Prognostic utility of right atrial emptying fractions in pulmonary arterial hypertension

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Abstract: Although left atrial function has been extensively studied in patients with heart failure, the determinants and clinical correlates of impaired right atrial (RA) function have been poorly studied. We investigated measures of RA function in pulmonary arterial hypertension (PAH). We identified all treatment-naïve patients with World Health Organization category 1 PAH seen at our center during 2000–2011 who had right heart catheterization and 6-minute walk test (6MWT) within 1 month of initial echocardiographic examination. Atrial size was measured using the monoplane area-length method, and atrial function was quantified using total, passive, and active RA emptying fractions (RAEFs). We compared measures of RAEF with known prognostic clinical, echocardiographic, and hemodynamic parameters. For the subset of patients with follow-up echocardiographic examination/6MWT within 6–18 months, we investigated the change in RAEF. In an exploratory analysis, we investigated the association between RAEF and mortality. Our population consisted of 39 patients with treatment-naïve (incident) PAH, 30 of whom had follow-up testing. The mean total, passive, and active RAEFs were $24.4\% \pm 15.1\%$, $8.5\% \pm 6.9\%$, and $17.6\% \pm 13.9\%$, respectively. Total and active RAEFs correlated with tricuspid annular plane systolic excursion ($P = 0.004$ and $P = 0.005$) and cardiac output ($P = 0.02$ and $P = 0.01$). The change in active RAEF correlated with change in 6-minute walk distance ($P = 0.02$). In our Cox regression analysis, low active and total RAEF were associated with mortality, with hazard ratios of 5.6 (95% confidence interval [CI], 1.2–26.2; $P = 0.03$) and 4.2 (95% CI, 1.1–15.5; $P = 0.03$), respectively. Passive RAEF was poorly reproducible and not associated with outcome. Measures of RAEF appear to have prognostic importance in PAH and warrant further study.

Keywords: pulmonary arterial hypertension, right atrial emptying fraction, echocardiography, prognosis.

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Pulmonary arterial hypertension (PAH) is an incurable disease caused by progressive narrowing of the small pulmonary arteries, culminating in increased pulmonary vascular resistance, right-sided heart failure, and death.^{1–3} In recent years, the function of the right ventricle (RV) has been identified as a highly important prognostic marker in PAH,^{4–6} because it reflects cardiac output (CO). However, the right atrium (RA) also contributes significantly to cardiac filling and function and may provide important prognostic information.⁷ For example, loss of atrial function in PAH can be observed in patients with atrial fibrillation and has been associated with clinical deterioration and poor outcome.^{8,9}

Atrial function is complex and has several components. It consists of a reservoir phase during atrial filling, a conduit phase during passive emptying of the atrium into the ventricle, and a pump phase during atrial systole.¹⁰ Emptying fractions measure changes in atrial volume between different phases of the cardiac cycle and are the most common metrics used to measure components of atrial

function. In patients with left heart disease, left atrial emptying fractions have been found to have prognostic implications and even predict the occurrence of atrial fibrillation.^{11–15} We hypothesized that RA emptying fractions (RAEFs) would be associated with parameters reflective of CO and that a low RAEF would be associated with poorer prognosis. We determined whether RAEF correlated with clinical, echocardiographic, and hemodynamic parameters both at baseline and during follow-up. Next, we performed an exploratory analysis of the association between RAEF and outcome in PAH.

METHODS

Study population

We performed a retrospective observational study of a well-characterized population of treatment-naïve patients with World Health Organization (WHO) category 1 PAH. Adults >18 years of

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age who were evaluated at Stanford University Medical Center during 2000–2011 and met criteria for diagnosis of PAH on cardiac catheterization (mean pulmonary artery pressure ≥ 25 mmHg, pulmonary capillary wedge pressure < 15 mmHg, pulmonary vascular resistance > 3 Wood units) were included. Only PAH treatment-naïve patients with 6-minute walk test (6MWT) performed within 1 month of diagnostic cardiac catheterization were included. We required all subjects to have 1 year of follow-up from the date of the first echocardiogram. We excluded all patients who had significant components of WHO category II–V disease. Patients with a history of atrial fibrillation or atrial flutter were excluded, because these conditions affect atrial function.¹⁶ Finally, patients with congenital heart disease and those with suboptimal image quality were also excluded from the analysis.

