Measurement of total pulmonary arterial compliance using invasive pressure monitoring and MR flow quantification during MR-guided cardiac catheterization

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PULMONARY HYPERTENSIVE DISEASE is characterized by narrowing and occlusion of the small pulmonary arteries, increased pulmonary vascular resistance (5), and right ventricular dysfunction. Vascular resistance can be calculated by invasively measuring pulmonary arterial pressure and flow. The calculated resistance and its response to nitric oxide (NO) and O2 are used to assess suitability for surgery in patients with congenital heart disease and the need for vasodilator therapy in patients with pulmonary hypertensive disease (1, 2, 9). However, ventricular load is dependent on total arterial compliance as well as resistance (8, 23, 24).

In pulmonary hypertensive disease, vessel wall distension and remodeling result in decreased arterial compliance (13, 26), causing an increase in pulse pressure, peak systolic pressure, and ventricular load. Morphological changes in the vessel wall, decreased segmental arterial compliance, and changes in compliance in response to vasodilators have been demonstrated in patients with pulmonary hypertensive disease (6, 22). Thus measuring total arterial compliance or elastance in the pulmonary arterial system in the clinical setting may provide additional diagnostic and prognostic information.

A simple approximation of compliance is the ratio of stroke volume to pulse pressure (Csv). However, it is thought to be an overestimate of true arterial compliance (23). The pulse pressure method (Cppm), based on the parameter optimization of a two-element windkessel model, is considered to be a more accurate estimate of true compliance (23, 27, 29). Both methods have been successfully used to calculate pulmonary arterial compliance in animals, and a close correlation between Csv and Cppm has been demonstrated (23). Thus Csv can be used to validate Cppm in vivo. Both methods require simultaneous measurement of arterial flow (stroke volume for Csv and flow curves for Cppm) and pulse pressure. In addition, the pulse pressure method requires calculation of vascular resistance. Such physiological information is difficult to acquire in humans in the clinical setting.

Velocity-encoded phase-contrast magnetic resonance (MR) enables quantification of volume flow in the pulmonary artery. Cardiac output and the pulmonary-to-systemic flow ratio (Qp/Qs) measured using this technique have been shown to be accurate (3, 4, 21). In addition, phase-contrast MR has been validated in numerous phantom experiments (3, 21). A new technique, MR-guided cardiac catheterization, allows simultaneous acquisition of phase-contrast MR information and invasive pressure measurements (18, 20). We previously demonstrated the feasibility of using this technique to calculate pulmonary vascular resistance in humans (18). We build on

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this previous work to evaluate the feasibility of calculating total arterial compliance in humans undergoing MR-guided cardiac catheterization. In this study, compliance was calculated using the pulse pressure method and the ratio of stroke volume to pulse pressure. In addition, measurement of other pulmonary hemodynamic parameters allowed a preliminary study of the relation between compliance and resistance and between compliance and pressure, particularly in response to NO.

MATERIALS AND METHODS

Study population. The study population consisted of 17 children and adults [mean 9.58 yr of age (SD12.95)]; inclusion criteria were suspected pulmonary hypertension or congenital heart disease requiring preoperative assessment. Twelve patients had suspected pulmonary arterial hypertension secondary to a congenital systemic-to-pulmonary shunt, three had pulmonary hypertension associated with disorders of the respiratory system, one patient had pulmonary arterial hypertension associated with human immunodeficiency virus infection, and one had pulmonary venous hypertension secondary to repaired mitral stenosis. All patients were in class I or II in the World Health Organization stratiﬁcation of pulmonary hypertension. There is overlap with the patient population from our previous study, in which the feasibility of measuring pulmonary vascular resistance with MR-guided cardiac catheterization was evaluated. However, patients were excluded if previous surgery of the pulmonary artery had been performed. All patients were in sinus rhythm. The study was approved by the Local Research Ethics Committee. Informed consent was given by the patient or a parent/guardian (patients <16 yr of age).

