A Simple Echocardiographic Prediction Rule for Hemodynamics in Pulmonary Hypertension

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Background—Pulmonary hypertension (PH) has diverse causes with heterogeneous physiology compelling distinct management. Differentiating patients with primarily elevated pulmonary vascular resistance (PVR) from those with PH predominantly because of elevated left-sided filling pressure is critical.

Methods and Results—We reviewed hemodynamics, echocardiography, and clinical data for 108 patients seen at a referral PH clinic with transthoracic echocardiogram and right heart catheterization within 1 year. We derived a simple echocardiographic prediction rule to allow hemodynamic differentiation of PH attributed to pulmonary vascular disease (PH\textsubscript{pvd}), defined as pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and PVR > 3 WU. Age averaged 61.3 ± 14.8 years, PAWP and PVR were 16.4 ± 7.1 mm Hg and 6.3 ± 4.0 WU, respectively, and 52 (48.1%) patients fulfilled PH\textsubscript{pvd} hemodynamic criteria. The derived prediction rule ranged from −2 to +2 with higher scores suggesting higher probability of PH\textsubscript{pvd}; +1 point for left atrial anterior–posterior dimension < 3.2 cm; +1 for presence of a mid systolic notch or acceleration time < 80 ms; −1 for lateral mitral E/e’ > 10; −1 for left atrial anterior–posterior dimension > 4.2 cm. PVR increased stepwise with score (for −2, 0, and +2, μPVR = 2.5, 4.5, and 8.1 WU, respectively), whereas the inverse was true for pulmonary artery wedge pressure (corresponding μPAWP = 21.5, 16.5, and 10.4 mm Hg). Among subjects with complete data, the score had an area under the curve (AUC) of 0.921 for PH\textsubscript{pvd}. A score ≥ 0 had 100% sensitivity and 69.3% positive predictive value for PH\textsubscript{pvd} with 62.3% specificity. No patients with a negative score and acceleration time > 100 ms had normal PVR (μPVR = 1.8 WU, range = 0.7–3.2 WU).

Conclusions—We present a simple echocardiographic prediction rule that accurately defines PH hemodynamics, facilitates improved screening and focused clinical investigation for PH diagnosis and management. (Circ Cardiovasc Imaging. 2012;5:765-775.)

Key Words: pulmonary heart disease ▪ echocardiography ▪ heart failure ▪ hemodynamics

Pulmonary hypertension (PH), defined by elevated mean pulmonary artery pressure (mPAP), has diverse clinical and hemodynamic causes resulting from varying contributions of elevated pulmonary vascular resistance (PVR), pulmonary artery stiffness, left atrial pressure, and pulmonary blood flow.1 The most common type of PH results from pulmonary venous hypertension (PVH) in patients with left heart disease. PH attributed to pulmonary vascular disease (PH\textsubscript{pvd}) is less common, and seen in pulmonary arterial hypertension (PAH) as well as non-PAH conditions (ie, chronic thromboembolic and chronic respiratory disease) with similar physiology. The most commonly used PH screening tool, estimation of pulmonary artery systolic pressure (PASP) using continuous wave Doppler transthricuspid flow velocity, does not differentiate PH\textsubscript{pvd} from PVH. The distinction between PH\textsubscript{pvd} and non-PH\textsubscript{pvd} conditions (ie, PVH, high-cardiac output) is critical given the prevalence of left heart disease, and the considerable differences in diagnostic and treatment strategies.2

Clinical Perspective on p 775

Right heart catheterization (RHC) is the gold standard for hemodynamic evaluation, and is essential for the diagnosis and appropriate management of PAH. RHC, however, is invasive and cannot practically be applied to all patients with suspected PH (eg, based on estimated PASP) given the large population with elevated PA pressure attributed to left heart disease. Noninvasive hemodynamic characterization of PH would provide a simple, practical method of classifying hemodynamic pathophysiology as being consistent with PH\textsubscript{pvd} (ie, PAH) or...
PH not attributed to PH\textsubscript{PVD}. Those likely to have PH\textsubscript{PVD} could be quickly referred for RHC. Those unlikely to have PH\textsubscript{PVD} physiology may be better served with further investigation into causes of their presentation, such as elevated pulmonary venous pressure and focusing therapy on those contributing conditions before invasive evaluation.

Transthoracic flow velocity is a limited PH screening tool. Only a subset of patients have interpretable data, and studies show this method is only moderately good for PH screening.\textsuperscript{3–5} Even when accurate, however, PASP (noninvasive or invasive) does not permit physiological classification of PH.\textsuperscript{3–5} Other individual echocardiographic variables provide information on PA pressure and PVR, but perhaps because of less intuitive interrelation or the lack of obvious validated cut-off values, none have been integrated into assessment of PH.\textsuperscript{6–13}

The literature and experience suggest that a carefully interpreted complete Doppler echocardiographic study provides a reliable comprehensive picture of pulmonary vascular hemodynamics. In practice, echocardiographic assessment rarely accomplishes this goal.

Our primary aim was to derive a simple prediction rule for PH\textsubscript{PVD} physiology among patients referred for suspected PH. We evaluated echocardiographic parameters in common clinical use or easily obtained from standard echocardiographic images. The variables chosen for investigation have been previously proposed to correlate with PVR, right heart function, and left-sided cardiac filling pressure. We hypothesized that a combination of several variables reflecting different aspects of PH physiology would allow confident hemodynamic differentiation.

