DIPYRIDAMOLE ATTENUATES REBOUND PULMONARY HYPERTENSION AFTER INHALED NITRIC OXIDE WITHDRAWAL IN POSTOPERATIVE CONGENITAL HEART DISEASE

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Objective: Inhaled nitric oxide therapy causes selective and sustained pulmonary vasodilation in patients with pulmonary hypertension; however, attempts to discontinue inhaled nitric oxide therapy may be complicated by abrupt life-threatening events. Dipyridamole, a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor, blocks the hydrolysis of cyclic guanosine monophosphate in vascular smooth muscle cells. **Methods:** We studied 23 consecutive children who were treated with inhaled nitric oxide because of clinically significant pulmonary hypertension after surgery for congenital heart disease. Inhaled nitric oxide therapy was withdrawn before and after dipyridamole treatment of children in whom sustained elevations of pulmonary artery pressure developed for over 30 minutes. **Results:** In 7 of 23 children, inhaled nitric oxide withdrawal caused a 40% increase in pulmonary artery pressure, a 17% decrease in systemic venous oxygen saturation, and a 46% increase in the ratio of mean pulmonary artery pressure to aortic pressure. Compared with children who had no significant increase in pulmonary artery pressure, children who experienced the development of prolonged pulmonary hypertension after inhaled nitric oxide therapy withdrawal had higher mean pulmonary artery pressure immediately before inhaled nitric oxide withdrawal (22 ± 1 mm Hg versus 27 ± 2 mm Hg; $p = 0.04$) and received inhaled nitric oxide for a longer duration (2 ± 1 days versus 4 ± 1 days; $p = 0.01$). Dipyridamole therapy attenuated the rise in pulmonary artery pressure and fall in systemic venous oxygen saturation in all six patients studied with rebound pulmonary hypertension after withdrawal of inhaled nitric oxide. **Conclusion:** We conclude that dipyridamole therapy acutely attenuates the adverse hemodynamic effects of rapid withdrawal of inhaled nitric oxide therapy. Children with higher pulmonary artery pressure and who are treated with inhaled nitric oxide for a longer duration may be at increased risk for adverse hemodynamic effects of inhaled nitric oxide therapy withdrawal. We speculate that dipyridamole therapy may sustain elevations of smooth muscle cyclic guanosine monophosphate induced by inhaled nitric oxide and that phosphodiesterase activity contributes to acute pulmonary hypertension after inhaled nitric oxide withdrawal. (J Thorac Cardiovasc Surg 1998;115:875-82)

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Inhaled nitric oxide (iNO) lowers pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) in many diseases associated with pulmonary hypertension, including postoperative congenital heart disease.¹⁻³ Although iNO therapy causes sustained decreases in PVR, iNO therapy may be complicated by adverse hemodynamic effects after abrupt withdrawal.^{4,5} These effects include increases in PAP and PVR, decreased cardiac output with a concomitant fall in systemic venous oxygen saturation (SV_{O_2}), decreased systemic arterial pressure (SAP), and decreased arterial oxygenation (PaO_2).⁵⁻⁷ The occurrence of these adverse hemodynamic effects after iNO withdrawal is highly variable among patients and may be transient and resolve over time^{6,8} or be mild and resolve with increases in inspired oxygen concentrations.⁵ Other studies have shown that withdrawal of iNO may cause life-threatening effects.⁴ The factors contributing to the variability in iNO responses or withdrawal effects remains unknown.

Mechanisms underlying the adverse effects of sudden iNO withdrawal are unknown but may include the presence of severe underlying pulmonary vascular disease with an imbalance of vasodilator stimuli, such as nitric oxide (NO),⁹ or increased production of endogenous vasoconstrictor stimuli, such as endothelin.¹⁰ Other mechanisms may include down-regulation of endogenous NO production.¹¹⁻¹³ Recently, persistent or increased degradation of cyclic guanosine monophosphate (cGMP) by the cGMP-specific phosphodiesterase enzymes (PDE5), has been found in animal models of pulmonary hypertension.^{14,15} Because iNO-induced pulmonary vasodilation is mediated through increased cGMP production in vascular smooth muscle cells, PDE5 inactivation of cGMP may limit the potency and duration of vasodilation by decreasing cGMP in smooth muscle cells. Experimental studies have shown that PDE5 inhibition augments and prolongs responses to iNO.¹⁶⁻¹⁸ Several agents, including dipyridamole, zaprinast, and E4021, inhibit

