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ORIGINAL RESEARCH

Assessment and Prognostic Impact of Right Ventricular Function in Patients with Pulmonary Arterial Hypertension Undergoing Pulmonary Artery Denervation: Central Role of Global Right Ventricular Longitudinal Peak Systolic Strain

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ABSTRACT

Background: Echocardiographic right ventricular (RV) functional parameters and longitudinal peak systolic strain (LS) are important determinants of prognosis in patients with pulmonary arterial hypertension (PAH). Pulmonary artery denervation (PADN) has been shown to reduce pulmonary artery pressures (PAP) in PAH. Whether this results in improved RV function is unknown. We therefore sought to evaluate serial changes in RV function and clinical outcomes after PADN, and determine the role of baseline RV-LS as a prognostic tool.

Methods: Between March 2014 and March 2016, 40 patients with PAH who underwent PADN were studied. RV function was evaluated at baseline, 1 week, 3 months, 6 months, and >1 year after PADN, and correlations between RV-LS, RV functional parameters, 6-minute walk distance (6MWD), and pulmonary vessel resistance (PVR) were examined. Receiver operating characteristic curve analysis was used to determine the optimal baseline RV-LS cutoff value to predict PADN responder status, and prognosis was assessed in these groups.

Results: PADN resulted in sustained changes in PVR and RV-LS over time (mean follow-up of 763 ± 254 days). By multivariate analysis, baseline RV-LS was the only independent predictor of ΔmPAP (β = −0.736, $p = 0.001$) and ΔPVR (β = −0.076, $p = 0.03$), and significantly correlated with 6MWD ($r = -0.586$, $p < 0.001$) at the end of follow-up. Baseline RV-LS ≥ −11.3% had a sensitivity of 78.1% and a specificity of 75.0% for predicting non-responders to PADN. During follow-up there were 10 (25%) PAH-related events, including 4 (10%) cardiac deaths. PAH-related events after PADN were more frequent in patients with RV-LS ≥ −11.3% vs. < −11.3% (46.2% vs. 14.8%, $p = 0.03$).

Conclusions: PADN results in sustained improvements in PVR and RV-LS. Baseline RV-LS is the strongest predictor of improved hemodynamic measures after PADN in patients with PAH, and is strongly associated with late 6MWD and prognosis. Specifically, baseline RV-LS ≥ −11.3% predicts non-responder status and PAH-related events after PADN, and thus may be useful to identify which PAH patients may benefit from the PADN procedure.

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KEYWORDS Clinical event; longitudinal peak systolic strain; pulmonary arterial hypertension; pulmonary artery denervation; right ventricle

Introduction

Pulmonary arterial hypertension (PAH) is an incurable disease of the pulmonary arterial tree, which leads to progressive right ventricular (RV) failure and premature death.[1] Because RV function plays a critical role in the prognosis of patients with PAH, measurement of RV function is essential to assess disease progression and to guide therapeutic decision-making.[1,2] RV function can be assessed with invasive and non-invasive imaging. Invasive right heart catheterization (RHC) allows direct assessment of right atrial (RA) pressure,[3] cardiac index,[4] and mean pulmonary arterial pressure (mPAP),[5] all of which have prognostic utility. However, serial RHC is not always practical. Alternatively, non-invasive assessment of RV volumes, pressures and function by echocardiography is globally accepted as prognostically useful.[1–6] In this regard, global RV longitudinal peak systolic strain (RV-LS) has been strongly correlated with clinical outcomes in patients with RV failure and has been recommended as a preferred prognostic parameter.[7–9]

We have previously reported the results of pulmonary artery denervation (PADN) in patients with PAH poorly responsive to medications, specifically demonstrating improved 3-month hemodynamic in patients with idiopathic PAH[10] and favorable 1-year clinical outcomes in patients with PAH of mixed etiologies.[11] Important unanswered issues include: (1) identifying which patients will respond to PADN; and (2) whether RV function improves after PADN. We therefore performed serial analysis of echocardiography-determined RV function and RV-LS in order to identify the correlation between RV function and hemodynamic parameters, and clinical outcomes before and after PADN treatment.

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Materials and methods

Study population

Between March 2014 and March 2016, 40 patients with Group I PAH,[1] poorly responsive to systemic medications who underwent PADN and had analyzable baseline echocardiographic images were included in this analysis (Figure 1). All patients were symptomatic, had been treated with maximally tolerated doses of at least one standard PAH medication within, had a rest mPAP ≥25 mmHg, and pulmonary capillary wedge pressure (PCWP) <15 mmHg. This cohort included five patients reported in previous publications[11] and 35 newly treated patients. Six additional group I PAH patients that underwent PADN did not have echocardiograms of sufficient quality for the present study, and were not included in this study. All patients provided informed written consent. This study was approved by the Nanjing Medical University & Nanjing First Hospital Institutional Review Board, and all patients provided informed consent.

Echocardiography

All echocardiographic studies were acquired at 40–90 frames/s with a commercially available echocardiography system equipped with a 3.5-MHz transducer (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway). Routine digital grayscale 2D and tissue Doppler cine loops were obtained at end-expiration from apical and parasternal views. All echocardiographic examinations were performed on the same day of RHC or performance of 6-minute walk distance (6MWD). Follow-up echocardiography was performed in patients at different time points (Figure 1).

Echocardiographic parameters of RV function were measured and calculated as previously described.[2] RV functional parameters included 3D RV ejection fraction (RVEF), tricuspid annulus plane systolic excursion (TAPSE), RV myocardial performance index (MPI), pulmonary artery (PA) acceleration time (PAAT), RV outflow tract velocity-time integral (RVOT VTI), systolic myocardial velocity (SMV), RV dp/dt, RV E', and RV E/E'.

