Living allogenic heart valve transplantation: Relative advantages and unanswered questions

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The Holy Grail in the field of pediatric cardiac valve surgery is to offer our patients an option that avoids the multiple reoperations needed to replace outgrown or structurally degraded valve prostheses. Cryopreserved human homografts historically have been 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. Reoperation and mortality rates associated with homograft implantation are high, especially for infants and neonates. Infants receiving a pulmonary homograft have a 5-year homograft survival rate of only 25%, and there is a 40% in-hospital mortality rate for neonates and infants receiving a homograft aortic valve replacement.

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. 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. Cellular viability facilitates homeostatic repair and remodeling, which is anticipated to underlie the homograft’s structural durability and reduce its thrombogenicity. 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. This represents an unmatched advantage that 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. This significantly enhances the range of surgical approaches available for treating complex congenital heart disease. LAVT also could improve outcomes in adult cardiac surgery by providing a structurally durable coumadin-free alternative to bioprostheses and mechanical valve replacements, thereby introducing a novel treatment option for young adults with contraindications to anticoagulation therapy, such as athletes or women who intend to become pregnant.

Notably, the valve’s “living,” transplanted nature also represents the origin of its greatest drawbacks: scarce donor availability, limited ex vivo viability, and immunogenicity. The first 2 of these introduce immense logistic and clinical challenges. A 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 (semiemergent 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. The first of which is how long fresh valvular homografts can 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. Recent work studying the viability of fresh valvular homografts ex vivo demonstrates preservation of tissue architecture and cellular metabolic activity after 48 hours of cold storage, with no increase in apoptotic markers. In the past, homovital homografts were regularly implanted well beyond this 48 hour time point, typically within 60 days of storage. Although tissue viability and microstructure 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, which represented a substantial increase from the viability observed when leaflet tissues were stored in electrolyte solution. Lupinetti and colleagues have shown that endothelial cell viability in rat valvular allografts decreases to 64% of baseline after 21 days of storage in nutrient medium. 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; nevertheless, systematic investigations have not been carried out to correlate this observation with tissue physiology at the time of implantation. Historically, tissue processing and storage strategies differed greatly among 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 cellular viability and resident cell phenotype, both spatially (throughout the valvular root) and temporally (over the course of storage). It also will be important to document preservation of the valvular microarchitecture, which underlies its biomechanical properties.

The question of ex vivo viability is crucial, 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 recent work noting that 10.8% of heart transplants are not used because of logistic challenges. This is most significant in the neonatal age group, in which 18% of hearts intended for transplantation are discarded due to procurement logistics.

An important question related to allograft viability is whether donor cells remain alive following implantation in the recipient. Understanding the viability of allogenic valves 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.

Next, questions regarding immunogenicity include the level of immunosuppression required to preserve the valve’s function and growth capacity in young patients, and the level (if any) of immunosuppression needed to maintain a functional, nongrowing valve in adults. A related question is the role of ABO and HLA matching. Although one can begin to glean answers from the outcomes of first-generation homovital homografts, the immunogenicity of valve tissue is not well understood, with some studies even suggesting immune privilege. 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, including 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. 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 is obtainable) are mostly targeted against donor HLA antigens. The antibodies’ implications for valve function are unknown; at a mean of 6 years of follow-up, patients with HLA antibodies demonstrated trends toward increased valve degeneration and higher aortic gradients, but these trends were nonsignificant. For cryopreserved allografts, a significant association has been noted between the formation of HLA class II antibodies and valve structural deterioration. When 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 compared to fresh syngeneic allografts, suggesting that cryopreservation may influence the implants’ subsequent immunogenicity.

Immunogenicity also may differ as a function of patient age, given the distinct immune environments in infants versus adults and these groups’ diverging inflammatory responses to cryopreserved homografts. In contrast to 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 needed to determine the ex vivo viability of valve tissue, allograft immunogenicity, and 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, whereas in the latter, sustained growth and self-repair capacity in situ are essential 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, preimplantation viability and immunosuppressive requirements may differ across 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 estimated retrospectively 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 multicenter studies that account for healthy valves explanted from patients undergoing a heart transplant (domino heart valve transplantation, carried out 3 times at 2 institutions so far). A concerted 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 Banking). Nevertheless, many standards remain 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. One question of great interest 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%24), how should grafts be distributed between cryopreservation and living transplantation, and what is the regulatory system that should be in charge of determining this 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 semiemergent 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 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.

Conflict of Interest Statement
The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

Key Words: allograft, congenital heart disease, living valve, valve transplantation