Prognostic Value of Echocardiographic Changes in Patients with Pulmonary Arterial Hypertension Receiving Parenteral Prostacyclin Therapy

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Background: It is unknown whether the echocardiographic changes observed after treatment of patients with pulmonary arterial hypertension have prognostic value.

Methods: Subjects with pulmonary arterial hypertension, confirmed by right heart catheterization, who underwent Doppler echocardiography before (baseline) and after 1 year of treatment (follow-up) with parenteral prostacyclin analogues were retrospectively identified. Echocardiographic parameters were measured offline by two investigators.

Results: A total of 48 patients were included (mean age, 45 ± 14 years; 83% women). Compared with baseline, follow-up echocardiography showed reductions in right atrial area (mean percentage change, 12 ± 25%; $P < .001$), right ventricular (RV) basal and middle cavity dimensions (mean percentage change, 8.5 ± 14% [$P < .001$] and 6.8 ± 17% [$P = .005$], respectively), and peak tricuspid regurgitant velocity (mean percentage change, 10 ± 14%; $P < .001$). Tricuspid annular plane systolic excursion (mean percentage change, 36 ± 43%; $P < .001$) and RV outflow tract time-velocity integral (mean percentage change, 48 ± 66%; $P < .001$) increased. During a median follow-up period of 52.5 months (interquartile range, 20.5–80 months), 18 patients (37.5%) died, mostly (n = 15 [83%]) from progression of pulmonary arterial hypertension. The changes in RV end-diastolic area (hazard ratio [HR per 10% decrease, 0.73; 95% confidence interval [CI], 0.57–0.93), tricuspid valve regurgitation velocity (HR per 10 cm/sec decrease, 0.58; 95% CI, 0.37–0.89), RV outflow tract velocity-time integral (HR per 10% increase, 0.90; 95% CI, 0.83–0.98), and subjective RV function (HR per 1 unit of improvement [e.g., from moderate to mild], 0.55; 95% CI, 0.31–0.96) were associated with overall mortality.

Conclusions: Echocardiographic parameters that estimate RV systolic pressure and assess RV morphology and function improve after 1 year of prostacyclin analogue treatment, and the degree of change has prognostic implications. (J Am Soc Echocardiogr 2014;27:733-41.)

Keywords: Pulmonary arterial hypertension, Prostacyclin analogues, Echocardiography, Outcome

Pulmonary arterial hypertension (PAH) is a severe and progressive pulmonary vascular condition due to narrowing of the blood vessels in the lung that can lead to right heart failure and premature death.[1] Nine pharmacologic agents are approved by the US Food and Drug Administration for the treatment of PAH, including two parenteral prostacyclin analogues: epoprostenol (intravenous [IV]) and treprostinil (IV and subcutaneous). These two parenteral therapies alleviated symptoms and improved exercise capacity and hemodynamic status in patients with PAH.[2-5] Furthermore, treatment with epoprostenol was associated with a survival benefit in patients with idiopathic PAH.[2] Notwithstanding major therapeutic advances in the past decade, the morbidity and mortality of PAH continue to be unacceptably high, with 1-, 3-, and 5-year survival rates from the time of diagnosis of 85%, 68%, and 57%, respectively.[6]

Echocardiography is a well-established and widely available technique that is routinely used during the initial assessment of patients suspected of having PAH. In addition, it continues to be an important method to follow patients with PAH and evaluate their treatment response.[7] This noninvasive technology permits the serial evaluation of right ventricular (RV) size and function as well as the estimated RV systolic pressure. Over the years, limited attention has been paid to the effects of PAH-specific treatment on echocardiographic parameters and their prognostic implications.[8]

Although a few echocardiographic parameters are known to improve after the initiation of PAH-specific therapies, it is not clear

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Abbreviations
CI = Confidence interval
HR = Hazard ratio
IQR = Interquartile range
IV = Intravenous
LV = Left ventricular
PAH = Pulmonary arterial hypertension
RV = Right ventricular

whether these changes have prognostic value. We hypothesized that improvements in certain echocardiographic parameters are associated with longer survival. We sought to investigate the effect of 1 year of treatment with parenteral prostacyclin analogues on echocardiographic parameters. Our main study objective is to determine whether changes in echocardiographic parameters resulting from advanced PAH-specific therapies have prognostic significance.

METHODS

Study Design and Inclusion and Exclusion Criteria

This retrospective study was approved by the Cleveland Clinic Institutional Review Board (Protocol No. 10-1127). We identified eligible subjects using the Cleveland Clinic Pulmonary Hypertension Registry. All patients had the diagnosis of precapillary pulmonary hypertension confirmed by right heart catheterization (mean pulmonary artery pressure $\geq$ 25 mm Hg with a pulmonary artery occlusion pressure $\leq$ 15 mm Hg). During right heart catheterization, patients were supine in a steady state, relaxed, and breathing room air or oxygen to maintain pulse oximetry $>$ 90%. Patient received no sedation. We cannulated preferably the right internal jugular vein using minimal local anesthesia (lidocaine 2%). We zeroed pressure transducers at the fourth intercostal space of the midaxillary line. Cardiac output was determined by thermodilution and Fick methodology. The resting oxygen consumption (milliliters per minute) for the Fick equation was estimated using the formula of Dehmer *et al.*,[9] whereas oxygen consumption = 125 $\times$ body surface area. Body surface area was calculated according to the formula of DuBois and DuBois.[10,11] Mixed venous oxygenation was measured in the blood obtained from the pulmonary artery during the right heart catheterization.

