Echocardiography based estimation of pulmonary vascular resistance in patients with pulmonary hypertension: a simultaneous Doppler echocardiography and cardiac catheterization study

Per Lindqvist 2,3*, Stefan Söderberg 1,3, Manuel C Gonzalez 1, Erik Tossavainen 1, and Michael Y Henein 1,3

1Department of Cardiology, Umeå University, Umeå, Sweden; 2Department of Clinical Physiology, Umeå University, Umeå, 5-90185 Sweden; and 3Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

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Aims
Pulmonary vascular resistance (PVR) is an important measurement for the diagnosis of patients with pulmonary hypertension (PH) but needs accurate determination of mean pulmonary artery pressure (PAMP). We aimed to test the accuracy of a Doppler-derived measurement of PVR, using the conventional invasive equation in patients with PH.

Methods and results
We investigated 30 patients undergoing right heart catheterization (RHC), mean age 62 ± 13 years, 21 females, with different diseases: idiopathic pulmonary arterial hypertension (PAH) (n = 5), associated PAH (n = 16), chronic thromboembolic PH (n = 6), interstitial lung disease (n = 2), and after closure of an atrial septal defect (n = 1). Patients with impaired left ventricular systolic function (EF, 50%) or elevated pulmonary capillary wedge pressure (PCWP ≥ 15 mmHg on RHC) were excluded. We used the formula: PAMP = PASPecho × 0.61 + 2 mmHg, where PASPecho is the peak tricuspid regurgitation pressure drop + 10 or 7 mmHg. Pulmonary vascular resistance was then calculated as PAMP echo/PCWP/cardiac output. Pulmonary capillary wedge pressure was estimated at 10 mmHg in all cases. The Doppler-derived estimation of PVRecho was achievable in 90% of patients, in whom accurate calculation of PAMP was obtainable. Pulmonary vascular resistance echo individual values strongly correlated with those from RHC (r = 0.85, P < 0.001 and r = 0.87, P < 0.001 for the two estimated values for right atrial pressure, respectively). The regression equation using this formula was PVR_rhc = 0.95 × PVR_echo – 0.29, and the regression line was close to identity. The Bland–Altman plot showed a good agreement between PVRecho and PVR_rhc values, with a mean difference of −0.66 ± 2.1 Wood unit.

Conclusion
The proposed Doppler-derived formula for estimating PVR based on the conventionally used invasive equation strongly correlates with invasive gold standard measures.

Keywords
Doppler echocardiography • Pulmonary vascular resistance • Right heart catheterization

Introduction
Estimation of pulmonary artery pressure (PAP) is important in refining the diagnosis, optimizing follow-up after treatment and predicting prognosis in patients with pulmonary hypertension (PH). Although non-invasive estimation of PAP by Doppler echocardiography is well established in clinical practice, it does not account for variations in the flow. A more accurate measurement

* Corresponding author. Tel: +46 9078 51965; fax: +46 9013 7633, Email: per.lindqvist@medicin.umu.se

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of PH is thus needed. Pulmonary vascular resistance (PVR) reflects better the disease process; hence its measurement should account for most accurate disease assessment. Furthermore, PVR is known as a strong predictor for reduced exercise capacity in thromboembolic patients after thrombendarterectomy. Right heart catheterization (RHC) is the gold standard investigation for determining pulmonary haemodynamics including vascular resistance, but its routine use is limited by its invasive nature and incurring cost. Other non-invasive resting and exercise methods have been proposed but with limited accuracy. The aim of this study was therefore to test a new Doppler-derived method, based on conventional invasive measurement in estimating PVR in patients with PH.

**Methods**

We investigated 30 patients with PH of different aetiologies, undergoing diagnostic and follow-up RHC of a mean age 62 ± 13 years and 21 were females. The aetiology of PH was classified according to guidelines as idiopathic PAH (n = 5), associated PAH (n = 16), chronic thromboembolic type of PH (n = 6), PH due to lung disease (n = 2), and closed atrial septal defect (n = 1). Patients were excluded from the study if they had signs of impaired left ventricular (LV) systolic function, as reduced ejection fraction (EF < 50%) or elevated mean pulmonary capillary wedge pressure (PCWP >15 mmHg on RHC).

