

## Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease

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**Background.** There has been a renewed interest in nitric oxide donor drugs, such as nitroglycerin, delivered by the inhalational route for treatment of pulmonary arterial hypertension (PAH). We investigated the acute effects of inhaled nitroglycerin on pulmonary and systemic haemodynamics in children with PAH associated with congenital heart disease.

**Methods.** Nineteen children with acyanotic congenital heart disease and a left to right shunt with severe PAH, undergoing routine diagnostic cardiac catheterization were included in this study. Systolic, diastolic and mean systemic as well as pulmonary artery pressures, right atrial pressure and pulmonary capillary wedge pressure (PCWP) were recorded and systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were calculated at room air, following 100% oxygen as well as after nitroglycerin inhalation in all patients.

**Results.** Systolic, diastolic and mean pulmonary artery pressure and PVRI decreased significantly, whereas heart rate, systolic, diastolic and mean systemic arterial pressure, PCWP and SVRI did not change significantly following 100% oxygen or inhalation of nitroglycerin.

**Conclusion.** Inhaled nitroglycerin significantly decreases systolic, diastolic and mean pulmonary artery pressure as well as PVRI without affecting systemic haemodynamics, and thus can be used as a therapeutic modality for acute reduction of PAH in children with congenital heart disease.

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Traditional therapeutic interventions for pulmonary arterial hypertension (PAH) include use of i.v. vasodilators<sup>1</sup> such as nitroglycerin or prostaglandins; however, lack of selectivity for pulmonary vasculature leads to systemic side-effects limiting their role in treatment of PAH.<sup>2</sup> Administering drugs by the inhalational route seems advantageous because large concentration of the drugs can be selectively administered to the pulmonary circulation, thus reducing their systemic side-effects. Commonly used therapy by the inhalational route is nitric oxide (iNO).<sup>3,4</sup> Administration of iNO requires special and expensive equipment which is not widely available. Apart from this, potential iNO toxicity<sup>5</sup> remains a concern, which stresses the importance of avoiding its indiscriminate use.<sup>6</sup>

Alternative modes of treatment for PAH include prostaglandin E<sub>1</sub>, prostaglandin I<sub>2</sub> (prostacyclin), phosphodiesterase inhibitors such as milrinone, sildenafil and zaprinast,

and nitric oxide donor drugs such as nitroglycerin and sodium nitroprusside.<sup>7</sup> There has been a renewed interest in the nitric oxide donor drugs such as nitroglycerin, administered via the inhalational route for the treatment of PAH. A previous study has demonstrated the efficacy of inhaled nitroglycerin in reducing PAH in adult patients undergoing mitral valve replacement surgery,<sup>8</sup> but data in children with PAH secondary to congenital heart disease and a left to right shunt are limited.<sup>9</sup>

We decided to study the acute effects of inhaled nitroglycerin on pulmonary and systemic haemodynamics in children with PAH associated with acyanotic congenital heart disease with left to right shunt. The study was conducted during routine diagnostic cardiac catheterization in these children so that the effects of anaesthetic drugs, high inspired oxygen concentration, controlled ventilation and surgical repair could be avoided.

## Methods

After approval from the Ethics Committee of the institute and written informed consent from the parents, 19 consecutive children below the age of 12 yr, suffering from acyanotic congenital heart disease and left to right shunt with severe PAH [defined by mean pulmonary arterial (PA) pressure >50 mm Hg] undergoing routine diagnostic cardiac catheterization were included in the study. Patients with associated mitral valve disease, left heart obstructive lesion, severe left ventricular (LV) dysfunction, mild to moderate PAH, severe pulmonary or tricuspid valvular regurgitation, trisomy 21, Eisenmenger syndrome and those already receiving vasodilator treatment were excluded.

