Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg. Pulmonary arterial hypertension (PAH), group 1 in the Dana Point Classification, requires a pulmonary wedge pressure (PWP) ≤ 15 mm Hg. Group 2, pulmonary venous hypertension (PVH), is defined by a PWP >15 mm Hg in addition to an elevated mPAP, and results from elevation in postcapillary pressure attributable to left ventricular (LV) systolic or diastolic dysfunction or left heart valvular disease.

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Clinical Perspective on p 122

Differentiating PAH from PVH is important to determine appropriate treatment. There are currently no medications approved specifically for the treatment of PVH. However, treatment with prostaglandins or endothelin receptor antagonists is not only ineffective, but also can potentially worsen patients with PVH. Furthermore, PAH-approved medications are extremely costly and impose an unnecessary burden on the healthcare system when prescribed for inappropriate indications. Therefore, accurate measurement of left heart filling pressure at the time of right heart catheterization (RHC), either directly by measuring left ventricular end-diastolic pressure (LVEDP) or, more commonly, indirectly by measuring PWP, is necessary to differentiate PAH from PVH.

Intravascular volume depletion may lead to underestimation of left heart filling pressure. Nearly all patients undergoing RHC are in a fasting state for ≥ 12 hours. Additionally, many patients have undergone marked diuresis before invasive hemodynamic evaluation. In 1970, Bush et al described rapid infusion of 1 L of normal saline (NS) to uncover latent pericardial constriction. In 2004, we began to administer a rapid fluid challenge in patients undergoing RHC as part of the evaluation of PH. Recent studies suggest that fluid challenge is a
Fluid Challenge in Pulmonary Hypertension

Robbins et al

useful and safe maneuver to uncover occult PVH (OPVH) as a contributing cause for PH. Two case series, 1 in patients with heart failure with preserved ejection fraction (HfPEF) and 1 in patients with scleroderma and PH, reported an increase in PWP to >15 mm Hg after rapid infusion of >0.5 L NS. We hypothesized that fluid challenge would identify a significant group of patients with PAH for whom OPVH contributes to PH.

Methods

This study was approved by the Institutional Review Board at Vanderbilt University Medical Center, IRB#130268. We reviewed all patients enrolled in our database from June 2004 to December 2011 who underwent RHC with fluid challenge for known or suspected PH. All patients were evaluated using published guidelines to determine the presence, severity, and pathogenesis of PH.11,12 PH was defined as a mPAP ≥25 mm Hg.13 The diagnosis of PAH required a PWP ≤15 mm Hg, whereas patients with a PWP >15 mm Hg were classified as having OPVH.14 Patients whose baseline hemodynamics met criteria for PH but developed a PWP >15 mm Hg after fluid challenge were classified as having OPVH. Patients were diagnosed with chronic thromboembolic PH if imaging studies were consistent with this diagnosis.15 Patients with chronic thromboembolic PH were included in the analysis of patients initially diagnosed with PH based on previous studies showing pathological changes identical to those found in PAH and in response to PAH-approved therapy.16,17 Patients with PH and restrictive (total lung capacity <60% predicted) or obstructive (FEV1/FVC [forced expiratory volume in 1 second/forced vital capacity] <70% with and FEV1 <60%) defects or a diffusing capacity <60% and more than mild lung disease on chest computed tomography were diagnosed with PH associated with parenchymal lung disease.18 In this study, PH associated with parenchymal lung disease or hypoxia (group 3 in the Dana Point Classification) or with unclear or multifactorial mechanisms (group 5) were classified as other. Patients with a reported LV ejection fraction <50% or in whom a reliable PWP tracing was not available were excluded from this study.

