Characterization of Right Ventricular Remodeling in Pulmonary Hypertension Associated With Patient Outcomes by 3-Dimensional Wall Motion Tracking Echocardiography

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Background—Adverse right ventricular (RV) remodeling has significant prognostic and therapeutic implications to patients with pulmonary hypertension (PH). However, differentiating RV adaption from adverse remodeling associated with poor outcomes is difficult. We hypothesized that novel 3-dimensional (3D) wall motion tracking echocardiography can differentiate morphological features of RV adaption from adverse remodeling heralding an unfavorable short-term prognosis in patients with PH.

Methods and Results—We studied 112 subjects: 92 patients with PH and 20 normal controls with 3D wall motion tracking for RV end-systolic volume index (ESVi), RV ejection fraction (EF), and RV global area strain. Patients with PH also had invasive hemodynamic measurements. Pressure–volume relations classified patients with PH into 3 groups, such as RV adapted, RV adapted–remodeled, and RV adverse–remodeled. The predefined combined end point was PH-related hospitalization, death, or lung surgery (lung transplantation or pulmonary endarterectomy) during 6 months. The 92 patients with PH had significantly larger RV volumes, lower RVEF and global area strain than normal controls as expected. Patients with PH classified as RV adapted (ESVi, ≤72 mL/m²) had a more favorable clinical outcome than those classified as RV adapted–remodeled (ESVi, 73–113 mL/m²) or RV adverse–remodeled (ESVi, ≥114 mL/m²): hazard ratio, 0.15; 95% confidence intervals, 0.07 to 0.39; P<0.0001. RV adverse–remodeled patients (ESVi, ≥114 mL/m²) had worse short-term outcome than the RV adapted–remodeled patients: hazard ratio, 2.2; 95% confidence interval, 0.91 to 5.39; P=0.04.

Conclusions—Quantitative 3D echocardiography in patients with PH demonstrated morphological subsets of RV adaption and remodeling associated with clinical outcomes. (Circ Cardiovasc Imaging. 2015;8:e003176. DOI: 10.1161/CIRCIMAGING.114.003176.)

Key Words: echocardiography ▪ outcomes assessment ▪ pulmonary hypertension

Pulmonary hypertension (PH) is a progressive disease associated with significant morbidity and mortality with advanced treatment options based on its stage of evolution.

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Patient outcomes in PH have been associated with right ventricular (RV) structural and functional changes described as RV adaptation where patients show minimal or no symptoms that progresses to a decompensated phase of RV adverse remodeling associated with catastrophic clinical deterioration and death within a year.1-3 The detection of RV adverse remodeling heralding RV failure in PH is of great importance to manage advanced treatment strategies, including continuous vasodilator infusions or lung transplantation. The contemporary clinical approach to assess for the advanced stage of PH is by invasive right heart catheterization hemodynamic data, which are important but imperfect. Morphological RV adverse remodeling in PH is clinically relevant,2,4 but a means to quantify these changes has been challenging because of complexities of RV anatomy. Direct noninvasive quantification of the RV pathophysiology has become recently possible with technological advances in 3-dimensional (3D) echocardiography, including RV time–volume and time–strain data.5 Accordingly, the objectives of this study were to (1) determine novel quantitative 3D echocardiographic RV structural and functional indices in patients with PH compared with normal subjects, and (2) to test the hypothesis that pathophysiological RV changes occurring with adaption and adverse remodeling in PH quantified by 3D echocardiography are associated with important patient outcomes.6-9 The practical clinical impact is to support the potential adjunctive role of noninvasive 3D echocardiography with invasive hemodynamic data.
for clinical decision making in PH, such as advancing medical therapy or lung transplantation.

