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Noninvasive Assessment of Pulmonary Artery Flow and Resistance by Cardiac Magnetic Resonance in Congenital Heart Diseases With Unrestricted Left-to-Right Shunt

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OBJECTIVES To determine whether noninvasive assessment of pulmonary artery flow (Qp) by cardiac magnetic resonance (CMR) would predict pulmonary vascular resistance (PVR) in patients with congenital heart disease characterized by an unrestricted left-to-right shunt.

BACKGROUND Patients with an unrestricted left-to-right shunt who are at risk of obstructive pulmonary vascular disease require PVR evaluation preoperatively. CMR cardiac catheter (XMR) combines noninvasive measurement of Qp by phase contrast imaging with invasive pressure measurement to accurately determine the PVR.

METHODS Patients referred for clinical assessment of the PVR were included. The XMR was used to determine the PVR. The noninvasive parameters, Qp and left-to-right shunt (Qp/Qs), were compared with the PVR using univariate regression models.

RESULTS The XMR was undertaken in 26 patients (median age 0.87 years)—ventricular septal defect 46.2%, atrioventricular septal defect 42.3%. Mean aortic flow was 2.24 ± 0.59 l/min/m^2, and mean Qp was 6.25 ± 2.78 l/min/m^2. Mean Qp/Qs was 2.77 ± 1.02. Mean pulmonary artery pressure was 34.8 ± 10.9 mm Hg. Mean/median PVR was 5.5/3.0 Woods Units (WU)/m^2 (range 1.7 to 31.4 WU/m^2). The PVR was related to both Qp and Qp/Qs in an inverse exponential fashion by the univariate regression equations PVR = exp(2.53 − 0.20[Qp]) and PVR = exp(2.75 − 0.52[Qp/Qs]). Receiver-operator characteristic (ROC) analysis was used to determine cutoff values for Qp and Qp/Qs above which the PVR could be regarded as clinically acceptable. A Qp of ≥6.05 l/min/m^2 predicted a PVR of ≤3.5 WU/m^2 with sensitivity 72%, specificity 100%, and area under the ROC curve 0.90 ($p = 0.002$). A Qp/Qs of ≥2.5/1 predicted a PVR of ≤3.5 WU/m^2 with sensitivity 83%, specificity 100%, and area under the curve ROC 0.94 ($p < 0.001$).

CONCLUSIONS Measurement of Qp or left-to-right shunt noninvasively by CMR has potential to predict the PVR in patients with an unrestricted left-to-right shunt and could potentially determine operability without having to undertake invasive testing. (J Am Coll Cardiol Img 2009;2:1285–91)

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Repair of congenital heart disease resulting in significant left-to-right shunt, such as ventricular septal defect, is usually undertaken in infancy to prevent progressive pulmonary vascular disease (1,2). However, some will present at an advanced age (3) or have other comorbidity (e.g., lung disease of prematurity) predisposing them to pulmonary vascular disease (4,5). This results in increased perioperative mortality, and repair might be contra-indicated (6,7).

The oximetric (Fick) method of assessing pulmonary vascular resistance (PVR) is limited at high flow rates and oxygen saturations (8–10). We have previously shown that, by combining phase contrast cardiac magnetic resonance (CMR) (11)—which precisely quantifies blood flow patients with congenital heart disease (12)—with simultaneous invasive pressure measurements in a combined X-ray and CMR cardiac catheterization laboratory (XMR), PVR can be precisely determined, overcoming the limitations of the oximetric method. Additionally, this method eliminates the need to measure oxygen consumption and reduces radiation dose (13,14). The XMR is now our standard technique for PVR assessment in patients with congenital heart disease.

