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Kheira Hireche, Ludovic Canaud, Pierre Antoine Peyron, Linda Sakhri, Isabelle Serres, et al.. Ex Vivo Comparison of the Elastic Properties of Vascular Substitutes Used for Pulmonary Artery Replacement. Journal of Surgical Research, 2024, 295, pp.222-230. 10.1016/j.jss.2023.10.022 . hal-04319076

HAL Id: hal-04319076 https://hal.science/hal-04319076

Submitted on 2 Dec 2023

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Ex Vivo Comparison of the Elastic Properties of Vascular Substitutes Used for Pulmonary Artery Replacement

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Keywords:

Compliance; Pulmonary artery; Stiffness; Vascular substitutes.

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abstract

Introduction:

Study aims were to evaluate the elastic properties of vascular substitutes frequently used for pulmonary artery (PA) replacement, and then to compare their compliance and stiffness indexes to those of human PA.

Methods:

A bench-test pulsatile flow experiment was developed to perfuse human cadaveric vascular substitutes (PA, thoracic aorta, human pericardial conduit), bovine pericardial conduit, and prosthetic vascular substitutes (polytetrafluorethylene and Dacron grafts) at a flow and low pulsed pressure mimicking pulmonary circulation. Intraluminal pressure was measured. An ultrasound system with an echo-tracking function was used to monitor vessel wall movements. The diameter, compliance, and stiffness index were calculated for each vascular substitute and compared to the human PA at mean pressures ranging from 10 to 50 mmHg.

Results:

The compliance of the PA and the thoracic aorta were similar at mean physiological pressures of 10 mmHg and 20 mmHg. The PA was significantly less compliant than the aorta at mean pressures above 30 mmHg (P ¹/₄ 0.017). However, there was no difference in stiffness index between the two substitutes over the entire pressure range. Compared to the PA, human pericardial conduit was less compliant at 10 mmHg (P ¹/₄ 0.033) and stiffer at 10 mmHg (P ¹/₄ 0.00038) and 20 mmHg (P ¹/₄ 0.026). Bovine pericardial conduit and synthetic prostheses were significantly less compliant and stiffer than the PA for mean pressures of 10, 20, and 30 mmHg. There were no differences at 40 and 50 mmHg.

Conclusions:

Allogenic arterial grafts appear to be the most suitable vascular substitutes in terms of compliance and stiffness for PA replacement.

Introduction

Acquired pulmonary artery (PA) anomalies are rare but some (aneurysm, dissection, neoplasm, arteritis) may require the replacement of the pulmonary trunk or the right or left main PAs.1-7 Several techniques have been reported in the literature and numerous vascular substitutes have been used for this purpose: autologous pericardium,8 xenograft pericardium,9 autologous pulmonary vein,10 allogenic arterial graft,11,12 and polytetrafluorethylene (PTFE) or Dacron (polyester) vascular prostheses.13 Despite the considerable advances in surgical procedures, there is currently no standardized technique or recommendation of the most suitable substitute to use. The choice of vascular substitute generally depends on reconstruction type, material availability, and the surgeon's preferences. However, from an ideal perspective, the most suitable substitute should be nonthrombogenic, biocompatible, and harbor similar viscoelasticity to native PA.

Previous studies have shown that differences in properties between the native tissue and vascular substitute can lead to abnormal wall shear stress at the anastomosis site and exacerbate peripheral vascular diseases.14 The elastic properties of the vascular substitute must thus be carefully considered when performing PA replacement. Disruption of the internal elastic lamina and loss of elastic tissue in the hilar PA has demonstrated a consistent association with decreased vascular compliance in animal models of induced pulmonary hypertension.15,16 In the same way, loss of vascular compliance in adult and neo-natal pulmonary hypertension has shown a clear association with collagen accumulation and loss of elastin in the proximal pulmonary arteries.17,18

Overall, these important aforementioned studies provide evidence that loss of proximal PA compliance could induce PA hypertension. However, the compliance of different vascular substitutes commonly used during PA replacement has not yet been investigated. Therefore, in this study we designed and developed a bench-test pulsatile flow experiment to investigate the ex vivo compliance properties and stiffness indexes of vascular substitutes commonly used for PA replacement at both pulsatile flow and low pressure. We then compared these properties to those of a human cadaveric PA. The secondary objective was to evaluate the influence of the elastic properties of nonhuman vascular substitutes (PTFE and bovine pericardium [BP]) on the compliance behavior of the PA.