Table I. Clinical characteristics and hemodynamic response to initial inhaled nitric oxide (iNO) withdrawal

Diagnosis	Age	mPAP (mm Hg)		mSAP (mm Hg)		SVO ₂ (%)	
		iNO on	iNO off	iNO on	iNO off	iNO on	iNO off
Rebound (<i>n</i> = 7)							
1. HLH/OCT	3 mo	22	34	86	70	73	61
2. HLH/OCT	4 mo	28	37	75	66	67	56
3. HLH/OCT	4 mo	25	37	63	48	70	60
4. HLH/OCT	5 mo	32	45	78	68	67	42
5. VSD/CoAo	5 mo	32	57	70	68	68	64
6. AS/MS	8 mo	34	62	77	72	73	69
7. TAPVR	12 mo	17	40	76	73	67	62
No rebound (<i>n</i> = 16)							
8. TAPVR	1 day	17	19	65	61	68	70
9. TAPVR	3 days	23	26	83	82	70	70
10. TAPVR	5 days	27	29	70	69	68	67
11. HLH/OCT	1 mo	20	20	65	63	77	77
12. HLH/OCT	1 mo	24	28	76	79	71	73
13. HLH/OCT	1 mo	26	28	66	65	70	67
14. HLH/OCT	1 mo	23	24	59	58	60	58
15. HLH/OCT	1 mo	19	20	64	63	72	73
16. HLH/OCT	2 mo	22	24	75	74	71	70
17. HLH/OCT	2 mo	24	26	80	80	81	82
18. HLH/OCT	3 mo	18	19	81	79	73	74
19. HLH/OCT	3 mo	24	26	62	60	81	78
20. HLH/OCT	3 mo	14	16	83	81	76	73
21. ASD	1 yr	21	24	70	70	74	71
22. CMP/OCT	4 yr	31	33	98	95	64	63
23. CMP/OCT	18 yr	19	21	81	79	72	71

Values are mean $\pm$ SEM; iNO off values 30 minutes after iNO withdrawal. mPAP, Mean pulmonary artery pressure; mSAP, mean systemic artery pressure; SV_{O₂}, systemic venous oxygen saturation; HLH/OCT, hypoplastic left heart syndrome/orthotopic cardiac transplantation; VSD/CoAo, ventricular septal defect/coarctation of the aorta; AS/MS, aortic stenosis/mitral stenosis; TAPVR, total anomalous pulmonary venous return; ASD, atrial septal defect; CMP/OCT, cardiomyopathy/orthotopic cardiac transplantation.

Table II. Baseline measurements comparing children with and without rebound pulmonary hypertension before inhaled nitric oxide (iNO) withdrawal

	No rebound (n = 16)	Rebound (n = 7)	p Value
iNO dose at withdrawal (ppm)	3.7 ± 0.3	2.8 ± 0.5	0.13
iNO treatment (days)	2 ± 1	4 ± 1	0.01
PAP (mm Hg)	22 ± 1	27 ± 2	0.04
SAP (mm Hg)	74 ± 4	72 ± 3	0.55
Svo ₂ (%)	71 ± 2	69 ± 1	0.49
PaO ₂ (mm Hg)	130 ± 10	127 ± 6	0.86
Paco ₂ (mm Hg)	34 ± 1	34 ± 1	0.93
pH (units)	7.49 ± 0.02	7.46 ± 0.02	0.24

Values are mean plus or minus standard error of the mean. PAP, Mean pulmonary artery pressure; SAP, mean systemic artery pressure; Svo₂, systemic venous oxygen saturation.

the PDE5 enzymes.^{14, 18, 19} In human beings, PDE5 inhibitors, such as dipyridamole, may augment the response to iNO^{20, 21} and may help in weaning iNO therapy.²² On the basis of these studies, we hypothesized that PDE5 contributes to the adverse hemodynamic effects after withdrawal of iNO. To test this hypothesis and to examine potential risk factors for the variability of this response between patients, we prospectively studied the effects of iNO withdrawal in consecutive patients treated with iNO for pulmonary hypertension after surgical repair of congenital heart disease.

