Editorial

Pulmonary Hypertension Associated With Heart Failure: A Challenge of Prediction or Persistence?

TODD F. DARDAS, MD, MS

Seattle, Washington

The ability to predict whether the pulmonary vascular bed will remodel with medical therapy, intravenous inotropes, or mechanical support remains a clinical challenge. Published reports suggest there is no predictive measure that precludes or guarantees normalization of pulmonary hypertension (PH) and no single PH therapy is demonstrably superior to others with multiple drug and device therapies required in some cases. In addition, measurement of PH remains controversial with some investigators supporting the concept that the transpulmonary gradient (TPG) is superior, only two pressures are required, to the pulmonary vascular resistance (PVR), which requires an additional measure of cardiac output introducing an additional source of error.

Lacking equipoise for quasi-experimental methods, the transplant community must now rely upon observational studies to understand novel therapies for PH and for evaluation of historic and novel indices of PH. In the current issue of the Journal, Uriel et al study a well characterized cohort of subjects enrolled in the prospective HeartMate II bridge to transplant trial. The authors provide analysis of pre-left ventricular assist device (LVAD) PH measured via the TPG and PVR and their effects on ultimate post-transplant survival. The authors begin by noting the poor correlation between pre-LVAD TPG and pre-LVAD PVR ($r^2 = 0.4$), suggesting the values are not synonymous and may provide different information on the state of PH. The authors demonstrate an association between post-transplant survival and TPG measured as either a continuous or dichotomous measure at 1 year. There was no definitive association between post-transplant outcomes and pre-LVAD PVR analyzed either continuously or dichotomized at the 75th percentile.

There are two main findings of the present work. First, TPG was superior to PVR in stratifying post-transplant survival at 1 year, but not at 30 days post-transplant. Notably, the original reports of PH as a risk factor for mortality and right ventricular failure identified a high incidence of mortality early in the post-transplant course (days or weeks).[1–3] In addition, these early reports included patients whose PH precludes transplant listing in the modern era with some cases of PVR >5 Wood units.[4] Among candidates with severe PH, oversizing the donor heart may have prevented early graft failure. Early reports using a direct measurement of the Fick cardiac output found that both PVR and TPG discriminated post-transplant mortality.[2] Transpulmonary gradient was not found to be superior to PVR in a large, modern sample of U.S. registry patients, where neither TPG ($P = .43$), nor PVR ($P = .774$) differentiated medium-term survival between the dichotomized grouping of PH measures.[5] In the current study, TPG was only found to be prognostic at 1 year, donor characteristics and graft dysfunction were not reported, and TPG was superior to PVR calculated with an estimated Fick cardiac output. The finding that only late survival was affected by TPG may indicate that transplant programs in the modern era have improved their ability to delay the effects of RV failure thereby unmasking effects of candidate PH on late graft performance. The effect of donor selection would have been of interest and modern selection practices mean that the historic experience with very high PVR is unlikely to be reproduced. The finding that TPG may be superior to PVR may be the result of sample size, but is consistent with other reports. Progress in transplanting candidates with PH is most likely to derive from novel agents and strategies to reduce PH and perhaps by pushing the boundaries of candidate PH with concerted efforts to oversize donor hearts.

Second, the authors suggest that prediction of post-transplant graft failure from pre-VAD values is possible and demands additional post-VAD follow-up. This finding omits PH information obligatorily obtained in the post-VAD interval and does not include measures of vasoreactivity. Pulmonary hypertension surveillance is standard of care in most programs and right heart catheterization is critical to understanding the interaction between LVAD and right ventricular performance and assures pulmonary

From the Division of Cardiology, University of Washington, Seattle, Washington.

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Reprint requests: Todd Dardas, MD, MS, 1959 NE Pacific Street, Box 356422, Seattle, WA 98195-6422. Phone: 206-543-2914; Fax: 206-616-4847. E-mail: tdardas@uw.edu

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vascular remodeling amenable to heart transplantation. Given the relatively short courses of inotropes or device support required to affect remodeling in the majority of patients with prohibitively high PH, follow-up of PH measurements 4−6 weeks after LVAD implant are warranted to assess whether further medical therapy or mechanical unloading is required.[6] Last, when evaluated and interpreted correctly, measures of vasoreactivity and the diastolic pressure difference (diastolic pressure gradient) may provide critical information as to the likelihood of PH resolution.[7] Future study is necessary to determine which PH markers best guide the therapeutic approach to PH modulation and by extension whether using any single measure to determine the likelihood of favorable remodeling could result in consignment of candidates with plastic pulmonary vascular beds to a non-transplantable state.

In summary, modulating pulmonary hypertension toward a transplantable state is more akin to an N-of-1 trial. Success in these trials is currently defined as a PH measure at or below guideline-recommended values and N-of-1 trialists are allowed to employ myriad treatment regimens and measure the primary outcome as many times as they choose. Selection of treatment, timing of PH resolution and clairvoyance around the ability to modulate PH may be obtained from carefully integrating all available static and dynamic PH measures, though the bulk of current evidence suggests that persistence with PH therapies may prove a more fruitful approach than prediction in reducing PH toward transplantable values.

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