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Impact of Lowering Pulmonary Vascular Resistance on Right and Left Ventricular Deformation in Pulmonary Arterial Hypertension

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Abstract

Objective—We aimed to determine the impact of therapy to reduce pulmonary vascular resistance (PVR) on right ventricular (RV) and left ventricular (LV) deformation in pulmonary arterial hypertension (PAH).

Background—PAH is associated with significant morbidity and mortality, particularly among patients with RV dysfunction.

Methods and Results—RV free wall longitudinal strain (FWLS) and LV global circumferential strain (CS) were measured at baseline, 12 weeks, and 24 weeks in 68 patients with advanced PAH randomized to imatinib or placebo in the Imatinib in Pulmonary arterial hypertension, a Randomized Efficacy Study (IMPRES) trial, and compared to 30 healthy controls. Compared to controls, PAH was associated with impaired RV FWLS (-15.9 ± 5.4 vs -30.8 ± 4.3 , respectively; $p < 0.0001$) and LV septal CS (-24.2 ± 8.2 vs -31.4 ± 5.3 respectively, $p < 0.0001$), but not LV global CS. Improvement in PVR and mean pulmonary artery pressure (MPAP) over a 24 week period was significantly associated with improvement in RV FWLS ($r = 0.39$, $p = 0.02$; 0.33 , $p = 0.04$ respectively), LV global CS ($r = 0.61$, $p = 0.0001$; $r = 0.60$, $p = 0.0001$ respectively), and LV septal CS ($r = 0.50$, $p = 0.005$; $r = 0.56$, $p = 0.002$ respectively). These associations were most robust with LV global and septal CS. Imatinib therapy was associated with improvement in RV FWLS compared to placebo.

Conclusions—PAH is associated with impaired biventricular deformation. Reduction in PVR is associated with improvements in both RV and LV deformation, coupled to improvements in MPAP and SVI, with LV global and septal CS the strongest correlates of these changes. RV FWLS is sensitive to treatment effect, demonstrating greater improvement with imatinib compared to placebo.

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Conflict of interest:

The remaining authors report no relevant financial conflicts.

Keywords

pulmonary heart disease; echocardiography; pulmonary hypertension; trials

Introduction

Pulmonary arterial hypertension (PAH) is associated with significant morbidity and mortality¹ and is characterized by elevated pulmonary vascular resistance (PVR),² pulmonary hypertension, and resulting right ventricular (RV) dilatation and dysfunction.^{3,4} Indeed, RV failure is a key prognostic determinant in PAH.⁵ RV dilatation and dysfunction may influence the left ventricle (LV) due to ventricular interdependence, mediated through both the shared interventricular septum and impaired LV filling. Measures of LV geometric distortion, such as degree of septal flattening quantified by the LV eccentricity index,⁶ have been consistently associated with increased risk of death in PAH.⁷ Beyond size and function, strain imaging allows for the quantification of biventricular deformation in PAH,⁸ and previous studies have demonstrated that both RV free wall longitudinal strain (FWLS) and LV global circumferential strain (CS) are impaired in PAH^{9,10} and prognostic of mortality.^{11,12} However, little data exists regarding the effect of therapy to improve pulmonary hemodynamics on biventricular deformation in PAH and whether these deformation measures are sensitive to therapeutic interventions.

We hypothesized that improvements in PVR and pulmonary hemodynamics in patients with advanced PAH will result in improvements in both RV and LV deformation. Specifically, we retrospectively quantified RV deformation (measured as RV FWLS) and LV deformation (measured as LV global, septal, and non-septal CS) among 68 patients enrolled in the echocardiographic sub-study of the Imatinib in PAH, a randomized, efficacy study (IMPRES),¹³ which randomized PAH patients with decreased exercise capacity and a $PVR > 800 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ despite therapy with two or more PAH-specific medications to add-on therapy with imatinib versus placebo. We determined the relationship between change in invasively determined pulmonary hemodynamics, RV deformation, and LV deformation following 24 weeks of therapy, and determined the impact of imatinib therapy on these deformation measures.

