The Healthcare Review
VOL 2: Article III
GSR
Beirut, LB

Biochemically Changing a Donor's Heart Valve

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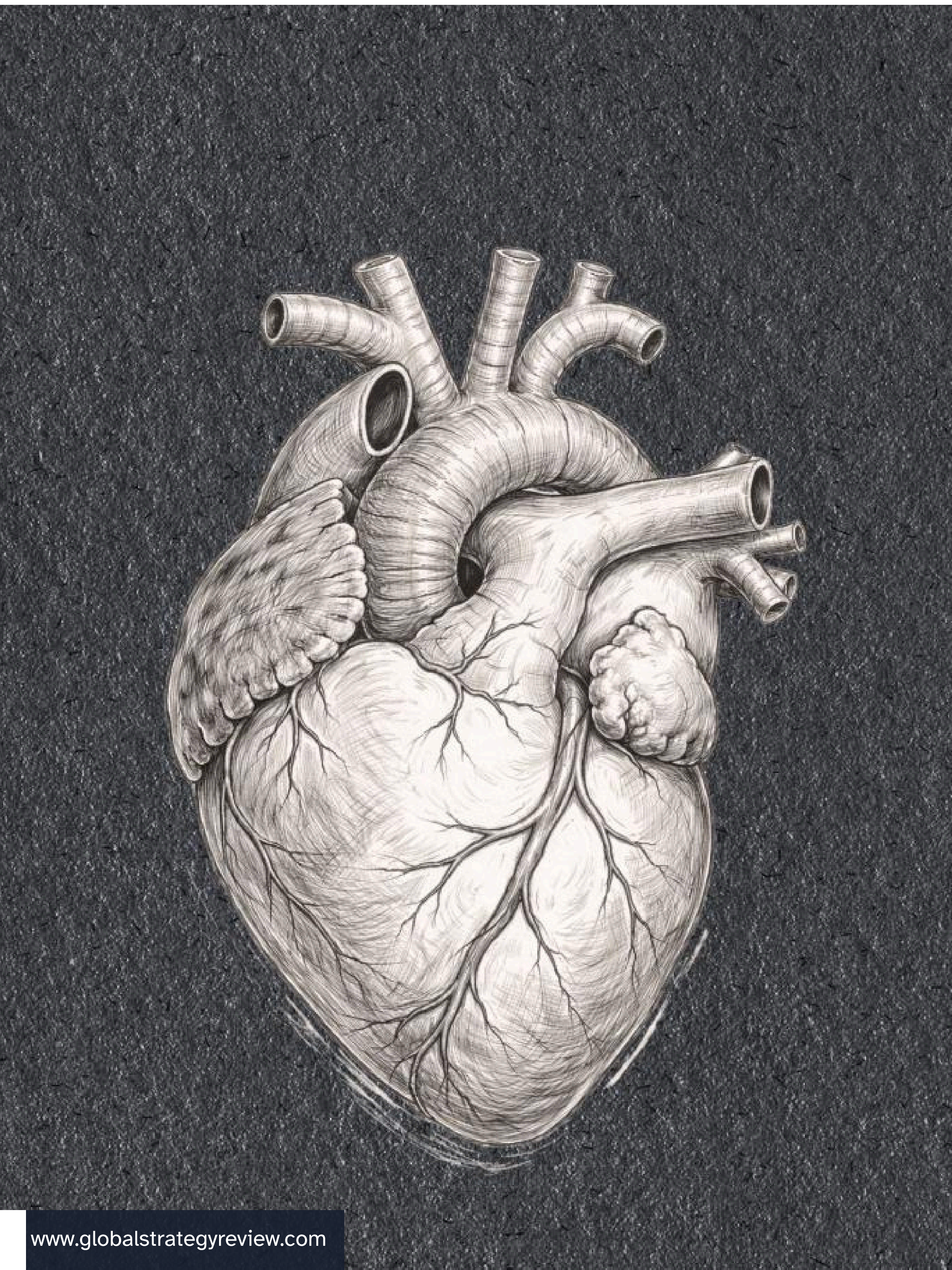