Echocardiography

The digitized transthoracic echocardiograms were analyzed by a single reader who was blinded to clinical outcomes (NWB). RA volumes were measured from the apical four-chamber view, using the single-plane area-length method according to the Guidelines of the American Society of Echocardiography (ASE; Fig. 1).¹⁷ RA areas were measured by direct planimetry of the RA endocardium, excluding the area between the tricuspid valve leaflets and the annulus, the superior and inferior vena cavae, and the right atrial appendage. RA lengths were measured from the center of the tricuspid annulus to the center of the superior wall, along a line parallel to the interatrial septum. The maximal and minimal RA volumes were measured immediately before the opening and immediately after the closure of the tricuspid valve, respectively. The preatrial systole RA volume was measured from the frame corresponding to the center of the P wave on the electrocardiogram. All reported RA volumes are indexed to body surface area. The echo reader was blinded to other study data at the time that the measurements were obtained.

Figure 1. Sample right atrial area and length measured at end diastole.

The total RAEF (tRAEF) is measured as the difference between the maximal and minimal RA volumes, divided by the maximal RA volume; the passive RAEF (pRAEF) corresponds to the difference between the maximal volume and the preatrial systole volume, divided by the maximal volume; and the active RAEF (aRAEF) corresponds to the difference between the preatrial systole volume and the minimal volume, divided by the preatrial systole volume.

The tricuspid annular plane systolic excursion (TAPSE) was measured for all patients in the manner described by Forfia and colleagues.⁴ Right ventricular systolic pressure (RVSP) and right ventricular basal diameter (RVd) as well as left ventricular dimensions and function were measured according to ASE guidelines.¹⁷ Also, RA pressure was estimated according to guidelines on the basis of the inferior vena cava size and collapsibility.

We also measured these parameters on echocardiograms obtained earlier from a population of prospectively recruited healthy volunteers. All volunteers reported no cardiovascular disease on enrollment. We compared the parameters measured for the patients with PAH versus healthy control subjects.

Clinical variables and outcomes

All demographic, clinical, and outcomes data were obtained from the Vera Moulton Wall Center Pulmonary Hypertension database, a prospective observational database encompassing all clinical data on patients seen at Stanford University Medical Center. Data were extracted by a trained research assistant (AH) and a physician (NWB). According to usual practice, echocardiographic examination and 6MWT are scheduled on the same day as clinic visits. New York Heart Association (NYHA) functional class was determined at the time of clinic visit by a pulmonary hypertension specialist. Other extracted clinical variables included age, sex, body mass index (BMI; defined as weight in kilograms divided by the square of height in meters), N-terminal pro-B type natriuretic, 6-minute walk distance (6MWD), and medical therapy at the time of follow-up echocardiographic examination. All 6MWTs were performed in accordance with American Thoracic Society standards.¹⁸ Community physician reporting, family contacts, and the social security death index were used to capture and validate mortality data.

Right heart catheterization (RHC)

RHC was performed by a single operator (RTZ) with an annual experience of more than 100 procedures. Measured pressures included mean right atrial pressure (mRAP), mean pulmonary arterial pressure (mPAP), and pulmonary artery wedge pressure (PAWP). All pressures were measured at end expiration, and zero was set at the level of the mid thorax. Hemodynamic characteristics were determined using traditional methods and calculations.¹⁹ Stroke volume was calculated as CO divided by heart rate at time of catheterization. Pulmonary arterial capacitance (PAC) was calculated as the ratio of the stroke volume to the pulmonary artery pulse pressure.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation for continuous variables or as number of cases and percentages for categori-

cal variables. The association between baseline RAEF and clinical, echocardiographic, and hemodynamic parameters of interest at baseline and follow-up were compared using linear regression analysis. Cox proportional hazards models were then created to compare survival between patients with high and low RAEF by dichotomizing the population by the mean value for RAEF. All *P* values presented are two-sided, and a value of less than 0.05 was considered statistically significant. For all baseline echocardiograms, two observers (NWB and FH) measured right atrial volumes independently to obtain estimates of interobserver variability. Intraclass correlation coefficients were measured for right atrial volumes and RAEF. Intraclass

correlation coefficients are also presented for TAPSE, measured on a subset of 25% of the baseline echocardiograms.

