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Inhaled nitric oxide differentiates pulmonary vasospasm from vascular obstruction after surgery for congenital heart disease

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Abstract *Objective:* To evaluate whether a trial of inhaled nitric oxide (NO) differentiates reversible pulmonary vasoconstriction from fixed anatomic obstruction to pulmonary blood flow after surgery for congenital heart disease in patients at risk for pulmonary hypertension.
Design: Prospective cohort study.
Setting: Tertiary care children's hospital.
Patients: 15 neonate and infants with elevated pulmonary artery or right ventricular pressure or with clinical signs suggestive of high pulmonary vascular resistance in the early postoperative period following repair of congenital heart disease.
Intervention: 30-min trial of 40 ppm inhaled NO.
Results: 5 patients responded to inhaled NO, 2 patients were weaned from extracorporeal support with NO. Four were maintained on continuous inhaled NO for 3 to 5 days. All the responders survived. Ten patients did not respond to NO. An important anatomic obstruction was found with echocardiography or angiography in all 10 patients. Reintervention was performed in 6/10 (4 stent placement, 1 balloon angioplasty of pulmonary arteries and 1 revision of systemic to pulmonary shunt). Six of the nonresponders died.
Conclusion: A trial of inhaled NO after cardiac surgery in neonates and infants may be useful to differentiate reversible pulmonary vasoconstriction from fixed anatomic obstruction and may provide useful information if temporary support with extracorporeal membrane oxygenation is considered. Failure to respond to inhaled NO should prompt further investigations to rule out a residual obstruction.

Key words Inhaled NO · Cardiac critical care

Introduction

Pulmonary hypertension after surgery for congenital heart disease may pose diagnostic and management dilemmas and complicate considerably the early postoperative course [1–4]. Pulmonary hypertension may be episodic or sustained in the immediate postoperative period with resolution once recovery from cardiopulmonary bypass is complete. Certain patients, particularly neonates with obstructed anomalous pulmonary venous drainage, truncus arteriosus and hypoplastic left heart syndrome, have marked pulmonary vascular lability postoperatively. Even with invasive monitoring it may be difficult to differentiate pulmonary vascular lability from residual obstruction at the surgical anastomosis. Indeed, the measurement of elevated pulmonary artery pressures from a proximally inserted catheter or the noninvasive recognition of an elevated right ventricular pressure by Doppler interrogation may represent distal pulmonary artery obstruction, amenable to treatment by surgical or interventional catheterisation techniques or pulmonary vasospasm. It is especially impor-

tant to resolve vasospasm from fixed obstruction to pulmonary blood flow when temporary support of the circulation with extracorporeal membrane oxygenation (ECMO) is considered [5, 6].

Therefore, we investigated the value of a trial of inhaled nitric oxide (NO) to facilitate differentiation between pulmonary vasospasm and fixed obstruction to pulmonary blood flow in postoperative patients with clinical or haemodynamic signs of an elevated pulmonary vascular resistance after congenital heart surgery.

Materials and methods

We enrolled consecutive patients over a 14-months period with echocardiographic or directly measured pulmonary hypertension (pulmonary artery pressure > half the systemic pressure) despite conventional treatment including high inspired oxygen, hyperventilation or alkalinisation, inotropic support, intravenous vasodilators, deep sedation and muscle paralysis. All patients underwent prior echocardiographic study to exclude the presence of residual shunts and proximal right ventricular outflow tract obstruction.

Inhaled NO (500 ppm, Matheson gases, Ontario, Canada) was administered at a dose of 40 ppm through the inspiratory limb of the ventilator (Siemens Servo 900 C) for 30 min. NO levels were measured with an electrochemical analyser (EIT Sensorstik, Extron, Penna., USA) [7]. NO_2 and methaemoglobin levels were measured daily if NO was delivered for $\geq$ 30 min [8–10]. Pulmonary or right ventricular and systemic arterial pressures and oxygen saturation were recorded before and after 30 min of inhaled NO in all except 2 patients receiving ECMO.

A positive response to inhaled NO was defined as a 20% decrease in the ratio between right ventricular or pulmonary arterial pressure to systemic arterial pressure (or a 10% increase in systemic oxygen saturation in 1 patient who underwent surgical creation of a systemic-to-pulmonary artery shunt as part of palliation for the hypoplastic left heart syndrome). In 2 patients who could not be separated from ECMO or cardiopulmonary bypass, a positive response to NO was inferred when a subsequent attempt with the delivery of NO resulted in successful separation from mechanical circulatory support.

