Impaired Left Ventricular Mechanics in Pulmonary Arterial Hypertension:
Identification of a Cohort at High Risk

Hardegree et al: LV Mechanics in PAH

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DOI: 10.1161/CIRCHEARTFAILURE.112.000098

Journal Subject Codes: 18, 31, 150
Abstract

**Background**—Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling and right heart failure. The right (RV) and left ventricles (LV) do not function in isolation, sharing a common pericardial sac and interventricular septum. We sought to define the clinical and prognostic significance of ventricular interdependence in PAH and its association with left ventricular filling patterns through speckle-tracking strain echocardiography.

**Methods and Results**—Echocardiography was performed in 71 adults with a new diagnosis of PAH. To separately analyze LV and RV function, we measured peak systolic longitudinal and circumferential strain of the LV and RV. Survival was assessed over two years. Patients had dilated right-sided chambers (RA volume index 44±19 mL/m²; RV end-diastolic area 34±9 cm²), and reduced RV function (RV fractional area change 28±12%). Speckle tracking echocardiography revealed significant reductions in RV free wall peak systolic strain (-15±3%). Despite normal LV size and normal conventional measures of LV systolic function (end-diastolic dimension 42±6 mm; ejection fraction 65±8%; cardiac index 2.6±0.8 L/min/m²), patients had reduced LV free wall systolic strain (-15±3%). Decreased LV free wall systolic strain was associated with a delayed relaxation mitral inflow Doppler pattern, p=0.0002. During 2 years follow-up, 19 patients (27%) died. LV strain was associated with increased mortality (unadjusted HR 2.40 per 5% decrease in LV free wall strain, 1.22-4.68), which remained significant when adjusted for age, sex, WHO functional class, and PAH etiology (HR 3.11, 1.38-7.20).

**Conclusions**—The pressure loading in PAH results in geometric alterations and functional decline of the RV, with marked reduction in RV systolic strain. Despite preservation of LVEF, LV systolic strain was also reduced and associated with early mortality, highlighting the significance of ventricular interdependence in PAH.

**Key Words:** diastolic function, echocardiography, pulmonary hypertension, right ventricle, risk prediction, strain rate
Abbreviations

**BNP**, B-type natriuretic peptide; **EF**, ejection fraction; **FC**, functional class; **GFR**, glomerular filtration rate; **LV**, left ventricle/ventricular; **PAH**, Pulmonary arterial hypertension; **PH**, pulmonary hypertension; **RHC**, right heart catheterization; **RV**, right ventricle; **RVSP**, (estimated) right ventricular systolic pressure; **RVDP**, (estimated) right ventricular diastolic pressure; **TVI**, time velocity integral; **WHO**, World Health Organization
Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling, right heart failure, and reduced survival.\textsuperscript{1} Both symptoms and extent of right heart failure predict mortality.\textsuperscript{2-4} Measures of RV filling pressure and systolic function have been shown to correlate with clinical disease progression and survival.\textsuperscript{5-8}

Right ventricular contraction is a complex process related to a variety of actions, the predominant being longitudinal motion, due to the arrangement of ventricular myofibrils.\textsuperscript{9-12} Right ventricular systolic strain assessment by speckle-tracking echocardiography is an angle-independent sensitive measure of RV contraction shown to correlate with clinical symptoms and invasive hemodynamic measures, and is predictive of disease progression and mortality.\textsuperscript{13-17}

PAH is a disease of the pulmonary circulation with resultant effects on the right heart. Conceptually, left heart anatomy and function should be normal in patients with PAH. However, the RV and LV do not function in isolation, sharing a common pericardial sac and interventricular septum.\textsuperscript{18} A delayed relaxation mitral inflow Doppler pattern on echocardiography (a feature seen in normal or low filling pressures and diastolic dysfunction) has been linked to severity of disease in PAH; however, it is unclear whether this Doppler pattern reflects impaired LV filling due to reduced RV output or intrinsic LV dysfunction.\textsuperscript{19} We sought to define the clinical and prognostic significance of ventricular interdependence in PAH and its association with LV filling patterns through speckle strain-based echocardiography.

