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Right atrial pressure/pulmonary artery wedge pressure ratio: A more specific predictor of survival in pulmonary arterial hypertension

Wassim H. Fares, MD, MSc,[a] Lavanya Bellumkonda, MD,[b] Adriano R. Tonelli, MD,[c] Shannon S. Carson, MD,[d] Paul M. Hassoun, MD,[e] Terence K. Trow, MD,[a] Erica L. Herzog, MD, PhD,[a] Naftali Kaminski, MD,[a] Cyrus A. Kholdani, MD,[a] Lixia Zhang, MD,[f] Yi Zhou, PhD,[f] Jeffrey P. Hammel, MS,[c] and Raed A. Dweik, MD[c]

From the [a]Department of Internal Medicine, Section of Pulmonary, Critical Care, & Sleep Medicine, Yale University, New Haven, Connecticut; [b]Department of Internal Medicine, Section of Cardiovascular Medicine, Yale University, New Haven, Connecticut; [c]Department of Pulmonary Medicine, Cleveland Clinic, Cleveland, Ohio; [d]Division of Pulmonary & Critical Care Medicine, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina; [e]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, Maryland; and the [f]United Therapeutics Corporation, Raleigh, North Carolina.

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BACKGROUND: Pulmonary arterial hypertension (PAH) is a progressive, fatal disease. Current prognostic models are not ideal, and identifying more accurate prognostic variables is needed. The objective of this study was to evaluate the relative prognostic value of the right atrial pressure/pulmonary artery wedge pressure (RAP/PAWP) ratio in PAH patients. We hypothesized that the RAP/PAWP ratio is more predictive of survival than any of the other measured or calculated hemodynamic variables.

METHODS: We performed a secondary analysis of a PAH cohort (Cohort 1) and validated our results in a separate cohort (Cohort 2). Cohort 1 included primarily patients enrolled in prospective, short-term, randomized clinical trials and subsequently followed long term. Cohort 2 included patients prospectively enrolled in a PAH registry at a tertiary PAH referral center.

RESULTS: Cohort 1 ($n = 847$) and Cohort 2 ($n = 697$) had a mean age of 47 and 54 years, respectively. Most were female (78% and 73%, respectively), Caucasian (83% and 82%), with advanced functional class disease status (New York Heart Association Functional Class III/IV 85% and 68%) and with significantly elevated hemodynamics (mean RAP/PAWP ratio: 1.2 and 1.0; pulmonary vascular resistance: 13.5 and 9.4 Wood units). RAP/PAWP ratio indicated a 1-year hazard ratio of 1.44 ($p = 0.0001$) and 1.35, respectively ($p < 0.0001$), and was the most consistently predictive hemodynamic variable across the 2 cohorts. These results remain valid even when adjusted for other covariables in multivariable regression models.

CONCLUSIONS: The RAP/PAWP ratio is a more specific predictor of survival than any other hemodynamic variable, and we recommend that it be used in clinical prognostication and PAH predictive models.

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Reprint requests: Wassim H. Fares, MD, MSc, Department of Internal Medicine, Section of Pulmonary, Critical Care, & Sleep Medicine, Yale University, 15 York Street, LCI 105-C, New Haven, CT 06510. Telephone: +203-785-4196. Fax: +203-785-3634.
E-mail address: wassim.fares@yale.edu

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease with poor morbidity and mortality rates.[1–3] Right ventricular (RV) function is a major determinant of

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functional capacity and prognosis in patients with pulmonary hypertension (PH).[4–8] The increase in pulmonary vascular resistance (PVR) and impedance of flow causes RV strain that impairs filling and causes RV volume and pressure overload.[9] Over time, this leads to elevation of right atrial pressure (RAP), which has been found to be an independent mortality predictive variable in PAH.[3]

The most common cause of right heart failure is left heart failure,[10] which manifests in increased left-sided filling pressures, the measured surrogate of which is the pulmonary artery wedge pressure (PAWP). Other causes of elevated PAWP, such as generalized fluid overload seen in kidney and liver failure, raise RAP as well. As long as RV function is maintained, RAP remains lower than PAWP, although, over time, both the RAP and PAWP are elevated. It is when the RV starts failing that the RAP may increase "out of proportion" to the PAWP, thus raising the RAP/PAWP ratio. This ratio has been commonly quoted in the literature for sub-categorizing patients with right heart failure.[11] Although this concept makes theoretical sense, it has not been validated in clinical practice.

We hypothesized that the RAP/PAWP ratio is strongly correlated with 1-year survival in patients with PAH, and is more predictive of survival than the RAP when not "indexed" for PAWP (primary hypothesis). We also hypothesized that the RAP/PAWP ratio is more predictive of survival than any other hemodynamic variable (secondary hypotheses).

