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Pulmonary Vascular Input Impedance is a Combined Measure of Pulmonary Vascular Resistance and Stiffness and Predicts Clinical Outcomes Better than PVR Alone in Pediatric Patients with Pulmonary Hypertension

Kendall S. Hunter, PhD¹, Po-Feng Lee, MSc², Craig J. Lanning, BSc¹, D. Dunbar Ivy, MD¹, K. Scott Kirby, RDCS¹, Lori R. Claussen, BSN, RN¹, K. Chen Chan, MD¹, and Robin Shandas, PhD^{1,3}

¹ Department of Pediatric Cardiology, University of Colorado Health Sciences Center, 1056 E. 19th Ave, Denver, CO 80218

² Department of Bioengineering, Texas A&M University, College Station, TX 77843

³ Department of Mechanical Engineering, University of Colorado at Boulder, Boulder, CO 80309-0427

Abstract

Background—Pulmonary vascular resistance (PVR) is the current standard for evaluating reactivity in children with pulmonary arterial hypertension (PAH). However, PVR measures only the mean component of right ventricular afterload and neglects pulsatile effects. We recently developed and validated an method to measure pulmonary vascular input impedance, which revealed excellent correlation between the zero-harmonic impedance value and PVR, and suggested a correlation between higher harmonic impedance values and pulmonary vascular stiffness (PVS). Here we show that input impedance can be measured routinely and easily in the catheterization laboratory, that impedance provides PVR and PVS from a single measurement, and that impedance is a better predictor of disease outcomes compared to PVR.

Methods—Pressure and velocity waveforms within the main PA were measured during right-heart catheterization of patients with normal PA hemodynamics (n=14) and those with PAH undergoing reactivity evaluation (49 subjects; 95 conditions). A correction factor needed to transform velocity into flow was obtained by calibrating against cardiac output. Input impedance was obtained off-line by dividing Fourier-transformed pressure and flow waveforms.

Results—Exceptional correlation was found between the indexed zero harmonic of impedance and indexed PVR ($y=1.095 \cdot x+1.381$, $R^2=0.9620$). Additionally, the modulus sum of the first two harmonics of impedance was found to best correlate with indexed pulse pressure over stroke volume (PP/SV) ($y=13.39 \cdot x-0.8058$, $R^2=0.7962$). Amongst a subset of PAH patients (n=25), cumulative logistic regression between outcomes to total indexed impedance was better ($R_L^2=0.4012$) than between outcomes and indexed PVR ($R_L^2=0.3131$).

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Address for Correspondence: Robin Shandas, Ph.D., Cardiovascular Flow Research Laboratory, Division of Cardiology, 1056 E. 19th Ave., B-100, The Children's Hospital, Denver, CO 80218, shandas.robin@tchden.org, Phone: (303) 837 2586, Fax: (303) 860 4056.

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Conclusions—Input impedance can be consistently and easily obtained from PW Doppler and a single catheter pressure measurement, provides comprehensive characterization of the main components of RV afterload, and better predicts patient outcomes compared to PVR alone.

Keywords

hypertension; pulmonary; pulmonary heart disease; pediatrics; echocardiography; hemodynamics

Introduction

The hemodynamic status of children with pulmonary arterial hypertension (PAH) is currently assessed through invasive measurement of pulmonary vascular resistance (PVR), which is the ratio of the mean pulmonary artery pressure drop across the pulmonary microvasculature to cardiac output. Because PVR is computed with mean values, it quantifies only the steady-state resistance presented to the heart, and ignores the dynamic impact of stiffness (or compliance) on the circuit [1–3]. In contrast, both static (PVR) and dynamic, i.e. pulmonary vascular stiffness (PVS) information is provided by the pulmonary vascular input impedance. Impedance is analogous to the ratio of the arterial pressure waveform to the blood flow waveform over an entire cardiac cycle, and thus includes both mean and pulse data. Here, we measure pressure and flow at the entrance to the main pulmonary artery, which yields the input impedance of the whole pulmonary vasculature. In an earlier study on a smaller number of patients we showed that this input impedance is both easily measured during a routine catheterization study and provides information on both steady and dynamic components of right ventricular afterload [4]. The importance of including dynamic (stiffness) components in evaluation of PAH has since been confirmed as a better predictor of mortality [5].