Methods

Study population and testing. Potential subjects were recruited from a registry of serial subjects newly diagnosed with pulmonary arterial hypertension. One patient was excluded because of a hemodynamically significant pericardial effusion and 5 because echocardiographic images were
inadequate for the assessment of LV strain by the speckle-tracking method. The remaining 71 patients comprised the study group.

All were adults (≥ 18 years) with PAH, first seen at Mayo Clinic Rochester, who were naïve to pulmonary vascular targeted therapy. Individuals were included if they fulfilled the contemporary diagnostic criteria for group 1 PH (mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, pulmonary capillary wedge pressure less than 15 mm Hg)\textsuperscript{20} and had echocardiographic images suitable for LV longitudinal strain analysis. Patients with congenital systemic-pulmonary shunts were excluded. Etiology of PAH was sub-classified as a) idiopathic, familial or related to anorexigenic drug use, b) portopulmonary, c) PAH associated with connective tissue disease, and d) other PAH. All patients consented to the use of their data for research, and the study was approved by the institutional review board.

We analyzed the following baseline characteristics at the time of initial evaluation: age; sex; WHO functional class (FC); 6-minute walk distance (6MW); B-type natriuretic peptide; diffusing capacity of carbon monoxide on pulmonary function testing normalized for age, gender, height;\textsuperscript{21} and estimated glomerular filtration rate (GFR). GFR was derived by the Modified Diet in Renal Disease equation.\textsuperscript{22} The 6MW test was performed under standard conditions under supervision from a PH clinic nurse. Survival status was available in all patients over a 2-year follow-up through clinical follow-up through our pulmonary hypertension clinic.

**Echocardiography.** Transthoracic echocardiography (2D and Doppler) was performed according to American Society of Echocardiography guidelines.\textsuperscript{23} Echocardiographic images were reviewed by a study echocardiologist (AS, JH, GCK), blinded to the clinical, laboratory and hemodynamic information. RA pressure estimation was based on interrogation of the inferior
vena cava (IVC) diameter and distensibility and pulsed wave Doppler interrogation of hepatic
vein flow and scored as 5 (normal sized IVC with >50% respiratory collapse and systolic
forward predominant flow on hepatic vein Doppler), 10 (borderline/normal sized IVC with
>50% respiratory collapse and equal degrees of systolic and diastolic forward flow on hepatic
vein Doppler), 15 (enlarged IVC with >25% respiratory collapse and predominant diastolic
forward flow on hepatic vein Doppler) or 20 mm Hg (enlarged IVC with minimal or no collapse
and solely diastolic forward flow or systolic flow reversal on hepatic vein Doppler). The mean
PA pressure (mPAP) was calculated as the mean trans-tricuspid valve gradient + estimated
RAP\textsuperscript{24} and the diastolic pressure derived from the equation: diastolic PA pressure =2(mPAP)−systolic PA pressure as there was insufficient subjects with end pulmonary regurgitant velocity
data. PA capacitance was calculated as the Doppler derived stroke volume/PA pulse pressure.\textsuperscript{25}
The RV index of myocardial performance (RIMP, Tei index) was calculated as previously
described.\textsuperscript{7} Two-dimensional and M-mode echocardiography (including tissue Doppler imaging)
were used to measure mitral peak velocity of early filling (E) and early diastolic medial mitral
annular velocity (e') in the standard fashion.\textsuperscript{26}

**Ventricular Strain Imaging.** Three beat 2-D digital clips of the apical two chamber and long-
axis views of the LV and apical 4 chamber views of the LV and RV (average frame rates 44±14
frames per second) were transferred to an independent Syngo Velocity Vector Imaging
workstation (Siemens Medical Solutions, Mountain View, CA) for analysis of regional and
global peak longitudinal and circumferential systolic strain. The ventricular endocardium was
traced with 10-15 points, starting and ending at the atrio-ventricular valve annulus. Negative
strain values indicate tissue contraction and positive values indicate tissue lengthening. The
ventricular septum is a shared wall that contributes to both the left and right ventricles. Hence
any deviations from normal of ventricular strain may reflect abnormalities of the LV, RV or both. To separately analyze LV and RV systolic function, strain measures of the shared intraventricular septum were excluded with analyses focused on the LV and RV free walls. The free wall of the LV was an average of the inferior, anterior and lateral walls i.e. the whole LV minus the basal, mid and apical septal segments. The RV free wall was an average of the basal, mid and apical segments from the anterior (free) wall of the RV from the apical 4 chamber view as described previously.

