Perspective

Pulmonary autograft in aortic position: is everything known?

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Comment on: Mookhoek A, Krishnan K, Chitsaz S, *et al*. Biomechanics of Failed Pulmonary Autografts Compared With Normal Pulmonary Roots. Ann Thorac Surg 2016;102:1996-2002.

Abstract: The Ross operation provides several advantages compared to other valve substitutes to manage aortic valve disease, such as growth potential, excellent hemodynamics, freedom from oral anticoagulation and hemolysis, and better durability. However, progressive dilatation of the pulmonary autografts after Ross operation reflects the inadequate remodeling of the native pulmonary root in the systemic circulation, which results in impaired adaptability to systemic pressure and risk of reoperation after the first decade. A recently published article showed that remodeling increased wall thickness and decreased stiffness in the failed specimens after Ross operation, and the increased compliance might play a key role in determining the progressive long-term autograft root dilatation. Late dilatation can be counteracted by an external barrier which prevents failure. Therefore, an inclusion cylinder technique with a native aorta or a synthetic external support, such as Dacron, might stabilize the autograft root and improve long-term outcomes. In this article, we offer a prospective about the importance of biomechanical features in future developments of the Ross operation. Pre-clinical and clinical evaluations of the biomechanical properties of these reinforced pulmonary autografts might shed new light on the current debate about the long-term fate of the pulmonary autograft after Ross procedure.

Keywords: Ross operation; pulmonary autograft; biomechanics

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The clinical problem

The Ross operation provides several advantages compared to other valve substitutes to manage aortic valve disease especially in the pediatric population, such as growth potential, excellent hemodynamics, freedom from oral anticoagulation and hemolysis, and better durability (1-19). Since Donald Ross performed the first successful operation in 1967 (1,2), survival rates have increased due to refinements of surgical techniques and improvements in medical management (3-8,20,21). Despite the technical complexity and modifications over years (22-29), this procedure gradually entered into the show in the cardiothoracic surgery scenario and the pulmonary autograft is considered the ideal substitute for both congenital and acquired disease of the left ventricular outflow tract. Currently, children and young adults who underwent Ross operation generally reach adulthood, with a 16-year survival rate of nearly 90% (30) and a life expectancy similar to that of the general population (31-33). However, the use of biological derivative poses some ethical issues related to the risk of reoperation due to autograft failure beyond the first decade (12,34). In the contest of pulmonary autograft implantation, the balance between pulmonary autograft root failure and the risk of structural valve degeneration with potential allogeneic valve dysfunction (23,30,35) versus favorable hemodynamic behavior, no requirement of prolonged anticoagulation treatment and a very low incidence of infection recurrence, which would require further complex redo-surgery and tissue demolition, should be taken into account when discussing with the patient the surgical options. Progressive dilatation of the pulmonary autografts after Ross operation reflects the inadequate remodeling of the native pulmonary root in the systemic circulation, which results in impaired adaptability to systemic pressure. Histologic analysis proved that loss and fragmentation of medial elastin fibers and increased adventitial collagen deposition occur after implantation (36-38). Since late autograft dysfunction remains a daunting issue in the Ross operation, our group and others tried to characterize the biomechanical aspects of pulmonary autograft failure (39-49) to understand in details the long-term effects and develop future frontiers in both surgical and basic researches.

The study described by Mookhoek and co-authors recently appeared in *Annals of Thoracic Surgery* reports the results concerning biomechanics of failed pulmonary autografts compared with normal pulmonary roots in a series of ten Ross patients and seven controls. The authors applied the mathematical-physical model in which the explanted autograft and pulmonary roots were assumed incompressible and nonlinear hyper-elastic materials (50). They found that non-linear stress-strain response was present in both failed and normal pulmonary roots, but remodeling increased wall thickness and decreased stiffness in the failed specimens after Ross operation. The increased compliance might play a key role in determining the progressive long-term autograft root dilatation. Interestingly, this remodeling determines detrimental macroscopic effects only after years from implantation, and might explain why autografts do not dilate immediately after implantation, confirming literature reports, which state that autograft dilatation generally occurs a decade later. This paper nourishes and expands the discussion about the failure of pulmonary autograft root in Ross operation occurring as a consequence of its active irreversible expansion and reopens the debate arisen in the previous meta-analysis and observational studies.

Evidence from trials and observational studies

In a large systematic review of thirty-nine articles (35), pooled rate of early death from any cause for consecutive, adult, and pediatric patients was 3.0% [95% confidence interval (CI), 1.8 to 4.9], 3.2% (95% CI, 1.5 to 6.6), and 4.2% (95% CI, 1.4 to 11.5). Overall late death rates were low and in subgroup analysis of adult series based on demographic and clinical characteristics, late mortality reflected general population. Autograft deterioration rates 0.78% (95% CI, 0.43 to 1.40) for adults, and 1.38%/patient-year for children (95% CI, 0.68 to 2.80), respectively, and for right ventricular outflow tract conduit were 0.55% (95% CI, 0.26 to 1.17), and 1.60%/patient-year (95% CI, 0.84 to 3.05), respectively.