Because impedance includes both resistive and stiffness components of right ventricular (RV) afterload, it should represent a simple-to-obtain measure of global pulmonary vascular function in patients with pulmonary hypertension. Further, we hypothesize that impedance, as a better measure of RV afterload, will be a superior predictor of patient outcomes compared to PVR alone. The goals of this study were: 1) measure pulmonary vascular input impedance in a large pediatric clinical population (63 subjects, 109 conditions); 2) determine an appropriate correction factor to convert Doppler velocity measurement into flow for impedance calculations; 3) correlate harmonic values of impedance against hemodynamically measured PVR and PVS; and 4) examine capabilities of impedance and PVR to predict 1-year outcomes for a sub-set of patients (n=25).

Methods

Clinical Study

Patient Selection—After institutional review board approval and informed consent and assent had been obtained, data were obtained during routine cardiac catheterization that is part of the regular evaluation and treatment of these subjects at the Children's Hospital in Denver, CO. The patient population was divided into two groups. Group 1 studies were conducted after intervention to correct congenital heart defects (8 PDA, 6 ASD), had normal MPA pressures, and were considered the control group (14 patients; median age = 2yrs, range = 1.66–16yrs; 10 females). The remainder of patients (49 patients, 95 reactivity conditions; median age = 3yrs, range = 0.25–17yrs; 18 females) suffered from PAH. 31 patients in the hypertensive group underwent tests for acute changes in hemodynamic parameters (reactivity) with the administration of oxygen, nitric oxide, or other therapeutic agents (Epoprostenol, Diltiazem, Sildenafil, Iloprost). The majority of these 31 patients underwent only a single reactivity study, but some patients underwent as many as four such

tests. A summary of patient characteristics, calculated at the patient level ($n=63$) is provided in Table 1; additionally, the quartiles of age and MPAP are plotted in Figures 1A & B.

Clinical Data Acquisition—Pressure measurements were made with standard fluid-filled catheters (Transpac IV, Abbot Critical Care Systems) within the main PA. PW Doppler velocity measurements were taken with a commercial ultrasound scanner (Vivid 5, GE Medical Systems Inc) from a parasternal short axis view within the midpoint of the main PA. Two dimensional echo and color Doppler was used to align the ultrasound beamline parallel to the main flow direction within the PA. We estimate minimal errors due to ultrasound beam angulation ($< 5^\circ$). Cardiac output was measured by Fick's method with measured oxygen consumption in cases where intracardiac shunts were in place and by thermodilution otherwise. Correct temporal alignment of the velocity and pressure signals was assured by storing the latter in digitized form on the auxiliary input of the ultrasound scanner simultaneously with PW Doppler (i.e. velocity) data. Measurements were made for 16 seconds for each patient; this typically encompassed 20 cardiac cycles. By definition impedance requires temporal histories of pressure and flow; here flow time-histories are calculated from Doppler velocity measurements, as explained below.

Data Analysis

MPA midline velocity time-histories were obtained semi-automatically from the recorded PW Doppler signals through the use of a custom edge-detection method to determine the appropriate envelope velocity in each PW Doppler time slice. Figure 2 shows the interface used for this method; in the figure, a red line superimposed upon the PW Doppler data on the main (upper) axes is the computed time-history, while the lower axes show both the AUX1 trace (pressure, in yellow) and the ECG trace (in blue) used to separate cardiac cycles. The method is referred to as “semi-automatic” in that user input was occasionally needed to remove velocity spikes due to noise and/or valve clicks from the time-history. From each velocity time-history $V(t)$ and mean cardiac output measurement (CO), the corresponding flow time-history $Q(t)$ was then computed as

