Echocardiographic Assessment of Estimated Right Atrial Pressure and Size Predicts Mortality in Pulmonary Arterial Hypertension

Christopher Austin, MD; Khadija Alassas, MD; Charles Burger, MD, FCCP; Robert Safford, MD, PhD; Ricardo Pagan, MD; Katherine Duello, MD; Preetham Kumar, MD; Tonya Zeiger, RRT; and Brian Shapiro, MD

BACKGROUND: Elevated mean right atrial pressure (RAP) measured by cardiac catheterization is an independent risk factor for mortality. Prior studies have demonstrated a modest correlation with invasive and noninvasive echocardiographic RAP, but the prognostic impact of estimated right atrial pressure (eRAP) has not been previously evaluated in patients with pulmonary arterial hypertension (PAH).

METHODS: A retrospective analysis of 121 consecutive patients with PAH based on right-sided heart catheterization and echocardiography was performed. The eRAP was calculated by inferior vena cava diameter and collapse using 2005 and 2010 American Society of Echocardiography (ASE) definitions. Accuracy and correlation of eRAP to RAP was assessed. Kaplan-Meier survival analysis by eRAP, right atrial area, and Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) risk criteria as well as univariate and multivariate analysis of echocardiographic findings was performed.

RESULTS: Elevation of eRAP was associated with decreased survival time compared with lower eRAP ($P < .001$, relative risk = 7.94 for eRAP > 15 mm Hg vs eRAP ≤ 5 mm Hg). Univariate analysis of echocardiographic parameters including eRAP > 15 mm Hg, right atrial area > 18 cm², presence of pericardial effusion, right ventricular fractional area change < 35%, and at least moderate tricuspid regurgitation was predictive of poor survival. However, multivariate analysis revealed that eRAP > 15 mm Hg was the only echocardiographic risk factor that was predictive of mortality (hazard ratio = 2.28, $P = .037$).

CONCLUSIONS: Elevation of eRAP by echocardiography at baseline assessment was strongly associated with increased risk of death or transplant in patients with PAH. This measurement may represent an important prognostic component in the comprehensive echocardiographic evaluation of PAH.

CHEST 2015; 147(1):198-208

Manuscript received December 31, 2013; revision accepted July 16, 2014; originally published Online First September 11, 2014.

ABBREVIATIONS: 6MWD = 6-min walk distance; ASE = American Society of Echocardiography; BNP = brain natriuretic peptide; ECHO = echocardiography; eRAP = estimated right atrial pressure; FAC = right ventricular fractional area change; GFR = glomerular filtration rate; HR = hazard ratio; IVC = inferior vena cava; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PEF = pericardial effusion; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrium; RAA = right atrial area; RAP = right atrial pressure; REVEAL Registry = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right-sided heart catheterization; RR = relative risk; WHO = World Health Organization

AFFILIATIONS: From the Division of Cardiovascular Disease (Drs Austin, Alassas, Safford, Duello, Kumar, and Shapiro), Division of Pulmonary Disease (Dr Burger and Ms Zeiger), and Division of Internal Medicine (Dr Pagan), Mayo Clinic, Mayo Foundation for Medical Education and Research, Jacksonville, FL.

FUNDING/SUPPORT: This work was supported by Center for Translational Science activities [Grant UL1 TR000135].

CORRESPONDENCE TO: Brian Shapiro, MD, Department of Cardiovascular Disease, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224; e-mail: shapiro.brian@mayo.edu

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.13-3035

Pulmonary arterial hypertension (PAH) is a progressive disease of proliferative and fibrotic changes of the pulmonary vasculature, ultimately leading to increased pulmonary vascular resistance (PVR), decreased pulmonary vascular compliance, right ventricular failure, and death.¹ Diagnosis of PAH is based on systematic hemodynamic measurements of the right heart and pulmonary circulation obtained by right-sided heart catheterization (RHC). Due to the risk of complications and invasiveness, RHC is limited in the longitudinal evaluation of patients with PAH.² Patients are typically monitored with careful clinical evaluation, echocardiography (ECHO), and standard functional and biomarker assessment.³

Elevated mean right atrial pressure (RAP) measured by RHC is an established risk factor for poor survival in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry) as well as other cohorts.⁴⁻⁸ ECHO estimates of right atrial pressure have been validated against RHC in the general population

and have shown modest correlation in patients with PAH.⁹⁻¹¹ While several methods have been studied, assessment of the inferior vena cava (IVC) size (eg, diameter) and percent collapsibility with inspiration or “sniff” is the most widely used and accepted.^{9,10,12,13} The estimated right atrial pressure (eRAP) is also required to calculate pulmonary artery systolic pressure or right ventricular systolic pressure (RVSP) using the modified Bernoulli equation: $RVSP = 4V^2 + eRAP$ where V = peak tricuspid regurgitant jet velocity.¹⁴⁻¹⁷ The prognostic significance of eRAP exclusively in patients with PAH has not been previously reported. However, IVC collapsibility > 50% was associated with favorable survival in a PAH cohort.¹⁸ The purpose of this study was to explore the association between eRAP and mortality in patients with PAH. In addition, because eRAP may be technically prohibitive in some patients, the association of right atrial size based on area (right atrial area [RAA]) to mortality was also assessed.¹⁰ Previously, enlarged RAA has been identified as a predictor of poor outcome in PAH.^{19,20}