Methods
This was a prospective study of 108 consecutive patients with the diagnosis of precapillary PH referred for right heart catheterization for clinical indications. This study received institutional review board approval, and all participants gave written informed consent. Patients with significant valvular heart disease, atrial fibrillation, cardiomyopathy, or coronary artery disease by coronary angiography with >50% stenosis in at least 1 major coronary artery were excluded (=15% of patients screened). There were 102 patients (94%) with mean pulmonary artery pressure (mPAP) >25 mmHg at rest and 6 (6%) considered at high risk for PH (3 with human immunodeficiency virus, 2 with scleroderma, and 1 with sickle cell disease) who had borderline mPAP 21–24 mmHg at rest and a significant increase >30 mmHg with exercise. All patients with PH received treatment according to standard guidelines. Three-dimensional echocardiography (Aplo Artida; Toshiba Medical Systems, Tochigi, Japan) was performed in general on the same day as the right heart catheterization (70% before and 30% after) as close in time as logistically possible. Sixteen patients (15%) were excluded because of 3D RV echocardiographic image quality unsuitable for quantitative analysis. Accordingly, there were 92 patients with PH, with a mean age of 52±14 years, of which 62 (67%) were women. Their functional class at referral was I in 4, II in 26, III in 46, and IV in 16 patients. Twenty healthy volunteers with no history of cardiovascular disease and normal complete 2D, Doppler, and 3D echocardiograms were normal controls.

Invasive Hemodynamic Studies
All patients with PH had invasive right heart catheterization (Edwards Co, CA) to measure systolic pulmonary arterial pressure (sPAP) and mean pulmonary arterial pressure, RV end-diastolic pressure, mean right atrial pressure, pulmonary capillary wedge pressure, Fick cardiac output and cardiac index, pulmonary vascular resistance (PVR) = (mPAP−pulmonary capillary wedge pressure)/ cardiac output, and transpulmonary gradient=(mPAP−left atrial pressure).

Echocardiographic Studies
Routine echocardiographic data were collected and analyzed using standard methods and guidelines of the American Society of Echocardiography. Tricuspid regurgitation graded as trace or mild was not considered significant and grades of moderate or severe were considered significant. Three-dimensional imaging used a matrix-array transducer (S3, 2–4 MHz; Toshiba Medical System) with gated 3D full-volume data sets within 1 breathhold combining 4 to 6 real-time subvolumes during consecutive cardiac cycles (mean volume rate, 28±5 volumes/s). Digital 3D data sets were analyzed off-line (Ultra Extend; Toshiba Medical Systems). The RV endocardium and epicardium was manually traced and adjusted for tracking throughout the cardiac cycle. We calculated RV end-diastolic volume (RV EDV), end-systolic volume (RV ESV), RV ejection fraction (RVEF), and RV global area strain (G-AS), which was the 3D endocardial surface % area change from combined longitudinal and circumferential strain (Figure 1). Pressure−volume loops were constructed using RV catheter pressure tracing and 3D RV volume curves matching representative beats and adjusting the time to achieve the most vertical isovolumic components. RV stroke work was calculated from the integral of the pressure−volume loops.

Interobserver and Intraobserver Variability
To determine the interobserver variability in the 3D analysis, RV EDV, RV ESV, and RVEF were repeated by a second observer, blinded to the values obtained by the first observer. All measurements were repeated for intraobserver variability using the stored images 1 month later by an observer who was blinded to the results of the previous measurements. Variability was calculated by intraclass correlation analysis.

Outcome Analysis and Determination of Predefined Right Ventricular Subgroups
Our predefined combined end point was PH-related hospitalization, death, or lung surgery (specifically, lung transplantation or pulmonary endarterectomy). Lung transplantation or pulmonary endarterectomy were considered as objective hard end points in our prognostic study because they are only performed at our institution on PH patients with advanced disease and limited anticipated survival without surgery. We used a simplified construct of pressure−volume relations by PAP and RV ESVi to determine RV structural−functional subgroups associated with clinical outcomes. Our 3 predefined subgroups of patients with PH based on RV morphology were RV adapted, RV adapted−remodeled, and RV adverse−remodeled. We used the relationship between sPAP and RV ESVi to estimate the transition from RV adaptation to RV adverse remodeling as the point where progressive RV enlargement was associated with less severe generation of elevated pulmonary artery pressures usually associated with impending RV failure. Polynomial regression analysis of sPAP versus RV ESVi was used to identify the PH patient group classified as RV adverse−remodeled at the highest risk for an unfavorable clinical outcome. We then separated RV adapted patients from RV adapted−remodeled using a RV ESVi cut-off value derived from receiver−operator characteristic (ROC) curve analysis using the predefined combined end point. The RV ESVi value of the optimal area under the ROC curve was used to subdivide these patients into 3 groups, such as RV adapted, RV adapted−remodeled, and RV adverse−remodeled groups.