Methods

Study Population

The IMPRES trial demonstrated significant improvements in exercise capacity (as assessed by the 6-minute walk test) and hemodynamics compared to placebo with imatinib mesylate, a tyrosine kinase inhibitor that inhibits platelet-derived growth factor and is thought to impede vascular remodeling by interfering with smooth muscle proliferation and migration. The IMPRES trial enrolled 202 patients at 71 sites in 14 countries on 3 continents. All patients provided written informed consent, which included consent for the echocardiographic analysis. Enrolled patients were males or females, at least 18 years of age, diagnosed with Pulmonary Hypertension Group 1, i.e. PAH, with decreased exercise capacity (defined as 6-minute walk distance < 450 meters) and a $PVR > 800 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$

despite therapy with two or more PAH-specific medications (endothelin receptor antagonists, phosphodiesterase 5 inhibitors, prostacyclin or prostacyclin analogues). Patients were randomized 1:1 to imatinib or placebo. Participation in the echocardiography sub-study of the IMPRES trial was voluntary and offered to all participating sites. The 27 sites in 8 countries that chose to participate in the echocardiography sub-study were asked to include all patients enrolled in the overall trial at that site to minimize selection bias. For participating sites, echocardiograms were performed by a study-specific protocol at baseline, week-12, and week-24.

In addition, 30 healthy controls of similar age and gender were retrospectively identified from patients referred to the echocardiographic laboratory at the Brigham and Women's Hospital (BWH) for one of the following indications: murmur, evaluation of LV function, syncope, or atypical chest pain. Patients with adequate image quality, LVEF>55%, no regional wall motion abnormalities, normal LV and LA size, normal LV wall thickness, and no valvular disease based on current recommendations of the American Society of Echocardiography (ASE)¹⁵ and who were free of prevalent cardiovascular disease, cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, renal dysfunction), and not taking any cardiovascular medications were identified by retrospective chart review of the electronic medical record. Study protocol was approved by the BWH Institutional Review Board.

Echocardiographic Methods

Details of the design and methods of the IMPRES echocardiographic sub-study have been previously described in detail.¹⁴ Briefly, all sonographers at participating sites underwent central training in the details of the echocardiographic views and techniques.

Echocardiograms were sent on digital storage media to the echocardiography core laboratory at the Brigham and Women's Hospital. Tricuspid annular peak systolic velocity (TA S'), tricuspid annular plane systolic excursion (TAPSE), RV Tei index, and RV fractional area change (RVFAC) were the primary prospectively defined RV functional measures for the echocardiographic sub-study and were measured in accordance with the ASE guidelines as previously described.^{14,16,17}

Further deformation analysis was performed on all digitally acquired studies in DICOM format with acceptable image quality using the Tomtec Cardiac Performance Analysis package (Munich, Germany). Strain analysis was not performed if there was poor visualization or poor tracking of two or more myocardial segments. From the apical four chamber view, the RV subendocardial border was traced at end-diastole. From the parasternal short axis view at the level of papillary muscle, the LV subendocardial border was traced at end-systole, defined by the QRS complex. The software then tracked speckles along the endocardial border throughout the cardiac cycle. RV free wall longitudinal strain (FWLS) and septal wall longitudinal strain was calculated as the mean of basal, mid and apical segments of the each RV wall and global longitudinal strain (GLS) as the average of all six segments (Figure 1). As previously published literature on RV LS has advocated the use of FWLS as opposed to GLS given the potential influence of LV function on septal longitudinal strain (LS), RV FWLS was used as the primary measure of RV deformation in

this analysis.^{10,18} From the parasternal short axis view at the papillary muscle level, global circumferential strain (CS) was measured as the average of all six segments. Septal CS was defined as the average of the two septal segments, and non-septal CS was calculated as the average of the 4 non-septal segments (Figure 1).

All measurements were performed by a single investigator blinded to clinical information and treatment allocation. Intra-observer variability for RV FWLS and LV global CS was assessed in a sample of 30 randomly selected patients (20 subjects from the IMPRES group and 10 subjects from the control group). Coefficient of variation was 12.8% and 6.3% for RV FWLS and LV global CS, respectively. Intraclass correlation coefficients were 0.93 (95% CI 0.88–0.98) for RV FWLS and 0.95 (95% CI 0.91–0.98) for LV global CS.