Cardiac catheterization. Subjects underwent cardiac catheterization in an MR interventional suite (maximum gradient performance = 30 mT/m amplitude, slew rate = 150 T/m·s; 1.5-T Intera I/T MRI scanner, Philips Medical Systems) with X-ray backup (BV Pulsera cardiac X-ray unit, Philips Medical Systems) in the same room (XMR suite). General anesthesia was induced and maintained with propofol. The catheter was advanced under MR guidance or with a combination of X-ray and MR guidance, depending on ease of catheter manipulation. Angiographic catheters (4- to 6-Fr) with CO2-filled balloons were used for all procedures, allowing visualization in both imaging modalities. Hemodynamic variables were collected at 30% O2 (condition 1) and at 20 ppm NO + 30% O2 (condition 2).

MR catheter visualization. All imaging was performed using an adult or pediatric two-element receive-only phased-array radio-frequency coil (Flex L or Flex M, Philips Medical Systems); transmission was performed using the body coil. An interactive steady-state free precession sequence (TR = 2.9 ms, TE = 1.45 ms, matrix = 128 × 128, field of view = 250–350 mm, 10–14 frames/s, flip angle = 45°, slice thickness = 6–8 mm, free breathing acquisition) was used to visualize the catheter balloon during manipulation within the heart and great vessels. The imaging plane could be manipulated in real time into any plane to follow the catheter (17).

Flow and pressure quantification. Pulmonary arterial flow data were acquired using a flow-sensitive, fast-field echo sequence (TR ~ 9 ms, TE ~ 5 ms, matrix = 128 × 192 × 256, field of view = 250–350 mm, flip angle = 15°, slice thickness = 5–7 mm, free breathing acquisition). 3 signal averages, retrospective gating, 40 phases, in-plane and through-plane resolution optimized to patient size). A dedicated nonlinear phase-correction filter, based on Chebichev polynomials (Philips Medical Systems), was used to correct for phase errors introduced by eddy currents and Maxwell terms. In addition, the image plane was centered in the bore of the magnet to further reduce the phase errors. Image planes were located at the midpoint of the pulmonary artery. Systolic pressure (P_systole), diastolic pressure (P_diastole), and mean pressure (P_mean) were collected during MR flow data acquisition by means of standard fluid-filled catheters coupled to a computerized data-recording system, with a quoted measurement error of ±2 mmHg (55 collect system, Datex Ohmeda). Pulse pressure (P_pulse) was calculated as P_systole − P_diastole.

Data analysis. Pulmonary blood flow curves and stroke volumes were generated from phase-contrast MR data using a semiautomatic vessel edge-detection algorithm (Flow, Medis) with operator correction. Pulmonary artery cardiac output is the product of pulmonary blood stroke volume and heart rate. Resistance (R) was calculated by dividing mean pulmonary arterial pressure by the pulmonary artery cardiac output and indexing to body surface area (23).

Calculation of total arterial compliance and elastance. The equation defining the two-element windkessel model is as follows (16)

\[ Q(t) = \frac{P(t)}{R} + \frac{dP(t)}{dt} \]

where \( P \) is pressure and \( C \) is total arterial compliance. A flow curve \( [Q(t)] \) with 50 cardiac cycles was constructed by repeating the single cardiac cycle phase-contrast MR flow curve. \( Q(t) \) was used as an input to the windkessel model. \( R \) was a known variable for each patient at each condition and was entered into the model. For a given \( C \), the equation was integrated using \( P(0) = 0 \) as an initial condition, generating a 50-cardiac-cycle pressure curve. The modeled \( P_{\text{diastole}} \) and \( P_{\text{systole}} \) are the minimum and maximum pressures between the 40th and 50th cycles, at which point the pressure curve has stabilized and is independent of initial conditions. The modeled \( P_{\text{pulse}} = \text{modeled } P_{\text{systole}} - \text{modeled } P_{\text{diastole}} \). A series of pressure curves were generated using values of \( C \) between 0.001 and 7 ml/mmHg. The modulus of the difference between the modeled \( P_{\text{pulse}} \) and the invasively measured \( P_{\text{pulse}} \) was calculated, and an error plot was produced. The compliance that coincides with the global minimum of the error plot is taken as the best estimate of \( C \) which was indexed to body surface area (which we call \( C_{\text{ppm}} \)). All windkessel modeling was performed using Matlab (Mathworks). Elastance (\( E \)) is the inverse of \( C \).