RESULTS

We identified 41 treatment-naïve patients with PAH who satisfied all inclusion and exclusion criteria. Two patients were excluded because of poor image quality. The baseline characteristics of the 39 patients included in the study are shown in Table 1. There was a weak correlation seen between RVSP measured with echocardiography and PASP measured at catheterization ($R^2 = 0.15$, $P = 0.02$).

Table 1. Baseline clinical, echocardiographic, and hemodynamic characteristics of the overall cohort

Clinical parameter	PAH (<i>n</i> = 39)	Survivors (<i>n</i> = 27)	Nonsurvivors (<i>n</i> = 12)	<i>P</i>
Age, years	40.5 ± 3.7	41.3 ± 12.6	38.8 ± 16.4	0.6
Female sex, no. (%) of patients	28 (72.0)	20 (74)	8 (67)	0.6
BMI	30.3 ± 6.5	30.2 ± 5.9	30.7 ± 8.3	0.8
Etiology, no. (%) of patients				0.4
Idiopathic and familial	14 (35.9)	9 (33)	5 (42)	
Drugs and toxins	12 (30.8)	10 (37)	2 (17)	
Connective tissue disease	12 (30.8)	7 (26)	5 (42)	
HIV infection	1 (2.6)	1 (3.7)	0	
NYHA 3 or 4, no. (%) of patients	29 (74.4)	21 (78)	8 (67)	0.5
Six-minute walk distance, m	382 ± 132	396 ± 147	350 ± 84	0.3
NT-proBNP, pg/mL	1,513 ± 1,202	1,506 ± 1,254	1,555 ± 1,008	0.9
Echocardiographic parameters				
Total RAEF, %	24.4 ± 15.1	27.6 ± 14.3	17.3 ± 14.9	0.05
Passive RAEF, %	8.5 ± 6.9	8.6 ± 6.9	8.3 ± 7.3	0.9
Active RAEF, %	17.6 ± 13.9	20.8 ± 13.4	10.3 ± 11.3	0.03
RVSP, mmHg	82.0 ± 20.1	82.3 ± 21.0	81.3 ± 18.6	0.1
Right atrial volume index, mL/m ²	54.0 ± 24.9	52.4 ± 29.7	56.0 ± 30.9	0.7
Right ventricular diameter, cm	5.3 ± 0.8	5.3 ± 0.8	5.4 ± 0.9	0.8
TAPSE, cm	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.4	0.6
LVEF, %	58 ± 4	59 ± 3	55 ± 6	0.08
Pericardial effusion, no. (%) of patients	17 (43.6)	12 (44)	5 (42)	1.0
Hemodynamic parameters				
mRAP, mmHg	9.8 ± 4.8	9.5 ± 4.6	10.6 ± 5.4	0.5
mPAP, mmHg	54.5 ± 11.6	53.8 ± 12.5	56.2 ± 9.4	0.6
CO, L/min	3.48 ± 1.07	3.53 ± 1.27	3.40 ± 0.49	0.7
PVR, WU	14.6 ± 7.2	14.6 ± 8.5	14.5 ± 3.3	1.0
PAC, mL/mmHg	1.10 ± 0.99	1.22 ± 1.20	0.88 ± 0.27	0.4

Note: Data are mean value ± standard deviation, unless otherwise indicated. BMI: body mass index, defined as weight in kilograms divided by the square of height in meters; CO: cardiac output; HIV: human immunodeficiency virus; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; NT-proBNP: N-terminal pro-B type natriuretic peptide; NYHA: New York Heart Association; PAC: pulmonary arterial compliance; PVR: pulmonary vascular resistance; RAEF: right atrial emptying fraction; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; WU: Wood units.

