



# Acute vasodilator testing: An opportunity to advance the precision care of pulmonary hypertension

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## ABSTRACT

The pulmonary arterial pressure of a child with severe pulmonary arterial hypertension immediately normalized while breathing nitric oxide during heart catheterization at 8 years of age. Her acute pulmonary vascular response to nitric oxide has persisted throughout her life. Her acute response to other medications has been similar to her long-term response to medications in the same class. Acute vasodilator testing with inhaled nitric oxide and other medications may be an opportunity to refine study design and advance precision care for patients with pulmonary hypertension.

## 1. Case report

An 8-year old female presented for evaluation in February 2003 after several months of syncopal and near syncopal episodes. Her past history was only remarkable for a severe respiratory infection at an age of 6 years. She was diagnosed with idiopathic pulmonary arterial hypertension and no cause of pulmonary vascular disease has been identified throughout her life (Table 1).

Table 2 lists the medications that were being used for long-term outpatient care and the medications that were used for acute vasodilator testing at the time of her hemodynamic evaluations. She consistently showed a marked decrease in mean pulmonary arterial pressure (mPAP) while breathing 20 parts per million (ppm) inhaled nitric oxide (iNO). The response occurs within 30–60 seconds as illustrated in Fig. 1 by the mPAP and abrupt change in the intensity of the second heart sound by acoustic cardiography.

She presented before the Sitbon criterion was published to identify patients that might respond favorably to calcium channel blocker (CCB) therapy. She was initially treated as an outpatient with medications that target the nitric oxide pathway of signal transduction, including sildenafil and intermittent transdermal nitroglycerin. Due to her history of syncope, iNO was approved for short-term emergency treatment by the Institutional Review Board of the University of Utah and an investigator sponsored Investigational New Drug application with the United States Food and Drug Administration. A delivery system was provided by Pulmonox and a source of nitric oxide was provided by SensorMedics, a

subsidiary of VIASYS Healthcare. She had no subsequent episodes of syncope. However, she could only be treated with iNO transiently for periods of 10–15 minutes a few times a day. Her mPAP progressively increased with this treatment strategy. She had little or no acute pulmonary vasodilator response to sildenafil or nitroglycerin during subsequent hemodynamic evaluations. Fig. 2 illustrates that sildenafil and tadalafil did not even prolong the pulmonary vasodilatory effect of iNO.

Her mPAP decreased when she was treated acutely with intravenous diltiazem during her second hemodynamic evaluation. Thereafter, sildenafil and nitroglycerin were discontinued and amlodipine has been the mainstay of her outpatient therapy. Fig. 3 illustrates the impact of long-term outpatient therapy on her baseline ratio of pulmonary to systemic vascular resistance (Rp:Rs) over time. Treatment with amlodipine therapy has been associated with a decrease in mPAP, Rp and Rp:Rs; however, these measurements have not decreased to levels that are readily achieved with iNO. The dose of amlodipine has been limited by severe gingival hyperplasia.

An increase in mPAP was observed while she was entering puberty at 12 years of age. She also experienced an adverse reaction to minocycline at 13–14 years of age with an increase in anti-nuclear antibody and an increase in serum transaminases. A four-month trial of nighttime iNO was approved by the Institutional Review Board of the University of Utah and a modified investigator sponsored Investigational New Drug application with the United States Food and Drug Administration. A delivery system and a source of nitric oxide were provided by INO Therapeutics. This trial was completed without complications. We did

*Abbreviations:* calcium channel blocker(s), CCB; inhaled nitric oxide, iNO; mean pulmonary arterial pressure, mPAP; parts per million, ppm

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**Table 1**  
Demographic and diagnostic evaluation.

Factors and Tests	Result
Family history of pulmonary hypertension	None
Altitude of residence	5500 and 4500 feet (home and college, respectively); < 500 feet (18 months from 19 to 20 years of age)
Anti-nuclear antibody	Only transiently detected at an age of 13–14 years while being treated with minocycline
Lupus anticoagulant	Not detected
Factor V Leiden	No variant
Prothrombin 20210G > A	No variant
Methylenetetrahydrofolate reductase	c.665C > T negative and c.1286A > C homozygous
Homocysteine	Normal
LDL Cholesterol	Normal
Thyroid function tests	Normal
Liver function tests	Only transiently abnormal at an age of 13–14 years while being treated with minocycline
Hepatitis A, B, and C serologies	Non-reactive
Asymmetric dimethyl arginine levels	(0.96 and 1.09 micromol/L, 95% reference interval 0.47–1.02 micromol/L)
Genomic microarray, 1 Mb chip	Normal female with several copy number variants that were considered clinically insignificant
Additional genetic testing	Not performed (not covered by insurance)
Pulmonary function tests	Normal spirometry
Oximetry	No hypoxemia while sleeping
Echocardiography	Patent foramen ovale with no structural cardiovascular anomalies
High-resolution CT scan of the chest	Normal airway and lung parenchyma
Pulmonary angiography	No evidence of thromboembolic disease

not have a delivery system or funding to continue treatment at home long-term. She was too young to be enrolled in clinical trials with iNO using an investigational outpatient delivery system.

