Shaping the future of paediatric pulmonary arterial hypertension
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CHAPTER 06

Pulmonary arterial pressure-area loops to assess vascular stiffness variables in paediatric pulmonary arterial hypertension

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In preparation
Abstract

Introduction. The purpose of this study was to develop a method to refine indices of pulmonary arterial stiffness using continuous pulmonary arterial pressure to cross-sectional area relationships and to investigate whether these relationships provide enhanced information on arterial stiffness and are related to disease severity and outcome in children with pulmonary arterial hypertension.

Methods and results. Pulmonary arterial pressure-area loops were constructed using transoesophageal tissue Doppler echocardiography and synchronized invasively measured pressure curves. These loops were used to determine indices of pulmonary arterial stiffness, including the continuous relation between pulmonary arterial cross-sectional area and pressure during systole (systolic loop compliance, $CL_{syst}$), diastole (Elastance, EL) and the total cardiac cycle (total loop compliance, $CL_{total}$), pulmonary arterial wall viscoelastic dissipated energy ($W_d$), pulmonary arterial wall peak velocity ($Vel_{max}$), acceleration (ACC) and acceleration time ($ACC_{time}$). Of these pulmonary arterial stiffness indices, $CL_{syst}$ and $CL_{total}$ were smaller in PAH compared to control patients and correlated with PVRi and outcome. Pulmonary arterial $W_d$ was increased in PAH and increased dissipated energy correlated with worse outcome. Increased $Vel_{max}$ and a delay in $ACC_{time}$ were both associated with higher WHO functional class and worse outcome.

Conclusion. We report the preliminary results of our quest to design a method that uses pulmonary arterial pressure-area loops to enhance and refine information regarding pulmonary arterial stiffness in patients with PAH. The new indices we measured in our first investigation appeared to be associated with disease severity and outcome in paediatric PAH and support the concept that pressure-area loop analysis can improve clinical diagnostics in patients with pulmonary arterial hypertension. The presented measurement methods, however, still have several limitations and need to be further refined.
Pulmonary arterial pressure-area loops

Introduction

Pulmonary arterial hypertension (PAH) is a severe progressive pulmonary vascular disease. The remodelling of the pulmonary vasculature in PAH alters its functional properties, including an increase in pulmonary vascular resistance and pulmonary arterial wall stiffness. As a consequence, the right ventricular afterload increases, requiring increased ventricular work and eventually leading to right ventricular failure and death. The introduction of PAH-targeted therapies, which may affect remodelling of the vascular wall, has improved the outcome of patients with PAH. Nevertheless, prognosis of PAH remains detrimental in both children and adults.

The right ventricular afterload consists of static and pulsatile components. The static components include net forward flow and mean pulmonary arterial to venous pressure decay, defined by the mean pulmonary arterial pressure (mPAP) and pulmonary capillary wedge pressure (mPCWP). The relation between mean pressure decay and net forward flow is expressed as the pulmonary vascular resistance (PVRI). PVRI and mPAP are key parameters used in clinical practice, but represent only partially the right ventricular afterload since it ignores the pulsatile components. The pulsatile components of the right ventricular afterload are determined by pulmonary arterial compliance and wave reflections, which are both affected by the pulmonary arterial stiffness. Emerging data indicates that indices of pulmonary arterial stiffness are important determinants of outcome in PAH. For instance, invasively measured pulmonary arterial capacitance index (PACi) and stroke volume were shown to be independent predictors of outcome in both adult and paediatric PAH. Furthermore, pulmonary arterial relative area change (RAC), distensibility and elastic strain index, either measured by transthoracic echocardiography or intravascular ultrasound were shown to be associated with outcome in paediatric and adult PAH. However, the optimal way of characterizing pulmonary arterial stiffness has yet to be determined.

Several indices for pulmonary arterial wall stiffness reported in the past (table 1) represent different aspects of pulmonary vascular wall dynamics. These include 1) variables such as the relative area change (RAC), that represent a change in pulmonary arterial size without taking into account pulmonary arterial pressure, 2) parameters such as pulmonary arterial capacitance (PACi), distensibility (D), dynamic compliance (Cdyn) and pressure-strain modulus (Ep), that represent the ability of pulmonary arteries to accommodate oscillatory changes in volume and 3) parameters such as the stiffness index (βind), and stiffness coefficient (βcoeff) that represent the intrinsic elastic properties of the pulmonary arterial wall. These indices are often calculated based on the average minimal to peak systolic cross-sectional pulmonary arterial area and pulmonary arterial pressure and therefore do not use the complete information captured in the continuous course of the pressure area relationship during the cardiac cycle. The latter, obviously offers more extensive information on the viscoelastic properties of the pulmonary arterial wall. The characterization of pulmonary arterial stiffness may therefore be improved using this continuous relationship, by analysing pulmonary arterial pressure-area loops. The proposed method may provide more sophisticated variables to
characterize pulmonary arterial wall stiffness and the ventricular-vascular interaction that eventually may improve the prediction of a patient’s outcome and the making of treatment decisions.