Methods

Subjects

The cohort included patients seen by the PH service at the Hospital of University of Pennsylvania who underwent RHC between January 2007 and June 2011 and had transthoracic echocardiography (TTE) within 1 year of RHC. Exclusions were interval initiation of pulmonary vasodilator or loop diuretic or cardiovascular/abdominal surgery between RHC/TTE. Intraoperative ventilators/vasopressors or positive pressure ventilation at the time of RHC/TTE. We excluded 3 out of 111 patients meeting these criteria because of absent pulsed wave Doppler of the right ventricular outflow tract (RVOT) resulting in n=108. Median time between TTE and RHC was 22.5 days (interquartile range=8–46.5 days). Patients were classified into World Health Organization (WHO) PH diagnostic group based on published recommendations.\textsuperscript{1}

Echocardiography and Hemodynamics

Patients underwent clinically indicated TTE; measurements were made by experienced echocardiographers blinded to invasive hemodynamics in accordance with American Society of Echocardiography guidelines and prior literature.\textsuperscript{14–19} RHC was performed using a 7 French balloon-tipped fluid-filled catheter. Right atrium, right ventricular (RV), PA, and pulmonary artery wedge pressure (PAWP) tracings were recorded. Cardiac output was measured by triplicate thermodilution. PH\textsubscript{PVD} physiology was defined as mPAP≥25 mm Hg, PAWP≤15 mm Hg, and PVR≥3 WU. See Online-only Data Supplement I for further details.

Analysis

Categorical data are expressed as number of patients (%), whereas continuous data are presented as mean±SD or median (interquartile range) as appropriate. Unpaired T-tests and Wilcoxon rank-sums were used to compare means for normally and nonnormally distributed continuous variables, respectively, whereas χ\textsuperscript{2} or Fisher exact test were performed to compare proportions for categorical variables.

The primary outcome of interest was whether hemodynamic criteria for PH\textsubscript{PVD} were fulfilled (PAWP≤15 mm Hg and PVR≤3 WU). Optimal cut-off points for continuous variables were estimated from receiver operating characteristic curves. Univariate logistic regression (LR) was performed for each predictor with PH\textsubscript{PVD} as the dependent variable. Echocardiographic predictors with univariate P>0.2 were excluded from further analysis. A priori, our goal was to select a parsimonious model containing ≤5 variables. The smallest absolute β coefficient was assigned a value of 1 and values for subsequent variables were assigned based on multiples of their respective β coefficients.\textsuperscript{20} Hosmer-Lemeshow goodness-of-fit χ\textsuperscript{2} was used to confirm overall model calibration.

We favored variables simple to measure and interpret (eg, left atrium [LA] anterior–posterior dimension preferable to LA area) to increase clinical utility. After development of the clinical prediction rule, we determined whether replacement of the simpler by more complex measurements provided important predictive improvement.

We used classification and regression tree analysis (CART 6.0, Salford Systems, San Diego, CA) to produce a decision tree analysis to provide additional evidence on the most predictive variables for PH\textsubscript{PVD}. CART involves repeated partitioning of the sample (root node) based on optimal cut-points of the variable that provides the 2 purest derivative nodes. Multiple clinically reasonable cut-points (eg, sysolic eccentricity index of >1, >1.2, >1.4) for each variable were specified to ensure the resulting tree could be useful in practice. We defined the cost of misidentifying a PH\textsubscript{PVD} case (false-negative) as twice that of misclassifying non-PH\textsubscript{PVD} as PH\textsubscript{PVD} given the greater negative clinical consequences.

Analyses were performed using GraphPad Prism 5.02 for Windows (GraphPad Software, San Diego, CA) and SAS for Windows 9.3 (SAS Institute, Inc., Cary, NC).

Results

Patient Characteristics

Patient characteristics are presented in Table 1. Average age was 61.3±14.8 years, and 63.9% were women. Patients with PH\textsubscript{PVD} physiology were younger and less likely to have atrial fibrillation or kidney disease than those with other PH physiology. Those with PH\textsubscript{PVD} had higher heart rate (80.3±17.0 versus 72.2±12.8 bpm; P<0.006) and transpulmonary gradient (35.7±10.8 versus 21.3±11.4 mm Hg; P<0.0001), but there was only a small difference in PA pressure (mPAP 46.5±10.4 versus 41.9±12.0 mm Hg; P=0.04). PH was classified as WHO Group I in 35.2%, II in 38.9%, III in 24.1%, and multifactorial in 1.9%. Among those with PH\textsubscript{PVD}, the breakdown was 65.4% Group I and 3.9%, 30.8%, and 0% Group II, III, and multifactorial, respectively. Among those without PH\textsubscript{PVD}, the equivalent figures were 7.1% I, 71.4% II, 17.9% III; 3.6% had multifactorial PH (combination Group II/III).

Score Derivation

Echocardiographic data stratified by physiology are presented in Table 2. Additional hemodynamic data and area under the curve (AUC) for PH\textsubscript{PVD} elevated PVR, and elevated PAWP for individual echocardiographic parameters are presented in the Online-only Data supplement appendix. β Coefficients for the variables (Table 3), which met the model selection criteria, were between 1.32 and 1.93, and we assigned each variable level a score of either −1 or +1. This score had an AUC=0.904 to predict PH\textsubscript{PVD}. Median score=0, with 12.0%, 18.5%, 23.2%, 29.6%, and 16.7% having scores of ≤−2 to 2, respectively. Assigning scores more precisely corresponding to the
magnitude of the $\beta$ coefficients (+4, –4, +5, –6 for notching or acceleration time (AccT)<80 ms, $E:e' > 10$, LA<3.2 cm, LA>4.2 cm, respectively) added little to the predictive value of the model ($AUC = 0.904 \rightarrow 0.914$). Because our goal was to develop a very simple score we adopted the simpler +1/–1 values. To ensure this was the most predictive 3-variable model, we substituted each potential variables (Table 2); none of the resulting models had equivalent or higher AUC. We then sequentially added single continuous variables (eg, AccT, LA dimension, LA area, TAPSE, RV fractional area change) to the model; none achieved statistical significance. The final score is presented in Table 4.

