Echocardiographic Assessment of Right Ventricular Function and Response to Therapy in Pulmonary Arterial Hypertension

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Echocardiography is a key tool in the management of patients with pulmonary arterial hypertension (PAH), but many potential parameters could be used to assess response to therapy. In this retrospective study of 48 patients with severe PAH at baseline, we examined echocardiographic variables before and after initiation of PAH-specific therapy to evaluate which measures of right ventricular (RV) function best correlated with clinical response to therapy as assessed by 6-minute walk distance (6MWD) and 3-year all-cause mortality. Tricuspid annular plane systolic excursion (TAPSE), mid-RV and basal-RV diameters, RV systolic pressure, and RV global longitudinal strain were all found to significantly improve after initiation of a PAH therapy. Decreases in right atrial area ($r = -0.50$, $p = 0.002$) and mid-RV diameter ($r = -0.36$, $p = 0.03$) were most strongly correlated with improvement in 6MWD. Pretreatment values of RA area (hazard ratio [HR] per 1 SD: 2.72; 95% confidence interval [CI] 1.58, 4.69), mid-RV diameter (HR 2.03; 1.20, 3.45), basal-RV diameter (HR 2.27; 1.40, 3.70), and RV global longitudinal strain (HR 2.36; 1.22, 4.56) were all associated with mortality risk. 6MWD and TAPSE were the 2 variables for which pretreatment measures (6MWD − HR 0.35; 0.17, 0.72; TAPSE − HR 0.41; 0.21, 0.82) and change with treatment (6MWD − HR 0.26; 0.10, 0.64; TAPSE − HR 0.40; 0.21, 0.77) were both significantly associated with 3-year mortality. Change in RV systolic pressure with treatment was significantly associated with mortality (HR 2.55; 1.23, 5.28,) but pretreatment baseline had no association (HR 1.48; 0.72, 3.06). Although many echocardiographic parameters change with initiation of PAH treatment, the strong association of both baseline TAPSE and change in TAPSE with mortality supports the ongoing use of TAPSE as an important measure in the assessment of disease severity and treatment response in PAH. **(Am J Cardiol 2019;124:1298−1304)**

Clinical monitoring of patients with pulmonary arterial hypertension (PAH) is challenging as symptoms are nonspecific and variable, and changes in right heart function can significantly precede clinical worsening.[1] Cardiac magnetic resonance imaging is considered the gold standard for assessment of right ventricular (RV) morphology and function, but its widespread use is limited by clinical availability, cost, and patient tolerance.[2,3] As a result, echocardiography has become a key tool for noninvasive assessment of the right heart. Multiple echocardiographic measures are used to provide information about RV function,[4] and many of these measures have been linked with clinical outcomes in patients with PAH.[5−7] Previously, serial assessment of RV longitudinal strain[8,9] and tricuspid annular plane systolic excursion (TAPSE)[10] have been shown to predict survival in patients with PAH. However, it is not well established which of these measures is the best predictor of response to treatment or disease progression in PAH.[11] The objectives of this study were to describe the echocardiographic changes following initiation of treatment for PAH and to determine which echocardiographic measures of RV function were best associated with disease progression and treatment response when measured sequentially.

Methods

This was a single-center, retrospective cohort study. Using the Duke Echo Lab database, we identified 48 patients with Group 1 PAH between the ages of 18 and 70 years old at time of imaging who had a transthoracic echocardiogram (TTE) performed from 2010 to 2013 at Duke University Hospital before (≤6 months) and after (≤6 months) initiation of PAH-specific therapy. Patient characteristics were extracted from the Duke Pulmonary Hypertension Database. Patients were excluded if the TTE images were of insufficient quality to perform strain analysis or if they had significant intercurrent illness,

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hospitalization (other than for initiation of PAH-specific medication) or surgery in the time between the performance of the pre- and post-treatment TTEs. All echocardiograms were performed as part of routine clinical practice and the patients' physicians, who were PAH specialists, had access to echocardiographic images and reports as they made decisions on medical therapy.