Materials and Methods

The Mayo Clinic Institutional Review Board approved this retrospective study (no. 12-004764) as minimal risk. Thus, patient consent was not required.

Study Design

A cohort of 121 consecutive patients who met World Health Organization (WHO) diagnostic criteria for group 1 PAH based on clinical evaluation, ECHO and RHC were retrospectively assessed. Comprehensive testing was performed at baseline only. Group 1 patients with PAH represented those with idiopathic or familial PAH, PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, drugs or toxins, or HIV infection.²¹ Inclusion criteria were mean pulmonary artery pressure (mPAP) > 25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg and PVR ≥ 3 Wood units based on RHC. Patients were evaluated by a board-certified pulmonologist (C. B.) or cardiologist (B. S. or R. S.) in the Pulmonary Hypertension Clinic.

Baseline Characteristics

In addition to a comprehensive clinical evaluation, patients underwent a 6-min walk distance (6MWD), comprehensive laboratory investigation including brain natriuretic peptide (BNP) level, ECHO, and RHC. Glomerular filtration rate (GFR) was estimated using the modified diet in renal disease equation.²² Renal insufficiency was defined as GFR of < 60 mL/min/1.73 m². Percent predicted of total lung capacity, % FEV₁, and % diffusion capacity of the lung for carbon monoxide were measured by pulmonary function testing. Hemodynamic assessment by RHC included mean RAP, mPAP, PCWP, and cardiac output. Left ventricular end diastolic pressure was obtained if the patient underwent simultaneous left-sided heart catheterization and RHC. The PVR was calculated using cardiac output and PCWP or left ventricular end diastolic pressure if PCWP was unavailable. All hemodynamic data were measured in triplicate and at quiet end-expiration. Patient information was collected using REDCap electronic data capture tools provided by the Mayo Clinic.²³

Echocardiography

All patients underwent a comprehensive transthoracic ECHO including two-dimensional and Doppler ECHO. All patients were breathing spontaneously without mechanical ventilation and did not require vasopressor support. Images of the IVC were obtained via the subcostal window. Measurements were analyzed by a single operator with direct supervision by a level 3, board-certified echocardiographer who was blinded to clinical information (B. S.). The IVC diameter was measured in the long axis within 1 to 2 cm of the junction with the right atrium (RA) during normal respiration as well as inspiratory sniff (Fig 1). Collapsibility index was calculated as:

$$\text{Collapsibility index} = \frac{\text{Minimum IVC diameter during sniff}}{\text{Maximum IVC diameter during normal respiration}} \times 100$$

Estimated RAP using the collapsibility index and maximum IVC diameter were used to categorize the patients into groups of increasing eRAP as defined by the 2005 and 2010 American Society of Echocardiography (ASE) guidelines, respectively^{10,13} (Table 1).

Right atrial size evaluation was performed via the apical four-chamber view (Fig 2). RAA was estimated by planimetry and was traced at the end of ventricular systole. Patients were stratified based on having a normal RAA (≤ 18 cm²) or enlarged RAA (> 18 cm²).

Survival

Vital status and date of death were obtained from the electronic medical record or Social Security Death Index as of June 7, 2013. Patients who underwent lung (n = 2) or liver transplantation (n = 5) at our institution were censored at date of transplant. Duration of follow-up was calculated as the total number of days between ECHO and death, transplant, or most recent patient contact including follow-up visits, hospitalizations, diagnostic testing, and phone correspondence.

Statistical Analysis

Statistical analysis was performed using JMP 9 software (SAS Institute Inc). The PAH cohort was divided into groups based on eRAP. Continuous

Figure 1 – Estimated right atrial pressure by echocardiography. A-D, The inferior vena cava (IVC) (*) during normal respiration (A) and inspiratory sniff (B) in a patient with estimated right atrial pressure of 5 mm Hg. Conversely, the IVC in a patient with estimated right atrial pressure of 20 mm Hg is dilated during normal respiration (C) and does not collapse with inspiratory sniff (D).

variables were presented as mean $\pm$ SD. One-way analysis of variance was used to compare continuous variables across groups. Categorical data were represented as a value and percentage. Comparisons were