Statistical Analysis
Continuous variables were compared using 2-tailed Student t tests for paired and unpaired data for comparisons of 2 groups or ANOVA method for the comparison among 3 groups. Variables were expressed as means±SD. All analyses were performed with MedCalc software version 10.4.0.0. (Mariakerke, Belgium). Categorical variables were compared by the χ² test. A cut-off value of RV ESVi was determined from polynomial regression formula of sPAP and RV ESVi. A second cut-off value was determined by ROC curve analyses. The statistical test based on DeLong test for the calculation of the difference between 2 ROC areas under the curves was used. Kaplan−Meier survival analyses were performed for RV morphology groups during 6-month follow-up and compared by log-rank tests. A 2-tailed P<0.05 was considered statistically significant.

Results
Clinical Characteristics and Echocardiographic Data in Normal Controls and Patients With PH
The study group consisted of 92 patients with PH and 20 normal controls (Table 1). Patients with PH compared with normal controls were older (59±14 years versus 52±12 years; P=0.03) had higher heart rates (80±16 bpm versus 60±10 bpm; P<0.001) and greater tricuspid regurgitation peak velocities (3.7±1.1 m/s versus 1.9±0.6 m/s; P<0.001) as expected. Patients with PH also had greater RA area (25.4±10.0 cm² versus 16.1±3.1 cm²; P<0.001) and RV volumes (RV EDVi, 111±38 mL/m² versus 75±15 mL/m²; RV ESVi, 76±32 mL/m² versus 36±8 mL/m²; both P<0.001). RV functional parameters were lower in patients with PH versus normal controls overall as expected, including TAPSE (18.9±6.0 mm versus 25.6±2.9 mm; P<0.001), RVEF (33±9% versus 52±4%; P<0.001) and RV G-AS (−21.2±6.5% versus −33.0±5.5%; P<0.001). About tricuspid regurgitation in patients with PH, 17 (18%) had trace, 29 (32%) had mild, 30 (33%) had moderate, and 16 (17%) had severe regurgitation. All normal control patients had only trace or mild tricuspid regurgitation. LVEF was similar in both normal controls and patients with PH.
Overall, there were 36 end point events within 6 months (39% of patients), including 24 PH-related hospitalizations (26%), 8 deaths (9%), and 4 lung surgery end points (4%), specifically 3 lung transplantations and 1 pulmonary endarterectomy. The results of ROC curve analysis of associations with outcomes for RV EDVi, RV ESVi, RVEF, and G-AS are shown in Table 2. Area under the curve for RV ESVi was significantly greater than G-AS ($P<0.05$) and RV EDVi ($P<0.01$). When comparing the ROC analysis of outcome associations with hemodynamic data, the area under the curve for RV ESVi remained significantly larger than that in PVR (0.84 versus 0.73; $P=0.03$), cardiac index (0.84 versus 0.69; $P=0.02$), and RA area (0.84 versus 0.69; $P=0.002$).