$$Q(t) = A_{corr} V(t), \quad (1)$$

in which the constant area correction factor A_{corr} is found from

$$A_{corr} = CO / \bar{V}, \quad (2)$$

where $\bar{V}$ is the mean velocity computed from the midline velocity time-history. This calculation relies on the assumption that the spatial profile of the velocity is nearly constant across the vessel (i.e. “top-hat” profile); this is not unreasonable since typical Womersley numbers found in the MPA are much greater than 1.0, indicating flat profiles [6]. Computational fluid dynamics studies from our group have confirmed that velocity profiles within the main PA are indeed flat over the pulsatile cycle [7]. The pressure and calculated velocity time-histories were then separated into individual cardiac cycles ($n > 20$) based on ECG gating. A discrete Fourier transform (DFT) was then performed on the pressure and flow time-histories for each cycle, yielding values for their spectral moduli and phase at discrete multiples (harmonics) of the cardiac cycle frequency. The input impedance modulus was readily obtained as

$$Z(\omega) = |P(\omega)|/|Q(\omega)|, \quad (3)$$

in which ω is the discrete frequency of interest. Two parameters were extracted from the impedance data: the zero harmonic impedance value (Z_0), which should correlate with distal vascular resistance, and the sum of the impedance values from the first two harmonics (Z_1+Z_2), which should correlate to the pulmonary vascular stiffness. Although higher harmonics of impedance ($> 2^{\text{nd}}$) also quantify stiffness and may contain additional information such as reflection strength, their modulus values contained sufficiently high uncertainty to preclude inclusion for statistical analysis or clinical relevance. Additionally, right ventricular power calculations [8] indicate that these higher harmonics carry negligible power and thus may be safely neglected in consideration of afterload.

Clinical follow-up was available for twenty-five patients (median age 4 yrs, range 0.25–19 years; 11 males). The majority of these patients had a septal defect closure ($n=18$); three had idiopathic PAH, two had undergone repair of a cognitive diaphragmatic hernia, and two had PDA closure. Median follow-up time was 12 months (range 1–33 months) after the initial assessment or procedure. Mean values of indexed impedance sum ($= \text{BSA} \cdot (Z_0 + Z_1 + Z_2)$), abbreviated hereafter as ZsumI, and PVRI (i.e., indexed PVR) over the baseline and challenge conditions were computed for each patient. Additionally, patients were placed into one of three numerical outcomes categories based on World Health Organization scores pre and post treatment [9]. A numerical score of 1 indicated improvement (change of ≥ 1 functional classes for the better, e.g. change in WHO grade from IV to II or III to II); a score of 2 indicated moderate worsening (change of one functional class for the worse); and a score of 3 indicated significant worsening (change of ≥ 2 functional classes for the worse) or death. Nine patients showed no change in WHO scores; these patients were placed into one of the three categories above based on their constant WHO classification. For example, a patient classified as WHO grade I and who did not show change in this grade during the follow-up examination was placed in outcomes category 1, while a constant WHO grade II or III was placed in outcomes category 2, etc. Generally, the categories are intended to represent patients who show excellent response to initial treatment (category 1), those who are unlikely to respond to the current standard of care may be candidates for more extensive early therapy (category 2), and those who are at great risk and need urgent attention (category 3).

Statistical Analysis

Linear regressions are obtained via the method of least-squares from the pooled data under the assumption that multiple observations of a single patient (i.e. reactivity conditions) may be considered independent degrees of freedom. This assumption is reasonable when there is a substantial change (taken here as $>20\%$) in the hemodynamic state due to the administration of therapeutic agents. Because inclusion of acute non-responder data – defined throughout the paper as data that show less than a 20% acute change in either Z_0 or Z_1+Z_2 due to reactivity challenges – have the potential to skew regressions, we examine the impact of these cases in more detail by comparing regressions obtained with and without them. Coefficients of determination for the regressions are calculated according to standard procedure (see, e.g. [10]). For the clinical follow-up analysis, single values for each patient were obtained in ZsumI and PVRI by averaging over all reactivity conditions, and an outcomes factor was assigned as noted above. Cumulative logistic regression between these parameters and the ordinal outcomes categories was performed with the PROC LOGISTIC procedure in SAS (SAS Institute Inc, Cary, NC) and goodness-of-fit statistics were computed as described in [11]. Finally, uncertainties for each measurement were obtained as described previously [4].