Right Heart Catheterization

All IMPRES patients underwent right heart catheterization on the same day as echocardiography at the baseline and 24-week visits per study protocol.¹³ Invasive hemodynamic measurements were not available in the control group.

Statistical Analysis

Continuous variables are presented as mean and standard deviation or median and interquartile range if not normally distributed. Categorical variables are presented as percentages. Comparisons between IMPRES patients overall and controls were performed using a Student's t-test for continuous variables and a Fisher exact test for categorical variables. We studied the association between strain measurements at baseline and invasive hemodynamic measurements and NT-proBNP using Pearson's correlation for normally distributed data. As both MPAP and PVR were non-normally distributed, we employed non-parametric statistical tests (Spearman's correlation and Wilcoxon rank sum test for between group comparisons) for these variables. The association of cardiac deformation measures with invasive hemodynamics and NT-proBNP beyond conventional measures of RV function was then assessed using multivariable linear regression models, adjusting for conventional echocardiographic measures of RV function including RVFAC, TAPSE, Tei Index and TA S'. Multivariable median regression was employed to assess the adjusted relationship of cardiac deformation measures with MPAP and PVR.

Changes in cardiac deformation between baseline and 12 week and baseline and 24 week were calculated. The relationship between the observed changes in RV FWLS, and LV global, septal, and non-septal CS and changes in invasive hemodynamic measures over the same period were assessed using both correlation analysis and ANCOVA analysis, adjusting for baseline strain and hemodynamic measure. To determine whether treatment allocation (imatinib versus placebo) significantly modified the relationship between change in hemodynamics and change in cardiac deformation, we performed a test for interaction. Finally, to determine between treatment-group differences in the changes in cardiac deformation measures from baseline to week-24, we used a mixed-effects repeated-measures model which included terms for randomized treatment, visit, treatment-by-visit interaction, and baseline value of the measure of interest as covariates. Changes from baseline to week-12 and week-24 were also assessed using the mixed-effects repeated-measures model.

In a sensitivity analysis, we repeated the analysis using an ANCOVA with the last observation carried forward (LOCF) and an observed case analysis. All analyses were performed using STATA 12.0 (StataCorp LP. 2009. Texas).

Results

Of the 74 patients included in the echocardiographic sub-study, 6 studies could not be analyzed due to technical issues. Of the remaining 68 patients, RV FWLS could not be analyzed at baseline in an additional 8 patients due to poor image quality (12%; analyzed n=60) and LV CS (global, septal, and non-septal) could not be analyzed at baseline in 4 patients (6%; analyzed n=64), with missing data balanced between study treatment arms (Figure 2). Patients included in the strain study did not significantly differ from the overall IMPRES population in demographics, clinical characteristics, or invasive hemodynamics at baseline and demonstrated similar changes in hemodynamics during follow up. Analyzable images were available in 60 patients at baseline, 44 patients at week 12, and 41 patients at week 24. Compared to those with follow-up echocardiographic data, those without follow-up studies had lower cardiac index (CI; 2.06 ± 0.42 L/min vs 2.33 ± 0.45 L/min respectively, $p=0.03$) and higher PVR (1224 ± 370 vs 1065 ± 222 dynes·sec·cm⁻⁵ respectively, $p=0.03$), but did not differ significantly in other clinical or echocardiographic measures.

IMPRES patients were 49.9 ± 13.3 years old, predominantly white, and the majority were women (Table 1). There was no significant difference in age, gender or BMI between the PAH and control groups. Compared to controls, patients with PAH had significantly lower blood pressure, higher heart rate, and significantly impaired values for all conventional echocardiographic measurements of RV function.