**Right heart catheterization**

Venous access was obtained by inserting an introducer in a medial cubital vein or in the femoral vein. A retrograde catheterization was then performed using a Swan-Ganz® Standard Thermodilution Catheters (Edwards Lifesciences). Mean right atrial pressure (RAP), systolic and end-diastolic right ventricular pressures, pulmonary artery systolic, mean and diastolic pressures (PASP, PAMP and PADP, respectively), and PCWP were measured. Blood samples for estimation of oxygen saturation were drawn from the superior and inferior caval veins, as well as right atrium, and that from the pulmonary and femoral arteries were used for screening for intra-cardiac shunts. Cardiac output was determined by thermodilution. Pulmonary vascular resistance was calculated from the equation PAMP – PCWP (trans-pulmonary gradient) divided by CO.

**Echocardiographic examination**

Echocardiographic examination was performed using a Vivid 7 system (GE Medical Systems, Horten, Norway) equipped with an adult 1.5–4 MHz phased array transducer. Standard views from the parasternal long and short axis and apical four-chamber views were used. Flow velocities were obtained using pulsed and continuous wave Doppler techniques as proposed by the American Society of Echocardiography. Stroke volume and COecho measurements were made at the level of the LV outflow tract because of the known limitations of acquiring accurate respective measurements from the right ventricular outflow tract (RVOT). Pulmonary artery flow was measured by placing the pulsed wave Doppler sample volume at the centre of the transpulmonary valve jet, obtained from the short-axis view. Retrograde systolic tricuspid flow was obtained from either parasternal right ventricular inflow view or apical four-chamber view for measuring peak tricuspid pressure drop using continuous wave Doppler. Right ventricular long-axis function (strain) was studied using speckle tracking echocardiography technique (STE). All Doppler recordings were made at a sweep speed of 50–100 mm/s with a superimposed ECG (lead II). Off-line analysis was made using a commercially available software system (General Electric, EchoPac version 5.0.1, Waukesha, Wisconsin, US) and mean of three consecutive tracings were calculated. The study protocol was approved by the Regional Ethics Committee of Umeå (DNR 07–092M) and all subjects signed an informed consent.

**Measurements**

Pulmonary vascular resistance was estimated using our proposed equation: $PVR = \frac{PAMP_{echo} - PCWP}{CO_{echo}}$ where $PAMP_{echo}$ is calculated as $PASP_{echo} \times 0.61 + 2$ mmHg, according to Chemla et al., with $PASP_{echo}$ peak transtricuspid retrograde pressure drop +10 and 7 mmHg (two proposed estimated values for RAP). Pulmonary capillary wedge pressure of 10 mmHg was also estimated for all cases. These results were compared with other previously published methods:

(i) $PAMP - PCWP/CO_{echo} $; where $PAMP$ was calculated as $PDP + 0.33 \times (PASP - PADP)$ and $PDP$ which was calculated as $4 \times (transtricuspid pressure drop at the time of pulmonary valve opening)^2 + \text{estimated RAP of 10}$. ($P$)

(ii) The ratio of transtricuspid peak pressure drop/RV outflow tract velocity time integral.

(iii) $PASP/(HR \times RVOT \text{velocity time integral})$. We also measured RV systolic deformation (strain) at the basal, mid-cavity and apical segments using STE.

**Statistical analysis**

Normally distributed continuous data were expressed as mean ± standard deviation. Relationships between variables were tested using Pearson’s correlation. Partial correlations were made to control for age, sex and type of PH. The Bland–Altman test was used to evaluate the mean difference ± 2SD between echocardiography and RHC. The statistical software package (PASW Statistics version 18) was used for all calculations.

**Results**

Clinical characteristics are shown in Table 1. The majority of patients were females and had PH, in most cases associated with connective tissue disease.