Inhaled NO therapy was continued in the responders at the lowest effective dose.

The study was approved by the hospital ethics committee. The parents of all patients gave informed and written consent for the administration of inhaled NO.

Results

Between January 1995 and March 1996, 15 patients (7 females, 8 males, median age: 8 weeks, range 1 to 32 weeks) fulfilled the above criteria. The demographic data, cardiac diagnoses and type of cardiac surgery are described in Table 1.

We assessed the preoperative anatomy and haemodynamics by echocardiography in all patients except patients 13 and 14. These 2 patients, with pulmonary atresia with ventricular septal defect and major aortopulmonary collaterals, underwent cardiac catheterisation to delineate the major aortopulmonary collaterals, the central pulmonary arteries and the number of lung segments supplied prior to unifocalisation. The response to NO, catheterisation and echocardiogram results, intervention and outcome are summarised in Table 2.

We observed a response to inhaled NO in 5/15 patients. All had undergone repair of obstructed total anomalous pulmonary venous drainage (TAPVD). In 2/5 patients, inhaled NO therapy facilitated weaning from extracorporeal support. We administered inhaled NO continuously for 3 to 5 days to all responders with progressive weaning. Patient 2, after an initial favourable response to inhaled NO, was weaned after 3 days from continuous NO. However, pulmonary hypertension recurred but was unresponsive to treatment with inhaled NO. Subsequent transoesophageal echocardiography revealed external compression of the pulmonary venous confluence by thrombus. He underwent successful surgical decompression with resolution of pulmonary hypertension. All the responders survived to hospital discharge. No complications or side effects related to inhaled NO therapy were noted.

We did not observe a response to NO in 10/15 patients. We documented an anatomic obstruction in all 10 nonresponders at subsequent cardiac catheterisation or echocardiographic or autopsy examination. Eight patients underwent cardiac catheterisation, in 7/8 with branch pulmonary artery obstruction, measurement of mean pulmonary arterial pressure distal to the stenosis was less than 22 mm Hg. In 1 patient, discrete obstruction to the Blalock-Taussig shunt was documented (pulmonary artery pressure measurement was not attempted) but with surgical revision of the shunt oxygen saturations improved. Six of 10 nonresponders underwent attempted surgical or transcatheter relief of branch pulmonary artery stenosis. In 3/10 the pulmonary arteries were considered diffusely hypoplastic and incapable of rehabilitation. A single patient with suprasystemic pulmonary artery pressures after repair of obstructed TAPVD failed to respond to a challenge with inhaled NO. Autopsy findings included marked pulmonary lymphangiectasia, muscularised and dilated pulmonary veins with many distal arteries that had failed to open. The lung histology was consistent with the pattern described in both fatal persistent pulmonary hypertension of the neonate [11] and TAPVD [12].

Six of the nonresponders died, despite reintervention in 3.

Discussion

The results of this study suggest that in infants and neonates with high right ventricular pressure, failure to respond to a brief trial of inhaled NO may be indicative of residual and surgically correctable anatomic obstruc-

Table 1 Patient diagnosis and surgical intervention (*RV* right ventricle, *PA* pulmonary artery, *LA* left atrium, *RPV* right pulmonary veins, *LPV* left pulmonary veins, *HLHS* hypoplastic left heart syndrome, *MAPCAs* major aortopulmonary collateral arteries, *PAT* pulmonary atresia, *PDA* patent ductus arteriosus, *VSD* ventricular septal defect, *TAPVD* total anomalous pulmonary venous drainage, *SVG* superior vena cava, *IAA* Interrupted aortic arch, *MPA* Main pulmonary artery)

	Diagnosis	Age	Sex	Surgery
Responders				
1	Obstructed infradiaphragmatic TAPVD	1 w	F	Confluence to LA anastomosis
2	Obstructed TAPVD to coronary sinus	2 w	F	Confluence to LA anastomosis
3	Obstructed supradiaphragmatic TAPVD	2.5 m	M	Confluence to LA anastomosis
4	Obstructed infradiaphragmatic TAPVD	5 w	F	Confluence to LA anastomosis
5	Obstructed mixed TAPVD	5 m	M	RPV baffle from SVC to LA LPV anastomosis to LA
Nonresponders				
6	Obstructed supradiaphragmatic TAPVD	1 w	F	Confluence to LA anastomosis
7	Truncus arteriosus type 1	1 w	F	RV to PA conduit VSD closure
8	Truncus arteriosus type 2	1 w	M	RV to PA conduit VSD closure
9	Truncus arteriosus type 2 and IAA	2 w	F	RV to PA conduit End to side anastomosis aorta VSD closure
10	Hemitruncus	1 m	M	Reimplantation right pulmonary artery
11	Truncus arteriosus type 1	6 w	F	Anastomosis MPA to RV with pericardial patch and monocusp valve VSD closure
12	PAT/VSD PDA	1 m	M	RV to PA conduit VSD closure
13	PAT/VSD MAPCAs	8 m	M	RV to PA conduit unifocalisation
14	PAT/VSD MAPCAs	8 m	M	RV to PA conduit VSD closure unifocalisation
15	HLHS	1 w	M	Norwood stage 1