Baseline RV and LV deformation in PAH compared to controls

Compared to controls, patients with PAH had significantly impaired RV longitudinal deformation (Table 1). LV septal CS was also significantly lower in PAH patients ($p<0.0001$), while LV non-septal CS was numerically higher in PAH patients ($p=0.07$), and no significant difference was noted in LV global CS ($p=0.34$) (Table 1). LV septal CS correlated with echocardiographic measurements of LV distortion, including the LV eccentricity index ($r=-0.43$, $p<0.0001$) and LV area/RV area ratio ($r=0.44$, $p<0.0001$). These differences between PAH patients and controls remained significant after adjusting for between group differences in heart rate and systemic systolic blood pressure. Among patients with PAH, the magnitude of impairment in LV septal and global CS was significantly related to the magnitude of impairment in RV FWLS ($r=0.69$, $p=0.001$ and $r=0.38$, $p=0.003$ respectively).

Baseline RV and LV deformation, and invasively measured pulmonary hemodynamics

At baseline RV FWLS was significantly related to PVR, MPAP, right atrial pressure (RAP), stroke volume index (SVI), and NT-proBNP level, associations which compared favorably to conventional echocardiographic measures of RV function (Table 2). Indeed, after adjustment for conventional echocardiographic measures of RV function (RVFAC, TAPSE, RV MPI, and TA S'), the association of RV FWLS with both PVR and SVI remained significant. In

contrast, LV septal and global CS at baseline were also associated with SVI, but not with other hemodynamic measures or NT-proBNP. Neither RV FWLS nor LV global, septal, or non-septal CS were associated with echocardiographic measures of LV diastolic function including E/A ratio, lateral E', and E/E' ratio (data not shown).

Relationship of change in pulmonary hemodynamics to change in RV and LV deformation

Among the 47 patients with complete data for either FWLS or LV global CS at baseline and 24 weeks, PVR decreased by 229 [-448, 0] dynes·sec·cm⁻⁵ ($p<0.001$), MPAP decreased by 4 [-12, 1] mmHg ($p=0.003$), and SVI increased by 6.3 ± 9.3 ml/m² ($p=0.0001$). The observed change in RV FWLS was significantly related to changes in PVR and MPAP, and with changes in conventional echocardiographic measures of RV function (Table 3; Figure 3). The change in RV longitudinal deformation was also associated with the change in LV global CS over the same period ($r=0.49$, $p=0.004$). Interestingly, the relationship of change in hemodynamic measures with change in both LV global and septal CS appeared more uniform and more robust than with change in RV functional measures. The change in LV global, septal and non-septal CS demonstrated robust associations with the observed change in PVR, MPAP, RAP, SVI, and CI (Table 3; Figure 3). The observed improvements in RV FWLS and LV global and septal CS were not associated with change in echocardiographic measures of LV diastolic function.

Impact of imatinib therapy on RV and LV deformation

Consistent with the findings in the overall IMPRES trial,¹³ in the echocardiographic sub-study imatinib therapy was associated with significant reduction in PVR (387 ± 371 vs 73 ± 332 dynes·sec·cm⁻⁵, $p=0.02$) and increase in SVI (10.0 ± 10.2 vs 3.9 ± 8.8 ml/m², $p=0.02$) at week 24. Using a mixed-effect repeated measures analysis, imatinib therapy was associated with significant improvement in RV FWLS compared to placebo (Table 4; Figure 4). The improvement in RV FWLS in the imatinib group compared to placebo achieved statistical significance at week-24, but not week-12. Sensitivity analysis using ANCOVA with last visit carried forward showed similar results (Supplemental Table 1) and qualitatively similar results were also noted in a sensitivity analysis using an observed cases analysis (Supplemental Table 2). Imatinib therapy was not associated with a significant improvement in LV global, septal, or non-septal CS compared to placebo. No significant effect modification of treatment assignment (imatinib versus placebo) on the relationship between change in RV LS or LV CS and change in hemodynamic measures was noted.

Discussion

There are three major findings of the current study. First, RV FWLS and LV septal, but not global, CS are reduced in PAH compared to controls and the magnitude of impairment in RV FWLS is robustly associated with hemodynamic measures of disease severity. Second, improvement in PVR and MPAP over a 24 week period was significantly associated with improvement in RV FWLS and LV global, septal and non-septal CS, although was most robustly associated with LV deformation. Third, the change in RV FWLS was sensitive to therapeutic intervention, in this study with imatinib, a therapy which was associated with greater reduction in PVR and improvement in pulmonary hemodynamics compared to

placebo. The latter two findings in particular are novel insights into cardiac deformation in PAH and, to our knowledge, have not been previously described.