Table 2. Comparison of parameters of right atrium (RA) function and other echocardiographic parameters for healthy control subjects versus patients with pulmonary arterial hypertension (PAH)

Parameter	Control subjects (n = 71)	PAH (n = 39)	P
Total RAEF, %	56.2 ± 10.0	24.4 ± 4.4	<0.001
Passive RAEF, %	27.6 ± 13.5	8.5 ± 6.9	<0.001
Active RAEF, %	39.7 ± 9.7	17.6 ± 13.9	<0.001
RVSP, mmHg	19.1 ± 9.1	82.0 ± 20.1	<0.001
RA volume index, mL/m ²	28.0 ± 8.0	54.0 ± 24.9	<0.001
RV diameter, cm	3.2 ± 0.2	5.3 ± 0.8	<0.001
TAPSE, cm	2.3 ± 0.3	1.5 ± 0.5	0.001
LVEF, %	62 ± 2	58 ± 4	0.5

Note: LVEF: left ventricular ejection fraction; RAEF: right atrial emptying fraction; RV: right ventricle; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion.

The mean tRAEF, pRAEF, and aRAEF were 24.4% ± 15.1%, 8.5% ± 6.9%, and 17.6% ± 13.9%, respectively. As shown in Table 1, baseline RVSP, TAPSE, and pulmonary hemodynamics were in keeping with severe PAH.

Table 2 compares the measures of RA function and other prognostic echocardiographic parameters for our PAH cohort versus healthy control subjects. The mean age of the control population was 43.3 ± 12.4 years, and the mean BMI was 24.2 ± 3.6. The control population was 73% female. RAEF was substantially reduced compared with control subjects for all measures of RAEF, showing that overall RA function, passive emptying, and active emptying are all reduced in pulmonary hypertension. Differences

in the other parameters tested were as expected. In the control population, age was associated with lower tRAEF ($r = -0.418$, $P < 0.001$) and pRAEF ($r = -0.498$, $P < 0.001$). There was no significant association between age and any measure of RAEF in the PAH population.

Correlates of baseline measures of RAEF

In our cohort, the correlation between tRAEF and aRAEF ($R^2 = 0.873$, $P < 0.001$) was stronger than that between tRAEF and pRAEF ($R^2 = 0.305$, $P < 0.001$). We found no association between pRAEF and aRAEF.

Table 3 shows the correlation between measures of RAEF and other known prognostic parameters. As expected, all measures of RAEF correlated with RA volume, although the correlation was strongest for tRAEF and aRAEF. TAPSE correlated with tRAEF ($R^2 = 0.206$, $P = 0.004$) and aRAEF ($R^2 = 0.198$, $P = 0.005$). Measures of RA function did not correlate with 6MWD.

For hemodynamic parameters, correlations were noted between CO and tRAEF ($R^2 = 0.143$, $P = 0.02$), aRAEF ($R^2 = 0.173$, $P = 0.01$), and TAPSE ($R^2 = 0.249$, $P = 0.002$). Right atrial pressure correlated with tRAEF ($R^2 = 0.125$, $P = 0.03$) alone. All measures of RAEF were not associated with the HR at the time of the study. There was no association between the presence of a pericardial effusion and any measure of RAEF. The estimated RA pressure on echocardiogram was associated with both tRAEF ($R^2 = 0.180$, $P = 0.007$) and aRAEF ($R^2 = 0.203$, $P = 0.004$).

Reproducibility of RAEF measurements

All baseline echocardiograms were interpreted by two observers (NWB and FH) independently. Intraclass correlation coefficients (ICCs) for maximal, minimal, and preatrial systole RA volumes were 0.97, 0.95, and 0.96, respectively. ICC was 0.72 for total RAEF, <0.4 for passive RAEF, and 0.70 for active RAEF. The ICC for TAPSE was 0.83.