Methods

This protocol was reviewed and approved by the institutional review board at the University of Colorado School of Medicine. After obtaining informed consent, we studied 27 consecutive children (median age: 4.5 months; range: 1 to 216 months) who were treated with iNO from July 1, 1995, to July 1, 1997, for pulmonary hypertension after surgery for congenital heart disease. Four patients died while receiving iNO therapy and are not included in this study because iNO could not be withdrawn. All remaining children in whom iNO was withdrawn were included in the study. Primary diagnoses of the remaining 23 children included orthotopic cardiac transplantation for hypoplastic left heart syndrome (14), repair of total anomalous pulmonary venous return (3), orthotopic cardiac transplantation for cardiomyopathy (2), revision of total anomalous pulmonary venous return repair (1), repair for congenital aortic and mitral stenosis (1), repair of atrial septal defect with associated bronchopulmonary dysplasia (1), and repair of ventricular septal defect after coarctation of the aorta repair and pulmonary artery banding (1).

Patients were selected for iNO therapy after cardiac surgery if the mean PAP exceeded 30 mm Hg with

Fig. 1. In the seven children with rebound pulmonary hypertension after withdrawal of iNO, the ratio of PAP to systemic artery pressure increased after withdrawal of iNO in comparison with the 16 patients without rebound.

hemodynamic compromise and/or inability to wean from cardiopulmonary bypass because of clinical signs of right heart failure. All patients had placement of an Opticath fiberoptic pulmonary artery catheter (5.5-7.5F; Abbott Laboratories, North Chicago, Ill.) and a systemic arterial line for hemodynamic monitoring. iNO therapy was initiated at 20 ppm and administered as previously described.²³ Methemoglobin, NO and NO₂ concentrations were frequently monitored.²³ iNO therapy was weaned by 50% daily, as tolerated based on hemodynamic stability, and was discontinued when a child's condition was hemodynamically stable, receiving less than 5 ppm of iNO for 8 hours or more. Hemodynamic stability was defined as a ratio of mean PAP to SAP of 0.50 or less, adequate gas exchange (Paco₂ ≤ 40 mm Hg; PaO₂ ≥ 100 mm Hg; fraction of inspired oxygen ≤ 0.40), and an Svo₂ of 60% or more. After iNO withdrawal, the fraction of inspired oxygen and ventilator settings remained constant. Study measurements included PAP, SAP, Svo₂, central venous pressure (CVP), arterial blood gas tensions, and systemic oxygen saturation (Sao₂) for 30 minutes after iNO withdrawal. *Acute pulmonary hypertension (rebound)* was defined as a persistent elevation of mean PAP of 20% or more above baseline with hemodynamic compromise for more than 30 minutes after iNO withdrawal. We chose a 20% change in mean PAP because many vasoreactivity studies have used this percentage as an indicator of a response to vasodilator therapy.³ Children with rebound pulmonary hypertension were given a trial of dipyridamole therapy. The children were not randomized but rather given a trial of dipyridamole therapy based on the response to withdrawal of iNO. In children with acute

Fig. 2. Effect of repeated withdrawal of iNO in a patient with pulmonary hypertension (patient 5). This patient was treated with iNO for 3 days; iNO was withdrawn at 2 ppm. In this patient, iNO withdrawal caused a sustained and repeatable increase in mean PAP after iNO withdrawal.

pulmonary hypertension, iNO was reinitiated after the 30-minute trial off iNO at the same dose before withdrawal. In these patients the iNO was given for 30 to 60 minutes with a return of hemodynamic variables to baseline values. Dipyridamole (0.6 mg/kg) was infused in the central venous catheter over 20 minutes. The iNO was again withdrawn, and measurements were obtained after 30 minutes. Patients 1, 2, 3, 4, 6, and 7 received dipyridamole therapy. Patient 5 inadvertently began receiving calcium channel blockade therapy after the initial three withdrawals of iNO at the discretion of the attending physician and therefore did not receive dipyridamole therapy.

Statistical analysis. All data are expressed as mean $\pm$ standard error of the mean. Confidence intervals (95% CI) are given where significant differences are found. Differences between children with rebound and those without rebound were analyzed by unpaired *t* test. Differences during dipyridamole treatment were analyzed by analysis of variance for repeated measures and Fisher's least significant difference test for post hoc comparisons (Super ANOVA, Berkeley, Calif.).