Results

Patients in the normotensive group (I) had normal pulmonary pressures (MPAP = 16.9 ± 4.7 mmHg), whereas the other group (II) displayed PAH (MPAP = 37.3 ± 18.7 mmHg, baseline condition); this difference was statistically significant ($p < 0.0001$). The mean cardiac indices of the normotensive and hypertensive groups, respectively, 6.7 ± 6.4 L/(min·m²) and 4.1 ± 2.3 L/(min·m²), and their mean heart rates, 105 ± 17.9 bpm and 109 ± 28.0 bpm, were not significantly different.

Obtaining impedance for each patient added no more than 5 minutes to each study. Representative impedance curves for each Group are shown in Figures 3A and 3B. As seen in the figures, the hypertensive patients typically displayed both larger values of Z_0 , indicating higher PVR [1–4,8], and larger values of the first several harmonics of impedance. Differences in Z_0 and Z_1+Z_2 between the normotensive and hypertensive patients were significant ($p < 0.05$). Quartiles of PVR, Z_0 , and Z_1+Z_2 are seen in Figures 1C, D, & E. In accord with our previous study, excellent agreement between indexed Z_0 and hemodynamically measured indexed PVR was found ($y = 1.095 \cdot x + 1.381$, $R^2 = 0.9620$; Figure 4). Three correlations were examined for the higher harmonics of impedance, listed in order from best of fit to poorest: Z_1+Z_2 compared to 1) indexed pulse pressure divided by stroke volume, or hemodynamically measured pulmonary vascular stiffness ($y = 13.39 \cdot x - 0.8058$, $R^2 = 0.7962$; Figure 5A); 2) hemodynamically measured PVRI ($y = 0.8528 \cdot x + 3.593$, $R^2 = 0.2997$; Figure 5B); and 3) mean pulmonary artery pressure ($y = 0.1525 \cdot x + 3.536$, $R^2 = 0.1307$; Figure 5C).

The regressions above were examined to quantify the impact of acute non-responders. For the indexed Z_0 vs PVRI regression, this imposed the removal of 19 data sets that were non-responsive in indexed Z_0 . The new regression (63 patients, 90 reactivity conditions) has the same slope (to three significant digits) and an intercept 4.3% larger than the original. This change in intercept (0.058 mm Hg/(L/min)) is less than 0.3% of the total range of indexed Z_0 data. For the PVS regressions 20 data sets were removed due to non-response; of interest is the overlap of 13 cases that were non-responsive in Z_0 and Z_1+Z_2 , leaving 6 cases that responded in Z_0 only and 7 cases that responded in Z_1+Z_2 only. The resulting reduced data set for Z_1+Z_2 (63 patients, 89 reactivity conditions) yielded regressions with slopes differing by -3.7% , -5.9% , and 14.6% , respectively, from the originals shown in Figure 4. The intercept values of all three regressions changed by as much as 24.2% in absolute value; however such a change represents less than 0.5% of the entire range of Z_1+Z_2 .

A_{corr} was calculated from measured cardiac output and linearly correlated against body surface area, patient age in months, mean pulmonary artery pressure, pulse pressure, and cardiac output, with both bivariate and multivariate methods. BSA ($y = 2.142 \cdot x + 0.3128$, $R^2 = 0.4263$) and CO ($y = 0.3632 \cdot x + 0.5064$, $R^2 = 0.6520$) displayed respectable correlation; additional regressions of A_{corr} against age, MPAP, and pulse pressure found lesser fits in each case ($R^2 = 0.3181$, $R^2 = 0.0885$, $R^2 = 0.0530$, respectively). Notable multivariate linear regressions of A_{corr} against these parameters produced little additional increase in goodness-of-fit, except one that considered BSA and CO [$A_{corr} = 0.2161 - 0.7402(\text{BSA}) + 0.2977(\text{CO})$, $R^2 = 0.6817$]. These indicate that BSA may be used to determine the area correction factor to convert Doppler-measured velocity to flow for impedance calculations in future studies.