TTEs were performed using a commercial GE Vivid E9 imaging system (GE Vingmed Ultrasound, Horten, Norway) or Philips iE-33 (Bothell, Washington) ultrasound equipment according to institutional protocol which has been previously described.[12] 2DSTE RV strain analysis was performed using vendor-independent image analysis software (TomTec 2D Cardiac Performance Analysis, Munich, Germany) on RV-focused views.[13] RV longitudinal strain was obtained by averaging basal, mid and apical strain values of the free wall and septal wall. Left ventricular (LV) and RV measurements of function and hemodynamics were calculated per the current American Society of Echocardiography guidelines by the interpreting cardiologist. All TTEs were initially read per routine clinical practice. An independent reviewer (J.T.) reviewed all images and performed additional strain analyses as required. All results were verified by a second independent reviewed before use in the study. Intra- and interobserver reliability was examined for strain analysis and found to be consistent with previous studies.[14,15] Reviewers were not blinded to patient characteristics at time of analysis.

Demographics, cardiac catheterization data, pulmonary function test results, and treatment information were extracted from the Duke Pulmonary Hypertension database and the electronic medical record. 6-minute walk distance (6MWD) assessments were performed as part of standard clinic visits at the Duke Center for Pulmonary Vascular Disease. Pretherapy 6MWD was included if performed in the 6 months before of therapy initiation. Post-therapy 6MWD included repeat assessment performed in the 6 months after therapy initiation and all subsequent assessments through May 2017. Mortality was evaluated starting at time of follow-up TTE by review of the medical record and Social Security death master file with follow-up censored at the earlier of 3 years or the time that the patient was last known to be alive.

Clinical, demographic, and echocardiographic variables were summarized for the included patients. Categorical variables were summarized with counts and proportions, and continuous variables were described by their median and interquartile range. Echocardiogram parameters and 6MWD were summarized at the "pre" and "post" time points. The change (pretreatment to post-treatment) was calculated and summarized for continuous and ordinal variables. The Wilcoxon signed rank test was used to evaluate whether the change was significantly different from zero. For binary variables, McNemar's test was used to evaluate whether the proportion with change in one direction was significantly different than the proportion with change in the other direction.

The change between post-treatment and pretreatment echo parameters were summarized and stratified by type of PAH therapy initiated and by whether the initiated therapy was initial or add-on. The Kruskal-Wallis test was used to compare continuous characteristics across strata. For patients in whom change in 6MWD could be evaluated, the change in 6MWD was compared with changes in TTE parameters by calculating Spearman rank-order correlations.

The Kaplan-Meier method was used to generate cumulative incidence curves stratified by factors of interest. Cox regression analysis was used to evaluate the association between echo parameters of specific interest, and the hazard of death during 3 years of follow-up. A separate model was run for each echo parameter and included as covariates the pretherapy assessment together with the pre- to postchange in value. The models were evaluated for linearity on the log-hazard scale and met linearity assumptions except where noted. In cases of nonlinearity, the continuous parameter was categorized into 3 groups in order to characterize the nonlinear relation. Hazard ratios for continuous measures are presented per 1 standard deviation increment of the parameter to allow more standardized comparisons between variables. p Values <0.05 were considered significant with no adjustment for multiple comparisons given the exploratory nature of this study. Statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina). The study was approved by the Duke Institutional Review Board. Need for informed consent was waived for this retrospective study.

Results

Our study included 48 patients who met inclusion criteria for the study and had pre- and post-treatment TTE's performed from 2010 through 2013. Of those patients, the majority were female and Caucasian, with median (Q1, Q3) age of 49 (35, 56) years old. Most patients had either idiopathic PAH (31%) or PAH related to connective tissue disorder (40%) and had severe PAH at baseline. Twenty-six (54%) patients had previously been on PAH specific therapy and were started on add-on therapy for this study. Baseline characteristics are summarized in Table 1. Therapies initiated at study onset included prostacyclin (n = 19), phosphodiesterase type 5 inhibitor (n = 15), and endothelin receptor antagonist (n = 10). Combination therapy was initiated in 4 patients.

