Living Allogenic Heart Valve Transplantation: Relative Advantages and Unanswered Questions

David Kalfa, MD, PhD1, Taufiek K. Rajab, MD2, Elizabeth Cordoves, BA3, Sitaram Emani, MD4, Emile Bacha, MD1, James Jaggers, MD5, Andrew Goldstone, MD, PhD1, Pirooz Eghtesady, MD, PhD6, Joseph Turek, MD, PhD, MBA7

1 Division of Cardiac, Thoracic, and Vascular Surgery, Section of Pediatric and Congenital Cardiac Surgery, New York-Presbyterian Morgan Stanley Children’s Hospital, Columbia University Medical Center, New York, NY
2 Section of Pediatric Cardiothoracic Surgery, Medical University of South Carolina Shawn Jenkin’s Children’s Hospital, Charleston, SC
3 Vagelos College of Physicians and Surgeons, Columbia University, New York, NY
4 Department of Cardiovascular Surgery, Boston Children’s Hospital, Boston, MA
5 Section of Congenital Heart Surgery, Children’s Hospital Colorado, University of Colorado, Aurora, CO
6 Section of Pediatric Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, MO
7 Division of Thoracic and Cardiovascular Surgery, Duke University, Duke Children’s Pediatric and Congenital Heart Center, Duke Children’s Hospital, Durham, NC

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Corresponding Author:
David M. Kalfa, MD, PhD
New York-Presbyterian Morgan Stanley Children’s Hospital
3959 Broadway
Babies North, Suite 274
New York, NY 10032
dk2757@cumc.columbia.edu
212-305-5975
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Central Message: Living allogenic valve transplantation can transform the treatment landscape for congenital valve disease by introducing a fully-viable valve with growth and self-repair capacity.

Central Picture: Columbia team (L to R: Drs. Kalfa, Bacha, Goldstone) performing a domino valve transplant.
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The Holy Grail in the field of pediatric cardiac valve surgery is to offer our patients an option which avoids the multiple reoperations required to replace outgrown or structurally degraded valve prostheses. Cryopreserved human allografts have historically represented the gold standard in pediatric valve replacements, and are commonly used to reconstruct the right ventricular outflow tract in neonates. Despite their widespread use in patients with congenital valve disease, cryopreserved homografts demonstrate recurrent failure modes of calcification and fibrosis.¹ Re-operation and mortality rates associated with homograft implantation are high, especially for infants and neonates. Infants receiving a pulmonary homograft demonstrate a 5-year allograft survival rate of only 25%,¹ and there is an 40% in-hospital mortality rate for neonates and infants receiving a homograft aortic valve replacement.²

Living allogenic heart valve transplantation (LAVT) – also known as partial heart transplantation – can disrupt the treatment landscape for pediatric patients with congenital valve disease by bringing to the table a fully-viable allogenic valve replacement.³ The presence of living resident cells within a physiologic tissue architecture enables valvular growth, envisioned to match the growth and durability of valves implanted within orthotopic heart transplants.⁴ Cellular viability facilitates homeostatic repair and remodeling, which is anticipated to underlie the homograft’s structural durability and reduce its thrombogenicity.⁵ Early preclinical and clinical studies support the graft’s predicted growth capacity, with growth of the valvular annulus and preserved valve function over the course of follow-up.⁵,⁶ This represents an unmatched advantage which is particularly relevant to young patients. Furthermore, procuring grafted tissue directly from the donor heart opens the door to different types of procedures, ranging from en bloc implantation of both donor outflow tracts together, to single-valve reconstruction using only the allograft cusps.⁷ This significantly enhances the range of surgical approaches available in
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treating complex congenital heart disease. LAVT could also improve outcomes in adult cardiac
surgery by providing a structurally durable coumadin-free alternative to bioprotheses and
mechanical valve replacements – thereby introducing a novel treatment option for young adults
with contraindications to anti-coagulation therapy, such as athletes or women who intend to
become pregnant. 8

Notably, the valve’s "living," transplanted nature also represents the origin of its greatest
drawbacks: scarce donor availability, limited ex vivo viability, and immunogenicity. Of these, the
first two introduce immense logistic and clinical challenges. Lack of donors causes doubt
regarding the relative benefits of waiting for LAVT, versus receiving an off-the-shelf valve
replacement. When a donor valve does become available, the required rapid transplant of the
homograft is a resource-intensive process (semi-emergent operations, procurement logistics and
costs). Importantly, the valve’s viability acts as a double-edged sword – living donor tissue is the
source of LAVT’s immunogenicity. Accordingly, patients undergoing LAVT are anticipated to
receive immunosuppression to prevent allograft rejection. Finally, there are uncertainties about
the optimal regulatory framework locally and nationally to oversee and provide equity among
recipients.

