



Commentary: Decellularized Versus Conventional Cryopreserved Pulmonary Allografts for Right Ventricular Outflow Tract Reconstruction During the Ross Procedure

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Our group recently shared our findings from a pooled analysis of four retrospective observational studies comparing the use of decellularized and cryopreserved pulmonary allografts for the reconstruction of the right ventricular outflow tract (RVOT) during the Ross procedure. This meta-analysis¹ published in the *Egyptian Heart Journal* consisted of 1,687 patients undergoing a Ross aortic valve replacement (812 decellularized, 875 cryopreserved). Our primary outcomes were early mortality and allograft dysfunction during follow-up, while additional outcomes included need for re-intervention and endocarditis. Pooled pairwise meta-analysis showed no difference between the use of decellularized and cryopreserved grafts during the Ross procedure. Of note, no significant difference was seen for allograft dysfunction at a weighted mean follow-up duration of 5.89 years. Of note, our findings were dissimilar to 2020 systematic review by Waqanivalagi et al.² who compared decellularized versus standard tissue conduits in patients undergoing RVOT reconstructions. In their analysis, the authors included patients that had undergone decellularized heart valves surgically implanted within the outflow tract position of human subjects. Compared to standard tissue conduits, decellularized heart valves led to a lower postoperative mortality and reoperation rate, although only the reoperation rate was statistically significant. In the 2019 European ESPOIR Trial, Boethig et al.³ prospectively enrolled 121 patients in the European ESPOIR Trial evaluating decellularized heart valves for pulmonary valve replacement. When compared to cryopreserved homografts, the combined decellularized heart valve cohort showed significantly lower explantation rates and less structural valve degeneration after three years. The previous findings are encouraging, but the use of exclusively Ross patients in our study should allow us to better compare the functionality of decellularized and cryopreserved conduits since the grafts can be sized precisely before being sutured into the bed of the transplanted autograft while preserving the patient's pulmonary tree. In writing this commentary, we hope to raise some points regarding the clinical implications of our investigation that may help readers properly interpret the findings reported in the paper.

Much contemporary literature has drawn attention to the clinical and echocardiographic benefits of the Ross procedure in young adults undergoing aortic valve replacement.^{4,5} However, one of the pertinent limitations of the operation is the long-term deterioration of the allograft used to repair the RVOT following the harvest of the

pulmonary autograft for aortic valve replacement. For this reason, we believe that follow-up allograft dysfunction is one of the most clinically relevant outcomes researchers must consider when investigating patient outcomes following the Ross procedure. Unfortunately, much heterogeneity exists in how allograft dysfunction is defined in contemporary literature, impeding the ability to make generalized clinical comparisons.⁶ In a 2005 retrospective analysis of 117 patients undergoing isolated RVOT reconstruction using an allograft conduit, Brown et al.⁷ defined allograft dysfunction as either moderate or greater allograft stenosis (>40 mmHg) or 2+ allograft insufficiency. Moreover, the authors considered the failure of the allograft to be need for explantation, balloon dilatation, or mortality. Conversely, in a study of 443 patients undergoing the Ross procedure, Fricke and colleagues⁸ defined pulmonary graft dysfunction to be any need for reintervention, moderate to severe pulmonary regurgitation, or a mean systolic gradient 25 mm Hg or greater. Given the meta-analytical methodology of our investigation, our definitions for outcomes were limited to those definitions reported in the included studies, which were not uniformly in what they considered allograft dysfunction. While two of the reports used peak pulmonary gradients to define allograft dysfunction,^{9,10} a third study that was pooled did not consider gradients in their definition, opting to define it as any complication requiring re-intervention.¹¹ We believe, therefore, that contemporary studies in the Ross procedure and allograft use may benefit from improved standardization of outcome definitions. One potential method is to urge researchers to apply established definitions for valvular outcomes, such as those put forth by the American Association for Thoracic Surgery, The Society of Thoracic Surgeons, and The European Association for Cardiothoracic Surgery, which included standardized definitions for both structural and non-structural valve dysfunction.¹²

Despite its well-documented long-term benefits, use of the Ross procedure continues to diminish and is currently estimated to constitute less than 1% of contemporary aortic valve replacements.¹³ Many factors may help explain this decline in its use. Firstly, many centers have limited experience with the Ross procedure due to its technical complexity. Moreover, contemporary advancements in mechanical or bioprosthetic aortic valve replacements and transcatheter valve-in-valve treatments have diminished interest in the operation.^{14,15} In addition to varying center expertise with the Ross procedure, we believe that limited global access to pulmonary grafts for RVOT repair during the second part of the operation has contributed to its waning use. Currently, cryopreserved conduits are the most widely used conduit for a pulmonary valve replacement with well-documented use in Europe and North America, although controversy has surrounded decreased access to them in lower-income nations.¹⁶

Although no differences were observed in any explored outcome between the decellularized and cryopreserved conduits in our analysis,¹ literature suggests endothelial maintenance in cryopreserved grafts causes heightened immunogenicity. In a 2020 study by Coti et al. comparing the immunogenicity of cryopreserved and decellularized heart valve allografts, the former was associated with increased immune responsiveness and human leukocyte antigen (HLA) class I and class II antibodies while the latter displayed minimal immune response.¹⁷ Similarly, Shaddy et al. noted that patients receiving a cryopreserved graft had increased levels of HLA class I panel reactive antibody (PRA) levels within months of operation, whereas such levels did not change significantly in the control group.¹⁸ Inflammatory mediators seen with cryopreservation then induce fibrosis and neointimal proliferation with progressive graft stenosis and degeneration.^{17,19,20} Decellularization opposes this immune response by lysis of allograft donor cells while preserving the extracellular matrix. This also allows for repopulation and remodeling by autologous cells.^{19,20} Unfortunately, complex harvesting and preservation techniques, have limited the availability and widespread use of decellularized allografts.^{21,22} Given such limitations to access, particularly in underrepresented nations, we do acknowledge that clinicians may be limited in their conduit options for RVOT repair in Ross patients. With the growing attention being directed to health inequities in cardiac care,^{23,24} we hope stakeholders will address this disparity to ensure Ross patients may receive the greatest quality of care possible.

To conclude, although no significant difference was found between the cryopreserved and decellularized allograft groups in our investigation of patients undergoing RVOT reconstruction during the Ross procedure, we hope that our paper will draw attention to limitations in contemporary literature regarding pulmonary allografts, as well as disparities in access to such conduits. We thank the journal for giving us the platform to share our position.

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None

Conflicts of Interest

None

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