**Association Between Pulmonary Pressure and Right Ventricular Remodeling**

In patients with PH, the transition from RV adaptation to RV adversely remodeling has been described as the point where progressive RV enlargement is associated with less severe elevation of pulmonary artery pressures because of impending RV failure. Polynomial regression analysis was fit the scatter plot of sPAP and RV ESVi in our patients with PH to determine this point: $y=-0.0064x^2+1.455x+3.51$; $r^2=0.52$; $P<0.001$ (Figure 2). Using this polynomial regression equation, a curvilinear relationship was observed with peak sPAP of 86 mm Hg and the corresponding RV ESVi value of 114 mL/m² used as a cut-off to divide patients with PH in 2 groups, such as RV adapted and RV adverse–remodeled. RV-adapted patients were then further subdivided to identify RV adapted–remodeled with greater RV enlargement among the RV-adapted patients, using the RV ESVi cut-off value identified by the previous ROC analysis (Table 2). Accordingly, the 3 PH groups based on 3D RV morphology were defined as: RV adapted (RV ESVi, ≤ 72 mL/m²; n=51), RV adapted–remodeled (RV ESVi, 73–113 mL/m²; n=28), and RV adverse–remodeled (RV ESVi, ≥114 mL/m²; n=13).

**RV Pressure–Volume Loops**

Pressure–volume loops were constructed from the RV pressure catheter and 3D RV volume curves in 86 patients (93%; Figure 3). Group estimates of stroke work were RV adapted patients (n=48) 1233 mm Hg* mL/m², RV adapted–remodeled patients (n=26) 1859 mm Hg* mL/m², and RV adverse–remodeled patients (n=12) 1695 mm Hg* mL/m² (RV adapted versus RV adapted–remodeled $P<0.001$ and RV adapted versus RV adverse–remodeled $P=0.01$).
Clinical Characteristics, Right Ventricular Morphology, and Patient Outcomes

Clinical characteristics of the 3 PH patient groups based on RV morphology showed no significant difference in age, sex, or PH causes (Table 3). Patients classified as RV adverse–remodeled had significantly lower body surface areas and higher New York Heart Association class. RV end-diastolic pressure, right atrial pressure, and transpulmonary gradient progressively worsened in the 3 RV classified groups, however, sPAP and mPAP did not distinguish between patients classified as RV adapted–remodeled from RV adverse–remodeled. Three-dimensional RV volumes, RVEF, and G-AS progressively worsen in the 3 RV morphology groups (Figure 4). However, TAPSE did not show significant difference between RV adapted–remodeled and RV adverse–remodeled, and RA area did not distinguish RV adapted and RV adapted–remodeled. Kaplan–Meier analysis demonstrated significant associations of PH groups based on RV morphological classifications with short-term patient outcomes during 6 months (Figure 5). RV-adapted patients had more favorable outcomes compared with RV adapted–remodeled and RV adverse–remodeled patients: hazard ratio, 0.15; 95% confidence interval (CI), 0.07 to 0.30; \( P < 0.0001 \). Patients classified as RV adverse–remodeled had an even worse outcome than RV adapted–remodeled patients: hazard ratio, 2.2; 95% CI, 0.91 to 5.39; \( P = 0.04 \).

Reproducibility

The interclass correlation coefficients for interobserver reproducibility were 0.89 (95% CI, 0.74–0.95) for RV EDV, 0.96 (95% CI, 0.91–0.99) for RV ESV, and 0.93 (95% CI, 0.71–0.98) for RVEF, respectively. The interclass correlation coefficients for intraobserver reproducibility of 3D echocardiography indices were 0.96 (95% CI, 0.90–0.98) for RV EDV, 0.96 (95% CI, 0.91–0.99) for RV ESV, and 0.94 (95% CI, 0.85–0.98) for RVEF, respectively.