These limitations bring up several unanswered questions. First, how long can fresh
valvular homografts remain viable ex vivo? It is hypothesized that to fully capture LAVT’s
advantages of remodeling and growth, stromal and endothelial cell populations should remain
alive. 3 Recent work studying the viability of fresh valvular homografts ex vivo demonstrates
preservation of tissue morphology and cellular metabolic activity after 48 hours of cold storage,
with no increase in apoptotic markers. 9 In the past, homovital homografts were regularly
implanted well beyond this 48 hour timepoint – typically within 60 days of storage. 10 While
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tissue viability\textsuperscript{11,12} and microstructure\textsuperscript{13} were assessed, these studies were restricted by the
techniques available at the time. El Janabi and Ross found that the viability of the mitral valve
leaflet (studied as a surrogate for aortic valve physiology) was 58\% of baseline after 56 days of
preservation in nutrient medium; this represented a substantial increase from the viability
observed when leaflet tissues were stored in electrolyte solution.\textsuperscript{11} Lupinetti et al. have shown
that endothelial cell viability in rat valvular allografts decreases to 64\% of baseline after 21 days
of storage in nutrient medium.\textsuperscript{12} Of note, longer storage times in this study were associated with
reduced graft immunogenicity, possibly pointing to the role of endothelial cells in inducing an
adverse host immune response to the graft.

When assessing the functional implications of storage time, one retrospective clinical
study suggested increased valvular regurgitation in the setting of extended (>4 weeks) storage
time;\textsuperscript{14} nevertheless, systematic investigations have not been carried out to correlate this
observation with tissue physiology at time of implantation. Historically, tissue processing and
storage strategies differed greatly between centers, complicating a large-scale analysis of the
effect of storage time on clinical outcomes. Therefore, it is not known at which point valvular
tissue is irreversibly injured, and whether rational design of transport/preservation conditions can
extend this timeline. Moving forward, parameters of interest include: i) cellular viability and ii)
resident cell phenotype, both spatially (throughout the valvular root) and temporally (over the
course of storage). It will also be critical to document preservation of the valvular
microarchitecture, which underlies its biomechanical properties.\textsuperscript{15}

The question of \textit{ex vivo} viability is critical, as long-term preservation of valve tissue
physiology allows for increased donor availability, diminishes the logistic burdens of
transplantation, and reduces clinical unpredictability. The clinical implications are highlighted by
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recent work noting that 10.8% of heart transplants are not used due to logistic challenges. This is most significant in the neonatal age group, where 18% of hearts intended for transplantation are discarded due to procurement logistics.\(^{16}\)

An important question related to allograft viability is: \textit{do donor cells remain alive following implantation in the recipient}? Understanding the viability of allogenic valves \textit{in situ} is important to predicting their capacity for growth and self-repair. Transgenic animal models with nuclei expressing fluorescent markers hold promise in answering this question. In this transplantation model, allografts from the transgenic donor would be implanted in a wild-type recipient. Following implantation, fluorescence of donor cells enables longitudinal studies of their persistence throughout the graft over time.\(^{17}\)

Next, regarding immunogenicity: \textit{what level of immunosuppression is required to preserve the valve’s function and growth capacity in young patients}? And, \textit{what level (if any) of immunosuppression is needed to maintain a functional, non-growing valve in adults}? Relatedly, \textit{what is the role of ABO- and HLA-matching}? Although one can begin to glean answers from the outcomes of first-generation homovital homografts\(^{10}\) the immunogenicity of valve tissue is not well understood, with some studies even suggesting immune privilege.\(^{18}\) The impressive durability of homovital homografts in the absence of immunosuppression begs the question as to whether long-term immunosuppression is required. In the largest study evaluating outcomes of homovital homografts (275 patients), with a maximum follow-up of 14 years post-implantation, freedom from degenerative valve failure was noted to be 94% at 5 years, and 89% at 10 years.\(^{10}\) This rivals or surpasses the durability observed today for bioprosthetic valves implanted in adults.
However, homovital homografts do evoke an immune response, with 80% of patients developing detectable HLA antibodies. These have been classified as mostly of the IgG subclass, and (where donor HLA typing was obtainable) are mostly targeted against donor HLA antigens.