**Invasive Hemodynamics.** Parameters of mPAP, RA pressure, pulmonary vascular resistance, cardiac index, and cardiac output were recorded at the time of cardiac catheterization. Right ventricular stroke work index (RVSWI) was calculated using the following formula: 

\[
RVSWI = \frac{(\text{mean PAP} - \text{mean RAP}) \times (\text{stroke volume index}) \times 0.0136}{\text{cardiac index}}
\]

where stroke volume index equals cardiac index divided by heart rate. Catheterization was performed within days of baseline echocardiography (median 2 days, interquartile range -10 to 19).

**Data analysis.** Statistical analyses were performed using JMP version 9.0 (SAS Institute Inc., Cary, NC). Continuous variables were presented as mean± SD or median with interquartile range and tested between groups using analysis of variance. Categorical variables were presented as number and percentage with comparisons by Pearson chi-square analysis.

The distribution of LV free wall systolic strain was separated into two groups based on a LV free wall systolic strain above or below -13%. This dichotomous value corresponded to the lowest quartile of the LV free wall systolic strain distribution. The relationship of LV free wall strain was assessed either as a continuous or dichotomous variable as outlined. Cox proportional
hazards regression models were used to identify correlates of all-cause mortality. Results are presented as hazard ratios (HR’s) with 95% CIs. Models were developed with stepwise techniques and by consideration of variables that were clinically relevant. Variables included were LV free wall strain, RV free wall strain, age, sex, WHO FC, PAH etiology, and estimated RAP by echocardiography. Follow-up of patients is presented based on the Kaplan-Meier product-limit method and compared between groups using the log-rank test. For all analyses, p<0.05 was considered to be significant.

Results

Clinical and echocardiographic characteristics. The characteristics of the 71 study subjects are presented in Table 1. The majority of patients were WHO FC III (65%) or IV (10%). Right heart catheterization demonstrated elevated RAP, PAP, and PVRI with depressed cardiac and stroke volume index. Patients had severe right atrial and RV enlargement and reduction in measures of RV contractile function, including fractional area change (RV FAC) and RV (Tei) index of myocardial performance. The average RV free wall longitudinal systolic strain was -15 ± 5% (average in normal subjects is -22%)\(^2\); Figure 1A and average RV longitudinal strain rate was -2.8 ± 1 cm/s.

LV function. Concomitantly, measures of LV size and ejection fraction were within normal limits (Table 1). However, measures of LV peak longitudinal systolic strain (Figure 1B) were reduced. The average LV free wall longitudinal systolic strain was -15 ± 3%.

The LV free wall longitudinal systolic strain separated into quartiles was as follows. 1) Less negative than or equal to -13% (n=15); 2) -13% to -16% (n=22); 3) -16% to -18% (n=15)
and 4) more negative than -18% (n=19). The average LV free wall strain rate was -0.95 ± 0.3 cm/s. Summarized in Table 2 and notably at similar PA pressure, an LV free wall longitudinal systolic strain < -13% correlated with smaller LA and LV dimensions (LA volume index, LV end-diastolic dimension), lower cardiac index, worse PA capacitance, and worse RV performance with a higher Tei index and lower RV stroke work index) as well as a greater frequency of clinical right heart failure as defined by the presence of significant peripheral edema despite diuretic use (58% [7/12] vs. 25% [12/48], p 0.02). LV free wall strain was not associated with body mass index (p=0.2), serum creatinine (p=0.73) or glomerular filtration rate (p=0.15).

