Development of A Noninvasive Ultrasound Color M-Mode Means of Estimating Pulmonary Vascular Resistance in Pediatric Pulmonary Hypertension

Mathematical Analysis, In Vitro Validation, and Preliminary Clinical Studies

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Background—Accurate determination of pulmonary vascular resistance (PVR) is an important component in the evaluation and treatment of pediatric patients with pulmonary hypertension. We developed a novel technique, based on the concept of flow propagation, to estimate PVR noninvasively. The hypothesis is that changes in PVR cause changes in the velocity propagation (Vel$_{prop}$) within the main pulmonary artery and that Vel$_{prop}$ can be quantified using color M-mode imaging.

Methods and Results—We tested the hypothesis using mathematical modeling, in vitro experiments, and preliminary clinical studies. The mathematical model showed that pressure and velocity tracings are closely correlated in time and that 6 to 18 ms time resolution was needed to resolve propagation times within typical main pulmonary artery lengths (2 to 5 cm). The in vitro experiments demonstrated that it was feasible to use color M-mode to measure Vel$_{prop}$ and that Vel$_{prop}$ correlated well with downstream resistance [$y = (-1.01x) + 22.77; R = 0.96$]. The method was then evaluated on patients undergoing acute pulmonary reactivity testing ($n = 22$ measurements). Good correlation between Vel$_{prop}$ and PVR was found [$y = (-1.71x) + 26.0; R = 0.90;$ SEE $= 2.41$].

Conclusion—This newly developed method promises to be useful in the noninvasive evaluation of adults and children with pulmonary hypertension. (Circulation. 2001;104:908-913.)

Key Words: hypertension, pulmonary echocardiography heart defects, congenital

Pulmonary hypertension is an important determinant of morbidity and mortality in children with congenital heart disease. Complications from pulmonary hypertension arise both preoperatively and postoperatively, and they can severely limit surgical repair or long-term survival.1-5 The accurate evaluation of pulmonary vascular resistance (PVR) is a key component in evaluating the operability of congenital cardiac lesions.1-4 The current standard for measuring PVR is by invasive measurement of flow and pressure in the pulmonary arteries (PAs). Although this technique is well established, its invasive nature precludes it from being used in the routine follow-up of patients undergoing treatment for pulmonary hypertension. A noninvasive method of evaluating PVR would (1) allow more frequent assessment of PVR, (2) facilitate the monitoring of individual patient responses, and (3) provide remote-site assessment of PVR.

Several noninvasive techniques using echocardiography and ultrasound Doppler have been proposed to evaluate pulmonary hypertension. These have focused on examining anatomy using echocardiography and estimating PA pressure by continuous-wave Doppler measurement of the tricuspid regurgitant jet velocity.6-10 Neither measurement has shown correlation to actual PVR, especially when PVR changes short-term. The use of Doppler methods to calculate pulmonary blood flow is also limited due to assumptions of a nondistendible arterial cross-section and a flat velocity profile.11,12

We hypothesized that short-term changes in PVR would cause concomitant changes in the speed of the pressure pulse propagation wave within the main PA and that, due to the close association between pressure and velocity fields, these changes would be reflected by changes in the centerline velocity trace along the PA. An estimate of PVR should therefore be possible by measuring the velocity propagation (Vel$_{prop}$) slope using ultrasound color M-mode imaging of flow along the centerline of the main PA. This hypothesis was...
tested using mathematical modeling, in vitro simulation, and clinically in the catheterization laboratory for 11 patients (total of 22 measurements) in whom PVR was altered in the short-term.

Methods

Theoretical Background

As the right ventricle ejects blood into the elastic PA, a pressure pulse propagation wave associated with the moving bolus of ejected fluid is created. The pressure pulse propagation wave speed is modulated primarily by 2 parameters, local compliance and downstream resistance.\textsuperscript{1,2,3,4} For short-term changes in PVR (as would occur with pulmonary vasodilators), no immediate morphological changes and, consequently, no significant local compliance changes in the PAs are expected. As a result, any changes in pressure propagation before and after early treatment would be primarily due to changes in downstream resistance.

Routinely measuring pressure pulse propagation speed in the clinical situation is not realistic because this involves either mounting strain gauges on the arterial wall or invasive pressure measurements.\textsuperscript{5,6,7} However, changes in local pressure (and so local pressure gradient) due to the changes in the pulse propagation wave speed should also affect local velocities within the artery due to the close association between velocity and pressure fields.\textsuperscript{8,9,10} By extension, pressure pulse propagation should also cause an equivalent \( \text{Vel}_{\text{prop}} \).

