Computational quantification of patient-specific changes in ventricular dynamics associated with pulmonary hypertension

**INTRODUCTION**

Pulmonary arterial hypertension (PAH) is a complex disorder caused by an increased vascular resistance in the pulmonary arterial circulatory system. As a consequence, pressure becomes elevated in the pulmonary artery and the right ventricle (RV). Unlike systemic hypertension, PAH is difficult to detect in routine clinical examination, and the current gold standard for diagnosis is through invasive right heart catheterization (13). Because of the difficulty in detecting PAH, the current estimated prevalence of this disease (15 to 50 per million) is most likely underestimated (39, 40, 43). Perhaps also because of this difficulty, PAH is arguably less well studied compared with systemic hypertension. Existing treatments are largely confined to relieving the symptoms and attenuating the disease progression (28). As the disease progresses, the RV remodels both structurally and geometrically, becomes dysfunctional as a result, and eventually this progression leads to decompensated heart failure and death.

A significant part of our current understanding of the ventricular mechanical alterations due to PAH has been developed using animal models (2, 10, 15, 25, 57), which may not fully reproduce the pathologies found in humans (53). Human studies have so far been largely confined to measuring ventricular function of patients with PAH at the global level (54). Specifically, global RV contractility and wall stress are typically quantified using the maximal elastance ($E_{\text{max}}$) (12, 41) and Laplace’s law (46), respectively. However, the accuracy of $E_{\text{max}}$, defined as the maximum ratio of ventricular pressure to volume during the cardiac cycle, is highly dependent on the applied methodology. The gold standard for $E_{\text{max}}$ estimation is through manipulation of venous return, but this is difficult to perform in practice (41). Estimates in patients are often confined to single beat methods, for which the accuracy has been questioned (30, 32). Similarly, the use of Laplace’s law is likely to be inaccurate when applied to the RV because of its irregular geometry (46). On the other hand, while magnetic resonance (MR) and echo imaging can quantify regional (including RV) myocardial strain or motion in vivo (11, 34, 60), strain is a load-dependent quantity and not truly a measure of myocardial contractility. As described by Reichek (50), the popular notion of equating myocardial contractility with (load...
dependent) strain measures is “off the mark [and] if contractility means anything, it is an expression of the ability of a given piece of myocardium to generate tension and shortening under any loading conditions.”

Computational modeling offers an opportunity to overcome these limitations through direct quantification of both passive and active ventricular mechanics under varying loading conditions. Such modeling has been used to assess left ventricular dynamics, and a small number of computational modeling studies have been conducted to investigate alterations of the RV mechanics in PAH (1, 7, 58). However, these studies are limited either by the use of nonhuman (rat) PAH data (7), the lack of consideration of patient-specific RV geometry (1), or the failure to consider the variability across patients with PAH (58). Consequently, there exists a gap in our current understanding of the changes in RV mechanics during the progression of PAH in humans. Here, we seek to narrow this gap by answering these questions will help us to a better understanding of how myocar-
dependent active tension generated by the tissue, altered load-independent active tension generated by the tissue, altered

### METHODS

**Patient cohort and data processing.** Twelve patients with PAH were recruited in the study and underwent both cardiac magnetic resonance (CMR) scans and right heart catheterization (RHC) that were performed at rest using standard techniques. Pulmonary arterial hypertension was defined as having a mean pulmonary artery pressure (mPAP) \( \geq 25 \text{ mmHg} \) with normal pulmonary capillary wedge pressure (\( \leq 15 \text{ mmHg} \)). The patients are from World Health Organization groups 1 (pulmonary arterial hypertension) with the majority associated with congenital heart disease. Six human subjects who had no known cardiovascular disease or other comorbidities also underwent CMR scans and served as control in this study. Invasive hemodynamics measurements were not acquired in the control group. Demographics of the study groups are summarized in Table 1. The protocol was approved by the Local Institutional Review Board, and informed consent was obtained from all subjects.

All subjects were imaged in a 3.0T Philips scanner (Philips-Ingenuity; Philips Healthcare, Best, The Netherlands). Balanced steady-state free precession (bSSFP) end-expiratory breath-hold cine images were acquired in multiple planes (short- and long-axis views). The typical imaging parameters were as follows: repetition time \( (T_R) \); echo time \( (T_E) \) ratio, 3/1 ms; matrix, 240 \( \times \) 240; flip angle, 45°; slice thickness, 8 mm; pixel bandwidth, 1,776 Hz; field of view, 300 \( \times \) 300 mm\(^2\); pixel spacing, 1.25 \( \times \) 1.25 mm; and 30 frames/cardiac cycle for both the control group and PAH group.