**Relationship of LV longitudinal systolic strain and mitral inflow patterns.** Diastolic mitral inflow Doppler patterns were assessed in the standard fashion.26, 28 A delayed relaxation mitral inflow pattern was associated with decreased LV systolic strain. Those patients with LV free wall longitudinal systolic strain < -13% were significantly more likely to demonstrate a delayed relaxation mitral inflow Doppler pattern (67% [10/15]) than those with LV systolic strain better than -13% (18% [10/56], p 0.0002). Patients with a delayed relaxation mitral inflow pattern demonstrated decreased average LV free wall longitudinal systolic strain (-12.7 ± 2.6) compared with those with normal LV diastolic filling patterns (-16.4 ± 3.2, p < 0.0001; Figure 2A). No difference was observed between patients with more versus less severe LV strain impairment in medial early diastolic mitral annular velocity (e' velocity 0.05 ± 0.04 vs 0.06 ± 0.02 cm/s, p 0.41) or E/medial e’ ratio (11.4 ± 5 vs 10.7 ± 5, p 0.66).
Predictors of overall mortality. The association of a delayed relaxation mitral inflow Doppler pattern with mortality has been previously reported in PAH, and was confirmed in our study. We demonstrated a greater 2-year all-cause mortality among patients with a delayed relaxation mitral inflow pattern (55%, 11/20) compared to those with normal LV diastolic filling (16%, 8/51; p 0.0002). Kaplan-Meier survival analysis over two year follow-up separated for mitral inflow pattern is displayed in Figure 2B.

In addition, an impairment in LV free wall longitudinal systolic strain was also associated with decreased survival (Figure 3). Those with LV free wall longitudinal systolic strain < -13% had a significantly higher 2-year mortality rate (53%, 8/15) compared with those with LV free wall longitudinal systolic strain ≥ -13% (21%, 12/56; p = 0.004). As demonstrated in Figure 4, for every 5% (1 SD) decline in LV free wall longitudinal systolic strain the mortality rate at two years doubled (age and sex adjusted 2 year HR, 2.37, 95% CI 1.11-5.36). This risk persisted when adjusted for age, sex, WHO FC, PAH etiology, and RA pressure. However when adjusted for the degree of RV dysfunction as measured by RV free wall systolic strain the association of LV free wall systolic strain with mortality disappeared.

Left ventricular circumferential strain. We analyzed an alternate vector of myocardial contractility. The average left ventricular circumferential strain was -20.1 ± 6%. The circumferential strain correlated modestly with the longitudinal strain (r²=0.1; p<0.008). Those subjects with the lowest quartile of circumferential strain (worse than -16%) had worse outcome with a 2 year mortality of 47% compared to 22% (p=0.04); although in the group overall, the circumferential strain did not confer a significant risk (age and sex adjusted HR 1.33 (0.64-2.99; p=0.46).
Discussion

Right ventricular systolic dysfunction is a recognized feature of PAH with the severity of RV dysfunction correlating with symptoms, mortality and 2-dimensional longitudinal strain, a sensitive quantitative measure of contractility emerging as a potent measure of RV function in PAH. While PAH is defined by normal LV filling pressures, prior reports have suggested LV mechanics may be altered, perhaps mediated through ventricular interdependence. Here we utilized strain imaging to evaluate whether, in the setting of normal LV ejection fraction and LV filling pressure in PAH, impairment in LV mechanical function was present in PAH and whether it was of clinical significance.

Our study demonstrates a relationship between LV and RV contractility in PAH. Here we describe the clinical, echocardiographic and hemodynamic correlates of LV strain reduction in PAH, including RV strain reduction, smaller LA and LV chamber dimensions, worse RV stroke work index and RV (Tei) index of myocardial performance, and a delayed relaxation mitral inflow Doppler pattern. Furthermore, we have demonstrated a strong correlation between reduced LV strain measures and delayed LV relaxation in patients with PAH and normal pulmonary capillary wedge pressures at catheterization.

The LV is designed to perform against systemic arterial pressures, the RV in comparison, has a thinner wall and higher compliance, resulting in a lower tolerance for elevated afterload. In PAH, chronic pressure loading results in geometric changes of the RV, including increased volume, hypertrophy, and transformation to a more spherical shape, resulting in functional decline over time. Studies have demonstrated that increased RV pressure and RV dilatation result in higher transseptal pressures, which as a result of the shared space within the pericardial sac, cause a bowing of the interventricular septum into the LV with resultant distortion of LV

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geometry and function. This underlies the important and clinically relevant concept of ventricular interdependence in PAH.