Pre- and post-treatment echocardiographic parameters and 6MWD results are summarized in Table 2. Most patients had been on treatment for 3 to 6 months at time of the post-treatment TTE. Pre- and post-treatment TTE's were separated by 6 to 12 months. Compared with pretreatment TTE parameters, post-treatment TTE's were significant for a decrease in RV basal diameter and RV mid-diameter. In addition, TAPSE increased by 0.3 cm (0.0, 0.6, $p < 0.001$) and RV global longitudinal strain (GLS) improved by −2.0% (−4.0, 1.0, $p = 0.02$), whereas RV systolic pressure (RVSP) decreased by 6 mm Hg (−26, 2, $p = 0.003$, $n = 35$). In the 37 patients with both pre- and post-treatment values, 6MWD increased by 26 m (−11, 75, $p = 0.006$). Of note, there was no significant change in subjective assessment of RV function, although the percentage with normal RV function increased slightly. Several echocardiographic assessments of the left heart were also noted to change with PAH treatment, with slight increase in LV internal diameter at end diastole and slight improvement in LV GLS. Changes in echocardiographic parameters were generally consistent across the different classes of treatment

Table 1
Baseline characteristics of study population

Characteristics	Distribution Median (Q1, Q3) for continuous variables n (%) for character or ordinal variables (n = 48)
Age (years)	49 (35, 56)
Men	13 (27%)
Women	35 (73%)
White	29 (60%)
Black	18 (38%)
Asian	1 (2%)
Height (inches)	64.0 (61.5, 68.0)
Weight (lbs)	171.5 (143.1, 223.8)
Body mass index (kg/m^2)	28.2 (25.1, 37.0)
Primary etiology of pulmonary hypertension	
Idiopathic	15 (31%)
Hereditary	2 (4%)
Connective tissue disorder	19 (40%)
Congenital heart disease − systemic-to-pulmonary shunts	4 (8%)
Drugs and toxins	3 (6%)
Left ventricular diastolic dysfunction	1 (2%)
Chronic obstructive pulmonary disease	1 (2%)
Interstitial lung disease	1 (2%)
Others	2 (4%)
Prior pulmonary hypertension treatment	26 (54%)
Endothelin receptor antagonist	5 (10%)
Prostacyclin/prostacyclin analog	6 (13%)
Phosphodiesterase type 5 inhibitor	6 (13%)
Combination	9 (19%)
Right atrial pressure (mm Hg)	10.0 (6.0, 15.0)
Peak systolic pulmonary arterial pressure (mm Hg)	79.0 (64.0, 93.0)
Diastolic pulmonary arterial pressure (mm Hg)	35.0 (27.0, 42.0)
Mean pulmonary arterial pressure (mm Hg)	50.0 (41.0, 60.0)
Pulmonary arterial oxygen saturation (%)	59.2 (53.1, 65.4)
Cardiac index (L/m^2)	2.1 (1.8, 2.9)
Pulmonary vascular resistance (Woods unit)	8.8 (5.6, 13.9)
Pulmonary capillary wedge pressure (mm Hg)	10.0 (8.0, 12.0)
Forced expiratory volume in 1 second (L)	1.7 (1.5, 2.6)
Forced expiratory volume in 1 second (% predicted)	67.5 (50.0, 82.0)
Forced vital capacity (L)	2.5 (1.9, 3.1)
Forced vital capacity (% predicted)	73.0 (54.5, 89.0)
Ratio of forced expiratory volume in 1 second to forced vital capacity	0.78 (0.72, 0.84)
Total lung capacity (L)	3.7 (3.0, 4.4)
Total lung capacity (% predicted)	78.5 (55.0, 86.0)
Diffusion capacity of the lung for carbon monoxide (% predicted)	47.0 (34.0, 67.5)

(see appendix − Table A). Stratification of echocardiographic parameters by previous treatment history is shown in Table 3. Changes in septal diameter and TAPSE were significantly larger with initial therapy compared with add-on therapy but were similar for other parameters regardless of previous treatment history.