Results

In nine of the 23 children (39%) iNO was initiated for difficulty weaning from cardiopulmonary bypass; the remainder of the children had a PAP that was greater than 50% of the SAP at the time of initial iNO treatment. Seven of the 23 children (30%) had a sustained and significant increase in mean PAP after iNO withdrawal (Table I). In children without rebound pulmonary hypertension, hemodynamic and blood gas variables did not change from treatment values at 30 minutes after iNO withdrawal

(Fig. 1). In comparison with patients without persistent hemodynamic changes after iNO withdrawal, there were no differences in age, sex, diagnosis, and use of cardiotoxic agents. In children with rebound pulmonary hypertension, there was a significant increase in the ratio of mean pulmonary artery to aortic pressure (Fig. 1; $0.38\% \pm 0.05\%$; 95% CI 0.31, 0.45 vs 0.68 ± 0.07 ; 95% CI 0.57, 0.79). Children with rebound pulmonary hypertension had a higher ratio of mean pulmonary artery to aortic pressure than those without rebound pulmonary hypertension (Fig. 1; $0.38\% \pm 0.05\%$; 95% CI 0.31, 0.45 vs $0.31\% \pm 0.02\%$; 95% CI 0.28, 0.34). In addition, the dose of iNO at the time the iNO therapy was stopped, SAP, CVP, Svo₂, Pao₂, Paco₂, pH, or Sao₂ were not different between the groups (Table II). However, immediately before iNO withdrawal, mean PAP was higher in children with rebound pulmonary hypertension (Table II; 22 ± 1 mm Hg; 95% CI 20, 24 vs 27 ± 2 mm Hg; 95% CI 24, 30). Children with acute pulmonary hypertension after iNO withdrawal had been treated with iNO for a longer duration than those children in whom acute pulmonary hypertension did not develop on iNO withdrawal (Table II; 2 ± 1 days; 95% CI 1.9, 2.8 vs 4 ± 1 days; 95% CI 3.2, 4.9).

In one child (patient 5), withdrawal of iNO therapy caused significant increases in mean PAP for over 30 minutes during three consecutive withdrawal attempts (Fig. 2). In the children with sus-

tained pulmonary hypertension after iNO therapy withdrawal, mean PAP and the ratio of PAP to SAP increased 40% and 46%, respectively (Figs. 1, 3, and 4). SvO_2 fell after iNO withdrawal in these six patients (Fig. 5; $70\% \pm 1\%$; 95% CI 67, 72 vs $58\% \pm 1\%$; 95% CI 51, 65). SAP also fell after iNO withdrawal ($p = 0.01$; 74 ± 5 mm Hg; 95% CI 66, 81 vs 66 ± 4 mm Hg; 95% CI 60, 72). CVP, SpO_2 , pH, $Paco_2$, and Pao_2 did not change. Hemodynamic variables rapidly returned to baseline values on reinitiation of iNO therapy. Dipyridamole therapy did not change any hemodynamic or blood gas variables but attenuated the adverse effects of iNO withdrawal (Figs. 3, 4, and 5). Dipyridamole therapy did not change SAP (71 ± 5 to 66 ± 5 mm Hg; $p = 0.18$) but blocked the fall in SAP at iNO withdrawal. In contrast to the 40% increase in mean PAP (Fig. 3; 26 ± 3 mm Hg; 95% CI 22, 30 vs 43 ± 4 mm Hg; 95% CI 35, 50) and 46% increase in the ratio of PAP/SAP without dipyridamole (Fig. 4; $0.36\% \pm 0.05\%$; 95% CI 0.28, 0.44 vs $0.65\% \pm 0.07\%$; 95% CI 0.53, 0.77), there was no change in PAP or the ratio of PAP/SAP after dipyridamole at withdrawal of iNO (Figs. 3 and 4). Similarly, dipyridamole therapy attenuated the 17% fall in SvO_2 (Fig. 5) and 11% fall in SAP at withdrawal of iNO. Two to three hours after dipyridamole therapy and withdrawal of iNO, three of the six children had hemodynamic instability that necessitated reinitiation of iNO therapy. For patient 5, iNO was withdrawn during calcium channel blockade. Each patient was subsequently weaned from iNO within 24 to 36 hours without dipyridamole therapy.

Four of the 14 (29%) patients with hypoplastic left heart syndrome who underwent orthotopic cardiac transplantation experienced the development of adverse hemodynamic events after withdrawal of iNO. All patients with hypoplastic left heart syndrome were treated with isoproterenol, dopamine, and milrinone in addition to iNO. Those patients with adverse hemodynamic effects were older at the time of transplantation ($p = 0.01$; 4.0 ± 0.4 months; 95% CI 3.2, 4.8 vs 1.8 ± 0.3 months; 95% CI 1.2, 2.4), were treated with iNO for a longer duration before withdrawal of iNO ($p = 0.01$; 4.8 ± 0.3 days; 95% CI 4.3, 5.3 vs 2.7 ± 0.3 days; 95% CI 2.1, 3.3), and had higher mean PAP before withdrawal of iNO ($p = 0.03$; 27 ± 2 mm Hg; 95% CI 23, 31 vs 21 ± 1 mm Hg; 95% CI 19, 23). The iNO dose at withdrawal, SAP, SvO_2 , and blood gas variables were not different between those children with or without adverse hemodynamic effects after iNO withdrawal.