Left ventricular pressure was measured through arterial access by left heart catheterization, and RV pressure was measured by right heart catheterization. Continuous LV pressure, RV pressure waveforms, and ECG signals were extracted from catheterization labora-

### Table 1. Demographics of the PAH patient and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>PAH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>52 ± 14</td>
<td>52 ± 11</td>
<td>0.989</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>1/5</td>
<td>2/10</td>
<td>0.755</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.5 ± 16.9</td>
<td>61.2 ± 12.3</td>
<td>0.739</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159 ± 8</td>
<td>161 ± 10</td>
<td>0.680</td>
</tr>
<tr>
<td>Clinical exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area, m(^2)</td>
<td>1.67 ± 0.25</td>
<td>1.65 ± 0.20</td>
<td>0.873</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>24.9 ± 4.0</td>
<td>23.6 ± 3.8</td>
<td>0.526</td>
</tr>
<tr>
<td>6-min walking test, m</td>
<td>N/A</td>
<td>326 ± 134</td>
<td>N/A</td>
</tr>
<tr>
<td>NT-ProBNP, pg/mL</td>
<td>N/A</td>
<td>1,188 ± 715</td>
<td>N/A</td>
</tr>
<tr>
<td>NYHA functional class I</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>NYHA functional class II</td>
<td>N/A</td>
<td>8</td>
<td>N/A</td>
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<tr>
<td>NYHA functional class III</td>
<td>N/A</td>
<td>3</td>
<td>N/A</td>
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<tr>
<td>NYHA functional class IV</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
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<tr>
<td>Cardiac magnetic resonance</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LV ejection fraction, %</td>
<td>73 ± 7</td>
<td>58 ± 12</td>
<td>0.014</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>93 ± 7</td>
<td>86 ± 30</td>
<td>0.574</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>25 ± 6</td>
<td>37 ± 21</td>
<td>0.198</td>
</tr>
<tr>
<td>LSVS, mL</td>
<td>68 ± 7</td>
<td>49 ± 14</td>
<td>0.009</td>
</tr>
<tr>
<td>LVFW ES wall thickness, mm</td>
<td>10.02 ± 1.25</td>
<td>10.87 ± 1.96</td>
<td>0.353</td>
</tr>
<tr>
<td>LVFW ED wall thickness, mm</td>
<td>5.42 ± 0.67</td>
<td>6.43 ± 1.29</td>
<td>0.093</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>54 ± 11</td>
<td>37 ± 14</td>
<td>0.020</td>
</tr>
<tr>
<td>RVEDV, mL</td>
<td>103 ± 13</td>
<td>134 ± 72</td>
<td>0.322</td>
</tr>
<tr>
<td>RVESV, mL</td>
<td>47 ± 12</td>
<td>91 ± 68</td>
<td>0.148</td>
</tr>
<tr>
<td>RVSV, mL</td>
<td>56 ± 14</td>
<td>43 ± 13</td>
<td>0.095</td>
</tr>
<tr>
<td>RVFW ES wall thickness, mm</td>
<td>2.77 ± 0.24</td>
<td>6.22 ± 1.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVFW ED wall thickness, mm</td>
<td>1.75 ± 0.17</td>
<td>3.83 ± 0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septum ES wall thickness, mm</td>
<td>9.21 ± 2.49</td>
<td>9.09 ± 2.75</td>
<td>0.926</td>
</tr>
<tr>
<td>Septum ED wall thickness, mm</td>
<td>6.13 ± 1.70</td>
<td>6.83 ± 2.20</td>
<td>0.508</td>
</tr>
</tbody>
</table>

