Extraction of Pulmonary Vascular Compliance, Pulmonary Vascular Resistance, and Right Ventricular Work From Single-Pressure and Doppler Flow Measurements in Children With Pulmonary Hypertension: a New Method for Evaluating Reactivity
In Vitro and Clinical Studies

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Background—Current evaluation of pulmonary hypertension (PH) in children involves measurement of pulmonary vascular resistance (PVR); however, PVR neglects important pulsatile components. Pulmonary artery (PA) input impedance and ventricular power (VP) include mean and pulsatile effects and have shown promise as alternative measures of vascular function. Here we report the utility of pulsed-wave (PW) Doppler–measured instantaneous flow and pressure measurements for estimation of input impedance and VP and use this method to develop a novel parameter: reactivity in compliance.

Methods and Results—An in vitro model of the general pulmonary vasculature was used to obtain impedance and VP, measured by PW Doppler and a reference flow meter. The method was then tested in a preliminary clinical study in subjects with normal PA hemodynamics (n=4) and patients with PH undergoing reactivity evaluation (8 patients; 23 data points). In vitro results showed good agreement between the impedance spectra computed from both flow-measurement methods. Excellent correlation was seen in vitro between actual resistance and the zero-frequency ($Z_0$) impedance value ($r^2=0.984$). Excellent agreement was also found between $Z_0$ and PVR in the clinical measurements ($y=1.075x+0.73$; $r=0.993$). Furthermore, total VP and VP/cardiac output increased significantly with hypertension (128.73 to 365.91 mW and 2.42 to 6.69 mW · mL$^{-1} · s^{-1}$, respectively). The first-harmonic value of impedance ($Z_1$) was used as a measure of compliance reactivity; older patients exhibited markedly less compliance reactivity than did younger patients.

Conclusions—Input impedance and VP calculated from Doppler measurements and a single-catheter pressure measurement provide comprehensive characterization of PH and reactivity. (Circulation. 2004;110:2609-2617.)

Key Words: hypertension, pulmonary heart disease, pediatrics, echocardiography, hemodynamics

The management of children with primary and secondary pulmonary hypertension (PH) continues to be a challenge for clinical cardiologists. Several recent advances such as the use of pharmaceutical agents to decrease pulmonary artery (PA) pressures and pulmonary vascular resistance (PVR) have facilitated the treatment of such patients.¹⁻⁵ Although assessment of the hemodynamic status of the pulmonary vasculature is a major component in treatment evaluation, the question of how best to do this is still unanswered.⁶⁻⁷ Current methods evaluate hypertension and vascular reactivity through measurement of PVR, which is the ratio of mean pressure drop across the pulmonary vasculature to mean pulmonary flow and which is based on the assumption of steady hemodynamics.⁸ This technique can be problematic, because right ventricular afterload (RVA) and consequently, PA hemodynamics can change owing to acute and chronic variations in proximal artery compliance and pressure and flow pulse reflections, neither of which is considered in current measurements.⁹⁻¹¹

The acquisition and processing of instantaneous pressure and flow measurements allow a more comprehensive characterization of PH and reactivity. Two parameters in particular,
glycerin-water mixture with a viscosity of 3.5 to 4.0 cP was used to simulate blood. Cornstarch (1% by weight) was added to the solution to enhance ultrasound backscatter.

Pressure, velocity, and flow were measured simultaneously at the same location in the proximal mock artery. Time calibration was performed for all acquisition systems to correct any time lags introduced by each measurement technique. The pressure measurements were made with a solid-state transducer (Millar Inc). Instantaneous flow was monitored by an ultrasonic transit-time flowmeter (Transonic). Instantaneous velocity was acquired through PW Doppler ultrasound measurements with a commercially available ultrasound scanner (Vivid 5, GE Medical Systems Inc) and postprocessing software (EchoDisp, GE Medical Systems Inc). Actual VR for the in vitro model was computed from pressure-drop and flow measurements. All pressure and flow measurements were digitized with a data acquisition system (LabView, National Instruments) sampled at 500 Hz. A total of 22 experimental conditions were produced with the 3 tube models and varying mean pressures.