Table 1. Clinical and Echocardiographic Characteristics in Patients With PH and Normal Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With PH (n=92)</th>
<th>Normal Controls (n=20)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59±14</td>
<td>52±12</td>
<td>0.03</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>62 (67)</td>
<td>11 (55)</td>
<td>0.14</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.8±0.2</td>
<td>1.7±0.8</td>
<td>0.07</td>
</tr>
<tr>
<td>NYHA class I/II/III/IV</td>
<td>4/26/46/16</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>80±16</td>
<td>60±10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Echo parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With PH (n=92)</th>
<th>Normal Controls (n=20)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR peak velocity, m/s</td>
<td>3.7±1.1</td>
<td>1.9±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>18.9±6.0</td>
<td>26.5±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial area, cm²</td>
<td>25.4±10.0</td>
<td>16.1±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>62±9</td>
<td>60±5</td>
<td>0.25</td>
</tr>
<tr>
<td>TR (moderate-severe, %)</td>
<td>46 (50)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3D RV end-diastolic volume index, mL/m²</td>
<td>111±38</td>
<td>75±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3D RV end-systolic volume index, mL/m²</td>
<td>76±32</td>
<td>36±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3D RV ejection fraction, %</td>
<td>33±9</td>
<td>52±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3D RV global area strain, %</td>
<td>−21.2±6.5</td>
<td>−33.0±5.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

3D indicates 3-dimensional; LV, left ventricular; NYHA, New York Heart Association, PH, pulmonary hypertension; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitation.

Table 2. Receiver–Operating Characteristic Curve Analysis of Associations With the Combined End Point of Hospitalization, Death, or Lung Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Cut-Off Value</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>0.75</td>
<td>90</td>
<td>44</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV end-diastolic pressure, mmHg</td>
<td>0.74</td>
<td>60</td>
<td>82</td>
<td>12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right atrial pressure, mmHg</td>
<td>0.75</td>
<td>61</td>
<td>87</td>
<td>11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR, Woods units</td>
<td>0.73</td>
<td>71</td>
<td>69</td>
<td>6.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>0.69</td>
<td>84</td>
<td>46</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transpulmonary gradient, mmHg</td>
<td>0.64</td>
<td>90</td>
<td>43</td>
<td>8.4</td>
<td>0.01</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>0.73</td>
<td>47</td>
<td>90</td>
<td>15.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right atrial area, cm²</td>
<td>0.69</td>
<td>74</td>
<td>61</td>
<td>23.6</td>
<td>0.002</td>
</tr>
<tr>
<td>3D RV end-diastolic volume index, mL/m²</td>
<td>0.77</td>
<td>68</td>
<td>80</td>
<td>123</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3D RV end-systolic volume index, mL/m²</td>
<td>0.84</td>
<td>81</td>
<td>74</td>
<td>72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3D RV ejection fraction, %</td>
<td>0.83</td>
<td>90</td>
<td>67</td>
<td>33.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3D RV global area strain, %</td>
<td>0.74</td>
<td>55</td>
<td>84</td>
<td>−17.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

3D indicates 3-dimensional; AUC, area under the curve; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; RV, right ventricular; and TAPSE, tricuspid annular plane systolic excursion.
Discussion

This study demonstrated the prognostic significance of RV volumes using 3D wall motion tracking echocardiography combined with routine invasive hemodynamics in patients with PH. The results showed the difference between normal and PH patients, and that large RV volumes (RV EDVi and RV ESVi) and low RVEF were associated with a poor prognosis. Specifically, 3D RV morphology was used to classify patients with PH into 3 groups, such as RV adapted, RV adapted–remodeled, and RV adverse–remodeled, whose clinical outcomes were not identified by invasive hemodynamic measurements alone.