For calculation of 3D RV volumes and EF, a fully sampled matrix-array transducer with almost 3000 active elements (4V-D; GE Vingmed Ultrasound AS) was used to acquire real-time 3D echocardiographic images in the apical four-chamber, two-chamber, and long-axis views. Acquisitions were recorded at the apex at a mean volume rate of ≥30 volumes/sec with multibeat acquisition to obtain correct spatial registration of all subvolumes and optimal temporal-spatial resolution. Within a single breath-hold lasting 6–8 sec and during a constant RR interval, four to six wedge-shaped subvolumes were required to acquire a full-volume data set. In patients with permanent atrial fibrillation, two or four cardiac cycles with ratios of the preceding to the preceding interval (RR1/RR2) of approximately 1 were acquired for data set selection. Acquired 2D and 3D data were digitally transferred to a separate workstation for offline analysis of ventricular volumes using EchoPAC BT08, GE Vingmed Ultrasound AS.

Echocardiographic measurements were performed by one of the authors (JPS) blinded to RHC and clinical data. Offline analysis was performed by a single experienced reader (ZJ), and analysis was confirmed by a separate experienced reader

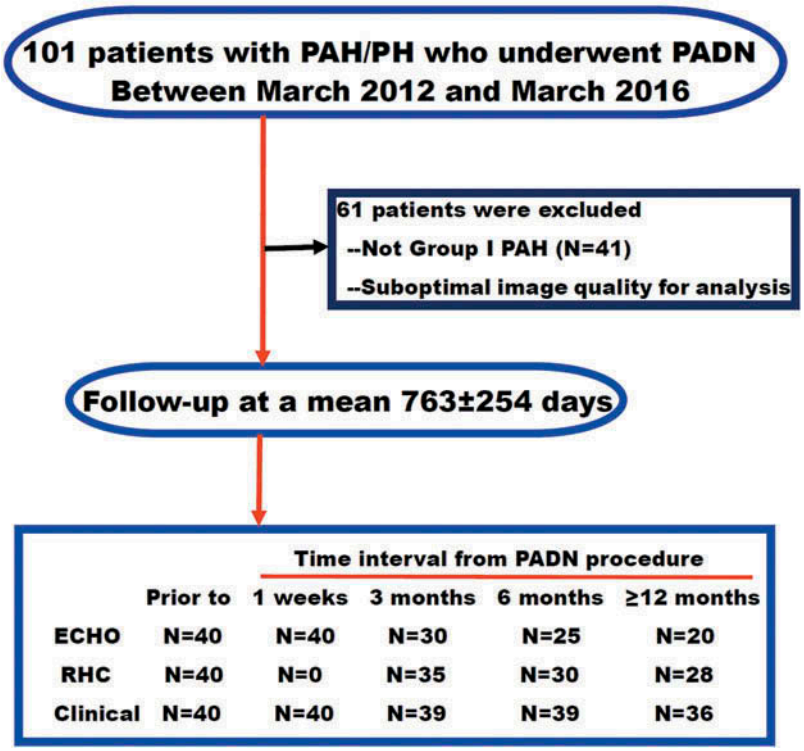

Figure 1. Study flowchart. A total of 40 patients with Group I PAH and echocardiographic images acceptable for detailed quantitative analysis were included in the present study.

(SJP). Intra-observer variability for conventional echocardiographic parameters was 2 ± 6% and inter-observer variability for RV-LS analysis was 1±7% (percentage mean difference [bias] ± coefficient of variation).

Global right ventricular longitudinal peak systolic strain

Only baseline echocardiographic images that provided appropriate tracking in all segments were used for this analysis (n = 40). Two-dimensional speckle-tracing echocardiographic analysis was performed from the RV-focused four-chamber view. Measurements were performed offline using dedicated software (EchoPAC version BTO8, GE Vingmed Ultrasound AS). A region of interest was traced on the endocardium at end-diastole in the RV from the modified apical four-chamber view. A larger region of interest was then generated and manually adjusted near the epicardium. Special care was taken to fine-tune the region of interest, using visual assessment during cine loop playback, to ensure that segments were tracked appropriately. The RV was divided into three layers (endothelial, middle, and epicardial), six standard segments (at the basal, middle, and apical level), and six corresponding time-strain curves were generated. Longitudinal speckle-tracking strain at the global RV, RV-free wall, and RV-septal wall on the endothelial layer was calculated by averaging each of regional peak systolic strains along the entire RV and analyzed in this study.

Right heart catheterization

Resting RA pressure, RV pressure, PAP, pulmonary artery occlusion pressure (PAOP), and thermodilution cardiac output (CO) were obtained with a 7 French flow-directed Swan-Ganz catheter. Pulmonary vessel resistance (PVR; [mPAP − PAOP]/CO) was then derived. All measurements were taken at end-expiration. If the PAOP measurement was unreliable, the LV end-diastolic pressure was used instead.[10,11] Blood samples from the right atrium (RA), RV, and PA were obtained, and if the oxygen saturation measurements varied by >7% between chambers, further sampling was performed to identify the location of an intra-cardiac shunt.

PADN procedure

PA ablation was performed using a dedicated 7 French temperature-sensing ablation catheter as previously described.[10,11] Briefly, PADN was performed in the peri-conjunctional area between the distal main trunk and the ostial left branch. The following ablation parameters were programmed at each point: temperature ≥45°C, energy ≤20 W, and time 120–240 seconds. The procedure was interrupted for 10 seconds if the patient reported severe chest pain. Electrocardiography and hemodynamic parameters were monitored and recorded continuously throughout the procedure.

Peri-procedural medications

A 5000 U IV heparin bolus was administered after the insertion of the venous sheath. Additional 2000–3000 U IV heparin boluses were administered if the procedural time was >1 h. Following the procedure, oral warfarin was prescribed and adjusted to an international normalized ratio of 1.5–2.5 in all patients. If contraindications to warfarin were present, aspirin (100 mg/d) and clopidogrel (75 mg/d) were prescribed indefinitely. Immediately after the PADN procedure, all target drugs (endothelial-receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin analogs) were discontinued. Diuretics were prescribed at a dosage less than or equal to that at baseline. Chronic oxygen therapy was used per physician discretion.

Follow-up

Patients were monitored in the critical care unit for at least 24 hours post-procedure. Hemodynamic measurements, 6MWD, and echocardiographic measurements were repeated at the intervals shown in Figure 1. Blood samples were obtained to measure N-terminal pro-brain natriuretic peptide (NT-proBNP) levels prior to each exercise test.