TABLE 1] eRAP Using Collapsibility Index and Maximum IVC Diameter to Categorize Groups of Increasing eRAP as Defined by ASE Guidelines

Measurement	eRAP
2005 ASE guidelines	
0-5 mm Hg	IVC maximum ≤ 1.7 cm and collapsibility index $\geq 50\%$
6-10 mm Hg	IVC maximum > 1.7 cm and collapsibility index $\geq 50\%$
11-15 mm Hg	IVC maximum > 1.7 cm and collapsibility index $< 50\%$
> 15 mm Hg	IVC maximum > 1.7 cm and collapsibility index $< 25\%$
2010 ASE guidelines	
Normal	IVC maximum ≤ 2.1 cm and collapsibility index $> 50\%$
Intermediate	IVC maximum ≤ 2.1 cm and collapsibility index $< 50\%$
High	IVC maximum > 2.1 cm and collapsibility index $< 50\%$

eRAP using collapsibility index and maximum IVC diameter were used to categorize the patients into groups of increasing eRAP as defined by the 2005 and 2010 ASE guidelines, respectively.^{10,13} ASE = American Society of Echocardiography; eRAP = estimated right atrial pressure; IVC = inferior vena cava.

performed with the χ^2 test. Accuracy analysis and correlation of eRAP vs RHC-measured RAP was performed using the Spearman rank correlation, with eRAP considered accurate if RHC-measured RAP was within 5 mm Hg of the mean of the eRAP range. Kaplan-Meier analysis by eRAP group was performed at 3 years and the survival curves were compared using the log-rank test. Univariate and multivariate analysis of REVEAL Registry calculator variables and ECHO findings was performed.⁴ Additionally, the cohort was divided into normal RAA (≤ 18 cm²) or enlarged RAA (> 18 cm²) groups. Kaplan-Meier survival analysis of these groups was completed in a similar fashion.

To compare this cohort to previously published subjects with PAH, REVEAL Registry 1-year predicted survival was calculated for each member using the following equation

$$\left[S_0(1)^{\exp(z/\beta\gamma)} \right],$$

Figure 2 – Right atrial size by echocardiography. A-B, The right atria (*) can be measured by echocardiography with area ≤ 18 cm² defined as normal (A) and > 18 cm² considered enlarged (B).

TABLE 2] Demographics and Characteristics of Analysis Cohort Based on 2005 ASE-Defined eRAP by ECHO

Characteristic	RAP				P Value ^a
	0-5 mm Hg	6-10 mm Hg	11-15 mm Hg	> 15 mm Hg	
Patient, No. (%)	30 (25)	45 (37)	31 (26)	15 (12)	...
Age at evaluation, mean $\pm$ SD, y	57.1 $\pm$ 13.3	57.0 $\pm$ 13.8	63.6 $\pm$ 14.0	63.4 $\pm$ 13.9	.103
Female, No. (%)	21 (70)	33 (73)	17 (55)	9 (60)	.358 ^b
Mean BMI at evaluation $\pm$ SD, kg/m ²	28.5 $\pm$ 5.3	28.6 $\pm$ 6.5	27.4 $\pm$ 4.6	29.4 $\pm$ 8.7	.717
PAH clinical classification, No. (%)					.571 ^c
Idiopathic	14 (47)	16 (36)	15 (48)	2 (13)	
CTD	9 (30)	15 (33)	9 (29)	11 (73)	
Portal hypertension	7 (23)	8 (18)	7 (22)	0 (0)	
Other	0 (0)	6 (13)	0 (0)	1 (7)	
Functional class at evaluation, No. (%)					.322 ^c
I	1 (3)	2 (4)	1 (3)	0 (0)	
II	14 (47)	14 (31)	9 (29)	2 (13)	
III	13 (43)	27 (60)	17 (55)	9 (60)	
IV	2 (7)	2 (4)	2 (6)	4 (27)	
Newly diagnosed, No. (%)	29 (97)	40 (89)	28 (90)	14 (93)	.617 ^b
Previously diagnosed, No. (%)	1 (3)	5 (11)	3 (10)	1 (7)	.617 ^b
6MWD at evaluation, mean $\pm$ SD, m	308 $\pm$ 104	303 $\pm$ 101	306 $\pm$ 89	179 $\pm$ 132	.002 ^d
Vital signs at evaluation					
Heart rate, mean $\pm$ SD, bpm	79 $\pm$ 13	79 $\pm$ 17	77 $\pm$ 13	83 $\pm$ 13	.654
Systolic BP, mean $\pm$ SD, mm Hg	123 $\pm$ 24	121 $\pm$ 23	119 $\pm$ 18	117 $\pm$ 14	.588
Pulmonary function testing, mean $\pm$ SD, % predicted					
DLCO	51 $\pm$ 16.4	59 $\pm$ 22	47.8 $\pm$ 16.9	46.5 $\pm$ 21.6	.076
TLC	91.7 $\pm$ 15.6	86 $\pm$ 18	84.0 $\pm$ 10.1	92.2 $\pm$ 8.3	.217
FEV ₁	82.0 $\pm$ 14.9	70 $\pm$ 19	72.0 $\pm$ 17.0	80.7 $\pm$ 20.6	.039 ^e
Hemodynamics at diagnostic RHC, mean $\pm$ SD					
RAP, mm Hg	7.1 $\pm$ 3.6	8.0 $\pm$ 4.3	8.8 $\pm$ 4.0	11.7 $\pm$ 6.1	.010 ^f
mPAP, mm Hg	41.4 $\pm$ 13.2	42.1 $\pm$ 11.8	43.3 $\pm$ 12.8	46.5 $\pm$ 9.6	.564
PCWP, mm Hg	9.3 $\pm$ 4.5	10.1 $\pm$ 3.1	10.4 $\pm$ 3.5	8.5 $\pm$ 3.9	.355