Statistical analysis. Values are means (SD) unless otherwise stated. A two-tailed \( t \)-test was used to compare the hemodynamic responses to NO. A two-tailed \( t \)-test, correlation coefficients, linear regression analysis, and Bland-Altman analysis (7) were used to compare \( C_{\text{ppm}} \) with \( C_{\text{sv}} \). Bias was the mean of the difference between the two methods, and agreement was the mean (2SD). \( P < 0.05 \) was taken as statistically significant. Correlation coefficients and linear regression analysis were also used to study the relation between steady-state hemodynamic variables and compliance. Statistical analysis was performed using Matlab.

RESULTS

Feasibility. In nine patients, catheterization of the pulmonary artery was achieved under MR guidance alone. In the other eight patients, the catheter was advanced using a combination of X-ray and MR guidance. Simultaneous invasive pressure and phase-contrast MR data (Fig. 1) were obtained in all 17 patients in conditions 1 and 2. Total arterial compliance in all patients in both conditions was calculated using the pulse pressure method and the ratio of stroke volume to pulse pressure.

Pulmonary hemodynamics: response to 20 ppm NO. Pulmonary hemodynamic parameters (\( P_{\text{mean}}, P_{\text{systole}}, P_{\text{diastole}}, P_{\text{pulse}} \)) were entered into the model. For a given \( C \), the equation was integrated using \( P(0) = 0 \) as an initial condition, generating a 50-cardiac-cycle pressure curve. The modeled \( P_{\text{pulse}} = \text{modeled } P_{\text{systole}} - \text{modeled } P_{\text{diastole}} \). A series of pressure curves were generated using values of \( C \) between 0.001 and 7 ml/mmHg. The modulus of the difference between the modeled \( P_{\text{pulse}} \) and the invasively measured \( P_{\text{pulse}} \) was calculated, and an error plot was produced.

Arterial compliance: \( C_{\text{ppm}} \) vs. \( C_{\text{sv}} \). The mean \( C_{\text{ppm}} \) and \( C_{\text{sv}} \) in conditions 1 and 2 are shown in Table 1. At baseline, pulmonary arterial pressures and resistance were raised compared with the normal quoted range. There were statistically significant declines in \( R \), \( P_{\text{systole}} \), and \( P_{\text{pulse}} \) in response to 20 ppm NO.

Arterial compliance: \( C_{\text{ppm}} \) vs. \( C_{\text{sv}} \). The mean \( C_{\text{ppm}} \) and \( C_{\text{sv}} \) in conditions 1 and 2 are shown in Table 1. Correlation between \( C_{\text{ppm}} \) and \( C_{\text{sv}} \) (Fig. 2) was excellent in condition 1 (\( r = 0.99, \)
P < 0.001), condition 2 (r = 0.97, P < 0.001), and overall (r = 0.98, P < 0.001). However, there was not a 1:1 relation between $C_{p}$ and $C_{v}$: $C_{v} = 1.86 \cdot C_{p} + 0.02$ (condition 1), $C_{v} = 1.83 \cdot C_{p} + 0.07$ (condition 2), and $C_{v} = 1.85 \cdot C_{p} + 0.04$ (overall). Bland-Altman analysis (Fig. 3) demonstrated a systematic bias with good limits of agreement in all cases: bias = 61%, upper level of agreement = 84%, and lower level of agreement = 38% for condition 1; bias = 61%, upper level of agreement = 85%, and lower level of agreement = 37% for condition 2; and bias = 61%, upper level of agreement = 84%, and lower level of agreement = 38% overall. In all cases, there was a significant difference between mean $C_{p}$ and $C_{v}$ ($P < 0.05$).