The antibodies’ implications for valve function are unknown; at a mean of 6 years follow-up, patients with HLA antibodies demonstrated trends towards increased valve degeneration and higher aortic gradients, but these trends were non-significant. For cryopreserved allografts, a significant association has been noted between formation of HLA Class II antibodies and valve structural deterioration. In interpreting these results, it is important to bear in mind that there may be inherent differences in the immunogenicity of fresh versus cryopreserved allografts. In a heterotopic rat implantation model, cryopreserved syngeneic allografts demonstrate increased macrophage and T-lymphocyte infiltration as compared to fresh syngeneic allografts, suggesting that cryopreservation may influence the implants’ subsequent immunogenicity.

Immunogenicity may also differ as a function of the patient’s age, given the distinct immune environments in infants versus adults, and these groups’ diverging inflammatory responses to cryopreserved homografts. In contrast with failed cryopreserved homografts explanted from adults, which primarily demonstrate fibrosis and calcification, explants from infants show inflammatory lymphocytic foci (including T lymphocytes) suggestive of graft rejection.

Therefore, scientific studies are required to determine: i) the *ex vivo* viability of valve tissue, ii) allografts’ immunogenicity, and iii) how viability and immunogenicity may influence valvular durability in both children and adults. This will guide the development of processing, storage, and immunosuppression protocols specific to LAVT. In determining these clinical protocols, a distinction must be made between the functional demands required of transplanted
allografts in adults versus children. In the former, the primary requirement for living allograft “functionality” is prolonged durability over time. In the latter, sustained growth and self-repair capacity in situ are critical to cope with a complex and incredibly demanding valvular environment, where valve tissue is exposed to rapidly evolving hemodynamics within a simultaneously growing valvular root. To deliver a valve that meets these unique sets of requirements, pre-implant viability and immunosuppressive requirements may differ between age groups.

Another element of critical importance to the clinical implementation of LAVT is the availability of valve transplants. Primary anticipated sources of living valvular allografts are hearts deemed unusable for transplantation. As retrospectively estimated from the UNOS registry, approximately 40% of donor hearts are discarded each year, with several of these being allocated to valvular allograft cryopreservation. Comprehensively evaluating the number of allografts available for LAVT requires multi-center studies which account for healthy valves explanted from patients undergoing a heart transplant (domino heart valve transplantation, carried out three times at two institutions so far). A consorted effort to register and appropriately distribute living valvular allografts may enhance valve availability, enabling inter-institutional distribution to meet patient needs.

Relatedly, a primary consideration in the clinical implementation of LAVT will be establishing quality-control metrics for assessing whether an allograft is suitable for transplantation. In this respect, LAVT can adapt protocols from organ transplantation, as well as already-existing systems for homograft biobanking and cryopreservation. Quality control metrics that have already been defined for the purposes of allograft cryopreservation include donor characteristics and tissue anatomy (largely derived from the American Association of Tissue
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Banking). Nevertheless, there are many standards that have yet to be defined for living transplantation – most notably, acceptable warm and cold ischemic times.

Many other questions related to growth potential and clinical outcomes, clinical indications balancing the risks of immunosuppression versus risks of repetitive valve surgery, regulatory framework, cost-effectiveness, and ethical considerations should be investigated. For example, what is the most effective means of distributing living allogenic valves? Given the significant proportion of non-transplanted hearts currently allocated to cryopreservation (between 25% and 35%), how should these grafts be distributed between cryopreservation and living transplantation? And, what is the regulatory system that should be in charge of determining distribution? Should it operate at the local or national level? And, how can this system ensure equity in the distribution of living valves? Finally, what are the cost-savings associated with this procedure? To answer the latter question, it will be necessary to balance the relative expenses inherent to tissue procurement and semi-emergent transplant against the cost-savings associated with reduced reoperation rates. Further scientific and clinical investigations as to the ex vivo viability, growth capacity, and durability of the allogenic valve are therefore needed.

Creating a consortium of centers proactive in this field and a prospective clinical registry of patients undergoing this procedure can be key steps to promote clinical and scientific collaborations to answer these questions. This crucial work holds promise in positioning the living allogenic valve as a historical game-changer in the future of heart valve replacements.
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References


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