Materials and Methods

The IRB of Montpellier University Hospital approved this study (IRB-MTP_2022_02_202100949). All procedures were performed under local and national regulations.

Description of the bench-test pulsatile flow experiment Figure 1A indicates the bench-test experiment which consisted in a pulsatile flow circuit with flexible plastic tubing connected to a fluid reservoir, a continuous flow pump (Jabsco 31,295-3512-3A), and an electric solenoid valve (SMC VX232DGAXB, Tokyo, Japan). The pump and the valve were connected to an

electronic control box from which the flow rate, frequency, and duration of valve occlusion were controlled. A loading compartment (C1), made by superimposing four cylinders of 25 cm in length of butyl rubber, was placed between the pump and the valve. A double compliance unit (C2) was used in series with the circuit. We made this C2 using a 3D printer; it consisted of a 50 mm diameter shore 40 silicone tube lined with a vinyl polychloride sleeve (Fig. 1B).

The concept of this bench-test experiment was to proceed from a continuous flow to a pulsed flow by alternative control of the valve. When the valve was in closed position, the C1 expanded and increased in pressure. When the valve opened, the elastic recoil of C1 ejected the fluid into the circuit through the valve, thus inducing pulsatility. The instantaneous flow rate was measured by a digital turbine flow meter (ASHATAuoygvginq9) used in series with the circuit. The pressure was changed by varying the diameter of an outflow resistance using a pinch valve sited at distance to the grafts and by changing the length of the return plastic tube to the expansion tank. Hence, pressure conditions (flow rate and frequency) were similar to physiological conditions and maintained throughout all experiments performed.

Vascular substitutes

Harvesting and preparation of human cadaveric substitutes With the permission of the legal department and in accordance with French regulations, fresh and healthy human vascular substitutes were harvested during autopsy of six adult subjects (Table 1) who had died a maximum of 4 days before (mean 2.1 days). The substitutes were immediately stored in physiological saline at 4_C until use in the bench-test experiment (mean delay <60 min). The pericardium was harvested from the right to the left pericardial pedicle, wrapped around a tubular support, and longitudinally sutured using a surgical stapler (Endo GIA, Medtronic, MN). This resulted in a pericardial conduit with a diameter of 2 cm and length of 10 cm. The PA was harvested from above the pulmonary valve up to the right superior mediastinal artery. The left PA was ligated 1 cm after the bifurcation of the pulmonary trunk. The descending thoracic aorta was harvested (10 cm long) and the intercostal arteries were then clipped (Fig.2A). Tissue sections of the PAs and aortas were sent to the pathology department for analysis to make sure that there was no arterial wall pathology that could affect arterial compliance.

Nonhuman substitutes

Commercially available BP (SJM; St Jude Medical, St Paul, MN) was obtained and tested. Three conduits of 18, 20, and 22 mm in diameter and 10 cm in length were created according to the same tubulation procedure used for the human pericardial conduits. Three PTFE tube grafts (Gore-Tex, W. L. Gore & Associates, Inc, Newark, DE) and three knitted Dacron grafts (Medox Medical, Newark, NJ) with diameters of 18, 20, and 22mmand a length of 10 cm were also studied. The prosthetic grafts were subjected to a precoating procedure to reduce intraluminal pressure loss related to transmural perfusate leakage. This was carried out by immersing the prosthesis in a mixture of gelatin and sodium alginate for up to 2 h. The grafts were then washed in physiological saline.