To compute the instantaneous flow rate from the PW Doppler measurements, the measured velocity must be multiplied by a scaling factor that corresponds to local instantaneous cross-sectional area and the coefficient of velocity. A correction factor for area, , was computed by recognizing that the mean flow during 1 cardiac cycle must be equal to the 2 measuring devices; thus, , where is the time-averaged flow from the perivascular flow meter and is the time-averaged PW Doppler velocity. Doppler flow was then calculated as

\[
Q(t)_{\text{pw}} = A_{\text{corr}} V(t)_{\text{pw}}
\]

Clinical Study

Patient Selection

After institutional review board approval and informed consent and assent (where appropriate) had been obtained, patients underwent cardiac catheterization for routine evaluation and treatment at The Children’s Hospital, Denver, Colo. A limited number of patients were considered; these were divided into 2 groups. Group 1 studies were conducted after closure of a small patent ductus arteriosus. These patients had normal mean PA pressures and were considered the control group (n=4). Group 2 consisted of patients with PH who were undergoing tests for PV reactivity with the use of oxygen and/or nitric oxide (8 patients; n=23 conditions). Table 1 provides hemodynamic data for each subject. For the reactivity studies, the initial data point was considered the baseline value, and each subsequent challenge was denoted as challenge 1, challenge 2, etc.

Clinical Data Acquisition

PW Doppler velocity measurements were taken within the middle section of the main PA with a commercial ultrasound scanner (Vivid 5) from a parasternal short-axis window. Two-dimensional echo and color Doppler flow imaging modalities were used to align the Doppler sample volume parallel to the main flow direction. For group 2 patients, data were obtained before and during nitric oxide and/or oxygen treatment. To determine the physiologic value of , cardiac output was used instead of \(Q_{\text{a}}\) in the aforementioned equation. Cardiac output was measured by Fick’s method with measured oxygen consumption in cases where intracardiac shunts were in place and by thermodilution otherwise. Main PA pressure was measured with standard fluid-filled catheters (Transpac IV, Abbott Critical Care Systems). To facilitate temporal alignment of velocity and pressure signals after acquisition, pressure tracings were digitized directly into the auxiliary input of the ultrasound scanner simultaneously with the PW Doppler information. Tracings were obtained for 16 seconds and transferred to an optical disc for offline analysis. All hemodynamic data were recorded before and during treatment for calculation of PVR.

Data Analysis

The recorded pressure and flow signals were separated into individual cardiac cycles for analysis (n>35 for the in vitro flow meter system; n>20 for the in vitro PW Doppler system; and n>20
Calculation of Input Impedance Spectrum

The input impedance modulus $Z$ and phase $\phi$ are defined by

$$Z(\omega) = \frac{|P(\omega)|}{|Q(\omega)|}$$

$$\phi(\omega) = \theta(\omega) - \varphi(\omega),$$

where $\omega$ is the frequency, $|P|$ is the modulus of the pressure spectrum, $|Q|$ is the modulus of the flow spectrum, $\theta$ is the pressure phase, and $\varphi$ is the flow phase.

Four parameters were extracted from the impedance data: distal VR, characteristic resistance, an index of compliance, and hydraulic reflection coefficient. Distal VR was obtained from the modulus data at the zero harmonic ($Z_0$). The characteristic resistance ($Z_c$) was estimated by averaging the impedance modulus from its first minimum up to the eighth harmonic. The index of compliance was obtained from the modulus of the impedance data at the first harmonic. The reflection coefficient $\Gamma$ was calculated by

