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Progressive Right Ventricular Dysfunction in Patients With Pulmonary Arterial Hypertension Responding to Therapy

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Objectives The purpose of this study was to examine the relationship between changes in pulmonary vascular resistance (PVR) and right ventricular ejection fraction (RVEF) and survival in patients with pulmonary arterial hypertension (PAH) under PAH-targeted therapies.

Background Despite the fact that medical therapies reduce PVR, the prognosis of patients with PAH is still poor. The primary cause of death is right ventricular (RV) failure. One possible explanation for this apparent paradox is the fact that a reduction in PVR is not automatically followed by an improvement in RV function.

Methods A cohort of 110 patients with incident PAH underwent baseline right heart catheterization, cardiac magnetic resonance imaging, and 6-min walk testing. These measurements were repeated in 76 patients after 12 months of therapy.

Results Two patients underwent lung transplantation, 13 patients died during the first year, and 17 patients died in the subsequent follow-up of 47 months. Baseline RVEF (hazard ratio [HR]: 0.938; $p = 0.001$) and PVR (HR: 1.001; $p = 0.031$) were predictors of mortality. During the first 12 months, changes in PVR were moderately correlated with changes in RVEF ($R = 0.330$; $p = 0.005$). Changes in RVEF (HR: 0.929; $p = 0.014$) were associated with survival, but changes in PVR (HR: 1.000; $p = 0.820$) were not. In 68% of patients, PVR decreased after medical therapy. Twenty-five percent of those patients with decreased PVR showed a deterioration of RV function and had a poor prognosis.

Conclusions After PAH-targeted therapy, RV function can deteriorate despite a reduction in PVR. Loss of RV function is associated with a poor outcome, irrespective of any changes in PVR. (J Am Coll Cardiol 2011;58:2511–9) © 2011 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature leading to increased pulmonary vascular resistance (PVR), elevated pulmonary artery pressure, right ventricular (RV) dysfunction, and ultimately, RV failure and death (1,2). Prognosis is strongly associated with RV parameters, such as cardiac index and right atrial pressure (3–5). Guided by the premise that RV failure follows an increased load, the current strategy to preserve RV function is by attempting to reduce the PVR. This strategy is effective when loading conditions can be normalized, which is the case in patients with PAH after lung transplantation and in patients with chronic thromboembolic pulmonary hypertension after pulmonary endarterectomy (6–8). Although PVR can be reduced by means of PAH-specific medication, PVR remains elevated in the vast majority of patients and the prognosis remains unsatisfactory (3,9). This apparent contrast between hemodynamic success and poor prognosis raises the question whether RV dysfunction can progress even when the PVR is lowered but not normalized by current medical therapies.

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Abbreviation and Acronyms

CMR = cardiac magnetic resonance
CO = cardiac output
EDVI = end-diastolic volume index
ESVI = end-systolic volume index
PAP = mean pulmonary artery pressure
PAH = pulmonary arterial hypertension
PCWP = pulmonary capillary wedge pressure
PVR = pulmonary vascular resistance
RHC = right heart catheterization
RV = right ventricular/ventricle
RVEF = right ventricular ejection fraction
6MWT = 6-min walk test

Therefore, the aim of the present study was to investigate the relationship between changes in PVR and right ventricular ejection fraction (RVEF) and survival, as assessed by means of right heart catheterization (RHC) and cardiac magnetic resonance (CMR) imaging in a cohort of patients with PAH receiving PAH-targeted medical therapy.

Methods

Patients. This study was part of a prospective ongoing research program to assess the value of CMR imaging in patients with pulmonary hypertension. Between March 2002 and March 2007, 657 patients were referred to the VU University Medical Center, Amsterdam, the Netherlands, because of a suspected diagnosis of pulmonary hypertension. Based on World Health Organization guidelines (10), 179 patients were diagnosed as having PAH. Inclusion criteria were: 1) patients diagnosed with PAH; and 2) RHC, CMR imaging, and 6-min walk test (6MWT) completed within 2 weeks of diagnosis and before the initiation of therapy. Exclusion criteria were: 1) congenital systemic-to-pulmonary shunts (n = 32); and 2) contraindications for CMR imaging (e.g., implanted devices, claustrophobia) (n = 28).

In total, 119 patients with PAH met the criteria and were enrolled. Nine patients were excluded because of incomplete data. Baseline measurements were completed in 110 patients. Thirteen patients died during the first year of follow-up. Seven patients did not undergo a second RHC and were excluded from the follow-up analysis. Ninety of the 110 patients underwent follow-up measurements consisting of a second RHC, CMR imaging, and 6MWT after 12 months of PAH-targeted medical treatment. Six patients were excluded from the final analysis because the time between the second RHC and CMR imaging was longer than 1 month. Five patients were excluded due to incomplete CMR data, and 3 patients were excluded due to insufficient CMR image quality. Seventy-six patients completed follow-up measurements (Fig. 1). All 110 patients were followed clinically on a regular basis by outpatient visits and telephone contacts until May 1, 2010.