**Hemodynamics**

| Heart rate, beats/min       | 78 ± 16 | 88 ± 15 | 0.216  |
| Diastolic blood pressure, mmHg | 81 ± 15 | 75 ± 14 | 0.397  |
| Systolic blood pressure, mmHg | 140 ± 19 | 122 ± 27 | 0.170  |
| Peak LV pressure, mmHg      | N/A     | 129 ± 16 | N/A    |
| Peak RV pressure, mmHg      | N/A     | 64 ± 15 | N/A    |
| LV end-diastolic pressure, mmHg | N/A     | 15 ± 2 | N/A    |
| RV end-diastolic pressure, mmHg | N/A     | 11 ± 5 | N/A    |
| LV dP/dt\(_{\text{max}}\), mmHg/s | N/A   | 1,245 ± 309 | N/A    |
| LV dP/dt\(_{\text{min}}\), mmHg/s | N/A   | −1,295 ± 275 | N/A    |
| RV dP/dt\(_{\text{max}}\), mmHg/s | N/A   | 444 ± 273 | N/A    |
| RV dP/dt\(_{\text{min}}\), mmHg/s | N/A   | −539 ± 232 | N/A    |
| Cardiac output, L/min       | 4.90 ± 1.16 | 3.98 ± 1.51 | 0.211  |
| Cardiac index, L-min\(^{-1}\)m\(^{-2}\) | 2.94 ± 0.57 | 2.39 ± 0.84 | 0.167  |
| Right atrial pressure, mmHg | N/A     | 9 ± 9 | N/A    |
| Mean pulmonary artery pressure, mmHg | N/A     | 39 ± 9 | N/A    |
| Pulmonary capillary wedge pressure, mmHg | N/A     | 11 ± 3 | N/A    |
| Systemic vascular resistance, dyn·cm\(^{-5}\) | N/A   | 1,889 ± 751 | N/A    |
| Pulmonary vascular resistance, dyn·cm\(^{-5}\) | N/A   | 535 ± 254 | N/A    |
| Pulmonary systemic flow ratio | N/A   | 0.99 ± 0.1 | N/A    |
| Pulmonary and systemic resistance ratio | N/A   | 0.33 ± 0.15 | N/A    |

Values are means ± SE; \( n \), number of subjects. PAH, pulmonary arterial hypertension; NT-ProBNP, NH\(_2\)-terminal-pro-brain natriuretic peptide; NYHA, New York Heart Association; LV, left ventricular; RV, right ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; PV, free wall; ES, end systole; ED, end diastole; dP/dt\(_{\text{max}}\), and dP/dt\(_{\text{min}}\), maximum and minimum first derivative of LV pressure, respectively; N/A, not applicable.
ory system and were aligned according to the simultaneously recorded ECG signals (R-R interval). These pressure waveforms were digitized using GetData Graph Digitizer (version 2.26). A total of three consecutive heart cycles were averaged to deal with the respiratory artifact if any. Pressure-volume (P-V) loops of the LV and RV of the patients with PAH were then reconstructed by synchronizing the LV and RV pressure waveforms measured from catheterization and volume waveforms, measured from the CMR images as described in Xi et al. (58). Because the ventricular pressure waveforms were not acquired in the control subjects, pressure waveforms acquired from normal humans in previous studies were used as surrogates to synchronize with the measured volume waveforms to reconstruct the P-V loops of each subject. Specifically, the normal mean RV pressure-waveform acquired from healthy human subjects in a previous study (49) was applied to all the control subjects. Based on a previous empirical study (29), a normal LV pressure-waveform with its end-systolic pressure scaled to be equal to 0.9 of the corresponding measured cuff pressure was applied to the control subjects. We have used this approach in our previous work (18, 58).

Regional circumferential strain ($E_{cc}$) and longitudinal strain ($E_{ll}$) were estimated from the cine CMR images using a hyperelastic warping method, which has been used in previous studies to measure ventricular strains (22, 23, 44, 55, 60). The hyperelastic warping method has also been evaluated and shown to produce good intra- and interobserver agreement for estimating $E_{cc}$ and $E_{ll}$ (60). Briefly, the biventricular geometry was segmented and reconstructed from the cine CMR images using MeVisLab (http://www.mevislab.de). The geometry was then partitioned into three regions consisting of the LVFW, RVFW, and SEPT (18, 60). The hyperelastic warping method was then applied to deform the reconstructed biventricular geometry from the template image into alignment with the corresponding object in the target image (22, 23). Normal strains in the circumferential and longitudinal directions at the LVFW, SEPT, and RVFW regions were computed from the displacement field. We used the end diastolic volume as the reference configuration. The circumferential and longitudinal directions in the biventricular unit were prescribed using a rule-based algorithm (8).