She had no decrease in mPAP when treated acutely with L-arginine. Riociguat was added to her outpatient regimen after an oral dose acutely decreased her mPAP. However, the dose of riociguat has been limited due to severe pain associated with gastroesophageal reflux despite treatment with multiple antacids. Of note, she developed severe exertional dyspnea and near syncope when a specialty pharmacy instructed her to stop amlodipine after starting riociguat. Her symptoms improved when the amlodipine was resumed. She had a limited acute response to epoprostenol and has not been treated with a prostacyclin analog as an outpatient. She has not been treated with an endothelin receptor antagonist.

## 2. Discussion

Inhaled nitric oxide has been used extensively for acute vasodilator testing since Pepke-Zaba and associates reported the selective pulmonary vasodilatory effects of this agent [1]. However, it is unknown whether the magnitude of one's response will improve or waver over time with treatment or disease progression. Further, it is unclear whether the acute effect of a medication can be used to predict the long-term effect of medications in a similar class. This case illustrates an opportunity to refine and advance the personalized care of patients with pulmonary hypertension based upon the results of acute vasodilator testing. Several aspects of this case underscore the fundamentals of precision care: treating the right patient with the right drug at the right time with the right dose and the right route.

### 2.1. Right patient

Our patient presented with severe pulmonary arterial hypertension. Her pulmonary vascular bed has the capacity to relax when treated with specific agents. Her response to iNO suggests that she may have inhibited or impaired function of pulmonary vascular nitric oxide synthase. She has a reliable phenotypic response to iNO and a CCB, even though we have not been able to test for a specific genetic variant to explain the cause of her pulmonary hypertension.

### 2.2. Right drug

Her immediate and long-term responses to oxygen, sildenafil, transdermal nitroglycerin and amlodipine were similar. Tolerance to nitroglycerin might explain the small difference between the acute and long-term effects of this medication. She had elevated levels of asymmetric dimethylarginine. We have not excluded the possibility that outpatient treatment with L-arginine had a small beneficial effect. We have not evaluated her long-term response to a prostacyclin analog or prostacyclin receptor stimulator.

Her mPAP decreased more with iNO than any other medication during acute vasodilator testing. Her immediate response to iNO has persisted throughout the course of her care. The acute response was not adversely influenced by treating her with nighttime iNO for four months. The immediate decrease in pulmonary arterial pressure after the onset of iNO, the limited response to nitroglycerin and the lack of prolonged iNO-mediated vasodilation following treatment with a phosphodiesterase V inhibitor suggest that iNO could be acting through a mechanism other than stimulation of guanylate cyclase [2]. Long-term treatment with amlodipine, with or without L-arginine, has not decreased her mPAP to a degree that can readily be achieved with iNO.

### 2.3. Right time

Our patient was treated with nighttime iNO when her pulmonary arterial pressure increased after the onset of puberty. We do not know whether iNO therapy had a favorable effect at that time because her amlodipine dose was adjusted for growth and she had an adverse reaction to minocycline between hemodynamic evaluations. The clinical features of pulmonary arterial hypertension are similar in children and adults [3]. We should not delay the treatment of children with effective drugs. Clinical trials or thorough treatment surveillance are needed to determine whether children respond differently to available medications.

### 2.4. Right dose

In patients with pulmonary hypertension, the acute effect of iNO is similar over a range of concentrations [4]. We do not know a dose of iNO that might prevent the progression of pulmonary hypertension in an outpatient setting. Short periods of treatment with iNO to avoid