(Continued)

TABLE 2] (continued)

Characteristic	RAP				P Value ^a
	0-5 mm Hg	6-10 mm Hg	11-15 mm Hg	> 15 mm Hg	
PVR, WU	7.4 ± 4.3	7.5 ± 4.3	9.2 ± 4.9	10.9 ± 3.9	.046 ^g
Cardiac index, L/min × m ²	2.7 ± 0.9	2.7 ± 1.0	2.3 ± 0.9	1.9 ± 0.7	.024 ^h
BNP, mean ± SD, pg/mL	168 ± 235	420 ± 573	346 ± 398	957 ± 740	< .001 ⁱ
Pericardial effusion present, No. (%)	6 (20)	9 (20)	9 (29)	7 (47)	.170 ^b
Renal insufficiency, No. (%)	8 (27)	17 (38)	14 (45)	8 (53)	.168 ^b
REVEAL Registry risk score	8.1 ± 2.8	8.8 ± 2.0	10.0 ± 2.5	11.4 ± 2.4	< .001 ^j
REVEAL Registry 1-y survival (%)	81.2 ± 21.5	85.3 ± 12.3	74.8 ± 20.9	63.0 ± 27.5	< .001 ^k

6MWD = 6-min walk distance; BNP = brain natriuretic peptide; bpm = beats/min; CTD = connective tissue disease; Dlco = diffusion capacity of the lung for carbon monoxide; ECHO = echocardiography;

mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; REVEAL

Registry = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right-sided heart catheterization; TLC = total lung capacity; WU = Wood unit. See Table 1 legend for expansion of other abbreviations.

^aCross-group contingency analysis performed.

^bContingency analysis is suspect due to inadequate population size.

^c $P < .01$ for when > 15 compared with all other groups.

^d $P < .01$ for 0-5 vs 6-10 and $P = .03$ for 0-5 vs 11-15.

^e $P = .02$ for 0-5 vs > 15 and 6-10 vs > 15.

^f $P = .03$ for 0-5 vs 6-10 and $P < .10$ for 0-5 vs > 15, 6-10 vs > 15, and 11-15 vs > 15.

^g $P < .01$ for 0-5 vs > 15 and 6-10 vs > 15.

^h $P = .03$ for 0-5 vs 6-10 and $P < .10$ for 0-5 vs > 15, 6-10 vs > 15, and 11-15 vs > 15.

ⁱ $P < .01$ for 0-5 vs 11-15, 0-5 vs > 15 and 6-10 vs > 15; $P = .04$ for 6-10 vs 11-15.

^j $P < .01$ for 0-5 vs > 15 and 6-10 vs > 15; $P = .02$ for 6-10 vs 11-15.

^k $P < .01$ for 0-5 vs > 15 and 6-10 vs > 15; $P = .02$ for 6-10 vs 11-15.

where $S_0(1) = 0.9698$, $\gamma = 0.939$, and $Z'\beta$ is the sum of the patient's individual characteristics multiplied by the β coefficients for each of the 19 parameters in the REVEAL Registry model.²⁴ Missing demographic and clinical data were handled as a "0" for each missing variable as was performed in the REVEAL Registry cohort.

REVEAL Registry simplified risk score was calculated using the REVEAL Registry risk calculator.⁴ Kaplan-Meier analyses of the cohort were performed according to the assigned REVEAL Registry risk stratum, and the survival curves were compared using the log-rank test.

Results

Clinical Characteristics

The cohort included 121 group 1 patients with PAH who were followed for $1,109 \pm 1,096$ days for the overall cohort and $1,366 \pm 1,172$ days for survivors. Baseline characteristics are summarized in Table 2. Of the 121 patients, 105 had ECHO within 1 year of RHC (average interval time 170 ± 706 days) and the majority ($n = 92$, 76.0%) underwent ECHO within 90 days of RHC. The mean age was 60 years and 66% were women. Most patients were characterized as having idiopathic PAH, associated with connective tissue disorder, or as having portopulmonary hypertension. The majority of patients were symptomatic and newly diagnosed ($> 90\%$) with PAH.