Construction of personalized models. Personalized computational models of biventricular mechanics that fit the corresponding patient’s pressure, volume, and regional strain data were created using previously described methods (18). Briefly, the computational models were formulated based on classical large-deformation solid mechanics, and active contraction of the ventricular wall was incorporated by a multiplicative decomposition of the deformation gradient (6):

$$
F = F^a F^p
$$

Here, $F = I + VU$ is the total deformation gradient computed from the displacement field $U$, $F^a$ is associated with an inelastic deformation resulting from the actively contracting muscle fibers, and $F^p = FF^a^{-1}$ is associated with the elastic deformation that preserves (kinematic) compatibility of the tissue under load. We employ the following form of $F^a$:

$$
F^a = (1 - \gamma)I_a \otimes I_0 + \frac{1}{\sqrt{1 - \gamma}}(I - I_a \otimes I_0)
$$

where $I_a$ is the unit fiber direction in the reference configuration, and $\gamma$ is a parameter that represents the relative active shortening strain along the muscle fibers, i.e., a measure of the local load-independent active tension generated by the tissue. Meanwhile, passive mechanics was modeled using a purely incompressible transversely isotropic hyperelastic material law (26) with an isochoric strain energy density given by

$$
\Psi(F^a_c) = \frac{a}{2b} \left[ e^{4b I^2} - 1 \right] + \frac{b_1}{2b} \left[ e^{2b I^2} - 1 \right]
$$

where $a$, $b$, $a_0$, and $b_0$ are material constants and $I_0^f, I^p_f$ are reduced (pseudo) invariants defined as

$$
I^f = tr C^f \bar{I}^f_0 - f_0 \cdot (C^f I_0)
$$

For each time point, we estimated $\Psi(F^a_c)$, assimilating the passive-phase measurements, starting from an initial unloaded, stress-free configuration of the ventricles, thus neglecting residual stresses (21). The passive parameter was then determined by assimilating the passive-phase measurements, starting from an initial guess of $a_{LV} = a_{RVFW} = 1.291 \text{ kPa}$. After fitting the model to the passive phase of the P-V curve and strain data, the parameters $a_{LV}$ and $a_{RVFW}$ were held fixed, and the relative active fiber shortening strain $\gamma$ in Eq. 2 was chosen as the control variable for the active phase. While the chosen optimization method would in principle allow efficient estimation of any number of parameters [see Finsberg et al. (18)], the fact that the passive parameters are constant while the active parameters are time dependent motivates the two-step optimization procedure. We allowed $\gamma$ associated with the LVFW ($\gamma_{LVFW}$), SEPT ($\gamma_{SEPT}$), and RVFW ($\gamma_{RVFW}$) to vary independently from each other to capture their spatial timing associated with active contraction. For each time point, we estimated $\gamma_{LVFW}$, $\gamma_{SEPT}$, and $\gamma_{RVFW}$ to obtain
their variation with time over a cardiac cycle. The spatially resolved, isotropic parameters \(a\) and \(b\)-waveforms were estimated with different linear transmural variation of the myofiber helix angles varying from \(-\alpha\) at the epicardium to \(+\alpha\) at the endocardium, with \(\alpha\) ranging from 30 to 80° (18). The set of parameters yielding the lowest mean square error between the predicted and measured strain and P-V data was taken to be the optimal one and used to post-process regional biventricular myofiber wall stresses \(\sigma_{cc}\).

RESULTS

Patient data and regional strains. The control and PAH groups have comparable demographic characteristics, with the majority of the patients in the latter group (8/12) classified in New York Heart Association functional class II. In terms of hemodynamics, the PAH group had an mPAP of 39 ± 9 mmHg with a pulmonary capillary wedge pressure (PCWP) of 11 ± 3 mmHg. No differences in the systemic hemodynamics measurements (i.e., blood pressure) were detected between the two groups.

Evaluation of CMR images revealed that the PAH group had significantly (\(P < 0.05\)) reduced right ventricular ejection fraction (RVEF) (37 ± 14 vs. 54 ± 11%), increased RVFW thickness at ED (3.83 ± 0.61 vs. 1.75 ± 0.17 mm), and ES (6.22 ± 1.88 vs. 2.27 ± 0.24 mm) compared with the control group. Left ventricular ejection fraction (LVEF) and stroke volume (LVSV) were also significantly reduced in the PAH group compared with the control group (LVEF: 58 ± 12 vs. 73 ± 7%; and LVSV: 49 ± 14 vs. 68 ± 7 mL). Right ventricular end-diastolic volume (RVEDV) and right ventricular end-systolic volume (RVESV) were larger, but not statistically significant, in the PAH group. Although LV function, indexed by EF and SV, was significantly reduced in the patient group compared with the controls, only two of the patients were characterized with reduced ejection fraction (LVEF < 50%).