Oral trichlofos and i.m. meperidine with promethazine was given for sedation and right heart catheterization was carried out under local anaesthesia using pulmonary artery catheter. During cardiac catheterization study, baseline heart rate, systolic, diastolic and mean systemic as well as PA pressures, right atrial pressure and pulmonary capillary wedge pressure (PCWP) were recorded for all the patients, while breathing room air. Haemodynamic data were obtained using MAC-LAB 6H, cath lab haemodynamic monitoring system (1996 Marquette Medical Systems Inc., now a part of GE Healthcare worldwide), which provided the electronic mean of all haemodynamic variables. Blood samples were collected from superior vena cava, pulmonary artery (PA) and from femoral artery in heparinized syringes to measure saturation and partial pressure of oxygen representing systemic venous, pulmonary arterial and systemic arterial blood, respectively. As pulmonary veins were not entered during cardiac catheterization study, pulmonary venous saturation was substituted with systemic arterial saturation as there was no right to left shunt in any of the patients.<sup>10</sup> Oxygen consumption ( $\text{VO}_2$ ) was obtained from a standard nomogram routinely used in the cardiac catheterization lab of our institute, based on age, sex and heart rate of the child.<sup>11</sup> Pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI) and pulmonary to systemic blood flow ratio ( $Q_p/Q_s$ ) was calculated using standard formulas based on Fick's principle. All patients received 100% oxygen for 10 min, as a part of routine cardiac catheterization study protocol; 100% oxygen was administered using a face mask and Jackson Rees system attached to Datex Ohmeda Excel 210 anaesthesia machine (Datex-Ohmeda Inc., MA, USA). Haemodynamic and oximetric data were recorded again in a similar manner as described above. Fifteen minutes after discontinuing the oxygen (time allowed for haemodynamic variables to return to baseline), with children breathing room air, nebulized nitroglycerin was given in the dose of  $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$  for a period of 10 min (i.e.  $25 \mu\text{g kg}^{-1}$  of nitroglycerin was needed during the 10 min period). Original nitroglycerin drug ( $5 \text{ mg ml}^{-1}$ ) was dissolved in normal saline (up to 20 ml) to make a solution of  $250 \mu\text{g ml}^{-1}$  of drug. The required amount of nitroglycerin

was taken with the help of 1 ml syringe bearing marks for each 0.1 ml, so that  $25 \mu\text{g}$  of drug could be taken precisely, then 0.1 ml of drug solution was taken for every 1 kg body weight of patient (i.e. 0.5 ml for a 5 kg child) and made up to 3 ml with normal saline and nebulized with the help of CIRBUS Jet Nebulizer (Inter Surgical Respiratory systems, Berkshire, UK) using  $8 \text{ litre min}^{-1}$  of medical air, delivering the particles from aqueous solution at a rate of  $0.25\text{--}0.3 \text{ ml min}^{-1}$ . After completion of nebulization, a complete set of haemodynamic and oximetric data were recorded again, as described for the baseline data.

## Statistical analysis

Patient characteristics were expressed as median (range), while haemodynamic variables were expressed as mean (SD). For the statistical analysis ANOVA with repeated measures using statistical package SAS 8.0 was used. Pairwise comparisons were made between baseline, post 100% oxygen and post nitroglycerin values of the haemodynamic variables that showed significant difference with ANOVA. *P*-value of <0.05 was considered as statistically significant.

## Results

Nineteen consecutive children with unrestricted ventricular septal defect and left to right shunt with severe PAH, undergoing routine diagnostic cardiac catheterization study in a catheterization lab were included in the study. Clinical characteristics of the patients are shown in Table 1. Haemodynamic variables, both measured and calculated, expressed as mean (SD) are shown in Table 2. Heart rate, systolic, diastolic and mean systemic arterial pressure, PCWP and SVRI did not show any significant change following 100% oxygen administration as well as after nitroglycerin inhalation. One patient (No. 17 in Tables 3 and 4) had moderate left ventricular dysfunction pre-procedure, while left ventricular contractility was normal in all other patients. No adverse effects such as an increase in heart rate, hypotension or a decrease in systemic arterial oxygen saturation ( $\text{SaO}_2$ ) were seen in any of the patients after nitroglycerin inhalation.