Figure 1 shows representative echocardiographic tracings from 2 patients. Patient A was diagnosed with heart failure

Table 1. Descriptive Statistics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>PH</th>
<th>No PH</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>108</td>
<td>52</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61.3±14.8</td>
<td>54.8±14.5</td>
<td>67.5±12.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>39 (36.1%)</td>
<td>18 (34.6%)</td>
<td>21 (37.5%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>White</td>
<td>61 (67.0%)</td>
<td>27 (57.5%)</td>
<td>34 (77.3%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16 (17.6%)</td>
<td>14 (29.8%)</td>
<td>2 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>Asian or other</td>
<td>5 (5.5%)</td>
<td>3 (6.7%)</td>
<td>2 (4.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Comorbidities

| Hypertension | 62 (57.4%) | 22 (42.3%) | 40 (71.4%) | 0.003 |
| Dyslipidemia | 29 (26.9%) | 11 (21.2%) | 18 (32.1%) | 0.28  |
| Coronary artery disease | 23 (21.3%) | 8 (15.4%) | 15 (26.8%) | 0.17  |
| Atrial fibrillation | 25 (23.2%) | 5 (9.6%) | 20 (35.7%) | 0.001 |
| Pacemaker or defibrillator | 3 (2.8%) | 1 (1.9%) | 2 (3.6%) | 1.00 |
| Congenital heart disease | 2 (1.9%) | 2 (3.9%) | 0 (0%) | 0.23  |
| Scleroderma | 10 (9.3%) | 7 (13.5%) | 3 (5.4%) | 0.19  |
| Pulmonary embolism | 4 (3.7%) | 1 (1.9%) | 3 (5.4%) | 0.62  |
| Chronic obstructive lung disease | 19 (17.6%) | 9 (17.3%) | 10 (17.9%) | 1.00  |
| Obstructive sleep apnea | 25 (23.2%) | 9 (17.3%) | 16 (28.6%) | 0.18  |
| Interstitial lung disease | 16 (14.8%) | 9 (17.3%) | 7 (12.5%) | 0.59  |
| Asthma | 2 (1.9%) | 2 (3.9%) | 0 (0%) | 0.23  |
| Chronic kidney disease | 11 (10.2%) | 0 (0%) | 11 (19.6%) | 0.0006 |
| Diabetes mellitus | 15 (13.9%) | 5 (9.6%) | 10 (17.9%) | 0.27  |
| Liver cirrhosis | 7 (6.5%) | 2 (3.9%) | 5 (8.9%) | 0.44  |
| Tobacco (>10 pack per year) | 47 (44.8%) | 27 (52.9%) | 20 (37.0%) | 0.72  |
| 6MWT distance, m | 309.9±153 | 341.3±177 | 277.8±116 | 0.04  |

Hemodynamics

| HR, bpm | 76.1±15.5 | 80.3±17.0 | 72.2±12.8 | 0.006 |
| sBP, mm Hg | 135.1±21.9 | 127.8±22.7 | 141.1±19.4 | 0.002 |
| RAP, mm Hg | 12±5.9 | 9.8±4.4 | 13±6.4 | 0.0002 |
| sPAP, mm Hg | 72.6±19.9 | 77.1±19.3 | 68±19.8 | 0.02 |
| mPAP, mm Hg | 44.1±11.5 | 46.5±10.4 | 41.9±12.0 | 0.04 |
| PAWP, mm Hg | 16±7.1 | 10.8±3.3 | 21.6±5.5 | <0.0001 |
| TPG, mm Hg | 29±13.1 | 35.7±10.8 | 21.3±11.4 | <0.0001 |
| PVR (WU) | 6±4.0 | 8.4±3.8 | 4.3±3.2 | <0.0001 |
| SV/PP | 2.6±0.7 | 2.5±0.6 | 2.7±0.8 | 0.07 |
| CI, L/min/m² | 37.4±24.5 | 35.7±33 | 39±12.5 | 0.49 |

PH indicates pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance; HR, heart rate; sBP, systolic blood pressure; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; SV, stroke volume; PP, pulmonary artery pulse pressure; CI, cardiac index; SVI, stroke volume index.

Descriptive data by PH PVD. $P$ values are for comparison ±PH PVD. Data presented as mean±SD or n(%) for continuous and categorical variables, respectively.

*Race not available for all subjects.
with a preserved ejection fraction (score=−2) and patient B with PAH (score=+2). The patients had similar mPAP but markedly different PH physiology.

Hemodynamics and Predictive Values for PHPVD

Patients with a negative score had elevated PAWP, but normal-to-mildly elevated transpulmonary gradient and PVR (Figure 2). Positive scores were associated with normal-to-mildly elevated PAWP but markedly elevated transpulmonary gradient and PVR. The difference in mPAP between scores was less pronounced than for PVR, PAWP, and transpulmonary gradient. There was only a modest difference in cardiac index by score (3.2±0.9, 2.5±0.7, 2.7±0.8, 2.3±0.5, 2.6±0.7 L/min/m² for score –2 to 2, respectively, \( P=0.02 \)).