We identified 112 consecutive patients who received parenteral prostacyclin analogues for $\geq$1 year, from January 1, 2004, until January 8, 2011. We selected the initiation date (January 1, 2004) on the basis of the availability of syngo Dynamics (Siemens Medical Solutions USA, Inc, Malvern, PA), a system that allows offline echocardiographic measurements.

Each patient underwent a thorough clinical evaluation to identify the cause of pulmonary hypertension. We excluded patients who had pulmonary hypertension other than group I as defined by the Fourth World Symposium on Pulmonary Hypertension[12] (chronic thromboembolic pulmonary hypertension [n = 10] and pulmonary hypertension due to sarcoidosis [n = 4]). We also excluded patients with complex congenital heart diseases or those in whom surgical correction was performed in the 2 years before initiation of the study (n = 5), moderate or severe mitral and/or aortic valve stenosis and/or insufficiency (n = 16), echocardiography either not done in the predetermined time window (n = 10) or not available for offline review (studies done at an outside hospital or not retrievable [n = 19]). Patients with pulmonary hypertension due to congenital intracardiac shunts were not excluded. No patient had evidence of left ventricular (LV) myocardial disease.

Measurements and Calculations

Transthoracic Doppler echocardiography was performed during the initial evaluation (before the initiation of parenteral prostacyclin analogues) and at the end of a 1-year treatment with parenteral prostacyclin analogues. We arbitrarily chose 1 year of treatment to assess patients receiving an adequate and stable dose of prostacyclin analogue and to allow enough time for this medication to exert a noticeable effect. Studies were performed according to American Society of Echocardiography guidelines.[13,14] All recordings were reviewed with our offline quantification system (syngo Dynamics). Measurements were obtained by experienced physicians blinded to the patients' clinical histories and survival status. All new determinations were compared with the ones provided in the report at the time of echocardiography. In cases of discrepancies, another physician reviewed the echocardiographic images, and consensus was obtained.

In all but three echocardiographic studies, the patients were in sinus rhythm during image acquisition. In three studies, patients had atrial fibrillation with well-controlled heart rates (two patients during the initial study and one during the 1-year study), so measurements were made on three beats and the results averaged. Left atrial area was measured using planimetry at end-ventricular systole in the apical four-chamber view. We measured RV basal and middle cavity and longitudinal dimensions of the right ventricle in the apical four-chamber view. In addition, RV area was obtained at end-diastole by tracing the endocardial border in the apical four-chamber view and including trabeculations, tricuspid leaflets, and chords as part of the chamber.[14] The intraclass correlation coefficients for RV end-diastolic area determination (n = 15) for the same and different raters were 0.95 (95% confidence interval [CI], 0.85–0.98) and 0.93 (95% CI, 0.81–0.97), respectively. Abnormal LV diastolic function was divided into three grades, according to recommendations from the American Society of Echocardiography and the European Association of Echocardiography (grade I, impaired LV relaxation; grade II, pseudonormal LV filling; grade III, restrictive LV filling).[15] RV systolic function was visually estimated as normal, mild, moderate, or severe by experienced operators. The severity of tricuspid regurgitation was graded as mild, moderate, or severe according to recommendations of the American Society of Echocardiography.[16] Pericardial effusion was evaluated on two-dimensional echocardiography at end-diastole and graded as trace (separation of pericardial layers only in systole), small (separation $<$ 1 cm), moderate (separation $\geq$ 1 but $<$ 2 cm), or large (separation $\geq$ 2 cm).[17]

The RV outflow acceleration time was measured between the onset and the maximal velocity of the pulsed-wave Doppler flow profile. In addition, we determined the time-velocity integral of the RV outflow tract and noted the presence or absence of midsystolic notching. Maximal tricuspid regurgitant jet velocity was obtained during quiet respiration after analyzing the continuous-wave Doppler from different echocardiographic views. In cases of noticeable respiratory spectral oscillations, measurements were obtained during brief held-expiration, or three consecutive signals were averaged. We estimated the pulmonary vascular resistance on echocardiography using the model proposed by Opotowsky *et al.*[18] (pulmonary vascular resistance = [pulmonary artery systolic pressure/RV outflow tract velocity-time integral] + 3 if RV outflow tract notch is present). For all echocardiographic measurements, absolute changes were calculated by subtracting the determination performed after 1 year of treatment from the baseline value. Percentage change was obtained by dividing the absolute change over the baseline value and multiplying by 100.

Follow-Up

Patients were followed in our clinic at least every 3 months after the initiation of parenteral prostacyclin analogues. Echocardiography was performed before the initiation of PAH-specific therapies and every 3 to 6 months. After 1 year of treatment, patients were continued on parenteral prostacyclin analogues unless they underwent lung transplantation or died. In no patient was prostacyclin analogue discontinued on the basis of echocardiographic deterioration or lack of improvement. Patients underwent transplantation in the event of refractory PAH, using criteria suggested by the International Society for Heart and Lung Transplantation.[19] Death of study participants was ascertained by reviewing our records and querying the US Social Security Death Index.

