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Case Report

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Histological examination of the pulmonary artery and aorta in an adolescent undergoing the Ross procedure

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Abstract

Background: The Ross procedure offers several advantages for adolescents requiring aortic valve replacement, but progressive pulmonary autograft dilation is a well-described risk. To provide novel insight into the pre-Ross histology in an adolescent with bicuspid aortic valve (BAV)-associated aortopathy, we describe the extracellular architecture of the pulmonary artery (PA) compared to the native ascending aorta. *Methods:* A 15-year-old with BAV, symptomatic moderate aortic insufficiency and aortic stenosis, and ascending aortic dilation underwent Ross. Intraoperative specimens included the main PA and ascending aorta. Tissue specimens were fixed, stained using 1) haematoxylin and eosin, 2) Verhoeff's van Gieson, and 3) trichrome, and compared using light microscopy. *Results:* Elastin van Gieson stain revealed that the aortic media in the dilated ascending aorta contained a greater concentration of dense elastin weaves and a regular distribution of collagen compared to the PA. In contrast to the dense and organised compaction of elastic fibres in the media of the aortic specimen, the PA, though grossly normal, demonstrated extensive disruption and fragmentation. Trichrome staining revealed minimal fibrosis in both specimens. *Conclusions:* Notable pre-Ross histological differences include marked disruption of elastin in the PA compared to the aorta. Age-based differences in Ross outcomes suggest that adolescents may experience proportionally more significant autograft dilation over time, so future studies should include prospective collection and histological analysis of specimens across the age spectrum, both pre- and post-Ross, to allow comparison to age-matched controls.

Introduction

In children with aortic valve pathology, the approach to management requires complex decision-making by the surgical team, patient, and caregivers. For patients with an aortic valve not amenable to surgical repair, the Ross procedure is an option in which the aortic valve is replaced with the patient's native pulmonary root and valve (pulmonary autograft). The Ross procedure is the standard of care for severe congenital aortic stenosis (AS) and other congenital defects in the paediatric population, and it is considered superior to a replacement with a prosthetic valve because of its growth potential, excellent durability compared to bioprosthetic valves, and the avoidance of lifelong anticoagulation compared to mechanical valves. However, the pulmonary and systemic circulations are comprised of vastly different physiologic conditions that may affect the function and durability of the pulmonary autograft after implantation, particularly across the age spectrum.

Following the Ross procedure, the pulmonary autograft is exposed to systemic pressures, and dilation of the pulmonary autograft, out of proportion to somatic growth, has been observed in mid- and long-term follow-up.[1–3] Prior reports suggest that pathologic autograft dilation is more likely in patients that undergo Ross at age 1 year or older.[4] Several authors have observed that the architecture of the pulmonary artery and aorta is similar at birth but adapts to their new environments over time; thus, the pulmonary artery may not be well suited to withstand systemic pressures in older children.[1–3] The rate, extent, and character of divergent aorta and pulmonary artery remodelling, both in native configuration and in post-Ross configuration, are not universally defined and remain areas for active research.[2]

Patients with congenitally bicuspid aortic valves undergoing the Ross procedure represent a group of particular interest. Bicuspid aortic valve (BAV) is the most common congenital cardiac abnormality, with reports demonstrating its high rate of co-incidence with other abnormalities such as coarctation of the aorta as well as pathological processes thought to be related to the

predilection for cystic medial necrosis of the aorta, including aortic dissection and annuloaortic ectasia. Studies of patients with BAV undergoing the Ross procedure suggest that medial changes in the ascending aorta are more clinically important than in patients with tricuspid aortic valves, perhaps contributing to progressive autograft dysfunction by distortion or dilation at the anastomosis to the ascending aorta.[4]

To provide novel and critical insight into pre-Ross histology in an older child, this report aims to describe the cellular and extracellular architecture of the pulmonary artery, aorta, and BAV in a patient with symptomatic mixed AS and aortic insufficiency (AI) and an ascending aortic aneurysm undergoing a Ross operation.

Material and methods

Clinical details

A 15-year-old boy had been followed since birth for congenital AS, BAV, and dilated ascending aorta. The patient had a history of balloon aortic valvuloplasty on the first day of life and again at 3 months. He was ultimately referred for surgery due to increasing symptoms of fatigue in the setting of moderate AI, moderate AS, and mild left ventricular hypertrophy. His ascending aorta measured 4.5 cm in maximal diameter. Aortic root size was normal. A transthoracic echocardiogram revealed a well-functioning, tri-leaflet pulmonary valve with an annulus measuring 21 mm in diameter. The patient was offered a "supported" Ross operation with a straight woven polyester vascular graft enclosing the pulmonary autograft vs. a modified Bentall procedure with a mechanical valve. The family and patient were counselled on valve replacement options. They opted for the Ross procedure due to the desire to avoid anticoagulation and the knowledge that at this near-adult size, the autograft could be supported within the vascular graft and thus would be unlikely to dilate. This study was deemed exempt from review by the Nemours Children's Hospital Institutional Review Board, and the patient's parent provided consent for publication.