Absolute peak circumferential strain \(E_{cc}\) in the PAH group was significantly lower (one tailed, \(P < 0.05\)) than the control group at the LVFW (13 ± 4 vs. 17 ± 2%) and RVFW (8 ± 4 vs. 11 ± 2%) (Fig. 1). Similarly, peak longitudinal strain \(E_{ll}\) in the PAH group was also significantly lower at the LVFW (13 ± 5 vs. 17 ± 3%) and RVFW (10 ± 4 vs. 15 ± 3%) compared with the control group. While both \(E_{cc}\) and \(E_{ll}\) at the septum were lower in the PAH group than the control group, these reductions were not statistically significant (one tailed, \(P = 0.11\) for \(E_{cc}\) and 0.05 for \(E_{ll}\)).

Model results and validation. Optimized models were compared with measurements of cardiac volumes and strains for validation. For all cases, good temporal matching for pressure transitions was achieved.
and volume was obtained, with Fig. 2 showing the simulated pressure and volume traces against measurements for all cases. The overall fit of the LV and RV volumes in the patient-specific computational models is very good, with the simulation results closely agreeing with the measurements in the cardiac cycle (Fig. 3). The overall root mean square error (RMSE) of the fit is 3.89 mL for the RV and 6.6 mL for the LV. When compared with the volumes, the fit of the regional strains in the cardiac cycle shows significantly more scatter, especially at lower LV systolic strains. The RMSEs of the regional circumferential strain fit are 4.7% for the LVFW, 1.9% for the SEPT, and 2.6% for the RVFW. Meanwhile, serving as an independent measure of model fit, model prediction of longitudinal strains, which were not included in the

![Figure 2](image-url)
optimization, has an RMSE of 6.2% for the LVFW, 6.2% for the SEPT, and 5.2% for the RVFW when compared with the measurements.

Figure 4 shows a comparison of model results for a single PAH patient and a healthy control. The figure illustrates the differences observed in the PAH group, including a shifted P-V loop of the RV, increased LV diastolic stress and RV systolic stress, and significant thickening of the RV. Note that the particular cross section shown in the figure tends to exaggerate the extent of RV wall thickening. The average RVFW thickness in patients with PAH was about two thirds of the septal thickness compared with about one third in the controls (Table 1).

Model results: contractility, stiffness, and stress. Regional contractility for the biventricular units was estimated using fitted values of the corresponding regional active strains \( \gamma_{\text{LVFW}}, \gamma_{\text{RVFW}}, \) and \( \gamma_{\text{SEPT}} \) during systole. Peak RVFW contractility \( \gamma_{\text{RVFW,max}} \) is not uniformly decreased in the PAH group, but instead presented a pattern with respect to the level of remodeling (Fig. 5). Using the ratio of RVEDV to LVEDV (i.e., RVEDV/LVEDV) as an indicator of remodeling, we found that RVEDV/LVEDV varies substantially in the PAH group (1.55 ± 0.50) but little in the control group (1.11 ± 0.12). With RVEDV/LVEDV = 1.5 (that is 3 SD from the mean value of the control group) serving as a threshold to delineate between patients with PAH and mild RV remodeling (RVEDV/LVEDV < 1.5) and those with severe RV remodeling (RVEDV/LVEDV ≥ 1.5), we found that in patients with PAH and mild RV remodeling, their peak RVFW contractility \( \gamma_{\text{RVFW,max}} \) is not significantly changed compared with the control group (P = 0.09). We note that the threshold RVEDV/LVEDV = 1.5 is approximately the midpoint for the range (1.27 ≤ RVEDV/LVEDV ≤ 1.69) proposed previously (5) to categorize “mild” RV dilation in patients with PAH. With increasing RVEDV/LVEDV, however, \( \gamma_{\text{RVFW,max}} \) decreases linearly so that \( \gamma_{\text{RVFW,max}} \) in patients with PAH and RVEDV/LVEDV ≥ 1.5 (severely remodeled PAH) is significantly less than that in the control group. The inverse linear relationship between \( \gamma_{\text{RVFW,max}} \) and RVEDV/LVEDV is strong and has a coefficient of determination \( R^2 = 0.77 \). By comparison, \( \gamma_{\text{LVFW,max}} \) has a weaker linear relationship with RVEF (\( R^2 = 0.50 \)) and RVEDV index (RVEDVi) (\( R^2 = 0.40 \). *P < 0.05.