Systolic pulmonary artery pressure significantly decreased from 94.6 (13.8) mm Hg to 85.0 (14.4) mm Hg

**Table 1** Patient characteristics. Data are expressed as median (range) or absolute numbers. BSA, body surface area; Hb, haemoglobin; VSD, ventricular septal defect

Age (months)	33 (8–54)
M:F	12:7
Weight (kg)	11 (5–17)
Height (cm)	89(64–115)
BSA ( $\text{m}^2$ )	0.52 (0.29–0.75)
Hb ( $\text{gm dl}^{-1}$ )	11.2 (10–14)
Type of VSD	
Perimembranous	15
Muscular	2
Multiple muscular	1
Perimembranous with muscular	1

**Table 2** Systemic and pulmonary haemodynamic variables expressed as mean (SD). HR, heart rate; NS, not significant; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index;  $Qp/Qs$ , ratio of pulmonary to systemic blood flow;  $Sa_{O_2}$ , systemic arterial oxygen saturation; SAP, DAP and MAP, systolic, diastolic and mean systemic arterial pressure, respectively; S\_PAP, D\_PAP and M\_PAP, systolic, diastolic and mean pulmonary artery pressure, respectively; SVRI, systemic vascular resistance index. \*Paired comparison between baseline and values after 100% oxygen; \*\*between values after 100% oxygen and after nitroglycerin; †between baseline and values after nitroglycerin

	Baseline (a)	Post 100% oxygen (b)	Post nitroglycerin (c)	ANOVA	Paired comparisons (a–b)* (b–c)**(a–c)†
HR (beats min <sup>-1</sup> )	140.9 (15.9)	136.3 (17.2)	137.7 (16.2)	NS	–
SAP (mm Hg)	97.6 (17.2)	97.3 (17.6)	97.1 (17.1)	NS	–
DAP (mm Hg)	65.4 (10.7)	65.2 (10.3)	63.8 (11.8)	NS	–
MAP (mm Hg)	76.3 (12.2)	75.8 (12.8)	75.8 (12.3)	NS	–
S_PAP (mm Hg)	94.6 (13.8)	85.0 (14.4)	75.5 (13.6)	<0.001	(<0.001) (<0.001) (<0.001)
D_PAP (mm Hg)	59.3 (9.4)	50.5 (7.9)	44.3 (10.0)	<0.001	(<0.001) (<0.001) (<0.001)
M_PAP (mm Hg)	71.9 (9.5)	63.2 (8.1)	55.1 (8.9)	<0.001	(<0.001) (<0.001) (<0.001)
PCWP (mm Hg)	9.1 (3.2)	8.8 (2.9)	8.6 (3.2)	NS	–
SVRI (units m <sup>2</sup> )	10.3 (2.8)	10.2 (3.0)	10.1 (3.3)	NS	–
PVRI (units m <sup>2</sup> )	5.4 (2.0)	2.1 (0.9)	1.2 (0.6)	<0.001	(<0.001) (<0.001) (<0.001)
$Qp/Qs$	1.79 (0.55)	3.44 (1.09)	4.53 (1.64)	<0.001	(<0.001) (<0.001) (<0.001)
$Sa_{O_2}$	92.8 (5.2)	97.6 (4.5)	97.4 (4.1)	<0.001	(<0.001) (NS) (<0.001)

**Table 3** Pulmonary haemodynamic variables in individual patients. (a) Baseline, (b) following 100% oxygen and (c) after nitroglycerin inhalation. PAP, pulmonary artery pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg); PVRI, pulmonary vascular resistance index (units m<sup>2</sup>);  $Qp/Qs$ , ratio of pulmonary to systemic blood flow