**Table 2**  
Results of heart catheterization and acute vasodilator testing.

	CI	mPAP	Rp	Rp:Rs or mPAP:mSAP <sup>a</sup>
	L/ min- m <sup>2</sup>	mm Hg	units-m <sup>2</sup>	
Age: 8 years and 7 months				
Outpatient therapy				
None				
Room Air	2.91	53	15.3	0.70
8 L/min Oxygen	2.68	56	18.3	0.75
8 L/min Oxygen, 20 ppm Nitric Oxide	2.69	22	4.46	0.19
8 L/min Oxygen, 10 ng/kg/min Epoprostenol		51		0.65
Age: 9 years and 9 months				
Outpatient therapies used since previous heart catheterization				
Sildenafil (75 mg/day or 1.9 mg/kg/day), Intermittent Transdermal Nitroglycerin (0.2 mg/hour), Digoxin, Aspirin, Vitamins, Nighttime Oxygen, Short Periods of Inhaled Nitric Oxide (~25 ppm)				
Room Air	2.36	73	28.4	0.96
8 L/min Oxygen	2.21	79	32.6	1.06
8 L/min Oxygen, 20 ppm Nitric Oxide	2.49	22	6.83	0.26
8 L/min Oxygen	1.94	77	34.5	1.01
8 L/min Oxygen, 20 mcg/kg/min Diltiazem	2.59	47	15.4	0.64
21% Oxygen <sup>a</sup>		73 <sup>a</sup>		1.06 <sup>a</sup>
21% Oxygen, 2 h after 50 mg Oral Sildenafil <sup>a</sup>		82 <sup>a</sup>		1.14 <sup>a</sup>
Age: 10 years and 10 months				
Outpatient therapies used since previous heart catheterization				
Amlodipine (7.5 mg/day or 0.14 mg/kg/day), Aspirin, Vitamins, L-arginine, Short Periods of Inhaled Nitric Oxide (~25 ppm)				
Room Air	3.01	41	10.6	0.52
12 L/min Oxygen	3.08	41	9.74	0.49
12 L/min Oxygen, 20 ppm Nitric Oxide	2.82	19	3.55	0.15
12 L/min Oxygen	2.83	42	11.7	0.46
12 L/min Oxygen, 50 meq L-arginine	3.02	41	10.6	0.50
Age: 12 years and 10 months				
Outpatient therapies used since previous heart catheterization				
Amlodipine (7.5 mg/day or 0.11 mg/kg/day), Aspirin, Vitamins				
12 L/min Air	3.70	47	10.8	0.61
12 L/min Air, 20 ppm Nitric Oxide	3.53	21	3.97	0.20
12 L/min Oxygen	3.36	50	12.8	0.56
12 L/min Oxygen, 20 ppm Nitric Oxide	3.22	18	3.42	0.16
Age: 14 years and 3 months				
Outpatient therapies used since previous heart catheterization				
Amlodipine (10 mg/day or 0.13 mg/kg/day), Aspirin, Vitamins, Nighttime Inhaled Nitric Oxide with Oxygen (~20 ppm)				
12 L/min Air	3.42	50	12.0	0.53
12 L/min Air, 20 ppm Nitric Oxide	3.42	24	4.02	0.17
12 L/min Oxygen	3.06	52	13.7	0.49
12 L/min Oxygen, 20 ppm Nitric Oxide	3.51	22	3.42	0.14
21% Oxygen	3.58	55	13.1	0.54
21% Oxygen, 4 mcg/kg/min Nitroglycerin	3.96	42	9.09	0.47
21% Oxygen	3.13	49	13.4	0.49
21% Oxygen, 30 mcg/kg/min Diltiazem	3.96	27	4.80	0.24
Age: 18 years and 0 months				
Outpatient therapies used since previous heart catheterization				
Amlodipine (10 mg/day or 0.13 mg/kg/day), Aspirin, Vitamins				
Room Air	3.45	30	6.38	0.34
15 L/min Air	3.20	31	7.19	0.35