Over the last two decades, major discoveries in both the medical and the science world have proven to be life changing. With new breakthroughs emerge new possibilities for treating complex illnesses, especially when biochemical advancements and medicine work hand in hand to find an optimal cure. In the span of the last decade, a new idea emerged combining the fields of biochemical science and medicine together. This idea involves biochemically replacing donor cells with the recipient's cells, thus allowing growth of the transplanted organ, while simultaneously reducing the risk of immune rejection. Clinical evidence suggests this idea is possible; however, the work is still under development and needs time before it can be implemented properly. Although research on biochemical engineering, host replacement, and growth exist separately, few studies have merged these three concepts together and specifically, in a pediatric transplant setting. The aim of this review is to close this research disparity, look for common gaps, and target specifically a heart valve transplant setting.

This matter has been an ongoing debate for some time now. That is because researchers have not reached consensus. Until now, there is no clear preferred method of choice when it comes to biochemical engineering and recellularization of a valve.

I. Growth as the Key to Success

Some of the key contributors to this ongoing conversation are Konsek et al. (2023). This clinically driven translational review written by surgeons and researchers that are directly involved in partial heart transplantation research focuses on the importance and impact that growth has in replacing donor cells with recipient cells. The procedure should begin with a live tissue/organ. Even though donor heart valve tissue is obtained from deceased donors, cellular viability is preserved through rapid recovery and specialized preservation. This allows the transplanted tissue

to remain biologically active, unlike standard heart valve transplants which are biologically inactive. Once the tissue is inside the recipient's body, mechanical forces (blood flow, pressure stretch from the implanted organ) will be sensed by and stimulate the "valve interstitial cells" (VICs) and the "Endothelial cells" (ECs) through Mechan transduction pathways involving integrins and the cytoskeleton. These mechanical cues activate downstream signaling pathways, including YAP/TAZ and TGF-β signaling. These signaling pathways amplify and sustain the Mechan transduction pathways.

Once stimulated, they will trigger the VICs to proliferate and upregulate gene expression of the ECM (such as collagen and elastin), while the ECs will produce nitric oxide (NO), anti-inflammatory signals, and paracrine growth factors to signal and regulate the VICs and maintain tissue homeostasis.

In parallel, recipient-derived endothelial and mesenchymal progenitor cells infiltrate the graft and under the influence of these biochemical and mechanical signals, differentiate into VIC-like and fibroblast-like cells that actively contribute to ECM production. Following that, the ECM will begin continuously remodeling through the elongation and realignment of the collagen, reversible stretch of the elastin, and regulation of the hydration and flexibility of the proteoglycans. As a consequence, both the valve annulus diameter and the leaflet surface area will increase, and the thickness will remain proportional. This suggests real growth rather than simple valve dilation (Konsek et al., 2023).

In summary, without a biologically active tissue that is capable of both signaling and growth, and without the VICs differentiating in the donor's tissue, the remodeling/reshaping as

well as the growth of the tissue inside the recipient's body would be unlikely. Thus, Konsek stresses the importance of growth in achieving recellularization of a donor's organ/tissue.

II. Growth as an Outcome of Remodeling

Tzavellas et al. (2025), examine the remodeling of heart valves through a review of multiple preclinical and clinical studies that included juvenile animal models and limited pediatric clinical studies. They emphasize that growth is an outcome of the remodeling process rather than a prerequisite for successful valve function. By comparing how researchers have experimentally created and assessed decellularized heart valve scaffolds, all of the reviewed studies begin by decellularizing the valve in vitro using either chemical or physical methods. These methods aim to decellularize the donor's valve while preserving the ECM's native fiber orientation, mechanical compliance, and biochemical signaling cues, so that the recipient's cells can recolonize. Some researchers additionally use enhancement strategies, such as surface modifications to improve cell recruitment and cross-linking agents to preserve mechanical properties while still allowing cell ingrowth. Following decellularization, the recipient-derived mesenchymal stem-cells (MSCs) and valvular endothelial cells (VECs) either migrate into the scaffold in vivo or, in some experimental setups, are seeded in vitro prior to implantation. The MSCs proliferate and differentiate into VIC-like and fibroblast-like cells, contributing to ECM recellularization, while the VECs form a lining that reduces thrombosis (the formation of clots within blood vessels) and secretes factors supporting deeper host cell integration. These cellular processes remodel the ECM, and consequently allow proportional valve growth (Tzavellas et al., 2025).