The PVR can be described by: PVR = trans-pulmonary gradient (TPG)/flow. In an unrestrictive cardiac defect, an inverse exponential relationship between pulmonary blood flow and PVR is expected (1). With the XMR technique, we hypothesize that PVR can be estimated from the degree of pulmonary blood flow or shunt magnitude. This might allow us to predict noninvasively whether PVR is within an acceptable range to proceed to surgery, avoiding catheterization. We tested this prospectively in children and adults with congenital heart disease who had been referred for PVR assessment.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CMR = cardiac magnetic resonance

MPAP = mean pulmonary artery pressure

MTPG = mean trans-pulmonary gradient

PVR = pulmonary vascular resistance

Qp = pulmonary flow

Qs = aortic flow

Qp/Qs = left-to-right shunt (pulmonary/systemic flow ratio)

ROC = receiver-operator characteristic

Rp/Rs = pulmonary/systemic resistance ratio

TPG = trans-pulmonary gradient

XMR = combined cardiac magnetic resonance and cardiac catheter

METHODS

Study population. Patients of all ages with congenital heart disease with a potentially unrestricted left-to-right shunt that had been referred for PVR assessment were included. Excluded were those with mechanical pulmonary obstruction (pulmonary artery band or bilateral branch stenosis), arrhythmia, and CMR contraindication. The local ethics committee approved the study and clinical use of the XMR for the assessment of PVR in adults and children. Informed consent was obtained from all patients or the parents/legal guardians of those under 16 years.

CMR catheterization. The CMR catheterization was performed as a single procedure in an XMR Suite with a 1.5-T Achieva MRI Scanner and a single plane Pulsera Cardiac X-Ray Unit (Philips Healthcare, Best, the Netherlands). Procedures were undertaken with general anesthesia and ventilation to normocarbia in 30% oxygen to overcome the potential effects of atelectasis (15). Pressures were measured (right atrial, left atrial or pulmonary artery wedge, pulmonary artery and systemic arterial pressures) with multipurpose catheters (Cordis Corporation, Miami, Florida) manipulated under fluoroscopic guidance. These were exchanged for nonbraided balloon-tipped angiographic catheters, which remain in situ for CMR scanning without risk of heating. Patients were transferred into the CMR scanner via an interconnecting table. Pulmonary artery and aortic phase contrast CMR flows were obtained from cross-sectional imaging planes with a free-breathing flow-sensitive segmented k-space fast field echo sequence (approximate echo time 3 ms, approximate repetition time 5 ms, matrix 128 × 256, field of view 250 to 350 mm, flip angle 15°, number of signal averages 3, retrospective gating, 40 phases). In patients with an arterial duct, pulmonary flow (Qp) was the sum of left and right branch flow. Simultaneous pressures were determined with the average of 5 consecutive cardiac cycles at the start of each flow sequence.

PVR and shunt assessment. Viewforum software (version 4.1, Philips Healthcare) with a semiautomatic border detection algorithm with manual correction was used to determine the stroke volume and cardiac output. The PVR was calculated by dividing the mean trans-pulmonary gradient (MTPG) by indexed Qp. Systemic vascular resistance was calculated with corresponding systemic parameters. Pulmonary to systemic resistance (Rp/Rs) and flow (Qp/Qs) ratios were calculated.

Statistical analysis. Continuous data are expressed as mean (±SD). Pearson correlation coefficient was used to compare measures of pulmonary resistance. Generalized linear models were used to assess the relationship between PVR and Qp/Qs, Qp, mean pulmonary artery pressure (MPAP), and MTPG. We used the Akaike information criterion (AIC) and the Schwarz Bayesian information criterion (BIC) to compare

linear (identity link) models with exponential models (log link). A statistical model is considered better-fitting if its AIC is smaller than the AIC of another. We calculated 95% confidence intervals (CIs) for the corresponding regression curves. Receiver-operator characteristic (ROC) analysis was used to determine cutoff values with sensitivity and specificity. The Student *t* test was used for the comparison between patients with and without Down syndrome. All statistical analyses were carried out with the statistical software packages SPSS (version 14.0, SPSS, Inc., Chicago, Illinois) and R version 2.6.016 (R Foundation for Statistical Computing, Vienna, Austria). The authors had full access to the data and take responsibility for its integrity.