Fig. 1 - (A) The bench-test pulsatile flow experiment set-up. (B) Effect of the double compliance unit on blood pressure. Arrows indicate transition areas in compliance. (A) Initial phase of ejection before the compliance chamber reaches the tube, compliance is then C2e. (B) Phase of ejection when the compliance chamber has exceeded the diameter of the vinyl polychloride sleeve, compliance becomes C2c.

Subjects (N)	Age (y)	Gende		
1	65	М		
2	58	М		
3	32	F		
4	71	F		
5	49	М		
6	62	F		



Fig. 2 — (A) Human substitutes: a human pericardial conduit, (B) pulmonary artery, (C) thoracic aorta. (B) Composite substitutes mounted on the circuit.

Composite substitutes

To evaluate the effects of the elastic properties of the nonhuman substitutes on the compliance of the upstream PA, the PTFE prosthesis and the BP conduit were anastomosed end-to-end to a previously tested cadaveric PA (Fig. 2B).

The flow circuit

A blood-mimicking perfusate consisting of 40% glycerol, 60% distilled water, and 0.9 g/L sodium salt was maintained by a heater at a temperature of 25°C for all experiments performed. The resulting dynamic viscosity and density of the blood mimicking perfusate were similar to those of blood.19 The vascular substitutes tested were mounted in series on the circuit, immersed in a distilled water bath, maintained at 25°C, and then exposed to flow. We adjusted the pulse of the valve to a frequency of 1 Hz (60 pulses/minute) and the pump to 5 L/min. The valve opening time was 40%. Intraluminal pressure along the tested substitute was measured using a punctured catheter introduced through a Y-connection port and connected to a pressure monitor (Smartsigns Compact monitor, Huntleigh Healthcare, UK). Compliance was measured over a mean pressure range of 10-50 mmHg (Video 1).

Principle and method of compliance measurement

The diameter measurements were taken using a GE Vivid S60 ultrasound (GE Healthcare, GE Medical Systems SCS, France) with an integrated high-resolution ultrasound tracking system. Briefly, a linear ultrasound probe (11 MHz) was immersed in the bath and positioned above the tested substitute. Sufficient pressure was applied to allow acoustic coupling without compression. The B-mode cursor was then positioned at the midpoint of each tested substitute and perpendicular to flow direction. The pressure loading cycles were repeated without interruption and the substitute was then continuously subjected to the pressure cycles for approximately 3 min. Measurements were made using longitudinal section images in transverse magnetic mode. Three consecutive measurements of end-systolic and end-diastolic diameters were made at each mean pressure, and the experiment was repeated three times for each substitute tested. The pressure diameter response was digitally recorded.20

Circumferential compliance of human substitutes was calculated using equation (1),21 and reported in units of percentage of radial change/mm Hg x 10^{-2}

$$c = \frac{((D_s - D_d)/D_d)}{P_s - P_d} \times 10^4$$
 (1)

Where Ds is maximum internal diameter and Dd minimum internal diameter, and Ps systolic pressure and Pd diastolic pressure.

Circumferential compliance of PTFE and Dacron substitutes was calculated according to the following formula²²:

$$C_{\chi}$$
(% change per mmHg) = $100 \times \frac{\Delta D}{D_{\chi} \times \Delta P}$ (2)

DD is the dimensional change (DD $\frac{1}{4}$ Dp - Dx) where Dp is the outer diameter at a pressure P and Dx is the initial outer diameter at a reference pressure (Px).

DP: change in pressure (P - Px) Peterson's pressure stiffness index (b) was calculated for each substitute using equation (3),²¹

$$\beta = \frac{Ps - Pd}{Ds - Dd} \times Dd$$
(3)

Statistical analysis

Statistical analyzes were performed using SPSS IBM software version 25 (IBM, Armonk, NY). Data are presented as mean +/- standard deviation. We used student's t-test for quantitative variables, as per the normality of the distribution, assessed with the ShapiroeWilk test. Compliance and stiffness results were compared using a single-factor analysis of variance for each mean pressure. P values < 0.05 were reported as significant. When results from single-factor analysis of variance testing were significant, a comparison of the values for each substitute with those of the human cadaveric PA was performed using the Tukey post hoc test.