Medical treatment comprised prostacyclins, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors, either alone or in various combinations. Patients with a positive response to an acute vasodilator challenge were treated with calcium antagonists (10). All patients received oral anticoagulants. During follow-up, many patients went through one or more treatment regimens.

This study was approved by the institutional "Review Board on Research Involving Human Projects" of the VU University Medical Center, Amsterdam, the Netherlands. All participants gave written informed consent.

Right heart catheterization. Hemodynamic assessment was performed with a 7-F balloon-tipped, flow directed Swan-Ganz catheter (131HF7, Baxter Healthcare Corp., Irvine, California) during continuous electrocardiography monitoring. PVR was calculated as: (mPAP − PCWP)/CO (mPAP is mean pulmonary artery pressure, PCWP is pulmonary capillary wedge pressure, and CO is cardiac output).

6-min walk test. The 6MWT was performed according to American Thoracic Society guidelines (11).

CMR imaging. CMR imaging was performed on a Siemens 1.5-T Sonato scanner (Siemens Medical Solutions, Erlangen, Germany), equipped with a 6-element phased-array receiver coil. electrocardiography-gated cine imaging was performed using a balanced steady-state precession pulse sequence during repeated breath-holds. Short-axis images from base to apex of the ventricles were obtained with a typical slice thickness of 5 mm and an interslice gap

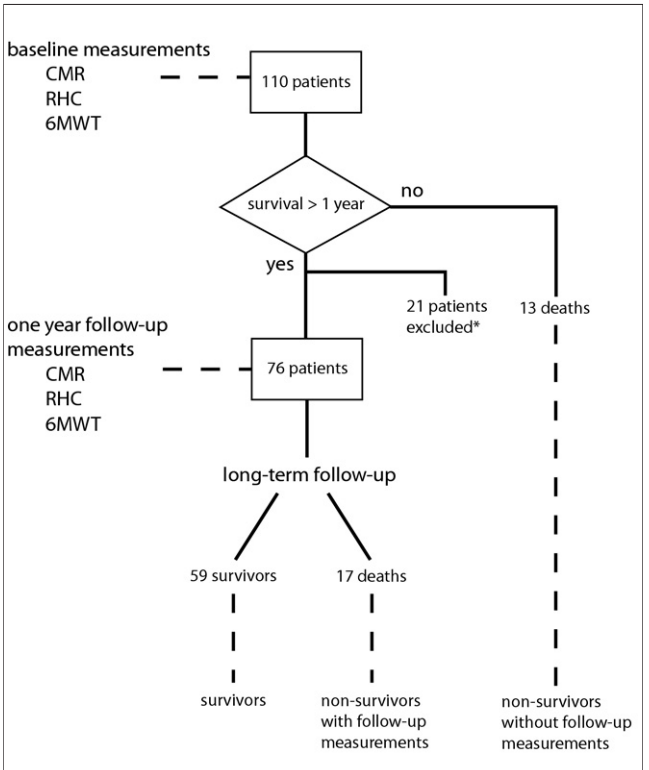

Figure 1 Study Profile

*Excluded because of a missing second right heart catheterization (RHC) (n = 7), interval between the second RHC and cardiac magnetic resonance (CMR) imaging >1 month (n = 6), incomplete CMR cines (n = 5), and insufficient CMR image quality (n = 3). 6MWT = 6-min walk test.

of 5 mm. MR parameters were: temporal resolution between 35 and 45 ms, typical voxel size 1.5 × 1.8 × 5.0 mm^3, flip angle 60°, receiver bandwidth 930 Hz/pixel, field of view 280 × 340 mm^2, repetition time/echo time 3.2/1.6 ms, and matrix 256 × 156.

During post-processing, a blinded observer analyzed the short-axis images with the MASS software package (MEDIS Medical Imaging Systems, Leiden, the Netherlands). On end-diastolic images (first cine after the R-wave trigger) and end-systolic images (cine with visually the smallest cavity area), endocardial contours of the left ventricle and RV were obtained by manual tracing. Papillary muscles and trabeculae were excluded from the cavity. Ventricular volumes were estimated using the Simpson rule. Ejection fraction was calculated as (EDV − ESV)/EDV, where EDV is end-diastolic volume and ESV is end-systolic volume. Ventricular volumes were indexed by correcting for body surface area.