**Compliance: response to 20 ppm NO.** An increase of ≥10% was considered a response to NO (30). A response in $C_{p}$ was demonstrated in 7 of 17 patients and in $C_{v}$ in 9 of 17 patients. The mean increase in $C_{p}$ was 16.9% (SD29.6), and the mean increase in $C_{v}$ was 17.0% (SD30.1). There was no significant difference between percent increase in $C_{p}$ and $C_{v}$ ($P = 0.48$). There was excellent correlation between the percent increase in $C_{p}$ and $C_{v}$ ($r = 0.89, P < 0.001, m = 0.87, c = 1.95$). As a population, although mean $C_{p}$ and $C_{v}$ increased in response to 20 ppm NO, statistical significance was not reached ($P = 0.12$ for both).

**Relation between steady-state hemodynamic variables and compliance.** As pulmonary hypertensive disease worsens, compliance is thought to decrease. Thus $R$ and $P_{mean}$ were correlated with $1/C_{p} = E$, rather than $C_{p}$ (Figs. 4 and 5). There was good correlation between $R$ and $E$ in condition 1 ($r = 0.86, P < 0.001, m = 0.54, c = -0.22$), condition 2 ($r = 0.92, P < 0.001, m = 0.56, c = -0.19$), and overall ($r = 0.89, P < 0.001, m = 0.55, c = -0.20$). There was moderate correlation between $P_{mean}$ and $E$ in condition 1 ($r = 0.72, P < 0.001, m = 12.6, c = 15.5$), condition 2 ($r = 0.73, P < 0.001, m = 14.0$,

Table 1. Mean pulmonary hemodynamic parameters in conditions 1 and 2

<table>
<thead>
<tr>
<th>Condition 1</th>
<th>Condition 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{systolic}$, mmHg</td>
<td>52.3 (24.1)</td>
<td>49.2 (23.7)</td>
</tr>
<tr>
<td>$P_{diastolic}$, mmHg</td>
<td>20.4 (12.2)</td>
<td>20.3 (12.2)</td>
</tr>
<tr>
<td>$P_{pp}$, mmHg</td>
<td>31.9 (15.0)</td>
<td>28.9 (14.5)</td>
</tr>
<tr>
<td>$P_{mean}$, mmHg</td>
<td>33.7 (16.1)</td>
<td>32.8 (16.9)</td>
</tr>
<tr>
<td>$Q$, ml/s</td>
<td>840 (45.6)</td>
<td>870 (42.2)</td>
</tr>
<tr>
<td>SV, ml/m2</td>
<td>50.9 (27.4)</td>
<td>51.7 (25.6)</td>
</tr>
<tr>
<td>$R$, mmHg/ml/m2s</td>
<td>0.56 (0.58)</td>
<td>0.50 (0.51)</td>
</tr>
<tr>
<td>$C_{pp}$, ml/m2/mmHg</td>
<td>0.99 (0.68)</td>
<td>1.06 (0.58)</td>
</tr>
<tr>
<td>$C_{sv}$, ml/m2/mmHg</td>
<td>1.87 (1.28)</td>
<td>2.01 (0.99)</td>
</tr>
</tbody>
</table>

Values are means (SD). $P_{mean}$, mean pulmonary arterial pressure; $P_{systolic}$, systolic pulmonary arterial pressure; $P_{diastolic}$, diastolic pulmonary arterial pressure; $P_{pp}$, pulse pressure; Q, pulmonary artery flow; SV, stroke volume; $R$, resistance; $C_{pp}$, pulse pressure compliance; $C_{sv}$, ratio of SV to $C_{pp}$. Significance is $P < 0.05$. 