	10 mmHg		20 mmHg		30 mmHg		40 mmHg		50 mmHg	
	C	β	C	β	C	β	C	β	С	β
PA	81.75 ± \$0.54	7.073 ± 4.62	25.25 ± 26.31	16.79 ± 11.42	17 ± 11.51	11.50 ± 7.92	13.75 ± 7.45	22.18 ± 13.72	16.3 ± 16.18	16.71 ± 14.31
Thoracic aorta	56.4 ± 14.84	16.01 ± 8.60	40 ± 8.16	7.70 ± 2.49	38.5 ± 7.32	7.27 ± 4.20	37.25 ± 11.14	5.67 ± 4.47	35.25 ± 20.03	5,43 ± 2,47
Human pericardium	21 ± 3.65	23.96 ± 1.09	11.75 ± 6.23	30.05 ± 11.25	6.5 ± 2.08	29.95 ± 10.07	5 ± 1.63	30.53 ± 18.54	7.25 ± 7.22	18.07 ± 7 0.34
BP	5.5 ± 2.38	85.50 ± 19.20	7.75 ± 4.34	30.31 ± 11.04	4.5 ± 1.80	50.15 ± 22.24	4 ± 1.82	34.30 ± 24.86	3.5 ± 1.29	24.72 ± 5 0.56
PA + PTFE	68 ± 73.79	9.90 ± 11.07	20.5 ± 18.08	7.20 ± 5.01	15.75 ± 7.49	7.61 ± 4.62	10.5 ± 3.10	29.09 ± 23.63	15 ± 2.44	5.59 ± 1.63
PA + BP	60.5 ± 71.29	16.38 ± 18.80	22.5 ± 24.18	8.13 ± 7.35	6.5 ± 2.38	20.54 ± 6.50	4.5 ± 1.29	22.29 ± 4.63	3±1.15	24.15 ± 11.09
Dacron	0.99 ± 0.45	69.69 ± 23.43	1.6 ± 1.13	24.86 ± 21.19	1.79 ± 1.26	20.98 ± 9.72	1.26 ± 0.91	16.48 ± 4.36	1.24 ± 0.93	16.48 ± 4.23
PTFE	2.64 ± 1.53	23.69 ± 14.89	1.4 ± 0.85	29.21 ± 15.07	0.8 ± 0.42	32.3 ± 23.68	0.8 ± 0.37	34.85 ± 17.39	0.73 ± 0.39	34.85 ± 16.78





Results

Diameter results

Healthy human vascular substitutes (1 PA, 1 descending thoracic aorta, and 1 pericardial conduit) were harvested and tested from six cadavers. Histologic analysis of the harvested PAs and aortas at the start of the study revealed no underlying arterial wall pathology. Pressurized diameter measurements yielded 30 value pairs (Ds and Dd) for each of the human substitutes: 15 value pairs (Ds and Dd) for each composite substitute and 15 value pairs (Ds and Dd) for the tested bovine pericardial conduits. The mean diameters (Ds and Dd) and

pressures (Ps and Pd) of the different substitutes are reported in Supplementary Material (Tables 1 and 2).

Compliance and stiffness

Table 2 reports compliances and stiffness indexes of the tested substitutes. Figure 3 shows the variation in compliance in response to mean pressure variation for the different substitutes tested. Despite the PA being highly compliant at a mean pressure of 10 mmHg, a high decline in compliance was exhibited at 20mmHg. The compliance of the human vascular substitutes had a nonlinear relationship with increasing mean perfusion pressure (Fig. 3A). Bovine pericardial conduits had similar elastic properties to those of the synthetic prostheses (Fig. 3B). The curves for compliance versus mean pressure for composite substitutes are overlapping with the curve for PA (Fig. 3C). The variance analysis revealed a significant difference in compliance and stiffness between the different substitutes for each mean pressure studied (P < 0.001).