Observational study (9,14-16,18) and more recent randomized study controlled (23-25) have updated the previous work by including higher-risk patients and reflecting changes in clinical and surgical practice. These studies included large numbers of patients with different aortic disease pathogenesis who were treated with reinforcement of pulmonary autograft (23-25,51). In the series of Elkins at 16 years (30), survival was 82%±6%, and hospital mortality was 3.9%. In children group, survival was 84%±8%, and freedom from autograft valve failure was 83%±6%. The study revealed a low rate of autograft failure, including autograft reoperation and valve-related death, estimated in 26%±5%, which required reoperation. A multivariate statistical analysis showed a higher incidence of autograft failure among males and in case of primary aortic valve regurgitation. The rate of right ventricular outflow tract structural and non-structural valve deterioration requiring reoperation was 18%±4% and rate of all valve-related events was 37%±6%.

In the systematic prospective German-Dutch Ross registry (11,23), 1,620 patients with 1,420 adults (mean age 39±16.2 years) and 200 children (mean age 8,4±5,1 years) were enrolled and surgical details were evaluated, with subcoronary implantation or root replacement, the latter with combined with external reinforcement of pulmonary autograft. Patients had a lower rate of early and late mortality, which was 1.2% and 3.6%, respectively.

Those studies are confirming that Ross operation is a safe and durable approach to treat aortic valve disease in the younger population. However, long-term pulmonary autograft dilatation after Ross procedure remains a daunting issue as results in reoperation and increased mortality. Also, newer surgical options to treat aortic valve disease with minimally invasive techniques are emerging as an important alternative. However, none of the current aortic valve replacement strategy offers the benefits related with the adaptation to the somatic growth proper of the Ross procedure and therefore it is vital to improve the long-term outcomes of the Ross procedure by reducing its most common side effect. Adequately addressed studies should investigate pulmonary autograft dilatation in details, with the aid of biomechanics, to improve surgical outcomes.

Pulmonary autograft failure

Ross operation can be performed with a complete preservation of pulmonary autograft root or with a subcoronary implantation technique (2). The technique of preservation includes individual variation of the application of the root replacement technique and many ways can be undertaken to achieve a correct insertion, and levels of proximal implantation and distal suture were chosen according to the preference of each surgeon. On the other hand, the subcoronary implantation technique is gradually being abandoned by most centers for multiple reasons, including its technical complexity related to the correct geometrical orientation of pulmonary autograft. Moreover, the increased biomechanical stress of the pulmonary valve leaflet can promote faster structural valve degeneration with increased risk of adverse events in children undergoing somatic growth. Late autograft dysfunction in the root replacement technique is generally related to the progressive root dilatation, which leads to aneurism formation and aortic regurgitation, while autograft failure after implant in the subcoronary position is generally, but not exclusively, caused by leaflet dysfunction (34,52-56).

Children and young adult arm of pulmonary autograft root insertion was associated with less favorable results compared to adult arm considering the same surgical implantation technique, and pulmonary autograft root dilatation plays a major role in long-term outcomes (35). These findings were directionally similar to those reported on the basis of the long-term results in other studies (11,13,30). Thus, it appears that the failure risk of pulmonary autograft root expansion associated with Ross operation is offset by a low occurrence of thromboembolic complications, bleeding, nonstructural valve failure, and endocarditis compared with other aortic valve substitutes that translates into increasing clinical benefit to at least 15 years.

A predictor of progression of pulmonary autograft root expansion and impaired long-term outcome is the presence of a congenital aortic valve disease. Accumulating evidence suggest that bicuspid aortic valves is previously associated with increased pulmonary autograft root diameter and sub-sequential higher risk of failure and durability (57), and therefore in this category of patients the problem of autograft dilatation seems greater.

Biomechanical and biological insights of the pulmonary failure

The study of Mookhoek *et al*. (50) adds a piece in the puzzle of the mechanical phenomena related to the dilatation of pulmonary autograft under systemic conditions. The authors focused their attention on the idea that failed pulmonary autografts retained nonlinear response to mechanical loading typical of healthy human arterial tissue, as nonlinear stress-strain response was present in both failed autografts and normal pulmonary roots. Remodeling process was demonstrated in failed explanted conduits with an increased wall thickness and decreased stiffness. Explanted pulmonary autograft were less stiff compared to that their native pulmonary root counterparts at 8 mmHg (134±42 *vs*. 175±49 kPa, respectively) and 25 mmHg (369±105 *vs*. 919±353 kPa, respectively), independently of age at the Ross procedure or time in the systemic circulation. As reported by the authors in the study, the increased compliance may explain progressive autograft root dilatation in autograft failures.