**Relationships between invasive and new Doppler-derived measure of pulmonary vascular resistance**

The new method (Lindqvist) was feasible in 90% of the cases and the results obtained correlated closely with PVRhc ($r = 0.85$, $P < 0.001$) with a regression equation of $0.95 \times PVR_{echo} - 0.29$ and the regression line close to identity (Figure 1A). The Bland–Altman plot showed an excellent agreement between $PVR_{echo}$ and $PVR_{hc}$ with a bias of $-0.66 \pm 2.1$ (Figure 1B). The sensitivity and specificity of the method for identifying patients with PVR >3 WU were 100 and 63%, respectively, and negative and positive predictive values were 100 and 86%, respectively (Table 2). Using an estimated RAP of 7 mmHg resulted in a stronger correlation ($r = 0.87$, $P < 0.001$) with a regression equation of $1 \times PVR_{echo} - 0.08$, (Figure 1C). The sensitivity and specificity of the method for identifying patients with PVR >3 WU were 95 and...
The linear regression equation was 0.74 between PVRecho and PVRrhc, bias of 1.8. Using the method by Selimovic et al., the estimated PVR was feasible in 76% and had a correlation with PVRrhc of $r = 0.77$, $P < 0.001$. The linear regression equation was $0.74 \times \text{PVRecho} + 0.98$ with the regression line slightly overestimating PVR, at all levels (Figure 2C). The Bland–Altman analysis showed an agreement between PVRecho and PVRrhc, bias of $6.4 \pm 4.1$ WU. The sensitivity and specificity using a cut-off value of $<0.04$ for identifying patients with elevated PVR was 94 and 100%, respectively, and the negative and positive predictive values were 88 and 100%, respectively (Table 2).

Assessment of RV strain function using STE at mid-segment showed an acceptable feasibility of 77% but only modest correlation with PVRrhc ($r = 0.59$, $P < 0.01$). The regression equation was $\text{PVRrhc} = \text{RV strain} \times 0.20 + 2$ (Figure 2D). The Bland–Altman analysis showed a low agreement between PVRecho and PVRrhc, bias of $21.0 \pm 7.9$ WU. The sensitivity and specificity using a cut-off value of $< -20\%$ for identifying patients with elevated PVR was 88 and 63%, respectively, and the negative and positive predictive values were 71 and 82%, respectively (Table 2).

The correlations between Doppler echocardiography and RHC were not influenced by age, sex, or aetiology of PH.

**Discussion**

**Findings**

This study shows that our Doppler-derived equation for estimating PVR proved very accurate in identifying patients with raised PVR. In the patient’s group, as a whole, results of individual patients strongly correlated with the respective catheter-based measurements of PVR as well as CO. Finally, this correlation was not influenced by age, sex, or type of PH.

**Data interpretation**

Right heart catheterization has been the gold standard method for confirming the diagnosis of PH, providing accurate measurements of PAP and pulmonary vascular resistance. However, the method is limited to be used in the regular follow-up of patients because of its invasive nature and potential risks, despite being rare. Doppler echocardiography has become the investigation of choice for studying cardiac structure and function as well as estimating intra-cardiac and transvalvular pressures. Doppler echocardiography has particularly revolutionized our cardiology practice for assessing PAP non-invasively. Retrograde transtricuspid pressure drop using continuous wave Doppler is a solid routine estimate of peak PAP in most patients undergoing echocardiographic examination. It has, however, certain limitations particularly when RAP rises, right ventricular systolic function drops and tricuspid regurgitation becomes severe. In addition, the known limitation of pulmonary pressure measurements, which reflects the pulmonary circulation status, makes assessment of pulmonary vascular resistance a serious need for optimal patient management.

A number of Doppler echocardiographic measurements and equations for estimating PVR have been proposed and proved to have at least one of the four measures of accuracy: sensitivity, specificity, positive, or negative predictive values. However, the negative and positive predictive values were 75 and 94%, respectively (Table 2).

The method by Haddad et al. was feasible in 80% and had a correlation of $r = 0.74$, $P < 0.001$ in predicting PVRrhc. The regression equation was $88.5 \times \text{PVRecho} + 0.98$ with the regression line slightly overestimating PVR, at all levels (Figure 2C). The Bland–Altman analysis showed an agreement between PVRecho and PVRrhc, bias of $6.4 \pm 4.1$ WU. The sensitivity and specificity using a cut-off value of $<0.04$ for identifying patients with elevated PVR was 94 and 100%, respectively, and the negative and positive predictive values were 88 and 100%, respectively (Table 2).