Definitions

PAH-related clinical events were defined as those caused by worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, atrial septostomy, or all-cause mortality. Worsening of PAH was defined as the occurrence of all three of the following: ≥15% decrease in 6MWD from baseline, confirmed by a second 6MWD performed on a different day within 14 days; worsening PAH symptoms; and the need for additional treatment(s) for PAH. Worsening PAH symptoms were defined as a change from baseline to a higher WHO functional class (or no change in WHO functional class IV from that at baseline) plus the appearance of or worsening signs of right heart failure not responsive to oral diuretic therapy. An independent clinical events committee adjudicated all deaths and events for their relationship to PAH. Additional secondary endpoints included changes in 6MWD, WHO functional class, NT-proBNP levels, PAH-related and all-cause mortality, echocardiographic measurements, and rehospitalization for PAH. The pre-specified definition of PADN procedural hemodynamic success was reduction in mPAP or sPAP immediately after PADN by ≥10%, without the occurrence of any intra-procedural complications.

Statistical analysis

Continuous variables are expressed as mean ± SD. Normality was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Data having unequal variances at different times were log transferred for comparison. Differences in continuous variables over time were analyzed with paired t tests. Proportional differences were evaluated using Fisher's exact tests or Chi-squared tests as appropriate. Univariate linear correlation analysis was used for comparison of echocardiographic data, RHC data and 6MWD. Multiple linear regression analysis with stepwise selection was performed to determine independent predictors of the change in hemodynamic measures and 6MWD over time.

PADN responders were defined as those with a ≥10% acute reduction in mPAP. Multivariable regression analysis was then

performed to identify the correlates of non-responder status. A receiver operating characteristic (ROC) curve identified the optimal baseline RV-LS cut-off value to predict non-responder status, and the area under the curve (AUC) was obtained for the calculation of sensitivity and specificity. Patients were classified as high-risk vs. low-risk according to this RV-LS cut-off value, and this categorization was examined for its relationship with long-term PAH-related events. Event rates during follow-up were estimated using the Kaplan-Meier method and compared with the log-rank test. A Cox proportional hazards model was calculated to identify independent determinants of PAH-related events. For the Cox model, baseline variables that were of clinical relevance or reached a significance level of $p < 0.10$ in Tables 1 and 2 were included. Stepwise inclusion and exclusion techniques selected the optimal model, with model fit assessed using Harrell's C-statistic and the Chi-squared test. Results were presented as hazard ratio (HR) with 95% confidence intervals. Statistical significance was defined as a two-sided p value <0.05. All analyses were performed with SPSS 16.0 (SPSS Institute Inc., Chicago, IL, USA).

Results

Patient population and baseline characteristics

The study consisted of 40 patients (average age, 43 years old) with Group I PAH (75% female, average symptomatic duration of 3.5 years; Table 1). WHO functional class III and IV was present in 34 patients (85%). PAH was classified as idiopathic in 25 patients (62.5%), as secondary to connective tissue disease in 10 patients (25%), and due to congenital heart disease after surgical repair (mean 5.2 years after surgery) in 5 patients (12.5%). Combination PAH drug therapy was prescribed in 20 (50%) of patients and single drug therapy in 19 patients (47.5%); 1 (2.5%) patient was not tolerant of any PAH medication. Mean baseline plasma concentration of NT-proBNP was 4917 pg/L (range 1025–17,028 pg/L).

Table 1. Baseline characteristics of the study population.

Variables	Values
Clinical	
Women, *n* (%)	30 (75.0)
Age, years	43 ± 14
Body mass index (kg/m^2)	37.5 ± 1.8
Heart rate (bpm)	79 ± 18
Systolic blood pressure (mmHg)	116 ± 13
Diastolic blood pressure (mmHg)	73 ± 10
Symptom duration, years (range)	3.5 (1.2–6.3)
WHO functional class, *n* (%)	
I	2 (5.0)
II	4 (10.0)
III	25 (62.5)
IV	9 (22.5)
6-minute walk distance (m)	347 ± 121
PAH etiology, n (%)	
Idiopathic PAH	25 (62.5)
Connective tissue disease related	10 (25.0)
Congenital heart disease after operation	5 (12.5)
Medications, n (%)	
Warfarin	3 (7.5)
Diuretics	16 (40.0)
Calcium blockers	2 (5.0)
Endothelin receptor antagonist	26 (65.0)
PDE_5 inhibitor	22 (55.0)
Prostacyclin	18 (45.0)
Combination therapy	20 (50.0)
None	1 (2.5)
NT-proBNP (pg/L) (range)	4917 (1025–17028)

Note. PAH, pulmonary arterial hypertension; ERA, endothelin receptor antagonist; PDE, phosphodiesterase; NT-proBNP, N-terminal pro brain natriuretic peptide.

Baseline echocardiography (Table 2) demonstrated severe RV systolic and diastolic dysfunction compared to accepted normal measures:[12] RVEF (19% observed vs. >45% normal), MPI (0.8 vs. <0.54), PAAT (62 ms vs. >105 ms), dp/dt (86 vs. >400), E/E' (7.5 vs. <6), SMV (4.2 m/s vs. >9.5 m/s), and TAPSE (13 mm vs. >15 mm).[12] RV-LS was significantly decreased (mean −13.8 ± 3.3%; Table 2), particularly in the free wall (−12.3 ± 2.6%) compared with the septal segment (−14.8 ± 3.5%, $p = 0.02$). Patients also had low cardiac output and increased mPAP (mean 60 ± 9 mmHg), with high PVR (mean 17 ± 5 Woods units (WU); Table 2). Baseline 6MWD was also decreased (mean 348 ± 130 m).

Serial measures of echocardiographic and hemodynamic measurements and 6MWD after PADN

PADN was successfully performed in all 40 patients without intra-procedural complications. The PADN procedure resulted in an average reduction of 12% in mPAP and sPAP immediately after intervention. mPAP and sPAP were significantly decreased 6 months after the procedure, but were no longer significantly decreased at last follow-up (mean 763 ± 254 days; Table 2). In contrast, PVR on RHC was reduced immediately after PADN, and this reduction was sustained through latest follow-up. Most parameters of RV systolic function were improved at 1 week and 3–6 months after PADN treatment. However, these improvements were not sustained at long-term follow-up. Conversely, RV-LS was improved significantly at each time period (Table 2).