$$\Gamma = \frac{Z_0 - Z}{Z_0 + Z}.$$

Calculation of Ventricular Power

Ventricular power (the rate of ventricular work) comprises potential energy (pressure energy) and kinetic energy. Kinetic energy has been shown to account for a small fraction of the total ventricular power and is neglected here. The mean power (mean energy per unit time) was calculated as $W_\text{tot} = P_0 \cdot Q_0$, where $P_0$ and $Q_0$ are the zero-frequency components of the pressure and flow moduli, respectively. The oscillatory power (pulsatile energy per unit time) was calculated as

$$W_\text{o} = \frac{1}{2} \sum_{l=1}^{8} |Q|^2 \cdot |P| \cdot \cos(\theta_l - \varphi_l),$$

where $l$ represents the harmonic of the fundamental frequency.

Finally, total RV power was calculated as $W_\text{T} = W_\text{tot} + W_\text{o}$. To quantify the total power expended per unit of forward flow, total power was divided by cardiac output ($W_\text{T}/CO$).

Statistics

With the exception of the input impedance modulus and phase (see next section), all data are presented as mean±SD. The in vitro
instantaneous flow data computed from PW Doppler measurements were compared with the results from the flow meter with Student’s t test. The same t test was used to identify differences between patients with normal and high mean pulmonary pressures. The level of significance for all statistical tests was set at 5%.

Experimental Uncertainty
For impedance modulus and phase calculations, it was necessary to determine the complete experimental uncertainty to ensure that subsequent statistical comparisons were robust. Uncertainty (u) in the mean modulus due to variance in the data at a specific frequency is defined as

\[
u(\omega) = t_{\omega,\alpha} \times \sqrt{\left(\frac{\sigma_\omega}{\bar{Z}(\omega)}\right)^2 + \left(\frac{\sigma_\phi}{\phi(\omega)}\right)^2},\]

where σ is the standard deviation of the data, n is the number of data points, and t(\omega) is the t value calculated from Student’s t distribution with \(\nu\) degrees of freedom and 95% confidence. The number of degrees of freedom was calculated from the Welch-Satterthwaite formula.22 The uncertainty in the impedance phase was calculated in a similar manner as described earlier.

Results
In Vitro Study
Mean pressures within the in vitro models ranged from 26.64 to 43.99 mm Hg for tube 1, 30.67 to 53.45 mm Hg for tube 2, and 29.49 to 59.56 mm Hg for tube 3. An average pulse pressure of 16.81 ± 3.55 mm Hg was observed for all models throughout all conditions. The mean flow rate was kept constant at 1.88 ± 0.23 L/min. Actual VR, measured as the mean pressure drop divided by mean flow within the in vitro models, ranged from 11.15 to 37.06 mm Hg · L⁻¹ · min⁻¹.

Figure 2 shows input impedance spectra (modulus, A; phase, B) obtained from the flow probe and PW Doppler data for tube 2 at a mean pressure of 41.98 mm Hg and a resistance of 22.35 mm Hg · L⁻¹ · min⁻¹. Good agreement was found in the impedance magnitudes calculated by flow probe and PW Doppler for the Z₀ component and the minimum impedance value for all tubes and conditions. However, PW Doppler overestimated the impedance modulus at higher harmonics. Similar results were seen for the other tube models. Excellent correlation was seen between Z₀ and the actual VR calculated from the drop in pressure across the system (see Figure 3A).

To investigate the impedance spectral response to changes in compliance independent of all other parameters, the most- and least-compliant tubes were exposed to equal hemodynamics and resistance. Figure 3B and 3C shows the impedance modulus and phase for the most-compliant and least-compliant in vitro tube models. The mean values and their uncertainties are presented. It can be seen that as compliance decreased, the impedance values at both the first and second harmonics increased. This indicates that either of these values may be useful for assessing compliance in the clinical situation.

No differences in mean power between the 2 flow measurement methods were seen (mean difference of 0.02 ± 0.44%; P = NS). However, PW Doppler underestimated the oscillatory component by 25.10 ± 19.14% (P = 0.05). No statistical difference was seen between total RV power expelled for fluid motion agreed between the 2 methods (mean difference of −0.26 ± 0.48%; P = NS). Measurement of total RV power expelled for fluid motion agreed between the 2 methods (mean difference of −0.33 ± 0.28%; P = NS).