Three-Dimensional Echocardiographic RV Assessment

Because 3D wall motion tracking echocardiography is a relatively new technique, we first included a control group of normal subjects for quantitative comparison. Three-dimensional RV analysis was feasible overall in 112 subjects (88%). As expected, patients with PH had significantly enlarged RV with decreased RVEF and RV strain overall.\(^7,19,20\) The 3D parameters of RV volumes, EF and G-AS, were significantly associated with the prognosis. Other markers of a poor prognosis included functional class, TAPSE, right atrial pressure, PVR, and cardiac index.\(^1,21–27\) Our current study of 3D RV morphology confirms and extends previous reports of outcome prediction in patients with PH. van Wolferen et al\(^28\) reported end-diastolic volume index \(\geq 84\) mL/m\(^2\) by cardiac magnetic resonance predicted a 3-year survival of \(\approx 60\%\) in patients with PH. Smith et al\(^5\) recently reported the usefulness of 3D RV strain analysis to predict the prognosis with 24 months outcome. We observed 3D RV volumes to have a greater prognostic value than RV strain in our patient series; in particular, 3D RV ESVi seemed useful to detect the transition to RV decompensation. We found 3D RV strain alone to be a less sensitive predictor in patients with severe RV dysfunction and low amplitude strain curves. van de Veerdonk et al\(^29\) also reported a progressive decrease in RV function and have worse outcomes, despite showing a decrease in PVR in response to PH therapies. These data suggest that there may

![Figure 2. Scatter plot of systolic pulmonary artery pressure (sPAP) and right ventricular (RV) end-systolic volume index (ESVi), showing associated peak sPAP (86 mm Hg) and corresponding RV ESVi value (114 mL/m\(^2\)) using a polynomial regression formula for pulmonary hypertension patients. Normal controls were shown as a reference but were not included in the formula. Proposed cut-offs for progression from RV adapted, to RV adapted-remodeled to RV adverse-remodeled based on RV ESVi are shown. PH indicates pulmonary hypertension.

![Figure 3. A, Left, Examples of right ventricular (RV) pressure–volume loops derived from RV 3-dimensional echocardiographic volumes from 3 representative patients with pulmonary hypertension (PH) from the RV-adapted group, RV adapted-remodeled group, and RV adverse-remodeled group. The adverse–remodeled patient with PH showed larger RV volumes and higher end-diastolic pressure. B, Right, The comparison of stroke work in 3 PH patient groups. RV adapted group was significantly smaller than the other 2 groups.

![Figure 3. B, Right, The comparison of stroke work in 3 PH patient groups. RV adapted group was significantly smaller than the other 2 groups.

**Figure 2.** Scatter plot of systolic pulmonary artery pressure (sPAP) and right ventricular (RV) end-systolic volume index (ESVi), showing associated peak sPAP (86 mm Hg) and corresponding RV ESVi value (114 mL/m\(^2\)) using a polynomial regression formula for pulmonary hypertension patients. Normal controls were shown as a reference but were not included in the formula. Proposed cut-offs for progression from RV adapted, to RV adapted-remodeled to RV adverse-remodeled based on RV ESVi are shown. PH indicates pulmonary hypertension.
be intrinsic myocardial mechanisms related to clinical deterioration of patients with PH, which is independent of RV afterload alone.

Assessment of the RV Remodeling and Its Association With Outcome

RV adaptation increased pressure overload is closely related to survival in PH, which was supported by this study, which showed differential RV remodeling patterns by RV ESVi associated with patient outcomes. By comparison, the routine measures PAP, PVR, and TAPSE were not significantly different between RV adapted–remodeled and RV adverse–remodeled patients with PH, whereas RV ESVi had additive prognostic value. Sutendra et al. used a rat model to define the decompensated RV as the stage, in which adverse RV remodeling was associated with decreasing RV systolic pressure and decreasing cardiac output. They showed that hypoxia-induced factor-1α inhibition and suppressed angiogenesis was accompanied by rapid deterioration of RV function. Myocardial fibrosis may also contribute to ventricular remodeling and response to therapy. Bogaard et al. reported that the RV failure in PH was complex and associated with variable degrees of fibrosis, myocardial apoptosis, and decreased RV capillary density. RV adverse remodeling is also associated with decreased vascular endothelial growth factor mRNA expression, despite increased nuclear stabilization of hypoxia-induced factor-1α. RV reverse remodeling after PH therapy has been associated with clinical improvements in survival. The addition of 3D RV morphology to predict outcomes has promise to contribute to this understanding and influence clinical applications.

