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Inhaled Nitric Oxide Selectively Decreases Pulmonary Vascular Resistance without Impairing Oxygenation during One-lung Ventilation in Patients Undergoing Cardiac Surgery

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Background: **Inhaled nitric oxide (NO), an endothelium-derived relaxing factor, is a selective pulmonary vasodilator. The authors investigated whether inhaled NO decreases pulmonary vascular resistance (PVR) while preserving hypoxic pulmonary vasoconstriction and whether it maintains or improves oxygenation in patients during one-lung ventilation.**

Methods: **In supine cardiac surgical patients with a normal mean pulmonary artery pressure (PAP) (< 25 mmHg, n = 10) or a moderately elevated PAP (25–35 mmHg, n = 10), one-lung ventilation was established with 80% oxygen and 20% nitrogen followed by the same gas mixture containing 20 ppm NO for 6 min.**

Results: **Inhaled NO decreased ($P < 0.05$) PAP from 30 ± 2 to 27 ± 2 mmHg in the patients with moderate pulmonary hypertension. Likewise, PVR decreased ($P < 0.05$) from 266 ± 10 to 205 ± 8 dyn·s·cm^{-5}. The PAP and PVR did not change significantly after NO inhalation in the patients without pulmonary hypertension. All other hemodynamic variables remained unchanged after inhalation of NO in both groups. In the patients with pulmonary hypertension, the PAP and PVR returned to baseline after discontinuation of inhaled NO. Inhaled NO did not significantly change the arterial oxygen tension or venous admixture in either group of patients. Ventilation, airway pressure, tidal volume, and lung compliance also were unaffected by inhaled NO.**

Conclusions: **This study demonstrates that 20 ppm inhaled NO is a selective pulmonary vasodilator in patients with moderate pulmonary hypertension secondary to cardiac disease who are undergoing one-lung ventilation. In contrast to what would be expected with intravenous vasodilators that inhibit hypoxic pulmonary vasoconstriction, inhaled NO does not increase the venous admixture or impair oxygenation. (Key words: Anesthetics, gases: nitric oxide. Blood vessels, vasodilation: endothelium-derived relaxing factor. Lungs: hypoxic pulmonary vasoconstriction; pulmonary hypertension; shunting; vasodilation. Oxygen: blood levels.)**

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 27A.

INHALED nitric oxide (NO), an endothelium-derived relaxing factor, is a selective pulmonary vasodilator in animal models[1–3] and in pediatric[4–6] and adult[7–9] patients with pulmonary hypertension. Vasodilation is limited to the pulmonary vasculature because inhaled NO is rapidly inactivated by hemoglobin as it enters the circulation.[10–12] Furthermore, inhaled NO should vasodilate only ventilated areas of the lung and should not alter hypoxic pulmonary vasoconstriction (HPV) in nonventilated areas. Therefore, in contrast to intravenous vasodilators that inhibit HPV,[13,14] inhaled NO may maintain[3] or improve[8] arterial oxygen tension (Pa_{O_2}) while decreasing pulmonary vascular resistance (PVR). This has been demonstrated by Rossaint *et al.*, who showed that inhaled NO decreases PVR while also decreasing intrapulmonary shunting and increasing Pa_{O_2} in patients with adult respiratory distress syndrome (ARDS).[8]

During one-lung ventilation oxygenation is partly dependent on HPV to increase blood flow to the ventilated lung and decrease shunting.[15] We hypothesized that in patients receiving one-lung ventilation, as in patients with ARDS, inhaled NO would selectively decrease PVR while preserving HPV and maintaining or improving oxygenation. To determine this we measured oxygenation and hemodynamics and calculated venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) before and after NO inhalation in

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supine cardiac surgical patients with normal and elevated pulmonary artery pressure (PAP) who were undergoing one-lung ventilation.