Operative details

The operation was performed on cardiopulmonary bypass utilising bi-caval cannulation and moderate hypothermia. The native BAV was observed to be functionally unicuspid, thickened, and dysplastic, with fusion of the right-noncoronary commissure and the right-left commissure. It was excised and sent for histological examination. The pulmonary autograft was harvested and measured 21 mm in diameter. The autograft was supported in a 26 mm straight tube graft. The right and left coronary artery buttons were reimplanted in the usual anatomic positions in the right and left facing sinuses. Right ventricle to pulmonary artery continuity was re-established with a 24 mm surgeon-fashioned (hand-sewn) polytetrafluoroethylene (PTFE) tri-leaflet valved conduit. After an unremarkable postoperative course, the patient was discharged home with trivially regurgitant and non-stenotic neoaortic and neopulmonary valves. The patient is doing well with unchanged echocardiographic findings at two years post-Ross.

Histological examination

Intraoperative specimens included the distal main pulmonary artery, dilated ascending aorta, and aortic valve cusps. Tissue specimens were fixed in 10% neutral buffered formalin followed by paraffin embedding. Samples were then sectioned and stained using 1) haematoxylin & eosin (H&E), 2) Elastic Verhoeff's van Gieson (EVG), and 3) Gomori' strichrome. They were examined at low and high-power magnifications using light microscopy.

Results

Aorta

The aortic specimen was grossly unremarkable. After H&E staining under low power, no significant intimal thickening was observed. At high-power magnification, regular and compact parallel lamellae of elastic tissue were noted with EVG stain (Figure 1b). Gomori's trichrome stain revealed no internal or mural fibrosis (Figure 1c). Figure 1a demonstrates minimal thickening of the aortic intima on H&E stain only.

Pulmonary artery

The pulmonary artery specimen was grossly unremarkable. Haematoxylin and eosin staining revealed minimal intimal thickening (Figure 2a). The Gomori's trichrome stain revealed no significant intimal or mural fibrosis (Figure 2b). However, the EVG stain on low- and medium-power magnification views showed extensive fragmentation of the elastic fibres. (Figure 3). In contrast to the dense and organised compaction of elastic fibres in the aortic specimen, Figure 3 demonstrates the extensive disruption and fragmentation of the elastic fibres in the media of this patient's pulmonary artery and represents an abnormal finding for a pulmonary artery in a 15-year-old.

Aortic valve

The aortic valve cusps showed myxoid change with minimal chronic inflammation after staining with H&E (Figure 4).

Comment

Remodelling of the pulmonary autograft starts immediately after exposure to higher systemic pressures, and while many patients will have a durable and well-functioning autograft valve for decades, some will develop autograft dilation and will require reoperation.[1,3–6] Studies have demonstrated that heart valves retain the capacity to adapt to their environment such that transcriptome profiles and collagen fibre thickness and orientation change from foetal to adult life.[7] The histological structure of the great vessels and valves therefore provides important information about their function.

Aorta and pulmonary artery

The walls of the aorta and the pulmonary artery exhibit significant differences in histological structure and mechanical properties. The intimal, medial, and adventitial layers of arteries have specific microstructures that preserve the integrity of the vessel during the cardiac cycle. At the lower pressures of diastole, elastin fibres in the media provide wall tension. At high pressures of systole, collagen fibres in the media and adventitia impart strength and limit distensibility. While all three layers are present in every artery of the body, the media of the aorta contains a greater concentration of dense elastin weaves and a regular distribution of collagen, allowing the aorta to withstand the much higher pressures of the systemic circulation, as demonstrated in Figure 1b.