Figure 3 shows PVR/PAWP for each subject by score. Positive scores (red/orange) are concentrated in the left-upper quadrant of low PAWP/high PVR, with fewer +1 scores in the right-upper quadrant (mixed PH: elevated PAWP/elevated PVR). Conversely, negative scores (blue/green) are concentrated in the right-lower quadrant with elevated PAWP/normal PVR. Subjects with a score of 0 ranged in physiology, although tended to have more moderate elevations in PVR or PAWP (PVR<10 and PAWP≤25). Mixed PH (ie, PAWP>15 mm Hg and PVR>3 WU) was present in 27 subjects, including 2 with score=−2, 12 with score=−1, 4 with score=0, and 9 with score=+1. None with a score of +2 had elevated PAWP. Most were classified with WHO Group II PH (55.6%), with 22.2% III, 14.8% I, and 7.4% V. More severe elevations in both PVR (>5 WU) and PAWP (>20 mm Hg) were present in 12 (11.1%), all of whom had scores between −1 and +1. Of those 11, 4 had clinically important mitral valve disease; 3 had a combination of parenchymal lung and mitral valve disease, whereas the fourth had mitral annular calcification with at least mild mitral stenosis.

Score ≥0 had 100% sensitivity for PH PVD, with specificity=59% (positive predictive value=69.3%, negative predictive value=100%, +LR=2.4, –LR=0). That is, no patient with a negative score had PHPVD. Only 1 subject with a score of −1 had group I PAH, but with mixed physiology, including

Table 2. Selected Candidate Variables, by PH<sub>pvp</sub> Hemodynamic Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>N With Data</th>
<th>Overall</th>
<th>SD</th>
<th>PH&lt;sub&gt;pvp&lt;/sub&gt;</th>
<th>SD</th>
<th>No PH&lt;sub&gt;pvp&lt;/sub&gt;</th>
<th>SD</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>107</td>
<td>63.0</td>
<td>11.1</td>
<td>62.6</td>
<td>10.0</td>
<td>63.3</td>
<td>12.2</td>
<td>0.76</td>
</tr>
<tr>
<td>LA AP dimension, cm</td>
<td>108</td>
<td>3.8</td>
<td>0.9</td>
<td>3.3</td>
<td>0.7</td>
<td>4.3</td>
<td>0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA area, apical 4 chamber view, cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>105</td>
<td>18.5</td>
<td>6.8</td>
<td>14.4</td>
<td>5.0</td>
<td>22.2</td>
<td>6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV septal wall thickness, cm</td>
<td>108</td>
<td>1.1</td>
<td>0.3</td>
<td>1.1</td>
<td>0.2</td>
<td>1.2</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>LV posterior wall thickness, cm</td>
<td>108</td>
<td>1.0</td>
<td>0.2</td>
<td>1.0</td>
<td>0.2</td>
<td>1.1</td>
<td>0.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>87</td>
<td>1.3</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
<td>1.6</td>
<td>0.9</td>
<td>0.0021</td>
</tr>
<tr>
<td>E′&lt;sub&gt;lateral&lt;/sub&gt;, lateral mitral</td>
<td>96</td>
<td>10.2</td>
<td>6.4</td>
<td>7.2</td>
<td>4.6</td>
<td>13.0</td>
<td>6.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TAPSE, cm</td>
<td>108</td>
<td>1.8</td>
<td>0.5</td>
<td>1.8</td>
<td>0.5</td>
<td>1.9</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>RV fractional area change, %</td>
<td>106</td>
<td>31.9</td>
<td>11.0</td>
<td>30.3</td>
<td>10.1</td>
<td>33.3</td>
<td>11.7</td>
<td>0.15</td>
</tr>
<tr>
<td>RV:LV ventricular inflow dimensions</td>
<td>103</td>
<td>1.0</td>
<td>0.4</td>
<td>1.1</td>
<td>0.4</td>
<td>0.9</td>
<td>0.2</td>
<td>0.004</td>
</tr>
<tr>
<td>RA dimension, cm</td>
<td>106</td>
<td>4.7</td>
<td>1.1</td>
<td>4.8</td>
<td>1.1</td>
<td>4.6</td>
<td>1.0</td>
<td>0.57</td>
</tr>
<tr>
<td>RA dimension: LA AP diameter</td>
<td>106</td>
<td>1.3</td>
<td>0.4</td>
<td>1.5</td>
<td>0.4</td>
<td>1.1</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eccentricity index, systole</td>
<td>100</td>
<td>1.4</td>
<td>0.5</td>
<td>1.5</td>
<td>0.5</td>
<td>1.3</td>
<td>0.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Eccentricity index, diastole</td>
<td>99</td>
<td>1.2</td>
<td>0.3</td>
<td>1.3</td>
<td>0.3</td>
<td>1.1</td>
<td>0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>AccT, m</td>
<td>107</td>
<td>83.7</td>
<td>27.5</td>
<td>72.6</td>
<td>21.9</td>
<td>94.3</td>
<td>28.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVOT VTI, cm</td>
<td>107</td>
<td>13.3</td>
<td>4.3</td>
<td>11.4</td>
<td>3.4</td>
<td>15.1</td>
<td>4.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; AP, anterior-posterior; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; RVOT VTI, right ventricular outflow tract velocity time integral.