Table 1: Previously reported indices of pulmonary arterial stiffness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial capacitance index (PACi)</td>
<td>ml/mmHg/m²</td>
<td>[ PACi = \frac{SV_i}{P_{Syst} - P_{Diast}} ]</td>
</tr>
<tr>
<td>Relative area change (RAC)</td>
<td>%</td>
<td>[ RAC = \frac{A_{Syst} - A_{Diast}}{A_{Diast}} \cdot 100% ]</td>
</tr>
<tr>
<td>Distensibility (D)</td>
<td>%/mmHg</td>
<td>[ D = \frac{A_{Syst} - A_{Diast}}{A_{Diast} (P_{Syst} - P_{Diast})} \cdot 100% ]</td>
</tr>
<tr>
<td>Dynamic compliance (C_{dy})</td>
<td>%/100mmHg</td>
<td>[ C_{dy} = \frac{R_{Syst} - R_{Diast}}{R_{Diast} (P_{Syst} - P_{Diast})} \cdot 10^{-4} ]</td>
</tr>
<tr>
<td>Pressure strain modulus (E_{p})</td>
<td>mmHg</td>
<td>[ E_{p} = \frac{R_{Diast} \cdot (P_{Syst} - P_{Diast})}{R_{Syst} - R_{Diast}} ]</td>
</tr>
<tr>
<td>Stiffness index (β_{ind})</td>
<td>Dimensionless</td>
<td>[ \beta_{ind} = \frac{\ln(P_{Syst}/P_{Diast})}{(A_{Syst} - A_{Diast})/A_{Diast}} ]</td>
</tr>
<tr>
<td>Stiffness coefficient (β_{coeff})</td>
<td>Dimensionless</td>
<td>[ \beta_{coeff} = \frac{\ln(P_{Syst}/P_{Diast})}{R_{Syst}/R_{Diast} - 1} ]</td>
</tr>
</tbody>
</table>

Calculation method of commonly used parameters of the dynamic properties of the right ventricular afterload, including: pulmonary arterial compliance index (PACi)\(^{7,8,14}\), relative area change (RAC)\(^{6,10,13}\), distensibility (D)\(^{6,9,10}\), dynamic compliance (D_{dy})\(^{15-17}\), pressure-strain modulus (E_{p})\(^{6,17,18}\), stiffness index (β_{ind})\(^{19,20}\), stiffness coefficient (β_{coeff})\(^{6}\), SV_{i}, Stroke volume indexed for body surface area (L/min/m²; calculated by dividing pulmonary flow index by heart rate); P_{syst/diast}, Systolic/diastolic pulmonary arterial pressure; A_{syst/diast}, Systolic/diastolic pulmonary arterial cross-sectional area; R_{syst/diast}, Systolic/diastolic pulmonary arterial cross-sectional radius; ln, natural logarithm.

In the human aorta it has been shown that the regression line of the arterial pressure-diameter loop of a total heart beat is a valuable indicator of the arterial stiffness, which is decreased in several diseases affecting the systemic arteries, including hypertension, diabetes and coronary artery disease.\(^{21-23}\) For the pulmonary artery, pressure-area loops can be constructed using tissue Doppler imaging with synchronized pulmonary arterial pressure measurements.\(^{15}\) These pressure-area loops will give the opportunity to determine the pulmonary arterial stiffness using the entire course of the cardiac cycle. Furthermore, the tissue Doppler data can be used to determine the velocity of the pulmonary arterial wall expansion, which is altered in stiffened pulmonary arteries.\(^{15}\) The continuous synchronised measurements al-
low to evaluate the timing and the associated pressure build up to reach the maximal wall velocity. Moreover, it can be used to calculate pulmonary arterial wall viscoelastic dissipated energy \( W_D \) represented by the area within a pressure-area loop.\textsuperscript{21,22,24-27} \( W_D \) represents the elastic energy that is lost due to the viscoelastic properties of the pulmonary arterial wall and as such characterizes pulmonary arterial wall viscoelasticity, a measure of the (in-)efficiency of the ventricular-vascular unit.\textsuperscript{24,28}

This report aims to describe the first results of our efforts to develop a method that refines indices of pulmonary arterial stiffness using continuous pulmonary arterial pressure to cross-sectional area relationships.

**Methods**

In the Netherlands, all paediatric PAH patients are cared for within the Dutch National Network for Paediatric Pulmonary Hypertension. Within this network all patients are referred to the University Medical Centre Groningen, the national referral centre, where the diagnosis of PAH is confirmed by heart catheterization, patients are treated according to the evolving ‘ESC guidelines for the diagnosis and treatment of PAH’, and all patients are regularly seen at standardized follow-up visits.\textsuperscript{29,30}

We performed a prospective paediatric PAH cohort study. From August 2011 to December 2015 all eligible IPAH/HPAH and PAH-CHD patients < 18 years that underwent a heart catheterization with complete hemodynamic evaluation and transoesophageal echocardiography either to confirm diagnosis or to evaluate treatment effect were included. A control group consisted of patients undergoing trans-catheter atrial septal defect closure under transoesophageal echocardiography guidance. Our institutional human research committee approved the protocol for the Dutch national clinical patient registry and the use of its data for observational studies. Patients or their legal guardians provided informed consent.

