Evaluation of pulmonary vascular resistance and vasoreactivity testing with oxygen in children with congenital heart disease and pulmonary arterial hypertension

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Estimating pulmonary vascular resistance index (PVRI) is of critical importance in determining the type of cardiac surgery, the decision to perform heart transplantation, the choice between surgery and drug treatment or combined modalities, even though it is not the only criterion for judgment (1, 2). A positive pulmonary vasoreactivity test (PVT) is accepted as an indicator of low perioperative risk and good prognosis. An acute positive response to PVT is reported in only 40% of patients (3). This test has been applied in many centers, following different protocols and different evaluation criteria. Most centers use nitric oxide (NO) or oxygen (O_2) inhalation, iloprost nebulization, or a combination thereof. A reduction by 20% of mean pulmonary artery pressure (PAPmean) or in the ratio of pulmonary resistance to systemic vascular resistance index (PVRI/SVRI) will define the patient as being a "responder" (4, 5). Reports on PVT performed with different drugs have been published recently (5-8). The aim of this study was to define the hemodynamic parameters of patients undergoing cardiac catheterization in our center for congenital heart disease and pulmonary arterial hypertension (PAH), characterize the efficacy of O_2 use in the PVT, and present the clinical findings in these patients with congenital intracardiac shunts. The present study was conducted on a cohort of 30 children diagnosed with PAH and congenital intracardiac shunts and placed under close surveillance at the pediatric cardiology department of the study center between October 2009 and November 2011 (Table 1). As described previously the criteria used for PAH definition and patient selection were considered as mean pulmonary arterial pressure (PAPmean) of ≥25 mm Hg, pulmonary capillary wedge pressure (PCWP) of ≤15 mm Hg, and PVR index (PVRI) of > 3 WU/m^2 at rest (6). The PVRI was calculated conventionally as the ratio of the difference between PAP and left atrial pressure or the pulmonary capillary wedge pressure to mean pulmonary flow, and the values were expressed as units per square meter. These parameters were also obtained before and after pulmonary vasoreactivity testing using 100% O_2 by simple face mask for 10 min when a high PAPmean was suspected. The PVT was considered positive if PAPmean or the PVRI/SVRI ratio exhibited a reduction by more than 20% (7, 8). Patients were evaluated in two groups according to PVT results, responders and non-responders (Table 2). The median age, height, weight, body surface area (BSA) and heart rate of the recruited patients were respectively 20.0 months, 76.5 cm, 9.2 kg, 0.41 m^2 and 112.0 beats/min. No significant difference was found in systolic PAP (PAPsystolic), SVRI, systemic flow (Qs) before and after PVT ($p>0.05$). The values of the other parameters before and after PVT were significantly different, with $p<0.05$. Average diastolic pulmonary arterial pressure (PAPdiastolic), PAPmean and median PVRI, PVRI/SVRI showed a significant decrease following PVT. Pulmonary blood flow (Qp) and its ratio to systemic blood flow (Qp/Qs) underwent a significant increase. The fall by more than 20% of PVRI and PVRI/SVRI was especially significant with regard to their PVT positivity (Table 3). No complication occurred in any patient during PVT testing with oxygen. No statistically significant difference in PVT-related measurements before and after the test was apparent within the non-responder patient group. All values in the responders, except Qs and SVRI ($p=0.541$ and $p=0.984$, respectively) were significantly different before and after the test ($p\leq0.05$). All of the significantly different parameters except the Qp/Qs ratio in the responders showed a reduction after the test, whereas Qp/Qs was increased ($p=0.019$). While 11 of 13 non-responders received medical treatment and the other two underwent full surgical correction, 14 of 17 responders were subjected to full surgical correction. Three patients of the recruited 30 patients were lost. Two of the deceased three patients had undergone surgery and one had had medical treat-

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Table 1. Clinical characteristics of patients

Variables	Min.	Max.	Median	IQR	Non-responders	Responders	PVT (–) vs. PVT (+)		
					Mean±1 S.D. Median (IQR)	Mean±1 S.D. Median (IQR)	t / Z *	*P*	*
Age, months	4.0	198.0	20.0	142.3	120 (197)	8 (7.8)	Z=2.481	0.012	†
Heart rate, bpm	64.0	150.0	112.0	42.5	94.0 (43.0)	124.0 (35.5)	Z=2.692	0.006	‡
Body weight, kg	3.7	75.0	9.2	30.7	27.0 (43.2)	6.8 (3.9)	Z=2.709	0.006	†
Height, cm	57.0	173.0	76.5	84.0	131.0 (94.1)	66.7 (15.3)	Z=2.626	0.008	†
BMI, kg/m^2	9.6	28.2	16.0	3.9	16.9 (4.4)	15.5 (3.6)	Z=0.847	0.415	†
Body Surface Area, m^2	0.22	1.80	0.41	0.92	0.98 (1.22)	0.33 (0.15)	Z=2.754	0.005	†

BMI - body mass index; PVT (+) responders; PVT(-) non-responders *t: Student's t-test; Z: Mann-Whitney U test
*† : PVT(–) > PVT(+) ‡: PVT(+) > PVT(-)

Table 2. Cardiac catheterization findings before and after the vasoreactivity test