RHCs were performed by 1 of 3 cardiologists with extensive experience with this procedure in patients with PH. Fluid challenge has become part of standard practice at our center during the past 5 years in patients with a right atrial pressure (RAP) of ≤15 mm Hg. Administration of a fluid challenge in patients with RAP or PWP >15 mm Hg and multiple risk factors for PVH was at the discretion of the cardiologist performing the RHC. Baseline hemodynamics were obtained, and an intravenous fluid bolus of 0.5 L normal NS was given during 5 to 10 minutes,19 and hemodynamic measurements were then repeated. The results of fluid challenge in 16 patients in this study have previously been reported.14 All patients with an mPAP >25 mm Hg at baseline and a PWP ≤15 mm Hg received inhaled nitric oxide at 40 ppm for 10 minutes, before fluid challenge, to assess acute vasodilator response. Although mPAP and PWP were obtained in all patients after fluid challenge, cardiac output (CO) and RAP were not measured in all patients.

CO was measured using either thermodilution method or Fick calculation, the latter using estimated oxygen uptake based on age and heart rate.20 Mean PAP was calculated using the formula: (systolic PAP–diastolic PAP)/3+diastolic PAP. Pulmonary vascular resistance was calculated using the formula: (mPAP–PWP)/CO. Transpulmonary gradient was calculated as mPAP–PWP. Diastolic PAP to PWP gradient (DPG) was calculated as dPAP–PWP. LVEDP was measured in a minority of patients undergoing left heart catheterization for additional reasons. Systolic and diastolic blood pressure was measured in a minority of patients undergoing left heart catheterization.

Statistics

Results are reported as means±SD unless otherwise noted. Between-group differences were compared by Kruskal–Wallis test or a χ2 test. We were interested in understanding differences between PAH and OPVH groups, which were further compared with the Mann–Whitney U test and logistic regression models. A logistic regression model was developed to predict a change in diagnosis from PH to OPVH after fluid challenge using the following clinical variables: age, hypertension, body mass index (BMI), and left ventricular hypertrophy. These variables were chosen based on previous finding of a strong association with PVH.14 Statistical analyses were performed with using SPSS for Windows (version 20.0; SPSS; Chicago, IL). The α level was set at 0.05 for all analyses, 95% confidence intervals were calculated, and all comparisons were 2-tailed.

Results

Demographics and Associated Conditions

RHC with fluid challenge was performed in 292 patients during the study period; 5 patients were excluded from the study because an accurate, end-expiratory PWP tracing could not be determined, leaving 287 patients for analysis. After baseline hemodynamics were obtained, 207 patients were classified as having PAH (PAH-BL), 32 with PVH, 23 with no PH, and 25 with other diagnoses including 2 patients with an elevated PWP but no PH (Figure 1). Demographics, relevant medications, and associated conditions are presented in Table 1.

The majority of patients in all groups were female and functional class 3. A group of 32 patients reported a history of appetite suppressant use, which included use of fenfluramine or dexfenfluramine in 23 patients.

After fluid challenge, 46 patients (22.2%) initially classified with PAH developed a PWP >15 mm Hg and were reclassified as OPVH. The PWP remained ≤15 mm Hg in the remaining 161 patients initially classified with PAH, and this group constitutes the PH final (PAH-F) group. The characteristics and hemodynamics of patients with OPVH are similar to those initially diagnosed with PVH and different from those of the patients with PAH-F (Tables 1 and 2). There was no difference between patients with OPVH and PAH-F in the proportion treated with PAH-approved medications, diuretics, or calcium channel blockers (Table 1). Including 5 patients with no PH at baseline who developed PVH after fluid challenge, the number of patients ultimately classified as having PVH contributing to their PH (PVH plus OPVH) increased to 83 or 28.9% of the entire cohort.