Transoesophageal echocardiographic images were made of a short and long axis transection of the right pulmonary arterial branch perpendicular to the pulmonary arterial wall, with tissue Doppler recordings of the pulmonary arterial wall movement, using a GE Vivid S6 ultrasound scanner with a high quality frame rate of at least 300 frames per second. During the echocardiography, simultaneous continuous pulmonary arterial pressure measurements were taken with a fluid filled catheter and stored on a MP150 Biopac System with a 1000/second sampling rate. These pressure measurements were taken in the main or left pulmonary artery so that the catheter movement could not disturb the tissue Doppler imaging of the right pulmonary arterial branch. At least 3-5 cardiac cycles were obtained and stored with simultaneous ECG registration for off-line analysis.

**Offline analyses**

The echocardiographic images were processed offline with Software Package for Echocardiographic Quantification Leuven (SPEQUE; University of Leuven, Leuven, Belgium). By tracking
the pulmonary arterial wall distal to the ultrasound transducer in the short axis cross-sectional image, the tissue Doppler velocity (cm/s) of the pulmonary arterial wall movement was extracted from the image frame to frame, while correcting for perpendicular movements. The pulmonary arterial wall velocity and pressure measurement were analysed with a Matlab (Mathworks, Natick, Massachusetts USA, 2014) based analysis program, specifically designed for this study.

Using this Matlab based program, first the signals were aligned by synchronising the point of minimal pressure with the zero velocity point marking the direction change of the pulmonary vascular wall at the beginning of the cardiac cycle, thereby correcting any potential delay in the pressure signal, for instance due to a conduction delay in the fluid filled catheter. The velocity and pressure signal were filtered using a third order zero phase low pass frequency filter with a cut-off value of 30 Hz, normalized for the half of the sample frequency. Furthermore 5 cardiac cycles were averaged to one average cycle to correct for beat-to-beat variations such as breathing artefacts. The tissue Doppler wall velocity was integrated to get a trace of the pulmonary arterial wall movement (radial change), with which the continuous pulmonary arterial diameter, area and relative area change were calculated using the pulmonary arterial diameter at the beginning of the echocardiographic image as a reference point. These data were used to plot the following images of the average cardiac cycle 1) synchronised pulmonary arterial wall velocity, radius, cross-sectional area and pressure to time traces 2) a relative pulmonary arterial area change (%) to pressure (mmHg) loop, 3) an absolute pulmonary arterial area to pressure loop. From these images the following indices of pulmonary arterial stiffness were obtained.

Indices of pulmonary arterial stiffness

The pulmonary arterial capacitance (PACi), was calculated from invasively measured stroke volume index (pulmonary flow index divided by heart rate) and pulmonary arterial pulse pressure. The end-diastolic and peak systolic pulmonary arterial pressure, diameter and area were extracted from the pressure, diameter and area to time traces of the average cardiac cycle (Figure 1A) and used to calculate previously reported indices of pulmonary arterial stiffness (Table 1), including relative area change (RAC), distensibility (D), dynamic compliance ($C_{dyn}$), pressure-strain modulus ($E_p$), Stiffness index ($\beta_{ind}$) and stiffness coefficient ($\beta_{coeff}$). The pressure-time curve was also used to calculate $dP/dT$ ((P$_{max}$ – P$_{min}$)/(Time$_{P_{max}-P_{min}}$)) from the beginning of the average cardiac cycle to the point of peak systolic pressure.

Because the pulmonary arterial cross-sectional area and diameter were calculated from the radius obtained from the echocardiographic images, there is an obligatory constant relation between radius, diameter and area. Therefore the distensibility, $C_{dyn}$ and their inverse, $E_p$, provide the same information and will have equal correlations with disease severity and outcome. We limited the analyses to the distensibility, while showing the mean $C_{dyn}$ and $E_p$ for reference to previous reports only.
New indices of pulmonary arterial stiffness included loop compliance (CL), elastance (EL) pulmonary arterial wall dissipated energy ($W_D$) and pulmonary arterial wall expansion velocity. Loop compliance (CL in %/mmHg) is the inverse of the regression coefficient (RC) of a linear regression line fitted over the relative area change (%) to pressure (mmHg) loop (Figure 1B). Loop compliance was determined for the systolic segment and total relative area change to pressure loop ($CL_{syst}$ and $CL_{total}$ respectively), for which the end of systole was defined as the point of peak systolic pulmonary arterial pressure. The diastolic segment of the relative area change (%) to pressure (mmHg) loop was used to measure pulmonary arterial elastance (EL in mmHg/%) by fitting a linear regression line over the diastolic segment. Pulmonary arterial $W_D$ (cm$^2$*mmHg) was determined by calculating the area within the absolute pulmonary arterial cross-sectional area to pressure loop (figure 1C).$^{20}$ Furthermore the velocity
and pressure to time traces were used to determine the maximum pulmonary arterial wall expansion velocity ($V_{el_{max}}$, cm/s), using the first velocity peak in this velocity trace. The time to the first velocity peak and the pulmonary arterial pressure rise during that time were also determined, and used to calculate the following parameters: the pulmonary arterial wall expansion acceleration ($ACC$, cm/s/ms), the acceleration time ($ACC_{time}$, ms), and the velocity increase per unit pressure ($Vel/Press$, cm/s/mmHg).