| Table 3. Clinical Characteristics of Pulmonary Hypertension Patient Subgroups |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Pulmonary Hypertension Subgroups                | RV Adapted (n=51) | RV Adapted–Remodeled (n=28) | RV Adverse–Remodeled (n=13) | PValue |
| Age, y                                          | 59±14           | 60±15           | 59±13           | 0.95 |
| Women, n (%)                                    | 34 (67)         | 19 (68)         | 9 (69)          | 0.98 |
| Body surface area, m²                           | 1.8±0.2*        | 1.9±0.3*        | 1.7±0.3         | 0.003 |
| Pathogenesis, WHO group 1/3/4/5                 | 37/83/2         | 20/53/1         | 9/13/0          | 0.45 |
| NYHA class I/II/III/IV                          | 4/16/29/2*      | 0/9/13/6*       | 0/14/8          | 0.002 |
| Heart rate, bpm                                 | 73±12†          | 82±18           | 87±10           | 0.002 |
| Medical therapy                                 |                 |                 |                 |      |
| Epoprostenol continuous infusion therapy        | 10 (20)         | 9 (32)          | 6 (46)          | 0.13 |
| Endothelin-1 receptor antagonists               | 21 (41)         | 14 (44)         | 5 (38)          | 0.70 |
| Phosphodiesterase inhibitor                     | 26 (51)         | 9 (32)          | 10 (77)         | 0.14 |
| Soluble guanylate cyclase stimulant             | 0 (0)           | 0 (0)           | 1 (8)           | 0.05 |
| Calcium antagonists                             | 12 (24)         | 4 (14)          | 0 (0)           | 0.12 |
| Prostacyclin inhalant                           | 6 (12)          | 4 (14)          | 1 (8)           | 0.84 |
| Hemodynamics                                    |                 |                 |                 |      |
| Systolic pulmonary artery pressure, mmHg        | 59.6±22.6†      | 84.3±23.2       | 80.5±14.5       | <0.001 |
| Mean pulmonary artery pressure, mmHg            | 36.9±13.0†      | 51.1±15.1       | 51.0±8.3        | <0.001 |
| RV end-diastolic pressure, mm Hg                | 8.1±3.6†        | 12.5±6.2*       | 16.8±5.9        | <0.001 |
| Right atrial pressure, mm Hg                    | 6.7±3.1†        | 10.6±6.4*       | 16.1±5.7        | <0.001 |
| Pulmonary vascular resistance, Woods units      | 5.4±3.5†        | 8.7±5.7         | 10.0±5.3        | <0.001 |
| Cardiac output, L/min                           | 5.2±1.4*        | 5.4±1.9*        | 4.0±1.4         | 0.03 |
| Cardiac index, L/min per m²                      | 2.9±0.8*        | 2.8±0.8*        | 2.3±0.5         | 0.03 |
| Transpulmonary gradient, mmHg                   | 25.5±12.9†      | 39.1±13.6*      | 35.2±10.7       | <0.001 |
| Echocardiographic parameters                    |                 |                 |                 |      |
| TAPSE, mm                                       | 21.1±6.1†       | 16.8±5.2        | 15.0±3.4        | <0.001 |
| Right atrial area, cm²                           | 22.1±6.9*       | 25.5±7.9*       | 37.4±14.4       | <0.001 |
| LV ejection fraction, %                         | 61±7            | 63±6            | 64±5            | 0.19 |
| Tricuspid regurgitation (moderate–severe; %)    | 17 (33)         | 16 (57)         | 13 (100)        | <0.001 |
| 3D RV end diastolic volume index, mL/m²         | 85±19†          | 128±16*         | 176±24          | <0.001 |
| 3D RV end systolic volume index, mL/m²          | 52±11†          | 91±12*          | 135±17          | <0.001 |
| 3D RV ejection fraction, %                      | 39±8†           | 29±7*           | 23±4            | <0.001 |
| 3D RV global area strain, %                     | −24.8±5.3†      | −18.0±5.0*      | −14.0±4.0       | <0.001 |