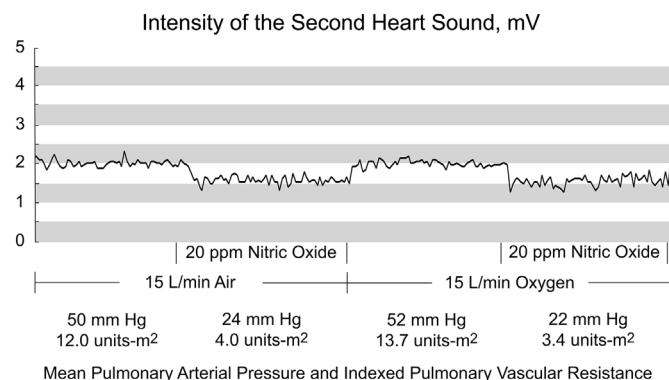
**Table 2 (continued)**

	CI	mPAP	Rp	Rp:Rs or mPAP:mSAP <sup>a</sup>
	L/ min- m <sup>2</sup>	mm Hg	units-m <sup>2</sup>	
15 L/min Oxygen, 20 ppm Nitric Oxide	3.03	18	2.97	0.13
Room Air	3.29	35	8.21	0.41
Room Air, 5 mg intravenous Sildenafil	3.62	32	6.91	0.42
Age: 21 years and 8 months				
Outpatient therapies used since previous heart catheterization				
Amlodipine (10 mg/day or 0.11 mg/kg/day), Aspirin, Vitamins				
Room Air	3.38	36	8.28	0.36
15 L/min Oxygen	3.22	32	8.70	0.37
15 L/min Oxygen, 20 ppm Nitric Oxide	3.09	16	3.92	0.15
Room Air <sup>a</sup>		28 <sup>a</sup>		0.42 <sup>a</sup>
Room Air, 2 hours after 2 mg oral Riociguat <sup>a</sup>		24 <sup>a</sup>		0.37 <sup>a</sup>

Heart catheterization was performed with procedural sedation. Outpatient medications were not given on the day of the procedure. The dose of outpatient vasodilators at the time of heart catheterization are shown in parentheses.

CI: cardiac index calculated by the Fick principle with an assumed oxygen consumption; mPAP: mean pulmonary arterial pressure; mPAP:mSAP: ratio of mean pulmonary arterial pressure and mean systemic arterial pressure; ppm: parts per million; Rp: indexed pulmonary vascular resistance; Rp:Rs: ratio of pulmonary vascular resistance and systemic vascular resistance.

<sup>a</sup> Measurements performed in the intensive care unit following heart catheterization: mPAP and the ratio of mean pulmonary artery pressure to mean systemic arterial pressure.



**Fig. 1.** Intensity of the second heart sound and mean pulmonary arterial pressure during acute vasodilator testing.

The intensity of the second heart sound was measured during heart catheterization at an age of 14 years by acoustic cardiography. The intensity of the second heart sound changed immediately in accordance with changes in pulmonary arterial pressure during 10- to 15-min intervals of acute vasodilator testing with inhaled nitric oxide while breathing air or supplemental oxygen. L/min: liters per minute, mV: millivolts, ppm: parts per million.

syncope did not prevent the progression of disease in our patient. Additional studies are needed to determine whether full- or part-time treatment with iNO will adequately prevent disease progression in acutely responsive patients.

The most appropriate doses of many oral, inhaled and parenteral medications for pulmonary hypertension are unknown in children. It is frequently necessary to empirically adjust the dose of medications to achieve a reasonable balance in safety and efficacy. Adverse effects have limited the dose of amlodipine and the dose of riociguat in our patient.

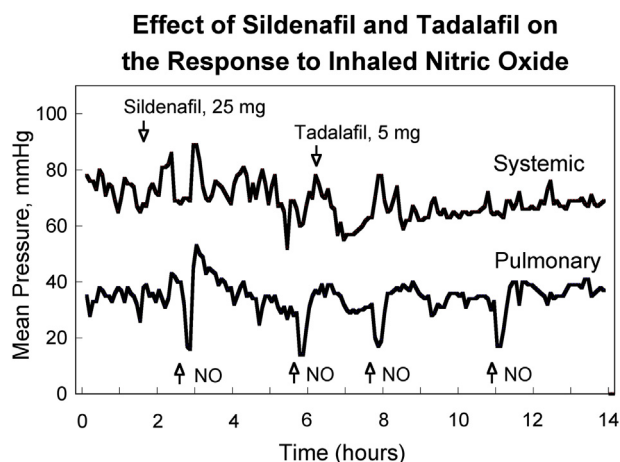


Fig. 2. Effect of phosphodiesterase V inhibitors on the pulmonary vasodilatory effect of inhaled nitric oxide.

The patient was monitored in the intensive care unit following heart catheterization at an age of 10 years. Pulmonary and systemic arterial pressures were measured continuously and recorded every 5 minutes for the graph. Adult doses of sildenafil (25 mg, 0.5 mg/kg) and tadalafil (5 mg, 0.1 mg/kg) were given while the patient was awake. Inhaled nitric oxide (20 parts per million) was administered for intervals of approximately 10 minutes. The pulmonary vasodilatory effect of inhaled nitric oxide was not appreciably prolonged by oral treatment with sildenafil or tadalafil. Less variability in her baseline pulmonary and systemic arterial pressures occurred while she was sleeping, between time points 8–14 hours.