Statistical Analysis

Means and standard deviations and numbers of patients with percentages are provided for continuous and categorical variables, respectively. Comparison of echocardiographic variables at baseline and after 1 year of treatment was performed using McNemar or paired Student *t* tests, as appropriate. Interrater and intrarater agreement for single measures was calculated using intraclass correlation coefficients and their respective 95% CIs. Each subject was rated by the same two raters. We tested for absolute agreement because systematic differences are considered relevant. Survival at each time point was assessed using Kaplan-Meier methodology. The start point was the date of the echocardiogram obtained after 1 year of parenteral treatment. The end of follow-up was marked by the patient's death. Patients were censored either at the time of lung transplantation or at the end of the study in May 2013. Cox proportional-hazards modeling adjusted for age and gender was used to examine the relationship between survival and selected echocardiographic variables. The results are expressed as hazard ratios (HRs) and the corresponding 95% CI. We generated models testing three outcome variables (overall mortality, PAH-associated death, and the combination of death and lung transplantation). Predictors with HRs < 1 are associated with lower risk for the outcome tested. As an example, an HR of 0.73 means that the outcome of interest (i.e., mortality) decreases by a factor of 0.73 (27% less) for each specified unit change of the predictor (e.g., a 10% decrease in RV end-diastolic area). For a 20% decrease in RV area, the HR for the outcome decreases by a factor of $(0.73)^2 = 0.53$ (47% lower risk for having the outcome).

Receiver operating characteristic curve analysis was used to determine the sensitivity and specificity of different cutoffs of the change in tricuspid regurgitation velocity to discriminate patients who died during follow-up. All *P* values reported are two tailed. *P* values $< .05$ were considered significant. The statistical analyses were performed using SPSS version 17 (SPSS, Inc, Chicago, IL).

RESULTS

Overall Characteristics of the Patients

We included a total of 48 patients (Table 1) with PAH, of whom 32 (67%) had either idiopathic (n = 25 [52%]) or heritable (n = 7 [15%]) PAH. A few patients had Eisenmenger syndrome due to ventricular septal defects (n = 2) and an atrial septal defect with anomalous pulmonary venous return (n = 1). Six-minute walk tests were performed the same day as echocardiography. Right heart catheterization was done within 1 month of the first echocardiographic assessment in 39 patients (81%).

Table 1 Patient characteristics immediately before the initiation of parental prostacyclin analogues

Variable	Value
Number of patients	48
Age (years)	44 ± 14
Women	40 (83%)
Caucasians	40 (83%)
Cause of PAH	
Idiopathic/heritable	32 (67%)
Connective tissue disease	10 (21%)
Portopulmonary	3 (6%)
Congenital heart diseases	3 (6%)
NYHA class*	
III	24 (57%)
IV	18 (43%)
6-min walk distance (m)	317 ± 107
6-min walk distance (% of predicted)[40]	54 ± 17
Hemodynamics	
RA pressure (mm Hg)	12 ± 7
Mean PAP (mm Hg)	54 ± 12
PAOP (mm Hg)	11 ± 5
CO by thermodilution (L/min)	4 ± 1
CO by Fick method (L/min)†	4 ± 1
PVR (Wood units)	13 ± 6
Mixed venous oxygenation (%)	60 ± 9

CO, Cardiac output; *NYHA*, New York Heart Association; *PAOP*, pulmonary artery occlusion pressure; *PAP*, pulmonary artery pressure; *RA*, right atrial.
Data are expressed as mean ± SD or number (percentage).
*NYHA functional class at the time of the initial echocardiographic study was available in 42 patients.
†Oxygen consumption was estimated using the formula of Dehmer *et al*.[9]

Prostacyclin Analogue Treatment

All patients were treated with parenteral prostacyclin analogues for ≥1 year. The prostacyclin analogues used during this period were IV epoprostenol in 42 patients (88%), IV treprostinil in three (6%), and subcutaneous treprostinil in two (4%). One patient (2%) was converted from IV epoprostenol to IV treprostinil during the first year of treatment. Twenty-five patients (52%) were receiving other PAH-specific therapies before the initiation of prostacyclin analogues (endothelin receptor antagonists, 17 [68%]; phosphodiesterase-5 inhibitors, three [12%]; combination of endothelin receptor antagonists and phosphodiesterase-5 inhibitors, five [20%]). One patient was initiated on a phosphodiesterase-5 inhibitor during the first year of treatment with prostacyclin analogue.

Serial Echocardiographic Determinations

We analyzed the initial echocardiogram and echocardiograms obtained after 1 year of treatment with parenteral prostacyclin analogues (Figure 1). The median time between these two echocardiograms was 12.9 months (interquartile range [IQR], 11–14.8 months). Significant echocardiographic differences between studies reflected an increase in the sizes of left-sided cardiac chambers, reductions of the sizes of right-sided heart cavities, improvements in LV and RV function, and a reduction in the leftward shifting of the interventricular septum (Table 2). On the