Changes in RA area ($r = -0.50$, $p = 0.002$) and RV mid-diameter (-0.36, $p = 0.03$) were significantly correlated with change in 6MWD, but there was no significant correlation for changes in TAPSE, RVSP, and RV GLS with change in 6MWD (Table 4).

In the 48 patients, there were 14 deaths in the 3-year period after the post-treatment TTE, corresponding to an all-cause mortality rate of 32%. Cox regression models were used to determine hazard ratios per standard deviation increment in each variable examined (Table 5, Figure 1). 6MWD and TAPSE were the 2 variables for which pretreatment measures and change with treatment were both significantly associated with 3-year mortality. Pretreatment RV GLS was associated with mortality but change in RV GLS had no significant association. Similarly, baseline values for RA, RV basal diameter, and mid-RV diameter were associated with mortality but there was no association of changes in these values with outcomes. In the 35 patients with both pre- and post-treatment measures available, change in RVSP with treatment was significantly associated with mortality but pretreatment baseline had no association.

Discussion

In the attempt to aid clinicians' ability to use echocardiograms to monitor patients with PAH, many previous studies have examined the relation between echocardiographic parameters and clinical outcomes.[5,6,9,16−18] However, it remains unclear which specific parameters are best suited for use in clinical practice and add information to clinical risk scores.[4,11] The purpose of our study was to compare and evaluate the association of multiple echocardiographic parameters with all-cause mortality and 6MWD, a validated surrogate end point used frequently in clinical practice and PAH clinical trials. One strength of our study is that it followed patients longitudinally to assess how echocardiograms changed with treatment of PAH and whether those changes were associated with clinical outcomes.

Given the multiple strategies to assess RV function echocardiographically, it is difficult to consistently and objectively define function.[10] TAPSE has been recommended by current guidelines as part of the assessment of RV function,[4] as it has proven to be simple, easily measured and reproducible in clinical practice and has been shown to be associated with outcomes in PAH.[10,11,17] Our study further supports that TAPSE is a useful tool in the assessment of disease severity and treatment response in patients with PAH. Along with several other echocardiographic parameters, pretreatment measures of TAPSE were associated with mortality. However, TAPSE was unique in our study in that both pretreatment measure and change with treatment were associated with mortality, which corroborates the findings of another recent study.[10] Our study did not show a significant association between change in TAPSE and change in 6MWD. This relation could have been obscured by incomplete 6MWD data in our study, as 21% of patients did not complete a 6MWD assessment before initiation of treatment. Furthermore, patients who did not complete a pretreatment 6MWD may have been sicker at baseline and unable to perform the assessment due to the severity of their illness.

RVSP is also frequently used in the diagnosis and evaluation of patients with pulmonary hypertension.[19] Our study demonstrated that change in RVSP was predictive of mortality, but pretreatment assessment was not. This suggests