Baseline RV and LV deformation in PAH compared to controls

Chronic pressure overload in PAH due to elevated PVR leads to RV hypertrophy, dilatation, and dysfunction.^{3,4} RV failure is associated with increased risk of mortality in PAH.⁵ Given the prominent contribution of longitudinal shortening to RV ejection, quantification of longitudinal deformation of the RV is an attractive method to quantify RV systolic dysfunction without relying on geometric assumptions of RV shape. Concordant with prior studies, we demonstrate significant impairments in RV FWLS in PAH patients compared to healthy controls of similar age and gender.^{8,9,10}

Due to the shared interventricular septum and to impaired LV filling resulting from RV dysfunction, PAH has also been associated with distortion of the LV geometry and function, possibly as a result of adverse effects on ventricular coupling. In this study, only septal CS was impaired, while LV global CS was preserved relative to healthy controls. This finding is consistent with impaired septal deformation related to marked RV overload despite globally preserved or hyperdynamic LV systolic function, and is supported by the correlation of LV septal CS with magnitude of LV distortion expressed as the LV eccentricity index and LV area/RV area ratio. This contrasts with the findings of Puwanant et al, who found significant reductions in both septal and LV lateral wall CS in pulmonary hypertension patients compared to controls.⁸ One explanation may be the severity of PAH and RV dysfunction, which was greater in our study and may have resulted in reduced LV filling and increased chamber level LV contractility.

Baseline RV and LV deformation and invasively measured pulmonary hemodynamics

Consistent with prior studies in PAH,¹⁸ we found significant associations between RV FWLS and invasive hemodynamic measures reflective of disease severity, including PVR, MPAP, RAP, and SVI. Furthermore, we compared these associations with those for conventional measures of RV function (RVFAC, TAPSE, TA S', and Tei index) and found that RV FWLS demonstrated more robust and uniform association with hemodynamic measures. RV FWLS demonstrated value beyond conventional measures, remaining significantly associated with hemodynamics even after adjusting for conventional measures. RV FWLS was also related to NT-proBNP, a biomarker reflecting myocardial wall stress and an emerging prognostic risk marker in PAH.¹⁹ In contrast to RV deformation, LV global and septal CS was primarily related to SVI but not to pulmonary hemodynamics, supporting the hypothesis that impaired LV function is related not only to septal distortion but also to LV underfilling due to reduced RV function.²⁰

Relationship of change in pulmonary hemodynamics to change in RV and LV deformation

Little data exists regarding the impact of therapy to reduce PVR on cardiac mechanics in PAH. Although Borges et al. have previously described improvement in RV strain with vasodilator therapy in a small observational single center study of 37 patients,²¹ the relationship between changes in RV and LV deformation and changes in pulmonary hemodynamics have not been previously reported. We demonstrate that improvement in

PVR over 24 weeks was associated with improvement in both RV and LV deformation, in concert with improvement in MPAP, RAP, and SVI. Interestingly, the strength of association of these changes was greater with LV global and septal CS than RV FWLS, suggesting that alteration in LV performance secondary to RV overload may be more sensitive to changes in pulmonary hemodynamics in PAH. Indeed, in previous therapeutic trials in PAH, indirect markers of RV overload – such as degree of septal flattening quantified by the LV eccentricity index – have been more consistently associated with increased risk of death than direct non-invasive measures of RV function.^{7,22,23}

Impact of imatinib therapy on RV and LV deformation

To our knowledge, ours is the first study to assess the impact of a PAH-specific therapy on myocardial deformation in the context of a multicenter randomized clinical trial. In the IMPRES trial and the echocardiographic sub-study, imatinib therapy was associated with significant improvements in MPAP, PVR, and SVI compared to placebo in PAH patients with elevated PVR (>800 dynes·sec·cm⁻⁵) despite therapy with two or more PAH-specific medications.^{13, 14} In this study, imatinib therapy was also associated with significant improvement in RV FWLS compared to placebo. These findings suggest that imatinib may be effective at attenuating the cardiac functional changes associated with PAH. Importantly, they also suggest that RV FWLS is a responsive measure to treatment effect in PAH. Further study is warranted to assess whether this non-invasive measure may be appropriate as an efficacy endpoint in future PAH trials.