Statistical analysis. Data were expressed as mean ± SD for continuous variables and absolute for categorical variables. $p < 0.05$ was considered significant. Comparisons between and within groups were calculated using unpaired and paired Student *t* tests. Correlation coefficients were calculated by the Pearson method. Univariate Cox proportional hazards analyses were applied to test the relationship between survival and selected demographic, New York Heart Association functional class, distance at 6MWT, and hemodynamic and CMR variables measured at baseline. Kaplan-Meier survival estimates were stratified by the optimal cut-off values of PVR and RVEF and compared by log-rank tests. The optimal cut-off values were identified from receiver-operating characteristic (ROC) curve analyses by taking the sum of the highest specificity and sensitivity. Bivariate Cox regression analysis was used to test the relationship between baseline RVEF and PVR and mortality. Survival was estimated from time of enrollment with cardiopulmonary death and lung transplantation as the endpoints (median period: 59 months [interquartile range (IQR): 30 to 74 months]). Other causes of death were censored. We performed a sensitivity analysis to test whether missing values influenced the results.

The follow-up analysis was performed in 76 patients after 12 months of follow-up. Univariate Cox proportional hazard analyses were performed to analyze the relationship between survival and the changes in 6MWT and selected hemodynamic and CMR variables during 1 year of follow-up. Multivariable Cox survival analyses were used to examine the independent effect of RVEF and PVR on survival after correction for potential confounders. These analyses take into account the number of events and the number of nonevents to achieve sufficient power of the test. Based on baseline RVEF and PVR and the changes in RVEF and PVR during follow-up, a backward multivariable survival

Table 1 Patient Demographics

Variable	Total Study Population (N = 110)	Population Without Follow-Up (n = 34)	Follow-Up Population (n = 76)	p Value
Age, yrs	53 ± 15	57 ± 17	50 ± 14	0.023
Female	84 (76)	21 (62)	63 (83)	0.139
Diagnosis				
Idiopathic PAH	73 (66)	19 (56)	54 (71)	0.445
Familial PAH	7 (6)	2 (6)	5 (7)	0.834
Associated PAH				
Connective-tissue disease	20 (18)	9 (26)	11 (14)	0.419
Portal hypertension	5 (5)	3 (9)	2 (3)	0.326
HIV infection	2 (2)	1 (3)	1 (1)	0.542
Drugs/toxins	3 (3)	0	3 (4)	0.550
Body surface area, m^2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.170
NYHA functional class				
I/II	53 (48)	16 (47)	37 (49)	0.222
III	51 (46)	17 (50)	34 (45)	0.217
IV	6 (6)	1 (3)	5 (7)	0.628
6MWT				
Distance, m	414 ± 135	405 ± 170	421 ± 117	0.675
Medical therapy*				
None	2 (2)	2 (6)	0	0.011
Calcium antagonists	3 (3)	2 (6)	1 (1)	0.966
Endothelin receptor antagonists	39 (35)	13 (38)	26 (34)	0.387
Phosphodiesterase inhibitor	17 (15)	7 (21)	10 (13)	0.291
Prostacyclin	15 (14)	7 (21)	8 (11)	0.251
Combination therapy	34 (31)	3 (9)	31 (41)	<0.001

Values are mean ± SD or n (%). *Refers to the period after baseline measurements.
HIV = human immunodeficiency virus; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; 6MWT = 6-min walk test.

analysis was applied to compare the prognostic values of baseline parameters with those of follow-up parameters.

Patients were considered to have a decreased PVR after a decrease of at least 15 dyne·s·cm^{-5}. In addition, according to the results of Bradlow et al. (12), a change of +3% defined an increased RVEF and a value of −3% defined a decreased RVEF. Patients with decreased PVR were dichotomized: decreased PVR + stable/increased RVEF and decreased PVR + decreased RVEF. A landmark analysis (landmark at month 12) was applied to compare survival rates of both subgroups. All statistical analyses were carried out with SPSS (version 15.0, SPSS, Inc., Chicago, Illinois).

Results

Patient characteristics. Table 1 summarizes the demographics of the study population, and Table 2 shows the hemodynamics and volume measurements. All baseline measures were obtained in treatment-naive patients with PAH. The mean age of the study population was 53 ± 15 years, 76% were female, and most patients (66%) were diagnosed as having idiopathic PAH. The time between baseline measurements and the end of the study represented a long-term median follow-up period of 59 months (IQR: 30 to 74 months). During that period, 30 patients died from cardiopulmonary causes and 2 patients underwent lung transplantation. Thirteen patients died during the first year, and 17 patients died during the median subsequent follow-up of 47 months. One patient who died during follow-up was treated as a censored case: the cause of death was given as lung cancer.

Baseline survival analyses. Table 3 shows univariate Cox regression analyses. It was found that both RVEF (hazard ratio [HR]: 0.938; 95% confidence interval [CI]: 0.902 to 0.975; p = 0.001) and PVR (HR: 1.001; 95% CI: 1.001 to 1.002; p = 0.031) were associated with survival. In addition, age and connective-tissue–disease PAH were associated with outcome. Multivariable analyses showed that RVEF and PVR remained significantly associated with survival after correction for age and type of underlying diagnosis (RVEF: HR: 0.921, 95% CI: 0.884 to 0.959, p < 0.001; PVR: HR: 1.001, 95% CI: 1.001 to 1.002, p = 0.002).