Those dynamic features are related to the histologic changes observed in "pulmonary autograft" with abnormal and dysregulated biological pathways within the pulmonary vessel wall, those represent the detrimental effect of a systemic circulation in a tissue, which was used to a low-pressure circulation, and ultimately result in increased compliance and long-term dilatation.

Stress strain and impaired compliance mediate injury by several mechanisms on the extracellular matrix protein, with loss and fragmentation of medial elastin fibers and increased adventitial collagen deposition (36-38), as in other cardiac conditions (58). Also, the imbalance of matrix metalloproteinase and their inhibitors leads to dysregulation of extracellular matrix metabolism, which results in apoptosis, delamination, inflammation and formation of aneurysms (47). A deficiency of Ki-67 and matrix metalloprotease-9 have been implicated in advanced pulmonary autograft dilatation. Production of inflammatory cytokines, activation of fibroblasts, and aneurysm formation are the acclaimed event. Moreover, the resulting matrix disruption and elastin and lamellar fragmentation lead to increased apoptosis of vascular smooth-muscle cells and disruption of the media layer, adversely affecting the structural integrity and flexibility of the pulmonary autograft root (47). Those biological alterations might be crucial in the development of macroscopic biomechanical defects of the pulmonary autograft and the consequent dilatation.

Future directions

Late dilatation can be counteracted by an external barrier, which prevents failure. Therefore, an inclusion cylinder technique with a native aorta or a synthetic external support, such as Dacron, might stabilize the autograft root and improve long-term outcomes (39,59).

Previous experience with a prosthetic Dacron graft with an artificial aortic root configuration (Valsalva graft) as external reinforcement of the pulmonary autograft has been reported by Carrel (60,61). This approach was attempted with the aim to prevent neoaortic root dilatation and prevent the dynamic function of Valsalva sinuses. Surely, this technique would carry the advantage to allow the most physiologic pressure and flow patterns within the autograft in respect to a straight Dacron graft. However, the autograft encased in a straight Dacron prosthetic graft would be dramatically impaired in its pulsatility and compliance. Moreover, we previously demonstrated as Dacron graft and other synthetic polyesters severely impair aortic compliance when used as vascular replacement and elicit a strong inflammatory reaction with significant damage to vessel wall when used a pulmonary artery reinforcement (46,62). From these standpoints, we focused in improving the biomechanical behavior of the reinforced pulmonary artery using a composite biodegradable and auxetic material. The aortic root anatomy presents an increased degree of complexity and cannot be approximated to a cylindrical geometry. Additionally, material deformation occurs not only in axial and lateral fashions, but a shear stress modulus is also applied determining a sliding of the conduit components. Clinical reports on the differential enlargement of the different sectors of the root and their potential for dilation brought us to reconsider the pulmonary autograft reinforcement strategy on the basis of the mathematical model developed and on our initial experience on resorbable reinforcement. The major disadvantages of synthetic materials used in pediatric cardiovascular surgery regard the inability to adapt to the vessels during their structural development and growth, and the induction of a strong inflammatory reaction, which affects the viability of the autografts interfering with the normal process of arterialization, and impairs their elastic compliance. For these reasons, we needed to select a material suitable to comply with both shear modulus requirements and differential dilation tendency of the root. ePFTE is a material currently used in surgery and known, from the elastomechanical standpoint, to have a so-called auxetic behavior. Its Poisson's ratio (63), i.e., the parameter to describe ability of a material to respond to applied forces, is negative which provides it with extremely advantageous compliance properties. ePTFE fibers, if subjected to a tensile stress, "open up" structurally and expand in the direction transverse to the stress; conversely, if these materials are subjected to compression they "close" structurally. In the Ross operation, the pulmonary autograft might be considered as an extensible solid cylinder to which the Hooke's law for linear-elastic bodies and membranes might be applied. Growth, remodeling and strain stress were studied by integrating the law of Hook, neo-Hookean incompressible hyperelastic behavior exploiting the Laplace formula and Lamè elastic shear modulus (64-67). In the light of these results, we developed a semi-resorbable composite scaffold originated from the need to reinforce the pulmonary autograft during the Ross procedure providing an increased stabilization and solidity of the neo-aortic root and preventing its dilation due to systemic pressure. This composite prosthesis prevented pulmonary autograft dilation while reabsorption of its PDS layer promoted a connective remodeling of the pulmonary autograft wall resulting in a neo-vessel formation, with increased elastin content and therefore potentially improved biomechanical properties. Moreover, application of a bio-resorbable reinforcement is able to modify the behavior of the curve of distensible materials, such as vessels wall, obtaining an increase of their elastic properties (41-43,46,49). Pre-clinical and clinical evaluations of the biomechanical properties of these reinforced pulmonary autografts might shed new light on the current debate about the long-term fate of the pulmonary autograft after Ross procedure, in order to improve the outcomes of the treated young patients.

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Footnote

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