![Figure 1. Patient diagnoses. A total of 207 patients were diagnosed with pulmonary arterial hypertension (PAH) after baseline hemodynamics were obtained. After fluid challenge, the pulmonary wedge pressure in 46 patients increased to >15 mm Hg, and they were reclassified as occult pulmonary venous hypertension (OPVH). PAH-BL indicates pulmonary arterial hypertension baseline; PAH-F, pulmonary arterial hypertension final; PVH, pulmonary venous hypertension; and No PH, no pulmonary hypertension.](http://circheartfailure.ahajournals.org/Downloaded from)
In the 161 patients whose PWP remain ≤15 mm Hg after fluid bolus, 60 patients (37.3%) were diagnosed with idiopathic or heritable PAH, 55 (34.2%) had connective tissue disease, 15 had (9.3%) portal hypertension, and 10 (6.2%) patients had congenital heart disease, which included 7 patients with an atrial septal defect (3 repaired), 2 with a repaired ventricular septal defect, and 1 with a repaired tetralogy of Fallot (Table 1). In the OPVH group, 18 patients (39.1%) had no identifiable risk factor for PAH, 7 (15.2%) had connective tissue disease, 5 (10.9%) had portal hypertension, 2 (4.3%) had congenital heart disease, which included 1 patient with a repaired ventricular septal defect and 1 with a repaired patent ductus arteriosus, and 1 had a family history of PAH (Table 1). Fourteen patients had chronic thromboembolic PH, 3 of which were additionally diagnosed with OPVH after fluid challenge. Seventeen patients were thought to have primarily parenchymal lung disease and hypoxia as the predominant cause of PH. All had significant parenchymal abnormalities on imaging with an average DLCO (diffusing capacity for carbon monoxide) of 45±14% of predicted. Seven of these patients exhibited an increase in PWP to >15 mm Hg after fluid challenge. Echocardiographic findings included mild left atrial enlargement in 5 of 7 patients, mild LVH in 3, and moderate LVH in 1 patient. Five patients had hypertension.

### Table 1. Baseline Demographics, Comorbid Illnesses, and Echocardiographic Findings

<table>
<thead>
<tr>
<th></th>
<th>PAH-F N=161</th>
<th>OPVH N=46</th>
<th>PVH N=32</th>
<th>No PH N=23</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% female)</td>
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<td>73.9</td>
<td>71.9</td>
<td>95.7</td>
<td>0.094</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.6±14.5</td>
<td>57.7±12.3*</td>
<td>59.3±12.2</td>
<td>54.0±16.0</td>
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<tr>
<td>Functional class 1/2, 3/4, %</td>
<td>36.7, 63.3</td>
<td>37.0, 63.0</td>
<td>21.9, 78.1</td>
<td>56.5, 43.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.9±6.8</td>
<td>30.9±6.9*</td>
<td>32.9±7.6</td>
<td>30.1±7.9</td>
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</tr>
<tr>
<td>Hypertension, %</td>
<td>32.9</td>
<td>63.0†</td>
<td>62.5</td>
<td>39.1</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>14.3</td>
<td>28.3*</td>
<td>28.1</td>
<td>17.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>14.9</td>
<td>21.7</td>
<td>40.6</td>
<td>30.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
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<td>8.7</td>
<td>15.6</td>
<td>13.0</td>
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</tr>
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<td>Obstructive sleep apnea, %</td>
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<td>23.9</td>
<td>25.0</td>
<td>26.1</td>
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</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
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<td>28.9*</td>
<td>13.5</td>
<td>21.7</td>
<td>0.177</td>
</tr>
<tr>
<td>Left atrial enlargement, %</td>
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<td>39.1*</td>
<td>56.2‡</td>
<td>26.1</td>
<td>0.005</td>
</tr>
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<td>PAH-specific medication, %</td>
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<td>41.3</td>
<td>18.8</td>
<td>13.0</td>
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</tr>
<tr>
<td>Calcium channel blockers, %</td>
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<td>34.4</td>
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</tr>
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<td>Diuretics, %</td>
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<td>69.6</td>
<td>71.9</td>
<td>47.8</td>
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<td>Risk factors for pulmonary hypertension</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite suppressant use, %</td>
<td>6.8</td>
<td>19.6*</td>
<td>21.9</td>
<td>26.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Connective tissue disease, %</td>
<td>34.2</td>
<td>15.2*</td>
<td>3.1</td>
<td>17.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congenital heart disease, %</td>
<td>6.2</td>
<td>4.3</td>
<td>6.3</td>
<td>4.3</td>
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<tr>
<td>Portal Hypertension, %</td>
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<td>10.9</td>
<td>6.3</td>
<td>0</td>
<td>0.416</td>
</tr>
<tr>
<td>HIV infection, %</td>
<td>3.1</td>
<td>0</td>
<td>0</td>
<td>4.3</td>
<td>0.433</td>
</tr>
<tr>
<td>CTEPH, %</td>
<td>6.8</td>
<td>6.5</td>
<td>6.3</td>
<td>0</td>
<td>0.646</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD. CTEPH indicates chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; No PH, no pulmonary hypertension; OPVH, occult pulmonary venous hypertension; PAH, pulmonary arterial hypertension; PAH-F, pulmonary arterial hypertension final; and PVH, pulmonary venous hypertension.