RESULTS

Demographic data. Between 2002 and 2007, 34 patients met the inclusion criteria; 8 were excluded (7 with pulmonary artery band, 1 with branch pulmonary stenosis), leaving 26 patients

Table 1. Case Summary Illustrating Demographic Data, Diagnosis, and Physiological Variables

Patient #	Age (yrs)	BSA (m^2)	Diagnosis	Trisomy 21	MPAP (mm Hg)	TPG (mm Hg)	PA Flow ($l/min/m^2$)	PVR (WU/m^2)	Rp/Rs	Qp/Qs
1	1.8	0.46	AVSD Previous repair, residual VSD	Yes	46	27	5.85	4.6	0.24	2.3
2	35.2	1.40	AVSD	No	18	9	8.60	1.7	*	4.0
3	0.9	0.41	Peri-membranous VSD	No	45	19	8.05	2.3	0.12	3.2
4	42.4	1.47	VSD, ASD Restrictive lung disease	No	26	14	4.80	2.9	0.17	2.0
5	0.5	0.35	AVSD	Yes	31	21	6.30	3.3	0.19	3.7
6	0.8	0.30	VSD	No	34	21	10.00	2.1	0.14	2.7
7	1.1	0.42	AVSD	Yes	43	38	4.40	8.6	0.36	2.0
8	0.3	0.32	AVSD, oxygen dependency	Yes	25	20	5.12	3.9	0.26	2.1
9	0.8	0.39	AVSD	Yes	45	33	2.72	12.0	0.73	1.3
10	2.5	0.52	AVSD	Yes	46	27	12.90	2.1	0.16	3.7
11	0.5	0.28	AVSD, oxygen dependency	Yes	34	22	6.25	3.5	0.21	3.2
12	0.3	0.22	VSD Congenital diaphragmatic hernia, oxygen dependency	No	35	25	7.50	3.3	0.14	4.6
13	0.7	0.34	Residual ascending vein after repair of TAPVC	No	24	15	5.70	2.6	0.12	3.0
14	0.8	0.30	AVSD, large residual VSD after repair	Yes	30	16	3.93	4.1	0.32	1.8
15	17.3	1.33	Large patent arterial duct	Yes	52	42	1.65	25.4	0.95	1.1
16	15.9	1.25	Double inlet left ventricle with malposed great arteries; no previous procedures	No	35	21	7.00	3.0	0.12	4.4
17	1.8	0.52	Peri-membranous VSD Previous coarctation repair	No	34	13	6.71	1.9	0.12	2.4
18	4.0	0.60	Multiple muscular VSDs	No	25	15	4.50	3.3	0.16	3.0
19	0.9	0.40	Peri-membranous VSD	No	31	18	9.40	1.9	0.14	3.3
20	3.9	0.65	AVSD repair Residual primum ASD	Yes	13	8	2.80	2.9	0.12	1.8
21	1.8	0.45	Peri-membranous VSD	No	40	24	9.64	2.5	0.14	3.4
22	0.3	0.23	AVSD, airway compression, oxygen dependency	No	24	12	4.78	2.5	0.11	2.8
23	0.4	0.28	Peri-membranous VSD Pulmonary hypertension without heart failure	No	33	25	4.89	5.1	0.38	2.1
24	0.4	0.30	Peri-membranous VSD, oxygen dependency	Yes	32	21	7.42	2.8	0.20	4.1
25	2.2	0.45	Peri-membranous VSD	No	41	24	10.10	2.4	0.13	3.4
26	21.8	2.08	Large multiple VSDs	No	62	48	1.53	31.4	1.54	0.7

*Right atrial pressure not recorded.
ASD = atrial septal defect; AVSD = atrioventricular septal defect; BSA = body surface area; MPAP = mean pulmonary artery pressure; PA = pulmonary artery; PVR = pulmonary vascular resistance; Qp/Qs = left-to-right shunt; Rp/Rs = pulmonary to systemic resistance ratio; TAPVC = total anomalous pulmonary venous connection; TPG = trans-pulmonary gradient; VSD = ventricular septal defect.

included in the analysis. The majority were infants and children, median age 0.87 years (range 0.25 to 42.4 years). Primary diagnosis was ventricular septal defect in 12 patients (46.2%) and atrioventricular septal defect in 11 (42%). Eleven (42%) had Down syndrome. Demographic and physiological parameters are detailed in Table 1.