Comparative characteristics and echocardiographic findings for 2005 ASE-defined eRAP groups are presented in Tables 2 and 3, respectively. Patients with high eRAP had lower 6MWD ($P < .001$, 179 ± 132 m for eRAP > 15 mm Hg vs 308 ± 104 m for eRAP ≤ 5 mm Hg) and higher BNP values ($P < .001$, 957 ± 740 pg/mL

for eRAP > 15 mm Hg vs 168 ± 235 pg/mL for eRAP ≤ 5 mm Hg). Accuracy assessment of RHC-measured RAP and eRAP revealed accuracy of 64.4% ($\rho = 0.222$, $P = .016$) and 68.6% ($\rho = 0.220$, $P = .017$) for 2005 and 2010 ASE guidelines, respectively (Table 4).

Survival Analysis

At 3 years of follow-up, there were 42 deaths, two lung transplants, and five liver transplants. The overall survival of the cohort at 3 years was 60%. Kaplan-Meier survival analysis by 2005 and 2010 eRAP groups was performed (Fig 3). Three-year survival ranged from 82% to 13% in the lowest and highest 2005 ASE-defined eRAP groups and 75% to 45% in the 2010 ASE-defined groups, respectively. Elevated eRAP was highly associated with death or transplant for both 2005 (relative risk [RR], 7.94; $P < .05$ for eRAP > 15 mm Hg vs eRAP ≤ 5 mm Hg) and 2010 (RR, 2.61; $P < .05$ for high vs normal) ASE-defined groups.

Univariate analysis of this cohort revealed WHO functional class IV, BNP > 180 pg/mL, eRAP > 15 , IVC collapse $< 50\%$, RAA > 18 cm², presence of pericardial

TABLE 3] Echocardiographic Characteristics of 2005 ASE-Defined eRAP Groups

Characteristic	RAP				P Value
	0-5 mm Hg	6-10 mm Hg	10-15 mm Hg	> 15 mm Hg	
IVC diameter, mean $\pm$ SD, cm					
Minimum	0.38 ± 0.2	0.64 ± 0.3	1.35 ± 0.4	1.94 ± 0.4	$< .001^a$
Maximum	1.31 ± 0.3	2.08 ± 0.3	2.03 ± 0.5	2.25 ± 0.4	$< .001^b$
IVC collapse index, %	70.1 ± 10	69.0 ± 12	33.2 ± 9.8	14.0 ± 7.2	$< .001^c$
RV area, mean $\pm$ SD, cm ²					
Systole	16.6 ± 8.5	19.8 ± 7.9	21.9 ± 9.0	24.0 ± 6.6	$.018^d$
Diastole	25.1 ± 9.3	29.1 ± 8.3	30.1 ± 8.7	32.3 ± 7.0	$.037^e$
Tricuspid regurgitation					
None to mild	19	20	6	2	^f
Moderate to severe	11	24	24	13	^f
RA area, mean $\pm$ SD, cm ²	17.2 ± 5.7	22.2 ± 7.8	24.4 ± 8.1	27.0 ± 6.7	$< .001^g$

RA = right atrium; RV = right ventricle. See Table 1 and 2 legends for expansions of other abbreviations.

^a $P < .01$ for all comparisons of all quartiles.

^b $P < .01$ for all comparisons of 0-5 mm Hg quartile vs other quartiles.

^c $P < .01$ for all comparisons except 0-5 mm Hg vs 6-10 mm Hg ($P = .68$).

^d $P = .01$ for 0-5 vs 10-15 and $P < .01$ for 0-5 vs > 15 quartiles.

^e $P = .02$ for 0-5 vs 10-15 and $P < .01$ for 0-5 vs > 15 quartiles.

^fContingency analysis not performed due to inadequate population size.

^g $P < .01$ for 0-5 vs 6-10, 0-5 vs 10-15, and 0-5 vs > 15 ; $P = .03$ for 6-10 vs > 15 quartiles.