ROC curve analysis revealed that RVEF and PVR at a cut-off of 35% and 650 dyne·s·cm^{-5}, respectively, were indicators of survival (RVEF: area under the ROC curve: 0.749, p = 0.007; PVR: area under the ROC curve: 0.628, p = 0.035). Univariate Cox regression analyses based on cut-off values showed that low RVEF (HR: 0.237; 95% CI: 0.102 to 0.551; p = 0.001) and high PVR (HR: 2.296; 95% CI: 1.016 to 5.184; p = 0.046) were associated with mortality. Bivariate analysis showed that a low RVEF was independently associated with poor survival (HR: 0.260; 95% CI: 0.101 to 0.670; p = 0.005). Figure 2 shows Kaplan-Meier survival analyses based on the cut-off values of PVR and RVEF. Patients with low RVEF (groups 3 and 4) had significantly poorer prognosis compared with patients with high RVEF (groups 1 and 2), regardless of their PVR (Fig. 2C). Bivariate Cox regression analysis applied to the combination of the binary values of RVEF and PVR showed that the patients with high RVEF/high PVR (group 2) did not have a different prognosis compared with the

Table 2 Baseline Hemodynamics and Volume Measurements

Variable	Baseline Population (N = 110)	Population Without Follow-Up (n = 34)	Follow-Up Population (n = 76)	p Value
Hemodynamics				
mPAP, mm Hg	49 ± 16	47 ± 17	50 ± 16	0.474
mRAP, mm Hg	7 ± 5	6 ± 5	7 ± 4	0.623
PCWP, mm Hg	7 ± 4	8 ± 4	7 ± 4	0.220
PVR, dyne·s·cm^{-5}	745 ± 432	720 ± 513	772 ± 384	0.463
CO, l/min	5.1 ± 1.9	5.2 ± 2.4	4.9 ± 1.3	0.444
Cardiac index, l/min/m^2	2.8 ± 1.0	2.8 ± 1.3	2.7 ± 0.7	0.325
Heart rate, beats/min	82 ± 14	80 ± 16	85 ± 16	0.313
SvO_2, %	66 ± 9	65 ± 10	66 ± 8	0.727
CMR measurements				
RVEDVI, ml/m^2	71 ± 23	69 ± 22	72 ± 24	0.611
RVESV, ml/m^2	47 ± 21	45 ± 18	48 ± 22	0.709
RVEF, %	36 ± 11	38 ± 12	35 ± 10	0.160
LVEDVI, ml/m^2	42 ± 14	45 ± 18	41 ± 13	0.268
LVESVI, ml/m^2	15 ± 9	16 ± 12	14 ± 7	0.364
LVEF, %	67 ± 10	68 ± 10	66 ± 10	0.323
SVI, ml/m^2	28 ± 9	30 ± 11	27 ± 8	0.133

Values are mean ± SD.

CMR = cardiac magnetic resonance; CO = cardiac output; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume index; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistance, RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index, SVI = stroke volume index, SvO_2 = mixed venous oxygen saturation.

Table 3 Univariate Cox Regression Analyses of Baseline Variables

Variable	Baseline Population (N = 110) Hazard Ratio	95% CI	p Value
Age, yrs	1.027	1.001–1.052	0.040
Sex			
Male	1.000		
Female	0.789	0.323–1.926	0.603
Diagnosis			
Idiopathic PAH	2.064	0.866–4.238	0.163
Familial PAH	0.982	0.862–1.119	0.784
Associated PAH			
Connective-tissue disease	0.306	0.143–0.654	0.002
Portal hypertension	0.364	0.086–1.544	0.170
HIV infection	0.876	0.545–1.408	0.585
Drugs/toxins	0.726	0.099–5.342	0.753
6MWT			
Distance, m	0.993	0.990–0.997	<0.001
Hemodynamics			
mPAP, mm Hg	0.998	0.976–1.020	0.850
mRAP, mm Hg	1.048	0.981–1.120	0.167
PCWP, mm Hg	0.986	0.898–1.082	0.761
PVR, dyne·s·cm^{-5}	1.001	1.001–1.002	0.031
CO, l/min	0.669	0.483–0.928	0.016
Cardiac index, l/min/m^2	0.560	0.323–0.970	0.039
Heart rate, beats/min	1.014	0.989–1.039	0.274
SvO_2, %	0.936	0.900–0.972	0.001
CMR measurements			
RVEDVI, ml/m^2	1.011	0.996–1.024	0.121
RVESVI, ml/m^2	1.014	1.001–1.027	0.048
RVEF, %	0.938	0.902–0.975	0.001
LVEDVI, ml/m^2	0.962	0.931–0.994	0.019
LVESVI, ml/m^2	0.942	0.888–0.998	0.045
LVEF, %	0.998	0.960–1.036	0.900
SVI, ml/m^2	0.945	0.899–0.993	0.025