No.	Age in months	Systolic/diastolic (mean) PAP			PVRI			PCWP			$Qp/Qs$		
		(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Group I—patients responding to both 100% oxygen and nitroglycerin (n=8)													
1	48	96/56 (78)	81/43 (65)	67/55 (56)	7.62	2.1	0.43	11	11	11	1.79	4.19	5.0
2	24	88/60 (69)	75/52 (60)	65/40 (48)	5.54	1.39	0.84	10	9	9	1.60	2.33	2.80
3	8	70/52 (58)	61/44 (50)	55/34 (41)	2.14	1.1	1.01	8	7	7	2.57	2.50	3.0
4	48	96/62 (73)	84/50 (61)	74/42 (53)	2.8	1.43	0.78	9	8	9	2.60	4.33	5.99
5	30	89/63 (72)	78/52 (61)	68/54 (59)	5.62	1.84	1.3	6	7	6	1.30	3.25	3.25
6	9	71/54 (60)	61/44 (50)	50/38 (42)	2.7	1.12	0.69	8	7	7	2.25	4.0	4.0
7	54	96/62 (73)	84/50 (61)	74/42 (53)	5.92	1.99	1.27	9	8	7	1.80	3.50	4.99
8	30	91/67 (75)	87/54 (65)	68/50 (56)	5.9	1.49	0.86	6	7	6	1.40	4.66	6.98
Group II—patients responding to nitroglycerin but not to 100% oxygen (n=8)													
9	24	97/60 (75)	92/48 (65)	90/47 (64)	5.71	1.51	1.12	7	11	11	1.33	3.33	3.20
10	9	91/51 (63)	77/46 (59)	74/30 (45)	2.72	1.5	0.77	13	11	12	1.86	1.83	2.50
11	36	98/64 (75)	82/57 (65)	70/44 (53)	4.66	1.69	1.05	4	5	5	2.14	5.0	5.0
12	42	100/68 (79)	94/62 (73)	85/50 (62)	7.23	3.59	1.52	9	8	8	1.18	2.0	3.99
13	42	120/70 (87)	108/60 (76)	98/58 (71)	5.67	1.65	1.09	10	9	6	1.67	4.33	6.94
14	12	96/51 (66)	85/46 (59)	74/35 (48)	3.03	1.57	0.89	13	11	12	1.86	2.75	3.32
15	36	100/64 (76)	86/57 (67)	72/54 (60)	6.25	1.78	1.06	4	5	5	1.67	4.66	6.99
16	33	100/72 (81)	92/61 (71)	82/49 (60)	8.07	3.54	2.05	8	7	7	1.33	2.66	4.24
Group III—patients not responding to either 100% oxygen or nitroglycerin (n=3)													
17	8	70/40 (50)	67/32 (48)	71/21 (44)	8.75	3.59	3.22	17	18	18	1.06	2.43	2.34
18	51	110/40 (70)	113/41 (68)	100/40 (60)	4.46	3.56	1.81	11	10	10	3.17	5.25	7.30
19	54	118/71 (87)	108/60 (76)	97/58 (71)	7.13	3.49	1.63	10	8	7	1.36	2.33	4.33

following 100% oxygen administration ( $P<0.001$ ) and decreased significantly to 75.5 (13.6) mm Hg after nitroglycerin inhalation ( $P<0.001$ ). Similarly diastolic and mean PA pressures significantly decreased from baseline of 59.3 (9.4) and 71.9 (9.5) mm Hg to 50.5 (7.9) and 63.2 (8.1) mm Hg, respectively following 100% oxygen administration ( $P<0.001$ ) and decreased significantly further to 44.3 (10.0) and 55.1 (8.9) mm Hg after nitroglycerin inhalation ( $P<0.001$ ). PVRI decreased significantly from a baseline of 5.4 (2.0) Wood units m<sup>2</sup> to 2.1 (0.9) Wood units m<sup>2</sup> ( $P<0.001$ ) following 100% oxygen administration and significantly decreased still further to 1.2 (0.6) Wood units m<sup>2</sup> after nitroglycerin inhalation ( $P<0.001$ ).

Pulmonary to systemic blood flow ratio ( $Qp/Qs$ ) increased significantly from baseline of 1.79 (0.55) to 3.44 (1.09) following 100% oxygen administration ( $P<0.001$ ) and significantly increased further to 4.53 (1.64) after nitroglycerin inhalation ( $P<0.001$ ).  $Sa_{O_2}$  increased significantly from a baseline of 92.8 (5.2) to 97.6 (4.5) following 100% oxygen administration ( $P<0.001$ ), increase was also significant from the baseline to 97.4 (4.1) after nitroglycerin inhalation ( $P<0.001$ ).