TABLE 4 Correlation of Initial RHC and eRAP by 2005 and 2010 ASE Guidelines

Characteristic	2005	2010
mRAP vs eRAP, No.	121	121
Spearman correlation	0.222	0.220
<i>P</i> value	.016	.017
Percent of ECHOs within 5 mm Hg, No. (%)		
ECHO underestimates	15 (12.4)	27 (22.3)
ECHO within 5 mm Hg RHC	77 (63.6)	83 (68.6)
ECHO overestimates	29 (24.0)	11 (9.1)

mRAP by RHC; eRAP by echocardiography. See Table 1 and 2 legends for expansion of abbreviations.

effusion (PEF), right ventricular fractional area change (FAC) < 35% and tricuspid regurgitation at least as moderate as significant risk factors for death or transplant (Table 5). Multivariate analysis of echocardiographic

Figure 3 – Survival by estimated right atrial pressure (eRAP). The pulmonary arterial hypertension cohort was stratified by eRAP and survival was analyzed by Kaplan-Meier. A-B, Analysis was performed for the 2005 (A) and 2010 (B) American Society of Echocardiography-defined eRAP. The groups were significantly different, and stratification by eRAP was similar for 2005 and 2010 eRAP definitions. Right atrial pressure > 15 mm Hg was significantly associated with decreased transplant-free survival at 3 y after baseline echocardiography.

findings including eRAP, RAA, PEF, FAC, and tricuspid regurgitation identified eRAP > 15 mm Hg as the only significant echocardiographic risk factor for this cohort (hazard ratio [HR] = 2.284, *P* = .037).

Survival analysis by RAA revealed similar results (Fig 4). At 3 years' follow-up, patients with normal RAA and enlarged RAA had survival rates of 76% and 50%, respectively. The RR of death or transplantation at 3 years was 2.56 for patients with enlarged RAA (*P* = .006). Finally, survival analysis by REVEAL Registry risk category successfully discriminated survival in our cohort (*P* < .001, Fig 5). Three-year survival was 91%, 62%, 64%, 49%, and 35% for the low, average, moderately high, high, and very high risk groups, respectively.

Discussion

As previously described, eRAP is an important measurement in PAH. Our findings confirm the hypothesis that eRAP, a noninvasive measure easily obtained by ultrasound, provides important prognostic information with potential implications on functional capacity and survival. Measures of cardiac function including cardiac index, 6MWD, and BNP were significantly worse with increased eRAP and its ability to stratify our cohort by REVEAL Registry risk score, and REVEAL Registry 1-year survival suggests eRAP is an inexpensive and easily obtained predictive measure for patients with PAH. Multivariate analysis revealed eRAP > 15 mm Hg as being the single most significant echocardiographic parameter (HR = 2.28, *P* = .037).

The secondary analysis of RAA revealed enlargement > 18 cm² as a significant risk factor for death or transplant in the PAH cohort. Right atrial enlargement and associated outcomes in the setting of PAH are not well described in the medical literature. Our cohort had better survival at 3 years (50%) than previously identified by Bustamante-Labarta et al²⁰ (20%), although their cohort consisted of only 22 patients with PAH. It is possible that ECHO assessment of eRAP and RA size reflect complementary tools for prognostic assessment.

Comparative analysis of the 2005 and 2010 ASE guidelines for eRAP revealed similar findings regarding prognosis. Accuracy between ECHO and catheterization was comparable for the 2005 (63.6%) and 2010 (68.6%) definitions and similar to data from Farber et al¹¹ (63.5%). However, while accuracy (< 5 mm Hg difference between ECHO and catheterization) was modest, correlation was poor and likely related to multiple confounders. The 2005 guidelines were more prone to eRAP overestimation (24%) when compared with 2010 (9%), which may have

TABLE 5] Univariate and Multivariate Analysis of PAH Cohort

Characteristic	Univariate Hazard Ratio	P Value	Multivariate Hazard Ratio ^a	P Value
Patient, No. (%)				
Age > 60 y at evaluation	0.933	.824	...	...
Female	0.916	.784	...	...
PAH clinical classification vs CTD				
Idiopathic	0.434	.028	...	...
Portal hypertension	0.880	.751	...	...
Other	1.800	.316	...	...
Functional class vs WHO class II				
I	1.030	.977	...	...
III	0.675	.297	...	...
IV	0.188	<.001	...	...
6MWD < 165 m	4.937	<.0001	...	...
Vital signs				
Heart rate > 92 bpm	2.038	.065	...	...
Systolic BP < 110 mm Hg	1.055	.947	...	...
Pulmonary function testing				
DLco ≤ 32% predicted	2.140	.101	...	...
Hemodynamics at diagnostic RHC				
RAP > 20 mm Hg	2.614	.414	...	...
PVR > 32 WU	1.000	1.000	...	...
Laboratory testing				
BNP > 180 pg/mL	2.568	.005	...	...
GFR < 60 mg/dL	1.175	.609	...	...
Echocardiographic findings				
eRAP ≤ 5 mm Hg	0.337	.009	0.527	.197
eRAP > 15 mm Hg	4.202	<.001	2.284	.037
IVC > 1.7 cm	1.663	.112	...	...
IVC > 2.1 cm	1.540	.174	...	...
IVC % collapse < 50%	2.055	.021	...	...
RA area > 18 cm ²	2.600	.006	1.141	.507
Pericardial effusion present	2.490	.004	1.797	.081
FAC < 35%	2.316	.014	1.521	.265
Tricuspid regurgitation ≥ moderate	2.619	.005	1.896	.088

FAC = right ventricular fractional area change; GFR = glomerular filtration rate; WHO = World Health Organization. See Table 1-3 legends for expansion of other abbreviations.