*P<0.05.
†P<0.001, PAH-F vs OPVH.
‡P<0.05, PVH vs OPVH.

### Hemodynamics

Before fluid administration, the 207 PAH-BL patients had a lower RAP, CO, and systolic blood pressure (P<0.05 for all 3), and a higher pulmonary vascular resistance (PVR) (P<0.001) compared with patients with PVH (Table 3). CI was similar between the 2 groups indicating that higher weight in patients with PVH accounted for much of the increased CO. There was no significant difference in systolic PAP (sPAP), diastolic PAP (dPAP), or mPAP between the 2 groups. RAP, mPAP, CO, CI, PWP, PVR, and systolic BP were significantly different between the 161 patients with PAH-F and the 46 patients with OPVH before fluid challenge despite the fact that all patients had a PWP ≤15 mm Hg (Table 2). After fluid bolus, the PWP pressure of both groups increased significantly. However, the average increase in the OPVH group was greater than in those with PAH-F, 6±3 mm Hg versus 2±4 mm Hg, (P<0.001). RAP, CO, CI, and PVR increased significantly in both groups although RAP and CO were measured in only 30 of 46 patients with OPVH and 125 of 163 patients with PAH-F (Table 2). PAP increased significantly only in the patients with OPVH. There was no effect of fluid administration on systemic BP in either group. The transpulmonary gradient (TPG) was significantly greater in the patients with PAH-F compared with the OPVH patients at baseline, 40±13 versus 29±10, respectively,
Predictors of PVH and OPVH

We analyzed demographic, hemodynamic, and echocardiographic factors that could predict a diagnosis of OPVH. Univariate analysis of the entire cohort identified that factors associated with the metabolic syndrome (hypertension, diabetes mellitus, and obesity), older age, and left atrial enlargement on echocardiogram were associated with a diagnosis of PVH. Confining the analysis to the patients with OPVH, hypertension, BMI, left atrial enlargement, and older age remain as predictive factors. Additionally, the presence of left ventricular hypertrophy on echocardiogram is predictive of OPVH (Figure 2). However, the adjusted odds ratio demonstrates that age, hypertension, and BMI are the only independent risk factors for OPVH (Table 4).

with a similar change in both groups, \( P<0.001 \) for both comparisons. LVEDP was measured in addition to PWP in 18 patients at baseline and 24 patients after fluid bolus. There was good correlation between the 2 values: average LVEDP \( =7±5 \), \( 9±3 \), and \( 12±2 \) \( \text{mm Hg} \), \( r=0.732 \).

Safety

Fluid challenge was tolerated without any side effects or clinical deterioration in all patients, including patients with RAP as high as 29 mm Hg. Although RAP increased significantly in the entire cohort from 8±5 to 10±5 mm Hg \( (P<0.001) \), in the 24 patients with prefluid RAP ≥15 mm Hg, 17 had a repeat RAP obtained, and there was no change in RAP after fluid administration, 19±6 versus 19±6, \( P=0.732 \).