Data on selected variables for model derivation, including mean±SD overall and by ±PHPVD. \( P \) values are for comparison ±PHPVD.

Table 3. Derivation of the Echocardiographic Prediction Model

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Variable Entered</th>
<th>ROC, Cumulative</th>
<th>( \beta ) Coefficient</th>
<th>( \chi^2 ) (Type III)</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA &lt;3.2 vs 3.2–4.2, cm</td>
<td>1</td>
<td>0.808</td>
<td>1.65</td>
<td>12.8</td>
<td>3.9</td>
<td>1</td>
<td>15.6</td>
</tr>
<tr>
<td>LA &gt;4.2 vs 3.2–4.2, cm</td>
<td>–1.93</td>
<td>0.11</td>
<td>0.02</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midsystolic notch or AccT &lt;80, ms</td>
<td>2</td>
<td>0.885</td>
<td>1.32</td>
<td>16.9</td>
<td>4</td>
<td>49.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E′&lt;sub&gt;lateral&lt;/sub&gt; &gt;10 vs &lt;10</td>
<td>3</td>
<td>0.916</td>
<td>–1.39</td>
<td>10.3</td>
<td>0.1</td>
<td>0.02</td>
<td>0.4</td>
</tr>
</tbody>
</table>

ROC indicates receiver operating characteristic; LA, left atrium.

Model building steps for derivation of prediction model for PH<sub>pvp</sub> (PVR>3WU and PAWP≤15 mm Hg).

*Other variables considered (none \( P<0.2 \)): MSN, AccT in 3 levels (≤90, 90–120, ≥120), LA <4 cm, RV fractional area change <30% or <40%, TAPSE <2 cm, RV:LV inflow diameter >1:1 or >1:1:1, mitral E:A >1, >1.3, or >1.5, posterior LV wall thickness ≥12 mm, LV septum ≥12 mm, systolic eccentricity index >1.4, RA minor dimension, RAL dimension, RVOT VTI continuous and 3 levels (<10 cm, 10–17 cm, and >17 cm), and transtricuspid flow velocity.

**n=12 missing data on E′<sub>lateral</sub>.”
PAWP=23 mm Hg. The sensitivity of score ≥1 for PH_PVD was 78.8% (specificity=83.9%, positive predictive value=82%, NPV=81.0%, +LR=4.9, –LR=0.25).

“Misclassified” Subjects

There were 9 subjects with score=+1 who did not meet hemodynamic criteria for PH_PVD. However, these subjects had significant PVD, with mean PVR=7.7±2.5 WU, albeit in combination with mean PAWP=20.2±4.3. All of these subjects had PVR >5 WU; this compares with PVR=3.7±2.9 WU among the 47 subjects without PHPVD with score ≤0. Two of 9 subjects had PAWP=16 mm Hg (PVR=5.7 and 13.7 WU), whereas 3 had PAWP≤19.

Excluding the 26 patients with mixed PH (PVR>3 WU, PAWP>15 mm Hg), the AUC=0.98. In this population (n=82), all subjects with a positive score had PH_PVD, and all with a negative score had elevated PAWP as the cause of PH.

Hemodynamic and WHO Group Classification Compared With PASP Estimates

The prediction rule was developed to predict hemodynamics, but much data on treatment are based on WHO Group classifications determined after integration of all available clinical data. A score ≥1 was 86.8% sensitive and 77.1% specific for Group I PH (PAH), whereas a score ≥0 had 97.4% sensitivity and 45.7% specificity. Figure 4 shows the number of patients classified into diagnostic/physiological categories (WHO Group, PAWP>15 mm Hg, PVR>3 WU, PH_PVD) by echo score and echocardiographic PASP estimates in 4 categories. It is visually apparent that PASP poorly differentiates these categories as compared with the derived score. Of note, more than 20% (4 out of 19) of those with estimated PASP<40 mm Hg had PH_PVD, a proportion unaffected by excluding those with suboptimal TR envelopes (3 out of 12, 25%).

Estimated PASP as a continuous variable had much lower discriminatory power (Figure 5A, AUC=0.689) than the derived clinical prediction rule (Figure 5B). Including only those with high-quality TR envelopes (n=81/108) did not improve these test characteristics (AUC=0.659).

Meaning of Score=0

Among n=25 with score=0, 16 had normal values for all variables (E′ data missing for 4 out of 16). Mean PVR=3.5±2.2 WU with PAWP=16.4±5.0 mm Hg; 9 out of 16 had PVR<3 WU and 12 out of 16 had PVR<4 WU. Of the other 9, n=5 had normal LA size but ↑E:e′ and evidence of notching or rapid AccT, n=3 had LA>4.2 cm but abnormal RVOT Doppler, and n=1 had LA<3.2 cm but ↑E:e′. PVR in this group (n=9) was 6.2±2.3 WU.
and PAWP=16.7±5.7 mmHg with 8 out of 9 having PVR>3 WU (values between the 3 subsets comprising this group were similar). Those with normal scores for each component variable had relatively normal PVR, whereas those with a combination of abnormal variables summing to 0 had elevated PVR.

**Identifying Normal PVR**

The model distinguished ↑PVR (PVR>3; n=79) well with AUC=0.873, although a sizable minority of those with a negative score had elevated PVR (for score<0, NPV=57.6%), few had markedly elevated PVR (for score<0, NPV for PVR>6 WU=87.8%). Score=–2 more strongly argued against PVR>3 (NPV=84.6%) or PVR>6 WU (NPV=100%).