CI = confidence interval; other abbreviations as in Tables 1 and 2.

patients with high RVEF/low PVR (group 1) (p = 0.579). Patients with low RVEF/low PVR (group 3) had similar prognosis compared with patients with low RVEF/high PVR (group 4) (p = 0.830). In addition, patients of group 3 and patients of group 4 had 5.2 times greater HRs compared with high RVEF/low PVR patients (group 1) (p < 0.01).

Table 4 Differences Between Characteristics at Baseline and at 12-Month Follow-Up

Variable	Follow-Up Population (n = 76) Baseline	Follow-Up	P value
6MWT			
Distance, m	421 ± 117	425 ± 139	0.727
Hemodynamics			
mPAP, mm Hg	50 ± 16	47 ± 16	0.176
mRAP, mm Hg	7 ± 4	7 ± 5	0.557
PCWP, mm Hg	7 ± 4	7 ± 4	0.966
PVR, dyne·s·cm^{-5}	772 ± 384	660 ± 378	0.003
CO, l/min	4.9 ± 1.3	5.4 ± 2.4	0.032
Cardiac index, l/min/m^2	2.7 ± 0.7	3.0 ± 1.2	0.026
Heart rate, beats/min	85 ± 16	83 ± 12	0.182
SvO_2, %	66 ± 8	65 ± 10	0.641
CMR measurements			
RVEDVI, ml/m^2	72 ± 24	76 ± 32	0.099
RVESVI, ml/m^2	48 ± 22	51 ± 30	0.167
RVEF, %	35 ± 10	36 ± 13	0.413
LVEDVI, ml/m^2	41 ± 13	43 ± 14	0.374
LVESVI, ml/m^2	14 ± 7	14 ± 8	0.965
LVEF, %	66 ± 10	67 ± 10	0.267
SVI, ml/m^2	27 ± 8	29 ± 8	0.224

Values are mean ± SD.
Abbreviations as in Tables 1 and 2.

Changes with follow-up. After a median period of 12 months (IQR: 10 to 16 months) of PAH-specific medical treatment, pulmonary pressures remained almost unaltered, whereas PVR was significantly decreased. In addition, cardiac index was improved and the 6MWT was stable. No other changes in cardiac functional parameters were observed (Table 4). Furthermore, with respect to the effects of

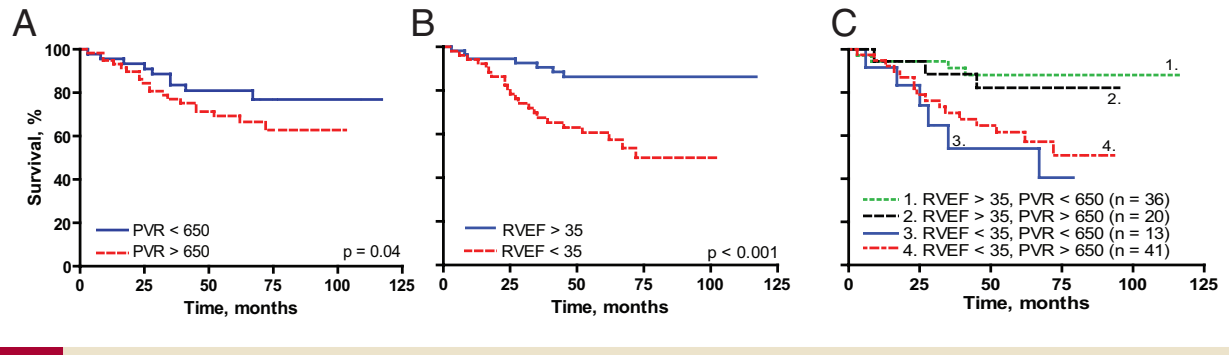

Figure 2 Survival Rates of Patients With PAH Stratified According to PVR and RVEF at Baseline

(A) Patients with pulmonary vascular resistance (PVR) <650 dyne·s·cm^{-5} showed better survival rates than patients with PVR >650 dyne·s·cm^{-5} (p = 0.04). **(B)** Patients with right ventricular ejection fraction (RVEF) >35% showed better survival rates compared with patients with RVEF <35% (p < 0.001). **(C)** Survival rates based on the coupling of PVR and RVEF. PAH = pulmonary arterial hypertension.