Table 3. R^2 table demonstrating association between right atrial emptying fraction (RAEF) and clinical, echocardiographic, and hemodynamic parameters

Parameter	tRAEF	pRAEF	aRAEF	RAvol	RVd	TAPSE	6MWD	CO	RAP	PAC
tRAEF	...	0.305***	0.873***	0.349***	0.099	0.206**	0.037	0.143*	0.125*	0.104
pRAEF	0.305***	...	0.051	0.165*	0.120*	0.040	0.007	0.005	0.057	0.163*
aRAEF	0.873***	0.051	...	0.254**	0.046	0.198**	0.058	0.173*	0.085	0.038
RAvol	0.349**	0.165*	0.254**	...	0.327**	0.242**	0.033	0.030	0.328***	0.026
RVd	0.099	0.120*	0.046	0.327***	...	0.079	0.001	0.001	0.144*	0.048
TAPSE	0.206**	0.040	0.198**	0.242**	0.079	...	0.166*	0.249**	0.125*	0.014

Note: aRAEF: active RAEF; CO: cardiac output; PAC: pulmonary artery compliance; pRAEF: passive RAEF; RAP: right atrial pressure; RAvol: right atrial volume index; RVd: right ventricular diameter; TAPSE: tricuspid annular plane systolic excursion; tRAEF: total RAEF; 6MWD: 6-minute walk distance.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

Correlates of the change in RAEF with time

Thirty patients (79%) in our original cohort had follow-up echocardiograms done within 6–18 months of their initial echocardiogram and within 1 month of a 6MWT. Table 4 demonstrates the characteristics of the patients at their follow-up visit. The mean time between echocardiograms was 10.8 ± 2.8 months. At follow-up, the vast majority (96.7%) of these patients were receiving pulmonary vasodilator therapy. Parenteral therapy was common (40.0%), as was combination therapy (43.3%). The majority of patients exhibited improvement in prognostic clinical and echocardiographic variables. On average, tRAEF, pRAEF, and aRAEF increased by $6.1\% \pm 15.9\%$, $2.6\% \pm 11.8\%$, and $4.4\% \pm 15.6\%$, respectively.

As shown in Figure 2, the changes in both aRAEF and TAPSE showed weak correlations with change in 6MWD ($R^2 = 0.186$, $P = 0.02$, and $R^2 = 0.137$, $P = 0.04$, respectively). None of the changes in RAEF correlated with the change in TAPSE.

Table 4. Changes at follow-up in the population with follow-up echocardiographic examination and 6-minute walk test (6MWT) results

Clinical parameter	Patients (n = 30)
Time between echocardiograms, months	10.8 ± 2.8
Therapy at follow-up, no. (%) of patients	
None	1 (3.3)
Prostanoid	18 (60.0)
ERA	6 (20.0)
PDE5-I	18 (60.0)
IV/SC therapy	12 (40.0)
Combination therapy	13 (43.3)
Improvement in NYHA class, no. (%) of patients	20 (66.7)
Change in 6MWD, m	$91.3 \pm 121.7^{**}$
Echocardiographic parameters	
Change in total RAEF, %	$6.1 \pm 15.9^*$
Change in passive RAEF, %	2.6 ± 11.8
Change in active RAEF, %	4.4 ± 15.6
Change in right atrial volume index, mL/m ²	$-10.8 \pm 17.9^{**}$
Change in right ventricular diameter, cm	$-0.5 \pm 0.8^{**}$
Change in TAPSE, cm	0.3 ± 0.6
Change in RVSP, mmHg	$-17 \pm 25^*$

Note: Data are mean value $\pm$ standard deviation, unless otherwise indicated. ERA: endothelin receptor antagonist; IV: intravenous; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-B type natriuretic peptide; PDE5-I: phosphodiesterase type 5 inhibitor; RAEF: right atrial emptying fraction; RVSP: right ventricular systolic pressure; SC: subcutaneous; TAPSE: tricuspid annular plane systolic excursion; 6MWD: 6-minute walk distance.

* $P < 0.05$.