Resistance, flow, and pressure relationships. The measures of pulmonary resistance, PVR and Rp/Rs (0.29 ± 0.07), had a very strong linear relationship (Pearson's correlation coefficient = 0.98). Therefore resistance is expressed by PVR alone. The mean physiological findings were: aortic flow (Qs) 2.24 ± 0.59 l/min/m^2, Qp 6.25 ± 2.78 l/min/m^2, Qp/Qs 2.77 ± 1.02, MPAP 34.8 ± 10.9 mm Hg, and MTPG 22.23 ± 9.6 mm Hg. The mean/median PVR was 5.5/3.0 Woods Units (WU)/m^2 (range 1.7 to 31.4 WU/m^2). Exponential relationships were observed between the PVR and all parameters (Table 2)—Qp/Qs and Qp, inversely; MPAP and MTPG, directly. Regression curves with CIs are described for Qp (Fig. 1A) and Qp/Qs (Fig. 1B). From these we calculated univariate prediction formulae of: PVR = exp(2.53 − 0.20[Qp]) and PVR = exp(2.75 − 0.52[Qp/Qs]).

Regression curves can also be described for the MPAP and MTPG (Fig. 2); however, the scatter of data and CIs are much wider. A Qp/Qs in excess of 2/1 is considered to be an indication for surgical intervention (16). In our patient group, the maximum PVR in patients with a shunt in excess of this (i.e., Qp/Qs > 2.5/1) was 3.5 WU/m^2. Because the normal range for PVR (17) is 1.0 to 3.0 WU/m^2, a cutoff value of 3.5 WU/m^2 seemed clinically reasonable. A ROC analysis was used to determine preliminary cutoff values for flow and shunt to estimate the PVR of ≤3.5 WU/m^2. A Qp/Qs ≥ 2.5/1 determined those with a PVR of ≤3.5 WU/m^2 with sensitivity 83% (95% CI: 64% to 98%), specificity 100% (95% CI: 60% to 100%), and positive predictive value (PPV) 62% (95% CI: 41% to 97%), and area under the ROC curve 0.94 ($p < 0.001$) (Figs. 3A and 3B). A Qp ≥6.05 l/min/m^2 determined those with a PVR of ≤3.5 WU/m^2 with sensitivity 78% (95% CI: 52% to 93%), specificity 100% (95% CI: 60% to 100%), and PPV 54%

Table 2. Comparison of Predictors of PVR by Identity (Linear) and Log (Exponential) Links

Explanatory Variable (Link)	AIC	BIC	Linear Predictor	p Value
QP/QS (identity)	166	170	18.25 − 4.61(Qp/Qs)	<0.001
QP/QS (log)	45	49	exp(2.75 − 0.52[Qp/Qs])	<0.001
Qp_i (identity)	169	172	15.34 − 1.58(Qp)	<0.001
Qp_i (log)	43	47	exp(2.53 − 0.20[Qp])	<0.001
MPAP (identity)	165	169	−9.95 + 0.44(MPAP)	<0.001
MPAP (log)	50	53	exp(−0.21 + 0.04[MPAP])	<0.001
MTPG (identity)	152.5	156.2	−8.05 + 0.61(TPG)	<0.001
MTPG (log)	30.7	34.5	exp(−0.14 + 0.065[TPG])	<0.001

AIC = Akaike information criterion; BIC = Schwarz Bayesian information criterion; MTPG = mean trans-pulmonary gradient; Qp = indexed pulmonary blood flow; other abbreviations as in Table 1.