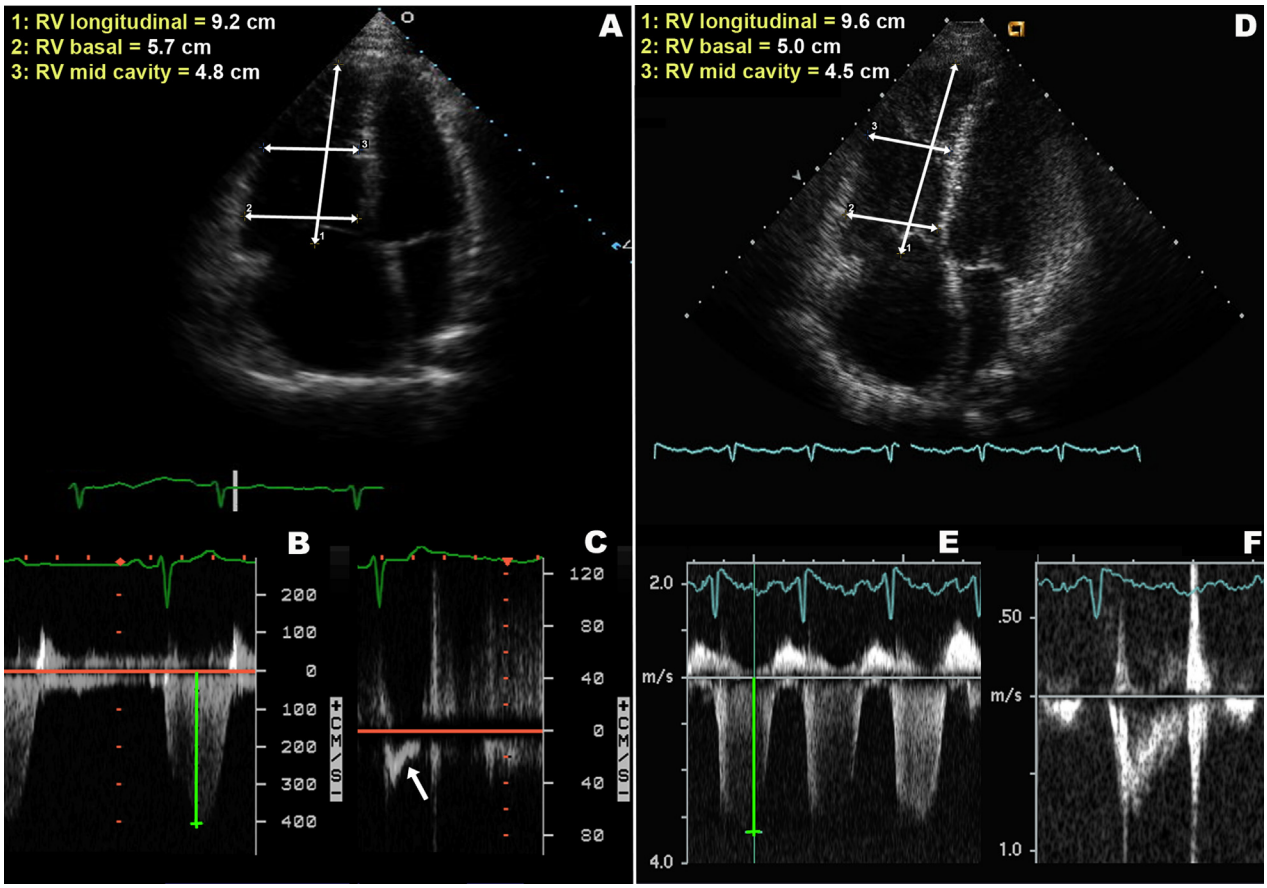

Figure 1 Echocardiograms at baseline and after 1 year of treatment with prostacyclin analogue. RV dimensions **(A)**, tricuspid regurgitant jet **(B)**, and RV outflow tract flow **(C)** of the baseline echocardiogram. RV basal and middle cavity and longitudinal dimensions were 5.7, 4.8, and 9.2 cm, respectively. The tricuspid regurgitation velocity was 4.1 m/sec. The RV outflow tract flow had a midsystolic notch (*arrow*), and the velocity-time integral was 7.4 cm. RV dimensions **(D)**, tricuspid regurgitant jet **(E)**, and RV outflow tract flow **(F)** of the echocardiogram after 1 year of treatment. RV basal and middle cavity and longitudinal dimensions were 5, 4.5, and 9.6 cm, respectively. The tricuspid regurgitation velocity was 3.3 m/sec. The RV outflow tract flow had no notch, and the velocity-time integral was 13.1 cm.

echocardiogram obtained after 1 year of prostacyclin analogue treatment, the peak tricuspid regurgitant velocity, estimated RV systolic pressure, ratio of tricuspid regurgitant velocity to RV outflow tract time-velocity integral, estimated pulmonary vascular resistance, percentage of studies showing RV outflow tract notching, and grade of LV diastolic dysfunction decreased, while RV outflow tract flow acceleration time increased (Table 3). Echocardiographic parameters that did not reach statistical significance are shown in Supplemental Table 1 (available at www.onlinejase.com).

Outcomes after Receiving Parenteral Prostacyclin Analogues for 1 Year

Patients were followed for a median of 52.5 months (IQR, 20.5–80 months). During this period, 18 patients died (37.5%), 15 from progression of PAH (83%) and three (17%) from other conditions (sepsis in two patients and gastrointestinal bleeding in one). The cumulative incidence of death from any cause is shown in Figure 2. All but five of the 48 patients received prostacyclin analogue treatments until death, transplantation, or the end of the study. The reasons for discontinuation of the parenteral prostacyclin analogue treatment were recurrent central venous catheter infection (n = 2), severe side effects (n = 2), and patient decision (n = 1). These five patients were started on oral and/or inhaled medications, and all but one were alive at the end of the study. In the patients who continued treatment with prostacyclin analogues (epoprostenol, n = 24 [56%]; treprostinil, n = 19 [44%]), the median doses of these medications were 50.5 ng/kg/min (IQR, 24.6–78.5 ng/kg/min) for epoprostenol and 98 ng/kg/min (IQR, 66–129 ng/kg/min) for treprostinil.