In summary, evidence from juvenile animal models and limited pediatric clinical studies have shown that with a biologically active valve and an intact ECM, remodeling and growth of a valve within a host is possible.

III. Growth as a Functional Outcome

Snyder and Jana (2022), discuss the remodeling of a donor's valve through a similar perspective to Konsek et al. (2023) and Tzavellas et al. (2025). By comparing many studies, their review article discusses the different strategies for remodeling a transplanted valve. The process begins with in vitro decellularization, using chemical, physical, and crosslinking methods to remove donor cells while preserving the ECM's fiber organization, mechanical compliance, and bioactive cues. Following the transplant, the ECs, MSCs, and M2-like macrophages are stimulated. The ECs secrete anti-inflammatory factors and an anti-thrombogenic lining to improve cellular infiltration, the MSCs proliferate and differentiate into VIC-like cells that recolonize the ECM, while the M2-like macrophages are known to secrete IL-10 and TGF-β that promote tissue repair, matrix remodeling, and anti-inflammatory progression. Through active cellular remodeling, Mechan transduction, and preserved ECM bioactivity, functional valve growth emerges. This is demonstrated by proportional expansion of leaflet area, elastin dynamics, and collagen reorganization. Preclinical evidence on juvenile sheep has shown that such remodeling can result in growth-compatible valve function, as measured by mechanical testing of strength, elasticity, and structural conformity (Snyder & Jana, 2022, section "Decellularization and Recellularization").

IV. The Common Gaps Found

Though these articles have certain differences, they share common ground regarding the biological activity of the graft, the structure of the ECM that is needed for recolonization, and the kinds of cells that are recruited for proliferation and infiltration. So consequently, they share certain, similar gaps:

1. Every article presents different methods to decellularize a donor's valve that is different from the other, which highlights the concern that there is no consensus or standardized protocol for the decellularization process.
2. While all studies show that recellularization occurs in vivo, the exact timing, rate, and completeness remain a mystery. Thus, this renders the recellularization process difficult to predict.
3. Although there is enough information regarding the mechanical forces and biochemical signals in remodeling the ECM, the specific pathway remains unmapped. This limits the ability to engineer scaffolds which properly direct growth, as well as our ability to understand the cues for optimal growth.
4. All of the existing clinical evidence is either theoretical or experimental, where the latter is currently exclusive for animals. This limits our knowledge for long-term growth on humans and the resulting outcome.
5. The immune cells involved in this process aid in anti-inflammation and remodeling, but their exact contribution and optimal regulation are still unclear. This could result in adverse consequences like fibrosis, calcification, or graft failure.
6. These studies have shown progressive remodeling and infiltration, but complete recellularization has not yet been guaranteed. Thus, methods are needed to ensure a uniform and functional recolonization of all the ECM layers.

In conclusion, evidence from current findings suggests that it is indeed possible to have a biochemically engineered, recellularized growing valve. However, much research is still needed to fully grasp the knowledge of recellularization of a transplanted tissue, as well as fill in the missing gaps. Whether it's decellularizing in vivo or in vitro, recellularizing uniformly and continuously, or even considering growth as a result of the process or as a necessity, many questions are still awaiting to be answered. Now, there is a need to focus on the gaps in order to turn this theoretical research into a surgical procedure that can reduce the effects of the immune response and the possibility of undergoing further operations.

References

Konsek, H., Sherard, C., Bisbee, C., Kang, L., Turek, J. W., & Rajab, T. K. (2023). Growing heart valve implants for children. *Journal of Cardiovascular Development and Disease*, 10(4), 148. https://doi.org/10.3390/jcdd10040148

Tzavellas, N. P., Simos, Y. V., & Tsamis, K. I. (2025). Decellularized scaffolds and heart valve treatment: Present techniques, long-standing hurdles and the challenging future. *Biomaterials Advances*, 177, 214367. https://doi.org/10.1016/j.bioadv.2025.214367

Snyder, Y., & Jana, S. (2022). Strategies for development of decellularized heart valve scaffolds for tissue engineering. *Biomaterials*, 288, 121675. https://doi.org/10.1016/j.biomaterials.2022.121675