Fig. 3. Effects of dipyridamole pretreatment on mean PAP after withdrawal of iNO ($n = 6$). As shown, mean PAP increased 40% after iNO withdrawal. Reinitiation of iNO rapidly returned PAP to baseline. Dipyridamole therapy did not lower PAP during iNO treatment but attenuated the rise in PAP on repeat withdrawal of iNO.

Discussion

Since the initial clinical reports of iNO therapy for persistent pulmonary hypertension of the newborn,²⁴ adult respiratory distress syndrome,⁷ and congenital heart disease,²⁵ it has been recognized that rapid withdrawal of iNO therapy may cause marked increases in PAP and decreased oxygenation.⁴⁻⁷ However, other studies⁸ have shown that iNO may be withdrawn in patients treated with iNO for total anomalous pulmonary venous return without adverse events, thus showing the variability in the response to withdrawal of iNO. To study the frequency of this response in postoperative congenital heart disease and the potential role of PDE5 in these acute changes, we studied children treated for postoperative congenital heart disease. In this pilot study, 30% (7/23) of children who were treated with iNO after surgery for congenital heart disease had acute pulmonary hypertension characterized by a 40% increase in PAP, a 17% decrease in SvO_2 , and an 11% decrease in SAP. In comparison with children in whom increased PAP did not develop after iNO withdrawal, patients with acute pulmonary hypertension had higher mean PAP before iNO was stopped and were treated with iNO for a longer

Fig. 4. Effects of dipyridamole pretreatment on the ratio of mean PAP to mean systemic artery pressure after iNO withdrawal ($n = 6$). As shown, PAP/SAP initially increased from 35% to 65% after acute iNO withdrawal. Dipyridamole therapy did not change the pulmonary to aortic pressure ratio during iNO treatment but attenuated the rise in pulmonary to aortic pressure ratio after repeat withdrawal of iNO.

duration. Dipyridamole therapy subsequently attenuated the adverse hemodynamic effects of iNO withdrawal in the six patients studied.

Atz and associates⁸ have shown that after prolonged treatment with iNO, PAP increased transiently in all patients when iNO was discontinued. In this study, the rebound effect was transient and the peak elevation in mean PAP was observed 7 ± 3 minutes after iNO withdrawal. Our results are similar in that no patient treated with iNO for the initial repair of total anomalous pulmonary venous return had an adverse hemodynamic effect 30 minutes after the withdrawal of iNO.

Pulmonary hypertension is a risk factor for children undergoing orthotopic cardiac transplantation.²⁶ Patients with hypoplastic left heart syndrome have systemic levels of PAP, elevated left atrial pressure, and hypoxia. Therefore it is likely that for some of our patients a sustained elevation in PAP developed after iNO withdrawal. This is supported by the fact that rebound pulmonary hypertension was more common in those patients with hypoplastic left heart syndrome undergoing

orthotopic cardiac transplantation who were older at the time of transplantation and had a higher mean PAP before withdrawal of iNO. In fact, during the last year only one of 12 patients (8%, patient 5) has had a rebound effect after withdrawal of iNO. This likely reflects a change in our patient population. The eight recent patients with hypoplastic left heart syndrome were an average of 1.9 ± 0.4 months at the time of transplantation and did not have a rebound effect after iNO withdrawal, supporting the theory that younger patients with hypoplastic left heart syndrome undergoing transplantation are less likely to experience the development of rebound effects after withdrawal of iNO. However, patients with hypoplastic left heart syndrome and rebound pulmonary hypertension were treated with iNO for a longer duration before withdrawal of iNO, suggesting that down-regulation of endogenous NO may play a role.