The Tukey post hoc test results are shown in Table 3. There was no significant difference between compliance of the PA and the thoracic aorta at mean pressure of 10 and 20 mmHg; however, the thoracic aorta was more compliant than the PA at mean pressures 30, 40, and 50 mmHg. Stiffness index values were similar across all mean pressures for the PA and aorta. A significantly lower compliance and increased stiffness were observed for the human pericardial conduits compared to the PA at mean pressures of 10 and 20 mmHg. These differences were lost >/=30 mmHg. The elastic properties of bovine pericardial conduits were similar to those of the synthetic prostheses, that is they all showed a significantly lower compliance and a significantly greater stiffness than the PA did at mean pressures 10, 20, and 30 mmHg. These differences were lost at 40 and 50 mmHg. Results for the composite substitutes revealed that the prosthesis and/or the BP had no impact on the compliance and stiffness of the upstream PA.

Substitute	10 mmHg		20 mmHg		30 mmHg		40 mmHg		50 mmHg	
	С	β	С	β	C	β	С	β	С	β
Thoracic aorta	0.067	0,081	0.094	0.461	0.017	0.578	0,015	0.167	0.048	0.198
Human pericardium	0.033	<0.001	0.053	0.026	0.122	0.078	0.061	0.236	0.34	0.080
PB	0,013	<0.001	0.024	0.028	0.04	0.037	0.076	0.45	0.165	0.149
PA + PTFE	0.891	0.064	0.631	0.231	0.186	0.074	0.671	0.33	0.579	0.092
PA + PB	0.070	0.456	0.089	0.363	0.059	0.138	0,092	0.082	0.662	0.239
PTFE	<0.001	800.0	0.03	0.04	0.013	0.01	0.11	0.062	0.1	0.234
Dacran	0.018	<0.001	0.038	0.002	0.015	0.036	0.12	0.078	0.11	0.569

Discussion

We investigated the elastic properties of different vascular substitutes used for PA replacement and compared these properties with those of healthy human cadaveric PA. An

experimental bench-test producing a pulsatile flow at low pressure was developed to apply a cyclic strain on the walls of the tested substitutes.

Several experimental studies have been conducted to assess the viscoelastic properties of synthetic vascular grafts.23-27 To our knowledge, only two studies have compared the compliance of synthetic and/or biologic substitutes to that of the human artery. Tai et al.28 compared the compliance properties of polycarbonate polyurethane prosthetic grafts with that of the human muscular artery, using a pulsed flow system, while Trambly et al.29 compared the mechanical and elastic properties of human and BP samples patch to that of the ascending aorta, using a tensile test. The present study is the first to compare the compliance of synthetic and biological vascular substitutes with those of a human PA, and the only one to study the elastic properties of human and bovine pericardial conduits under physiological flow. Furthermore, the specificity of our bench test here is the use of a continuous flow pump controlled by a pulse width modulator, which allows a switch from continuous to pulsed flow, whereas the mock circulatory loop described previously used a piston pump with a calibrated ejection volume. The use of a butyl rubber C1 and a C2 is also an original concept, and mimicks the ventricular function and the vascular tree compliance, in order to accurately reproduce the physiological conditions at low pressure.

An ultrasound system with arterial wall tracking was used to monitor the diameter changes of the tested grafts during each pulsatile cycle. This method is associated with a 6% coefficient of variation for diameter measurements according to Gamble et al.20 Nevertheless, a clear ultrasonographic visualization of both anterior and posterior walls of the substitute is required. We were required to consider the outer rather than the internal diameter given that PTFE and Dacron are nonechogenic materials. Indeed, the diameter measurement type used does not affect the compliance outcomes when the wall thickness is much smaller than the diameter 30