Assessment of RV strain function using STE at mid-segment showed an acceptable feasibility of 77% but only modest correlation with PVRrhc ($r = 0.59$, $P < 0.01$). The regression equation was $\text{PVRrhc} = \text{RV strain} \times 0.20 + 2$ (Figure 2D). The Bland–Altman analysis showed a low agreement between PVRecho and PVRrhc, bias of $21.0 \pm 7.9$ WU. The sensitivity and specificity using a cut-off value of $< -20\%$ for identifying patients with elevated PVR was 88 and 63%, respectively, and the negative and positive predictive values were 71 and 82%, respectively (Table 2).

The correlations between Doppler echocardiography and RHC were not influenced by age, sex, or aetiology of PH.

**Table 1** Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 13</td>
</tr>
<tr>
<td>Male/female</td>
<td>6/24</td>
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<tr>
<td>Aetiology of PH</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension (PAH)</td>
<td>5</td>
</tr>
<tr>
<td>Associated PAH</td>
<td>16</td>
</tr>
<tr>
<td>Thromboembolic PH</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
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</tbody>
</table>

Right heart catheterization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP (mmHg)</td>
<td>58 ± 23</td>
</tr>
<tr>
<td>PAMP (mmHg)</td>
<td>37 ± 15</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>RVEDP (mmHg)</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.1 ± 1.5</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>5.7 ± 4.0</td>
</tr>
<tr>
<td>RV longs axis function, tissue Doppler echocardiography (TDI)</td>
<td>$s'$ (cm/s) 10.4 ± 3.0, $e'$ (cm/s) 9.6 ± 4.7, $a'$ (cm/s) 14.0 ± 5.3</td>
</tr>
</tbody>
</table>

75%, respectively, and negative and positive predictive values were 90 and 86%, respectively (Table 2). The correlation coefficient between CO from rhc and echo was $r = 0.76$, $P < 0.001$.

**Comparison between the newly proposed model and previous methods**

Using the method by Selimovic et al., the estimated PVR was feasible in 76% and had a correlation with PVRrhc of $r = 0.77$, $P < 0.001$. The linear regression equation was $0.74 \times \text{PVRecho} + 0.29$, and the regression line was close to identity only at low PVR but slightly overestimated PVR at higher levels (Figure 2A). The Bland–Altman analysis showed an acceptable agreement between PVRecho and PVRrhc, bias of $-1.8 \pm 2.9$ WU. The sensitivity and specificity of this method for identifying patients with elevated PVR, $>3$ WU, were 100 and 14%, respectively, with negative and positive predictive values of 100 and 66%, respectively (Table 2).

The method proposed by Abbas et al. was feasible in 83% and showed a good correlation with PVRrhc of $r = 0.78$, $P < 0.001$. The regression equation was $22.5 \times \text{PVRecho} + 0.62$ with the regression line continuously overestimating PVR at all levels (Figure 2B). The Bland–Altman analysis showed an agreement between PVRecho and PVRrhc, bias of $6.1 \pm 4.0$ WU. The sensitivity and specificity using a cut-off value of $>0.175$ for identifying patients with elevated PVR was 88 and 86%, respectively, and
Figure 1 Linear correlation (A) and the Bland–Altman plot (B) comparing invasive pulmonary vascular resistance right heart catheterization (PVR_{rhc}) and pulmonary vascular resistance from the new method (M1) using estimated right atrial pressure (RAP) of 10 mmHg. Additionally the correlation (C) and the Bland–Altman plot (D) comparing invasive pulmonary vascular resistance right heart catheterization and pulmonary vascular resistance from the new method (M1) using estimated right atrial pressure of 7 mmHg.