\( \text{Vel}_{\text{prop}} \) can be calculated from a color M-mode trace of flow down the centerline of the PA by tracking the location of fluid moving at one particular velocity. By manipulating the aliasing velocity on the color M-mode trace, the location of this isovelocity as a function of time and space can be visually tracked as the point of color change. Such a method should provide an easy yet quantitative means of estimating \( \text{Vel}_{\text{prop}} \) in the clinical situation.

Mathematical Analysis

The goals of the mathematical analysis were to (1) study the time-correlation between pressure and velocity traces within the tube and (2) quantify typical time lags seen in the pressure propagation wave as it travels down the artery. We focused this model on the main PA segment. The motion of the blood can be governed by the quasi one-dimensional unsteady equations of motion for incompressible and viscous fluid.\textsuperscript{11,12} Tube length was 16 cm; however, only a central section 5 cm in length was used for the numerical study. This was done to minimize end-effects while maintaining a length that resembled the in vitro model and was a reasonable approximation of the main PA. The governing equations of a deformable tube of varying cross-section may be expressed as the continuity equation:

\[
\frac{\partial S}{\partial t} + \frac{\partial (Sv)}{\partial x} = 0
\]

and the momentum equation:

\[
\frac{\partial v}{\partial t} + \frac{\partial}{\partial x}\left(\frac{v^2}{2} + p \right) - F = 0
\]

where

\[
F = -8\pi \frac{1}{S} \frac{\partial p}{\partial \rho}
\]

In these equations, \( S \) indicates cross-sectional area; \( v \), blood velocity averaged over the local cross-section; \( p \), locally-averaged transmural pressure; \( \rho \), blood density; \( t \), time; \( x \), axial coordinate; \( \partial \), differential operator; \( \mu \), viscosity; and \( F \), a viscous resistance factor.

We can assume a linear relationship between cross-sectional area and transmural pressure of all large vessels\textsuperscript{13} (diameter \( >1000 \mu\text{m} \)), and this relationship can be expressed as follows:

\[
S = S_0 + \alpha p
\]

In this equation, \( S_0 \) indicates the relaxed (diastolic) cross-sectional area; \( S \), the cross-sectional area; \( \alpha \), the average compliance of the tube segment; and \( p \), locally-averaged transmural pressure. The above equations were combined and solved using the MacCormack predictor-corrector method. Further details on this method are given elsewhere.\textsuperscript{14}

In Vitro Studies

The in vitro studies were designed to (1) test the color M-mode technique as a means of calculating \( \text{Vel}_{\text{prop}} \) and (2) correlate \( \text{Vel}_{\text{prop}} \) to downstream PVR. As Figure 1 shows, the in vitro system consisted of a pulsatile pump (Harvard Apparatus) that was used to deliver pulsatile flow (33% glycerin:water mixture; viscosity, 3.5cP; density, 1.04 g/mL) at variable frequencies (60 to 100 bpm) and stroke volumes (20 to 100 cc/beat) into a compliant test section. Cornstarch (0.5% by weight) was also added for ultrasound reflectivity. The compliant test section, which served as the model PA, was custom made from silicone rubber using a dip process whereby thin layers (0.2 mm) were added to the tube. Tube diameter was 1.9 cm, and pulse pressure varied from 10 to 40 mm Hg. Total tube length was 16 cm but, as in the numerical studies, measurements were taken within a central section 5 cm in length. Instantaneous flow rate (Transonics Inc) and pressure (Millar Inc) were monitored. Downstream resistance varied from 0.5 to 16 Wood Units to simulate PVR changes.

Color M-Mode Studies

Ultrasound color M-mode Doppler recordings of flow within the main PA were performed using a VingMed System 800 (GE Medical Systems). The transducer was placed proximal to the PA, and the ultrasound beam was aimed parallel to the flow direction. Two-dimensional color Doppler flow imaging was used to align the color M-mode cursor directly along the centerline of the tube. Color M-mode tracings (10 beats) were obtained at various Nyquist limits (0.25 to 0.75 m/s) and digitally transferred to an analysis computer (Echosp, VingMed Sound Inc) for off-line analysis.