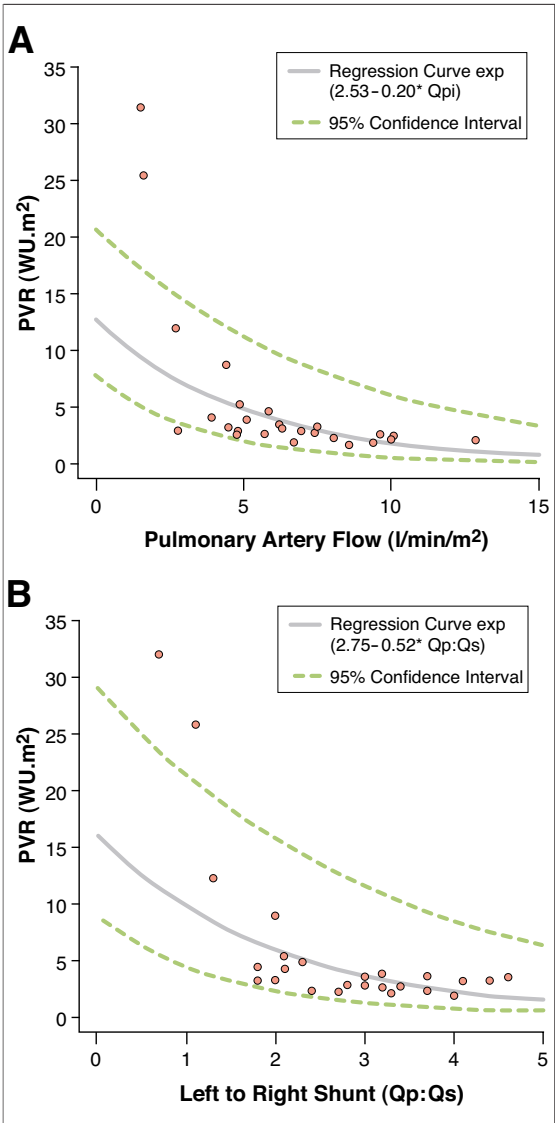

Figure 1. Relationship Between Resistance and Flow Parameters

Univariate regression models with 95% confidence intervals (CIs) are shown demonstrating the inverse exponential relationship between pulmonary vascular resistance (PVR) and **(A)** pulmonary artery flow (Qp) and **(B)** left-to-right shunt. Given the patient numbers, the CIs are quite wide; however, all patients with an elevated Qp or shunt in excess of 2.5/1 have a PVR ≤3.5 Woods Units (WU)/m^2. Of note, only a small number of patients had an elevated PVR.