3D indicates 3-dimensional; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and WHO, World Health Organization.
*P≤0.05 vs RV adverse–remodeled.
†P≤0.05 vs both RV adapted–remodeled and adverse–remodeled.
Limitations

The consecutive patients included with chronic PH were referred for clinical invasive right heart catheterization. The medical therapy was at the discretion of the clinicians, and this study was not designed to determine potential effects of PH therapy on RV remodeling. A limitation was that...
fluid-filled pressure catheters were used and high-fidelity catheters may have been advantageous. An additional limitation was that 3D echocardiograms were not acquired simultaneously with the invasive study but performed within a short time. There was no comparison of RV volumes from our 3D wall motion tracking method with cardiac magnetic resonance studies in our patients, although 3D echocardiographic RV volumes have been shown to compare favorably with cardiac magnetic resonance data. Another limitation was that quantification of scar by cardiac magnetic resonance was not performed. Also, invasive or echocardiographic measures of diastolic function were not part of our study. Limitations of 3D echocardiography include the need for a regular rhythm to acquire 4 to 6 successive beats, suboptimal spatial resolution with poor windows and relatively lower volume rates. However, this 3D approach has been reported as clinically useful in patients with LV dysfunction. Therefore, RV 3D wall motion tracking might provide a clinically adequate model to quantitatively evaluate RV morphology in PH.

Conclusions and Clinical Implications
Quantitative RV analysis using 3D wall motion tracking echocardiography is feasible in the large majority of attempted studies in patients with PH and has potential for clinical use. Three-dimensional RV morphology demonstrated progressive changes and adaptation to afterload and the transition to adverse remodeling associated with poor short-term outcome. Three-dimensional echocardiographic RV assessment may provide additional new information about risk, which may influence the PH patient management. Further prospective 3D echocardiographic RV study in a larger PH patient series is warranted.

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Disclosures
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CLINICAL PERSPECTIVE

Adverse right ventricular (RV) remodeling has significant clinical, prognostic, and therapeutic implications in patients with pulmonary hypertension (PH). Identification of patients who progress from adapted RV remodeling to adverse remodeling is clinically important to allow consideration of advanced pharmacological interventions or lung transplantation. This study used novel 3-dimensional wall motion tracking echocardiography in 92 patients with PH who also had invasive hemodynamic assessment. Pressure–volume relations classified patients with PH into 3 groups, such as RV adapted, RV adapted–remodeled, and RV adverse–remodeled. The outcome variables measured were the predefined combined end point of hospitalization, death, or lung surgery (lung transplantation or pulmonary endarterectomy) during 6 months. We classified patients with PH as RV adapted with end-systolic volume index ≤72 mL/m² who had a more favorable outcome than those with RV adapted–remodeled (end-systolic volume index, 73–113 mL/m²) or RV adverse–remodeled (end-systolic volume index, ≥114 mL/m²) with respect to death or lung surgery: hazard ratio, 0.15; 95% confidence interval, 0.07 to 0.39; P<0.0001. RV adverse–remodeled patients (end-systolic volume index, ≥114 mL/m²) had worse short-term outcome than the RV adapted–remodeled patients: hazard ratio, 2.2; 95% confidence interval, 0.91 to 5.39; P=0.04. These data suggest that quantitative 3D echocardiography in patients with PH, in conjunction with invasive hemodynamics, can characterize morphological subsets of RV adaptation and remodeling, which seem to identify high-risk subgroups of these patients.
Characterization of Right Ventricular Remodeling in Pulmonary Hypertension Associated With Patient Outcomes by 3-Dimensional Wall Motion Tracking Echocardiography
Keiko Ryo, Akiko Goda, Tetsuari Onishi, Antonia Delgado-Montero, Bhupendar Tayal, Hunter C. Champion, Marc A. Simon, Michael A. Mathier, Mark T. Gladwin and John Gorcsan III

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