Echocardiographic Changes at 1 Year and Impact on Survival

Overall mortality, adjusted by age and gender, was associated with percentage change in RV midcavity dimension (HR per 10% decrease, 0.76; 95% CI, 0.58–0.99), RV end-diastolic area (HR per 10% decrease, 0.73; 95% CI, 0.57–0.93), RV outflow tract velocity-time integral (HR per 10% increase, 0.90; 95% CI, 0.83–0.98), tricuspid valve regurgitation velocity (HR per 10% decrease, 0.58; 95% CI, 0.37–0.89), estimated RV systolic pressure (HR per 10% decrease, 0.79; 95% CI, 0.63–1.00), and difference in qualitative RV function (HR per 1 unit of improvement [e.g., from moderate to mild], 0.55; 95% CI, 0.31–0.96). Other echocardiographic determinations did not reach statistical significance (Supplemental

Table 2 M-mode and two-dimensional echocardiographic determinations before and after 1 year of parenteral prostacyclin analogue treatment in patients with PAH

Variable	*n*	Initial echocardiographic study	Echocardiographic study after 1 year of treatment	Difference between studies	Difference between studies		Percentage change	*P* (paired Student *t* or McNemar test)
					Lower 95% confidence limit	Upper 95% confidence limit		
Heart rate (beats/min)	45	87.7 ± 15	81.9 ± 10	5.8 ± 18	0.5	11.2	3.3 ± 26	.03
Body surface area (kg/m^2)	48	1.9 ± 0.3	1.9 ± 0.3	0.02 ± 0.1	−0.02	0.06	0.4 ± 7.4	.38
Left atrial area (cm^2)	45	14.4 ± 5	16.2 ± 4	1.7 ± 4	0.4	3.1	20 ± 39	.01
LV end-diastolic diameter (cm)	44	3.3 ± 0.6	4 ± 0.7	0.7 ± 0.7	0.5	0.9	24 ± 27	<.001
LV end-systolic diameter (cm)	44	2.1 ± 0.5	2.5 ± 0.6	0.4 ± 0.7	0.2	0.6	26 ± 40	<.001
LV ejection fraction (%)	46	55.5 ± 3	57.5 ± 4	1.9 ± 6	0.2	3.7	4 ± 11	.03
Right atrial area (cm^2)	45	25.1 ± 7	21.4 ± 8	−3.6 ± 6	−5.6	−1.7	−12 ± 25	<.001
RV end-diastolic basal dimension (cm)	48	5.3 ± 0.8	4.6 ± 0.8	−0.5 ± 0.7	−0.7	−0.3	−8.5 ± 14	<.001
RV end-diastolic mid cavity dimension (cm)	48	4.2 ± 0.7	3.9 ± 0.9	−0.3 ± 0.7	−0.5	−0.1	−6.8 ± 17	.005
RV end-diastolic longitudinal dimension (cm)	48	8 ± 1	8 ± 1	−0.04	−0.3	0.2	0.1 ± 10	.75
RV end-diastolic area (cm^2)	44	33.9 ± 9	31 ± 8	−2.9	−5	−0.8	−7 ± 22	.008
TAPSE (cm)	44	1.5 ± 0.5	1.9 ± 0.5	0.42	0.3	0.6	36 ± 43	<.001
RV function	47							
Normal		0 (0%)	4 (9%)					<.001
Mild		5 (11%)	13 (28%)					
Moderate		19 (40%)	19 (40%)					
Severe		23 (49%)	11 (23%)					
Leftward shifting of the IVS	45							
Absent		6 (13%)	20 (44%)					.001
Present		39 (87%)	25 (56%)					
Inferior vena cava collapse	40							
Absent		20 (50%)	11 (28%)					.035
Present		20 (50%)	29 (72%)					

IVS, Interventricular septum, *TAPSE*, tricuspid annular plane systolic excursion.
Data are expressed as mean ± SD or number (percentage).

Table 2). Results were similar when considering a composite event that included overall death and lung transplantation (data not shown).

Three variables remained significant predictors of long-term mortality in a multivariate model that included age, gender, and percentage change in RV midcavity dimension, difference in qualitative RV function, RV outflow tract velocity-time integral, and tricuspid valve regurgitation velocity. These variables were RV midcavity dimension (HR per 10% decrease, 0.68; 95% CI, 0.49–0.93), RV outflow tract velocity-time integral (HR per 10% increase, 0.87; 95% CI, 0.79–0.96), and tricuspid valve regurgitation velocity (HR per 10% decrease, 0.53; 95% CI, 0.27–1.00). Of these three variables, only percentage change in tricuspid valve regurgitation velocity (HR per 10% decrease, 0.61; 95% CI, 0.37–0.98) remained a significant predictor of long-term mortality in a multivariate model that included baseline New York Heart Association functional class, pulmonary vascular resistance, and 6-min walk distance.

The areas under the receiver operating characteristic curves were significant for percentage change in RV midcavity dimension (0.69; 95% CI, 0.54–0.82; $P = .04$) and tricuspid valve regurgitation velocity (0.73; 95% CI, 0.58–0.88; $P = .008$) in predicting mortality after 1 year of prostacyclin analogue treatment. In the event that the tricuspid valve regurgitation velocity does not decrease during the first year of treatment, the sensitivity and specificity for dying are 50% and 86%, respectively. If tricuspid valve regurgitation velocity decreases by <4.5% during the first year of treatment, the sensitivity and specificity for overall death are 72% and 75%, respectively (Figure 3).

When the three patients who died of conditions other than PAH progression were excluded, we observed that change in RV end-diastolic area (HR per 10% decrease, 0.81; 95% CI, 0.66–0.98), pulmonary artery acceleration time (HR per 10% increase, 0.83; 95% CI, 0.69–1.00), estimated RV systolic pressure (HR per 10 mm Hg decrease, 0.87; 95% CI, 0.76–0.98), tricuspid valve regurgitation velocity (HR per 10 cm/sec decrease, 0.68; 95% CI, 0.51–0.92), and improvement in the leftward shifting of the interventricular septum (HR, 0.38; 95% CI, 0.16–0.89) were predictors of mortality due to PAH progression. Using forward stepwise Cox regression, only the change in RV end-diastolic area and tricuspid regurgitation velocity were included in the model.