Materials and Methods

This study was approved by the Human Investigation Committee at the University of Virginia, and informed consent was obtained from all patients. Patients were selected if they were undergoing coronary artery bypass graft surgery with a left internal mammary artery and had either a normal preoperative mean PAP (< 25 mmHg, n = 10) or had moderate pulmonary hypertension secondary to cardiac disease (PAP 25–35 mmHg, n = 10). Patients were excluded if they had chronic pulmonary disease. All patients received morphine sulfate (0.1 mg/kg) and scopolamine (0.3 mg) as a premedication. Anesthetic induction consisted of sufentanil (10–15 μg/kg) or fentanyl (40–60 μg/kg) in combination with midazolam (2–6 mg). Metocurine (0.1–0.2 mg/kg) and pancuronium (0.04–0.6 mg/kg) were used for muscle relaxation. The patient's trachea was intubated with an 8.0-mm (ID) Univent tracheal tube containing a bronchial blocker (Fuji Systems, Tokyo, Japan) positioned to occlude the left mainstem bronchus. The position of the tracheal tube and bronchial blocker was verified by auscultation and bronchoscopy. All preoperative medications were continued until the morning of surgery, but no intravenous vasodilators or inotropic agents were administered during the study.

Patient monitoring included a triple-lumen pulmonary artery catheter (7.5-French, Baxter, Irvine, CA), electrocardiogram, pulse oximetry, and a 20-G radial artery catheter (Arrow, Reading, PA). Central venous pressure, PAP, pulmonary artery occlusion pressure, and mean arterial pressure were determined using Viggo-Spectromed T4812ADR transducers (Oxnard, CA) and monitored using a 500 Tram monitoring system (Marquette, Milwaukee, WI). Cardiac output was determined using triplicate room temperature thermodilution, computed through the Marquette monitoring system. Arterial and mixed venous blood gases and saturations were analyzed at 37° C (Mallinckrodt Sensor Systems, Ann Arbor, MI). Peak and plateau airway pressures and tidal volume were recorded from the ventilator (IIB, North American Dräger, Telford, PA).

After induction of anesthesia, two-lung ventilation was initiated with a tidal volume of 10 ml/kg and with a respiratory frequency adjusted to maintain end-tidal carbon dioxide at 30–35 mmHg and the fraction of inspired oxygen ($F_{I_{O_2}}$) at 0.8 using blended oxygen (O_2) and air. After a 15-min equilibration period, blood gases and hemodynamics were recorded. The bronchial blocker was inflated and one-lung ventilation instituted. The $F_{I_{O_2}}$ and tidal volume were kept constant and the respiratory frequency adjusted if needed to maintain a similar end-tidal carbon dioxide. A median sternotomy was performed, and right-sided one-lung ventilation was confirmed. After 20 min of one-lung ventilation, the data were recorded again. NO (20 ppm) was added to the inspiratory limb of the breathing circuit for 6 min, and again the data were collected. Six minutes after discontinuation of NO the variables again were recorded. All data obtained during one-lung ventilation were recorded during dissection of the left internal mammary artery to minimize variations in surgical stimulation. Six additional patients received nitrogen (N_2) rather than NO and served as controls.

When NO (100 ppm in N_2) was added to the inspiratory limb of the circle breathing circuit, the O_2 concentration from the ventilator was adjusted to maintain a constant $F_{I_{O_2}}$ (0.8) and fresh gas flow. The NO and O_2 flow rates were 1 and 4 l/min, respectively, which results in delivery at 20 ppm NO. The inhaled NO concentration was confirmed using an electrochemical sensor (Exidyne Instrumentation Technologies, Exton, PA). O_2 and N_2 concentrations were continuously monitored by Raman spectroscopy (Ohmeda, Salt Lake City, UT).

Vascular resistances and $\dot{Q}_{VA}/\dot{Q}_T$ on 80% O_2 were calculated using standard formulas.[16] Lung compliance was calculated by dividing the tidal volume by the plateau airway pressure.[16] All variables were compared before, during, and after NO by repeated-measures analysis of variance and are expressed as the mean ± standard error of the mean. Significance was stated for $P < 0.05$.

Results

The 20 patients were ASA physical status 3 or 4, aged 60 ± 3 yr, and weighing 78 ± 4 kg. Preoperative room air *p*H, Pa_{O_2}, and arterial carbon dioxide tension were 7.42 ± 0.01, 73 ± 4 mmHg, and 40 ± 1 mmHg, respectively, without a difference between groups. Four additional patients were studied but not included in the results because of technical difficulties with the bronchial blocker or the pulmonary artery catheter.