Clinical Data
Patients 1 through 4 had normal pulmonary pressures (group 1), whereas patients 5 through 12 had PH (see Table 1). The mean cardiac index was 5.76 ± 0.94 L · min⁻¹ · m⁻² for group 1 patients and 4.62 ± 2.49 L · min⁻¹ · m⁻² for group 2 (P = NS). Figure 4A shows the impedance modulus, and Figure 4B shows the phase for group 1 subjects. Input impedance (magnitude and phase) for the PH patients are presented in Figure 5. For brevity, only 4 patients are presented here, but these values were representative of the population. Z₀ increased with hypertension, as would be expected (see Figure 5A).

Significant differences were seen in Z₀ between normal and hypertensive patients (P < 0.05). As with the in vitro data, excellent agreement was found between Z₀ and hemodynamic measurement of PVR (y = 1.07x + 0.73, r = 0.993; Figure 6). On the basis of the in vitro observations of changes in impedance values at the first and second harmonics with compliance changes, we used the percent change in impedance value at the first harmonic (Z₁) with challenge as a measure of reactivity in compliance for the clinical studies. These data, along with reactivity in PVR, are presented in
All challenges except 1 produced negative changes (ie, decrease in $Z_1$), indicating some increase in compliance with challenge. How much the compliance increased varied from patient to patient and from challenge to challenge. A reactivity threshold of $10\%$ change in $Z_1$ change could be used to gauge the change in compliance with reactivity. When reactivity in PVR was examined along with reactivity in compliance, as defined earlier, the data showed that most patients who were reactive in PVR were also reactive in compliance (Figure 7), with 2 exceptions: patients 8 and 9, who are discussed later. These data provide initial evidence for using input impedance to gauge reactivity in both resistance (based on changes in $Z_0$) and compliance (based on $Z_1$).

No differences in $Z_0$ were seen ($P=NS$) between group 1 and 2 data. However, the PA reflection coefficient increased significantly from $0.45\pm0.11$ to $0.75\pm0.15$ with PH ($P=0.05$). Significant increases were seen in both mean power (group 1, $120\pm42$ mW; group 2, $346\pm391$ mW) and oscillatory power (group 1, $8.45\pm3.27$ mW; group 2, $19.4\pm19.0$ mW) with hypertension ($P=0.05$ for both). Furthermore, the average total power increased from $128.73\pm44.84$ to $365.91\pm409.38$ mW ($P=0.05$) between the 2 groups. Table 2 summarizes these data. Maximum interobserver and intraobserver variabilities in impedance were $3.2\%$ and $3.9\%$, respectively.

**Discussion**

This project addressed several difficulties related to the evaluation of PH in pediatric subjects, including patients undergoing reactivity testing and evaluation of new treatments. These patients are already in the catheterization laboratory during such evaluation; the intent here was to determine whether the addition of an easy-to-use Doppler measurement would provide important additional data on PV status. The input impedance (and parameters derived from impedance data) and RV power were chosen as key markers.
Previous investigators, using more invasive cuff-type flow probes, have identified these as useful parameters of vascular function.\textsuperscript{23–28}

Utility of PW Doppler for Impedance and Power Measurements

Although the utility of PW Doppler for cardiac output and pulmonary-to-systemic flow-ratio measurements has been examined by investigators in our laboratory and others,\textsuperscript{29–31} evaluation of Doppler as a tool for impedance and power calculations, especially in the pediatric pulmonary vasculature, has not been performed. The first concern in using Doppler methods to obtain instantaneous flow involves conversion of velocity to flow through a correction factor for local area. In the clinical studies, a mean value of 1.70 cm\textsuperscript{2} was found for $A_{corr}$. The assumption of constant area will affect the pulsatile content of the calculated flow and therefore, the final response of the impedance spectra. For most accurate calculations, the instantaneous area of the PA must be measured over time.

