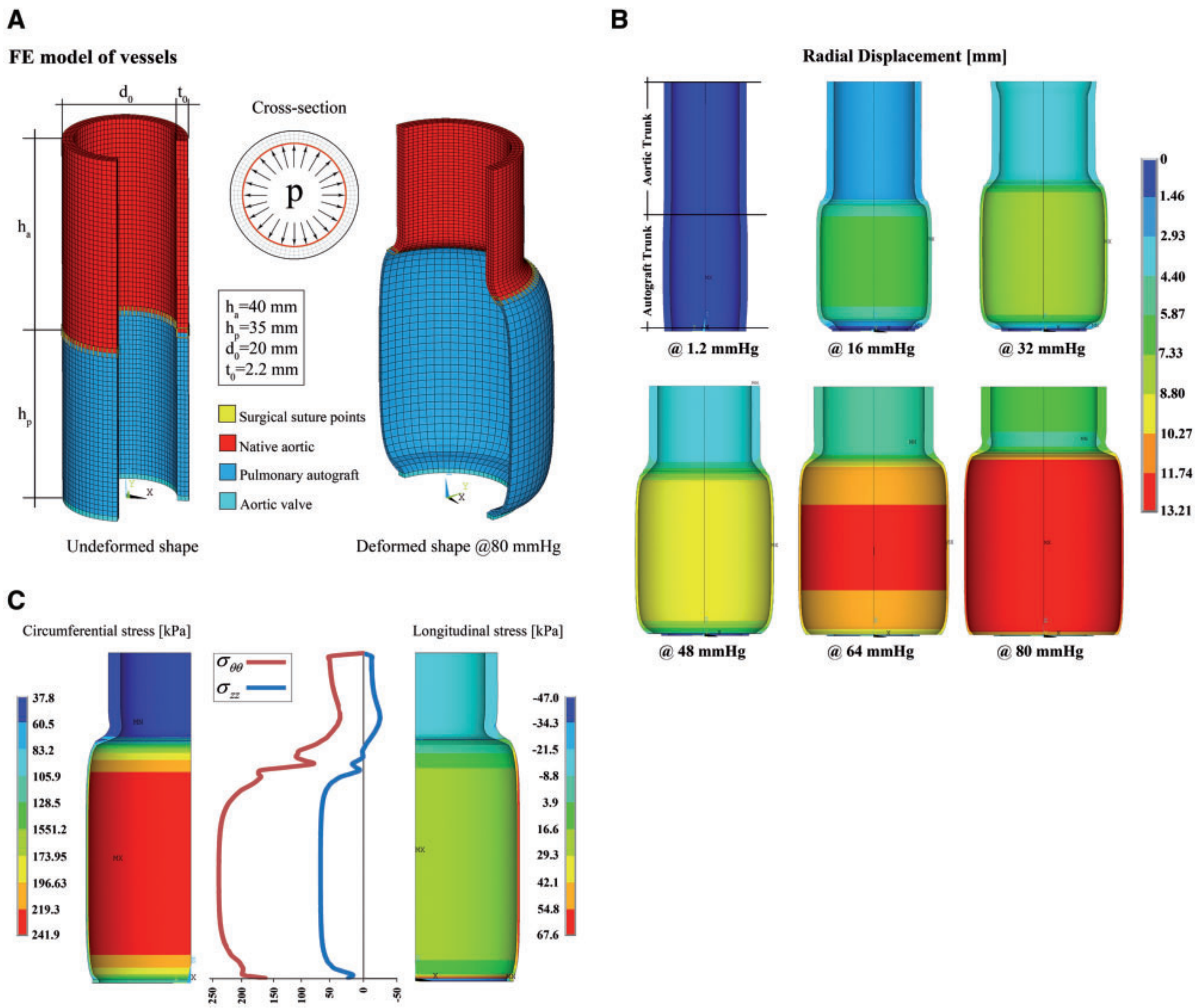


Figure 4: (**A**) Overall sketch of the FE model reconstruction of the aorta–suture–autograft–annulus ensemble: undeformed system (left); deformed (at the maximum pressure level) model (right) and cross-section with applied pressure. At the bottom, the legend with the details of the elements used and distinguished for material properties. (**B**) Sequence of deformations at increasing pressure levels up to 80 mmHg. The contour plots refer to the displacements along the radial direction (in mm). (**C**) Hoop (circumferential) and longitudinal (axial) stress profiles as a function of the vessel axis (middle), with contour plot details showing the spatially inhomogeneous distribution of the stresses (in kPa). FE: finite element.