To test our hypotheses, we performed an analysis of a database that included pooled PAH patients from multiple prospective, randomized, controlled trials (RCTs) and cohorts. We subsequently analyzed a different non-RCT "real-life" PAH cohort to validate our results. The purpose of these two cohort analyses is to evaluate the consistency of the predictability of the RAP/PAWP ratio in different populations and to shed light on the potential differential value of the RAP/PAWP ratio in different clinical populations.

Methods

Cohort 1: PAH population

This de-identified cohort included PAH patients enrolled in prospective, short-term RCTs that compared vasodilators (specifically subcutaneous treprostinil infusion) with placebo, and were then followed for multiple years in an observational, non-randomized cohort study[12–15] (Figure 1). All hemodynamic measurements were made before initiation of the study drug in these RCTs. There were also patients in this database who were directly enrolled in the long-term observational cohort study without being enrolled first in the short-term RCTs.

Studies P01:03, P01:04 and P01:05 were multicenter, double-blind, randomized, parallel-group studies, conducted between April 1998 and February 2000. Study P01:06 was a long-term follow-up study of 776 patients who were either enrolled in the aforementioned short-term RCTs ($n = 403$)[13] or newly recruited ($n = 373$). Additional details about these studies are presented in Supplementary material E1 (available online at www.jhltonline.org). These original studies included pediatric patients (age <18 years old) and patients with chronic thromboembolic PH (World Health Organization [WHO] Group 4 PH), but we excluded these patients from this analysis to limit it to adult PAH (WHO Group 1 PH) patients.

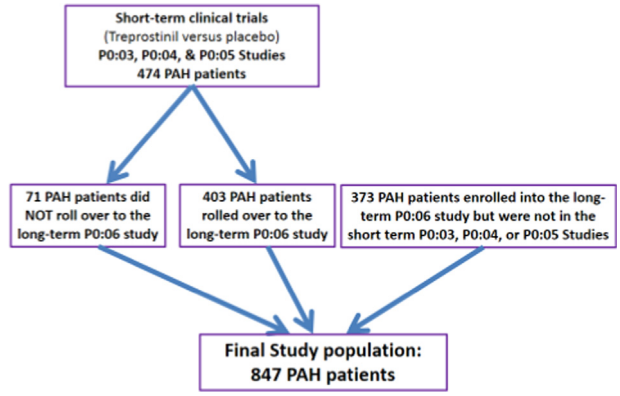

Figure 1 Flowchart for the studies from which the patients in Cohort 1 were included. These are prospective, randomized, controlled clinical trials that compared subcutaneous treprostinil to placebo over an 8- to 12-week period, and then had long-term extensions up to 4 years. The P0:03, 04 and 05 studies were short-term follow-up studies for 6-minute walk test distance as a primary outcome. The P0:06 study was the long-term follow-up study.

Cohort 2: Cleveland Clinic validation PAH population

This de-identified prospective cohort included patients managed in a tertiary-care PAH referral center (Cleveland Clinic, Cleveland, Ohio, USA). They were not part of any specific RCT, and were receiving care as dictated by their PH specialist, which included oral, inhaled and/or infused PAH therapies. Patients were enrolled in this database from 1990 to 2013. (The data for 2014 had not been finalized at the time of preparation of this manuscript, so they were not included in our analysis.)

Statistical analysis

Sample descriptive data are expressed as mean ± standard deviation. Categorical variables are expressed as counts or percentages. We used a 2-sample Student's *t*-test to compare means of continuous variables between two groups (the *p*-value for Type III sum of square was provided for continuous comparison if normality was satisfied for both variables; otherwise, a non-parametric approach, Wilcoxon's rank-sum test, was applied). Bivariable relationships, including changes over time, between continuous variables were evaluated by Pearson's correlation coefficient (r).

Simple and multiple linear regression and proportional hazard models were performed. As mentioned earlier, the primary outcome variable of this study was 1-year survival, and the primary exposure variable was RAP/PAWP ratio as a continuous variable. Based on a data-driven discriminatory value of a RAP/PAWP ratio of 1 (see Results), we also analyzed data using the RAP/PAWP ratio as a dichotomous variable (<1 vs ≥ 1).

For the multivariable regression model, we adjusted for age and functional class, which were decided beforehand. We did not adjust for many of the REVEAL risk score variables[3] because they were either missing (e.g., echocardiographic variables and blood work, including kidney function) or were variables of interest in the secondary analyses (e.g., RAP and PVR). We hypothesized that