Table 2
Pre- and post-treatment echocardiographic parameters

Echo variable	Pretreatment Median (Q1, Q3) (n = 48)	Post-treatment Median (Q1, Q3) (n = 48)	Change Median (Q1, Q3) (n = 48)	p Value
Right atrial area (cm^2)	22.0 (18.0, 26.0)	21.5 (18.5, 26.5)	0.0 (−1.0, 2.0)	0.31
Left atrial area (cm^2)	17.0 (15.0, 21.0)	18.0 (16.0, 21.5)	1.0 (0.0, 2.0)	**0.01**
E-wave velocity (cm/s)	62.5 (46.5, 75.0)	77.0 (66.0, 84.0)	13.0 (2.0, 26.0)	**<0.001**
A-wave velocity (cm/s)	62.0 (50.5, 71.5)	64.0 (53.0, 83.0)	5.0 (−4.0, 20.0)	**0.02**
Septal diameter (mm)	5.8 (4.2, 7.4)	6.3 (5.1, 8.6)	0.7 (−0.5, 2.0)	**0.02**
Lateral wall diameter (mm)	9.8 (7.3, 11.5)	11.0 (8.0, 12.1)	0.7 (−1.0, 2.9)	0.07
Left ventricular internal diameter—end diastole (cm)	4.1 (3.7, 4.4)	4.3 (3.8, 4.7)	0.3 (0.0, 0.5)	**<0.001**
Left ventricular internal diameter—end systole (cm)	2.5 (2.1, 2.8)	2.8 (2.2, 3.3)	0.1 (−0.2, 0.6)	0.05
Right ventricular basal diameter (cm)	4.9 (4.5, 5.3)	4.7 (4.2, 5.2)	−0.1 (−0.4, 0.1)	**0.01**
Right ventricular mid-diameter (cm)	3.9 (3.5, 4.4)	3.7 (3.2, 4.1)	−0.2 (−0.5, 0.0)	**<0.001**
Right ventricular length (cm)	8.4 (7.9, 9.2)	8.7 (7.9, 9.3)	0.1 (−0.2, 0.3)	0.26
Inferior vena cava diameter (cm)	1.9 (1.5, 2.4)	1.7 (1.4, 2.3)	0.1 (−0.6, 0.3)	0.50
Inferior vena cava collapse*	26 (54%)	32 (67%)	4% | 17%	0.06
Tricuspid annular plane systolic excursion (cm)	1.6 (1.3, 2.0)	1.9 (1.6, 2.3)	0.3 (0.0, 0.6)	**<0.001**
Tricuspid regurgitation grade			0.0 (−1.0, 0.0)	0.24
Trivial	15 (32%)	19 (40%)		
Mild	18 (38%)	17 (35%)		
Moderate	8 (17%)	7 (15%)		
Severe	6 (13%)	5 (10%)		
Right ventricular systolic pressure (mm Hg, n = 35)	75 (63, 92)	70 (46, 78)	−6 (−26, 2)	**0.003**
Right ventricular function (n = 35)			0 (0, 0)	0.55
Normal	7 (20%)	9 (26%)		
Mild	11 (31%)	11 (31%)		
Moderate	12 (34%)	9 (26%)		
Severe	5 (14%)	6 (17%)		
Right ventricular global longitudinal strain (%)	−14.0 (−18.0, −12.0)	−15.0 (−21.0, −13.0)	−2.0 (−4.0, 1.0)	**0.02**
Left ventricular global longitudinal strain in 4-chamber view (%)	−16.5 (−19.5, −15.0)	−19.0 (-20.0, -17.0)	−2.0 (−3.0, 1.0)	**0.02**
6-minute walk distance (m)				
N	38	44		
Median (Q1, Q3)	340.5 (263.0, 477.0)	385.5 (271.0, 505.5)		
6-minute walk distance (m) − patients with both measures (N = 37)	342.0 (263.0, 477.0)	419.0 (273.0, 517.0)	26.0 (−11.0, 75.0)	**0.01**

p values < 0.05 shown in bold.
* Change column − proportion of patients who went (pre-treatment to post-treatment) from Yes to No and No to Yes.

Table 3
Comparison of echocardiographic changes with treatment stratified by initial vs. add-on therapy for pulmonary hypertension

