Reversible but risky: Pulmonary hypertension in advanced heart failure is the Achilles' heel of cardiac transplantation

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Central Message

Tsukashita and colleagues examined the influence of LVAD use in heart transplant candidates with pulmonary hypertension, but important questions remain unanswered.

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In this issue of the *Journal*, Tsukashita and colleagues¹ report the effect of continuous-flow left ventricular assist device (LVAD) support on pulmonary vascular resistance (PVR) in 227 candidates for orthotopic heart transplant (OHT) and compared posttransplantation outcomes in 150 of these patients, including 30 with severe pulmonary hypertension (PH) (ie, PVR >5 WU pre-LVAD). Despite a significant decrease in the mean pulmonary artery pressure with LVAD support (to a level commensurate with LVAD recipients classified as having low PVR), the presence of severe PH was associated with increased in-hospital mortality (20% vs 5.8%) after OHT with a strong predictive value. The authors conclude that PVR was reduced after LVAD implantation even in patients with severe PH refractory to pulmonary vasodilators, despite the improvement in PVR, patients with severe PH had higher early mortality after OHT, and the long-term survival did not differ between OHT recipients with high and low PVR (Figure 1).

PH is present in 40% to 75% of patients with advanced heart failure.² LVAD implantation decreases PVR by unloading the left ventricle, reducing pulmonary venous pressure, and augmenting cardiac output. This reduction in PVR seems to be durable and maintained after OHT.³⁻¹¹ The reduction in PVR imparted by LVAD support is highly relevant in patients supported with an LVAD as a bridge to OHT. It may allow OHT candidacy of patients previously deemed not transplant-eligible, and no improvement or a marginal improvement in PVR after LVAD implantation may be associated with prohibitive surgical risk for OHT. Initially, some series demonstrated comparable early and late outcomes in patients with PH supported with an LVAD.^{7,10} However, other reports have noted higher perioperative mortality and more right ventricular failure in patients with severe PH who received an OHT.^{3,6,8} It is important to note that the severity of PH, criteria for LVAD implantation, and definition of responsiveness to treatment have been

heterogeneous across previously published studies. The time needed for the pulmonary pressure to decrease to allow consideration for OHT has also been variable among published series—from days to weeks after LVAD implantation—and 1 series suggested no additional benefit after 6 months of LVAD support.^{3,7,12}

The study by Tsukashita and colleagues¹ is the largest single-center experience to date on the effects of preexisting PH on OHT outcomes in patients bridged with continuous-flow LVADs, and provides relevant information on the use of continuous-flow LVADs at a highly specialized center. With an optimistic interpretation, the authors confirm that 66% of patients with severe PH, who in the absence of LVAD would have not been OHT candidates, underwent transplant. The vast majority of these patients presented with a significant improvement in PH as early as 37 days after LVAD placement, although only 40% received pulmonary vasodilator treatment during LVAD support. At the same time, the higher perioperative mortality of 20%, mostly due to primary graft dysfunction, reminds us that this patient population should still be considered high risk.

Not infrequently, patients with severe PH before LVAD implantation will present with severe primary graft dysfunction after OHT, commonly triggered by right ventricular dysfunction,^{3,8} consistent with the findings of the study by Tsukashita and colleagues.¹ One possible reason is that although PVR decreases with LVAD

FIGURE 1. Kaplan-Meier survival curve during left ventricular assist device support.¹ PVR, Pulmonary vascular resistance.

support, reversal of pulmonary vascular remodeling is heterogeneous or incomplete, and the pulmonary arteriopathy that remains may provide a substrate for a pulmonary hypertensive crisis triggered by perioperative insults, including insulin resistance from cardiopulmonary bypass and depletion of nitric oxide associated with the transfusion of stored packed red cells.

Unfortunately, there are scarce data on the efficacy of pulmonary vasodilator therapy in patients with severe PH on long-term LVAD support. Tedford and colleagues¹³ demonstrated an encouraging drop in PVR (from 5.8 to 2.96 WU) in patients who received sildenafil, a PDE-5 inhibitor. LaRue and colleagues¹⁴ identified a drop in PVR (from 3.9 to 1.5 WU) in patients who were treated with an endothelin-receptor antagonist (ERA).¹⁴ We hope to learn more about the tolerability and efficacy of ERAs during an upcoming randomized clinical trial of ERA treatment initiated within 1 month of LVAD implantation in patients with increased PVR (the SOPRANO [macitentan in pulmonary hypertenSiOn Post left ventRiculAr assist device implanTatiOn] study).

The elegant study by Tsukashita and colleagues¹ helps us understand the effects of continuous-flow LVAD implantation in secondary PH and outcomes of OHT, but important questions remain unanswered, including the potential role of adjunctive pulmonary vasodilator therapy and the time of support needed to minimize the perioperative risks of OHT. Given the higher risk of

perioperative mortality in patients with severe PH before continuous-flow LVAD support in this study¹ and consistent with our clinical experience, LVAD therapy is not a universal solution. In selected cases, maintaining LVAD support, even in the presence of right-sided heart failure, may be superior strategy to forging ahead with a high-risk heart transplant.

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