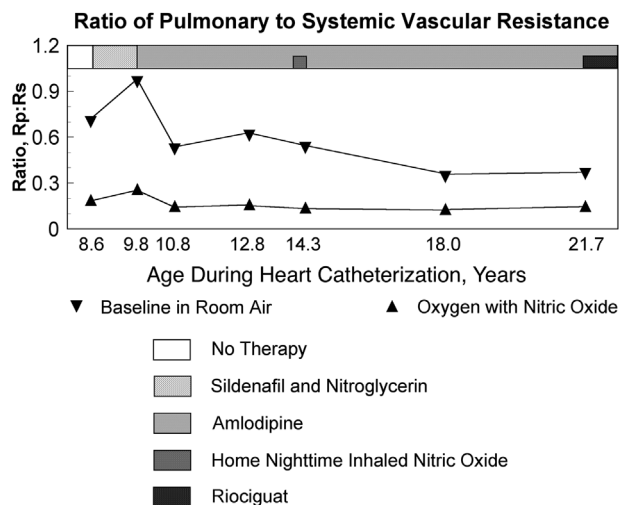


Fig. 3. Timeline of acute vasodilator testing with supplemental oxygen and 20 parts per million inhaled nitric oxide and long-term outpatient therapy.

The baseline ratio of pulmonary to systemic vascular resistance increased while being treated with sildenafil (25 mg/day to 75 mg/day, 0.7 mg/kg/day to 1.9 mg/kg/day) and intermittent transdermal nitroglycerin (0.2 mg/hour). A decrease in the baseline ratio of pulmonary to systemic vascular resistance occurred while being treated with amlodipine (5 mg/day to 15 mg/day, 0.11 mg/kg/day to 0.23 mg/kg/day). The ratio of pulmonary vascular resistance to systemic vascular resistance transiently increased at the onset of puberty. The effect of long-term treatment with amlodipine has not decreased the ratio of pulmonary vascular resistance to systemic vascular resistance to a level that can readily be achieved while breathing nitric oxide.

## 2.5. Right route

Inhaled nitric oxide has a good safety profile because it does not have a direct effect on the systemic circulation. In clinical practice, iNO does not cause significant methemoglobinemia when used at a dose near 20 ppm.

## 2.6. Future directions

Inhaled nitric oxide was approved for the treatment of newborns with respiratory failure associated with pulmonary hypertension in 1999. Outpatient treatment with iNO is still not available, even though some patients acutely respond well to this agent. A recent clinical trial was discontinued with an interim analysis when iNO failed to effectively improve the functional capacity of patients with pulmonary arterial hypertension [5]. The trial demonstrated the feasibility of long-term iNO therapy in an outpatient setting, but patients were enrolled independent of their acute response to iNO and were only eligible if already on an endothelin receptor antagonist, phosphodiesterase V inhibitor or prostacyclin analog. An alternative study might focus on a subset of patients to evaluate the long-term efficacy of iNO: randomizing acute iNO responders to CCB treatment with, or without, concurrent iNO treatment using clinical worsening or an escalation in care as an end-point for treatment failure. A subset of early responders to a CCB ultimately fail therapy over time [6]. The Sitbon criterion for selecting patients for CCB therapy only had a sensitivity of 87%, a specificity of 69%, a positive predictive value of 77%, a negative predictive value of 81%, and an accuracy of 79% [7]. Accordingly, we have an opportunity to determine whether precision care with iNO will improve the outcome of more patients on CCB therapy.

## 3. Conclusion

Our patient has an immediate decrease in pulmonary arterial pressure when she breathes nitric oxide. This response has persisted throughout the course of her care. Her acute response to several medications has been similar to her long-term response to medications in the same class. Acute vasodilator testing with iNO and other medications may be an overlooked opportunity to advance precision care for subsets of patients with pulmonary hypertension.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the University of Utah (Study Numbers 00011458 and 00033414) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of interest

None.

## Conflicts of interest

Pulmonox, SensorMedics and INOTherapeutics provided supplies for the treatment of our patient with inhaled nitric oxide at home. No other funding or support was provided for the treatment of our patient with any medications described in this report. Ronald Day filed an investigator sponsored investigational new drug application with the United States Food and Drug Administration in order to treat this patient with inhaled nitric oxide at home, IND Number 41,844. Pulmonox, SensorMedics and INOTherapeutics were not sponsors and did not participate in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Ronald Day has discussed potential research projects for nitric oxide with Nu-Med Plus without any financial compensation or support for research. The authors have

not invested in any company that has provided, provides, or intends to provide, inhaled nitric oxide therapy. The authors have no financial/personal interest or belief that could affect their objectivity concerning the content of this report.

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