**Statistical Analyses**

All individual echocardiographic images and pressure traces were analysed and synchronized by two independent investigators (JMD and MJP). Interobserver variability of parameters characterizing the continuous pressure and area measurements was tested using Two-way mixed Intraclass Correlation Coefficient (ICC). Comparisons between PAH patients and control subjects were made using student t-test for independent groups for continuous normally distributed variables and Mann-Withney U test for not normally distributed variables. Chi-square or Fishe’s exact test were used to compare categorical variables as appropriate. The association of the indices of stiffness with disease severity was tested using Pearson and Spearman correlation coefficients, using WHO functional class and PVRi to represent disease severity. Outcome analysis was performed from heart catheterization until adverse outcome, defined as death, lung-transplantation or initiation of intravenous prostacyclin analogues, or until last follow-up visit. Indices of pulmonary arterial stiffness were split up in their tertiles, after which outcome difference between the tertile subgroups per parameter were tested using Kaplan-Meier curves with log rank tests. Furthermore, univariate Cox regression analysis was used to evaluate the associations with outcome on a continuous scale. Because of a limited patient number no multivariate outcome analyses were performed. Analyses were performed using IBM SPSS Statistics version 23 (IBM, North Castle, New York USA). P-values of $<0.05$ were considered statistically significant.

**Results**

From August 2011 – December 2015, 24 children with PAH, including 17 IPAH/HPAH and 7 PAH-CHD patients, and 15 control subjects were included in the study. Patient characteristics are shown in table 2. Control subjects were younger compared to the PAH patients. PAH patients with a shunt defect were younger than patients without a shunt. Patients were treated according to the guidelines for diagnosis and treatment for pulmonary hypertension. The study group included 5 treatment naive patients and 19 patients already on PAH targeted therapy.

**Indices of pulmonary arterial stiffness**

Both the conventional and the new, pressure-area loop derived indices of pulmonary arterial stiffness, analysed by two independent, blinded investigators showed high single measures intraclass correlation coefficients of 0.90 or higher with $p<0.001$ (Table 3).
Children with pulmonary arterial hypertension had larger end-diastolic cross-sectional pulmonary arterial area compared to control subjects, whereas the maximal systolic cross-sectional areas were comparable. The conventional indices of pulmonary arterial stiffness differed significantly between PAH patients and control subjects, with lower distensibility.
### Table 3: Indices of pulmonary arterial stiffness

<table>
<thead>
<tr>
<th>Pulmonary arterial characteristics</th>
<th>All study subjects:</th>
<th>PAH patients:</th>
<th>Intraclass correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=24</td>
<td>N=15</td>
<td>p-value</td>
</tr>
<tr>
<td>End-diastolic Pressure (mmHg)</td>
<td>38 ± 15</td>
<td>8 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak systolic Pressure (mmHg)</td>
<td>79 ± 23</td>
<td>22 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-diastolic Area (cm²)</td>
<td>0.8 (0.7-1.5)</td>
<td>0.5 (0.2-0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak systolic Area (cm²)</td>
<td>1.8 (1.5-3.4)</td>
<td>1.8 (1.4-2.2)</td>
<td>0.386</td>
</tr>
</tbody>
</table>

Traditional indices

| PACi (ml/mmHg/m²) | 1.2 ± 0.6 | 7.4 ± 3.6 | <0.001 | 1.2 ± 0.6 | 1.2 ± 0.5 | 0.996 | Not applicable |
| RAC (%)           | 122 (96-172) | 333 (137-459) | 0.001 | 125 (84-184) | 118 (117-136) | 0.972 | 0.97 (0.94-0.98) | <0.001 |
| Distensibility (%/mmHg) | 3.0 (2.3-5.3) | 19.2 (11.4-33.0) | <0.001 | 3.1 (2.3-5.6) | 2.7 (2.7-3.6) | 0.972 | 0.98 (0.97-0.99) | <0.001 |
| Dynamic Compliance (%/100mmHg) | 122 (95-202) | 731 (409-932) | <0.001 | 133 (89-222) | 109 (107-134) | 0.915 | 0.99 (0.98-0.99) | <0.001 |
| Ep (mmHg)         | 85.2 ± 38.3 | 15.7 ± 7.4 | <0.001 | 85.3 ± 42.7 | 84.7 ± 14.6 | 0.958 | 0.99 (0.97-0.99) | <0.001 |
| Stiffness Index   | 0.6 ± 0.3 | 0.4 ± 0.3 | 0.028 | 0.6 ± 0.3 | 0.7 ± 0.2 | 0.711 | 0.97 (0.94-0.98) | <0.001 |
| Stiffness Coefficient | 1.6 ± 0.7 | 1.2 ± 0.7 | 0.069 | 1.6 ± 0.7 | 1.7 ± 0.5 | 0.622 | 0.97 (0.95-0.99) | <0.001 |

