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Use of bioresorbable scaffold for neopulmonary artery in simple transposition of great arteries: Tissue engineering moves steps in pediatric cardiac surgery

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ABSTRACT

Background: Supravalvular pulmonary stenosis (SPS) remains a worrisome complication in the long term of simple transposition of the great arteries. Issues of scar formation and inability to grow are considered at the base of this phenomenon. We pioneered the use of a tissue engineering approach to guide the maturation and the growth of pulmonary autograft in the Ross procedure with encouraging results. We therefore sought to investigate the use of a similar approach in the reconstruction of neopulmonary trunk (NPT) with the aim to recreate a vascular conduit that retains the structural architecture and the same biological potential of native pulmonary artery and prevents long-term SPS.
Methods: A model of NPT reconstruction in growing lambs was used. NPT was constructed with autologous pericardium and reinforced with a four-layered knitted polydioxanone mesh (PDS n = 10) or left unreinforced (control n = 10). Animals were left growing for 6 months and angiographic and transesophageal echocardiographic measurements were performed at day 1 and at the end of the study together with histological analysis.
Results: Control group developed SPS while PDS reinforcement allowed a progressive increase in diameter with an optimal size to match the pulmonary artery of healthy growing controls. Histological analysis showed in the control group disruption of endothelial lining with fibrosis, while demonstrated in the PDS group a trilaminar vessel-like structure.
Conclusions: The bioresorbable reinforcement induced the formation over time of a neopulmonary conduit able to both face the hemodynamic load of the pulmonary system and guarantee a harmonious increase in size during the somatic growth.

1. Introduction

Supravalvular pulmonary stenosis (SPS) remains a worrisome complication in the long term of simple transposition of the great arteries (sTGA) (1). The extensive mobilization of the pulmonary arteries (PA) and the creation of a longer neopulmonary trunk (NPT) often are not often sufficient to prevent the inconvenience of re-interventions at distance (2,3). The use of the biological valves conduits and the pulmonary homograft (PH) conduit inserted in orthotropic and heterotopic positions is still proposed for many complex congenital cardiac lesions involving the right ventricular outflow tract (RVOT). These two alternatives are not suitable in neonates with sTGA undergoing arterial switch operation (ASO) (4–7) and the use of autologous pericardium has been claimed to be the best choice to reconstruct the NPT in these procedures even if carrying the risk of SPS.

We have successfully pioneered the use of fibrillar scaffold made with polydioxanone for reinforcement of the pulmonary autograft in a model of the Root Ross procedure in the growing lamb (8). In vivo application of this biomaterial elicited a phenomenon of histoarchitectural rearrangement of PA resulting in medial thickening and in an increase in the elastic wall component leading to the formation of a "neovessel" with characteristics similar to the native aorta (9,10). We might reliably speculate that the temporary interaction between the bioresorbable reinforcement and the PA might have orchestrated a complex process of vascular remodeling based on a balance between inflammation and extracellular matrix production resulting, after biomaterial resorption, in an arterial-like vessel still biologically alive and capable of growth (11). Indeed, on a side the biomaterial accompanied and accelerated

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the naturally occurring pressure-load adaptation phenomena by attenuating the load exerted on the pulmonary artery and compensating the tendency to dilation and aneurysmal degeneration. On the other side it still permitted and respected somatic growth of vascular structure over time (12,13). This concept might be extended to other conditions involving a pressure-load conditioning of vascular structures normally bearing non-arterial regimens. With this in mind, we thought that the biological reinforcement might be used to prevent the complications of the arterial switch operations (ASO) for transposition of great artery (13), which mainly regard neo-aortic root enlargement and regurgitation for the left outflow tract repair, and the onset of supravalvular pulmonary stenosis for the right ventricular to pulmonary artery (RV-PA) reconstruction.

The objective of this study was therefore to recreate a vascular conduit that retains the structural architecture and the same biological potential of native pulmonary artery and prevents long-term supravalvular pulmonary stenosis in the anatomical correction of simple transposition of the great arteries.

2. Methods

2.1. Experimental protocol

A typical reconstruction of the right outflow tract for transposition of the great arteries was simulated in two months old growing lambs in order to reproduce the pediatric clinical scenario. The neopulmonary trunk was obtained with autologous pericardium. In ten animals pericardium was reinforced with a commercially available four-layered knitted polydioxanone mesh (Ethicon, NJ, USA) (group PDS n = 10) (Fig. 1). The remaining ten were used as control (group control n = 10).

The age of the animal at the moment of the implant was about 2 months (8–10 weeks) and baseline mean weight was 18 ± 2 kg (BSA 0.754 with a PA mean diameter 14.4 ± 1.3 mm) allowing to observe the progression of NPT diameter during the period of fastest growth of the subject (first 3 months). Animals were left growing and observed over a six-month period, in consideration of the resorbing time of the biomaterial used (9). Angiography and transesophageal echocardiography were performed immediately after the operation at the time of day one (D1) and after six months. Animals were then humanely sacrificed and histological analysis with Hematoxylin-Eosin staining was performed.

All animal experiments have been performed in respect of guidelines for animal care and handling and the protocol was approved by the institutional animal care committee.