In our study, we demonstrated ventricular interdependence by identifying impairment in LV contractility, correlating reduction in longitudinal systolic strain of the LV free wall with a reduction in longitudinal systolic strain in the RV free wall in patients with PAH. We also showed that while conventional measures of LV systolic function remained normal, LV systolic strain was significantly reduced in concert with reduced RV systolic strain, and was predictive of outcome.

Experimental models have demonstrated that approximately one third of RV output is attributable to LV contraction. Furthermore, RV pressure- or volume-overload leads to a leftward shift of the interventricular septum and increased LV constraint by the pericardium and the LV is small, D-shaped and underfilled with reduced LV distensibility, increased end-diastolic pressure, reduced preload and reduced cardiac output. Markers of diastolic dysfunction are common and are associated with the degrees of LV and RV structural change, hemodynamics and outcome. Here we demonstrate that sensitive markers of LV systolic function (strain / strain rate) are abnormal in this setting and associated with poor outcome. What is less clear is the mechanism(s) by which enlarged dysfunctional RV may lead to underfilling of the LV. Two logical explanations are a) a direct ventricular interaction leading to a limitation in LV diastolic filling or b) a hemodynamic effect where a low RV cardiac output in the setting of a high pulmonary vascular resistance leads to an underfilled LV. Aspects of our work and others support these concepts and indeed we cannot exclude that the reduction is LV strain measures, that correlate with measures of abnormal LV filling and predict poor outcome, are a result of rather than a cause of LV underfilling.
Here, decreased LV free wall longitudinal systolic strain corresponded to the presence of a delayed relaxation mitral inflow Doppler pattern. Those with lower LV strain tended to have smaller LA volumes and smaller LV cavities. This may point toward impaired filling as a contributing factor in LV functional impairment. Other groups have also noted similar findings of LV diastolic dysfunction in patients with PAH, as demonstrated by impaired LV relaxation. Proposed mechanisms include an early diastolic left-to-right septal displacement with reduced LV compliance, decreased LV torsion with delayed diastolic untwisting, increased RV tension leading to prolonged myocardial shortening with impairment of RV systole and LV diastole, RV conduction slowing and action potential prolongation with resultant ventricular dyssynchrony and diastolic delay, and impaired LV filling through preload reduction. Indeed, patients tended to have a reduction in the early peak diastolic tissue velocities of the mitral annulus (E), although neither E’ velocity nor E/E’ ratio was different between those with or without severe LV systolic strain reduction. It must be recognized that any reduction in medial annular tissue relaxation velocities may reflect RV abnormalities due to the shared septum. Measures of lateral wall myocardial relaxation would be of interest in this cohort, but were not acquired. However, this was the reason that LV systolic strain analysis was focused on the free wall rather than the shared septum, as any deviations from normal of ventricular strain may reflect abnormalities of the LV, RV or both. Some prior studies have evaluated LV strain in PAH and found a range of longitudinal strain values but on average no clear difference compared to normals, however these studies used the more variable technique of Doppler-based, rather than 2D-speckle-based, strain and included only small cohorts of patients (≤20 subjects), rather than the 71 subjects in the current study.
All subjects included in this study met the conventional Dana Point classification of group 1 pulmonary hypertension with a mean PA pressure $\geq 25$ mm Hg and a pulmonary arterial wedge pressure $\leq 15$ mm Hg.\textsuperscript{20} The lower LA volume indices seen in those patients with the worst LV strain suggest that this subset did not display elevations in LA pressure. This was corroborated by the fact that there was no difference in pulmonary capillary wedge pressure seen between groups. Some subjects had ‘mildly elevated’ LA volume indexes. Whether this is related to prior elevations in left atrial pressure is unknown. No patient had a history of prior left heart disease or prior invasive measurements of left-sided pressures prior to their index catheterization (when all wedge pressures were $\leq 15$ mm Hg). However we cannot exclude that subjects may have had elevations in LA pressure at some stage in their past, which plausibly could explain the mild elevations in LA size seen in some subjects. The inverse correlation of LA size and LV strain abnormalities suggest that this was not a major factor in the LV strain abnormalities seen. Tonelli et al. similarly demonstrated lower left atrial volumes in PAH patients with diastolic dysfunction compared to PAH patients with normal diastolic function.\textsuperscript{30}