Indices derived from echocardiography with synchronised pressure

| CL_syst (%)/mmHg | 2.7 (2.2-4.2) | 15.5 (12.3-27.5) | <0.001 | 2.9 (2.1-5.1) | 2.4 (2.3-2.4) | 0.644 | 0.97 (0.95-0.99) | <0.001 |
| CL_total (%)/mmHg | 3.4 (2.6-5.5) | 23.3 (15.2-42.1) | <0.001 | 3.7 (2.5-5.6) | 3.2 (2.7-3.6) | 0.749 | 0.99 (0.98-1.00) | <0.001 |
| EL (mmHg%)       | 0.32 (0.18-0.38) | 0.04 (0.02-0.06) | <0.001 | 0.32 (0.18-0.38) | 0.30 (0.27-0.35) | 0.804 | 0.99 (0.98-0.99) | <0.001 |
| Wp (cm²/mmHg)    | 5.4 (4.0-17.1) | 3.2 (1.7-5.4) | 0.046 | 5.5 (4.1-19.4) | 4.2 (3.9-9.5) | 0.337 | 0.98 (0.96-0.99) | <0.001 |
| dP/dT (mmHg/ms)  | 0.2 ± 0.1 | 0.1 ± 0.1 | <0.001 | 0.2 ± 0.1 | 0.3 ± 0.1 | 0.131 | 1.00 (1.00-1.00) | <0.001 |
| Velmax (cm/s)    | 2.6 ± 0.9 | 2.1 ± 1.0 | 0.173 | 2.6 ± 1.0 | 2.4 ± 0.3 | 0.412 | 0.90 (0.80-0.95) | <0.001 |
| ACC (cm/s/ms)    | 0.09 ± 0.03 | 0.09 ± 0.05 | 0.906 | 0.09 ± 0.04 | 0.08 ± 0.02 | 0.829 | 0.94 (0.89-0.97) | <0.001 |
| ACCtime (ms)     | 30.2 ± 7.2 | 29.5 ± 15.4 | 0.883 | 30.3 ± 7.0 | 29.8 ± 9.0 | 0.902 | 0.91 (0.83-0.95) | <0.001 |
| Vel/Press (cm/s/mmHg) | 0.6 (0.4-1.2) | 0.6 (0.3-1.1) | 0.954 | 0.7 (0.4-1.2) | 0.6 (0.3-1.3) | 0.859 | 0.93 (0.88-0.97) | <0.001 |

Values are median (interquartile range [IQR]), n (%), or mean ± SD unless otherwise indicated. P-value from student T-test, Mann-Whitney U test or Chi-square test as appropriate. PAH, pulmonary arterial hypertension; PACi, pulmonary arterial capacitance index; RAC, relative area change; Ep, pressure strain modulus; CL_syst, Loop compliance of systole; EL, Elastance; CL_total, Loop compliance of total heart beat; Wp, pulmonary arterial wall dissipated energy; Vel, pulmonary arterial wall expansion velocity; ACC, pulmonary arterial wall expansion acceleration.
and increased pulmonary arterial stiffness in patients with PAH. No differences in indices of pulmonary arterial stiffness were observed between patients with PAH associated with a shunt compared to those without a shunt. PACi, RAC, and distensibility correlated with PVRI.

Of the new indices $CL_{syst}$ and $CL_{total}$ were significantly lower in PAH patients compared to controls, whereas $EL$ was higher in PAH patients. The $W_D$ and dP/dT were increased in PAH patients. For the $Vel_{max}$, ACC, ACCtime and Vel/Press no significant differences could be demonstrated between PAH patients and control subjects. The $CL_{syst}$, $CL_{total}$ and $EL$ correlated with PVRI, whereas the correlation between dP/dT and PVRI just failed to reach statistical significance. $Vel_{max}$ and ACC both correlated with WHO-FC, whereas the $W_D$ tended to have an association with WHO-FC (Table 4).