in longitudinal and circumferential stress and deformation of the PA root. This change indicates the stress-shielding characteristic of the PA root, which allows for a uniform distribution of forces to be imparted within the walls and could guarantee relatively long durability. Although the study had insufficient power to allow us to draw definitive conclusions about the relative effects of the 2 types of the stresses on the pulmonary conduit, we can speculate that the duration of the application of stress and the rates of dilation might be associated with the length of the conduit implanted. For these reasons, a miniroot technique with a reinforcement represents the most appropriate option, and the use of reinforcing materials that do not impair the compliance of the native PA is important at this stage [21]. Results from a large series comprising young adults demonstrated the importance of reinforcing the PA by showing a 6-fold increase in the reoperation rate in subjects who did not receive PA reinforcement [24]. There was a linearized occurrence rate of reoperation for aortic valve dysfunction of more than 1.8% per patient-year in the case of a non-reinforced PA and 0.32% per patient-year in the case of a reinforced PA using the miniroot approach [25]. In contrast, reports from a large series from the German–Dutch registry demonstrated the superiority of the subcoronary technique in the adult population in terms of autograft durability with freedom from autograft reintervention (97% at 10 years and 91% at 12 years) even in the absence of external support [20, 25], probably related to the improved stabilization of the annulus when the subcoronary technique was used. These results should theoretically encourage the implant of the PA in the subcoronary position and reinforce the concept that pulmonary leaflets do not deteriorate when they are over-pressurized. However, besides the progressive clinical abandoning of this technique, our results also revealed its biomechanical limitations: The absence of the entire root determines a non-homogeneous distribution of forces concentrating on a few points on the leaflets and resulting in degeneration of the cusp. Indeed, the areas in which the major haemodynamic and biomechanical loads are imparted constitute an initial point of weakness with further leaflet tears normally at the level of the right and left cusps and sparing the non-coronary cusp, as confirmed by results from recent biomechanical studies [26, 27]. In contrast, the main issue with the miniroot technique is the expansion of the STJ as well as the loss of relationship between the expansion of the Valsalva sinus and the STJ. If the diameter of the STJ remains smaller than that of the Valsalva sinus, the potential for aortic regurgitation is avoided, as reflected by the results of a recent systematic review of the literature [28]. Although further confirmatory studies are needed, these concepts are also confirmed by the report on the long-term outcomes of the German–Dutch Ross registry, which showed that the leading cause of autograft valve failure with the need for reoperation in the subcoronary group was structural valve deterioration (80% of all reoperations) due to cusp prolapse (69% of all structural valve deteriorations) [20, 25, 29]. Therefore, we strongly support the advantage of the miniroot technique, which preserves the geometry and the function of the pulmonary valve because it imparts a homogeneous distribution of circumferential and longitudinal forces within the entire system of the root, annulus and valve.

External reinforcement of the pulmonary autograft. The biomechanical behaviour of the PA elucidated in this study confirms the need to support the conduit with a reinforcement that could prevent overstressing and dilation but that also has to comply with the somatic growth process of the patient. These thoughts inspired the design of a semiresorbable reinforcement to be applied during the Ross operation [21]. The results of this study advance our understanding of the relative benefits of PA for the management of severe aortic valve disease [30], especially with the use of the miniroot technique. However, it also emphasizes a warning about the importance of the choice of the length of the conduits because mechanical deformation and, therefore, potential failure, increase with the length of the segment subjected to stress. Strengthening the distal pulmonary root anastomosis using external reinforcement and modifying the ascending phase of the circumferential stress curve might be advisable as previously described [21]. The tendency to withstand longitudinal mechanical overloads of PA confirms the potential for remodelling. Indeed, it can still be improved with the use of external bioresorbable scaffolds that can control the circumferential expansion of the PA.

The PA is an ideal substitute for aortic valve replacement not only in Mr. Ross's dreams but also from the biomechanical point of view.

Limitations

The authors acknowledge that tests should have been performed considering 3 axes in order to achieve a fully accurate simulation. A CT reconstruction at different ages has not yet been performed but is the subject of a future study. Also, the target population was aged 16 months to 62 years with severe aortic valve disease and therefore few infants were included in this series. Unfortunately, FEA simulation cannot be directly integrated with the imaging methods currently in use in the clinical setting, and the limited clinical translatability of this approach surely constitutes a limitation of this study. However, we are confident that the new technologies will be able to provide additional *post hoc* analysis software to integrate these interesting data to the routine imaging methods such as echocardiography or CT scans. On the other hand, the current echographic technique of stress–strain measurement by tissue Doppler is currently validated for myocardial function and has not been widely explored for valve tissues; therefore, we could not provide echocardiographic data analogous to the results of the FEA.

We also acknowledge the general limitations of the *in silico* simulation. In this study, although clinical data were used as a confirmatory multicentric representative series to contextualize the problem and to feed the FEA, we elected, unlike in other studies already performed, to work on aortic and pulmonary tissues of normal organ donors to simulate the biomechanical conditions experienced by the PA during the Ross operation. We sought to acquire data on the regions prone to dilation and on the factors involved in PA failure before its implant. For this reason, we performed this analysis on healthy PAs, thus simulating the actual conduits used in the operation. The final aim was to determine the ideal geometrical parameters of the PA and the best implant strategy to prevent failure and repeat surgery. Our intention was therefore to obtain a predictive simulation of the postimplant conditions that, besides the possible limitations related to the methods, could provide useful information. We also electively avoided bench tests on reinforced and non-reinforced PAs because these investigations might be affected by the lack of control of important haemodynamic and haemorheological parameters (e.g. resistance, blood viscosity) that can otherwise be easily integrated into an FEA model. More investigations are therefore needed to validate the findings on the dimensional modification of the root.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

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