Variable (change from pre- to post-treatment echocardiogram)	Overall (n = 48)	Initial therapy (n = 22)	Add-on therapy (n = 26)	p Value
Right atrial area (cm^2)	0.0 (−1.0, 2.0)	0.0 (−2.0, 2.0)	1.0 (−1.0, 2.0)	0.20
Left atrial area (cm^2)	1.0 (0.0, 2.0)	0.0 (−1.0, 1.0)	2.0 (0.0, 2.0)	0.09
E-wave velocity (cm/s)	13.0 (2.0, 26.0)	12.0 (0.0, 33.0)	14.5 (3.5, 25.0)	0.94
A-wave velocity (cm/s)	5.0 (−4.0, 20.0)	−0.5 (−5.0, 19.0)	7.0 (−2.0, 25.0)	0.22
Septal diameter (mm)	0.7 (−0.5, 2.0)	1.9 (0.1, 3.3)	0.1 (−1.3, 1.1)	**0.003**
Lateral wall diameter (mm)	0.7 (−1.0, 2.9)	0.8 (−1.0, 3.9)	0.7 (−0.6, 1.3)	0.62
Left ventricular internal diameter—end diastole (cm)	0.3 (0.0, 0.5)	0.3 (0.1, 0.6)	0.2 (−0.1, 0.5)	0.24
Left ventricular internal diameter—end systole (cm)	0.1 (−0.2, 0.6)	−0.1 (−0.3, 0.3)	0.4 (0.0, 0.8)	0.09
Right ventricular basal diameter (cm)	−0.1 (−0.4, 0.1)	−0.1 (−0.5, 0.2)	−0.1 (−0.3, 0.1)	0.86
Right ventricular mid-diameter (cm)	−0.2 (−0.5, 0.0)	−0.1 (−0.3, 0.0)	−0.2 (−0.5, 0.0)	0.40
Right ventricular length (cm)	0.1 (−0.2, 0.3)	0.0 (−0.3, 0.2)	0.1 (0.0, 0.3)	0.25
Inferior vena cava diameter (cm)	0.1 (−0.6, 0.3)	−0.2 (−0.6, 0.2)	0.2 (−0.3, 0.3)	0.13
Tricuspid annular plane systolic excursion (cm)	0.3 (0.0, 0.6)	0.5 (0.3, 0.8)	0.1 (−0.1, 0.4)	**0.009**
Right ventricular global longitudinal strain (%)	−2.0 (−4.0, 1.0)	−2.0 (−4.0, 0.5)	−1.0 (−3.0, 2.0)	0.32
Left ventricular global longitudinal strain in 4-chamber view (%)	−2.0 (−3.0, 1.0)	−1.0 (−3.0, 1.0)	−2.0 (−3.0, 1.0)	0.83
RVSP				
N	35	15	20	
Median (m)	−6 (−26, 2)	−6 (−26, 5)	−7 (−27, 0)	0.59
6MWD				
N	37	13	24	
Median (m)	26.0 (−11.0, 75.0)	50.0 (17.0, 99.0)	13.5 (−22.0, 55.0)	0.08

p values < 0.05 shown in bold.

Table 4
Correlation of change in echo parameters with change in 6-minute walk distance

Variable (change from pre- to post-treatment echocardiogram)	N	Spearman correlation	p Value
Right atrial area	36	−0.50	**0.002**
Left atrial area	36	−0.18	0.28
E-wave velocity	35	−0.12	0.49
A-wave velocity	32	−0.24	0.19
Septal diameter	35	0.056	0.75
Lateral wall diameter	34	0.092	0.60
Inferior vena cava diameter	37	−0.085	0.62
Right ventricular basal diameter	36	−0.22	0.20
Right ventricular mid-diameter	36	−0.36	**0.03**
Right ventricular length	36	0.058	0.73
Tricuspid annular plane systolic excursion	36	0.10	0.55
Left ventricular internal diameter—end diastole	37	0.15	0.36
Left ventricular internal diameter—end systole	37	0.030	0.86
Right ventricular global longitudinal strain	32	−0.16	0.37
Left ventricular global longitudinal strain in 4-chamber view	22	−0.058	0.80
Tricuspid regurgitation grade	36	-0.17	0.31
Right ventricular systolic pressure	26	−0.32	0.12
Right ventricular function	26	0.11	0.60

p values < 0.05 shown in bold.