Table 2. Baseline and Postfluid Hemodynamics in Patients With PAH-F and OPVH

<table>
<thead>
<tr>
<th></th>
<th>PAH-F</th>
<th>OPVH</th>
<th>N=207</th>
<th>N=32</th>
<th>No PH</th>
<th>N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prefluid</td>
<td>Postfluid</td>
<td>Prefluid</td>
<td>Postfluid</td>
<td>Prefluid</td>
<td>Postfluid</td>
</tr>
<tr>
<td>RAP</td>
<td>7±5</td>
<td>9±5‡</td>
<td>10±5</td>
<td>12±7‡</td>
<td>7±5</td>
<td>9±5‡</td>
</tr>
<tr>
<td>sPAP</td>
<td>80±20</td>
<td>70±15‡</td>
<td>81±19</td>
<td>74±15**</td>
<td>80±20</td>
<td>70±15‡</td>
</tr>
<tr>
<td>dPAP</td>
<td>33±10</td>
<td>28±9‡</td>
<td>34±9</td>
<td>32±8**</td>
<td>33±10</td>
<td>28±9‡</td>
</tr>
<tr>
<td>mPAP</td>
<td>50±13</td>
<td>42±10§</td>
<td>49±12</td>
<td>46±8**</td>
<td>50±13</td>
<td>42±10§</td>
</tr>
<tr>
<td>PWP</td>
<td>9±3</td>
<td>12±2§</td>
<td>11±4</td>
<td>19±3**</td>
<td>9±3</td>
<td>12±2§</td>
</tr>
<tr>
<td>CO</td>
<td>4.5±1.5</td>
<td>5.3±1.5‡</td>
<td>4.9±1.6</td>
<td>5.6±1.6‡</td>
<td>4.5±1.5</td>
<td>5.3±1.5‡</td>
</tr>
<tr>
<td>CI</td>
<td>2.5±0.8</td>
<td>2.8±0.7‡</td>
<td>2.7±0.9</td>
<td>2.9±0.7</td>
<td>2.5±0.8</td>
<td>2.8±0.7‡</td>
</tr>
<tr>
<td>PVR</td>
<td>10.1±5.4</td>
<td>6.0±2.6§</td>
<td>8.8±4.3</td>
<td>5.5±2.7§</td>
<td>10.1±5.4</td>
<td>6.0±2.6§</td>
</tr>
<tr>
<td>TPG</td>
<td>40±13</td>
<td>30±10§</td>
<td>39±12≠</td>
<td>27±9§</td>
<td>40±13</td>
<td>30±10§</td>
</tr>
<tr>
<td>SvO₂†</td>
<td>66±9</td>
<td>67±7</td>
<td>68±8</td>
<td>68±10</td>
<td>66±9</td>
<td>67±7</td>
</tr>
<tr>
<td>HR</td>
<td>78±14</td>
<td>76±16</td>
<td>77±14</td>
<td>74±13</td>
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<td>76±16</td>
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<tr>
<td>sBP</td>
<td>125±20</td>
<td>132±21§</td>
<td>125±18</td>
<td>132±20</td>
<td>125±20</td>
<td>132±21§</td>
</tr>
<tr>
<td>dBP</td>
<td>80±13</td>
<td>80±12</td>
<td>79±13</td>
<td>79±15</td>
<td>80±13</td>
<td>80±12</td>
</tr>
<tr>
<td>Sat</td>
<td>96±4</td>
<td>95±3</td>
<td>96±3</td>
<td>95±4</td>
<td>96±4</td>
<td>95±3</td>
</tr>
</tbody>
</table>

*Measured in only 112 PAH-F and 23 OPVH patients postfluid.
†Measured in only 125 PAH-F and 30 OPVH patients postfluid.
‡\( P<0.05 \), §\( P<0.001 \), PAH-F vs OPVH.
§\( P<0.05 \), ¶\( P<0.001 \), PAH-F, pre- vs postfluid.
#\( P=0.05 \), #\( P=0.001 \), OPVH, pre- vs postfluid.

Continuous variables are presented as mean±SD. CI indicates cardiac index; CO, cardiac output; dBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary artery pressure to pulmonary wedge pressure gradient; HR, heart rate; mPAP, mean pulmonary artery pressure; OPVH, occult pulmonary venous hypertension; PAH-F, pulmonary arterial hypertension final; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; RAP, right atrial pressure; Sat, peripheral saturation; sBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SvO₂, mixed venous saturation; and TPG, transpulmonary gradient.