Table 5 Differences Between Different Classes of Medical Therapies (n = 76)

Variable*	Endothelin Receptor Antagonists (n = 26)	Phosphodiesterase Inhibitors (n = 10)	Prostacyclins (n = 8)	Combination Therapy (n = 31)	p Value
Changes in PVR, dyne·s·cm^{-5}	−133 ± 315	−33 ± 271	95 ± 201	−180 ± 271	0.311
Changes in RVEF, %	1 ± 8	−1 ± 6	−3 ± 10	2 ± 9	0.360

Values are mean ± SD. *One patient was treated with calcium antagonists and was not included in the analysis.
Abbreviations as in Table 2.

the different classes of drugs, we found no significant differences between groups (Table 5).

Follow-up survival analyses. Changes in PVR correlated moderately with changes in RVEF (R = 0.330; p = 0.005) (Fig. 3). PVR decreased in both survivors (−121 ± 297 dyne·s·cm^{-5}) and nonsurvivors (−132 ± 432 dyne·s·cm^{-5}) (p = 0.927). Changes in RVEF differed significantly between survivors (+3% ± 9%) and nonsurvivors (−5% ± 6%) (p < 0.001) (Fig. 4). Similar results were found for the relative changes in PVR (survivors −13%, nonsurvivors −11%; p = 0.765) and relative changes in RVEF (survivors +10%, nonsurvivors −20%; p < 0.001). Changes in PVR were not associated with outcome (HR: 1.000; 95% CI: 0.998 to 1.001; p = 0.820), whereas changes in RVEF were independently related to mortality (HR: 0.929; 95% CI: 0.875 to 0.985; p = 0.014). Table 6 shows univariate analyses of changes in hemodynamic and CMR variables during follow-up. After correction for age and connective-tissue–disease PAH, changes in RVEF remained significantly associated with survival (HR: 0.928; 95% CI: 0.870 to 0.991; p = 0.026).

A backward multivariable survival analysis based on baseline RVEF and PVR and the changes in RVEF and PVR showed that baseline RVEF and the changes in RVEF during follow-up had similar prognostic value (baseline RVEF: HR: 0.926, 95% CI: 0.876 to 0.978, p = 0.006; changes in RVEF: HR: 0.909, 95% CI: 0.846 to 0.976, p = 0.009).

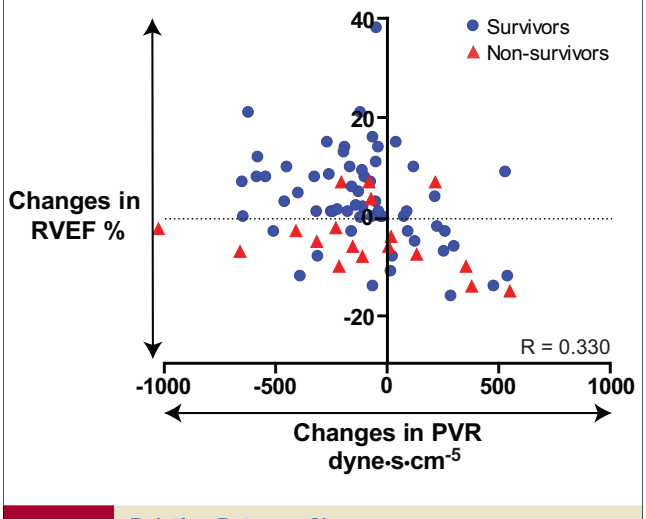

Figure 3 Relation Between Changes in PVR and Changes in RVEF

Changes in PVR were moderately correlated with changes in RVEF (R = 0.330; p = 0.005). Abbreviations as in Figure 2.

In total, 52 patients (68%) showed a significant decrease in PVR after therapy and were included in the landmark analysis. In this group, patients with a decreased RVEF had significantly poorer survival than patients with stable/increased RVEF (p < 0.001) (Fig. 5). Both groups had a similar decrease in PVR (mean −284 ± 248 dyne·s·cm^{-5}; difference in PVR p = 0.437). We observed no differences in the baseline characteristics that could account for a different RV response to a similar decrease in PVR (Online Table A1). Online Table A2 shows the characteristics of both groups after follow-up.

Thirteen patients did not survive the first year and therefore did not undergo follow-up measurements. The nonsurvivors without follow-up measurements showed similar characteristics to the 17 nonsurvivors with follow-up measurements (Online Table A3).

Discussion

Our study shows that in a large group of World Health Organization group 1 patients with PAH on PAH-targeted therapies, RVEF measured at baseline was a better predictor of mortality than PVR. Changes in RVEF after 12 months predicted long-term outcome, whereas changes in PVR did not. In addition, we found that changes in PVR were moderately related to changes in RVEF and that after medical therapy, RV dysfunction could progress despite a decrease in PVR.