### Table 4: Correlations in PAH patients

<table>
<thead>
<tr>
<th></th>
<th>PVRi</th>
<th>WHO-FC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Traditional indices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACi (ml/mmHg/m²)</td>
<td>-0.744</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAC (%)</td>
<td>-0.406</td>
<td>0.049</td>
</tr>
<tr>
<td>Distensibility (%/mmHg)</td>
<td>-0.676</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stiffness Index</td>
<td>0.030</td>
<td>0.889</td>
</tr>
<tr>
<td>Stiffness Coefficient</td>
<td>-0.010</td>
<td>0.962</td>
</tr>
<tr>
<td><strong>Indices derived from echocardiography with synchronised pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{syst}$ (%/mmHg)</td>
<td>-0.634</td>
<td>0.001</td>
</tr>
<tr>
<td>$CL_{total}$ (%/mmHg)</td>
<td>-0.508</td>
<td>0.011</td>
</tr>
<tr>
<td>$EL$ (mmHg/%)</td>
<td>0.547</td>
<td>0.006</td>
</tr>
<tr>
<td>$W_D$ (cm²/mmHg)</td>
<td>0.277</td>
<td>0.191</td>
</tr>
<tr>
<td>dP/dT (mmHg/ms)</td>
<td>0.393</td>
<td>0.058</td>
</tr>
<tr>
<td>$Vel_{max}$ (cm/s)</td>
<td>0.181</td>
<td>0.397</td>
</tr>
<tr>
<td>ACC (cm/s/ms)</td>
<td>0.077</td>
<td>0.719</td>
</tr>
<tr>
<td>ACCtime (ms)</td>
<td>0.200</td>
<td>0.348</td>
</tr>
<tr>
<td>Vel/Press (cm/s/mmHg)</td>
<td>0.228</td>
<td>0.284</td>
</tr>
</tbody>
</table>

Correlations using Spearman or Pearson correlation coefficient, as appropriate. PAH, pulmonary arterial hypertension; PACi, pulmonary arterial capacitance index; RAC, relative area change; Ep, pressure strain modulus; $CL_{syst}$, Loop compliance of systole; $EL$, Elastance; $CL_{total}$, Loop compliance of total heart beat; $W_D$, pulmonary arterial dissipated energy; Vel, pulmonary arterial wall expansion velocity; ACC, pulmonary arterial wall expansion acceleration.

### Outcome

A lower PACi and distensibility were associated with a shorter time to adverse outcome (figure 2). The PACi specifically identified the tertile of patients with better outcome, while the distensibility specifically identified those patients with worse outcome. Relative area
change, stiffness coefficient and stiffness index showed no significant correlation with time to adverse outcome.

**Figure 2: Kaplan Meier survival analyses of traditional indices of pulmonary stiffness**

Kaplan Meier survival analyses of traditional indices of pulmonary stiffness, separated for their tertiles. PACi tertiles cut-off values: (I) PACI ≤ 0.86 ml/mmHg/m²; (II) 0.86 ml/mmHg/m² < PACi < 1.37 ml/mmHg/m²; (III) PACi ≥ 0.37 ml/mmHg/m². Distensibility tertiles cut-off values: (I) D ≤ 2.4 %/mmHg; (II) 2.4 %/mmHg < D < 3.8 %/mmHg; (III) D ≥ 3.8 %/mmHg.

Of the new variables derived from pressure area loops, a high $CL_{syst}$ and $CL_{total}$ was associated with a better outcome (figure 3). A lower $W_D$ was associated with excellent outcome, compared to the two higher tertiles of $W_D$. Both a low pulmonary arterial wall expansion velocity and a short $ACC_{time}$ tended to be associated with improved outcome. Cox regression analyses showed that on a continuous scale both the $W_D$ (HR 1.03 (1.00-1.058), $p=0.024$) and $ACC_{time}$ (1.10 (1.00-1.21), $p=0.047$) were significantly associated with outcome. No correlation with outcome could be demonstrated for the variables EL, ACC, Vel/Press and dP/dT.

**Discussion**

The current study introduces a new method to determine indices of pulmonary arterial stiffness and to enhance characterization of the pulsatile components of the right ventricular afterload, based on continuous pulmonary arterial cross-sectional area to pressure relationships. These indices could be calculated from measurements collected during routine right heart catheterization and simultaneously recorded transoesophageal echocardiography. Our preliminary data suggests that these indices are related to disease severity and outcome.
Kaplan Meier survival analyses of new indices of pulmonary stiffness, separated for their tertiles. Loop compliance of systole tertiles cut-off values: (I) $CL_{\text{syst}} \leq 2.2 \%$/mmHg; (II) $2.2 \%$/mmHg < $CL_{\text{syst}} < 3.1 \%$/mmHg; (III) $CL_{\text{syst}} \geq 3.1 \%$/mmHg. Loop compliance of total heart beat tertiles cut-off values: (I) $CL_{\text{total}} \leq 2.7 \%$/mmHg; (II) $2.7 \%$/mmHg < $CL_{\text{total}} < 5.0 \%$/mmHg; (III) $CL_{\text{total}} \geq 5.0 \%$/mmHg. Elastance tertiles cut-off values: (I) $EL \leq 0.20 \text{mmHg/%}$; (II) $0.20 \text{mmHg/%} < EL < 0.37 \text{mmHg/%}$; (III) $EL \geq 0.37 \text{mmHg/%}$. Stroke work tertiles cut-off values: (I) $W_D \leq 4.2\text{cm}^2\text{mmHg}$; (II) $4.2\text{cm}^2\text{mmHg} < W_D < 13.5\text{cm}^2\text{mmHg}$; (III) $W_D \geq 13.5\text{cm}^2\text{mmHg}$. Maximum velocity tertiles cut-off values: (I) $Vel_{\text{max}} \leq 2.3\text{cm/s}$; (II) $2.3\text{cm/s} < Vel_{\text{max}} < 2.8\text{cm/s}$; (III) $Vel_{\text{max}} \geq 2.8\text{cm/s}$. Acceleration time cut-off values: (I) $ACC_{\text{time}} \leq 26\text{ms}$; (II) $26\text{ms} < ACC_{\text{time}} < 33\text{ms}$; (III) $ACC_{\text{time}} \geq 33\text{ms}$. 
In the process, we encountered some methodological problems that need to be further investigated and refined.