** $P < 0.01$.

Figure 2. Relationships between change in active right atrium emptying fraction (RAEF) and change in 6-minute walk distance (6MWD; A), change in tricuspid annular plane systolic excursion (TAPSE) and change in 6MWD (B), and change in active RAEF and TAPSE (C).

The change in aRAEF was greater for patients treated with combination therapy than for those treated with monotherapy (11.1% vs. -0.6% , $P = 0.04$). Patients who received prostanoid agents enjoyed greater improvement in aRAEF and tRAEF than did patients who received other classes of therapy (9.4% vs. -3.0% , $P = 0.03$, and 10.6% vs. -0.6% , $P = 0.04$, respectively), whereas the change in TAPSE did not differ by type of therapy.

Survival analysis

Mean duration of follow-up in the overall cohort was 4.2 ± 2.3 years. At the end of follow-up, 12 (30.8%) of the population had died.

Survival was worse for subjects with low aRAEF and tRAEF, as shown in Figure 3. The hazard ratios (HRs) for time to death for low aRAEF and tRAEF were 5.6 (95% confidence interval [CI], 1.2–26.2; $P = 0.03$) and 4.2 (95% CI, 1.1–15.5; $P = 0.03$), respectively. Passive RAEF was not predictive of survival. There was no association between high (>15 mm) and low (≤ 15 mm) TAPSE and time to death in our population, with HR = 0.81 (95% CI, 0.2–2.6; $P = 0.7$). This lack of association persisted when other cutoff points were used. The survival analysis was repeated using maximal and minimal RA volumes, and neither was predictive of survival.

DISCUSSION

This is, to our knowledge, the first study to characterize and determine the clinical correlates of RA function in treatment-naïve patients with PAH. In our study cohort with severe PAH, RA function as assessed by measures of RAEF was substantially reduced compared with that of healthy control subjects, suggesting that pressure overload of the RA impairs all aspects of right atrial function. Our correlations between RAEF and the other parameters tested were not strong. Because all measures of RAEF are derived by the subtraction of similar volumes, errors in the volume measurements are therefore magnified. This, coupled with our small sample size, is the reason why the correlations—even the correla-

tions with other volume measures—were fairly weak. Nevertheless, some of the weak associations between RAEF and other parameters were interesting.

We found a relationship between RA enlargement and RAEF in patients with PAH. This finding parallels similar findings in studies investigating left atrial emptying fractions in left-sided heart failure.^{11,12} Also, the correlations identified between TAPSE, which is a measure of RV systolic function, and tRAEF and aRAEF suggest a link between RA systolic dysfunction and RV systolic dysfunction in PAH. These findings are in agreement with a previous study that assessed RA function using Doppler measures of the velocity of flow through the tricuspid valve.²⁰

We did not see any correlation between any measure of RAEF and baseline 6MWD, despite correlations being seen between this parameter and baseline TAPSE. However, it should be noted that baseline 6MWD is an imperfect surrogate for disease severity.²¹

Increased tRAEF and aRAEF were associated with increased CO in our population, although there may be confounding due to the association between atrial function and TAPSE. Although lower tRAEF was associated with higher invasively measured mRAP, aRAEF was not. Although one might postulate that such an association should exist, because higher RAP should trigger RA systolic dysfunction, it is important to consider that mean RAP will vary in response to diuresis and that the RAP during atrial systole (A wave) is itself partly dependent on RA systolic function. The RA pressures estimated on the basis of echocardiogram findings did correlate significantly with both tRAEF and aRAEF, however.

Despite excellent ICC for the measured right atrial volumes, the ICC for tRAEF and aRAEF showed only fair-to-good interobserver reliability. The ICC for pRAEF was poor. As mentioned above, this is suspected to be due to the magnification of measurement error given subtraction of RA volumes in the calculation of RAEF. Measures of RAEF thus become less reliable as RA function worsens. Caution is warranted when interpreting measures of RAEF in cases where RA function is substantially reduced. In our population with severe PAH, RA volume often changed very little during the passive emptying phase. Thus, the poor reproducibility of pRAEF is to be expected.