Significance of baseline parameters. In accordance with previous studies, we showed that RVEF as assessed by CMR imaging had a strong prognostic value (13,14). Kawut et al. (15) showed that RVEF was an independent predictor of long-term outcome. In correspondence with earlier studies, we found that baseline PVR was a prognostic predictor (3,4). However, we showed that although a high PVR at baseline was associated with outcome, the prognosis was primarily determined by RVEF. Previously, Ghio et al. (16) found similar results in patients with pulmonary hypertension secondary to left heart disease.

Effects of medical therapies. Thus far, only a few studies have studied the therapeutic effects on changes in PVR and RV function. It was previously shown by Roeleveld et al. (17) that epoprostenol therapy lowered PVR but did not affect RV dilation and hypertrophy. Chin et al. (18) reported that although bosentan reduced PVR, it did not

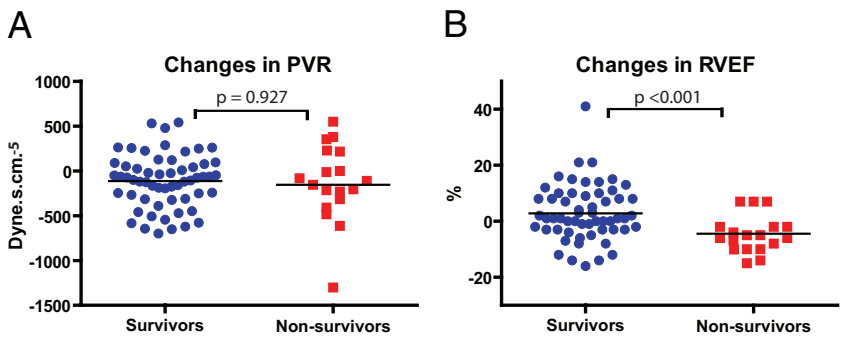

Figure 4 Changes in PVR and RVEF After 12 Months of Follow-Up According to Survival

(A) Changes in PVR did not differ between survivors **(blue)** and nonsurvivors **(red). (B)** Survivors **(blue)** showed increased RVEF, whereas nonsurvivors **(red)** showed decreased RVEF during follow-up. Abbreviations as in Figure 2.

affect either RVEF or RVEDV. Wilkins et al. (19) showed that RV mass decreased after sildenafil treatment and remained stable after bosentan therapy. A randomized clinical trial by Galie et al. (20) showed that bosentan treatment was associated with improvement in RV systolic function as assessed by the RV Doppler index. The last 2 studies cited did not include hemodynamic measures in the analyses. Although the former studies analyzed treatment effects in patients with PAH, the relationship between changes in load and RV function was not been quantified.

The majority of patients in our cohort (68%) had reduced PVR after medical treatment. However, the reduction in PVR was modest (−12%) and mPAP remained almost unaltered (−5%). Despite the small patient groups, we found nonheterogeneity in the effects among different classes of medical treatment. These results are in correspondence with meta-analyses of randomized controlled trials showing moderate reductions in PVR and only small reductions in mPAP over an average study duration of 14 weeks (9). Furthermore, our results agreed with the findings of previous studies reporting lowered PVR (ranging from −11% to −39%) after a long-term treatment period (21–26).

Significance of follow-up parameters. Our results on PVR showed that although this parameter measured at baseline was of prognostic significance, a change over time of this parameter was not. However, we cannot conclude from this result that a change in PVR is not important. It was found in an earlier study that PVR reduction will lead to an improvement in survival only if reduced to more than 30% (25). Because this was the case in a minority of our patients, no conclusions can be made whether a larger

Table 6 Univariate Survival Analyses of Changes in Follow-Up Variables

Variable	Follow-Up Population (n = 76) Hazard Ratio	95% CI	p Value
Changes in 6MWT			
Distance, m	0.996	0.989–1.003	0.239
Changes in hemodynamics			
mPAP, mm Hg	1.013	0.975–1.053	0.504
mRAP, mm Hg	1.050	0.945–1.167	0.360
PCWP, mm Hg	1.027	0.944–1.118	0.530
PVR, dyne·s·cm^{-5}	1.000	0.998–1.001	0.820
CO, l/min	0.811	0.619–1.062	0.128
Cardiac index, l/min/m^2	0.705	0.443–1.123	0.141
Heart rate, beats/min	0.986	0.950–1.024	0.475
SvO_2, %	0.965	0.911–1.096	0.314
Changes in CMR measurements			
RVEDVI, ml/m^2	1.029	1.013–1.045	<0.001
RVESVI, ml/m^2	1.036	1.018–1.053	<0.001
RVEF, %	0.929	0.875–0.985	0.014
LVEDVI, ml/m^2	0.928	0.937–1.014	0.179
LVESVI, ml/m^2	0.971	0.909–1.037	0.377
LVEF, %	0.988	0.947–1.031	0.576
SVI, ml/m^2	0.928	0.843–1.015	0.110

Abbreviations as in Tables 1, 2, and 3.