The aorta and the PA are anisotropic materials, that is there is a nonlinear relationship between the degree of radial deformation of the arteries in response to increased intraluminal pressure.31 In this study, we found no significant difference between the compliance of the PA and the thoracic aorta at mean pressures of 10 and 20 mmHg. However, a pressure above 20 mmHg resulted in decreased PA distensibility, leading to compliance mismatch. Wolinsky and Glagov32 previously investigated the mechanical properties and organization of the collagen and elastin of the aortic media. The authors revealed that collagen and fibrin are in a folded loop configuration at low pressure. Elastin increasingly unfolds as pressure increases, until the elastin is completely unwound. At this point, the vessel diameter depends on smooth muscle tone, and thus maximum vessel diameter is reached while collagen fibers are still in a folded state; that is the vessel is in compliance. If the rigid collagen fibers unfold, vessel wall distension reaches a limit; that is the vessel is not in compliance. The PA wall contains less elastin and smooth muscle than the aortic wall.33 Therefore, the PA is incompliant when exposed to mean pressures above physiological pulmonary circulation pressures. However, it is worth noting that the stiffness indexes for both the PA and the thoracic aorta were similar over the range of mean pressures reported. Unlike arterial compliance, the arterial wall stiffness index (b) does not depend on quantitative pressure changes and has therefore been advocated as more useful for describing the viscoelastic behavior of the artery.34 Indeed, stiffness of the PA is being increasingly recognized for its prognostic value in pulmonary hypertension.35,36

Human and bovine pericardial conduits were significantly less compliant and stiffer than the PA at mean pressures of 10 and 20 mmHg. Our results are in line with previous experimental studies investigating the mechanical properties of human and BP using tensile tests.37,38 Tremblay et al.29 showed that anisotropy of the aorta significantly increases with increasing strain, while that of fresh human pericardium decreases with increasing strain; from 1.2 times to only 1.05 times the axial value. The authors also reported that human (11 times) and bovine (22 times) pericardium were stiffer than the ascending aorta.

PTFE and Dacron substitutes were considerably stiffer and less compliant than the PA. These results are consistent with previous studies comparing the elastic properties of prosthetic grafts and arteries.28,39 The reduction in PA distensibility at mean pressures above 30 mmHg resulted in the absence of a statistically significant difference in compliance and stiffness at 40 and 50 mmHg between the PA and synthetic prostheses. Investigation of the elastic properties of composite substitutes did not show significant differences with those of the PA, suggesting that the implantation of a nonhuman substitute has no influence on the compliance of the PA. However, these results should be considered with caution. For instance, reports from Kelly et al.40 showed that implantation of nonhuman substitutes in the aorta limits the redistribution of energy between systolic to diastolic phases, and increases oxygen consumption in the myocardium during exercise. In vivo studies under physiological conditions that take into account right ventricle afterload would be more appropriate for addressing this issue.

The results from this study could overestimate the elastic proprieties of the tested substitutes, and particularly those of the PA. Compliance depends on both increase in diameter (circumferential deformation) and axial elongation (longitudinal deformation). Fixing the substitutes to the connectors in our study allowed us to measure circumferential changes, but we could not investigate changes in longitudinal properties. Furthermore, the connective tissues adjacent to the arteries and the periprosthetic fibrous scarring may limit vessel wall expansion in the in vivo physiological setting, which would be manifested by lower compliance values than those observed in this study. Next, despite the viscosity and density of the blood-mimicking perfusate being similar to those of blood, the bench test would not permit the thrombogenic properties of the different substitutes to be studied. This should also be factored into the choice of surrogate to be grafted.

Conclusions

Biological arterial grafts appear to be the most suitable substitutes for PA replacement in terms of compliance and stiffness at low mean pressures of 10 and 20 mmHg. Compared to the PA, the elastic properties of the bovine pericardial conduits were not different to those of the synthetic prostheses. Additional in vivo studies are needed to evaluate the impact of prosthetic replacement on PA compliance and right heart function.

Author Contributions

KH Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing original draft. LC: Conceptualization; Methodology; Formal analysis. PAP: Data curation; Formal analysis. LS: Visualization; Writing, review. IS: Conceptualization; Resources; Validation. SK: Data curation, Primary analyses, Review, editing. YL: Statistical

analysis; Results interpretation. TG: Methodology; Validation; Visualization. PA: Methodology; Supervision; Validation.

Disclosure

None declared.

Funding

None.

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