Among 33 patients with negative scores, none had PH PVD, but 42.4% had PVR>3 WU and 24.2% had PVR>5 WU. Patients with a negative echo score and TAPSE ≥1.8 cm (n=19) were much less likely than those with TAPSE<1.8 cm to have PVR>3 WU (15.8% versus 78.6%) or PVR>5 WU (5.3% versus 50%). RVOT AccT was >100 ms in 11 out of 33, and 1 had PVR>3 WU (PVR=3.2 WU); none had PVR>5 WU. Among patients with a negative score, all with TAPSE<1.8 cm had AccT<100 ms. Thus, in patients with a negative score, the presence of preserved RV function or normal AccT is consistent with normal or minimally elevated PVR.

For patients with either a negative score or a score=0 but normal component variables (n=49), only 4 out of 22 patients with AccT>100 ms had PVR>3 WU and only 1 (4.6%) had PVR>5 WU. However, among those with AccT<100 ms (n=27), 63.0% had PVR>3 WU and 44.4% had PVR>4 WU. Preserved TAPSE was not as predictive of normal PVR; 16.1% of 31 patients with TAPSE ≥1.8 cm had PVR>5 WU (versus 38.9% with TAPSE<1.8 cm).

**Sensitivity Analysis**

Delay between TTE/RHC: The score had similar test characteristics when applied to subjects with TTE/RHC within 90 days (n=97, AUC=0.908), 30 days (n=67, AUC=0.894), or 14 days (n=26, AUC=0.927). Delay >30 days did not impair discrimination of PHPVD (n=41, AUC=0.943).

Tissue Doppler: We did not specify incomplete tissue Doppler data as an exclusion criterion, and included 12 (11.1%) subjects missing E:e′ data. The score for those subjects could range from –1 to +2. Excluding these subjects, AUC→0.921 and test characteristics improved slightly (score≥0 +LR=2.7, −LR=0; for score≥1 +LR=5.7, −LR 0.2).

LV Systolic Dysfunction: Excluding n=5 with LVEF<45% did not affect the results. Furthermore, 2 out of 5 actually had PH_{PVD} (PVR/PAWP 7.9 WU/12 mm Hg and 7.5 WU/10 mm Hg). Both subjects with PH_{PVD} had score=1, whereas 1 without PH_{PVD} had a score=1 and the others had score=−1.
WHO Group I versus II: Among n=80 (74.1%) with group I or II PH, the model had improved test characteristics for predicting PH PVD (AUC=0.949; for score>0 positive predictive value=88.5%, NPV=88.9%), and distinguished group I versus II PH (AUC=0.967; for score>0 positive predictive value=97.1%, NPV=91.1%).

CART Analysis
Results of CART analysis are presented in Figure 6. The variables found to provide optimal splits (LA dimension, notching, AccT, and E:e') were the same as we derived using LR. LA diameter >4.2 cm identified a group very unlikely to have PH PVD. Among those with LA diameter≤4.2 cm, notching or AccT<80 ms identified patients likely to have PH PVD. In the absence of abnormal RVOT Doppler, E:e'>10 identified patients unlikely to have PH PVD. Even when E:e'≤10, those with truly normal AccT (>120 ms) were unlikely to have PH PVD.

Put another way, patients with either (1) LA>4.2 cm and E:e'>10 without a notch or (2) normal RVOT Doppler with either E:e'>10 or AccT>120 were very unlikely to have PH PVD (3.1%, 1 out of 32). Among those not meeting these criteria,
67.1% (51 out of 76) had PH<sub>pvD</sub> (OR=21.5, 95% CI 3.1–149). The resulting tree had an receiver operating characteristic AUC=0.881.

Discussion

We present a simple echocardiographic score to predict the hemodynamic basis of PH among a diverse referral population. The distinction between elevated PVR as the primary cause of elevated PA pressure (ie, PH<sub>pvD</sub>) from PVH (eg, WHO Group II PH) is critical in the initial assessment of PH; ensuing diagnostic steps and therapeutic choices differ dramatically. The proposed score integrates assessment of the likelihood of both elevated LA pressure and PVR. A negative score argues strongly against PH<sub>pvD</sub> physiology. In addition, a negative score in conjunction with normal RVOT AccT (>100 ms) and preserved RV function (TAPSE≥1.8 cm) essentially excludes elevated PVR.

A positive score, on the other hand, is highly suggestive of PH<sub>pvD</sub> and all patients with a score=±2 had PH<sub>pvD</sub>. We see 4 potential clinical roles for this score. First, among patients in whom PH is thought related to elevated left-heart filling pressure, a score of ±2 (or ±1 to a lesser extent) suggests important PH<sub>pvD</sub> and invasive evaluation should be considered. Second, a negative score in conjunction with relatively low pretest probability of PH<sub>pvD</sub>, especially with normal TAPSE and AccT, will encourage focus on alternative explanations for symptoms (ie, left heart failure) and avoid delay in appropriate diagnosis. Third, the score may help when catheterization reveals borderline values for PVR or PAWP, or in mixed PH when both PVR and PAWP are elevated, a relatively common clinically challenging situation. Appropriate application of this score in such situations merits additional study. Finally, we think a positive score (especially ±2) will prove highly predictive of PH<sub>pvD</sub> even in the absence of prior suspicion for PH. This requires further investigation, because the current data derive from a PH referral population. Prior literature, however, strongly supports that those with a small LA and either very short AccT or midsystolic notching are very likely to have importantly elevated PVR.