tion to pulmonary blood flow. Inhaled NO has been shown to be an effective treatment of postoperative pulmonary hypertension in patients with congenital heart defects. However, few studies have assessed the diagnostic value of a postoperative challenge to inhaled NO despite animal and human studies demonstrating that inhaled NO has little or no effect in the absence of pulmonary vasoconstriction [13]. The normal pulmonary arterial pressure measured beyond the anatomic obstruction, in the nonresponders in the present study, is in agreement with these findings.

All 5 responders to inhaled NO survived and in 2 patients inhaled NO facilitated weaning from extracorporeal support. Indeed, weaning patients with high pulmonary vascular resistance from cardiopulmonary bypass or ECMO may be an important application of inhaled NO. As others have demonstrated, there were no complications attributable to inhaled NO therapy [3, 4, 10]. However, we recommend gradual reduction in NO dose with cautious monitoring to reduce the risk of rebound pulmonary hypertension after prolonged therapy [14].

All 10 nonresponders presented immediately after surgery with high right ventricular or pulmonary arterial pressure and signs of low cardiac output. Nine had an anatomic obstruction to pulmonary blood flow and 1 had severe pulmonary vascular disease with lymphangiectasia as described by Yamaki et al. in fatal cases of TAPVD [12]. The mortality in the nonresponders was high (60 %) and suggests that in such patients failure to respond to a brief inhaled NO test should prompt further aggressive investigation to exclude residual anatomical obstruction before embarking on demanding and expensive supportive therapy such as ECMO, which has a poor outcome in cardiac patients with residual defects [15, 16].

We found, as previously reported, that postoperative patients with TAPVD were extremely sensitive to inhaled NO [13, 14], and it is of interest that in 1 patient loss of a pulmonary vasodilator response prompted fur-

Table 2 Response to NO, imaging, intervention and outcome (*LPA* left pulmonary artery, *RPA* right pulmonary artery, *BT* Blalock-Taussig shunt, *CPB* cardiopulmonary bypass, *ECMO* extracorporeal membrane oxygenation, *RV* right ventricle, *PAP* pulmonary arterial pressure, *SAP* systemic arterial pressure)

	RV or PAP/SAP		Imaging	Intervention	Outcome
	pre-NO	On NO			
Responders					
1	0.6	0.2	Unobstructed pulmonary veins	Conventional treatment	Alive
2	Weaned from ECMO with NO	0.6	Unobstructed pulmonary veins	Continuous NO for 5 days	Alive
3	1.2	0.7	Confluence obstructed by clots	Failed repeat trial of NO Surgical decompression	Alive
4	Weaned from CPB with NO	0.6	Unobstructed pulmonary veins	Continuous NO for 3 days	Alive
5	0.6	0.3	Unobstructed pulmonary veins	Continuous NO for 3 days	Alive
Nonresponders					
6	1.1	1.1	Unobstructed pulmonary veins	None	Died
7	1.0	1.0	Proximal LPA stenosis	Stent LPA	Alive
8	0.7	0.7	Proximal RPA stenosis	None	Died
9	1.0	1.0	Hypoplastic bilateral distal PAs	None	Died
10	0.5	0.6	RPA stenosis	Stent RPA	Alive
11	0.8	0.8	Bilateral proximal PAs stenosis	Stent L&RPA	Died
12	1.1	1.1	Severe bilateral distal hypoplasia of PAs	Balloon angioplasty of PAs	Died
13	1.1	1.0	Proximal LPA stenosis	Stent LPA	
14	1.0	1.0	Bilateral distal PAs hypoplasia	None	Died
15	55 %[a]	55[a]	Narrowing distal insertion BT shunt	Revision BT shunt	Alive

[a] Patient's response assessed by oxygen saturation changes

ther investigation and treatment of a late haematoma compressing the pulmonary venous anastomosis. The pattern of response to inhaled NO has been reported to be of value to differentiate reversible persistent pulmonary hypertension of the neonate from pulmonary hypoplasia [6]. However, neonates with pulmonary hypoplasia, in contrast to patients with postoperative fixed pulmonary obstruction, respond to NO with an improved oxygenation but require prolonged therapy with higher NO doses [6].