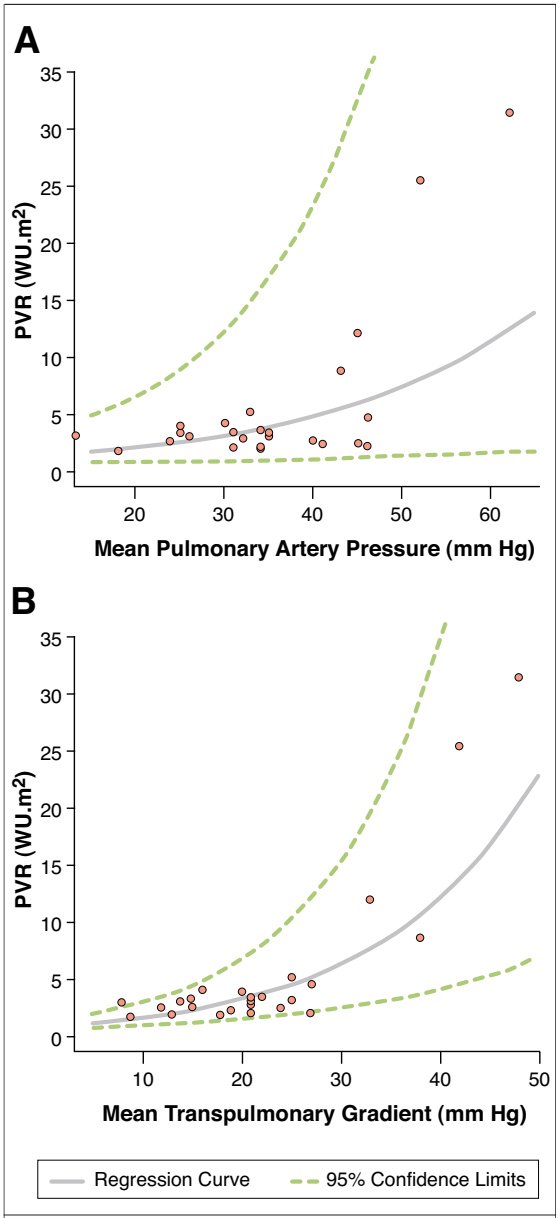

Figure 2. Relationship Between Resistance and Pressure Parameters

Univariate regression models with 95% CIs are shown demonstrating the direct exponential relationship between PVR and **(A)** mean pulmonary artery pressure (MPAP) (mm Hg) and **(B)** the mean transpulmonary gradient. The CIs for MPAP are very wide, and the MPAP can be in excess of 40 mm Hg with the PVR remaining within an acceptable range. This illustrates that pulmonary artery pressure measurements alone provide an incomplete picture, and clinical decisions should not be based on pressure parameters alone. Abbreviations as in Figure 1.

(95% CI: 34% to 74%), with the area under the ROC curve 0.90 ($p = 0.002$) (Figs. 3C and 3D).

To test the cutoff values derived from the ROC analysis, they were applied to the regression equations. The Qp performed well; a flow of 6.05 l/min/m^2 would predict a PVR of 3.59 WU/m^2. Left-to-right shunt performs less well, with a shunt of 2.5/1 predicting a PVR of 3.94 WU/m^2. With the same formula, a shunt of 2.8/1 would predict a PVR of 3.5 WU/m^2.

Down syndrome. Data for patients with and without Down syndrome are shown in Table 3. No difference in any of the physiological parameters was detected.

DISCUSSION

This study focuses on the small but important group of patients with a large left-to-right shunt with potentially elevated PVR. The CMR catheter gives us a unique opportunity to examine the relationship between PVR and a noninvasive measure of flow in these patients.

Relationship of PVR to flow and pressure. The PVR is determined by dividing the MTPG by Qp; therefore, PVR would be expected to be directly related to pressure and inversely related to flow in an exponential fashion. We were able to demonstrate this and generate univariate regression equations that were most powerful when based on flow followed by shunt. In contrast, MPAP was found to give a poor estimate of PVR with a wide scatter. Importantly, there were patients with a normal PVR who had an MPAP in excess of 40 mm Hg, indicating that indirect estimates of pulmonary artery pressure, although demonstrating pulmonary hypertension, might not accurately reflect the PVR.

Patients with Down syndrome and atrioventricular septal defect have been shown to be at greater risk of developing pulmonary vascular disease. This has been demonstrated in children <1 year of age, and early repair is recommended (18,19). We did not demonstrate any difference in the PVR of patients with or without Down syndrome and atrioventricular septal defect. This is likely to be a reflection of the sample size and the study population, because those who clearly have Eisenmengers syndrome are not referred for preoperative evaluation. There were 7 patients over 1 year old, including patients ages 15, 35, and 42 years. All had a PVR that would make them amenable for surgery. This suggests that, when considering patients with chronically elevated pulmonary blood flow, even with Down syndrome, a diagnosis of pulmonary vascular disease and inoperability cannot be assumed, and further investigation might be warranted.