Table 5
Cox regression hazard ratios for 3-year all-cause mortality with baseline and change in echocardiographic measures and 6-minute walk distance as predictors of mortality

Variable	Hazard ratio (95% CI)	Standard deviation	p Value
Right atrial area (baseline)	2.72 (1.58, 4.69)	7.3 cm^2	**<0.001**
Right atrial area (change)	0.86 (0.44, 1.69)	2.9 cm^2	0.67
Right ventricular basal diameter (baseline)	2.27 (1.40, 3.70)	0.66 cm	**<0.001**
Right ventricular basal diameter (change)	1.14 (0.59, 2.22)	0.35 cm	0.70
Right ventricular mid-diameter (baseline)	2.03 (1.20, 3.45)	0.68 cm	**0.009**
Right ventricular mid-diameter (change)	1.58 (0.85, 2.96)	0.44 cm	0.15
Tricuspid annular plane systolic excursion (baseline)	0.41 (0.21, 0.82)	0.50 cm	**0.01**
Tricuspid annular plane systolic excursion (change)	0.40 (0.21, 0.77)	0.54 cm	**0.006**
Right ventricular systolic pressure (baseline)	1.48 (0.72, 3.06)	22.1 mm Hg	0.29
Right ventricular systolic pressure (change)	2.55 (1.23, 5.28)	21.3 mm Hg	**0.01**
6-minute walk distance (baseline)	0.35 (0.17, 0.72)	121 m	**0.004**
6-minute walk distance (change)	0.26 (0.10, 0.64)	91.6 m	**0.004**
Right ventricular global longitudinal strain (baseline)	2.36 (1.22, 4.56)	4.7%	**0.01**
Right ventricular global longitudinal strain (change): Decrease (by 0 to −5) vs increase	1.17 (0.29, 4.67)		0.83
Right ventricular global longitudinal strain (change): Decrease (by more than −5) vs increase	1.69 (0.36, 7.95)		0.51

p values < 0.05 shown in bold.
HR (hazard ratio) is for one unit increment in standard deviation of predictor variable, except when variables split into categories as indicated above.

that RVSP is an informative measure of treatment response if followed longitudinally but that a single measurement in isolation may be less predictive of disease severity. This may be because pressures can drop in the setting of RV failure due to a fall in cardiac output without any change in PVR. Our study also highlighted the limitation that RVSP cannot be reliably measured in certain patients, as pre- and post-treatment measures were not available in 13 patients in our cohort (27%).

As a relatively newer technology, RV strain analysis using speckle tracking technology has emerged as a modality to assess abnormal RV function in a variety of settings including PAH.[5,6,13] It has also been shown to predict outcomes in patients with known or suspected PAH and has been independently associated with mortality.[6,9,20] Our study supports the view that RV GLS is a useful assessment of disease severity at baseline, as pretreatment values of RV GLS were significantly associated with mortality. However, our study did not find change in RV strain between pre- and post-treatment echocardiograms to be predictive of mortality or change in 6MWD, which is in contrast to the findings of another recent study.[8] This is likely due to the fact that, compared with that study, our patients had a relatively small change in RV GLS with median improvement of only 2% with less than a quarter of patients experiencing >4% decrease in RV GLS. This follow-up period for our study was relatively short at 6 to 12 months, so it is possible that in patients responding to treatment, RV GLS would improve further over time.

Our study included a relatively small sample size drawn from a single center, impairing the generalizability of the results. As a retrospective analysis, our study was limited to data collected during TTEs or captured by clinicians in the clinical record or PAH database which may obscure some potentially useful measures. Utility of 6MWD as a clinical assessment in our trial is limited given that pretreatment data are missing in >1/5 of the study population, likely due to illness severity. Our study is also susceptible to false positive findings given the exploratory nature of the multiple statistical comparisons used given the number of echocardiographic parameters examined.