Based on a positive response to 100% oxygen administration or to nitroglycerin inhalation (defined by a greater than 15% decrease in mean pulmonary artery pressure to mean systemic arterial pressure ratio),<sup>12</sup> patients were

**Table 4** Systemic haemodynamic variables in individual patients in the three groups. (a) Baseline, (b) following 100% oxygen administration and (c) after nitroglycerin inhalation. AP, systemic arterial pressure (in mm Hg); HR, heart rate (beats min<sup>-1</sup>); SVRI, systemic vascular resistance index (units m<sup>2</sup>)

No.	Systolic/diastolic (mean) AP			SVRI			HR		
	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Group I—patients responding to both 100% oxygen and nitroglycerin ( <i>n</i> =8)									
1	89/73 (77)	89/61 (76)	105/65 (80)	14.76	13.7	14.62	137	120	137
2	92/65 (74)	95/66 (76)	95/65 (75)	10.45	9.5	9.28	136	132	138
3	69/50 (56)	70/52 (58)	68/50 (56)	7.91	9.24	9.34	165	162	163
4	98/64 (75)	96/65 (74)	94/65 (75)	8.18	8.23	7.62	135	121	124
5	98/73 (81)	102/74 (83)	100/72 (81)	8.6	8.83	8.49	138	132	131
6	72/48 (56)	69/50 (56)	71/50 (57)	8.0	8.29	7.39	161	159	158
7	115/75 (88)	114/75 (88)	112/75 (87)	13.97	11.09	11.58	130	121	124
8	99/72 (81)	103/74 (84)	101/73 (82)	9.1	10.42	9.39	138	136	132
Group II—patients responding to nitroglycerin but not to 100% oxygen ( <i>n</i> =8)									
9	92/60 (73)	93/60 (70)	108/67 (87)	7.84	11.51	12.54	133	134	135
10	92/57 (68)	86/57 (63)	89/52 (68)	6.27	5.05	4.98	158	146	142
11	108/70 (83)	105/68 (80)	102/65 (77)	10.86	10.68	10.13	130	132	135
12	110/70 (83)	112/72 (85)	106/70 (82)	9.74	9.22	8.84	129	130	126
13	120/78 (92)	118/80 (93)	116/77 (90)	10.72	9.26	9.79	141	138	142
14	98/57 (71)	94/55 (68)	92/54 (67)	6.86	5.75	5.12	154	146	147
15	110/72 (85)	108/70 (83)	107/70 (82)	11.52	10.62	10.57	128	130	132
16	104/73 (83)	106/72 (83)	102/69 (80)	11.64	11.65	11.86	143	138	137
Group III—patients not responding to either 100% oxygen or nitroglycerin ( <i>n</i> =3)									
17	57/40 (48)	55/42 (46)	51/30 (44)	10.44	10.76	11.01	180	182	180
18	110/68 (82)	113/70 (84)	110/67 (81)	17.53	19.71	19.89	114	107	106
19	122/78 (93)	120/76 (91)	116/76 (89)	11.12	10.15	9.28	128	124	128

divided into three groups; those responding both to 100% oxygen and nitroglycerin inhalation (8 patients, Group I), those not responding to 100% oxygen but responding to nitroglycerin inhalation (8 patients, Group II), and those neither responding to 100% oxygen nor to nitroglycerin inhalation (3 patients, Group III). There was no patient who responded to 100% oxygen administration and did not respond to nitroglycerin inhalation. Tables 3 and 4 show pulmonary and systemic haemodynamic data respectively of all the patients in these three groups.