Fig. 2. Scatter plot of compliance estimated using the ratio of stroke volume to pulse pressure ($C_{sv}$) and the pulse pressure method ($C_{pp}$). Plotted line represents line of regression.
Innovative Methodology

A METHOD TO ASSESS PULMONARY ARTERIAL COMPLIANCE

H1304

DISCUSSION

We have demonstrated the feasibility of combining invasive pressure measurements and MR flow data to quantify total pulmonary arterial compliance in humans. Calculation of vascular resistance is essential in the management of patients with suspected pulmonary hypertension. However, arterial pressure and ventricular load are also dependent on total arterial compliance. Thus complete hemodynamic assessment of patients with pulmonary hypertensive disease requires measurement of resistance and compliance. Traditionally, because of difficulties in measuring compliance in the clinical environment, pulmonary hypertensive disease is assessed on the basis of pulmonic pressure and resistance method and has been used to estimate pulmonary arterial compliance in humans. It is believed that

Estimates of total arterial compliance. Several methods have been proposed to calculate total arterial compliance. The ratio of stroke volume to pulse pressure (Cvsv) is the simplest method and has been used to estimate pulmonary arterial compliance in humans. However, Cvsv is an overestimate of arterial compliance, inasmuch as it fails to take into consideration outflow from the arterial system during the ejection phase. Nevertheless, Cvsv has been shown to correlate strongly with other measures of compliance, and it also represents the upper limit of arterial compliance. It is therefore a useful method of validating other estimates of arterial compliance. Most other estimates of arterial compliance are based on the arterial windkessel model (16, 29). The diastolic decay method (19) and the area method (16) are widely used to estimate systemic arterial compliance based on the two-element windkessel model. Both require detailed pressure curves and are only applicable when there is zero flow in diastole (27, 29). These methods may not be suited to patients with pulmonary hypertension and pulmonary regurgitation. A method based on parameter optimization of a three-element windkessel model has also been used to calculate total pulmonary arterial compliance (23, 24), but this method overestimates pulmonary arterial compliance (23). The pulse pressure method is based on parameter estimation of a two-element windkessel model and has been found to be an accurate method of calculating the total arterial compliance in the pulmonary (23) and systemic vasculatures (27–29). It does not require measurement of a detailed pressure curve or zero flow conditions in diastole and is well suited to patients with pulmonary hypertension (29).

This method requires measurement of volume flow as a function of time (flow curves), pulse pressure, and vascular resistance (R). In the pulmonary artery, pressure can be measured at the beginning of the pulmonary catheterization with invasive manometry. In animal studies, perivascular flow probes can be used to accurately measure flow curves (23); unfortunately, use of such methods is difficult in humans. In humans, blood flow velocity curves can be measured invasively (15) or noninvasively (14, 30). Combining this data with a measurement of cardiac output (using an indicator-dilution method) allows generation of flow curves (14, 15, 30). However, inaccuracies in measurement of cardiac output by indicator-dilution methods (10, 11) and measurement of blood flow velocities can lead to errors in measurement of volume flow.

MR-guided cardiac catheterization. Velocity-encoded phase-contrast MR is a validated technique that enables measurement of flow curves in major vessels (3, 4, 18). It is therefore well suited to generate flow curves for estimation of pulmonary arterial compliance by the pulse pressure method. MR-guided cardiac catheterization is a new technique that allows greater access to physiological and anatomic information (20). We previously demonstrated the feasibility of simultaneously acquiring phase-contrast MR and invasive pressure data in patients undergoing MR-guided cardiac catheterization to calculate pulmonary vascular resistance (18). In this study, we have used these data to calculate total arterial compliance by the pulse pressure method and as the ratio of stroke volume to pulse pressure.

Total arterial compliance. We have demonstrated the feasibility of calculating total pulmonary arterial compliance in patients undergoing MR-guided cardiac catheterization. As reported in other studies, Cvsv was consistently higher than Cppm (23). It is believed that Cvsv overestimates total arterial compliance, inasmuch as it assumes that the total stroke volume is buffered in the arteries (23). In fact, the volume buffered in the arteries is the stroke volume minus the arterial outflow volume.

Fig. 4. Scatter plot of resistance (R) vs. 1/Cppm. Plotted line represents line of regression.