Correlation between RV-LS, RV functional variables, hemodynamic measurements and 6MWD

Baseline RV-LS was well correlated with RV functional parameters (E/E', RVOT VTI, and TAPSE) and PVR by RHC (Table 3). Multivariate analysis revealed that RV-LS and RV MPI were independent predictors of ΔmPAP ($\beta = -0.736$, $p = 0.001$, and $\beta = -0.853$, $p < 0.001$) and ΔPVR ($\beta = -0.076$, $p = 0.03$, and $\beta = -0.041$, $p < 0.001$) after PADN. RV-LS was the only baseline parameter which significantly correlated (negatively) with 6MWD at the end of the study ($r = -0.586$, $p < 0.001$, Table 3 and Figure 2A [central illustration]).

Baseline echocardiographic predictors of acute PADN non-responders

Four patients (10%) were non-responders (reduction of mPAP <10% post-PADN). By multivariable analysis baseline RV-LS was the only independent predictor of non-responder status (HR 5.66, 95% CI 2.11–18.65, $p = 0.001$). By ROC curve analysis (Figure 2B [central illustration]), the optimal cut-off value of baseline RV-LS was −11.3%, providing sensitivity of 83.3%, specificity of 76.5% and an AUC of 0.85 (95% CI 0.70–0.99, $p = 0.007$) of predicting non-responder status to PADN.

Patients with baseline RV-LS ≥ −11.3% had more severely abnormal baseline values of TAPSE, RVOT VTI, E/E', RV MPI, and PVR than patients with RV-LS < −11.3% (Table 4, Figure 3).

Table 2. Changes in RV function and longitudinal strain, hemodynamic measures, and 6MWD after PADN at different time intervals (paired measures).

	1-week follow-up (n = 40)			3-month follow-up (n = 30)			6-month follow-up (n = 25)			≥12-month follow-up (n = 20)		
Variables	Baseline	1-week	p	Baseline	3-m	p	Baseline	6-m	p	Baseline	≥12-m	p
Systolic function												
TAPSE (mm)	13 ± 4	16 ± 5	<0.001	14 ± 4	16 ± 4	0.008	15 ± 4	18 ± 5	0.006	15 ± 6	18 ± 7	0.74
RVEF (%)	19 ± 13	22 ± 15	0.37	18 ± 13	29 ± 15	0.02	19 ± 15	24 ± 12	0.40	19 ± 16	26 ± 17	0.08
RV MPI	0.8 ± 0.1	0.6 ± 0.2	0.04	0.7 ± 0.2	0.5 ± 0.1	0.04	0.7 ± 0.1	0.5 ± 0.1	0.06	0.8 ± 0.3	0.6 ± 0.2	0.78
PAAT (ms)	62 ± 19	74 ± 21	0.002	69 ± 22	76 ± 22	0.41	69 ± 21	81 ± 20	0.15	63 ± 14	80 ± 15	0.22
Diastolic function												
RVOT VTI	10 ± 4	12 ± 4	<0.001	11 ± 5	13 ± 5	0.004	13 ± 5	11 ± 5	0.05	8 ± 3	13 ± 3	0.008
RV dp/dt	86 ± 21	228 ± 25	0.001	99 ± 20	230 ± 16	0.008	87 ± 17	219 ± 22	0.02	89 ± 275	277 ± 25	<0.001
E′ (RV)	8.9 ± 3.3	9.9 ± 3.8	0.15	8.9 ± 4.5	8.8 ± 3.5	0.46	8.1 ± 4.4	11 ± 4.5	0.02	7.5 ± 1.0	8.5 ± 4.7	0.42
E/E′ (RV)	7.5 ± 2.4	7.5 ± 3.1	0.94	8.1 ± 2.1	6.9 ± 2.4	0.02	8.5 ± 1.7	6.6 ± 2.7	0.09	10 ± 1.1	5.6 ± 1.7	0.03
PE (mm)	7.3 ± 4.5	4.6 ± 3.5	0.02	6.5 ± 4.3	4.1 ± 1.5	0.02	6.7 ± 1.2	2.9 ± 0.6	<0.001	6.3 ± 3.5	1.6 ± 0.4	0.02
SMV (m/s)	4.2 ± 0.8	4.4 ± 0.8	0.72	4.1 ± 0.8	4.7 ± 0.8	0.01	4.2 ± 0.9	4.4 ± 0.9	0.051	3.9 ± 0.6	4.6 ± 0.6	0.01
RV-LS (%)	−14 ± 3	−16 ± 2	<0.001	−14 ± 7	−16 ± 8	0.001	−14 ± 5	−17 ± 4	<0.001	−14 ± 5	−17 ± 6	<0.001
Free wall	−12 ± 3[a]	−15 ± 4	<0.001	−13 ± 4	−15 ± 7	<0.001	−13 ± 5	−15 ± 7	0.001	−13 ± 5	−16 ± 5	<0.001
Septal	−15 ± 4	−17 ± 6	<0.001	−15 ± 6	−18 ± 6	<0.001	−15 ± 7	−18 ± 5	<0.001	−15 ± 6	−18 ± 7	<0.001
RHC												
CO (L)	3.5 ± 1.0	4.1 ± 0.7[b]	<0.001	3.5 ± 0.8	4.3 ± 0.9	<0.001	3.5 ± 1.0	4.5 ± 1.0	<0.001	3.3 ± 1.0	4.6 ± 1.0	<0.001
PVR (WU)	17 ± 5	10 ± 3[b]	<0.001	16 ± 4	9 ± 3	<0.001	14 ± 5	8 ± 5	<0.001	16 ± 5	11 ± 4	<0.001
sPAP (mmHg)	97 ± 29	89 ± 30[b]	<0.001	97 ± 30	86 ± 29	<0.001	94 ± 36	87 ± 38	0.004	97 ± 25	92 ± 20	0.28
mPAP (mmHg)	60 ± 9	54 ± 10[b]	<0.001	58 ± 10	52 ± 8	<0.001	57 ± 13	53 ± 30	<0.001	61 ± 15	58 ± 10	0.16
6MWD	348 ± 130	376 ± 121	0.37	359 ± 127	408 ± 100	<0.001	356 ± 129	421 ± 97	<0.001	344 ± 127	411 ± 45	<0.001

Note. [a]p = 0.04 compared with free-wall; [b]At 24 h post-PADN.