Peak contractility in the LVFW \( \gamma_{\text{LVFW,max}} \), unlike \( \gamma_{\text{RVFW,max}} \), did not exhibit any relationship with the level of remodeling as measured by RVEDV/LVEDV (Fig. 6). Specifically, we found that peak contractility in \( \gamma_{\text{LVFW,max}} \) is significantly smaller in the mildly remodeled PAH group with RVEDV/LVEDV < 1.5 (0.33 ± 0.02) compared with the control (0.38 ± 0.03) (P < 0.05). On the other hand, while the average \( \gamma_{\text{LVFW,max}} \) in the severely remodeled PAH group (0.33 ± 0.07) is decreased compared with the control group, that decrease is not statistically significant, possibly due to high standard deviation and low sample size (P = 0.14; power = 0.35).

Fitted values of the regional material isotropic parameters \( a_{\text{LV}} \) and \( a_{\text{RVFW}} \) are measures of the tissue passive stiffness in the LVFW + SEPT and RVFW of the biventricular unit, respectively. Separating the fitted values in the PAH group based on the degree of remodeling (i.e., RVEDV/LVEDV) revealed a progressive increase in the mean value of \( a_{\text{LV}} \) and \( a_{\text{RVFW}} \) with remodeling (Fig. 7). The value of \( a_{\text{RVFW}} \) of one patient in the severely remodeled PAH group (RVEDV/LVEDV ≥ 1.5) is disregarded as it appears to be an outlier (Z score > 2, \( a = 36.78 \) kPa). In the severely remodeled PAH group, the mean value of \( a_{\text{RVFW}} \) (4.3 ± 3.5 kPa) is 2.4 times higher than that of the control group (1.8 ± 0.6 kPa), but that increase is not significant, possibly due to the large standard deviation and low sample size in the former group (power = 0.34). On the other hand, the average \( a_{\text{LV}} \) in the severely remodeled PAH group (3.00 ± 2.5 kPa) is significantly higher (P < 0.05) than that of the control (0.48 ± 0.12 kPa).

Fig. 3. Overall data assimilation errors in the control (circle) and pulmonary arterial hypertension (diamond) populations. Comparison between measured and simulated volumes for both the right ventricular (RV; blue) and left ventricular (LV; red) (A) and circumferential strain for the LV free wall (LVFW; red), septum (green), and RV free wall X (RVFW; blue) at all cardiac time points (B). A y = x line is also plotted to show the zero-error reference.

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Using the data-assimilated computational models, we computed the peak regional wall stress in the myofiber direction ($\sigma_{ff,max}$) (i.e., maximum myofiber load) (Fig. 8). We found $\sigma_{ff,max}$ at the RVFW is, on average, the same between the control (36.4 ± 5.7 kPa) and the mildly remodeled PAH (36.5 ± 12.0 kPa) groups. In the severely remodeled PAH group, however, the RVFW is on average 1.5 times larger (54.3 ± 25.1 kPa) than these two groups, but that difference is not significant ($P = 0.14$, power = 0.33) due to its large standard deviation. In comparison, the LVFW is significantly reduced in the mildly remodeled PAH group (55.4 ± 7.4 kPa) compared with the control group (84.0 ± 17.6 kPa). In the severely remodeled PAH group, the LVFW of two patients are disregarded since they appeared to be outliers with substantially large values ($Z$ score > 2, $\sigma_{ff,max} = 544:1$, 1659:9 kPa), which is likely due to the presence of local stress-concentration in the model. Peak myofiber stress at the LVFW in this group (71.22 ± 7.8 kPa) is significantly larger than the mildly remodeled PAH group but lower (not statistically significant) than the control.