Added Value of Percentage Difference versus Baseline or 1-Year Echocardiographic Variables

We compared the changes in echocardiographic variables between baseline and 1-year determinations to assess whether the change augmented the prognostic information of each independent component of the equation. Baseline RV basal (HR per 1-cm increase,

Table 3 Doppler echocardiographic determinations before and after 1 year of parenteral prostacyclin analogue treatment in patients with PAH

Variable	*n*	Initial echocardiographic study	Echocardiographic study at 1 year of treatment	Difference between studies	Difference between studies		Percentage change	*P* (paired Student *t* or McNemar test)
					Lower 95% confidence limit	Upper 95% confidence limit		
Tricuspid regurgitation severity	46							
Mild		9 (20%)	26 (57%)					<.001
Moderate		22 (48%)	14 (30%)					
Severe		15 (32%)	6 (13%)					
Peak tricuspid regurgitant velocity (m/sec)	46	4.3 ± 0.5	3.8 ± 0.6	−0.5 ± 0.6	−0.6	−0.3	−10 ± 14	<.001
RVSP (mm Hg)	46	82.4 ± 16	67.4 ± 18	−15 ± 17	−20.1	−9.8	−17 ± 21	<.001
RV outflow tract flow acceleration time (msec)	35	55.1 ± 17	73 ± 20	18.4 ± 17	10.7	26.1	43 ± 50	<.001
RV outflow tract time-velocity integral (cm)	42	12.6 ± 3.6	17.5 ± 6.6	4.9 ± 7	2.8	7.1	48 ± 66	<.001
Doppler RV outflow tract notching	40							
Absent		15 (35%)	29 (67%)					<.001
Present		28 (65%)	14 (33%)					
Ratio of tricuspid regurgitant velocity to RV outflow tract time-velocity integral	40	0.37 ± 0.1	0.25 ± 0.1	−0.13 ± 0.1	−0.2	0.09	−30 ± 28	<.001
PVR estimation[18]	38	9 ± 3.2	5.3 ± 2.6	−3.7	−4.8	−2.7	−38 ± 28	<.001
Peak E velocity (cm/sec)	45	60.5 ± 25	76.8 ± 22	16.2 ± 30	7.1	25	46 ± 76	.001
E/A ratio	43	0.91 ± 0.5	1.1 ± 0.4	0.19 ± 0.6	0.01	0.38	47 ± 77	.04
Peak S velocity (cm/sec)	33	49 ± 12	54 ± 13	5 ± 10	1.5	8	12 ± 22	.006
Peak D velocity (cm/sec)	33	39 ± 15	48 ± 13	9.1 ± 16	3.4	14.7	33 ± 42	.002
S/D ratio	33	1.4 ± 0.4	1.2 ± 0.4	−0.18	−0.31	−0.06	−10 ± 24	.004
LV diastolic function	47							
Normal		15 (32%)	28 (60%)					.02
Grade I		31 (66%)	17 (36%)					
Grade II		1 (2%)	2 (4%)					

PVR, Pulmonary vascular resistance, *RVSP*, RV systolic pressure.
Data are expressed as mean ± SD or number (percentage).

2.23; 95% CI, 1.23–4.06) and RV midcavity (HR per 1-cm increase, 2.34; 95% CI, 1.27–4.35) dimensions were the only baseline echocardiographic variables associated with long-term mortality. RV end-diastolic area (HR per 10-cm^2 decrease, 0.54; 95% CI, 0.30–0.96), RV basal (HR per 1-cm increase, 2.79; 95% CI, 1.47–5.30) and RV midcavity (HR per 1-cm increase, 2.67; 95% CI, 1.56–4.58) dimensions, tricuspid valve regurgitation velocity (HR per 1 m/sec decrease, 0.3; 95% CI, 0.12–0.89), and qualitative RV function (HR per unit [e.g., mild = 1, moderate = 2], 0.46; 95% CI, 0.24–0.87) at 1 year were significant predictors of survival. The basal and middle cavity dimension at 1 year of treatment and the change in RV end-diastolic area and tricuspid valve regurgitation velocity were selected by backward stepwise Cox regression models that included the measure at 1 year and the difference between echocardiograms.

DISCUSSION

Using detailed assessments, our study demonstrates that 1 year of parenteral prostacyclin analogue treatment improves several echocardiographic parameters in patients with PAH, suggesting a favorable effect on disease progression in patients who continue treatment for this long. More important, we show that the degrees of improvement in RV size, peak tricuspid regurgitant velocity, estimated RV systolic pressure, RV outflow tract velocity-time integral, and subjective RV function are associated with overall survival.

A limited number of studies have investigated the predictive role of echocardiographic parameters in patients with PAH. The presence of pericardial effusion, a reflection of RV dysfunction, has been frequently associated with mortality.[20–22] Other echocardiographic determinations that have demonstrated prognostic implications include tricuspid annular plane systolic excursion,[23,24] right atrial area,[20,25] RV diameter,[26] and degree of tricuspid valve regurgitation.[24,25]

Echocardiography permits a serial noninvasive evaluation of cardiac morphology and function; therefore, it remains the imaging option of choice to follow patients with PAH. A trial that randomized patients with PAH to bosentan or placebo (Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy 1) showed a decrease in pericardial effusion, an increase in LV diastolic area, and improvements in LV systolic eccentricity index, RV-to-LV diastolic area ratio, RV ejection time, LV stroke volume, and early diastolic filling after 16 weeks of therapy.[27] The effects of long-term