In the current discussion we will start with a discussion of the preliminary results, followed by a discussion on the limitations and potential future refinements of the method itself.

Pulmonary arterial cross-sectional area to pressure loops were used to determine pulmonary arterial loop compliance (CL). We found that $CL_{total}$ is decreased in children with PAH and is related to disease severity and outcome. The $CL_{total}$ provides a representation of both the systolic and the diastolic component of the area – pressure loop. In contrast to the conventional indices of pulmonary arterial stiffness, the area-pressure loop gives us the opportunity to analyse these components separately. This may in theory have surplus value, since the loop compliance of systole and elastance determined during diastole may represent different pulmonary arterial properties. The systolic component of the continuous area pressure relationship represents the pulsatile right ventricular afterload or the pulsatile forces the right ventricle encounters while ejecting. The diastolic area-pressure relationship is, however, not a component of the right ventricular afterload but characterizes the elastance during pulmonary arterial recoil in diastole. This recoil is influenced by intrinsic pulmonary arterial wall properties and may represent pulmonary arterial wall stiffness independent of the right ventricular function. Furthermore it may affect the shear forces on the endothelium of the pulmonary vascular bed. Therefore, we analysed the systolic loop compliance and elastance separately.

The $CL_{syst}$ correlated with disease severity (PVRi) and showed to be a predictor of outcome. The $CL_{syst}$ is a parameter comparable to distensibility. However, the benefit of loop compliance is that it represents the direct effect of the pressure rise in the pulmonary artery on its cross-sectional diameter instead of being based on the peak systolic relation only. In theory, it therefore more completely represents the compliance and thus the right ventricular load throughout the systole.

Pulmonary arterial elastance represents the tendency of the pulmonary artery to recoil during diastole, and as such represents pulmonary arterial wall stiffness. It may however also represent PVR, considering that the PVR determines the afterload of the pulmonary arterial recoil. The $EL$ correlated with PVRi, but we could not demonstrate a significant relation of $EL$ to outcome. The stiffness index and coefficient, that are presumed to be less pressure-dependent than pulmonary arterial distensibility and therefore better represent the intrinsic pulmonary arterial wall stiffness, were not associated with outcome.

$WD$ was shown to be larger in PAH patients compared to controls and was associated with outcome in the current study. $WD$ has previously been shown to be increased in the aorta of patients with hypertension, which was considered due to viscoelastic changes in the arterial wall in hypertensive patients. Increased viscoelasticity of the pulmonary artery has been previously shown in experimental models of chronic hypoxic pulmonary hypertension and was suggested to be due to collagen accumulation in the pulmonary arterial wall. Our
findings suggest that the viscoelastic properties of the pulmonary arteries is altered in PAH also and that progressed change of the pulmonary arterial wall viscoelasticity may be associated with worse outcome. This may be a consequence of pulmonary arterial remodelling, as suggested by previous literature. However, it could also be due to pulmonary arterial wall stretching because of exposure to an increased pressure level. Considering the negative effect of increased viscoelasticity to the right ventricular afterload the mechanism behind increased viscoelasticity may not matter, when measured to determine a patient’s prognosis or disease severity.

Arterial wall expansion velocity has been reported to represent arterial wall stiffness of the aorta in patients with Marfan syndrome, in whom the relation between arterial wall velocity and arterial stiffness cannot be attributed to an increased arterial pressure. Furthermore, in the aorta lower arterial wall expansion velocity has been shown to be associated with higher arterial wall stiffness, in patients with systemic hypertension. In the current study no significant difference in \( \text{Vel}_{\text{max}} \) between PAH patients with increased pulmonary arterial stiffness and control patients could be demonstrated. Within the PAH patient group, high \( \text{Vel}_{\text{max}} \) was associated with high WHO-FC and tended to be associated with worse outcome. The high \( \text{Vel}_{\text{max}} \) in patients with worse outcome may be the consequence of an increased hydraulic power, caused by a combination of an increased blood flow velocity and increased pulmonary arterial pressure build up due to both a higher PVRI and the presence of early pressure reflection waves, in these patients with pulmonary arterial hypertension.