**DISCUSSION**

We have used a previously established data assimilation technique (17, 18) to quantify changes in regional myocardial properties and stresses in PAH based on measurements of P-V loops and myocardial strains from patients and a cohort of healthy subjects serving as control. The major finding of this study is a strong inverse linear relationship between the RVFW load-independent contractility, as indexed by the fitted model’s active strain parameter $\gamma_{RVFW,max}$ and the degree of remodeling as indexed by RVEDV/LVEDV in patients with PAH. We have previously suggested that the contractility parameter $\gamma_{RVFW,max}$ could possibly be a biomarker of ventricular failure (17), and its relationship to RVEDV/LVEDV ($R^2 = 0.77$) is stronger than that with RVEF ($R^2 = 0.50$) or RVEDVi ($R^2 = 0.40$) in patients with PAH. We also found that RVFW contractility is increased by ~20% in patients with PAH when little remodeling is present (i.e., RVEDV/LVEDV < 1.5) but decreases linearly with increasing RVEDV/LVEDV.
The strong RVFW,max-RVEDV/LVEDV relationship also suggests a mechanistic explanation for recent clinical findings that RVEDV/LVEDV is a better metric (with a higher sensitivity) than RVEDVi for identifying patients with PAH based on all-cause mortality (5), as well as for detecting RV enlargement (4). Besides PAH, this metric is also used for assessing RV dilation and indicating pulmonary valve replacement in patients who have tetralogy of Fallot (19, 35). There is, however, no other clear mechanistic basis for applying RVEDV/LVEDV to delineate the severity of PAH or electing surgery, other than a statistical association of this metric with clinical end points (5) or from clinical experience (35). Our finding suggests that the underlying reason why RVEDV/LVEDV is a better metric in determining PAH severity is because of its close association with RVFW contractility in PAH. Based on this relationship (Fig. 5A), the threshold of RVEDV/LVEDV of ~2 for distinguishing patients with PAH with severe RV dilation, as well as electing patients for pulmonary valve replacement, is associated with a reduction of RVFW contractility by ~30% from normal.

Fundamentally, our study also provides an insight into the changes in regional contractility during the progression of PAH. Our result suggests there is an increase in the RV contractility in early stages of PAH (RVEDV/LVEDV < 1.5), perhaps as a compensatory mechanism to maintain RVEF in response to the increased RV pressure, before it decreases as the disease progresses. The similarity in RVEF in patients with PAH with RVEDV/LVEDV < 1.5 (49 ± 5%) compared with normal (54 ± 11%) (Fig. 5) supports this theory. Because wall thickness is already accounted for geometrically in the computational models, the increase in RVFW contractility indicates that RV cardiomyocytes become hypercontractile in an attempt to normalize RVEF in the presence of increased pulmonary afterload at early stages of PAH. This finding is supported by a recent study which shows that the maximal tension of skinned myocytes of idiopathic patients with PAH is 28% higher than normal in early stages of disease with RVEF at 46 ± 7% (27), close to that found in patients with PAH with RVEDV/LVEDV < 1.5 in this study. Other than affecting the RV, we also found that LV contractility γLVFW in patients with PAH is reduced. This reduction is observed even in patients with PAH exhibiting little RV remodeling, suggesting that there is some early influence on LV function in this disease, a result broadly consistent with findings of reduced myocyte contractility in the LV of patients with PAH (37).

Fig. 5. Analysis of peak right ventricular free wall (RVFW) contractility γRVFW,max for control and pulmonary arterial hypertension (PAH) groups. A: graphical depiction of γRVFW,max for both controls (diamonds) and patients (black dots) as a function of the ratio of right ventricular end-diastolic volume to left ventricular end-diastolic volume (RVEDV/LVEDV). Dashed line shows a linear fit to the patients with PAH group (γRVFW,max = −0.13 (RVEDV/LVEDV) +0.44, $R^2 = 0.77$). B: average γRVFW,max for controls, patients with RVEDV/LVEDV < 1.5, and patients with RVEDV/LVEDV ≥ 1.5. C: linear fit of γRVFW,max with RVEDV index (RVEDVi; γRVFW,max = −0.001 (RVEDVi) +0.32, $R^2 = 0.40$). D: linear fit of γRVFW,max with right ventricular ejection fraction (RVEF; γRVFW,max = 0.39 (RVEF) +0.09, $R^2 = 0.50$). *P < 0.05.
Besides contractility, we found that there is, on average, an increase in the LV and RV passive stiffness (reflected by $a_{LV, RVFW}$) with increased RVEDV/LVEDV in the PAH groups. While this increase is largely not statistically significant due to the large variance of the fitted parameter values, the result is consistent with experimental (47) and clinical (27) findings that PAH is associated with cardiac fibrosis and passive tissue stiffening. Interestingly, we also find that the peak LV fiber stress is reduced in patients with PAH with mild RV remodeling but is relatively unchanged in those with severe RV remodeling compared with the controls. This result could be due to changes in LV dynamics associated with a change in passive tissue stiffening and septal loading. Computation of the peak RV fiber stress using the fitted parameters, on the other hand, revealed that it is increased only in the severely remodeled patients with PAH, with RVEDV/LVEDV $\geq 1.5$, although that increase is not statistically significant ($P = 0.14$, Fig. 8). Because myocardial wall stress is directly correlated with myocardial oxygen consumption (MV$\dot{O}_2$), this result suggests that MV$\dot{O}_2$ is increased in the RV of patients with PAH with RVEDV/LVEDV $\geq 1.5$ but less so in patients without substantial RV remodeling. When considered with our finding that RVFW contractility is reduced in patients with PAH with RVFW/LVEDV $\geq 1.5$, this result further suggests that coronary flow may not be sufficient to meet the increase in MV$\dot{O}_2$ due to a higher workload in the RV, and as a result, ischemia develops in this cohort of patients producing a lower contractility. Our finding that RVEDV/LVEDV $\geq 1.5$ may represent the threshold at which RV may become ischemic (with reduced contractility) is also consistent with clinical observations that RV ischemia may play a role in later stages of the disease (24, 42).