Table 3. Baseline Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>PAH-BL</th>
<th>N=207</th>
<th>PVH</th>
<th>N=32</th>
<th>No PH</th>
<th>N=23</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP</td>
<td>8±5</td>
<td>12±5*</td>
<td>4±3</td>
<td>&lt;0.001</td>
<td>32±10</td>
<td>32±10</td>
<td>11±3</td>
</tr>
<tr>
<td>sPAP</td>
<td>78±19</td>
<td>73±21</td>
<td>27±8</td>
<td>&lt;0.001</td>
<td>47±13</td>
<td>46±13</td>
<td>16±5</td>
</tr>
<tr>
<td>dPAP</td>
<td>32±10</td>
<td>32±10</td>
<td>11±3</td>
<td>&lt;0.001</td>
<td>10±4</td>
<td>19±3</td>
<td>8±3</td>
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<td>PWP</td>
<td>14±7.5</td>
<td>5.7±1.9*</td>
<td>6.0±1.7</td>
<td>&lt;0.001</td>
<td>2.5±0.8</td>
<td>2.8±1.0</td>
<td>3.5±1.1</td>
</tr>
<tr>
<td>CO</td>
<td>2.5±0.8</td>
<td>2.8±1.0</td>
<td>3.5±1.1</td>
<td>&lt;0.001</td>
<td>9.2±5.2</td>
<td>5.8±5.2†</td>
<td>1.4±0.9</td>
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<td>&lt;0.001</td>
<td>66±8</td>
<td>68±10</td>
<td>74±8</td>
</tr>
<tr>
<td>SvO₂</td>
<td>78±15</td>
<td>75±13</td>
<td>74±14</td>
<td>0.247</td>
<td>127±20</td>
<td>135±21*</td>
<td>138±18</td>
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<td>CI</td>
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<td>0.007</td>
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<tr>
<td>dBP</td>
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<td>94±6</td>
<td>98±2</td>
<td>0.007</td>
</tr>
<tr>
<td>Sat</td>
<td>95±4</td>
<td>94±6</td>
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<td>0.007</td>
<td>94±6</td>
<td>98±2</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD. P value reflects comparison by ANOVA across all groups. CI indicates cardiac index; CO, cardiac output, dBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; HR, heart rate; mPAP, mean pulmonary artery pressure; No PH, no pulmonary hypertension; PAH-BL, pulmonary arterial hypertension baseline; PVH, pulmonary venous hypertension; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; RAP, right atrial pressure; Sat, peripheral saturation; sBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SvO₂, mixed venous saturation; and TPG, transpulmonary gradient.

*\( P<0.001 \), PAH-Baseline vs PVH.
†\( P<0.001 \), OPVH, pre- vs postfluid.
HFpEF, Fujimoto et al 9 studied 60 subjects without cardio-
in PWP with fluid challenge.16 Whereas this was not per-
can help identify those patients who exhibit an increase
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in PWP with fluid challenge was significantly greater in
Although their results indicate that PWP can increase to
10±2 to 20±3 mm
Hg after rapid infusion of 0.5 L NS, and the slope of the increase
mild dehydration reduced the PWP to normal levels in some
patients with OPVH, and diastolic dysfunction was revealed
only after volume infusion. Prospective hemodynamic stud-
ies of fluid loading and outcomes are needed to determine
whether there is a cut point for increase in PWP, which dif-
derentiates PAH from PVH.

There is a substantial group of patients with PVH or
OPVH who have considerable elevations of PAP along with
large TPGs and dPAP to PWP gradient. In our study, which
excluded patients with more than mild LV systolic dysfunc-
tion, 84.3% of patients categorized as having PVH, either
pre- or postfluid challenge, had a transpulmonary gradient
≥15 mmHg, ranging from 15 to 51 mmHg. These patients
have features of both PAH and PVH, and have previously
been described as having PH out of proportion to the degree
of PWP elevation,2 but may be more aptly described as hav-
ing combined disease. There is no universal definition of
combined disease,17 although previous studies have reported
a transpulmonary gradient <12 or <15 mmHg as indicative
of predominantly passive PH resulting from elevated post-
capillary pressure.18,19 It is clear from this study and other
recent publications that combined disease is common in
patients with PH.14,18,20