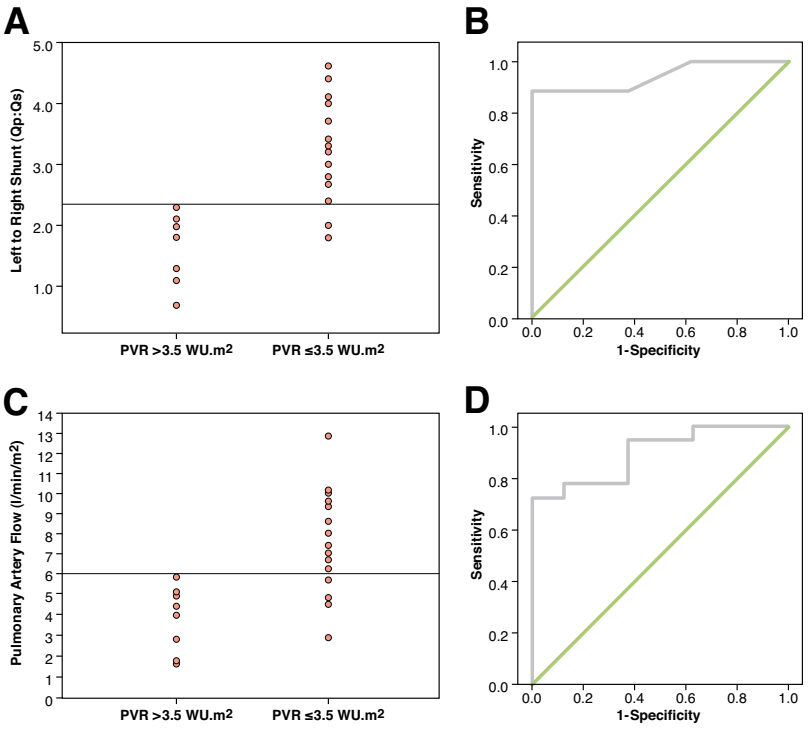

Figure 3. Cutoff Values for PVR

Scatterplot and corresponding receiver-operator characteristic (ROC) curves for shunt magnitude (left-to-right shunt [Qp/Qs]) **(A, B)** and Qp **(C, D)**. All patients with a PVR ≥3.5 WU/m^2 had a Qp/Qs <2.5/1 with an area under the ROC curve of 0.94 or a Qp <6.05 l/min/m^2, area under the ROC curve of 0.90. With future validation these values could be applied clinically, where those with a Qp of ≥6.05 l/min/m^2 or a shunt ≥2.5/1 measured by phase contrast cardiac magnetic resonance could proceed to surgery without invasive assessment. Abbreviations as in Figure 1.

Can we now estimate PVR from Qp? In our group only 4 patients had a PVR >6 WU/m^2. We cannot draw conclusions when PVR is elevated, but consideration of the predictive value of Qp might be justified in the group where PVR is borderline or normal. We found that we could estimate a PVR of ≤3.5 WU/m^2 if Qp was ≥6.05 l/min/m^2 or if Qp/Qs was ≥2.5/1 with high sensitivity. These figures do need to be viewed with caution, given the sample size, and this is reflected within the confidence limits; however, it does suggest that with further large studies a more robust model of PVR in this setting might be achievable.

Table 3. Comparison of Parameters for Down Syndrome Demonstrating Mean (±SD) and Probability Value

Parameters	Down Syndrome		
	Present	Not Present	p Value
n	11	15	—
Age (yrs)*	0.83 (0.33–16.97)	1.75 (0.25–42.18)	0.19
BSA (m^2)	0.48 (±0.30)	0.69 (±0.57)	0.24
MPAP (mm Hg)	36.1 (±11.5)	33.8 (±10.7)	0.61
MTPG (mm Hg)	25.0 (±9.2)	20.2 (±9.8)	0.22
Qp (l/min/m^2)	5.39 (±3.05)	6.88 (±2.50)	0.19
Qp/Qs	2.46 (±1.04)	3.00 (±0.98)	0.19
PVR (WU/m^2)	6.65 (±6.88)	4.60 (±7.46)	0.48
Rp/Rs	0.34 (±0.27)	0.25 (±0.38)	0.52

*Median (range).
Abbreviations as in Tables 1 and 2.

Study limitations. Patients with an unrestrictive ventricular or atrioventricular septal defect not repaired at the appropriate time are rare in the developed world, significantly limiting the number of patients we are able to include in this study and additionally limiting the conclusions that can be drawn from the statistical analysis. Because the majority had a borderline or normal PVR, we cannot comment on those with elevated PVR.

CONCLUSIONS

Our study describes the exponential relationship among PVR, Qp, and shunt in patients with an

unrestrictive cardiac defect. It is unique in that this is with a noninvasive measure of flow. We have suggested preliminary regression equations with which the PVR can be estimated from noninvasive Qp measurements alone, and these seem reasonable in patients with borderline or normal PVR. However, further studies are needed to validate this, especially with elevated PVR. Our results hold promise that, in future, prediction of PVR and the operability of patients with an unrestrictive cardiac defect might be able to be performed by PC-CMR flow alone.

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Key Words: cardiac magnetic resonance ■ congenital ■ heart defects ■ pediatrics ■ pulmonary vascular resistance ■ shunts.