Fig. 5. Scatter plot of mean pulmonary arterial pressure (Pmean) vs. 1/Cppm. Plotted line represents line of regression.
during ejection. Our results demonstrated excellent correlation between \( C_{sv} \) and \( C_{ppm} \) in conditions 1 and 2 and overall, as well as good correlation between the percent change in \( C_{sv} \) and \( C_{ppm} \), in agreement with previous studies (23). These results suggest that \( C_{ppm} \) is a precise estimate of true arterial compliance, although we are unable to verify its accuracy, inasmuch as there is no in vivo “gold standard” method of measuring arterial compliance. However, previous work using models of the arterial system has shown \( C_{ppm} \) to be an accurate estimate of total arterial compliance (27).

**Relation to hemodynamic variables and response to NO.**
Our results show that, within our study population, \( R \) and \( P_{mean} \) are inversely related to \( C_{ppm} \), with good to moderate correlation. There are two possible explanations for these findings: 1) Vascular remodeling, which leads to an increase in \( R \) and, thus, in \( P_{mean} \), causes vessel distension and reduced compliance. Studies have shown that reduced compliance in systemic arteries is secondary to distension. 2) Vascular remodeling occurs in the large conduit arteries as well as the resistance arteries as part of the pulmonary hypertensive disease process. Vessel wall thickening in large pulmonary arteries has been demonstrated using intravascular ultrasound and is associated with decreased vessel compliance (6, 22). It is probable that both factors contribute to the relation between \( R \), \( P_{mean} \), and \( C_{ppm} \). However, the strong correlation between \( P_{mean} \) and \( C_{ppm} \) do suggest that distension of the conduit arteries is an important factor. To fully understand the relation between \( R \), \( P_{mean} \), and \( C_{ppm} \), this technique will need to be performed on a larger group of patients with pulmonary hypertensive disease.

Inhaled NO acts on pulmonary vascular smooth muscle, causing smooth muscle relaxation (12). NO causes a fall in resistance due to vasodilation of resistance arteries. In this study, we have demonstrated a hemodynamically significant increase in \( C_{ppm} \) in response to NO in seven patients. However, the population change was small and not statistically significant. There was mild correlation between the percent change in \( R \) and \( 1/C_{ppm} \). A possible explanation for these findings is that a decrease in \( R \) leads to a decrease in \( P_{mean} \), causing less distension and an increase in \( C_{ppm} \). In this study group, there was little correlation between the percent change in \( P_{mean} \) and \( 1/C_{ppm} \). Therefore, increase in compliance in response to NO cannot be explained purely in terms of reduced distension. Another explanation is that NO decreases resistance and increases compliance through its actions on smooth muscle distributed throughout the pulmonary vasculature. However, it should be noted that inhaled NO may not have significant bioavailability in the large conduit arteries.

**Limitations.** Phase-contrast MR flow is less accurate in patients with arrhythmias during acquisition and/or turbulent blood flow; the presence of these conditions is a general limitation of this technique, however, we did not encounter these events in our study. We did not repeat previous work internally validating phase-contrast MR in our patient population, inasmuch as we did not wish to prolong the procedure times. The study population was small and inhomogeneous. In addition, the change in hemodynamic parameters in response to NO was limited, possibly because of general anesthesia. This population was sufficient to prove the feasibility of this technique. However, study of the relation between the various hemodynamic parameters was hampered.

**Conclusion.** Using simultaneously acquired invasive pressure measurements and MR flow data, we have demonstrated the feasibility of quantifying total arterial compliance. This additional information can be combined with information regarding resistance to tailor patient management, particularly with the advent of new medical therapies. With proof of the feasibility of this technique, it will be possible to investigate the relation between compliance and other hemodynamic parameters in a larger more homogeneous population. In our facility, cardiac catheterization was accomplished by MR guidance with X-ray backup. Pulmonary artery catheterization can be accomplished without imaging before MR scanning, thus potentially allowing this technique to be used in a conventional cardiac MR scanner. Further investigation using this technique is required to fully elucidate the relation between compliance, pulmonary hypertensive disease, and medical intervention. In conclusion, we believe that measurement of pulmonary arterial compliance will give new insights into the pathophysiology of pulmonary hypertension and may be important in assessing suitability for long-term medical therapy.

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**REFERENCES**