In support of a combined pathogenesis of PH in the major-
ity of our OPVH patients, +40% of them were treated with
PAH-approved therapies. Several of them were treated with
phosphodiesterase type 5 inhibitors based on studies show-
ing some benefit, and no deterioration, in patients with ele-
vated postcapillary pressure attributable to either systolic or
diastolic LV dysfunction.21,22 This may be the safest approach
in the treatment of patients with combined disease and only
mildly elevated PVR or TPG. A small group of patients was
treated with other PAH-approved therapy because their PH
was thought to be markedly out of proportion to the eleva-
tion in PWP. Although many of these patients had several risk
factors for PVH, they also had risk factors for PAH, further
highlighting the weakness of the current classification of PH
and the need to study PAH therapies specifically in patients
with combined disease.

The results of the current study have implications not
only for the classification of PH, but also for clinical tri-
als in PAH. Based on our findings, more than one fifth of
patients enrolled in PAH clinical trials may have a com-
ponent of PVH. Whether an increase in PWP ≥15 mmHg
after fluid challenge should be a criterion for exclusion

Discussion

Our results demonstrate that >20% of patients initially meet-
the hemodynamic criteria for PAH develop a PWP >15
mmHg when given a rapid infusion of 0.5 L NS. Although
PWP pressure was ≤15 mmHg in the 46 patients with OPVH
before fluid challenge, it was significantly higher than that in
the 161 patients with PAH-F, suggesting that these are 2 dis-
tinct hemodynamic groups. In support of a different pheno-
type between the PAH-F and OPVH groups, although PWP
increased in both after fluid challenge, the increase was sig-
nificantly greater in the OPVH group. Conversely, patients
with OPVH have a hemodynamic profile similar to that seen
in patients with PVH. They also have clinical characteristics
similar to those of patients with PVH including older age,
higher BMI, and a greater prevalence of hypertension and
diabetes mellitus when compared with patients with PAH-F.
Patients with these characteristics or LVH on echocardiogram,
despite a normal PWP, should raise the possibility of PVH as
a contributing factor to PH, and a fluid challenge can help to
diagnose this.

Our findings confirm those recently reported in 2 smaller
studies of rapid fluid loading during RHC. Fujimoto et al9
reported an increase in PWP from 14±4 to 20±4 mmHg
in 11 patients with HFpEF after an average saline chal-
just more than half a liter. Fox et al10 studied fluid challenge
in patients with scleroderma and found that 6
of 29 patients with PH and a PWP <15 mm Hg developed
an elevated PWP after rapid infusion of 0.5 L of NS. Our
results extend their findings to a larger and broader group
of patients with PH. It may be that a fluid challenge is
not necessary to elicit this change. A previous study of
patients with HFpEF found that simply elevating the legs
can help identify those patients who exhibit an increase
in PWP with fluid challenge.16 Whereas this was not per-
formed in our cohort, this should be considered in futures
studies of patients with PH.

In addition to studying fluid challenge in patients with
HFpEF, Fujimoto et al9 studied 60 subjects without cardio-
pulmonary disease and reported an increase in PWP from
10±2 to 20±3 mm Hg after rapid infusion of ≥2 L of NS.
Although their results indicate that PWP can increase to
>15 mm Hg in normal subjects, it is difficult to extrapolate
this finding to patients with PH. Furthermore, none of the
normal subjects seem to have had an increase in PWP >15
mm Hg after just 0.5 L of NS, and the slope of the increase
in PWP with fluid challenge was significantly greater in
those with HFpEF.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.030</td>
<td>1.001–1.060</td>
<td>0.046</td>
</tr>
<tr>
<td>HTN</td>
<td>2.337</td>
<td>1.106–4.938</td>
<td>0.026</td>
</tr>
<tr>
<td>BMI</td>
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<tr>
<td>LVH</td>
<td>1.910</td>
<td>0.830–4.395</td>
<td>0.113</td>
</tr>
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</table>

BMI indicates body mass index; CI, confidence intervals; HTN, hypertension;
LVH, left ventricular Hypertrophy; OPVH, occult pulmonary venous hypertension;
OR, odds ratio; and PAH, pulmonary arterial hypertension.