Changing from two- to one-lung ventilation significantly ($P < 0.05$) decreased Pa_{O_2}, tidal volume, and lung compliance, while $\dot{Q}_{VA}/\dot{Q}_T$ and peak and plateau airway pressures significantly ($P < 0.05$) increased (table 1). Stabilization of hemodynamics, oxygenation, and ventilation after 20 min of one-lung ventilation was established in the six placebo (N_2 only) studies.

Inhaled NO (20 ppm) decreased ($P < 0.05$) the PAP from 30 ± 2 to 27 ± 2 mmHg in the group of patients with pulmonary hypertension (table 2). Likewise, the PVR decreased ($P < 0.05$) from 266 ± 10 to 205 ± 8 $dyn \cdot s \cdot cm^{-5}$ (fig. 1). The PAP and PVR did not change significantly after NO inhalation in patients with a normal PAP. All other hemodynamic variables remained unchanged in both groups after inhalation of NO. In the patients with pulmonary hypertension the PAP and PVR returned to baseline within 6 min after discontinuation of NO.

Inhaled NO (20 ppm) did not significantly alter the Pa_{O_2} or the calculated $\dot{Q}_{VA}/\dot{Q}_T$ in the patients with normal or moderately elevated PAP (fig. 1). Likewise, ventilation, peak and plateau airway pressures, tidal volume, and lung compliance were not significantly affected by inhaled NO (table 1).

Discussion

Low concentrations of inhaled NO (< 80 ppm) have been demonstrated to produce rapid, reversible pulmonary vasodilation in cardiac surgical patients,[9] patients with ARDS,[8] and pediatric patients with pulmonary hypertension due to congenital heart disease,[6] as well as in animal models.[1-5] Pulmonary vasodilation occurs without altering SVR, cardiac output, or ventricular preload. The decrease in PVR is proportional to the baseline PVR in adults with chronic pulmonary hypertension secondary to mitral valve disease[9] and in patients with ARDS.[17] The 23% decrease in PVR observed in this study in patients with moderate pulmonary hypertension and the insignificant change in PVR in patients without pulmonary hypertension are consistent with previous results.[8,9] This study demonstrates that inhaled NO produces selective pulmonary vasodilation in patients with pulmonary hypertension secondary to cardiac disease without impairing oxygenation during one-lung ventilation.

Inhaled NO relaxes pulmonary vessels by activating guanylate cyclase and increasing cyclic guanosine 3′,5′-monophosphate.[18] The nitrovasodilators nitroglycerin and sodium nitroprusside are believed to act by the same mechanism.[19] However, systemic vasodilation does not occur with inhaled NO because upon entering the pulmonary circulation it is rapidly inactivated by hemoglobin.[10-12] We have shown previously that NO is rapidly inactivated even at extremely low hematocrits (*e.g.*, 5%).[20] Most importantly, this rapid reaction with hemoglobin probably prevents NO that is delivered to ventilated regions from reaching areas of the lung that are not ventilated, thus preserving HPV.

Intravenous vasodilators decrease PVR but may also decrease oxygenation. Rossaint *et al.* demonstrated in patients with ARDS that a 35% decrease in PVR resulting from intravenous prostacyclin decreased Pa_{O_2}/FI_{O_2} by 19% because of a 25% increase in pulmonary shunting.[8] Likewise, Casthely *et al.* demonstrated that a 31–37% decrease in PVR caused by sodium nitroprusside and nitroglycerin increased pulmonary shunting by 20–70% in patients with normal lung function.[21] The decrease in Pa_{O_2} secondary to intravenous nitrovasodilators has been demonstrated in animal models to be the result of inhibition of HPV.[13,14] HPV is an important compensatory mechanism in preventing hypoxemia by diverting pulmonary blood flow from hypoxic areas to areas with higher alveolar O_2 concentrations. Consequently, in patients dependent on HPV to maintain oxygenation, the use of intravenous vasodilators to decrease PVR may result in a decrease in Pa_{O_2}. Inhaled anesthetics, which diffuse into the circulation and act as intravenous vasodilators, also may inhibit HPV and decrease Pa_{O_2} during one-lung ventilation.[15,16]