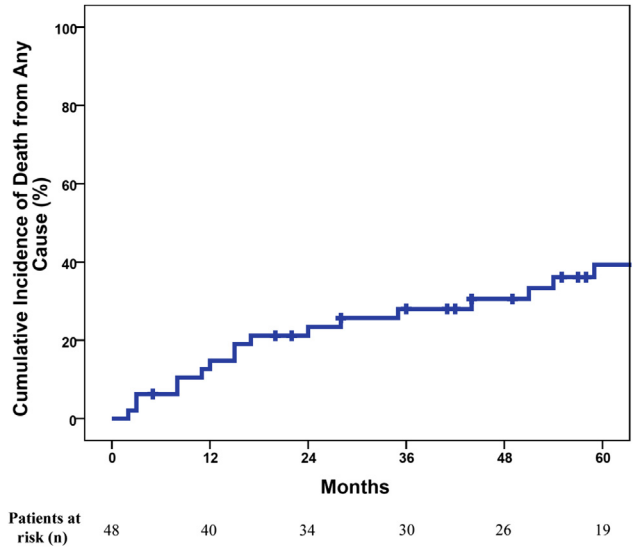

Figure 2 Cumulative Kaplan-Meier estimates from the time of echocardiography after 1 year of parenteral prostacyclin analogues to the time to death from any cause.

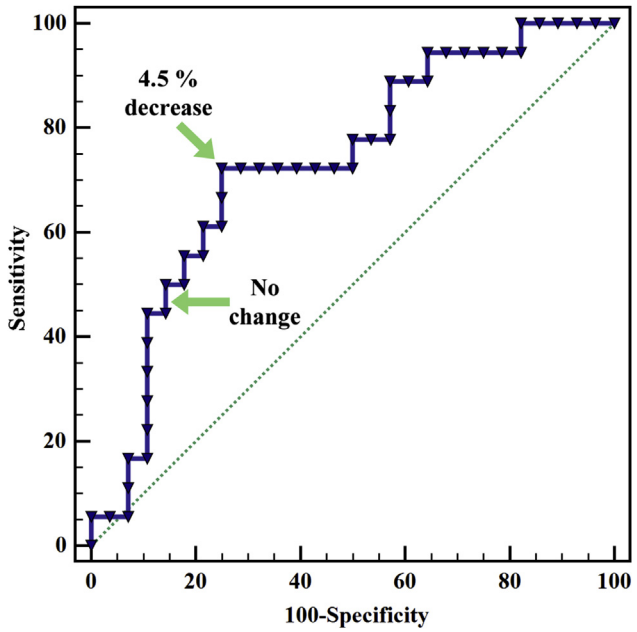

Figure 3 Receiver operating characteristic curve analysis of percentage change in tricuspid regurgitation velocity and survival status. The area under the curve was 0.73 (95% CI, 0.58–0.88; P = .008). The sensitivity and specificity for dying are 50% and 86%, respectively, when the tricuspid valve regurgitation velocity does not decrease during the first year of treatment. The sensitivity and specificity for overall death are 72% and 75%, respectively, when the tricuspid valve regurgitation velocity decreases by <4.5% during the same interval.

epoprostenol therapy on echocardiographic parameters have not been adequately investigated. A study that randomized patients to epoprostenol or placebo demonstrated a beneficial effect of epoprostenol in reducing RV size, curvature of the interventricular septum, and maximal tricuspid regurgitant jet velocity at 12 weeks.[28] Long-term studies of epoprostenol treatment failed to show an improvement in RV size, but one demonstrated an improvement in RV function.[29,30]

After 1 year of parenteral prostacyclin analogue treatment, we observed increases in left atrial and LV sizes; reductions in right atrial and RV sizes; improvements in tricuspid annular plane systolic excursion, RV outflow acceleration time, RV outflow tract time-velocity integral, qualitative RV function, LV systolic and diastolic function; and reductions in tricuspid regurgitation severity, peak tricuspid regurgitant velocity, and RV systolic pressure. These favorable changes support that parenteral analogue therapies are certainly efficacious in PAH. However, it is unclear whether the measured changes in the echocardiographic variables have inherent prognostic significance and if this percentage difference has better predictive value than either the baseline or 1-year determinations.

In our cohort, with the exception of RV basal and middle cavity dimensions, only the echocardiographic values obtained after 1 year of receiving parenteral prostacyclin analogue treatment and their respective changes from baseline were significant predictors of long-term mortality. Particularly, the percentage change in RV end-diastolic area and tricuspid regurgitation velocity were predictors of overall and PAH-associated mortality. RV failure was the main cause of death in our cohort, and we found an improvement in subjective measurements of RV morphology and function after 1 year of parenteral prostacyclin therapy, suggesting that the right ventricle is able to adapt and remains a critical factor to determine long-term patient survival.[8]

We have previously reported a high prevalence of grade I LV diastolic dysfunction in patients with severe PAH.[31] Impaired relaxation (i.e., grade I LV diastolic dysfunction) is due predominantly to displacement of the interventricular septum toward the left ventricle during early diastole, resulting in decreased LV chamber size and filling.[32–34] This reciprocal relation of the ventricles (ventricular interdependence) is also observed at the auricular level, given the limited space for the right atrium to expand.[35] After 1 year of treatment with IV prostacyclin analogues, we observed that LV diastolic function improved and that the transmitral (E/A) ratio increased, in association with increases in left atrial area and LV end-systolic and end-diastolic diameters and a decrease in the proportion of patients with leftward displacement of the interventricular septum. Similarly, other investigators have found an increase in the E/A ratio after treatment with PAH-specific therapies.[27,36]

