Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) $\geq 25$ mm Hg. Pulmonary arterial hypertension (PAH), group 1 in the Dana Point Classification, requires a pulmonary wedge pressure (PWP) $\leq 15$ 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.

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) 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 $\geq 12$ 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
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 (HfP EF) 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.\(^3\)\(^5\) 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.\(^1\)\(^3\) PH was defined as a mPAP ≥25 mm Hg.\(^1\) The diagnosis of PAH required a PWP ≤15 mm Hg, whereas patients with a PWP >15 mm Hg were classified as having PVH.\(^1\) Patients whose baseline hemodynamics met criteria for PAH 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.\(^3\) Patients with chronic thromboembolic PH were included in the analysis of patients initially diagnosed with PAH based on previous studies showing pathological changes identical to those found in PAH and in response to PAH-approved therapy.\(^1\)\(^3\) Patients with PH and restrictive (total lung capacity <60% predicted) or obstructive (FEV\(_1\)/FVC [forced expiratory volume in 1 second/forced vital capacity] <70% with and FEV\(_1\) <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.\(^1\) 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 NS.\(^9\)\(^10\) We hypothesized that fluid challenge would identify a significant group of patients with PAH for whom OPVH contributes to PH.

Statistics

Results are reported as means±SD unless otherwise noted. Between-group differences were compared by Kruskal–Wallis test or a \(χ^2\) 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 PAH 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.\(^1\)\(^4\) 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 PAH 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.
In the 161 patients whose PWP remain \( \leq 15 \text{ mm Hg} \) 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.

### Hemodynamics

Before fluid administration, the 207 PAH-BL patients had a lower RAP, CO, and systolic blood pressure \((P<0.05 \text{ for all } 3)\), 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 \( \leq 15 \text{ mm Hg} \) (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, and remained that way postfluid, 39±12 versus 27±9, 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, hyperlipidemia, 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).

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±4 versus 19±6, P=0.732.

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Our results demonstrate that >20% of patients initially meeting the hemodynamic criteria for PAH develop a PWP >15 mm Hg when given a rapid infusion of 0.5 L NS. Although PWP pressure was ≤15 mm Hg 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 distinct hemodynamic groups. In support of a different phenotype between the PAH-F and OPVH groups, although PWP increased in both after fluid challenge, the increase was significantly 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, diabetes mellitus when compared with patients with PAH-F, higher BMI, and a greater prevalence of hypertension and 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 studies of fluid loading and outcomes are needed to determine whether there is a cut point for increase in PWP, which differentiates 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 dysfunction, 84.3% of patients categorized as having PVH, either pre- or postfluid challenge, had a transpulmonary gradient ≥15 mm Hg, ranging from 15 to 51 mm Hg. 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, but may be more aptly described as having combined disease. There is no universal definition of combined disease, although previous studies have reported a transpulmonary gradient <12 or <15 mm Hg as indicative of predominantly passive PH resulting from elevated postcapillary pressure. It is clear from this study and other recent publications that combined disease is common in patients with PH.

In support of a combined pathogenesis of PH in the majority 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 showing some benefit, and no deterioration, in patients with elevated postcapillary pressure attributable to either systolic or diastolic LV dysfunction. 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 elevation 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 trials in PAH. Based on our findings, more than one fifth of patients enrolled in PAH clinical trials may have a component of PVH. Whether an increase in PWP ≥15 mm Hg after fluid challenge should be a criterion for exclusion

### Table 4. Multivariate Predictors of Change From PAH to OPVH

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</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>
<td>1.057</td>
<td>1.005–1.113</td>
<td>0.032</td>
</tr>
<tr>
<td>LVH</td>
<td>1.910</td>
<td>0.830–4.395</td>
<td>0.113</td>
</tr>
</tbody>
</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.
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. 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


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**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.
High Prevalence of Occult Pulmonary Venous Hypertension Revealed by Fluid Challenge in Pulmonary Hypertension

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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