The \( \text{Vel}_{\text{prop}} \) calculation method involved tracking the location of fluid moving at one particular velocity as a function of time and distance down the PA. Such a measurement was facilitated by adjusting the aliasing velocity of the ultrasound system, because a clear color change occurred at the point where local velocity exceeded the aliasing limit. Baseline shifting was used on the off-line images to change the aliasing velocity until a clear delineation of isovelocity slope was seen. The slope of \( \text{Vel}_{\text{prop}} \) was then calculated from the slope using the following equation:

\[
\text{Vel}_{\text{prop}} = \frac{(d_2 - d_1)}{(t_2 - t_1)}
\]

In this equation, \( d \) and \( \delta \), are the distance points corresponding to the beginning and end of the propagation slope, and \( t_2 \) and \( t_1 \) are the corresponding time points. Thus, \( \text{Vel}_{\text{prop}} \) has units of velocity (distance/time) and corresponds to the velocity at which the flow is propagating down the artery. The above method was used to calculate \( \text{Vel}_{\text{prop}} \) for both in vitro and clinical studies.

Preliminary Clinical Studies

All clinical studies were conducted with patient consent and institutional review board approval. During cardiac catheterization, color M-mode imaging was performed through a parasternal short-axis approach using the VingMed 800 system. Two-dimensional echo
and color Doppler were used to align the color M-mode cursor parallel to the main flow direction within the PA. Data were obtained during an evaluation of reactivity under conditions of room air, O₂, inhaled nitric oxide (20 ppm via pulsed nasal or mask delivery), or diltiazem infusion. Inhaled NO was given as previously described.³ Cardiac output was measured using the method of Fick while on room air and assumed oxygen consumption²⁴ or by thermodilution in the absence of intra-cardiac shunts.³ Main PA pressure was measured using standard fluid-filled catheters. Pulmonary venous pressures were obtained using pulmonary wedge pressure. All hemodynamic data were recorded before and during treatment to calculate PVR.

Statistical Analysis
All values are given as mean±SD. Linear regression was used to examine whether Velₚₑₒₚₚ was correlated with measured PVR for both in vitro and clinical data. Intraobserver variability was calculated by comparing the differences in 5 consecutive measurements of Velₚₑₒₚₚ performed by the main observer. A subset of the measurements (25%) was repeated by a second blinded observer to calculate interobserver variability. A value of 5% was used to designate statistical significance.

Results
Mathematical Model
Figure 2 shows pressure tracings at 2 downstream points 5 cm apart within the elastic artery. The time lag between the proximal (8 cm) pressure trace and distal (13 cm) trace is clearly seen. As Figure 2 also shows, it is difficult to measure the time lag by visually tracking the peak due to the small lag values. However, the mathematical technique of cross-correlation can be applied to quantify time lag accurately for such traces.²⁵ When applied to these results, the cross-correlation analysis revealed that a time lag of 6 to 18 ms is present for pressure traces from locations between 2 and 5 cm apart, respectively. Such time resolution is well within the range of most modern ultrasound imaging systems.

In Vitro Studies
Figure 3 shows typical in vitro color M-mode tracings for PVR values of 4.08, 8.83, and 16.40 Wood Units. The aliasing velocity was baseline-shifted to produce a clear velocity propagation slope, which was measured using Velₚₑₒₚₚ. As PVR increases, the slope of the alias line decreases from 20.27 cm/s for PVR of 4.08 to 9.21 cm/s for a PVR of 16.40. Figure 4 shows color M-mode–measured Velₚₑₒₚₚ versus PVR (Wood Units) for the in vitro experiments; these measurements showed excellent correlation, indicating that Velₚₑₒₚₚ can be used to follow PVR.

Clinical Studies
A total of 11 patients were studied. Mean age was 7.0±6.3 years. In some cases, the patient underwent multiple challenges to evaluate pulmonary vascular reactivity. Each challenge produced a distinct PVR value resulting in a total of 22 separate conditions. The Table summarizes the clinical data. Figure 5 shows color M-mode traces for a patient with pulmonary hypertension under normal (room air) conditions who was then treated with 100% O₂, which caused a short-term decrease in PVR. The slope of the color M-mode alias increases perceptibly from the high to low PVR condition. Measuring Velₚₑₒₚₚ shows a corresponding increase from 8.8 cm/s at a PVR of 8.4 Wood Units to 19.4 when PVR was decreased to 5.4 Wood Units.