There were limitations to this study, including its retrospective nature and the fact that our results apply only to patients with PAH who received ≥1 year of parenteral prostacyclin analogue treatment. Only a few patients had data on RV function parameters that are less afterload dependent, such as tricuspid lateral annular systolic velocity, isovolumic contraction peak velocity, or isovolumic acceleration by Doppler tissue imaging and RV longitudinal systolic strain by speckle-tracking imaging.[37,38] In patients with atrial fibrillation (n = 3), we averaged only three beats instead of the more reliable approach of averaging ≥5 beats or using the index-beat method (a single beat is selected when the ratio of the preceding R-R interval to the pre-preceding R-R interval is closer to 1).[39] Nevertheless, this study adds important information to the sparse evidence regarding the long-term effects of PAH-specific therapy on diverse echocardiographic parameters. Even when there was a marked response to therapy in our cohort, only a few echocardiographic parameters, such as changes in tricuspid regurgitant jet velocity, RV morphology, and function, predicted long-term survival. Those patients who do not show such favorable echocardiographic changes may need to be

treated more aggressively or referred earlier for lung transplantation evaluation. Future studies are needed to determine the best time interval to repeat studies (i.e., the 6-min walk test, echocardiography, and right heart catheterization) after the initiation of PAH-specific therapies and which parameter variation (alone or in combination) is able to predict long-term outcomes.

CONCLUSION

Echocardiographic parameters that estimate RV systolic pressure and assess RV morphology and function improve after 1 year of prostacyclin analogue treatment, and the degree of change has prognostic implications.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2014.03.012.

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Supplementary Table 1 Echocardiographic determinations before and after a year of parenteral prostacyclin analogue treatment in patients with PAH.

	n	Initial echocardiogram Mean ± SD, n (%)	Echocardiogram at 1 year of treatment Mean ± SD, n (%)	Difference between studies Mean ± SD	Difference between studies		Percentage change Mean ± SD	*P* (paired student t-or McNemar test)
					Lower 95% CI	Upper 95% CI		
Left atrium diameter (cm)	45	3.4 ± 0.7	3.6 ± 0.7	0.17 ± 0.7	−0.04	0.37	7 ± 22	.12
Aortic diameter (cm)	44	2.8 ± 0.5	2.9 ±0.5	0.08	−0.04	0.2	4 ± 15	.18
Interventricular septum (cm)	44	1.2 ± 0.3	1.1 ± 0.2	−0.07 ± 0.3	−0.16	0.01	−3 ± 22	.09
Posterior left ventricular wall (cm)	44	1.1 ± 0.2	1 ± 0.2	−0.07 ± 0.2	−0.14	0.01	−3 ± 21	.07
Inferior vena cava diameter (cm)	37	2.2 ± 0.4	2 ± 0.6	−0.19 ±0.6	−0.39	0.01	−8 ± 28	.06
Peak A wave velocity (cm/s)	43	70 ± 21	73 ± 19	0.4 ± 9	−2.6	3.5	9 ± 32	.4
Deceleration time of the E wave (ms)	30	218 ± 67	224 ± 52	6 ± 85	−26	38	13 ± 43	.71
Ar wave velocity (cm/s)	32	27 ± 6	28 ± 6	0.4 ± 8	−2.6	3.5	6 ± 29	.77
Degree of pericardial effusion	47							.7
None or trivial		30 (64)	29 (62)					
Mild		13 (28)	16 (34)					
Moderate		4 (8)	2 (4)					

CI, confidence interval; *SD,* standard deviation.

Supplementary Table 2 Univariate Cox regression analysis with overall mortality as outcome and echocardiographic variables as covariates, adjusted by age and gender

	HR	95% CI	*P*
Left atrial area % change	1.01	0.99-1.02	.34
Left ventricular end-diastolic diameter % change	0.99	0.98-1.01	.39
Left ventricular end-systolic diameter % change	1	0.99-1.01	.92
Left ventricular ejection fraction % change	1	0.95-1.04	.85
RV basal dimension % change	0.99	0.95	1.02
RV longitudinal dimension % change	0.98	0.93	1.03
Right atrial area % change	0.98	0.96-1.01	.11
Basal RV diameter % change	0.97	0.94-1.02	.1
Tricuspid regurgitation severity change (per unit of improvement)	0.8	0.35-1.81	.59
TAPSE % change	0.99	0.97-1.01	.43
Leftward shifting of the IVS (present to absent)	0.49	0.20-1.18	.11
Inferior vena cava collapse change (present to absent)	0.68	0.26-1.79	.44
RV outflow flow acceleration time % change	1.1	1-10.03	.08
Doppler RV outflow tract notching (present to absent)	0.56	0.19-1.65	.29
Tricuspid regurgitation velocity / RV outflow tract time-velocity integral % change	0.99	0.98	1.02
Estimate PVR[18] % change	1	0.98	1.02
E wave velocity % change	1	1-1.01	.1
E/A ratio % change	1	0.99-1.01	.31
Peak S wave velocity % change	0.97	0.94-10	.07
Pulmonary vein peak D wave velocity % change	0.99	0.97-1.10	.13
S/D ratio % change	1.1	0.98-1.04	.55
Diastolic dysfunction grade (per grade of improvement)	0.99	0.49-2	.98

CI, confidence interval; *HR,* hazard ratio; *IV,* interventricular septum; *RV,* right ventricular; *TAPSE,* tricuspid annular plane systolic excursion.
HR is based on 1% decrease or 1 Unit decrease on the echocardiogram performed a 1-year compared to the initial one.