For the 25 patients for whom clinical follow-up data was examined, indexed impedance sum and PVRI were regressed against outcomes category to determine outcomes likelihood (i.e. probability); Table 2 contains regression parameters and their statistical significance, while Table 3 lists means & standard deviations for each outcomes category. Both models more than satisfied the proportional odds assumption ($p > 0.3$ for both). Figure 6 shows likelihood

curves for each outcomes category & normalized predictor; black curves correspond to ZsumI and red curves correspond to PVRI, while solid, dashed, and dot-dashed lines are used to represent categories 1, 2, and 3, respectively. We see that ZsumI has a higher probability of a category 2 outcome (66.1% probability to 52.8%) over a broader normalized range (40.1% of range to 28.6%), while having nearly identical odds of improvement (i.e. category 1) at low parameter values and of worsening (category 3) at high parameter values. Thus, ZsumI is better at differentiating between the three categories. This is borne out by goodness-of-fit statistic, which for ZsumI and outcomes is better ($R_L^2=0.4012$) than for PVRI and outcomes ($R_L^2=0.3131$). We also examined the ability of indexed PP/SV to predict outcomes; interestingly, its goodness-of-fit was worse ($R_L^2=0.2112$) than both ZsumI and PVRI.

Discussion

Evaluation of PVR and reactivity in PVR are currently the primary means of determining the severity of pediatric pulmonary hypertension, classifying patients pre-operatively, and determining appropriate therapy for PAH [12]. Although PVR is a dominant component of RV afterload, it is not the only component. Pulmonary vascular stiffness can play a significant role in maintaining low RV afterload in healthy patients and conversely, exacerbating afterload in patients with pulmonary hypertension. Vascular input impedance, which theoretically includes both resistance and stiffness components, should thus be the best global measure of RV afterload, and consequently should also provide a better means of predicting outcomes than PVR alone [1–4,8]. Although impedance is not a new concept, its application to clinically relevant diagnostics has been hampered by the lack of an easy-to-implement method to obtain it. We have shown [4] using in vitro and preliminary clinical data the utility of a method combining measurement of main PA pressure with computation of instantaneous PA flow using Doppler velocity measurements to obtain impedance easily during routine cardiac catheterization of patients with PAH. This study extends this prior work significantly by: 1) studying a larger number of patients; 2) providing explicit correlations between Z_0 and PVR, and between Z_1+Z_2 and hemodynamically measured pulmonary vascular stiffness; 3) correlating the correction factor, required to “correct” Doppler-measured velocities and obtain instantaneous flow, to facilitate future use of this method; and 4) obtaining regressions of outcomes against impedance and PVR to show the clinical utility of impedance measurement. Results show impedance is a highly promising clinically realizable measurement for comprehensively evaluating pulmonary vascular function in patients with PAH.

Measurement of impedance possesses several advantages over the traditionally derived hemodynamic variables (PVR, PP/SV) obtained through right-heart catheterization. First, it enables quantification of both system resistance and stiffness with a single measurement, which is important given the relatively moderate correlations that have been found between reactivity in PVR and clinical outcomes [12]. Because impedance is measured at a single position in the vasculature, it also does not require the measurement of wedge pressure, which may be problematic in certain patients. Through use of the presented correlation A_{corr} with BSA, or with imaging measurements of MPA area, measurement of instantaneous flow with or without measured cardiac output becomes much simpler. Note that if cardiac output were available it would only add confidence to the instantaneous flow measurement obtained from Doppler since the correction factor can be explicitly calculated for each patient and condition. Finally, the measurement of impedance adds roughly 5 minutes to the catheterization study, primarily for the Doppler measurement.

The importance of vascular stiffness in determining ventricular afterload is becoming increasingly recognized in hypertension management strategies in the pulmonary circulation

[5] and on the systemic side [13–16]. Links between arterial stiffening and systemic hypertension are well established [17,18]. Here we demonstrate the same on the pulmonary side, and additionally establish that impedance well-quantifies stiffness in the clinical situation, as Z_1+Z_2 is clearly a good correlate of indexed pulse pressure over stroke volume (BSA·PP/SV), or pulmonary vascular stiffness (PVS). Of the three hemodynamics variables with which correlation was attempted, PVS is the best constitutive measure in that it expresses the ratio of a given change in a kinetic or force variable (pulse pressure) over a resulting change in a kinematic or displacement variable (normalized vascular displacement, SV/BSA). We have explored other constitutive measures such as the dynamic compliance [19]; although promising as well, these require measurement of both pressure and arterial wall displacements. PVRI is purely indicative of viscous flow losses, whereas the mean pulmonary pressure is simply a kinetic measure, without any link to a resultant displacement; hence it is no surprise that both have lesser correlations with Z_1+Z_2 . We note that stiffness as represented by Z_1+Z_2 , unlike resistance and the other clinical measures it is compared to, is already independent of body mass; thus it is not normalized with BSA prior to comparison.