The purpose of our study was to examine the potential role of PDE5 in the elevation of PAP after iNO withdrawal and to determine potential risk factors for this effect. This pilot study did not examine whether chronic dipyridamole treatment would continue to sustain its effects for prolonged periods. We found that dipyridamole, a cGMP-specific PDE5 inhibitor, attenuated the adverse hemodynamic effects after iNO withdrawal in some patients after surgery for congenital heart disease. NO causes vasodilation by stimulating cGMP in vascular smooth muscle. cGMP is hydrolyzed and inactivated by the PDE5 enzymes. Inhibitors of the PDE5 enzymes have been shown to lower PVR in fetal and newborn lambs^{18,19} and adult rats with chronic hypoxia.¹⁴ Furthermore, PDE5 inhibitors augment and prolong the response to iNO in experimental models of pulmonary hypertension.^{16,17} In human beings, PDE5 inhibitors, such as dipyridamole, may augment the response to iNO.^{20,21} Although we speculate that the adverse effects of iNO withdrawal were attenuated by an increase in cGMP, dipyridamole therapy may prevent the adverse hemodynamic effects as a nonspecific pulmonary vasodilator. Previous studies have shown that inhibition of hypoxic pulmonary vasoconstriction by dipyridamole is not due to its platelet-mediated effects.²⁷ Furthermore, dipyridamole-induced pulmonary vasodilation in the ovine fetal lung is not mediated by adenosine,¹⁸ and nitric oxide synthase inhibitors completely block dipyridamole-induced vasodilation,²⁸ suggesting that the dipyridamole

causes vasodilation primarily through increasing smooth muscle cGMP.

Marked elevations of PAP with diminished cardiac output and systemic hypotension have been described on rapid withdrawal of iNO.⁴⁻⁷ In some instances, the adverse rebound effects of iNO withdrawal may be avoided by slow weaning of iNO and careful attention to adequate oxygenation and hemodynamic stability. The purpose of our study was not to determine the efficacy of dipyridamole as a weaning agent in withdrawal of iNO but rather to determine risk factors for rebound and the potential role of PDE5 in rebound. Moreover, rebound effects of rapid withdrawal of iNO diminish with repeated attempts to discontinue iNO over time.⁵ However, despite adequate blood gas variables, hemodynamic stability, and sedation during low-dose iNO therapy, adverse hemodynamic events on discontinuation of iNO developed in 30% of children with postoperative pulmonary hypertension.

Clinical and laboratory studies have termed the acute increase in PAP after iNO withdrawal a rebound phenomenon.^{6, 11, 13, 29} The mechanisms responsible for the adverse effects of rapid iNO withdrawal are unknown. iNO-induced down-regulation of endogenous NO synthase may play an important role.^{11, 12} Recent reports suggest that in hypoxic rats, endogenous NO production is reversibly reduced after short-term NO inhalation and is likely due to NO synthase inhibition.¹³ NO donors, such as nitroglycerin, may be associated with increased superoxide anion production and subsequent inhibition of NO-mediated vasodilation, suggesting decreased NO sensitivity.²⁹ However, similar rebound effects occur in patients with severe pulmonary hypertension after sudden withdrawal of other vasodilators, such as prostacyclin.³⁰ An imbalance of vasodilator and vasoconstrictor stimuli may also contribute to rebound effects. For example, increased production of vasoconstrictors, such as endothelin,¹⁰ may augment rebound increases in PAP after sudden discontinuation of iNO. Thus the rebound phenomenon of elevated PAP may not be exclusively due to decreased endogenous NO production with iNO therapy. The underlying state of the pulmonary vasculature may also contribute to this phenomenon. Our data support the rebound phenomenon as being a combination of diminished endogenous NO production (children with rebound were treated for a longer duration than those who did not have rebound) and more severe pulmonary vascular disease (greater PAP

Fig. 5. Effects of dipyridamole pretreatment on systemic Svo_2 after iNO withdrawal ($n = 6$). As shown, Svo_2 fell 17% from baseline, suggesting a fall in cardiac output. Dipyridamole therapy did not change Svo_2 but attenuated the fall in Svo_2 after repeat withdrawal of iNO.

at the time of iNO withdrawal in children with rebound).

In summary, children treated with low-dose iNO for pulmonary hypertension after surgery for congenital heart disease are at risk for severe pulmonary hypertension after iNO therapy is stopped. Adverse hemodynamic effects of rapid withdrawal of iNO are attenuated with dipyridamole therapy. Children treated with iNO for a longer duration and with a higher mean PAP at the time of iNO discontinuation may be at greatest risk for the development of these hemodynamic effects and may benefit from dipyridamole therapy before iNO withdrawal. In patients with hypoplastic left heart syndrome treated with orthotopic cardiac transplantation, patients with adverse hemodynamic effects were older at the time of transplantation, were treated with iNO for a longer duration before withdrawal of iNO, and had a higher mean PAP before withdrawal of iNO. We speculate that PDE5 activity contributes to rebound pulmonary hypertension after iNO withdrawal.

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