Limitations

Several limitations of this exploratory, hypothesis generating post-hoc analysis should be noted. As the echocardiographic sub-study was voluntary, only a subset of patients enrolled in the IMPRES trial participated. In addition, missing data was present at 12-weeks and 24-weeks, due to either patient drop out from the main study, the echocardiogram not being received by the core laboratory, or images not being analyzable for deformation measurements. Strain analysis was not prespecified for the echo study, possibly contributing to missing data due to image quality. Of patients with baseline data, those without follow-up echocardiographic data had modestly lower PVR and CI compared to those with follow-up data. For our analysis of treatment effect, we addressed missing data by using a mixed-effects repeated measures analysis. Furthermore, we performed sensitivity analyses using both an observed case analysis and a LOCF, which is often considered to be more conservative than an observed case analysis,^{24,25} both of which demonstrated similar results. However, despite the consistent results of these sensitivity analyses, we cannot exclude the possibility that differential loss of follow-up of patients with more severe PAH may influence our results. Analysis of LV longitudinal strain among IMPRES PAH patients was not technically feasible due to the magnitude of LV compression and distortion by the markedly enlarged RV in the apical views. IMPRES was not powered for outcomes, limiting our ability to study the predictive value of measurements of RV and LV deformation. However, our novel findings of the ability of deformation measurements to reflect changes in invasive hemodynamics, which have known prognostic relevance in PAH, highlight the potential prognostic value of deformation measurements in PAH. In addition, these findings

suggest the potential utility of changes in myocardial deformation in assessing treatment response.

Conclusions

RV and LV deformation are impaired in patients with severe PAH, and the magnitude of impairment in RV FWLS is significantly associated with hemodynamic measures and biomarkers reflective of disease severity. Reduction in PVR in PAH is associated with improvements in both RV and LV deformation, coupled to improvements in MPAP and SVI, with LV global and septal CS the strongest correlate of these changes. Finally, RV FWLS is a measure that is sensitive to treatment effect, demonstrating greater improvement with imatinib compared to placebo as add-on therapy in this sub-study of a multicenter randomized controlled trial in advanced PAH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Representative examples of deformation measurements in a patient with PAH. (A) RV global longitudinal strain (RV GLS); white – segments comprising RV free wall (FWLS), light grey – segments comprising RV septal wall (SLS). (B) LV circumferential strain (LV global CS); light grey – segments comprising LV septal segments (Septal), white – segments comprising non-septal LV segments (Non-septal). The right-most panel demonstrates average and segmental strain curves for both RV LS (top) and LV CS (bottom). From top to bottom: RV

longitudinal strain: (A.1) IMPRES patient. (A.2) Control patient; LV circumferential strain:
(B.1) IMPRES patient. (B.2) Control patient.

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Figure 2.

Study population, including IMPRES patients with PAH and healthy controls. LS – longitudinal strain; CS – circumferential strain.

Figure 3.

Scatter plot showing the correlation between change in deformation measures (left – RV FWLS; right – LV global CS) and change in invasively measured hemodynamics (MPAP, SVI, PVR). Correlation coefficients (Pearson's correlation for SVI; Spearman's correlations for MPAP and PVR) and p value are provided.

Figure 4.

Cardiac deformation (left – RV FWLS; right – LV global CS) at baseline, 12 weeks, and 24 weeks in IMPRES patients treated with imatinib versus placebo. Values provided are mean and standard errors. P value is for the combined difference between groups, derived from mixed-effects repeated measures models, adjusting for baseline value.

Baseline demographic and standard echocardiographic characteristics of IMPRES and controls groups. The control group did not undergo right heart catheterization.