When compared with previous patient data assimilation techniques that have so far been only applied to the LV (17, 20,
Specifically, patients with PAH recruited in this study had those found in the general heterogeneous PAH population. A sizable patient cohort (when applied to the biventricular unit is robust in regard to have shown that the semiautomatic data assimilation pipeline is needed to determine the most appropriate boundary conditions to be used for this type of analysis. It should also be noted that longitudinal strains are correlated to the circumferential strains through the incompressibility condition, and therefore the validation is not as strong as it would have been using an independent observation. In addition, even with this connection, the absolute errors in the longitudinal strain remain relatively large in our simulations. Second, the cohort size (n = 12) is fairly small, although it is still larger than many other patient-specific computational modeling studies. This limited sample size, especially with the need to further refine the patient group by level of remodeling, creates a somewhat underpowered study to investigate all the mechanical factors that could be important. Additional work is needed in larger cohorts to verify and refine some results, especially the relationship between LV and RV dynamics. For instance, our results indicated an increase in LV passive stiffness in patients with PAH, which is consistent with previous experimental and clinical findings. A sensitivity analysis (see supplementary material) of passive stiffness to LV diastolic pressure further supports that the increase is not a modeling artifact but a real difference between the groups. However, because of the large variability of fitted parameter values, the results are not statistically significant and will need to be confirmed in a larger cohort. Nevertheless, we are able to suggest a broad mechanistic explanation as to why some clinical indexes are better at characterizing PAH severity as well as features found during the progression of PAH, which are also supported by other clinical studies. A larger cohort needs to be considered in future studies. Third, we have applied surrogate pressure waveforms to the control subjects since RHC was not performed on them. Future studies can consider estimating pressures in control healthy subjects using Doppler echocardiography or including human subjects who have had false-positive diagnosis of PAH after undergoing RHC. Lastly, although an active strain formulation is able to provide information on the contraction dynamics and relative twitch strength, it is difficult to contextualize these results against other studies based on the active stress framework. In the supplementary material, we

![Fig. 8. Comparison of peak myofiber wall stress between control and pulmonary arterial hypertension (PAH) groups in the left ventricular free wall (LVFW; A) and right ventricular free wall (RVFW; B) regions. RVEDV/LVEDV, ratio of right ventricular end-diastolic volume to left ventricular end-diastolic volume. *P < 0.01, statistical significance between groups.](image-url)
show that essential properties such as the force-length relationship are captured by the formulation of active strain, but additional work is needed to link active strain dynamics with the more physiologically derived active stress frameworks. Detailed studies of this kind will be important for comparing our findings with other studies and standards and would be particularly useful in optimizations that use dynamic information such as myofiber force generation over the entire twitch.

Conclusion. In conclusion, we have shown that RVEDV/LVEDV is strongly associated with the RVFW load-independent contractility estimated from assimilating a computational model of active biventricular mechanics with clinical imaging and hemodynamics data acquired from patients with PAH and control subjects. Our study therefore suggests a mechanistic basis for using RVEDV/LVEDV as a noninvasive metric for assessing PAH severity as well as a noninvasive approach of estimating RV contractility from measurements of RVEDV/LVEDV.

ENDNOTE

C.X., L.C.L., and S.T.W. approved final version of manuscript; L.C.L., M.G., and S.T.W. edited and revised manuscript; and H.N.T.F., J.S.S., C.X., performed experiments; H.N.T.F., C.X., and M.G. analyzed data; L.C.L. and S.T.W. drafted manuscript; H.N.T.F., J.S.S., C.X., prepared figures; L.C.L. and S.T.W. edited and revised manuscript; and C.X., Forfia PR, Han Y. Institute Grant R01-HL-134841 (to L. C. Lee); and the Center for Cardiological Innovation (Research Council of Norway).

DISCLOSURES

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