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Commentary: Building Bridges to Recovery in VAD Patients

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**Central Message:** HiCT treatment provides a promising preclinical strategy to supplement VAD as a Bridge-to-Recovery. Large animal models with LVAD implantation are the next step towards clinical applicability.

**Central Picture Legend:** Paige E. Brlecic, MD and Ravi K. Ghanta, MD

**Main Text:**

In 1963 Dr. DeBakey published the first experience with an early implantable artificial ventricle. This accomplishment inspired the inception of the NIH's Artificial Heart Program, sparking an era of innovation in the field of mechanical circulatory support. After the REMATCH trial, left ventricular assist devices (LVADs) are standard clinical practice as a Bridge-to-Transplantation, Destination therapy, Bridge-to-the-Decision, and - in select patients – as a Bridge-to-Recovery. However, as LVADs introduce their own complication profile, alternative strategies, including cell-based therapies, are under investigation, particularly as a Bridge-to-Recovery.

In this issue of *The Journal of Thoracic and Cardiovascular Surgery*, Heima and colleagues explore the potential of human iPS cell-derived cardiac tissue (HiCT) treatment as an adjunctive Bridge-to-Recovery strategy for VAD patients with ischemia-induced end-stage heart failure. The authors found that HiCT treatment promotes graft survival, reduces infarct remodeling, and stimulates neovascularization. Albeit encouraging, the current work does not delve into the respective mechanisms of action. In this context, it is understood that unloading through LVAD alone is generally insufficient in achieving complete functional recovery, making device explantation after prolonged use rare. A deeper mechanistic understanding of HiCT as an
adjunctive approach may aid in identifying candidates for VAD explantation and tailoring adjunctive Bridge-to-Recovery treatment strategies. Additionally, understanding the mechanisms of functional recovery in HiCT treatment could enhance other adjunctive heart failure treatments, such as cardiac reprogramming, cell therapies, angiogenic therapies, and bioenergetic approaches. Combining these strategies with HiCT may amplify their benefits, addressing current limitations in clinical applications.

A notable aspect of this study is the exploration of how HiCT treatment affects CM atrophy, a debated hurdle associated with prolonged VAD treatment and important limitation in Bridge-to-Recovery therapy. The authors found that HiCT treatment mitigated CM atrophy by suppressing a muscle-specific ubiquitin ligase. Another noteworthy aspect of the current work lies in the epicardial placement of HiCT – hydrogel grafts, ameliorating risks associated with intramyocardial cell injection while preserving the beneficial effects associated with iPSC treatment.

While these early findings are promising, much work remains in building the Bridge-to-Recovery for VAD patients. As acknowledged by the authors, a large animal model utilizing implantable LVADs in chronic ischemic cardiomyopathy is the next step in testing the clinical applicability of this adjunctive HiCT treatment strategy. A model with implantable VADs would consider the pathophysiologic effects of RV failure in LVAD patients, a factor not addressed in the proposed heterotopic heart transplant model. While Heima and colleagues report promising surrogate measures that allude to enhanced functional recovery with HiCT treatment, quantifying the grafts’ functional contribution remains a crucial aspect yet to be substantiated, and we eagerly await the authors’ future work.
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