Table 1

	CONTROLS		IMPRES		P Value
	N		N		
Demographics					
Age (years)	30	49.23±12.3	68	49.9±13.3	0.82
Female n(%)	30	20 (67)	68	56 (82)	0.12
White (%)	30	20 (67)	68	58 (85)	0.04
Clinical Exam					
Body mass index	30	23.9±3.9	68	25.4±5.6	0.14
WHO class III & IV (%)	N/A	N/A	68	44 (65)	N/A
6 minute walk distance (m)	N/A	N/A	68	355±71	N/A
NT-proBNP (pg/mL)	N/A	N/A	65	101 [44, 224]	N/A
Hemodynamics					
Heart rate (bpm)	29	69±11	59	81±12	0.0001
Systolic blood pressure (mmHg)	27	124±12	63	107±14	<0.0001
Diastolic blood pressure (mmHg)	27	71±9	63	66±10	0.035
Right atrial pressure (mmHg)	N/A	N/A	68	10±5	N/A
Mean pulmonary artery pressure (mmHg)	N/A	N/A	68	60 [51, 66]	N/A
Pulmonary capillary wedge pressure (mmHg)	N/A	N/A	68	10±3	N/A
Pulmonary vascular resistance (dyne-sec-cm ⁻⁵)	N/A	N/A	68	1113 [932, 1334]	N/A
Stroke volume index (ml/min)	N/A	N/A	67	27.3±6.4	N/A
Standard Echocardiography: RV function					
TA S' (m/sec)	12	14.19±2.3	66	10.55±2.5	<0.0001
TAPSE (mm)	4	2.15±0.11	56	1.74±0.38	0.035
RVFAC (%)	29	54±6	67	23±8	<0.0001
RV Tei index	26	0.24±0.14	60	0.69±0.21	<0.0001
Standard Echocardiography: Right side dimensions					
RAA (cm ²)	29	15.1±3.3	68	25.3±9.1	<0.0001
IVC width (cm)	27	1.57±0.35	62	1.88±0.54	<0.008

	CONTROLS		IMPRES		P Value
	N		N		
RVEDA (cm ²)	29	19.7±4.5	67	35.9±11.4	<0.0001
LV eccentricity index	30	0.98±0.10	62	0.77±0.13	<0.0001
Standard Echocardiography: LV dimension and function					
LVEDD (cm)	30	4.3±0.5	67	3.6±0.5	<0.0001
LVEF (%)	30	61±5	62	58±6	0.02
E wave (cm/sec)	27	78.6±11.3	64	68.0±18.3	0.007
E'	29	12.7±3.6	63	10.5±2.9	0.003
E/E'	27	6.6±1.7	60	7.0±3.1	0.53
Deceleration Time	26	0.22±0.03	58	0.25±0.06	0.01
Echocardiography: RV deformation					
RV GLS	30	-27.0±3.8	60	-14.7±4.6	<0.0001
RV FWLS	30	-30.8±4.3	60	-15.9±5.4	<0.0001
RV SPLS	30	-23.2±4.8	60	-13.5±5.0	<0.0001
Echocardiography: LV deformation					
LV Global CS	30	-27.6±4.2	64	-26.6±5.5	0.34
LV Septal CS	30	-31.4±5.3	64	-24.2±8.2	<0.0001
LV Non-septal CS	30	-25.7±4.8	64	-27.8±6.2	0.07

Table 2

Correlations between baseline RV invasive hemodynamics and NT-proBNP with RV FWLS and LV global, septal and non-septal CS as well as with other standard echocardiographic measurements of RV function, in PAH patients.

	FW RV LS (N=60)	LV global CS (N=64)	LV septal CS (N=64)	LV non- septal CS (N=64)	TA S' (N=66)	TAPSE (N=56)	RVEAC (N=67)	RV Tei Index (N=60)
Mean RAP	0.34 P=0.007 [§]	0.20 P=0.11	0.07 P=0.59	0.22 P=0.08	0.03 P=0.83	-0.14 P=0.30	-0.17 P=0.17	0.003 P=0.98
Mean PAP*	0.36 P=0.005 [§]	0.23 P=0.07	0.02 P=0.85	0.30 P=0.02	-0.17 P=0.17	-0.13 P=0.32	-0.26 P=0.03	0.002 P=0.99
RV SVI	-0.43 P=0.0007 [§]	-0.37 P=0.003	-0.32 P=0.01	-0.28 P=0.03	0.18 P=0.15	0.37 P=0.006	0.34 P=0.005	-0.08 P=0.62
PVR*	0.31 P=0.02 [§]	0.20 P=0.11	0.05 P=0.69	0.21 P=0.10	-0.30 P=0.02	-0.35 P=0.009	-0.18 P=0.15	0.02 P=0.88
PCWP	0.17 P=0.18	0.24 P=0.06	0.02 P=0.85	0.21 P=0.09	0.14 P=0.26	0.06 P=0.64	0.06 P=0.64	-0.14 P=0.28
NT-proBNP[‡]	0.39 P=0.003	0.04 P=0.78	0.05 P=0.07	0.05 P=0.69	-0.19 P=0.16	-0.44 P=0.002	-0.32 P=0.02	0.31 P=0.03