In conclusion, this study demonstrates and confirms that the response to an inhaled NO trial, after surgical repair of congenital heart defects, is helpful to differentiate reversible pulmonary vasoconstriction from residual anatomic obstruction or pulmonary hypoplasia [13]. A 30-min trial of inhaled NO is simple to administer and free of side effects and may be incorporated with ease into the management algorithm of these fragile patients. The absence of a response to inhaled NO after neonatal repair of truncus arteriosus, pulmonary atresia with ventricular septal defect, TAPVD or systemic-to-pulmonary artery shunt suggests an anatomical or fixed pulmonary vascular obstruction and should prompt further investigations. Early diagnosis and intervention secondary to an early trial of inhaled NO may improve the outcome of these very precarious patients and avoid the use of ECMO in patients with residual defects.

References

1. Jones ODH, Shore DF, Rigby ML et al (1981) The use of tolazoline hydrochloride as a pulmonary vasodilator in potentially fatal episodes of pulmonary vasoconstriction after cardiac surgery in children. Circulation 64 [Suppl II]: II 134–II 139
2. Hopkins RA, Bull C, Haworth SG, de Leval MR, Stark J (1991) Pulmonary hypertensive crises following surgery for congenital heart defects in young children. Eur J Cardiothorac Surg 5: 628–634
3. Beghetti M, Habre W, Berner M (1995) Continuous low dose inhaled nitric oxide for treatment of severe pulmonary hypertension after cardiac surgery in paediatric patients. Heart 73: 65–68

4. Miller OI, Celermeyer DS, Deanfield JE, Macrae DJ (1994) Very low dose inhaled nitric oxide: a selective pulmonary vasodilator after operations for congenital heart disease. J Thorac Cardiovasc Surg 108: 487–494
5. Dhillon R, Pearson G, Firmin R, Chan K, Leanage R (1995) Extracorporeal membrane oxygenation and the treatment of critical pulmonary hypertension in congenital heart disease. Eur J Cardiothorac Surg 9: 553–556
6. Goldman AP, Tasker RC, Haworth SG, Sigston PE, Macrae DJ (1996) Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics 98: 706–713
7. Petros AJ, Cox P, Bohn D (1994) A simple method for monitoring the concentration of inhaled nitric oxide. Anaesthesia 49: 317–319
8. Adatia I, Perry S, Moore P, Landzberg M, Wessel DL (1995) Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. J Am Coll Cardiol 25: 1652–1664
9. Berner M, Beghetti M, Spahr-Schopfer I, Oberhänsli I, Friedli B (1994) Inhaled nitric oxide to test the vasodilator capacity of the pulmonary vascular bed in children with long-standing pulmonary hypertension and congenital heart disease. Am J Cardiol 77: 532–535
10. Wessel DL, Adatia I, Thompson JE, Hickey PR (1994) Delivery and monitoring of inhaled nitric oxide in patients with pulmonary hypertension. Crit Care Med 22: 930–938
11. Raine J, Hislop A, Redington A, Haworth S, Shinebourne E (1991) Fatal persistent pulmonary hypertension presenting late in the neonatal period. Arch Dis Child 66: 398–402
12. Yamaki S, Tsunemoto M, Shimada M et al (1992) Quantitative analysis of pulmonary vascular disease in total anomalous pulmonary venous connection in sixty infants. J Thorac Cardiovasc Surg 104: 728–735
13. Adatia I, Atz AM, Jonas RA, Wessel DL (1996) Diagnostic use of inhaled nitric oxide after neonatal cardiac operations. J Thorac Cardiovasc Surg 112: 1403–1405
14. Atz AM, Adatia I, Wessel DL (1996) Rebound pulmonary hypertension after inhalation of nitric oxide. Ann Thorac Surg 62: 1759–1764
15. Black MD, Coles JG, Williams WG et al (1995) Determinants of success in pediatric cardiac patients undergoing extracorporeal membrane oxygenation. Ann Thorac Surg 60: 133–138
16. Beghetti M, Bohn D, Adatia I (1997) Extracorporeal membrane oxygenation and the treatment of critical pulmonary hypertension in congenital heart disease. Eur J Cardiothorac Surg 11: 796–797