## Discussion

The acute effects of nitroglycerin inhalation on pulmonary circulation, in 19 children with congenital heart disease and severe PAH in our study, demonstrate a significant decrease in systolic, diastolic and mean PA pressure as well as PVRI, without any significant change in heart rate or systemic arterial pressure. Our findings are similar to those by Yurtseven and colleagues<sup>8</sup> in adult patients with PAH undergoing mitral valve replacement surgery. A significant increase in  $Q_p/Q_s$  following 100% oxygen and nitroglycerin inhalation, in our study, was a result of the decrease in PVRI with no significant effect on SVRI.  $Sa_{O_2}$  after nitroglycerin inhalation in our study was significantly higher than baseline values and was comparable with values obtained following 100% oxygen administration, indicating the advantage of the inhalational route of administration, in which vasodilator drug is preferentially distributed to well-ventilated lung areas, effecting a redistribution of blood flow from non-ventilated regions to these areas,<sup>13</sup> thereby reducing

the ventilation-perfusion mismatch and intrapulmonary shunt fraction.

We have excluded patients with mild and moderate PAH and included only the patients with severe PAH (mean PA pressure >50 mm Hg) secondary to unrestricted ventricular septal defect and a left to right shunt, which might have contributed to relatively high baseline PA pressures in our study. Administration of meperidine may theoretically increase PA pressure if given as i.v. bolus, however, pre-medication with i.m. meperidine in combination with promethazine is widely used for sedation of children during cardiac catheterization.<sup>14</sup> Studies demonstrating the effects of meperidine and promethazine on pulmonary and systemic circulation have mainly used animal data and have shown reduction in mean PA pressure along with an increase in PVR following i.v. meperidine alone or in combination with promethazine and chlorpromazine.<sup>15</sup> There are no data regarding the effects of meperidine on pulmonary haemodynamics in children after i.m. administration. Moreover, the administration of alternate drugs for sedation of children during cardiac catheterization is also not without any confounding effects on various haemodynamic variables. Propofol can result in clinically important changes in cardiac shunt direction and flow.<sup>16</sup> Ketamine has been shown to increase  $VO_2$ , heart rate, cardiac output and PA pressure and can confuse interpretation of cardiac catheterization data especially if  $VO_2$  is assumed (derived from standard nomogram) and not actually measured,<sup>17</sup> as was the case in our study. Considering all of the above issues, the sedation protocol formulated for children at our institute's cardiac catheterization lab is oral trichlofos



with i.m. meperidine and promethazine, and the same was used in our study.

A decrease in PVRI after 100% oxygen administration was very marked in Groups I and II but was not accompanied by a similar decrease in mean PA pressure (Table 3). This is because passive distension and recruitment of pulmonary arteries or an increase in cardiac index can affect the calculation of pulmonary vascular resistance without necessarily indicating a decrease in vascular tone.<sup>12</sup> Similarly assumed  $\text{VO}_2$  values can also produce inaccurate calculations of PVRI and SVRI.<sup>10</sup> Reduction in systemic blood pressure can be associated with a decrease in pulmonary artery pressure without necessarily influencing the pulmonary vascular bed directly. We therefore defined a positive response to 100% oxygen administration or nitroglycerin inhalation as >15% decrease in mean pulmonary artery pressure to mean systemic arterial pressure ratio<sup>12</sup> and without a significant change in systemic arterial pressure. According to this definition we found positive response to nitroglycerin inhalation in 16 (Groups I and II) of a total of 19 patients. Of these 16 patients who had positive response to nitroglycerin inhalation, 8 patients had negative response to a prior 100% oxygen administration (Group II), whereas all the patients with positive response to 100% oxygen responded to nitroglycerin inhalation, indicating that nitroglycerin inhalation is superior to 100% oxygen as pulmonary vasodilator. The negative response was not an all or none phenomenon, other patients also responded but did not cross the limit of 15% reduction in mean pulmonary artery pressure to mean systemic arterial pressure ratio.