The second measurement problem involves the inherent higher-frequency noise found in the velocity data, which results in disagreement in high-frequency impedance spectra calculated from Doppler versus flow meter data. These differences affect parameters containing significant oscillatory components, such as oscillatory power, characteristic resistance, and reflection coefficient. No differences between Doppler-derived and flow meter--obtained data were found in

**Figure 5.** Input impedance for limited number of group 2 patients is shown. A, Impedance modulus ($Z$, mm Hg \cdot L \cdot \text{min}^{-1}$) and B, phase ($\phi$, radians) as function of harmonics of heart rate. Means are shown, with error bars as uncertainty in means. For patient 5, 35% $O_2$ (■); patient 8, room air (○); patient 9, 100% $O_2$, +40 ppm NO (□); and patient 10, room air (+). Abbreviations are as defined in text.

**Figure 6.** $Z_o$ vs hemodynamically measured values of PVR for all subjects. Excellent agreement was seen, indicating value of $Z_o$ in following PVR clinically. Abbreviations are as defined in text.

**Figure 7.** Reactivity in PVR (A) and reactivity in compliance (B, measured here as change in $Z_1$) for PH patients subjected to various clinical challenges (see Table 1), plotted with mean PA pressure at each condition. In general, reactivity in PVR (defined as $> -20\%$ change) was correlated to reactivity in compliance (defined here as $> -10\%$ change) except for patients 8 and 9. Abbreviations are as defined in text.
mean and total ventricular power, input impedance at lower harmonics, and mean VR. Thus, it is in the evaluation of these latter parameters for which PW Doppler should be useful in the clinical setting.

Evaluation of Impedance and Power in PH

No problems were encountered in the use of PW Doppler for impedance and power measurements in the preliminary clinical studies. Although lack of prior impedance data after closure of patent ductus arteriosus prevents direct comparison of our data with those in the literature, the input impedance spectra in our clinical studies display general frequency-response characteristics and patient-to-patient variance representative of previously published in vivo data for children who were evaluated with perivascular cuff-type flow probes.\(^23\)\(^{-25}\)

Clinically, no differences were seen in characteristic resistance between patients with or without PH. In previously published studies with cuff-type flow meters by Lucas et al\(^24\) and Wilcox and Lucas,\(^25\) the characteristic resistance for children with normal mean pulmonary pressures was reported as 1.46±0.75 and 1.43±0.88 L · min\(^{-1}\) · m\(^{-2}\), respectively. Our values were higher (normal patients at \(Z_0 = 2.27\)±0.96 L · min\(^{-1}\) · m\(^{-2}\)), presumably because of the Doppler-based overestimation that was also seen in vitro. The reflection coefficient was seen to increase significantly (from 0.43 to 0.76) with PH, although no prior data are available in the literature to verify the hypertensive value. The normal value (0.43) is consistent with that reported in the literature.\(^14\)\(^,\)\(^21\)

Our clinical measurements of mean RV power were consistent with those in the study by Lucas et al,\(^23\) who used the more invasive flow meters. Normalization of total power by cardiac output may provide a better means of comparing values among various patients. Lucas et al\(^23\) obtained an average of 2.77 mW · mL\(^{-1}\) · s\(^{-1}\) in normalized power for patients with normal mean pulmonary pressures. This value is similar to that obtained in the group 1 subjects (2.60 mW · mL\(^{-1}\) · s\(^{-1}\)). Hypertensive patients displayed a significant increase in the ratio (6.96 mW · mL\(^{-1}\) · s\(^{-1}\)). It is thus clear that significant changes in RV workload occur with the onset