In our analysis of the change in RAEF with time, patients receiving stronger treatment regimens, such as combination therapy or prostanoid therapy, had greater improvement in aRAEF. Thus, rather than being fixed, RA systolic dysfunction appears to reverse in the presence of aggressive pulmonary vasodilator therapy. Moreover, this improvement in RA function also appears to correlate with increased 6MWD, providing further evidence that RA function contributes to CO.

We found evidence of improved survival with aRAEF and tRAEF in our exploratory survival analysis. This is the first time that such an association has been shown, albeit in a univariate analysis. This finding requires confirmation and should be investigated in larger multicenter studies. Longitudinal studies using alternate means of assessing RA function, such as RA speckle-tracking echocardiography²² and cardiac magnetic resonance imaging (MRI), will also be helpful.

Figure 3. Kaplan-Meier curves for survival for active right atrial emptying (A) and total right atrial emptying (B). aRAEF: active right atrial emptying fraction.

The lack of correlation seen between TAPSE and survival in our population is somewhat surprising, because TAPSE has been shown to have prognostic importance in several PH populations.⁴⁻⁶ This lack of correlation may have been due to our relatively small sample size or to less dispersion in TAPSE than in tRAEF and aRAEF. However, it may also be due to the fact that our population had significantly worse disease and longer follow-up periods than populations in previous studies.

Only one other study has reported on volumetric RAEF in a population with PAH. Using volumetric measures similar but not identical to ours, Willens and colleagues²³ showed that the active emptying phase contributed more to atrial function in patients with PAH than in matched control subjects, as we confirm in our study. As in the study by Willens et al.,²³ we found a correlation between age and passive RAEF in a healthy population but also found a correlation with total RAEF. This association does not persist in the PAH population, suggesting that RAEF is influenced more by the disease state than by age.

RA function has also been studied using MRI, using volumetric measures that are similar but not identical to ours.²⁴ As in our study, Sato et al.²⁴ found that measures of total and passive right atrial emptying are decreased in individuals with PAH compared with control subjects, and active right atrial emptying is reduced in patients with advanced functional class (WHO class IV). However, they also found that active RA function was increased in patients with better functional class. Although this signal was not seen in our study, this may simply reflect the very advanced disease present in our patient population. The study by Sato et al.²⁴ also contrasted with our work in finding that right atrial emptying observed on MRI correlated with PA pressure and RV function. Measures of reproducibility were better than those seen in our study. As is the case with volumetric measures of RV function, MRI appears to provide superior assessment of RA function compared with echocardiography. However, at present, the availability of cardiac MRI for the routine follow-up of patients with PAH is limited in most centers. Because transthoracic echocardiography remains the primary means of following up patients with PAH, determining the value of measures of RAEF should remain an important priority.

Right atrial function is currently being investigated in populations with PAH using other novel means, such as RA strain and 3D echocardiography.^{22,25} However, these measures often require special training and software. Volumetric measures of RA function, like RAEF, are simple measures that can be obtained from standard echocardiographic views with minimal extra training.

This study does have several limitations. Our study was retrospective in nature, which inherently introduces the possibility of bias. Also, our sample size was small, which is a function of the rarity of PAH. Although we could have included patients who were receiving therapy at the time of initial echocardiogram or who had non-PAH PH, this would have seriously impacted the homogeneity of our cohort. Although echocardiograms, 6MWTs, and right heart catheterizations occurred within 1 month of each another, they were often not performed on the same day. However, it is doubtful that

the time interval between tests was long enough to result in significant changes in disease severity.

Our study is the first to demonstrate an association between 2D-echocardiographic measures of RA function—*aRAEF* and *tRAEF*—and RV systolic function, CO, and survival in a population of treatment-naïve patients with WHO category I PAH. Moreover, we are the first to show an association between improvement in RA systolic function and improvement in 6MWD after initiation of therapy. These associations require additional study in the form of larger prospective studies that permit multivariate analyses and confirmatory studies using other imaging modalities.

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Conflict of Interest: RTZ is a consultant to Actelion, United Therapeutics, Ikaria, Bayer, and Gilead Pharmaceuticals.

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