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Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension

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Abstract. The purpose of this study was to evaluate the hemodynamic effects of inhaled nitric oxide in oxygen ($NO + O_2$) in patients with pulmonary hypertension. Eighteen patients (median age 31.5 months) with pulmonary hypertension inhaled through a mask 100% O_2 and 20 parts per million NO + inspired O_2 fraction (FiO_2) at 0.4. Hemodynamic measurements were made at baseline and after O_2 and $NO + O_2$ administration. The pulmonary vascular resistance index decreased after inhalation of O_2 and $NO + O_2$ ($p = 0.0018$ and $p = 0.0003$, respectively), the decrease being significantly greater after $NO + O_2$ ($p = 0.0311$). Concerning the transpulmonary pressure gradient, a reduction occurred in values after O_2 and $NO + O_2$ inhalation when compared with baseline values ($p = 0.0014$ and $p = 0.0008$). In patients with congenital heart disease, an increase occurred in pulmonary blood flow after O_2 ($p = 0.0089$) and $NO + O_2$ ($p = 0.0019$) compared with baseline values, and an increase also occurred in the pulmonary/systemic blood flow ratio after $NO + O_2$ ($p = 0.0017$). The main side effect related to $NO + O_2$ was pulmonary congestion in 3 patients. Low doses of NO combined with O_2 demonstrated a selective pulmonary vasodilator response in patients with pulmonary hypertension. Despite its use for testing pulmonary reactivity, inhalation of $NO + O_2$ should be carefully administered because of the potential risk of pulmonary congestion.

Key words: Pulmonary hypertension — Nitric oxide — Oxygen — Pulmonary congestion

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Endothelial cells play an important role in modulation of the vascular tone of pulmonary circulation by synthesizing and releasing a variety of substances, one of which is endothelium-derived relaxing factor (EDRF), identified as nitric oxide (NO) [13] or as an NO-related substance [28]. Impairment of endothelium-dependent pulmonary artery relaxation has been described as an important early event in pulmonary vascular disease [12, 14].

Pulmonary vascular disease and pulmonary hypertension affect the clinical course and outcome of some types of cardiac disease or end-stage pulmonary disease [2, 6, 7, 10, 34]. The reactivity of pulmonary circulation obtained in acute pulmonary vasodilator testing is very important in patients with pulmonary hypertension because decisions regarding suitability for corrective surgery, transplantation, and assessment of the long-term prognosis depend on this information [24].

In clinical trials [1, 18, 21, 31, 35, 36] inhaled NO has been shown to be a selective pulmonary vasodilator with minimal systemic effects and without increasing intrapulmonary shunting. However, scarce information exists concerning optimal dosing and the period of administration of NO effective for determining pulmonary vasodilation during cardiac catheterization.

Currently, breathing oxygen is still a standard method of pulmonary vasodilator testing in patients with pulmonary hypertension during cardiac catheterization. However, nonresponders to oxygen have been identified among patients with reactive pulmonary circulation [24]. Therefore, a safe and accurate method for identifying reactive pulmonary vasculature in pulmonary hypertensive patients at cardiac catheterization still remains an important goal.

The aim of this study was to assess the effects of inhaled NO in oxygen used as a screening method for identifying the reversibility of pulmonary vaso-

Table 1. Patient demographics

Patient no.	Age (years)	Sex	Weight (kg)	Diagnosis
1	1.3	M	7.2	Double ventricle outlet, atrial septal defect
2	0.9	M	6.8	Atrioventricular canal defect, PDA, Down's syndrome
3	2.9	M	10.4	Dilated cardiomyopathy
4	7.7	M	24.7	Dilated cardiomyopathy
5	1.7	M	8.3	Atrioventricular canal defect
6	2.0	M	11	Ventricular septal defect
7	1.8	M	10	Right double ventricle outlet, ventricular septal defect
8	1.1	F	7.2	Ventricular septal defect
9	8.0	F	19	Dilated cardiomyopathy
10	30.2	F	47	Atrial septal defect
11	2.6	M	13.6	Dilated cardiomyopathy
12	12.8	F	29	Primary pulmonary hypertension
13	14.0	F	32.5	Dilated cardiomyopathy
14	2.4	F	8.1	Atrioventricular canal defect
15	1.7	M	8	Ventricular septal defect
16	2.9	M	12	Ventricular septal defect
17	2.5	M	8.9	Ventricular septal defect
18	8.0	F	19.2	Ventricular septal defect

F, female; M, male; PDA, patent ductus arteriosus.

constriction in patients with pulmonary arterial hypertension caused by congenital heart disease, primary pulmonary hypertension, and severe cardiomyopathy and also to compare its pulmonary vasodilator effects with those of oxygen.

