Life presents us with many opportunities and challenges; in heart transplantation, the fear of rejection is always looming. We must respect the fear, but the benefit our patients can receive from these therapies must not give us complete pause. Bakir and colleagues⁷ provide compelling data that the classic belief of increased allosensitization with VADs may not be as detrimental as traditionally taught. We must work toward understanding these, take an educated leap of faith, and face the fear of rejection head on.

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Commentary: The anticlimax of the left ventricular assist devices—associated antibodies

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With limited organ availability, left ventricular assist devices (LVADs) become an important strategy in bridging patients with end-stage heart failure to heart transplant (HT).¹⁻³ LVAD usage increases the patients' antibody

CENTRAL MESSAGE

In a low immunologic risk group of patients, LVADs did not increase risk of post-HT ACR. However, it remains unclear how LVADs affect post-HT rates of DSAs, AMR, and CAV.

response through poorly understood mechanisms. Immunogenicity of the LVAD surface, upregulation of cytokines caused by the implant, and blood product transfusions have been postulated to be important contributors.^{4,5} However, an unanswered question is whether allosensitization in patients with LVADs has a long-term immunologic footprint that persists post-HT and heightens the risk of adverse outcomes.

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In this issue of the *Journal*, Bakir and colleagues⁶ investigate acute cellular rejection (ACR) incidence in a propensity-matched cohort of patients who had undergone HT with or without LVAD support at a single center. The authors report no difference in moderate-to-severe histologic ACR rates between the 2 groups at 12 and 24 months post-HT, consistent with previous reports. The caveat of these findings is that the studied population represents a low immunologic risk group, as at time of listing approximately 90% of patients in both groups have panel reactive antibodies <10%. Rates of preformed donor-specific antibodies (DSAs) and LVAD-associated infections are not reported despite their established role in elevating the immunologic risk peri-HT. In addition, the study lacks sufficient granularity to explore the full immunologic sequelae of continuous-flow LVADs post-HT, including the absence of a consistent DSA-monitoring protocol post-HT or routine assessment for antibody-mediated rejection on surveillance biopsies. Furthermore, despite ACR being a risk factor for coronary allograft vasculopathy,^{1,2} the authors do not address differences in coronary allograft vasculopathy rates.

How these results compare with an LVAD-bridged population with heightened pre-HT allosensitization rates remains unknown. The sensitized patients with bridge-to-transplant LVAD represent a particularly challenging group to manage. Elevated panel reactive antibodies pre-HT lead to an increased waitlist time with greater morbidity and mortality,⁷ whereas desensitization therapies to broaden the donor pool have significant infectious risk.^{4,5} Yet, there is no robust evidence whether preformed DSAs portend the same immunologic risk in LVAD-bridged patients as in patients who undergo HT without LVAD support. In one of the largest studies comprising 514 HT recipients, crossing DSAs with progressively greater mean fluorescent intensity decreased freedom from antibody-mediated rejection compared with patients with no DSA, with no difference in survival rates between the groups.⁸ However, outcomes

were not stratified per mechanical support strategy employed. One might postulate that device explant at the time of HT might alter the kinetics of preformed antibodies, hence leading to differences in the immunologic milieu post-HT between LVAD bridged and primary HT recipients. Further studies are needed to elucidate this important question.

The current United Network for Organ Sharing allocation system is changing the landscape of LVAD usage for hemodynamic support in patients awaiting HT.⁹ Inevitably, the allosensitization consequences need a treatment approach guided by knowledge of outcomes. The study by Bakir and colleagues⁶ is adding to our emerging understanding of the role of antibodies in LVAD-bridged HT recipients, and we sincerely applaud them for their contribution to this field.

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