Arterial wall acceleration time was shown to be increased in the aorta in patients with hypertension and higher aorta stiffness. In the current study no significant difference in \( \text{ACC}_{\text{time}} \) between PAH and control patients could be demonstrated. However, a longer \( \text{ACC}_{\text{time}} \) was associated with higher WHO-FC and worse outcome within the group of paediatric PAH patients having an increased pulmonary arterial stiffness. The great advantage of \( \text{Vel}_{\text{max}} \) and \( \text{ACC}_{\text{time}} \) is that no pressure measurement is needed to determine these indices of pulmonary arterial stiffness, allowing for non-invasive follow-up measurements.

The traditional indices of pulmonary arterial stiffness, PACi, distensibility, dynamic compliance and elastic modulus, proved lower in PAH compared to control patients and correlated with pulmonary vascular resistance and outcome, as has been shown previously for pulmonary arterial capacitance and distensibility.

The RAC was lower in PAH patients compared to controls and associated with PVRI. An association with outcome could, however, not be demonstrated. This can be explained because the pulmonary arterial pressure is not included in its calculation. The relative area change by itself provides limited information on the pulmonary arterial stiffness when not related to the pulmonary arterial pressure differences.

The control group of this study was composed of patients with atrial septal defects. These patients have a left to right shunt with increased volume load for the pulmonary circulation,
known to be associated with increased pulmonary arterial diameter. Therefore, these control patients may have decreased pulmonary arterial compliance compared to healthy individuals.\textsuperscript{5} They did however have normal PVRI and mPAP and so were considered appropriate to serve as a control group of patients that do not have progressed pulmonary vascular disease.

\textbf{The analysis method}

We consider our method used to evaluate continuous pulmonary arterial pressure-area relationships as work that is still in progress. The method still has some limitations that need to be perfected in future.

Comparing the results of our study to previous reports in literature, the values for relative area change and distensibility measurements in our study, differ from those previously reported in both patients and controls.\textsuperscript{9-11,13,36} This disparity may be due to both an underestimation of the end diastolic pulmonary arterial cross-sectional area and an overestimation of the peak systolic area in the current study. An explanation could be that in our study, the pulmonary arterial radial change was measured solely from the pulmonary arterial wall distal to the ultrasound transducer, while the proximal pulmonary arterial wall movement might have been restricted due to its position close to the transducer. The movement of the distal pulmonary arterial wall could therefore have been larger than the actual arterial radial change, causing an overestimation of the relative area change and distensibility. Also, by measuring solely the distal pulmonary arterial wall, movements are potentially affected by distortion due to movements of the pulmonary artery parallel and perpendicular to the measurement direction. Nevertheless, we have put maximal efforts in correcting for these errors: The pulmonary arterial wall tracking, used to extract the pulmonary arterial wall velocity from the ultrasound images, was corrected for perpendicular movements. Furthermore, multiple cardiac cycles were averaged to one average cycle to correct for beat to beat variations including extrinsic artery movements. However, this may not completely abolish the effect of these extrinsic movements. Further optimization of our method should include either a correction of these potential errors or an alternative approach enabling us to measure both sides of the pulmonary arterial wall (such as transthoracic ultrasound).

Our method uses linear regression to extract systolic loop compliance and elastance from the pulmonary arterial cross-sectional area to pressure loops. However, considering the shape of the area to pressure loops and the viscoelastic properties of an arterial wall this relationship is not linear. For future perspective an analyses of the best mathematical fit to the area pressure relationship should be performed to derive the full set of information from these loops and to further improve the indices to characterize pulmonary arterial stiffness.

Paediatric PAH is a rare disease and including large numbers of patients in a prospective study is challenging. Relatively small patient numbers may have limited our analyses. In the current study we could not yet determine an additional value of the proposed new indices of pulmonary arterial stiffness compared to traditional indices, since the number of patients
prohibited multivariate analyses. Also, we could not test whether the observed correlations between the new stiffness indices and clinical disease severity and outcome were dependent or independent from pulmonary arterial pressure. Therefore, we could not determine whether the increased pulmonary vascular stiffness is a consequence of pulmonary arterial wall remodelling or a mechanical consequence of increased pulmonary arterial pressure exposure. However, when considering pulmonary arterial stiffness indices as a measure of right ventricular afterload, the underlying mechanism of increased pulmonary arterials stiffness may not be important.

Furthermore, due to ethical considerations we included as control patient, those that needed a heart catheterization with transoesophageal echocardiography for clinical reasons. Therefore, inclusion of control subjects was limited to patients that were presented for transcatheter closure of atrial septal defect and no age and sex matching was possible.

And last, potential differences in frequency response between the pressure and area acquisition systems were not tested for. Such a difference could cause dyssynchrony between the two signals and should therefore be investigated in future.

To move forward we need to optimize the current measurement and analyses methods by addressing the above mentioned limitations. When we succeed in this and we are able to use the complete information from the continuous pulmonary arterial pressure area relation, and thus enhance the characterization of pulmonary arterial stiffness, we may identify the value of this new approach and its clinical relevance in the evaluation of patients with PAH.
References