This study has implications for standardizing the echocardiographic assessment on patients with PAH. We found that TAPSE is predictive of both disease severity at the onset of treatment and treatment response, which supports the use of TAPSE as an important noninvasive assessment in patients with PAH. Similarly, our study confirmed that RVSP and 6MWD are important tools for assessment of treatment response but highlighted the need for other

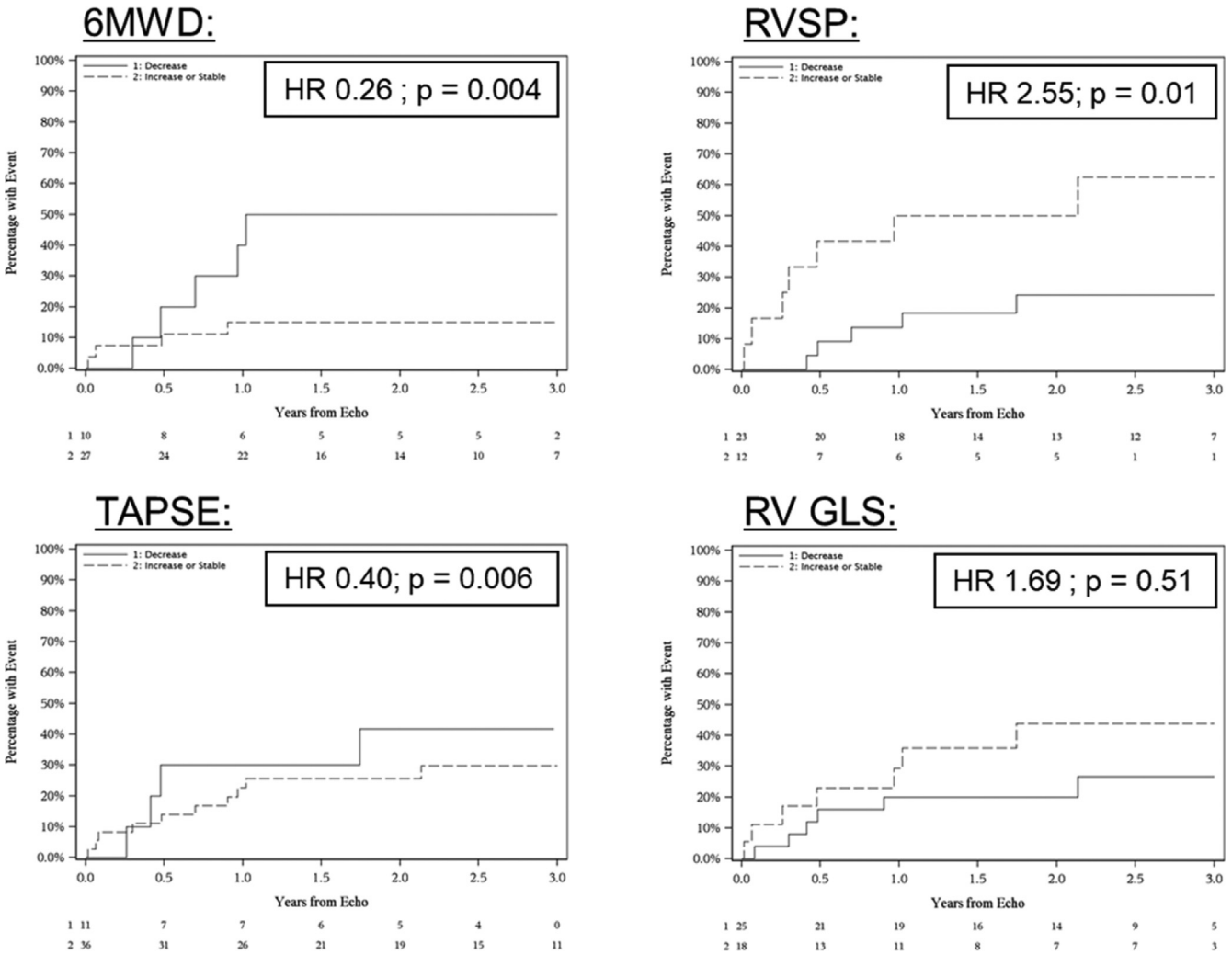

Figure 1. Cumulative incidence of mortality within 3 years after post-treatment echo stratified by decrease/increase in echocardiographic or clinical parameter

measures such as TAPSE as they cannot be reliably measured in all patients.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.026.

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