^aMultivariate analysis limited to echocardiographic findings.

been related to smaller cutoff for a normal IVC diameter (1.7 cm vs 2.1 cm). However, the 2005 eRAP guidelines resulted in superior stratification of the survival curves as compared with the newer recommendations (Fig 3).

The presence of PEF is a well-established predictor of poor outcome in patients with PAH.^{25,26} Intergroup analysis did not demonstrate a significant difference in the rate of PEF. However, our patients with highest

eRAP were more likely to have PEF present. Although the presence of elevated RAP has previously been associated with PEF, Fenstad et al⁶ noted this relationship in a cohort with higher RAP (13.5 ± 6.7 mm Hg for at least trivial effusion). Shimony et al²⁷ demonstrated an association between the incidence of at least moderate size PEF and increased mortality. Previous studies also suggest a strong relationship between connective tissue disease associated PAH and the presence of PEF.^{6,7,28}

Figure 4 – Survival by estimated right atrial area. Enlarged right atrial area ($> 18 \text{ cm}^2$) was associated with increased death or transplant at 3 y by Kaplan-Meier analysis.

Overall survival of this cohort was worse at 1 year when compared with REVEAL Registry and the French PAH Network cohorts. However, survival at 2 and 3 years was similar.^{24,29} Furthermore, our cohort had high percentages of incident cases, portopulmonary hypertension, and connective tissue disease, all of which are associated with poor prognosis.²⁹⁻³¹ Stratification of this cohort by REVEAL Registry 1-year risk demonstrated worse than anticipated survival in the very high risk category (40% vs $65.9\% \pm 7.2\%$) at 1 year. However, other categories performed similarly to the REVEAL Registry cohort.⁴

There are few prior studies that analyzed survival in patients with PAH by eRAP group. In a study to evaluate right ventricular free-wall systolic strain assessment, Fine et al³² found eRAP > 5 to be a risk factor for all-cause mortality among 406 patients with groups 1, 3, or 4 pulmonary hypertension (HR, 2.62; $P < .001$). Ghio et al¹⁸ showed IVC collapsibility as protective in a cohort of 59 patients with PAH (HR, 0.36; $P = .023$).

Limitations

One important limitation was that ECHO and RHC were not performed simultaneously, which likely contributed to poor correlation between measurements of RAP. However, accuracy of eRAP was comparable to

Figure 5 – Survival by Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) 1-y risk. The pulmonary arterial hypertension cohort was stratified by calculated REVEAL Registry 1-y risk and survival analyzed by Kaplan-Meier. Very high risk patients were significantly more likely to experience death or transplantation at 3 y.

that previously reported in the setting of PAH.¹¹ Furthermore, these tests were performed within 90 days for 76% of the patients, a timeframe that has previously been shown to be acceptable for baseline analysis.¹¹

Conclusions

Elevation of eRAP and RA enlargement are associated with decreased overall and transplant-free survival in this cohort of patients with group 1 PAH. Echocardiographic assessment of RAP is an essential component of the right heart evaluation. Multiple echocardiographic modalities of right ventricular function have also been shown to provide prognostic importance³³⁻³⁸ but there is no current general consensus on the appropriate technique for echocardiographic evaluation of the right heart in PAH.³⁹ As suggested by guideline statements, eRAP is essential in the estimation of echocardiographic pulmonary pressures. These authors also speculate that elevated eRAP and enlarged RAA may provide additional value in providing prognostic estimates. Future scoring systems may incorporate these findings, but further prospective studies are warranted for confirmation and validation.

Acknowledgments

Author contributions: B. S. had full access to all the data in the study and takes full responsibility for the integrity of the data and data analysis. C. A. and B. S. contributed to study design, data acquisition, analysis, and interpretation, and drafting of the manuscript; K. A. contributed to study design, data acquisition and interpretation, and drafting of the manuscript; C. B. contributed to study design, data acquisition and interpretation, drafting of the manuscript, and critical revision based on content expertise; R. S. contributed to data acquisition and interpretation, drafting of the manuscript, and critical revision based on content expertise; and R. P., K. D., P. K., and T. Z. contributed to data acquisition and drafting of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The work was performed at Mayo Clinic, Jacksonville, FL. We thank the Center for Translational Science Activities grant support (UL1 TR000135) for assistance with this study.