The predictive ability of any single variable for PH<sub>pvD</sub> was limited, and we report more modest test characteristics for several variables than published in prior studies. One reason is that we included studies performed up to 1 year apart, whereas much previous research included studies done within a very short time. While in a sense a scientific limitation, any echocardiographic model should be able to predict a patient’s long-term hemodynamic physiology. The fact that the prediction rule still retained its predictive value supports that the
root physiological cause of PH in a given patient is consistent over time and typically does not shift between PHpvD and PVH. Additionally, this study included a larger sample size than most prior studies and also included mixed PVH and elevated PVR. A single variable would naturally have trouble capturing the multifaceted physiological definition of PHpvD. Hence, the overall echo score was superior to any single variable alone in detecting PHpvD. For example, E:e’ ratio had an AUC=0.79, and a cutoff of 9.2 had sensitivity=80.9% and specificity=67.4% for PHpvD.

The decision to combine mid-systolic notching and AccT into a single variable was not arbitrary. These phenomena derive from equivalent pathophysiology: mid-to-late systolic flow deceleration and shortened ejection time resulting from the combined effects of increased PVR and increased conduit artery stiffness, leading to early return of a reflected pressure wave.22 Some patients have notching of the RVOT Doppler envelope, whereas others have shortened ejection time. These patients may have other manifestations of wave reflection, such as shortened AccT or a shift in timing of peak flow to peak pressure, which can be determined using RVOT and TR Doppler envelopes.23

The proposed score is simple and easy to integrate into practice for even the busiest clinical echocardiographic services. The component variables are either (1) already ubiquitously obtained and reported in routine practice (LA dimension, E:e’) or (2) quickly assessed from universally acquired images (ie, RVOT pulsed wave Doppler). The simplicity and practicality of this prediction rule, coupled with impressive test characteristics, makes clinical application of the score particularly appealing.

Of note, variables previously validated to predict PH outcome do not predict physiology well, ie, TAPSE.15,23 TAPSE is a validated correlate of stroke volume and predicts PAH outcomes, but did not differentiate PHpvD. This is not surprising; TAPSE can be decreased because of primary myocardial dysfunction, increased total pulmonary resistance from LA hypertension, or increased PVR.

The score does not perfectly predict PHpvD. Reasons may include time delay between studies, hemodynamic variation, or limitations inherent in echocardiography. In part, however, this relates to the outcome definition, a combination of normal PAWP and elevated PVR. Much misclassification was in subjects with both elevated PVR and elevated PAWP, as witnessed by the predictive capability (AUC=0.98) after excluding subjects with mixed PH physiology. Subjects with a positive score invariably had ↑PVR, and most without PHpvD who had positive scores had only mildly elevated PAWP. A cutoff PAWP=15 mmHg does not reflect an absolute physiological truth, and some patients have ↑PAWP attributed to ventricular interaction. Underlying physiology in such cases may appropriately be categorized as PHpvD by noninvasive examination, thus providing complimentary information over “spot” invasive assessment of left heart filling pressures alone. However, chronically elevated pulmonary venous pressure can cause pulmonary vascular remodeling and elevated PVR. Such remodeling seems to have real prognostic import, although the mechanisms and role for pulmonary vasodilator therapy are as yet undefined. Study is warranted to define the role of the derived model in chronic left heart failure.

It should be noted that invasive hemodynamics obtained by fluid-filled catheter, with cardiac output estimated with thermodilution or Fick using assumed VO₂, are far from a comprehensive gold standard.24 Precision is limited and data represent average flow over several beats and provide a resting snapshot of a dynamic system.25,26 While often considered a linear relationship between pressure drop and flow, PVR varies with flow attributed to variable pulmonary vascular distention and recruitment.27 Finally, PVR ignores the marked pulsatility of the pulmonary circulation.24,28 Abnormal flow may also relate to conduit vessel stiffness or asymmetrical downstream impedance.18,29 Echocardiographic variables, such as LA size, provide a time-averaged view of hemodynamics (eg, LA pressure), while systolic notching and AccT integrate elements of pulmonary vascular load, namely opposition to mean flow (resistance) and opposition to pulsatile flow (pulse wave velocity, wave reflection). As such, comprehensive understanding of PH should include integrated assessment of imaging data, such as the proposed score, along with invasive hemodynamics.

Limitations
TTE and RHC were not simultaneous, although this delay should weaken observed predictive ability (ie, bias results toward the null). Moreover, delays between echo-Doppler and catheterization are ubiquitous in clinical practice. Importantly, we studied a referral population who underwent invasive evaluation after clinical assessment. Most patients had elevated PVR; our findings may not be generalizable to the general population referred for TTE without suspicion for PH. This score was derived from a retrospective analysis of clinical data in a single center, and requires independent validation.

This prediction rule (“Echo Score”) was derived in a population with suspected PH who, after consultation with experienced PH providers, were referred for RHC. Normal subjects should have score=0 (or +1 because LA dimension may be <3.2 cm, especially for smaller or female patients).14 Thus, these findings apply to patients with clinically suspected PH, and should not be applied to other populations without investigation. In addition, clinically important hemodynamically mixed PH is not easily characterized by a single score, but rather requires an understanding of the score components and overall clinical picture. This issue is fundamental to diagnosing and treating PH and is not specific to this model. Our understanding of the mechanisms, clinical significance, and role of specific therapy of pulmonary vascular remodeling in various associated diseases, most notably parenchymal lung disease and chronic heart failure, is incomplete. Available PH classification schemes, based on a combination of hemodynamics and the presence of associated disease, do not directly reflect the pathology or physiology of underlying PHpvD. We opted for a purely hemodynamic primary end point (PHpvD), although sensitivity analysis demonstrates the score also distinguishes WHO Group and identifies ↑PVR.