In contrast, inhaled NO should vasodilate only ventilated areas without affecting HPV in hypoxic nonventilated areas. Rossaint *et al.* demonstrated in patients with ARDS that 18 ppm inhaled NO decreased PVR by 18% while increasing Pa_{O_2}/FI_{O_2} by 31%.[8] The increase in Pa_{O_2} resulted from a 3% decrease in the pulmonary shunt fraction and improved ventilation/perfusion matching. Using a hypoxic sheep model, Pison *et al.* also demonstrated that PVR is decreased by 20 ppm inhaled NO while ventilation/perfusion matching improved and Pa_{O_2} is maintained.[3] The quantitative effects of inhaled NO and intravenous vasodilators on Pa_{O_2} and shunting will undoubtedly depend on the baseline PVR and shunt.[17]

Inhaled NO may not be expected to improve oxygenation in patients with a normal PAP undergoing one-lung ventilation. Animal studies have indicated that inhaled NO does not vasodilate nonconstricted pulmonary vessels.[1,2,20] Therefore, we may not expect vasodilation and increased pulmonary blood flow in patients

Table 1. Gas Exchange with Inhaled Nitric Oxide

	Normotensive				Moderate Pulmonary Hypertension			
	2LV	1LV	1LVNO	1LV	2LV	1LV	1LVNO	1LV
Pa_{O_2} (mmHg)	298 ± 11	86 ± 8*	86 ± 8	86 ± 9	254 ± 10	77 ± 7*	78 ± 8	77 ± 8
Pa_{CO_2} (mmHg)	35 ± 1	36 ± 1	36 ± 1	36 ± 1	36 ± 1	36 ± 1	35 ± 1	35 ± 1
*p*H	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
$P\bar{v}_{O_2}$ (mmHg)	42 ± 1	40 ± 1	40 ± 1	40 ± 1	43 ± 1	39 ± 1	39 ± 1	39 ± 1
$\dot{Q}_{VA}/\dot{Q}_T$ (%)	14 ± 1	34 ± 2*	34 ± 2	35 ± 2	14 ± 1	39 ± 2*	37 ± 2	38 ± 2
Paw_{pk} (cmH_2O)	26 ± 1	28 ± 2*	29 ± 2	28 ± 2	27 ± 2	29 ± 2*	29 ± 2	29 ± 2
Paw_{pl} (cmH_2O)	18 ± 1	21 ± 1*	22 ± 1	21 ± 1	18 ± 1	21 ± 1*	21 ± 1	21 ± 1
V_T (ml)	711 ± 12	642 ± 13*	647 ± 12	640 ± 12	721 ± 12	640 ± 11*	648 ± 11	646 ± 12
C_{ST} (ml/cmH_2O)	39 ± 2	31 ± 2*	30 ± 2	30 ± 2	40 ± 2	30 ± 2*	31 ± 2	31 ± 2

Gas exchange (mean ± SEM) with inhaled nitric oxide in patients with moderate pulmonary hypertension and in normotensive patients.

2LV = two-lung ventilation; 1LV, 1LVNO, and 1LV = one-lung ventilation before, during, and after nitric oxide, respectively; Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension; *p*H = arterial *p*H; $P\bar{v}_{O_2}$ = mixed venous oxygen tension; $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture; Paw_{pk} = peak airway pressure; Paw_{pl} = plateau airway pressure; V_T = tidal volume; C_{ST} = lung compliance.

* Significantly ($P < 0.05$) different from 2LV by analysis of variance.

without pulmonary hypertension. In contrast to normotensive patients, we expected oxygenation to improve in patients with pulmonary hypertension, for two reasons. First, the decrease in PVR should have resulted from vasodilation only in the ventilated lung. Consequently, this vasodilation may be expected to increase pulmonary blood flow to the ventilated lung and increase Pa_{O_2}. Second, a decrease in PAP should enhance HPV in the nonventilated lung, which should decrease pulmonary shunting and improve oxygenation.[22] An increase in Pa_{O_2}, which previously has been observed after NO inhalation in ARDS patients, results from a decrease in intrapulmonary shunting and an improvement in ventilation/perfusion matching.[8] Inhaled NO did not decrease $\dot{Q}_{VA}/\dot{Q}_T$ (which, measured on 80% O_2, is close to shunt) in our study, despite what was likely a similar baseline shunt fraction and decrease in PVR. We did not attempt to determine the effects of inhaled NO on ventilation/perfusion matching in our patients. Theoretically, the effects of inhaled NO on $\dot{Q}_{VA}/\dot{Q}_T$ depend on the baseline shunt and the flow distribution. Therefore, it is possible that different disease states, *i.e.*, ARDS *versus* pulmonary hypertension secondary to cardiac disease, can explain the difference in the