Table 2 Diagnostic accuracy using different Doppler echocardiographic methods in estimating pulmonary vascular resistance

<table>
<thead>
<tr>
<th>Echocardiographic variables</th>
<th>Cut-off analysis</th>
<th>Bland–Altman analysis</th>
<th>Feasibility (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
</tr>
<tr>
<td>PVR (Lindqvist et al., RAP 10 mmHg) (WU &gt; 3)</td>
<td>100</td>
<td>63</td>
<td>86</td>
</tr>
<tr>
<td>PVR (Lindqvist et al., RAP 7 mmHg) (WU &gt; 3)</td>
<td>95</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>PVR (Selimovic et al.) (WU &gt; 3)</td>
<td>100</td>
<td>14</td>
<td>66</td>
</tr>
<tr>
<td>TRV_{peak}/VTI_{rvo} (Abbas et al.), (&gt;0.175)</td>
<td>88</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>PASP/HR × VTI_{rvo} (Haddad et al.), (&lt;0.04)</td>
<td>94</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>RV Strain (STE), mid, % (&lt; − 20)</td>
<td>88</td>
<td>63</td>
<td>82</td>
</tr>
</tbody>
</table>

PVR, pulmonary vascular resistance; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; TRV, tricuspid regurgitation velocity; VTI, velocity time integral; rvo, right ventricular outflow tract; RV, right ventricular; STE, speckle tracking echocardiography; PPV, positive predictive value; NPV, negative predictive value; HR, heart rate.
direct comparison of our proposed equation showed high feasibility and significantly higher specificity and accuracy in identifying patients with raised pulmonary vascular resistance of >3 WU compared with previously published methods. Several factors can explain the higher accuracy of our method. We acquired our Doppler echocardiographic recordings at the same time of the direct invasive measurements, virtually simultaneously; therefore we limited potential variations in pressure and flow. We also did not factor for Doppler time measurements, which are generally dictated by the cycle length as well as the functional status of the right ventricular myocardium. Furthermore, our method used the same equation conventionally used during RHC to calculate PVR, thus comparing similar ingredients. In addition, we adhered to estimating PAMP using the same equation proposed by Aduen et al. and Chemla et al., which has been well investigated. To our knowledge, this calculation of PAMP has not been previously used in the estimation of PVR. Finally, we did not include exact estimations of RAP or PCWP but instead a constant value of ‘10 or 7’ for RAP and ‘10’ for PCWP, having excluded patients with potential causes for raised atrial pressures. The reason behind this approach was the serious inaccuracies previously reported from using exact estimations of atrial pressures in patients with preserved LV ejection fraction.

It seems, therefore, that we have succeeded in avoiding potential sources of under or overestimation of PVR using Doppler echocardiographic measurements. Furthermore, using 10 mmHg for RAP has been shown accurate in estimating pulmonary artery systolic pressures. The correlation between our estimated values of the PVR and those obtained directly from RHC showed a value of $r = 0.85$ and $r = 0.87$ and gave a sensitivity and negative predictive values of 100% for both using 10 mmHg for RAP and 95 and 86%, respectively, using an RAP of 7 mmHg. This supports the proposed equation as a very viable non-invasive method for monitoring patients with pulmonary vascular disease.

**Clinical application**

We have proposed a simple Doppler-derived model for estimating PVR which is based on the invasive concept and
proved to have excellent accuracy, high sensitivity and negative predictive value for monitoring patients with raised PVR. The sensitivity of this method in differentiating raised pulmonary pressures secondary to raised left atrial pressure remains to be determined.

Limitations
We intentionally excluded patients with poor LV function and those with raised left atrial pressure in order to obtain a pure form of raised PVR rather than values potentially clouded by left-side cardiac disease. Likewise, we excluded patients with severe tricuspid and aortic regurgitation as potential causes of inaccurate stroke volume measurement. Thus, our findings need to be re-tested in such groups of patients. None of our patients had more than moderate tricuspid regurgitation, making our equation potentially limited.

Conclusion
The proposed catheter based non-invasive formula for estimating PVR using Doppler-derived measurements strongly correlates with invasive gold standard measures and has high accuracy in identifying patients with raised pulmonary vascular resistance.

Conflict of interest: none declared.

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References