### Table 2. Impedance (\(Z_0, Z_c\)) and Power Values for the Clinical Data

<table>
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<tr>
<th>Indexed CO, L/min per m(^2)</th>
<th>(Z_0^*), mm Hg/L per min</th>
<th>(Z_c), mm Hg/L per min</th>
<th>(W/O/W_T), %</th>
<th>(W_T/CO), mW/mL per s</th>
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<tr>
<td>5.84</td>
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<tr>
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<td>15.13±0.41</td>
<td>2.45</td>
<td>0.72</td>
<td>5.28</td>
</tr>
</tbody>
</table>

Values for \(Z_0\) are mean±uncertainty. \(W_T\) indicates total RV power; and \(W_O\) oscillatory RV power. All other abbreviations are as defined in text.

\(*P < 0.05.\)
of PH in children; this parameter will also need to be examined in a larger clinical study.

The ability to obtain the type of data presented here from a single pressure measurement (ie, without wedge pressure measurements) and Doppler allows evaluation of not only distal vascular bed reactivity but also proximal vascular reactivity through the examination of how compliance varies with mean PA pressure. With PH, compliance of the proximal PAs decreases because of 2 mechanisms: an acute decrease as a result of increased PA pressures (strain stiffening) and a chronic decrease because of structural changes (fibroblast proliferation, increase in medial thickness, overexpression of structural proteins, etc) in the arterial wall as the PA adapts to the chronically higher pressures. Compliance can be increased to normal values in strain-stiffened arteries simply by lowering mean PA pressure; however, chronically adapted arteries will require long-term treatment to reverse the structural remodeling. Measuring PVR alone will not differentiate these scenarios; however, input impedance should allow evaluation of proximal PA reactivity (through compliance) as well as distal bed reactivity (through Zt). If compliance changes with vasodilator therapy, this would indicate that the proximal PAs have not undergone structural remodeling. Conversely, if compliance does not change with mean PA pressure, this would indicate that structural alterations have taken place. Here we propose use of the first-harmonic value of impedance (Zt) as an index of pulmonary vascular compliance. Based on the in vitro data, it is clear that this value (as well as the second-harmonic value) varies with compliance.

When applied to the reactivity studies, we found that Zt decreased for all but 1 challenge, indicating increasing compliance with vasodilator challenge. The degree to which compliance increased varied depending on the challenge; based on these data, a nominal value of −10% can be proposed as a figure of merit. Patients in whom Zt decreased more than −10% with challenge can then be classified as reactive in compliance. It is interesting to note that the oldest patients (No. 7, 14 years; No. 8, 6 years; and No. 12, 12 years) exhibited the smallest changes in Zt with challenge. This fits with our hypothesis that the pulmonary vasculature of these patients exposed to PH over a longer time period would have undergone chronic structural adaptation. When compared with reactivity in PVR, we found a general correlation between a patient’s being reactive in compliance and reactive in PVR. Two exceptions, patients 8 and 9, were found. Patient 8 was reactive in compliance by our classification (although the actual percent change was only −20%) but would not be classified as reactive in PVR (percent change in PVR = −15%). For patient 9, true baseline (ie, room air or reduced oxygen) values could not be obtained and thus, the baseline value reported here is that with a nitric oxide plus oxygen challenge, making it difficult to gauge true reactivity.

We conclude that the use of a single pressure measurement combined with Doppler measurement of flow in the main PA provides a promising and relatively easy-to-implement method to quantify both PV compliance and PVR for reactivity studies. Such additional information may provide a means to further categorize patients for subsequent treatment, including surgical correction of congenital heart defects, as recently described in the INOP study. Studies to further evaluate these parameters in a larger clinical population and in animal models of PH are under way.

Acknowledgments

This project was supported in part by grants from the National Institutes of Health (HL 67393 and HL 72738) and the General Clinical Research Centers Program, National Center for Research Resources, National Institutes of Health (MO1 RR00069).

References

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_Circulation_. 2004;110:2609-2617; originally published online October 18, 2004;
doi: 10.1161/01.CIR.0000146818.60588.40
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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