2.2. Animal model

An animal model previously developed to simulate pulmonary artery transposition during Ross procedure has been used with some modifications (9). Briefly, lambs were premeditated with ketamine (25 mg/kg IM) and anesthesia was guaranteed by the injection of sodium thiopental (6–8 mg/kg) via the internal jugular. Animal received 100 mg of lidocaine intravenously as prophylaxis against rhythm disturbance. After endotracheal intubation, ventilation was provided up to animal awakening and the anesthesia was maintained with inhalation isoflurane (1% to 2.5%). The electrocardiogram was monitored. Chest was prepped and shaved. The heart was approached via left thoracotomy. After opening the pericardium, the right atrium was exposed for cannulation and the trunk of the pulmonary artery was dissected free from its right ventricular origin up to its bifurcation in the pulmonary arteries. The same was done for the ascending thoracic aorta. Three mg/kg of heparin was given intravenously, and cardiopulmonary bypass was started between right atrium and descending aorta. The cerebral circulation of the animal was guaranteed on a beating heart. Pulmonary trunk was removed and replaced with a neocylinder obtained from autologous pericardium constructed around a Hegar's probe. This autograft was alternatively reinforced or not reinforced with the bioresorbable scaffold before implantation to reconstruct the right outflow tract. The neopulmonary graft was implanted with a proximal and distal end-to-end anastomosis in 5–0 Prolene, as in the TGA correction operation. Left thoracotomy was closed and aspiration drainage left in place.

The bioresorbable scaffold was realized in four layered 15 mm wide bands of knitted PDS. Meshes were cut into a rectangle measuring 30 mm in height matching with the height of autograft and rolled out on a metallic candle and then reassured by a suture to create a cylinder with an internal diameter of 15 mm (30 mm in height in 15 mm diameter directly adherent to the pericardium neopulmonary trunk) (Fig. 2). The autograft was then inserted into the fibrillar cylinder and was anastomosed suturing both its margins and those of the prosthetic structure to the neopulmonary autograft trunk. The mesh was oriented to allow maximal extensibility in the longitudinal direction (which allows the growth in length) and minimal transverse extensibility (limiting the enlargement of the diameter).

2.3. Data acquisition

Animals underwent two sets of angiographic and echocardiographic measurements at day 1 (D1) and 6 months (M6). Eventually, animals were humanely sacrificed and tissue harvested for histopathological analysis. Measurements of the NPT proximally and distally were made in order to obtain a reference to be compared to the diameter of the PA. A weight curve for each animal during the growing period was processed in parallel. The diameter of the PA was determined by arteriography of the NPT in using radiopaque markers to determine the diameter of its basal side and height. The transesophageal echocardiography was also used to assess the size of the neo-PA. This measurement was made at day one, using a short axis view. The pulmonary artery growth in healthy control lambs was used as a reference value. At the sacrifice of the animal, the NPT was examined and the severity of adhesions with neighboring structures was evaluated with a graded scale based on anatomic parameters from 1 to 3. The NPT was fixed and processed for Hematoxylin-Eosin staining.

2.4. Statistical analysis

Continuous data are presented as mean ± standard deviation. Continuous variables were compared using unpaired Student's t-test and analysis of variance (one-way ANOVA) was performed to compare groups with different reinforcements, followed by multiple pairwise comparison procedure. P values less than 0.05 (two-tailed) were taken to indicate statistical significance. Analysis was performed with the SPSS version 20.0 software for Mac.

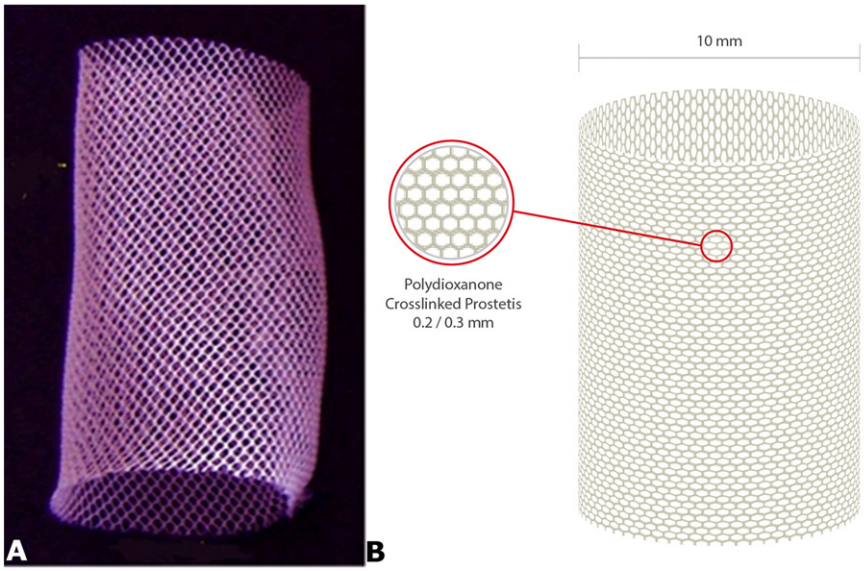

Fig. 1. A. PDS mesh used as resorbable reinforcement for NPT. B. Schematic diagram of resorbable mesh. Note PDS layer is arranged in a frame of hexagonal cells. Measure of mesh openings is reported in figure.