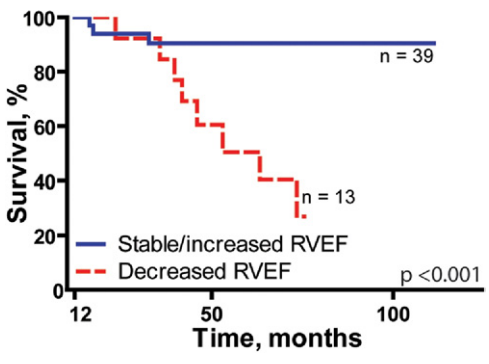

Figure 5 Landmark Analysis

Landmark analysis at month 12 of 52 patients with decreased PVR after therapy. Patients with stable/increased RVEF (n = 39) had better survival rates than patients with decreased RVEF (n = 13) (p < 0.001). Abbreviations as in Figure 2.

reduction in PVR would lead to an improved survival in our study.

In the present study, we showed that the changes in RVEF during follow-up had similar prognostic value in comparison with baseline RVEF. In addition, a previous study of our group found that the changes in stroke volume index and RV and left ventricular volumes were associated with mortality (13). The results of both studies suggest that follow-up parameters may provide important prognostic insights.

The paradox of progressive RV dysfunction despite decreased PVR. We found that the changes in RVEF were moderately correlated to the changes in PVR. The most important finding of this study was that in 25% of the patients with reduced PVR, RV function deteriorated further after follow-up. We showed that the group with deteriorating RV function had a poor outcome. This deterioration was not explained by the PVR because the reduction in PVR occurred to a similar extent in patients with improving and deteriorating RVEF.

RV load consists of peripheral resistance, arterial compliance and characteristic impedance of the proximal pulmonary artery. In previous studies of our group (27,28), it was shown that resistance and compliance are inversely related (resistance = constant × 1/compliance). As a consequence, compliance is strongly correlated to PVR (= peripheral resistance + characteristic impedance), and therefore, we do not think that compliance can explain additional variance in relation to RVEF. Recently, we showed that RV total power (associated with total load [i.e., compliance and PVR]) and mean power (associated with nonpulsatile load [i.e., PVR]) are proportional (29). These findings emphasized that PVR is a valid reflection of the load on the RV.

The moderate correlation between PVR and RVEF indicated that RV function does not fully adapt to changes in vascular properties, as is expected in healthy individuals due to "coupling" of the heart and arterial functions. Therefore, we expected that other factors play an important role in the changes in RVEF over time. Kawut et al. (30) showed that older age, male sex, and higher level of von Willebrand factor were associated with lower RVEF. We speculate that genetic differences in RV adaptation to pressure overload (2) and possible direct effects of current PAH treatments on the heart are responsible for different RV responses. In addition, we hypothesize that the deterioration in RV function might possibly be explained by an important physiological principle: ventricular wall tension. The current results showed that despite a reduction in PVR, pulmonary pressures were unaltered after medical treatment; consequently, ventricular wall tension will remain unchanged (31). If wall tension is the driving force for the RV to fail, therapies will not prevent the failure if failing conditions were already present at baseline.

Implications. Here we showed that changes in PVR as accomplished by currently available therapies do not prevent RV deterioration in 25% of the patients. Therefore, because RV function is the primary determinant of prognosis, it is important to analyze the factors that predict RV dysfunction.

It has been shown that larger reductions in PVR and mPAP (e.g., after lung transplantation or endarterectomy) can result in improved RV function. We therefore consider that a medical treatment strategy that is more effective at onset could have a more pronounced effect on patient outcome. Furthermore, understanding the pathways that underlie RV failure could lead to the development of strategies that are directly targeted at improving RV function.

Study limitations. A limitation of this study is that RHC and CMR measurements could not be obtained simultaneously, which may have potentially resulted in measurements in different hemodynamic states. However, the median time between CMR imaging and RHC was 2 days; therefore, it was unlikely that the delay affected our conclusions.

In addition, because our study required follow-up measurements, patients who died between baseline and follow-up measurements could not be included in the follow-up analyses (immortal time bias) (32). However, we observed no differences in baseline characteristics between the nonsurvivors without follow-up measurements and the nonsurvivors with follow-up measurements.

Conclusions

In PAH, baseline RVEF was a stronger prognostic predictor than baseline PVR. Changes in PVR after follow-up were moderately correlated with changes in RVEF. Moreover, this study showed that in the presence of PAH, right heart dysfunction may progress despite a reduced PVR by PAH-targeted medical therapies. A deterioration of RV function was associated with poor outcome, irrespective of any changes in PVR.

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Key Words: hemodynamics ■ magnetic resonance imaging ■ pulmonary arterial hypertension ■ right ventricular function ■ survival.

APPENDIX

For the supplementary tables, please see the online version of this article.