Predicting Long-Term Survival in Pulmonary Arterial Hypertension

More Than Just Pulmonary Vascular Resistance*

Reda E. Girgis, MB, BC H

Baltimore, Maryland

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily reflect the views of JACC or the American College of Cardiology.

From the Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland. The author has reported that he has received clinical research support from Actelion, United Therapeutics, and Bayer; has been a consultant for Actelion, Gilead, and Bayer; and is supported by NIH/NHLBI R01 HL092831 and P50 HL084946.

In a cohort of 110 patients with PAH, a lower baseline RVEF was a strong predictor of death (p = 0.001), outperforming PVR (p = 0.031). Although RVEF generally correlates inversely with PVR (6), the former was an independent determinant of survival. Remarkably, an RVEF above the optimal cut-off value of 35% was associated with similarly good long-term survival among patients with a PVR below or above the cut-off value of 650 dynes·s·cm⁻² that best predicted mortality. Baseline cardiac output (CO) and 6-min walk distance were also linked with survival.

Follow-up right heart catheterization and MRI were obtained after 1 year of therapy in 76 patients. In this group, there was a small but significant decline in PVR that was brought about primarily as a result of an increase in CO, with minimal reduction in mean pulmonary artery pressure, hemodynamic changes typically observed in response to PAH therapy (7,8). RVEF was unchanged. However, subsequent survival was significantly associated with changes in RVEF, whereas no relationship was observed between survival and change in PVR or CO. There was only a weak correlation between changes in PVR and RVEF (R = 0.33). In 52 patients, PVR decreased by at least 15 dynes·s·cm⁻² (mean reduction of 284). Thirteen of these patients had a fall in RVEF of 3% or more. Long-term survival in this subset was dramatically worse than that in the 39 patients with a fall in PVR combined with a stable or increased RVEF, in whom survival exceeded 90% beyond 5 years.

This study raises several provocative issues. There is general agreement that the RV response is the key determinant of clinical outcomes in PAH. A key question is how best to assess RV function. How can we identify a healthy RV as opposed to one that is destined to fail? New York Heart Association class and 6-min walk distance are likely surrogate markers of CO, a major component of PVR. All of these have previously been shown to predict survival, both at baseline and in response to therapy, particularly during a medium-range follow-up time of 2 to 3 years (7–9). A major strength of this series by van de Veerdonk et al. (4) is the relatively long median follow-up time of nearly 5 years. Pulmonary hypertension clinicians, and certainly patients and their families, are no longer satisfied with 1-, 3-, or even 5-year survival. We need to identify reliable surrogate markers of durable, long-term survival. Medical therapy would then be intensified until such an endpoint is met. If not, and one could be fairly certain that the RV was about to fail, then early referral for lung transplantation would be considered.

A higher CO or stroke volume (SV) does not necessarily indicate better function. A rise in SV can be achieved through an increase in right ventricular end-diastolic volume (RVEDV) and/or improvement in RVEF. An interesting observation from this study is that although CO was significantly higher, and PVR lower, after 1 year of therapy,
there was a marginal trend for RVEDV to increase. Importantly, increasing RVEDV and RV end-systolic volume after 1 year were the follow-up variables most significantly associated with mortality, more so than change in RVEF. According to the Laplace relationship, a dilated ventricular chamber will develop higher wall tension, particularly when combined with elevated intraluminal pressure. Thus, an enlarged RV, even if capable of generating a normal CO and maintaining normal filling pressures, may ultimately decompensate because of persistently elevated wall stress that increases myocardial oxygen demand and at the same time impairs perfusion.

Such a scenario would presumably be reflected by an elevated brain natriuretic peptide level, which unfortunately was not reported. The relative importance of RV size versus contractility is unclear. In a previous study from this group, RVEDV and smaller left ventricular end-diastolic volume and SV were significant predictors of mortality (10). If RVEF is a good surrogate marker, what should the target be? A baseline value of 35% was found to be the best cut-off (4). Is there a similar threshold level at follow-up? Hopefully, these and other questions will be answered in the near future as more MRI data are accumulated.

Currently, what is the role of cardiac MRI in PAH? This study adds to the growing body of literature supporting the utility of this noninvasive procedure in the management of PAH (11,12). However, further validation and standardization are required before its routine clinical application can be recommended. In the meantime, clinical trials should incorporate MRI variables as outcome measures. Another important question is whether echocardiography could have similar utility in RV assessment (12). Systolic RV function can be reasonably quantified with the echo-derived tricuspid annular plane systolic excursion, which has been associated with survival in PAH (3). With use of a centralized laboratory, a significant reduction in the ratio between RV and LV end-diastolic areas was demonstrated in bosentan-treated patients relative to placebo (13). However, the reproducibility and reliability of echocardiography may not be adequate for clinical decision making in routine practice (11,12).

Our utopian goal in PAH therapy is to reduce PVR to normal or near-normal levels. Although our research efforts should continue to aim for this, unfortunately it may be an unrealistic expectation in the majority of patients, despite maximal medical therapy. Current guidelines for treatment goals in PAH emphasize the attainment of New York Heart Association functional class I to II symptoms, near-normal exercise capacity, low brain natriuretic peptide level, the absence of clinical right heart failure, and normal CO and right atrial pressure (14). Good RV systolic function as measured by tricuspid annular plane systolic excursion is also included, but serial assessments remain to be validated. The current study by van de Veerendonk et al. (4), taken together with their previous work (10), suggests that targeting a small RV with good contractile function may ultimately prove to be the best surrogate marker of truly long-term survival.

Reprint requests and correspondence: Dr. Reda E. Girgis, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, Room 523, Baltimore, Maryland 21205. E-mail: rgirgis@jhmi.edu.

REFERENCES


Key Words: hemodynamics – magnetic resonance imaging – pulmonary arterial hypertension – right ventricular function – survival.