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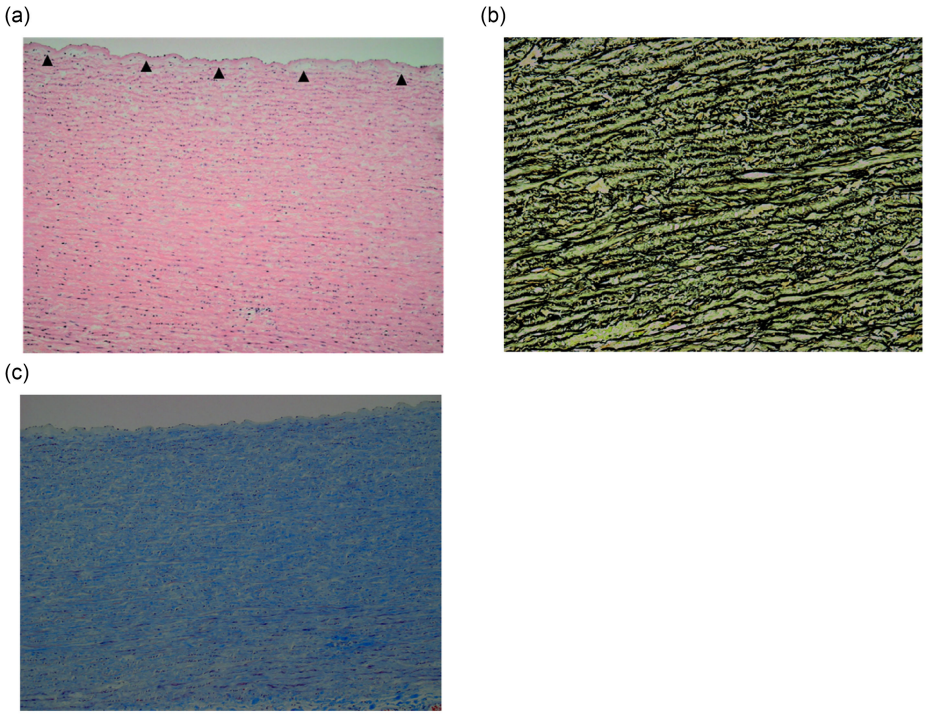

Figure 1. (***a***) Low-power view of the aorta with arrowheads indicating minimal intimal thickening (haematoxylin and eosin, 10x). (***b***) Medium-power view of elastic stain highlighting the compact, parallel lamellae of elastic tissue in the ascending aorta (Elastic van Gieson, 20 x). (***c***) Low-power magnification view of the aorta showing no significant increase in fibrous intimal thickening (Gomori's trichrome, 10x).

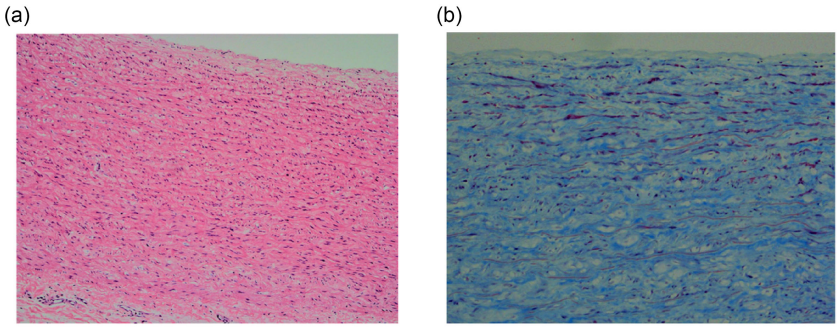

Figure 2. (***a***) Low-power view of pulmonary artery showing minimal intimal thickening (haematoxylin and Eosin 10 x). (***b***) Medium-power magnification view of the pulmonary artery showing no fibrous intimal thickening (Gomori's trichrome 20x).

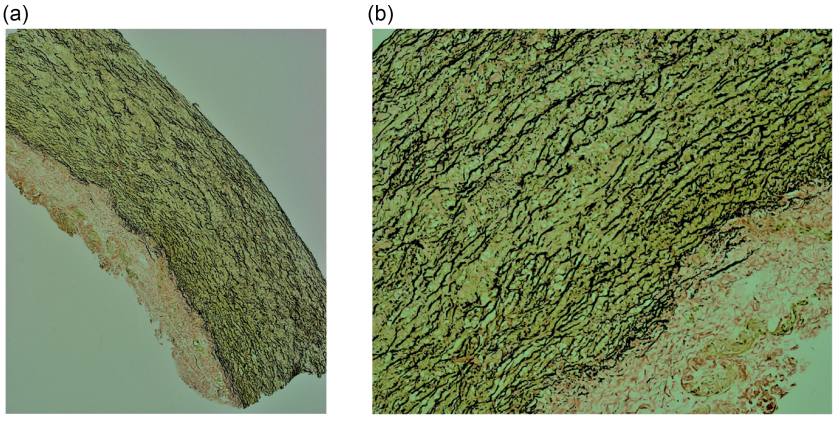

Figure 3. (***a***) Low-power view of elastic stain showing extensive fragmentation of the medial elastic tissue of the pulmonary artery (Elastic van Gieson 4x). (***b***) Medium-power view of disrupted elastic fibres in the pulmonary artery (Elastic van Gieson 10x).