Because of selective pulmonary vasodilatory effect, iNO is considered a standard therapy for treatment of PAH in various adult and paediatric cardiac patients<sup>3,4</sup> but its administration requires a special and expensive equipment which is not widely available. Secondly, it has a number of potential toxic effects on various organ systems of the body<sup>5</sup> including the formation of  $\text{NO}_2$  and free radicals,<sup>18</sup> direct pulmonary cytotoxicity in the form of immune pulmonary fibrosis reaction (bronchiolitis fibrosa obliterans), the risk of methaemoglobinaemia especially in patients with inadequate methaemoglobin reductase activity, pulmonary oedema by increasing left ventricular filling pressure in patients with preexisting LV dysfunction,<sup>19</sup> rebound pulmonary hypertension and arterial desaturation after withdrawal of iNO, and modification of platelet aggregation and agglutination in a non-dose-dependent manner. The unresolved issue of possible side-effects of iNO therapy necessitate the search for alternative inhaled drug therapies for the treatment of PAH, some of which are prostaglandin  $\text{I}_2$ ,<sup>20-22</sup> iloprost, prostaglandin  $\text{E}_1$ , phosphodiesterase inhibitors such as milrinone,<sup>21</sup> sildenafil<sup>23</sup> and zaprinast, and nitric oxide donor drugs such as nitroglycerin and sodium nitroprusside.<sup>24,25</sup>

Inhaled prostacyclin has been found to reduce pulmonary artery pressure and PVR as well as improve the systemic

haemodynamics in patients with mitral stenosis and PAH undergoing mitral valve replacement surgery,<sup>20</sup> and in new born with unobstructed total anomalous pulmonary venous connection with PAH after surgical correction under cardiopulmonary bypass.<sup>22</sup> Inhaled prostacyclin combined with inhaled milrinone produces prolonged reduction of PVR and increases stroke volume without affecting mean systemic pressure and SVR.<sup>21</sup> The disadvantages of administering prostacyclin and prostaglandin  $\text{E}_1$  are their high cost, local toxicity of commercial preparations of  $\text{PGI}_2$  (glycine buffer, pH 10.5) and  $\text{PGE}_1$  (ethanol-saline), limited period of stability of the solution once dissolved and the need for protection from light to avoid photodegradation.

Efficiency of various aerosolized nitric oxide donor drugs (including nitroglycerin and sodium nitroprusside) in selectively reducing PA pressure and PVR has been demonstrated in various animal studies,<sup>24,25</sup> but human studies on the role of inhaled nitric oxide donor drugs in the treatment of PAH are limited.<sup>8,9</sup>

Nitroglycerin inhalation is less expensive and easy to administer as compared with iNO and prostacyclin inhalation. Nitroglycerin is metabolized to nitric oxide, which produces smooth muscle relaxation in the vascular endothelial cells, thereby causing vasodilatation. Nitroglycerin is a safe drug and does not produce any toxicity in contrast with iNO. The suggested precautions are to keep the dose below  $5 \text{ mg kg}^{-1} \text{ day}^{-1}$  to prevent methaemoglobinaemia<sup>26</sup> and to remember the possibility of increased peripheral air flow resistance, with inhaled nitroglycerin therapy.<sup>27</sup>

In our study, inhalation of nitroglycerin in normal saline was done with the help of CIRRUS jet nebulizer. At a driving gas flow of  $8 \text{ litre min}^{-1}$ , it produces particles with a mass mean diameter of  $2.75 \mu\text{m}$ , which are suitable for alveolar deposition.<sup>28,29</sup> Targeting efficiency to alveolar region can be increased up to 96% with breath-holding manoeuvre during drug inhalation.<sup>30</sup> Although breath holding could not be applied in small children in our study, it can be used to improve the drug delivery in older children and adults with PAH, who can follow the instructions.

PA pressure and PVR is reduced by 100% oxygen, which is routinely used during diagnostic cardiac catheterization, after baseline study to determine the decrease in PA pressure and PVR, and to establish operability/non-operability of a particular congenital heart defect. After determining the extent of decrease in systolic, diastolic and mean PA pressure as well as in PVRI following 100% oxygen, we administered nitroglycerin by the inhalational route, which further decreased systolic, diastolic and mean PA pressure and PVRI significantly over the post 100% oxygen values, but without any significant effect on systolic, diastolic and mean systemic arterial pressure or on SVRI.

Our study was carried out in a cardiac catheterization lab, where the underlying congenital heart defect was not corrected, and the haemodynamic parameters were not affected by surgical repair of congenital heart defect, anaesthetic

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With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

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Sync your system to PACER to automate legal marketing.