Figure 6 shows Velₚₑₒₚₚ versus PVR for all preliminary clinical data. Good correlation between the 2 variables was seen, again indicating the value of Velₚₑₒₚₚ in following actual PVR. Intraobserver and interobserver variabilities were 8.2% and 9.3%, respectively. To assess the ability of this method to distinguish between high resistance and high pressure, Velₚₑₒₚₚ was also regressed against mean PA pressure for patients with
high right side pressure (mean PA pressure >45 mm Hg; n=7). In this limited group of patients, we found that Vel_corr correlates better to PVR \[y = (-1.55x) + 24.0; R = 0.87\] than to pressure \[y = (-0.58x) + 39.93; R = 0.73\].

**Figure 5.** Example of clinical color M-mode tracings for a patient with high PVR (A) who was subsequently treated with 100% O2 (B). Treatment with oxygen lowered PVR significantly. The change from high to low PVR is clearly delineated in the slope of the color M-mode alias pattern and in the actual Vel_corr value, which changed from 12.4 to 23.1 cm/s when PVR was lowered.

**Figure 6.** Vel_corr vs PVR is shown here for the preliminary clinical data. As seen by the regression curve, our method was able to distinguish among varying levels of PVR.

**Discussion**

In this investigation, we examined the relationship between color M-mode-derived Vel_corr of the main PA and downstream resistance. The goal was to obtain a noninvasive means of estimating PVR. Using mathematical modeling, we showed that pressure traces along an elastic artery exhibit a time lag and that this time lag should have theoretical limits...
of between 6 and 18 ms for arterial lengths between 2 and 5 cm. We also showed that pressure and center-line velocity time-traces within the elastic artery are well correlated in time, indicating that velocity traces can be used to compute a velocity propagation parameter that should be equivalent to pressure pulse propagation. The subsequent in vitro studies demonstrated that color M-mode imaging can be used to measure this $V_{elprop}$, and that $V_{elprop}$ correlates well to downstream resistance. Finally, we obtained preliminary clinical data that showed good correlation between color M-mode-derived $V_{elprop}$ and PVR. To our knowledge, these studies represent the first attempt at using color M-mode velocity propagation to derive PVR.

The quantitative assessment of PVR continues to be important in the evaluation and treatment of children with pulmonary hypertension. Hemodynamic measurements during cardiac catheterization, quantitative pulmonary wedge angiograms, and lung biopsies have been proposed as a progressive approach to determine surgical risk and outcome. Findings from cardiac catheterization, including right atrial pressure and PVR, correlate with survival and outcome in primary pulmonary hypertension. However, invasive procedures such as catheterization to measure pressure and flow have been associated with increased patient risk.

It is therefore no surprise that echocardiographers continue to search for accurate, noninvasive means of quantifying PVR. Conventional echocardiography only provides structural information and so is limited to evaluating acute hemodynamic changes. Ultrasound Doppler techniques have fallen into either estimation of PA flow acceleration time or measuring the tricuspid regurgitant jet velocity and using the Bernoulli equation to estimate PA pressure. However, both methods have significant problems, including variation due to other factors such as heart rate, ventricular function, right ventricular preload, and afterload and assumptions inherent in the use of the Bernoulli equation. More importantly, Doppler velocity measurements provide only a measure of pulmonary pressures and not PVR.

**Limitations**

It is important to recognize several limitations in our study. The mathematical model was only a one-dimensional model representing centerline hemodynamics, and results from this model should be viewed as the theoretical ideal. We did not evaluate other variables such as cardiac output, tube compliance, or transient flow changes. These are obviously important clinical considerations and will be examined in upcoming studies. The clinical studies were intended to prove initial feasibility only, and further stratification of the data were not performed due to the small numbers present.

**Clinical Application of the Method**

This method may be an important additional tool in the overall evaluation of pediatric pulmonary hypertension, especially for patients awaiting surgery in whom PVR may predict improved long-term surgical outcomes. The technique may also provide information to complement that obtained from other novel methods currently being evaluated to assess right heart function, such as MRI and SPECT equilibrium radionuclide angiography. The method may also be useful when evaluating pulmonary reactivity, because a decrease in PVR should produce a corresponding increase in $V_{elprop}$. On the basis of the preliminary results, a $V_{elprop}$ value $>18$ cm/s seems to indicate a PVR $<6$ Wood Units · m$^{-2}$. The $V_{elprop}$ technique may thereby reduce the number of catheterizations required to measure PVR. Further collection of clinical data to examine the utility of the method when both pressure and output are high but PVR is low, such as in left-to-right shunt lesions in a young patient, is needed.

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