PADN, pulmonary artery denervation; RV, right ventricle; WT, wall thickness; D, diameter; TAPSE, tricuspid annulus plane systolic excursion; EF, eject fraction; MPI, myocardial performance index; PAAT, pulmonary artery acceleration time; RVOT, right ventricular outer tract; VTI, velocity time integral; RHC, right heart catheterization; sPAP, pulmonary arterial systolic peak pressure; SMV, systolic myocardial velocity; PE, pericardial effusion; CO, cardiac output; PVR, pulmonary vessel resistance; RV-LS, right ventricular longitudinal strain.

Table 3. Univariate correlations between echocardiographic and hemodynamic parameters of RV performance before and after PADN.

	Baseline		End of study	
	r	*p* value	*r*	*p* value
Right ventricular longitudinal peak systolic strain vs. baseline or follow-up values of:				
E/E′ (right ventricle)	0.412	0.03	0.408	0.03
Pulmonary vessel resistance	0.589	<0.001	0.583	<0.001
Right ventricular outflow tract velocity-time integral	−0.553	<0.001	−0.550	<0.001
Tricuspid annulus plane systolic excursion	−0.527	<0.001	−0.522	<0.001
	Baseline mPAP		**Reduction of mPAP[a]**	
	r	*p* value	*r*	*p* value
Echocardiography-derived parameters vs. mean pulmonary arterial pressure (mPAP)				
Right ventricular dp/dt	-0.485	0.02	0.102	0.81
Right ventricular longitudinal peak systolic strain	0.476	0.02	−0.447	0.006
Right ventricular myocardial performance index	0.455	0.01	−0.466	0.02
	Baseline PVR		**Reduction of PVR[a]**	
	r	*p* value	*r*	*p* value
Echocardiography-derived parameters vs. pulmonary vascular resistance (PVR)				
Right ventricular dp/dt	−0.449	0.04	0.137	0.89
Right ventricular longitudinal peak systolic strain	0.347	0.03	−0.438	0.007
Right ventricular myocardial performance index	0.409	0.04	−0.403	0.04
	Baseline 6MWD		**6MWD at end of study**	
	r	*p* value	*r*	*p* value
Echocardiography-derived parameters vs. 6-minute walk distance (6MWD)				
Pulmonary vessel resistance by RHC	−0.558	<0.001	−0.461	0.01
Pulmonary arterial acceleration time	0.405	0.01	0.257	0.19
Right ventricular E/E′	0.539	0.003	−0.076	0.76
Right ventricular longitudinal peak systolic strain	−0.512	0.001	−0.586	<0.001

Note. [a] is the comparison of septal vs. free wall ($p = 0.04$).

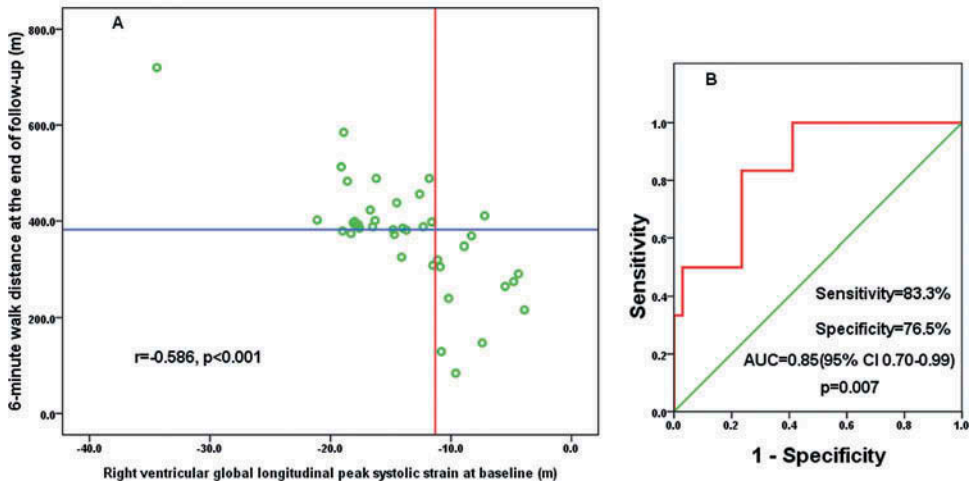

Figure 2. Central illustration: Correlation and receiver operator curve (ROC) analysis. (A) Baseline right ventricular global longitudinal strain (RV-LS) significantly correlated with 6-minute walk distance (6MWD) at the end of follow-up. (B) From ROC curve analysis, baseline RV-LS ≥ −11.3% had a sensitivity of 83.3% and specificity of 76.5% for the diagnosis of non-responders to pulmonary artery denervation.

The improvements in these parameters after PADN in patients with RV-LS ≥ −11.3% were significantly less than the changes observed in patients with RV-LS < −11.3% (Figure 3).

Improvement of RV function, and baseline echocardiographic predictors of improvement in hemodynamic measures and 6MWD after PADN

Baseline RV-LS and RV MPI were univariable (Table 3) and multivariable predictors of ΔmPAP (β = −0.736, $p = 0.001$, and β = −0.853, $p < 0.001$ respectively) and ΔPVR (β = −0.076, $p = 0.03$, and β = −0.041, $p < 0.001$ respectively) after PADN from baseline to latest follow-up. Baseline RV-LS (r = −0.586, $p < 0.001$) and PVR ($r = -0.461$, $p = 0.010$) were well correlated with the increase of 6MWD at the end of follow-up (Table 3).