Our study did have some limitations. First, this study was retrospective in nature. These original images were obtained on 3 different echo-vendor systems with subsequent strain data acquired with a single vendor analysis software, although no difference has been found between systems in a normal cohort.\textsuperscript{27} We did not evaluate radial strain or LV torsion, which could be the subject of a future study of ventricular mechanics in PH. Further, our study included patients with different underlying etiologies of PH, but those with congenital systemic-pulmonary shunts were excluded. As such, our conclusions cannot be extrapolated to that population. Finally, 75% of our patients had WHO FC III or IV symptoms at the time of evaluation. Thus, the utility of LV strain in milder disease is not described.
In summary, our study illustrates the presence and clinical significance of ventricular interdependence in PAH. The degree of RV dysfunction, a known correlate of PAH disease severity, was associated with decreased longitudinal LV strain, which is a sensitive measure of LV contractility, underscoring the significance of ventricular interdependence which has implications for PAH patient prognosis.

**Sources of Funding**

This work was supported by the Mayo Clinic CR20 program.

**Disclosures**

Dr. McGoon’s institution has received research funding from Medtronic and Gilead. He has served on advisory, steering, and/or endpoint/DSMB committees for Actelion, Gilead, Lung LLC, GSK, and Medtronic. He has received honoraria for speaking at conferences supported by Actelion and Gilead. Dr. Frantz has received consulting fees from Pfizer and contracted research support from United Therapeutics. There are no other financial disclosures for any of the other authors.

**References**


Table 1. Baseline characteristics of the study population

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<tr>
<td>Sex, % female</td>
<td>54 (76%)</td>
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<td>57 ± 14</td>
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<td>WHO Class I / II</td>
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<tr>
<td>WHO Class III / IV</td>
<td>46 (65%) / 7 (10%)</td>
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<td>6 minute walk test, mean (±SD) meters</td>
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<td>Idiopathic and familial PAH</td>
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<td>PAH with connective tissue disease</td>
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<td>Portopulmonary Hypertension</td>
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<td>Creatinine, mg/dL</td>
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<td>Diffusing capacity of carbon monoxide (%)</td>
<td>56 ± 19</td>
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<td>PA systolic/diastolic pressure, mm Hg</td>
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<td>Estimated RA pressure, mm Hg</td>
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<td>RV fractional area change, %</td>
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<td>Left atrial volume index, cc/m²</td>
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<td>Left ventricular end diastolic dimension, mm</td>
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<td>Left ventricular ejection fraction, %</td>
<td>65 ± 8</td>
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<td>Medial mitral annular peak systolic velocity, cm/s</td>
<td>6.8±2</td>
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<td>20 (28%)</td>
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<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>8 ± 3</td>
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<td>Mean PA pressure, mm Hg</td>
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<td>Mean RA pressure, mm Hg</td>
<td>9 ± 5</td>
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<td>2.6 ± 0.8</td>
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<td>Stroke volume index, mL/min/m²</td>
<td>32.5 ± 12.3</td>
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<td>RV stroke work index, g.m/m²/beat</td>
<td>17.4 ± 6.9</td>
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Table 2. Comparison of patients with LV free wall longitudinal systolic strain < -13% versus ≥ -13%