Table 2. Hemodynamics with Inhaled Nitric Oxide

	Normotensive				Moderate Pulmonary Hypertension			
	2LV	1LV	1LVNO	1LV	2LV	1LV	1LVNO	1LV
HR (beats · min^{-1})	64 ± 2	64 ± 2	64 ± 2	65 ± 2	66 ± 3	64 ± 2	64 ± 2	64 ± 2
CVP (mmHg)	13 ± 1	13 ± 1	13 ± 1	13 ± 1	14 ± 1	15 ± 1	15 ± 1	15 ± 1
PAP (mmHg)	20 ± 2	21 ± 2	21 ± 2	21 ± 2	30 ± 1	30 ± 2	27 ± 2*	30 ± 2
PAOP (mmHg)	11 ± 1	12 ± 1	12 ± 1	12 ± 1	17 ± 1	17 ± 1	17 ± 1	17 ± 1
MAP (mmHg)	84 ± 5	82 ± 4	84 ± 4	84 ± 4	88 ± 4	84 ± 4	85 ± 4	85 ± 4
CO ($l \cdot min^{-1}$)	4.2 ± 0.5	4.4 ± 0.4	4.5 ± 0.6	4.4 ± 0.5	4.1 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	4.1 ± 0.4
PVR (dyn · s · cm^{-5})	170 ± 12	173 ± 11	164 ± 12	172 ± 13	248 ± 10	266 ± 10	205 ± 8*	256 ± 10
SVR (dyn · s · cm^{-5})	1352 ± 21	1251 ± 24	1260 ± 20	1287 ± 22	1409 ± 21	1376 ± 22	1366 ± 22	1366 ± 20

Hemodynamics (mean ± SEM) with inhaled nitric oxide in patients with moderate pulmonary hypertension and in normotensive patients.

2LV = two-lung ventilation; 1LV, 1LVNO, and 1LV = one-lung ventilation before, during, and after nitric oxide, respectively; HR = heart rate; CVP = central venous pressure; PAP = pulmonary artery pressure; PAOP = pulmonary artery occlusion pressure; MAP = mean arterial pressure; CO = cardiac output; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

* Significantly ($P < 0.05$) different from 1LV by analysis of variance.