Clinical outcomes after PADN

During follow-up 10 patients (25.0%) experienced PAH-related events, mostly reductions in 6MWD by >15% ($n = 6$, 15.0%). Four (10.0%) patients died after PADN: one patient with idiopathic PAH suddenly died at 388 days; one patient died from RV failure at 16 days; and two deaths occurred during lung transplantation at 473 days and 502 days after PADN, respectively. The baseline RV-LS of all four of these

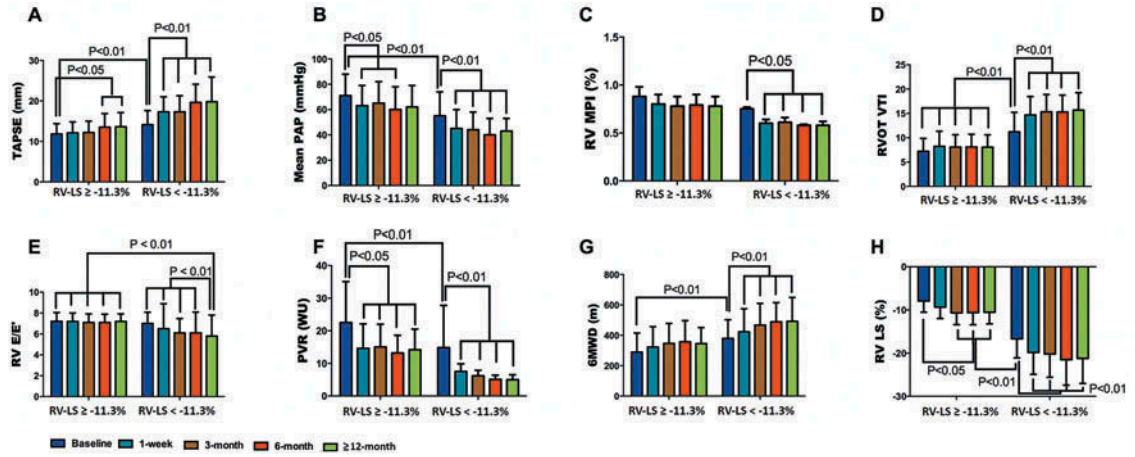

Figure 3. Improvement of right ventricular function, hemodynamic, 6-minute walk distance (6MWD), and global longitudinal peak systolic strain (RV-LS) in patients with RV-LS ≥ −11.3% and with RV-LS < −11.3% after pulmonary artery denervation. At the end of follow-up, tricuspid annulus plane systolic excursion (TAPSE), mean pulmonary arterial pressure (mPAP), right ventricular (RV) E/E′, and RV-LS in patients with RV-LS ≥ −11.3% were improved compared to baseline, but less so than in patients with RV-LS < −11.3%. However, the significant reduction of pulmonary vessel resistance (PVR) in patients with RV-LS ≥ −11.3% was not associated with the profound increase of 6MWD. In contrast, all measured parameters were significantly improved in patients with RV-LS< −11.3%.

patients was ≥ −9% despite the fact that RV MPI and 6MWD had significantly improved after PADN.

By univariate analysis age (HR 1.07, 95% CI 1.02–1.13, p = 0.02), male sex (HR 3.29, 95% CI 1.17–11.20, p = 0.045), WHO functional class III/IV (HR 13.07, 95% CI 2.96–179.42, p = 0.01), TAPSE (HR 1.66, 95% CI 1.35–3.04, p = 0.04), RV MPI (HR 1.08, 95% CI 1.01–2.01, p = 0.03), 6MWD (HR 0.94, 95% CI 0.90–0.99, p = 0.01), and RV-LS ≥-11.3% (HR 2.76, 95% CI 1.29–3.93, p = 0.001) correlated with PAH-related events during follow-up.

Patients were classified as high-risk (baseline RV-LS ≥ −11.3%) and low-risk (baseline RV-LS < −11.3%) according to the ROC curve analysis for prediction of non-responder status. Patients with baseline RV-LS ≥ −11.3% had lower baseline 6MWD, TAPSE, and RV dp/dt, but higher baseline RV MPI, RV-LS, and sPAP/mPAP (Table 4). Baseline RV-LS strongly correlated with improvement in 6MWD over time (Figure 3B). The rate of PAH-related events in high-risk patients (baseline RV-LS ≥ −11.3%) was significantly greater than that in low-risk patients (Kaplan-Meier event rate 46.2% vs. 14.8%, log-rank p = 0.03, Table 4 and Figure 4A). By multivariable analysis baseline RV-LS ≥ −11.3% was the only significant predictor of PAH-related events during follow-up (HR 4.51, 95% CI 2.25–18.35, p = 0.001). By ROC curve analysis, baseline RV-LS had a sensitivity of 81.5%, a specificity of 86.2%, and an AUC of 0.87 (95% CI: 0.64–0.98, p = 0.003) for prediction of PAH-related events (Figure 4B).

Table 4. Baseline echocardiographic and hemodynamic measures, exercise capacity, and long-term clinical outcomes according to baseline RV-LS.

Variables	RV-LS ≥ −11.3% (n = 13)	RV-LS < −11.3% (n = 27)	p value
Clinical			
Age, years	41 ± 16	45 ± 14	0.47
Heart rate, bpm	80 ± 23	78 ± 16	0.80
6MWD, m	289 ± 126	379 ± 123	0.04
NT-proBNP, pg/ml	2098 ± 1052	862 ± 948	0.001
Echocardiography			
RV wall thickness, mm	4.1 ± 0.9	4.8 ± 1.2	0.21
TAPSE, mm	11.8 ± 2.6	14.1 ± 3.5	0.045
SPAP, mmHg	108 ± 33	92 ± 28	0.15
RVOT-VTI	7.19 ± 2.68	11.19 ± 4.03	0.001
PAAT, ms	55.42 ± 19.53	64.58 ± 18.57	0.18
E′ (RV)	9.25 ± 1.83	8.57 ± 3.64	0.62
E/E (RV)	5.61 ± 0.84	8.19 ± 2.38	<0.001
RV dp/dt	863 ± 185	767 ± 224	0.28
RAEF, %	12.2 ± 17.8	17.2 ± 18.8	0.43
RVEF, %	15.49 ± 7.95	21.01 ± 8.19	0.39
RV MPI (%)	0.88 ± 0.10	0.63 ± 0.02	0.001
Pericardial effusion, mm	7.0 ± 1.4	6.2 ± 5.7	0.76
RV-LS (%)	−7.92 ± 2.6	−16.67 ± 4.43	<0.001
Right heart catheterization			
SPAP, mmHg	108 ± 22	92 ± 21	0.03
MPAP, mmHg	71 ± 17	55 ± 19	0.02
Right atrial pressure, mmHg	11.06 ± 6.7	9.7 ± 5.2	0.32
Cardiac output, L/min	3.0 ± 1.2	3.7 ± 1.4	0.17
PAP, Woods Unit	22.5 ± 12.6	14.8 ± 13.0	0.03
PAH-related events, n (%)	6 (46.2)	4 (14.8)	0.03
Cardiac death, *n* (%)	3 (23.1)	1 (3.7)	0.03

Note. Abbreviations same as used in Table 2.

