Optimal Timing for Lung Transplantation: Why Not Include RVEF As an Indicator?

Section Editor
Myung H. Park, MD

Myung H. Park, MD
Director, Pulmonary Vascular Diseases Program
University of Maryland School of Medicine

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-24 via free access

One of the most challenging questions to answer in pulmonary arterial hypertension (PAH) is: "When is the optimal time to proceed with lung transplantation?" The current lung allocation scoring (LAS) system prioritizes donor organ resources based on severity of illness. Factors used to assign LAS do not account for known predictors of outcome for PAH patients—including determinants of right ventricular (RV) function. It has been recognized that the system places PAH patients at a distinct disadvantage, and concerted efforts are being made to correct this by considering variables that reflect RV function, specifically mean right atrial pressure (mRAP) and cardiac index (CI).

However, how accurate are these hemodynamic indices as markers of RV function? Recent reports have illustrated the potential utility of cardiac MRI (cMRI) in quantitatively measuring RV dimension and function as prognostic markers in PAH.[1] The study by van de Veerdonk et al,[2] discussed in the Clinical Trials column in this issue, challenges some current thinking which guides our PAH management. Their study evaluated patients on PAH-directed therapy with serial cMRI and forces us to reconsider some of our current thinking: 1) mRAP and CI are the best prognostic indicators of RV function in PAH; 2) persistently elevated pulmonary artery pressure (PAP) despite PAH-specific therapies is acceptable as long as CI has improved; and 3) PVR is a reliable surrogate of RV function.

This study demonstrates that despite PAH-specific treatments, the reduction in PVR was only modest (-12%) and mPAP generally remained unchanged. The finding that PAPs do not normalize on treatment has been shown in prior studies, including a large cohort of epoprostenol-treated patients.[3] Thus, our current practice goal is to optimize cardiac output (CO), recognizing that treatments will generally have a greater impact in reducing PVR than in reducing PAP. Improving CI and reducing PVR have been major goals in utilizing combination treatments, with epoprostenol usually considered as the "gold standard" in supporting RV function.

However, as this most recent cMRI study has shown, PVR is not a reliable marker of RV function. The authors made several key observations: decreasing PVR via augmenting CO does not change the source of the wall stress on the RV, namely the elevated pulmonary pressure. Second, therapies that increase CI without reducing PAP may just force the RV to work harder, not necessarily smarter. Finally, this study clearly demonstrated that RV ejection fraction (RVEF) obtained at baseline is a better predictor of mortality than PVR, and that changes in RVEF on treatment predicted long-term survival while changes in PVR did not. Patients with high RVEF did better, regardless of PVR, while those with low RVEF did poorly.

This study provides compelling data for a shift in thinking that has recently begun among many experts. It has already been recommended that we should use stroke volume as a surrogate of RV function since CO is influenced by heart rate. These data reinforce what we have learned from left ventricular (LV) systolic heart failure: therapies that aim to increase CI can result in detrimental outcome. In fact, there is considerable degree of parallel between this study and the management of patients with LV systolic heart failure—for one, the LV ejection fraction (LVEF) is one of the major determinants in listing for cardiac transplantation. Due to the difficulty in obtaining reliable and reproducible RVEF, we have not previously been able to assess the prognostic importance of this measurement. The Dutch study now demonstrates that EF is a key prognostic factor for RV, as in LV.

Finally, this study attempts to shed some light on a common clinical conundrum in PAH: the variability in response to treatment among patients. van de Veerdonk and colleagues report that 25% of the patients progressed to RV failure despite decrease in PVR with PAH-specific therapies. Two important questions remain: "How can we identify these refractory patients?" and further "Can we change this trajectory by proactively treating them more aggressively at the time of diagnosis?" The authors discuss potential mechanisms, including genetic differences in RV adaptation to pressure overload. In the final analysis, the study underscores the major weakness of our current medical regimen: we cannot normalize PAP.

Although it is not practical or feasible to obtain cMRI in all PAH patients, it is critical to recognize the importance of RVEF as a predictor of outcome, independent of changes in PVR. We need to remember the benefit of normalizing the PAPs as we evaluate our treatment effi-

Correspondence: mpark@medicine.umaryland.edu

cacy in individual patients and ask the question: "How hard is that RV working?" That single question may help to better triage which patient should be evaluated for lung transplant sooner rather than later.

References

1. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J*. 2007;28(10):1250-1257.
2. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol*. 2011; 58(24):25112519
3. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002;106(12): 1477-1482.

Guest Editor's Memo

(continued from page 2)

20% penetrance of these mutations and a beautiful summary of the potential therapies we might ultimately test to improve pulmonary vascular signaling in all of our patients, even those without BMPR-2 mutations. Duncan Stewart's team from Ottawa offered a comprehensive state-of-the-art paper on the promise of endothelial and mesenchymal progenitor cells, especially those genetically engineered to optimize endothelial function. Our regular columns complement the full-length articles by providing practical guidance on the use of warfarin for pulmonary hypertension and exploring the utility of cardiac magnetic resonance imaging to evaluate the right ventricle. The roundtable digs into the recently presented imatinib data from the IMPRES trial.

On the cover, the artist illustrates the endothelial, medial, and adventitial changes that ultimately disconnect the microcirculation of our patients from the right heart. The insets are micro CT scans from rats in my laboratory and provide yet another example of how the rapid technological advances at the bench are giving us new ways to measure and study the diseased pulmonary circulation. Images like this for our patients are probably less than 10 years away. From bench to bedside and back to the bench, we collectively strive to reconnect the microcirculation and appropriately couple the right ventricle to the pulmonary artery, especially for our sickest patients. Clearly, new understanding has led to—and will continue to generate—better treatment approaches. I hope that you enjoy learning from this issue as much as I have enjoyed putting it together.

R. James White, MD, PhD
Assistant Professor of Medicine,
Pharmacology, and Physiology
University of Rochester

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-24 via free access