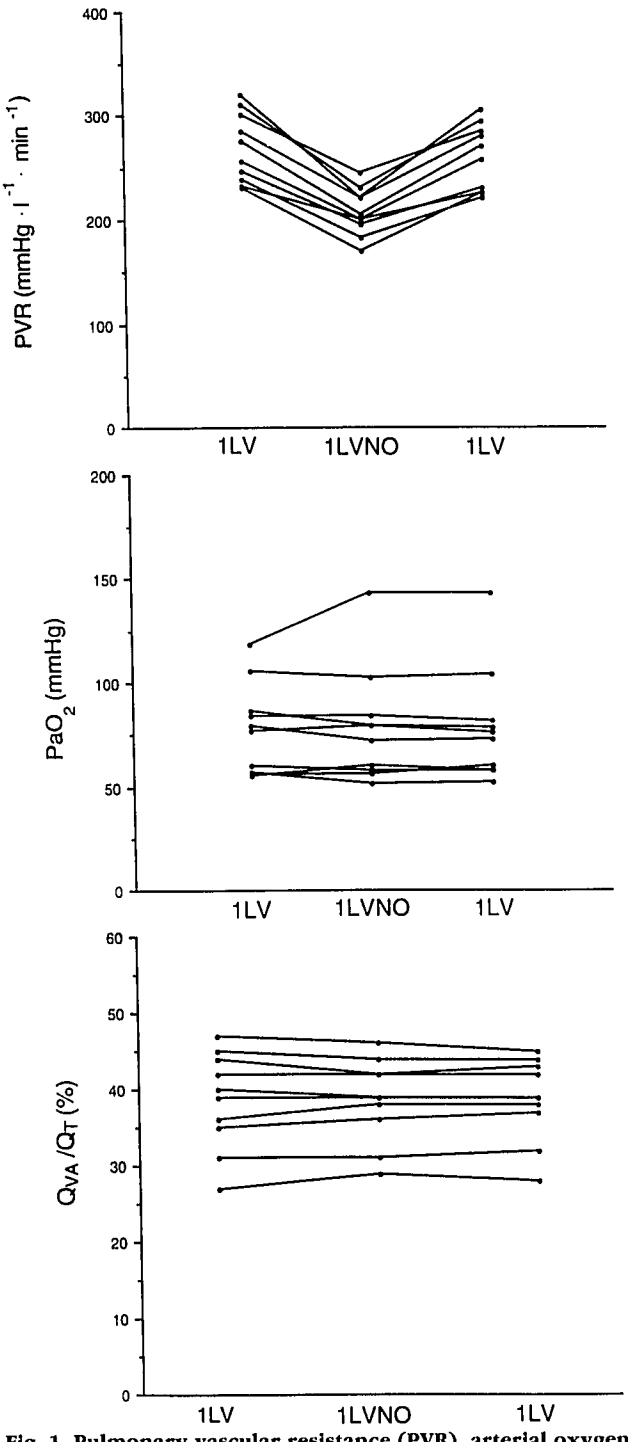

Fig. 1. Pulmonary vascular resistance (PVR), arterial oxygen tension (Pa_{O_2}), and venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) during one-lung ventilation before nitric oxide (1LV), during nitric oxide (1LVNO), and after nitric oxide (1LV) in ten patients with moderate pulmonary hypertension. PVR decreased significantly ($P < 0.05$) with inhaled nitric oxide.

results. The patients in our study had normal room-air blood gases, unlike ARDS patients with severe respiratory compromise. In Pison and colleagues' sheep study, the lungs were normal, and the decrease in PVR was not associated with an increase in Pa_{O_2}.[3] Although unlikely, we also cannot rule out the possibility that NO leaked into the nonventilated lung even though collapse of the left lung was observed. An NO leak to the nonventilated lung may inhibit HPV and negate the positive effects of vasodilation in the ventilated lung.

Although Pa_{O_2} was not increased, the positive aspect of this study is that it was not decreased, as would be expected with intravenous vasodilators. A direct comparison of the effects of sodium nitroprusside or nitroglycerin *versus* inhaled NO may be difficult because intravenous vasodilators also alter systemic hemodynamics. Changes in cardiac output alone can alter HPV and pulmonary shunting. Nevertheless, as demonstrated by the response of patients with ARDS and patients with one-lung ventilation, inhaled NO therapy may be beneficial to patients who require therapy for pulmonary hypertension but would not tolerate a decrease in Pa_{O_2}. The results of our study agree with those of Pison *et al.*[3] and demonstrate that inhaled NO selectively vasodilates the pulmonary vasculature without impairing oxygenation. However, it is yet to be determined if thoracotomy patients who are hypoxemic and who are undergoing one-lung ventilation in lateral decubitus will benefit from inhaled NO.

Inhaled NO (5–300 ppm) has been reported to be a bronchodilator and also to increase lung compliance in a methacholine bronchoconstricted guinea pig lung model.[23,24] Although none of the patients in our study had bronchoconstrictive disease, we did not observe a change in peak or plateau airway pressure, tidal volume, or lung compliance after inhalation of 20 ppm NO. It remains to be determined if any concentration of inhaled NO produces bronchodilation in humans with bronchoconstrictive disease.

In conclusion, inhaled NO selectively decreased PAP and PVR in patients with pulmonary hypertension secondary to cardiac disease who were undergoing one-lung ventilation. These hemodynamic variables were unaffected by inhaled NO in patients without pulmonary hypertension. Most importantly, inhaled NO decreased PVR in patients with pulmonary hypertension without impairing oxygenation or altering $\dot{Q}_{VA}/\dot{Q}_T$ during one-lung ventilation.

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