References

- Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and non-invasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. *Circulation*. 2009;120(11):992-1007.
- McLaughlin VV, Archer SL, Badesch DB, et al; ACCF/AHA. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc, and the Pulmonary Hypertension Association [published correction appears in *Circulation*. 2009;120(2):e13]. *Circulation*. 2009;119(16):2250-2294.
- Schannwell CM, Steiner S, Strauer BE. Diagnostics in pulmonary hypertension. *J Physiol Pharmacol*. 2007;58(suppl 5)(pt 2):591-602.
- Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest*. 2012;141(2):354-362.
- D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115(5):343-349.
- Fenstad ER, Le RJ, Sinak LJ, et al. Pericardial effusions in pulmonary arterial hypertension: characteristics, prognosis, and role of drainage. *Chest*. 2013;144(5):1530-1538.
- Honeycutt GR, Safdar Z. Pulmonary hypertension complicated by pericardial effusion: a single center experience. *Ther Adv Respir Dis*. 2013;7(3):151-159.
- Lee WT, Ling Y, Sheares KK, Pepke-Zaba J, Peacock AJ, Johnson MK. Predicting survival in pulmonary arterial hypertension in the UK. *Eur Respir J*. 2012;40(3):604-611.
- Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol*. 1990;66(4):493-496.
- Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713.
- Farber HW, Foreman AJ, Miller DP, McGoon MD. REVEAL Registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension. *Congest Heart Fail*. 2011;17(2):56-64.
- Prekker ME, Scott NL, Hart D, Sprenkle MD, Leatherman JW. Point-of-care ultrasound to estimate central venous pressure: a comparison of three techniques. *Crit Care Med*. 2013;41(3):833-841.
- Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440-1463.
- Baque-Juston MC, Wells AU, Hansell DM. Pericardial thickening or effusion in patients with pulmonary artery hypertension: a CT study. *AJR Am J Roentgenol*. 1999;172(2):361-364.
- Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation*. 1983;68(2):302-309.
- Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation*. 1984;70(4):657-662.
- Currie PJ, Seward JB, Chan KL, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. *J Am Coll Cardiol*. 1985;6(4):750-756.
- Ghio S, Klersy C, Magrini G, et al. Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension. *Int J Cardiol*. 2010;140(3):272-278.
- Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol*. 2002;39(7):1214-1219.
- Bustamante-Labarta M, Perrone S, De La Fuente RL, et al. Right atrial size and tricuspid regurgitation severity predict mortality or transplantation in primary pulmonary hypertension. *J Am Soc Echocardiogr*. 2002;15(10 pt 2):1160-1164.
- Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009;54(suppl 1):S43-S54.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
- Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122(2):164-172.
- Galiè N, Torbicki A, Barst R, et al; Task Force. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J*. 2004;25(24):2243-2278.
- Hinderliter AL, Willis PW 4th, Long W, et al. Frequency and prognostic significance of pericardial effusion in primary pulmonary hypertension. PPH Study Group. Primary pulmonary hypertension. *Am J Cardiol*. 1999;84(4):481-484.
- Shimony A, Fox BD, Langleben D, Rudski LG. Incidence and significance of pericardial effusion in patients with pulmonary arterial hypertension. *Can J Cardiol*. 2013;29(6):678-682.
- Ngian GS, Stevens W, Prior D, et al. Predictors of mortality in connective tissue disease-associated pulmonary arterial hypertension: a cohort study. *Arthritis Res Ther*. 2012;14(5):R213.
- Humbert M, Sitbon O, Yaïci A, et al; French Pulmonary Arterial Hypertension Network. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;36(3):549-555.
- McLaughlin VV, Presberg KW, Doyle RL, et al; American College of Chest Physicians. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical

- practice guidelines. *Chest*. 2004;126 (suppl 1):78S-92S.
31. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. *Eur Respir J*. 2007;30(6):1103-1110.
 32. Fine NM, Chen L, Bastiansen PM, et al. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. *Circ Cardiovasc Imaging*. 2013;6(5):711-721.
 33. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med*. 2006;174(9):1034-1041.
 34. Sachdev A, Villarraga HR, Frantz RP, et al. Right ventricular strain for prediction of survival in patients with pulmonary arterial hypertension. *Chest*. 2011;139(6):1299-1309.
 35. Tei C, Dujardin KS, Hodge DO, et al. Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr*. 1996;9(6):838-847.
 36. Ruan Q, Nagueh SF. Clinical application of tissue Doppler imaging in patients with idiopathic pulmonary hypertension. *Chest*. 2007;131(2):395-401.
 37. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation*. 2008;117(11):1436-1448.
 38. Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. *Heart*. 2006;92(suppl 1):i2-i13.
 39. Celermajer DS, Marwick T. Echocardiographic and right heart catheterization techniques in patients with pulmonary arterial hypertension. *Int J Cardiol*. 2008;125(3):294-303.