* Based on Spearman correlation.

[‡] Based on logarithmic transformed values.

[§] Association remains significant after adjusting by other RV echocardiographic measures of RV function.

Table 3

Correlations between changes after 24 weeks in invasive hemodynamics and changes in RV FWLS, LV global, septal and non-septal CS and other standard echocardiographic measurements of RV function in PAH patients. Pearson correlation for RAP, SVI, and PCWP; Spearman correlation for MPAP and PVR.

	FWLS (N=39)	LV global CS (N=38)	LV septal CS (N=38)	LV non- septal CS (N=38)	TA S' (N=42)	TAPSE (N=32)	RVFAC (N=42)	RV Tei Index (N=33)
RAP	0.17 P=0.31	0.33 P=0.04	0.22 P=0.09	0.34 P=0.04	-0.29 P=0.06	-0.08 P=0.66	-0.07 P=0.65	0.006 P=0.97
MPAP	0.33 P=0.04	0.60 P=0.0001	0.56 P=0.002	0.46 P=0.004	-0.40 P=0.009	0.08 P=0.63	-0.22 P=0.21	0.27 P=0.12
SVI	-0.25 P=0.14	-0.55 P=0.0005	-0.45 P=0.006	-0.48 P=0.003	0.36 P=0.02	0.17 P=0.37	-0.05 P=0.75	-0.49 P=0.005
PVR	0.39 P=0.02	0.61 P=0.0001	0.50 P=0.005	0.56 P=0.0004	-0.41 P=0.005	-0.09 P=0.92	-0.22 P=0.16	0.47 P=0.006
PCWP	-0.12 P=0.49	0.13 P=0.46	0.28 P=0.09	0.14 P=0.60	0.04 P=0.80	-0.02 P=0.90	0.18 P=0.26	-0.32 P=0.08

Changes in right ventricle free wall longitudinal strain (FWLS), left ventricle global circumferential strain (LV global CS), LV septal CS, and LV non-septal CS associated with imatinib therapy during follow-up. Estimates and P values are derived from mixed-effects repeated measures models, adjusting for baseline value. Effect estimates and P values at 12 week and 24 week visits are provided. Total N includes patients with any follow up at 12 week or 24 week

Table 4

Combined follow-up			12 weeks		24 weeks		Treat- ment × Visit Inter- action P
N	Effect estimate (95% CI)	P value	Effect estimate (95% CI)	P value	Effect estimate (95% CI)	P value	
Right Ventricle Free Wall Longitudinal Strain							
FWLS (%)	53	-3.11 (-5.84 – -0.38)	0.026	-1.71 (-4.69 – 1.27)	0.26	-4.69 (-7.72 – -1.66)	0.002
Left Ventricle Global Circumferential Strain							
LV global CS	55	-2.28 (-5.52 – 0.97)	0.17	-2.57 (-6.27 – 1.12)	0.17	-1.90 (-5.84 – 2.05)	0.35
Left Ventricle Septal Circumferential Strain							
LV septal CS	55	-3.49 (-8.35 – 1.37)	0.16	-5.00 (-10.58 – 0.59)	0.08	-1.62 (-7.61 – 4.37)	0.60
Left Ventricle Non-septal Circumferential Strain							
LV non-septal CS	55	-1.57 (-4.80 – 1.66)	0.34	-1.24 (-4.89 – 2.40)	0.50	-1.99 (-5.89 – 1.90)	0.32
							0.70