There are several ways this method may be used clinically. For example, this study provides some guidance on how to classify indexed impedance sum values, similar to how PVRI values are used clinically. From the outcomes analysis (Fig 6, Table 3) we see that, in general, $Z_{sumI} < 10$ indicates a relatively healthy pulmonary circulation and appear to predict good to moderately good outcomes. $Z_{sumI} > 18$ appears to indicate high RV afterloads and predict poorer outcomes. Based purely on comparison to PVRI, we calculate that Z_{sumI} predicts a PVRI of $> 3 \text{ m}^2 \text{ mm Hg}/(\text{L}/\text{min})$ with an 87.2% sensitivity and an 91.7% specificity; thus pre-operative evaluation may alternatively use a Z_{sumI} value of 8 as indicative of onset of PAH ($= \text{PVRI} > 3$) and of 18 as a means of generally classifying patients into outcomes categories. Although the outcomes analysis is preliminary in nature ($n=25$), it reveals that inclusion of stiffness effects enhances outcomes prediction in terms of goodness-of-fit and changes the form of outcomes probabilities for patients in poor health. Future studies will investigate Z_0 and Z_1+Z_2 as independent predictors of outcomes (i.e. multivariate regression); for the current small data set, such models were not statistically significant and thus were not included. Impedance may also provide a means of distinguishing effects of novel therapies, especially those that may affect upstream vascular tone and therefore alter pulmonary vascular stiffness versus those that affect downstream vascular tone and therefore alter pulmonary vascular resistance. We continue to perform impedance studies in our catheterization laboratory and will continue to expand our database of impedance correlations to further cement these findings.

There are several limitations that must be acknowledged. Impedance values at higher harmonics (beyond the 2nd) were not included due to their higher levels of measurement uncertainty and minuscule power content. In certain patients, this may underestimate true RV afterload since wave reflections, which typically manifest at higher harmonics, are not taken into account. The use of a constant area factor does affect the calculation of flow, although previous in-vitro studies on compliant models [4] suggest only a moderate impact on the harmonics of impedance. The regression for the area correction factor may need to be further refined for reactivity testing since we found as much as 20% variation in this factor due to reactivity. This could be done through additional secondary and/or tertiary correlates, such as the systolic acceleration time or the ratio of this time to the ejection time, which may influence the velocity profile and correspondingly the area correction factor. Other methods such as MRI could also be used to measure instantaneous flow directly without any need for correction factors. We did not examine reactivity in impedance as another potential predictor of outcomes, nor did we evaluate how impedance changes with the administration of different therapies; this work is ongoing. We note that exclusion of the non-responder data –

which may represent dependent observations – was seen to have a minor impact on the regressions performed. Thus, inclusion of such data does not appear to invalidate the statistical analysis. We note that the Doppler data was acquired at 100Hz, which provides useful frequency information up to 50Hz; additionally, the fluid-filled catheters used have been shown to have flat frequency response up to 15Hz. Thus, we may have confidence in the harmonics of impedance up to at least the sixth harmonic (for a heart rate of 120BPM), and to higher harmonics for lower heart rates.

In summary, we have shown in a relatively large pediatric patient population that pulmonary vascular input impedance provides a comprehensive yet easy-to-obtain measure of RV afterload in that it includes both resistance and vascular stiffness effects. Using a sub-set of patients where we also obtained outcomes, we also show impedance as a better and more significant predictor of clinical outcomes than PVR alone.