Materials and Methods

Study Population

The study population consisted of 18 consecutive patients (11 males and 7 females) with pulmonary arterial hypertension referred to the cardiac catheterization laboratory at the Heart Institute (InCor), University of São Paulo Medical School. Twelve patients had congenital heart disease: interventricular septal defect in 6, atrioventricular (AV) canal defect in 3, double-outlet right ventricle in 2, and atrial septal defect in 1. Five children had dilated cardiomyopathy with a mean shortening fraction of 15 ± 2.2% and mean radionuclide left ventricular ejection fraction of 17.2 ± 2.9% and they were candidates for heart or heart–lung transplantation. One child had primary pulmonary hypertension. Their median age was 31.5 months (11 months–30 years). Characteristics of this population are shown in Table 1.

Patients included in this study were cardiomyopathy or primary pulmonary hypertension candidates for heart, heart–lung, or lung transplantation and those with congenital heart disease and pulmonary arterial hypertension (PAMP ≥ 30 mmHg). Those excluded from the study were hemodynamically unstable patients using inotropic drugs, on ventilatory mechanical support, or both.

Written informed consent was obtained from each patient or legal guardian before catheterization. The ethics committee of our hospital approved this study.

Study Protocol

All patients underwent cardiac catheterization as part of an investigation of their disease. During cardiac catheterization, we compared both the hemodynamic effects of inhaling oxygen at an inspired oxygen concentration (FiO_2) of 1.0 and inhaling 20 ppm NO at FiO_2 of 0.4. Cardiac catheterization was performed through the femoral vein and, when clinically indicated, the femoral artery as well. General anesthesia was obtained by association of intravenous midazolam, fentanyl, and ketamine. Once the main pulmonary artery had been accessed and baseline measurements taken, the patients underwent mask inhalation of oxygen with FiO_2 of 1.0 for 10 minutes. After the inhalation of oxygen had been stopped and the cardiopulmonary parameters had returned to baseline, the patients inhaled NO by face mask at a flow rate calculated to deliver inspired NO at a concentration of 20 ppm at FiO_2 of 0.4 for 20 minutes.

Hemodynamic Assessment

Hemodynamic measurements were carried out at baseline, after mask inhalation of oxygen, and after inhalation of nitric oxide plus oxygen.

The following hemodynamic parameters were recorded: right atrial, left atrial, pulmonary, and systemic arterial pressures. In patients with intracardiac shunt, the left atrial pressure was obtained directly; in patients without intracardiac shunt, the left atrial pressure was measured via pulmonary wedge pressure. Cardiac output was determined by the thermodilution technique in patients without intracardiac shunt (group A) or by the Fick oxygen technique in patients with intracardiac shunt (group B). Oxygen consumption was estimated and was assumed to be constant throughout the study. Derived hemodynamic variables were calculated according to standard formulas: cardiac index (L/min/m^2), transpulmonary pressure gradient (TPG), systemic vascular resistance index, pulmonary vascular resistance index (PVRI), pulmonary blood flow, and pulmonary/systemic blood flow ratio (Q_p/Q_s).

A significant acute vasodilator response was defined by a reduction in PVRI of 20% or more from the baseline [4].

Table 2. Hemodynamic variables evaluated in patients without intracardiac shunt (group A) and with intracardiac shunt (group B) at baseline, after oxygen (O_2), and after nitric oxide in oxygen (NO + O_2)

Variable	Baseline	O_2	NO + O_2
Pulmonary vascular resistance index (U/m^2)			
Group A	12.89 ± 7.50	7.42 ± 3.74	4.69 ± 2.37
Group B	9.39 ± 6.52	6.09 ± 6.08	4.83 ± 3.13
Mean pulmonary artery pressure (mmHg)			
Group A	47.50 ± 10.60	43.67 ± 5.28	37.00 ± 10.73
Group B	51.58 ± 9.37	47.83 ± 8.82	49.25 ± 7.07
Left atrial pressure (mmHg)			
Group A	13.33 ± 9.37	21.33 ± 11.09	23.50 ± 10.33
Group B	8.92 ± 4.70	10.33 ± 6.80	10.83 ± 7.07
Cardiac index (L/min/m^2)			
Group A	2.30 ± 0.54	2.62 ± 0.70	2.88 ± 1.01
Group B	1.97 ± 1.11	2.39 ± 1.32	2.04 ± 0.84
Right atrial pressure (mmHg)			
Group A	8.60 ± 3.36	9.20 ± 1.92	9.80 ± 3.42
Group B	4.33 ± 3.63	3.92 ± 2.47	4.0 ± 2.92
Mean arterial blood pressure (mmHg)			
Group A	65.00 ± 13.59	66.83 ± 8.23	72.17 ± 11.09
Group B	65.08 ± 12.62	66.25 ± 12.31	67.17 ± 13.71
SVRI (U/m^2)			
Group A	20.16 ± 9.31	18.44 ± 6.78	18.43 ± 6.24
Group B	18.27 ± 9.88	18.71 ± 17.5	17.92 ± 8.62
Transpulmonary gradient pressure (mmHg)			
Group A	34.17 ± 10.40	23.67 ± 9.79	19.33 ± 11.62
Group B	43.17 ± 11.42	38.42 ± 13.31	39.25 ± 10.52
Pulmonary blood flow (L/min/m^2)			
Group B	3.29 ± 1.76	4.86 ± 2.32	4.91 ± 2.03
Q_p/Q_s			
Group B	1.71 ± 0.76	2.32 ± 0.99	2.56 ± 1.1