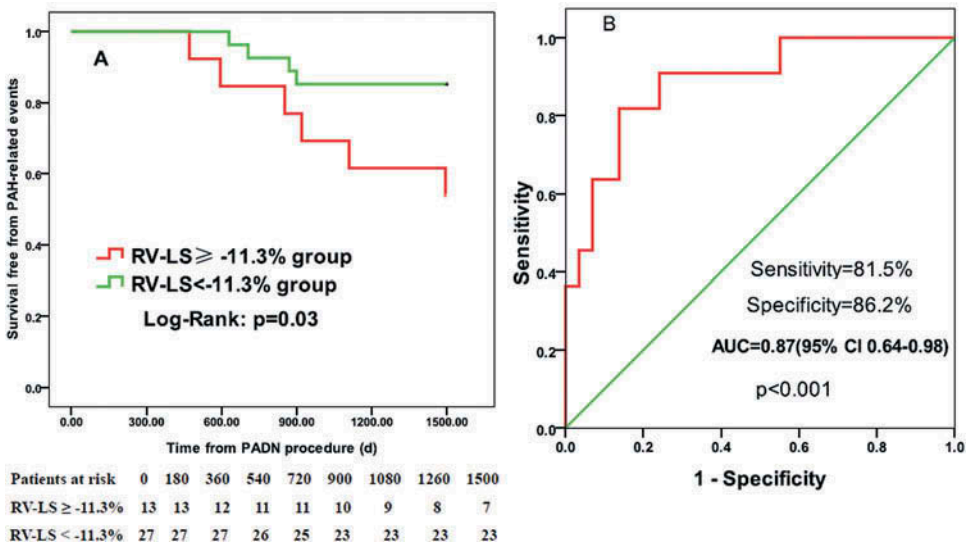

Figure 4. Kaplan-Meier estimated pulmonary arterial hypertension (PAH)-related event rates according to global right ventricular peak systolic strain (RV-LS). (A) Patients with RV-LS ≥ −11.3% had a higher rate of PAH-related events than those with RV-LS < −11.3% (46.2% vs. 14.8%, $p = 0.03$). (B) RV-LS had high sensitivity and specificity in predicting PAH-related events.

Discussion

The present study for the first time has reported the changes in RV functional measures and their correlates after PADN in patients with Group I PAH. The major findings are: (1) Baseline RV-LS was the most useful prognostic echocardiographic measure, and strongly correlated with baseline hemodynamic parameters (including mPAP and PVR), as well as long-term reductions in mPAP and PVR and improvement in 6MWD after PADN; (2) PADN resulted in durable improvements in PVR, CO, RV-LS and measures of RV diastolic function, whereas the early observed reductions in PAP and measures of RV systolic function were not sustained at long-term follow-up; and (3) The cut-off value of RV-LS ≥ −11.3% had good sensitivity and specificity to predict non-responder status to PADN, poor functional improvement in exercise capacity (6MWD), and the occurrence of PAH-related events during long-term follow-up after PADN.

PAH is a progressive, incurable disease that is characterized by chronic increases in PVR and PAP, resulting in RV failure.[1] RV function has been shown to be an important determinant of prognosis in PAH patients.[1–6] Unfortunately, assessment of RV function by conventional echocardiographic parameters is problematic due to the complex shape of the RV and its pattern of longitudinal shortening during systole (mainly in the longitudinal plane with the RV base moving toward the apex). Thus, there is no accepted standard as to which RV parameter(s) to use to establish and follow prognosis in PAH, and prior studies have reported conflicting and at times paradoxical data. For example, in 76 PAH patients who survived at least 1 year to undergo RHC and cardiac magnetic resonance imaging after initiation of targeted therapy,[13] changes in RVEF predicted long-term survival whereas changes in PVR did not. In this study 25% of patients in whom PVR decreased after initiation of medical therapy had deterioration in RVEF over time and high mortality, findings similar to the results from another study using radionuclide angiography.[14] Whether the observed dissociation between long-term changes in PVR and RV function and clinical outcomes is due to difficulties in accurately assessing these parameters vs. the complex inter-relationships that dictate prognosis in PAH is unknown.

In the present study we examined numerous measures of RV function for their prognostic utility. RVEF measured from 3D echocardiography (as performed in our study) has been reported to be superior to fractional area change (FAC) in assessing global RV function.[15] We therefore used RVEF rather than FAC to assess global RV function. However, RVEF did not correlate with either baseline hemodynamic measures or exercise capacity. TAPSE, reflecting RV systolic performance, in general correlates well with RVEF. However, TAPSE is load- and angle-dependent (like RVEF), and is subject to cardiac translation.[6–10] In the present study baseline TAPSE did not correlate with mPAP, PVR or clinical outcomes. RV MPI, defined as (IVCT+IVRT)/RV ejection time (ET), reflects both systolic and diastolic RV function. RV MPI has been reported to be correlated with baseline 6MWD[10–12,16] and survival after medication therapy in PAH.[17] In our study baseline RV MPI significantly correlated with baseline mPAP and PVR and their reduction over time after PADN, but was not predictive of either baseline 6MWD, improvement in 6MWD during follow-up, or PAH-related events. These differences may be due to: (1) the use of pulse wave rather than continuous wave Doppler in prior studies;[10,11,16,17] (2) the fact that IVRT may be shortened when RA pressure is elevated,[18] resulting in pseudo-normalization of RV MPI; and/or (3) the variable influence of loading conditions on RV MPI.