Variables	Before-test	After-test	before vs.after	
	Mean±1 S.D. Median (IQR)	Mean±1 S.D. Median (IQR)	t / Z*	*P*
PAPsystolic, mm Hg	82.73±24.48	78.57±30.50	t=1.810	0.081
PAPdiastolic, mm Hg	33.50 (39.00)	24.00 (40.00)	Z=2.657	0.008
PAPmean, mm Hg	57.53±22.00	53.60±24.41	t=2.334	0.027
Qp, L/min/m^2	6.50 (9.04)	8.05 (9.83)	Z=2.202	0.028
Qs, L/min/m^2	3.50 (1.23)	3.35 (1.78)	Z=0.057	0.955
Qp/Qs	1.76 (2.25)	1.92 (3.00)	Z=2.059	0.039
PVRI, WU/m^2	5.75 (11.53)	3.89 (9.23)	Z=2.844	0.004
SVRI, WU/m^2	19.73±8.79	20.09±8.79	t=0.446	0.659
PVRI/SVRI	0.32 (0.44)	0.23 (0.53)	Z=2.357	0.018

*t: Paired sample t-test; Z - Wilcoxon signed-rank test; PAP - pulmonary arterial pressure; Qp - pulmonary flow; Qs - systemic flow; PVRI - pulmonary resistance index; SVRI - systemic resistance index

Table 3. Catheter angiography results before and after the vasoreactivity test, according to response

Variables	Non-responders				Responders			
	Pre-test	Post-test	Pre vs. Post		Pre-test	Post-test	Pre vs. Post	
	Mean±SD Median (IQR)	Mean±SD Median (IQR)	t / Z*	*P*	Mean±SD Median (IQR)	Mean±SD Median (IQR)	t / Z*	*P*
PAP (systolic), mm Hg	90.94±23.24	93.39±28.13	t=1.046	0.310	70.42±21.68	56.33±18.18	t=5.187	<0.001
PAP (diastolic), mm Hg	46.50 (43.25)	45.00 (45.75)	Z=0.986	0.324	23.50 (27.25)	13.00 (14.75)	Z=2.552	0.011
PAP (mean), mm Hg	64.11±22.58	63.89±24.59	t=0.118	0.907	47.67±17.64	38.17±14.24	t=3.946	0.002
Qp, L/min/m^2	5.60 (7.75)	5.75 (7.38)	Z=0.873	0.383	10.00 (8.25)	9.75 (20.18)	Z=1.961	0.050
Qs, L/min/m^2	3.45 (1.00)	3.09 (1.18)	Z=0.370	0.711	4.05 (1.00)	3.90 (2.45)	Z=0.612	0.541
Qp/Qs	1.23 (2.13)	1.45 (1.15)	Z=0.525	0.600	2.20 (2.24)	3.65 (3.88)	Z=2.353	0.019
PVRI, WU/m^2	11.50 (11.43)	9.70 (12.13)	Z=1.278	0.201	4.30 (8.11)	2.50 (3.59)	Z=2.824	0.005
SVRI, WU/m^2	21.22±9.95	21.81±9.41	t=0.474	0.642	17.49±6.46	17.51±7.40	t=0.020	0.984
PVRI/SVRI	0.43 (.045)	0.41 (0.48)	Z=1.199	0.231	0.20 (0.44)	0.11 (0.20)	Z=2.080	0.037

SD - standard deviation; IQR - interquartile range-Paired sample t-test; Z - Wilcoxon signed-rank test; PAP - pulmonary arterial pressure; Qp - pulmonary flow; Qs - systemic flow; PVRI - pulmonary vascular resistance index; SVRI - systemic vascular resistance index; PAP (mean) t=3.946, *P*=0.002; Rp Z=2.824, *P*=0.005; Rp/Rs Z=2.080, *P*=0.037

ment targeted towards pulmonary hypertension and heart failure. The PVT was negative in two deceased patients and positive in the remaining deceased patient.

Pulmonary arterial hypertension is a life-threatening disease which affects all age groups and increases both PAPmean and PVRI. A review of the relevant literature shows that studies on

pediatric PAH and PVT are very limited in scope, while results relative to adult patients are relatively more available (8-10). This creates certain difficulties with regard to the evaluation of PAH in children with congenital intracardiac shunts. Today, iNO or intravenous epoprostenol are recommended as agents that can be used in PVT testing in adult patients with PAH. The ideal agent for PVT testing should have a short half-life and pulmonary-selectivity. Today, there is, however, no evidence-based guideline that can be used in children with childhood PAH and congenital heart disease. Implementing PVT with O_2 in present study was followed by a significant decrease in PAP diastolic, PAP mean, PVRI and PVRI/SVRI. All values in the responders, except Qs and SVRI ($p=0.541$ and $p=0.984$, respectively) were significantly different before and after the test ($p\leq0.05$). Our findings indicate that O_2 can be used alone for PVT in congenital intracardiac shunts.

The correct characterization of PVRI and PVT in pediatric PAH with congenital intracardiac shunt is of critical importance in patient management. The present study suggests that O_2, being both easy to use and free of side effects as a pharmacological agent, maintains its value in PVT performed especially for children with PAH related to congenital heart disease with intracardiac shunt.

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