The pulmonary artery is typically part of a low-pressure system that facilitates efficient intrapulmonary circulation for the process of gas exchange. Thus, the pulmonary artery's walls (and each individual layer) are usually thinner with approximately 50% fewer rows of elastic lamellae compared to the aorta, and the elastin fibres are stiffer at systemic pressures.[2] Normally, in the pulmonary artery, the elastic lamellae are intact and aligned in a parallel arrangement. In Figure 2, similar minimal intimal thickening to

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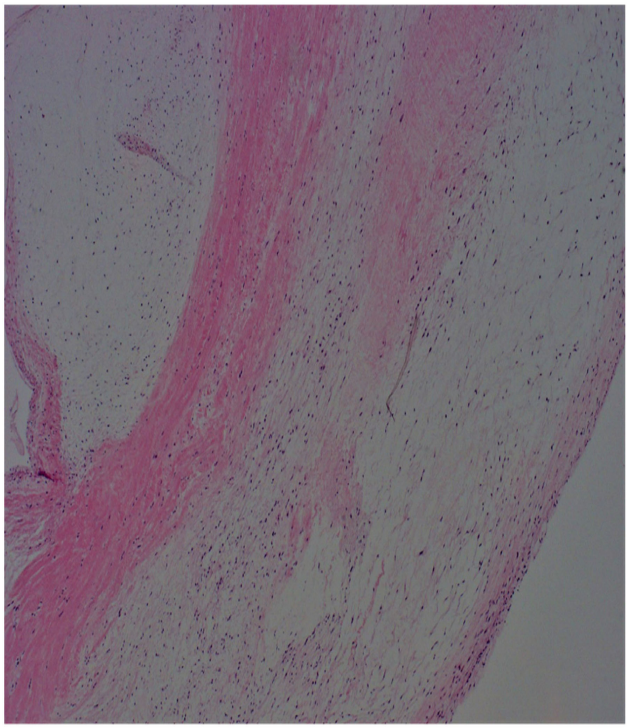

Figure 4. Low-power view of aortic valve leaflet. There is myxoid change with minimal chronic inflammation (haematoxylin and eosin, 4x).

that of the patient's aorta can be appreciated. In contrast to the dense and organised compaction of elastic fibres in the aortic specimen, Figure 3 demonstrated the extensive disruption and fragmentation of the elastic fibres in the media of this patient's pulmonary artery, which is abnormal.

Bicuspid aortic valve

While the arterial walls of the pulmonary artery and aorta exhibit notable differences allowing for optimal physiological performance under different pressure conditions, the aortic and pulmonary valves have a similar tri-layered structure delineated by endothelium on the arterial and ventricular side.[8]

The fibrosa, the first layer on the arterial side of the aortic valve, is composed primarily of type I and type II collagen that form a dense fibre network which maintains tensile strength while also remaining quite flexible under tension. The middle layer is the spongiosa, a glycosaminoglycan-rich tissue that confers flexibility and maintains integrity during the dynamic motion of the leaflets. On the ventricular side of the valve, the ventricle is rich in elastic sheets, allowing it to serve as the load-bearing layer of the leaflet at low strains.

As observed in this patient, bicuspid aortic valves are often associated with aortic root and ascending aortic dilation.[1] Histological findings of such BAV-associated pathology often include cystic medial degeneration of the aortic wall. Cystic medial necrosis is a complex degenerative process affecting predominantly large-sized elastic arteries, and consensus is lacking on the exact histopathological changes that define it. The extracellular matrix is severely affected, and elastin fibre disorganisation, thinning, and fragmentation can be observed in the media. Smooth muscle cells undergo alterations that include the breakdown and reduction of these smooth muscle cells, leading to necrosis and disrupting the normal architecture of the wall. The cyst-like appearance on an H&E stain results from mucoid extracellular matrix accumulation.[8] Myxoid change of the BAV leaflets with minimal chronic inflammation can be appreciated in Figure 4 and was thus consistent with the pathway of myxoid change to cystic medial degeneration that is seen in BAV-associated aortopathy.

The long-term success of the Ross procedure is dependent upon the ability of the pulmonary autograft to perform reliably within the systemic circulation. Understanding the histological characteristics of the valvular components is imperative to elucidating the potential adaptation process of a paediatric patient's autograft valve after the Ross procedure. Ultimately, deepening knowledge of the extent of adaptation of the pulmonary root when exposed to the systemic circulation can assist surgeons in determining the optimal timing for the Ross procedure and mitigate the risk of autograft failure.

This report offers limited generalisability, as it describes the histological findings of one patient. The results are therefore presented as hypothesis generating, rather than conclusive, regarding Ross's outcomes. Additionally, PTFE-graft reinforcement of the autograft, as was performed in this patient, may have an impact on the future remodelling of the neoaortic root. Lastly, this report represents a single time point rather than a longitudinal evaluation of changes over time." Therefore, future studies will include 1) age-matched control specimens, 2) the prospective collection of aortic and pulmonary artery specimens in patients of varying ages at time of Ross, and 3) histological findings of explanted autograft specimens across the age spectrum considering age at implant and interval time in situ.

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