A significant minority of patients with negative scores had elevated PVR. This is largely attributable to the referral
population studied, 73% of whom had PVR>3 WU. While no score in itself could exclude PH, all patients who had a negative score in combination with normal AccT (or preserved RV function) had essentially normal PVR.

We focused on echocardiographic variables commonly obtained in clinical practice. Including more quantitative or advanced parameters, such as LA area, RV isovolumic AccT, adjusting AccT for heart rate, RV strain, RV Tei index, estimated PVR or multivariable regression formulae might be more predictive of PH physiology. However, these complicated parameters require additional effort and would limit clinical implementation. Finally, we relied on PAWP, which may not always reflect LVEDP, although PA occlusion was confirmed with fluoroscopy and oximetry. We would expect misclassification to be related to stochastic variation (nondifferential); however, this would tend to underestimate the model’s predictive ability.

Clinical Implications and Conclusions

We present a simple clinical prediction rule that describes PH physiology among a diverse cohort of patients with suspected PH. A negative score essentially excludes PH physiology and should prompt further investigation and treatment of left heart disease. A positive score is highly suggestive of PH physiology, and strongly argues for invasive hemodynamic investigation with anticipation of PH physiology even in the absence of increased Doppler-estimated PA systolic pressure.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

This article describes a simple echocardiographic prediction rule to define the hemodynamic physiology of pulmonary hypertension (PH). The score uses ubiquitously acquired echocardiographic data (LA size, lateral mitral E:e’, and pulse wave Doppler of the right ventricular outflow tract) to predict the likelihood that a given patient has PH attributed to pulmonary vascular disease (PHpvD, normal left heart filling pressure and elevated PVR) or whether the PH is more likely related to left heart disease with elevated left atrial pressure. A positive score is highly suggestive of PHpvD physiology, and strongly argues for invasive hemodynamic investigation with anticipation of pulmonary vascular disease, even in the absence of elevated Doppler-estimated pulmonary artery systolic pressure. A negative score essentially excludes PHpvD physiology and should prompt further investigation and treatment of left heart disease. The simplicity and practicality of this prediction rule, coupled with impressive test characteristics, will facilitate widespread clinical application.
A Simple Echocardiographic Prediction Rule for Hemodynamics in Pulmonary Hypertension


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SUPPLEMENTAL MATERIAL (Expanded Methods)

Echocardiography

Patients underwent clinically indicated TTE with Philips Sonos (Philips Medical Systems, Andover, MA) or GE Vingmed Vivid 7 Ultrasound (GE, Vingmed Ultrasound, Horten, Norway). Measurements were made by experienced echocardiographers blinded to invasive hemodynamics in accordance with American Society of Echocardiography guidelines\textsuperscript{1} using the Acuson KinetDx digital system (WS 3000 Diagnostic Workstation, Siemens Medical Solutions USA Inc., Mountain View, CA). At least three cardiac cycles were measured (5-10 with irregular rhythms) and average values were used.

Left atrial (LA) AP dimension in end-systole, interventricular septum and LV posterior wall thickness in end-diastole were measured from the parasternal long axis view. TAPSE, RV and LV inflow diameters in diastole, RV end-systolic and end-diastolic length and area, RA and LA end-systolic areas, and LA length and RA minor dimension measured from the apical 4-chamber view. RV fractional area change was calculated as (RV diastolic area-RV systolic area)/RV diastolic area.\textsuperscript{1-3} Systolic and diastolic eccentricity index was calculated as described previously.\textsuperscript{4} RVOT and LVOT PW Doppler interrogation were performed from the basal short axis and apical 3-chamber views ~1cm proximal to the pulmonic and aortic valves respectively. By inspecting the PW Doppler signal from the RVOT, the presence of a mid-systolic notch (MSN) was characterized as a distinct notch or nadir within the initial two-thirds of the systolic ejection period, as described previously.\textsuperscript{5} TTFV was obtained from continuous wave Doppler interrogation in the view which view provided the best envelope with highest estimates. PW Doppler of the LV inflow was used to measure peak E/A velocities and E deceleration time. Lateral mitral annular Tissue Doppler was used to measure e’ velocity.\textsuperscript{6}
Invasive Hemodynamics

RHC was performed using a 7 French balloon-tipped fluid filled catheter, with care taken to obtain optimally damped hemodynamic tracings. RA, RV, PA, and PA wedge pressure (PAWP) tracings were recorded, with measurement at end-expiration; RA and PAWP estimates used the end-diastolic point of the hemodynamic tracing. Catheter position was confirmed by waveform analysis and, when indicated, by fluoroscopy and/or oximetry. Cardiac output was measured by triplicate thermodilution. Pressure tracings were reviewed and quantified by a single observer (PRF) and occurred prior to TTE quantification (i.e. investigator blinded to TTE parameters). Variables of interest included cardiac output, stroke volume, systolic, diastolic and mean PA pressure (mPAP), RA pressure, PAWP, and PVR expressed in Wood’s units (WU; mmHg/l/min). PH_{PVD} physiology was defined as mPAP≥25mmHg, PAWP≤15mmHg and PVR>3WU.

References