In contrast to these disappointing findings, in our study baseline RV-LS was an independent predictor of improved 6MWD and clinical events during follow-up. The major advantage of RV-LS is that it allows quantitative assessment of global and segmental RV function relatively independent of angle and load.[1,2,6–9,12,13,16] Because of the paucity of data, different reference limits were reported by previous studies,[19–21] ranging from > −25% (which allowed the prediction of RVEF >50% with a sensitivity of 81% in PAH patients),[19] to > −21% (which identified a high risk of adverse cardiac events in patients with congestive heart failure),[20] to > −19.4% (which facilitated identification of patients at high

risk of mortality).[21] The findings from our study confirms a prior report by Rajagopal and colleagues, who found that among 40 medically-treated patients with PAH, global or regional (RV free wall) RV-LS was superior to any other 2D echocardiographic parameter in terms of correlation with RV function, mPAP and PVR.[12] In that study patients with baseline RV-LS ≥ −11.3% had a lower 6MWD (337 ± 221 m) and the highest REVAEL risk score (10.5 ± 3.3). By ROC analysis our study identified the exact same baseline RV-LS value as the optimal discriminative cut-off of non-responder status to PADN. This cutoff value also strongly correlated with 6MWD during follow-up, and was an independent predictor of late PAH-related events. These findings thus strongly suggest that baseline RV-LS may have an important prognostic role in PAH patients undergoing treatment with either medical therapy or PADN. Nonetheless, as our patients were at extremely high-risk as reflected by profoundly reduced RV function, high PAP, WHO function class III and IV in most, and by study criteria unresponsive to target therapy for 2–3 years, the cut-off value of RV-LS ≥ −11.3% should be verified in a larger and more representative PAH patient population.

PADN is an invasive procedure in which the PA sympathetic nerves are denervated via a catheter with 10 pre-mounted electrodes. We have previously demonstrated[22] that in dogs the PA sympathetic nerves mainly localize at the left lateral side of PA, and are closest to the intima near the distal bifurcation, an anatomical feature which allows for successful percutaneous denervation.[23,24] Our first-in-human study[10] and the PADN I Phase II study[11] in which 66 consecutive patients with PAH of different etiologies were treated by PADN demonstrated hemodynamic improvements and potential clinical benefits of PADN. However, RV function is an important prognostic variable in PAH which does not necessarily track with hemodynamic changes in PAH, and we had not previously examined the responses of the RV to PADN. Moreover, the exact role of PA sympathetic hyperactivity in the progression of RV failure in PAH is unknown. The present study suggests that in addition to resulting in long-term reductions in PVR and improved CO, PADN may result in a durable improvement of RV diastolic function, more so than for RV systolic function. Recovery of RV systolic function may take longer to emerge, and/or RV diastolic function may be more sensitive to changes in sympathetic activity. In this regard a previous study reported fewer and less responsive β-adrenergic receptors in the myocardium of the failing RV in PAH patients (down-regulation and desensitization),[25] which may explain in part why nebivolol, a novel β1-antagonist and β2,3-agonist was more effective than metoprolol in promoting PA remodeling and improving RV function.[26] Theoretically, over-activation of PA sympathetic nerves may not only worsen RV function but also reduce coronary artery blood flow,[25,26] causing biventricular ischemia. More study is required to understand the mechanistic benefits of PADN in improving RV function over time.

Combining the present data with our previous report,[11] among 66 PADN-treated patients (5 of whom were included in this analysis), the rate of non-responders was 7.9% (8/101), and may be predicted by baseline RV-LS ≥ −11.3%. First-time non-responders to PADN had more frequent PAH-related events during follow-up, and whether such patients may benefit from a repeat PADN procedure months later is unknown. Further studies are required to examine this hypothesis.

The present study has several limitations, starting with the absence of a control group. However, there were relatively few deaths, and analysis of paired studies allowed examination of correlations between baseline measures, changes in RV function over time, and long-term outcomes. The improvement in 6MWD with PADN is difficult to place in context without a control group. However, control groups in PAH trials typically show no change or a reduction in exercise capacity.[27] It is less likely that serial echocardiographic measures are biased (as the echocardiographic readers did not know whether patients underwent PADN), although Hawthorne effects from close clinical follow-up may have contributed to the relatively favorable outcomes of our patients. Sham-controlled randomized trials of PADN in refractory PAH are essential and are currently being planned to overcome this limitation. In addition, the sample size of the present study is modest, follow-up durations were variable, 20/60 PADN-treated patients with type I PAH had echocardiograms of sub-optimal quality for quantitative analysis, and not all patients had serial testing at all time periods. While our reporting of only paired data from sequential studies may have in part reduced bias, our study should be replicated in a larger number of patients with routine and regular follow-up. The small sample size at long-term follow-up may also explain why a durable effect of PADN in reducing PAP or measures of RV systolic function were not evident. Finally, we did not use a cut-off value of RV-free wall LS < −20% as recommended by echocardiographic guidelines,[28] because RV-free wall LS was similar to global RV-LS.[12] Moreover, different RV-free wall LS cut-off values have been proposed from other studies.[29,30] The relatively high global RV-LS cut-off value from our study and a previous report[12] may be explained by smaller patient numbers than were used by the American Society of Echocardiography (ASE) in determining their recommended cutoff value.[29] Thus, although our high-risk cut-off value of RV-LS of ≥ −11.3% was identical to that found in the study of Rajagopal and colleagues,[12] prospective studies in larger PAH cohorts should be examined to confirm whether this is indeed the optimal value to both determine acute non-responsiveness to the PADN procedure and adverse prognosis during follow-up.

Conclusions

In conclusion, baseline measurement of RV-LS is valuable in assessing the severity and prognosis of PAH, and the functional and clinical outcomes following PADN. Specifically, baseline RV-LS ≥ −11.3% may predict which patients are less likely to respond to PADN, and have a poor long-term prognosis after the procedure. PADN in refractory patients with PAH is associated with long-term improvements in PVR, CO, and RV-LS, and may have a more durable beneficial effect on RV diastolic function than RV systolic function. Sham-controlled randomized trials are required to confirm the long-term benefits of PADN on hemodynamic parameters, RV function, exercise capacity and prognosis in patients with PAH.

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Disclosure Statement

The authors have no disclosures.

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