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Figure 1. Quartiles of A) age, B) mean pulmonary artery pressure (MPAP), C) pulmonary vascular resistance (PVR), D) 0th harmonic of impedance (Z_0), and E) higher-harmonic sum of impedance (Z_1+Z_2).

Figure 2. Graphical user interface for semi-automatic impedance computation. At center top is transient PW-Doppler data with an overlain computed envelope trace; at center bottom, the corresponding AUX1 (pressure) and ECG signals in yellow and blue, respectively.

Figure 03A

Figure 03B

Figure 3.

Typical impedance curves from A) Group I and B) Group II patients. Diagnoses: Patient 1, ASD, secundum, device closure; Patient 2, PDA coil embolization, minimal residual shunting; Patients 3-4, PDA coil embolization, no residual shunting; Patient 10, secondary PAH, ASD, secundum + A-P Collateral arteries; Patient 14, secondary PAH, Down's Syndrome, ASD device closure; Patient 31, primary PAH; Patient 41, secondary PAH, ASD, secundum.

Figure 4. Indexed Z_0 –vs– clinically measured indexed pulmonary vascular resistance (PVRI) for all subjects (63 patients; 109 reactivity conditions).

Figure 05A

Figure 05B

Figure 05C

Figure 5.

Z_1+Z_2 -vs- clinically measured value of A) PVS_I (indexed pulse pressure over stroke volume) B) PVR_I, and C) main pulmonary artery pressure, for all subjects (63 patients; 109 reactivity conditions).

Figure 6. Cumulative logistic regression of outcomes –vs– Z sum (black) and PVR (red) (n=25).

Table 1

Baseline patient characteristics (mean $\pm$ standard deviation) at control (Group 1) and with PAH (Group 2). p-values for significantly different quantities are shown in bold.

	Control (Group 1)	PAH (Group 2)	p
Demographics			
N	14	49	na
Age (Months)	58 $\pm$ 58	61 $\pm$ 60	0.8337
BSA (m ²)	0.76 $\pm$ 0.47	0.70 $\pm$ 0.38	0.6213
Female/Male	10/4	18/29	na
Hemodynamics			
Mean Pulmonary Artery Pressure (mmHg)	16.9 $\pm$ 4.7	37.3 $\pm$ 18.7	<0.0001
Cardiac Index (L/min m ²)	6.7 $\pm$ 6.4	4.1 $\pm$ 2.3	0.1524
Stroke Volume (mL)	54.5 $\pm$ 53	36.7 $\pm$ 27	0.2482
Pulse Pressure (mmHg)	17.6 $\pm$ 5.2	31.2 $\pm$ 12.8	<0.0001
Pulmonary Artery Resistance (mmHg/(L/min))	3.2 $\pm$ 2.0	12.8 $\pm$ 13.0	<0.0001
Pulmonary Artery Stiffness (PP/SV, mmHg/(L/min))	0.65 $\pm$ 0.55	1.41 $\pm$ 1.58	0.0069
Heart Rate (bpm)	105 $\pm$ 17.9	109 $\pm$ 28.0	0.5137
Derived Quantities (mmHg/(L/min))			
Z ₀	5.1 $\pm$ 3.3	14.3 $\pm$ 13.0	<0.0001
Z ₁ +Z ₂	3.6 $\pm$ 3.0	8.6 $\pm$ 6.8	0.0002
Z Sum	8.7 $\pm$ 6.2	22.9 $\pm$ 19.1	<0.0001

Table 2

Fit parameters for outcomes cumulative logistic regressions.

	Indexed Z sum	PVRI
Max (mmHg/(L/min))	34.3	17.7
Min (mmHg/(L/min))	5.8	2.0
Intercept 2 (p-value)	-7.3732 (0.0014)	-5.4909 (0.0004)
Intercept 3 (p-value)	-4.1947 (0.0009)	-3.1379 (0.0018)
Predictor (p-value)	0.2627 (0.0017)	0.4326 (0.0017)

Table 3

Means and standard deviations of each outcomes category.

Outcomes Category	n	Indexed Z sum	PVRI
1	15	10.23±3.52	4.67±2.30
2	6	17.95±9.36	6.97±4.11
3	4	30.13±4.52	14.27±3.58