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<td>&lt; -13%</td>
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<tr>
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<td>n = 15</td>
<td>n = 56</td>
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<tr>
<td><strong>Clinical</strong></td>
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<tr>
<td>Sex, % female</td>
<td>67% (10/15)</td>
<td>79% (44/56)</td>
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<tr>
<td>Age, years</td>
<td>47 ± 16</td>
<td>60 ± 13</td>
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<td>WHO Class I / II, %</td>
<td>13 (2/15)</td>
<td>32 (18/56)</td>
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<tr>
<td>WHO Class III / IV, %</td>
<td>87 (13/15)</td>
<td>68 (38/56)</td>
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<tr>
<td>6 minute walk test, mean (±SD) meters</td>
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<td>333±125</td>
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<tr>
<td>BNP, pg/mL (median and IQR)</td>
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<td>164 (60, 430)</td>
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<td><strong>Echocardiography</strong></td>
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<tr>
<td>Mid-RV diameter, mm</td>
<td>41 ± 8</td>
<td>39 ± 7</td>
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<tr>
<td>RA volume index, cc/m²</td>
<td>47 ± 15</td>
<td>43 ± 19</td>
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<td>RV index of myocardial performance</td>
<td>0.81 ± 0.3</td>
<td>0.62 ± 0.2</td>
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<td>RV fractional area change, %</td>
<td>24.7 ± 10</td>
<td>28.3 ± 11</td>
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<td>Tricuspid annular plane systolic excursion, mm</td>
<td>10 ± 5</td>
<td>13 ± 4</td>
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<td>PA capacitance, ml/mm Hg</td>
<td>1.2 ± 0.6</td>
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<td>LV end diastolic dimension, mm</td>
<td>38 ± 6</td>
<td>43 ± 6</td>
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<td>LV ejection fraction, %</td>
<td>64 ± 12</td>
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<td>Left atrial volume index, cc/m²</td>
<td>21 ± 6</td>
<td>30 ± 11</td>
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<tr>
<td>Delayed relaxation mitral inflow pattern, %</td>
<td>67 (10/15)</td>
<td>18 (10/56)</td>
</tr>
<tr>
<td><strong>Right heart catheterization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary cap. wedge pressure, mm Hg</td>
<td>8 ± 3</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Mean RA pressure, mm Hg</td>
<td>11.5 ± 4</td>
<td>8.8 ± 5</td>
</tr>
<tr>
<td>Mean PA pressure, mm Hg</td>
<td>53 ± 9</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>1.9 ± 0.5</td>
<td>2.8 ± 0.8</td>
</tr>
<tr>
<td>Stroke volume index, mL/min/m²</td>
<td>22 ± 8</td>
<td>36 ± 12</td>
</tr>
<tr>
<td>RV stroke work index, g.m/m²/beat</td>
<td>12.0 ± 4.2</td>
<td>19.0 ± 6.8</td>
</tr>
</tbody>
</table>

* ANOVA across groups
Figure Legends

**Figure 1.** A) Graphical representation of RV peak systolic strain of the basal, mid and apex of the RV septum and RV free wall (total 6), with mean ± standard deviation values displayed for each. **B)** Graphical representation of the LV strain segments (total 18) with three concentric circles representing the apex (inner circle), mid and base (outer circle). Hatch marks indicate the free wall segments averaged in the RV and LV free walls.

**Figure 2.** A) Association of delayed relaxation mitral inflow Doppler pattern with decreased LV free wall systolic strain (p=0.0002). **B)** Significantly worse two-year mortality was seen among those with a delayed relaxation mitral inflow Doppler pattern.

**Figure 3.** A severe reduction in LV free wall longitudinal systolic strain (less negative than -13%) was associated with increased mortality over 2 years of subsequent follow-up.

**Figure 4.** Multivariate analyses demonstrated that for every 5% worsening in LV free wall systolic longitudinal systolic strain there was an associated increase in mortality (unadjusted HR 2.19, 95% C.I. 1.11-4.31) which remained significant when adjusted for age, sex, functional class, and PH etiology (HR 2.82, 1.23-6.92) however not when adjusted for the degree of RV dysfunction as measured by RV free wall systolic strain.
Fig. 2A

Mean LV Free Wall Longitudinal Systolic Strain

-25

-20

-15

-10

Delayed Relaxation

Normal

$\text{p} = 0.0002$
Surviving

- Normal LV diastolic function
- Delayed relaxation

Follow-up, years

Number at risk
- 51
- 18

Surviving

- 100%
- 80%
- 60%
- 40%
- 20%

Follow-up, years

- 0
- 1
- 2

p = 0.0002

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Fig. 3

Surviving

Mild-Moderate (LV strain ≥ -13%)

Severe (LV strain < -13%)

Follow-up, years

Number at risk

56

52

48

46

44

15

12

8

8

7

p = 0.004
Impaired Left Ventricular Mechanics in Pulmonary Arterial Hypertension: Identification of a Cohort at High Risk

Circ Heart Fail. published online May 24, 2013;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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