The lower increase in PWP with fluid challenge in our
patients with PAH is consistent with disease in the resistance
pulmonary arteries, which would limit the effects of fluid
loading on the postcapillary circulation. RAP was similar in
PAH-F and OPVH patients at baseline, indicating that it is
not a sensitive marker of left heart filling pressure. This is
supported by the finding of a similar increase in RAP in both
groups with fluid challenge despite the significantly greater
increase in PWP in the patients with OPVH. As with the
findings reported in patients with HFpEF,9 the filling pres-
sure in a less compliant LV increases more rapidly and to a
greater extent when subjected to increased flow from a rapid
fluid challenge. Thus, greater increases in PWP may be used
to differentiate the 2 groups. It is possible that diuresis or
mild dehydration reduced the PWP to normal levels in some
patients with OPVH, and diastolic dysfunction was revealed
only after volume infusion. Prospective hemodynamic stud-
ies of fluid loading and outcomes are needed to determine
whether there is a cut point for increase in PWP, which dif-
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Table 4. Multivariate Predictors of Change From PAH to OPVH

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LVH, left ventricular Hypertrophy; OPVH, occult pulmonary venous hypertension;
OR, odds ratio; and PAH, pulmonary arterial hypertension.
from PAH clinical trials requires validation of our results but should be considered in patients with multiple risk factors for PVH before enrollment in studies evaluating new PAH treatments.

There are several limitations to this study. This is a single-center study but a large number of patients with multiple pathogeneses for PAH argues for general applicability of the results. LVEDP was measured in only a minority of patients, and 1 study has suggested that there is not infrequently a discrepancy between LVEDP and PWP in the same patient. However, we found a good correlation between the 2 measurements in our cohort and excluded patients with PWP tracings that were not interpretable. PWP is routinely used at our center, and most centers, and endorsed in guidelines for evaluation of PH as a measure of left heart filling pressure, making our results applicable to standard practice. It should also be noted that an accurate PWP, or even LVEDP, cannot be obtained in a small number of patients despite multiple attempts attributable to body habitus and large pleural pressure swings. Echocardiogram results used in this study were not reviewed by a single cardiologist, and we included studies not performed at our institution. None of these limitations invalidates our results used in this study were not reviewed by a single cardiologist, and we included studies not performed at our institution. However, this supports a more general applicability of our results.

In conclusion, administration of a rapid infusion of 0.5 L NS during RHC was associated with an increase in PWP in 22% of patients in our cohort. Fluid challenge is an easy and safe maneuver that can be performed in any catheterization laboratory without specialized equipment. Our results support the use of a fluid challenge in patients undergoing diagnostic RHC with risk factors for PVH.

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Patients undergoing hemodynamic evaluation for pulmonary hypertension may be intravascularly volume depleted, potentially leading to a falsely low measurement of pulmonary wedge pressure and an erroneous diagnosis of pulmonary arterial hypertension, which by definition requires a pulmonary wedge pressure of ≤15 mm Hg. This study describes our results with a 500 mL fluid bolus during right heart catheterization in 287 patients with known or suspected pulmonary hypertension. We found that 22% of patients initially classified as having pulmonary arterial hypertension demonstrated an increase in pulmonary wedge pressure to >15 mm Hg after fluid challenge. The patients with an increase in pulmonary wedge pressure were similar to patients with pulmonary venous hypertension in terms of demographics, comorbid illnesses, and baseline hemodynamics. Fluid challenge is easy to perform and can assist in identifying a group of patients with occult pulmonary venous hypertension, that is, patients initially diagnosed with pulmonary arterial hypertension but for whom pulmonary venous hypertension contributes to pulmonary hypertension. Our results support the use of a fluid challenge in patients undergoing diagnostic right heart catheterization with risk factors for pulmonary venous hypertension, and have implications for the diagnosis and treatment of pulmonary hypertension and for clinical trials evaluating therapies for pulmonary arterial hypertension.
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Ivan M. Robbins, Anna R. Hemnes, Meredith E. Pugh, Evan L. Brittain, David X. Zhao, Robert N. Piana, Pete P. Fong and John H. Newman

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