Delivery and Monitoring of NO

A tank containing 500 ppm of NO in nitrogen (N_2) (White & Martins, São Paulo, Brazil) was connected to a specially designed low-flow blender. The mixture of NO and N_2 was continuously delivered and entered the inspiratory limb of the closed breathing circuit attached to the face mask. Before patient inhalation, the inspiratory mixture was passed through a soda lime canister placed close to the patient on the inspiratory limb for scavenging nitrogen dioxide (NO_2). NO and NO_2 levels were continuously monitored by on-line electrochemical analyzers (PAC II NO and PAC II NO_2, respectively; Drager, Germany). The concentrations of NO_2 levels in the inhaled air never exceeded 1 ppm.

Statistics

The results were expressed as mean values ± SEM. The statistical analysis was performed by repeated measures of analysis of variance where appropriate. A value of $p < 0.05$ was considered significant.

Results

Mean values for central hemodynamic variables during control, O_2, and NO + O_2 are given in Table 2. The decrease in PVRI, after inhalation of O_2 and NO + O_2 in relation to baseline, was significant ($p = 0.0018$ and $p = 0.0003$, respectively), and the decrease was significantly greater when NO + O_2 was used in comparison with O_2 effect ($p = 0.0311$) (Fig. 1). In relation to group A, the decrease in PVRI was significant after O_2 and NO + O_2 ($p = 0.0016$ and $p = 0.0021$, respectively). The decrease was

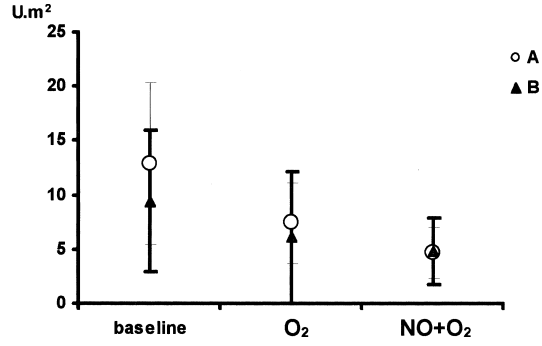

Fig. 1. Effects of oxygen (O_2) and nitric oxide in oxygen (NO + O_2) inhalation on pulmonary vascular resistance index. Group A, patients without intracardiac shunt; group B, patients with intracardiac shunt.

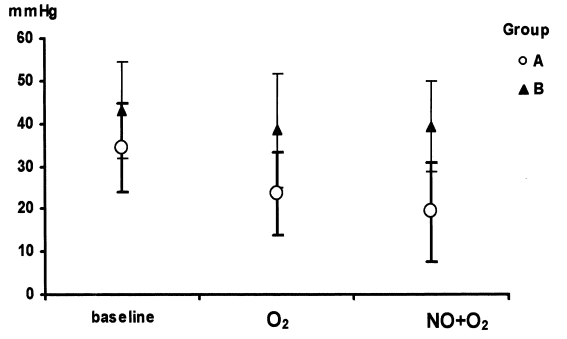

Fig. 2. Effects of oxygen (O_2) and nitric oxide in oxygen (NO + O_2) inhalation on transpulmonary gradient pressure. Group A, patients without intracardiac shunt; group B, patients with intracardiac shunt.

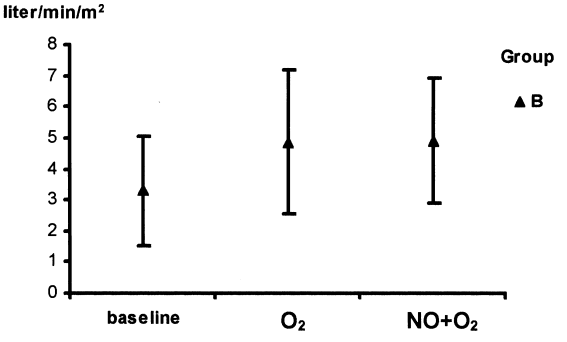

Fig. 3. Effects of oxygen (O_2) and nitric oxide in oxygen (NO + O_2) inhalation on pulmonary blood flow. Group B, patients with intracardiac shunt.

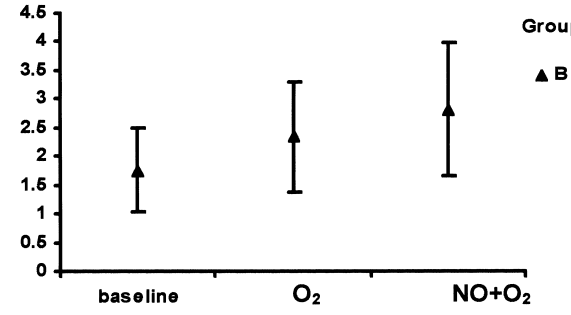

Fig. 4. Effects of oxygen (O_2) and nitric oxide in oxygen (NO + O_2) inhalation on pulmonary blood flow/systemic blood flow ratio (Q_p/Q_s). Group B, patients with intracardiac shunt.

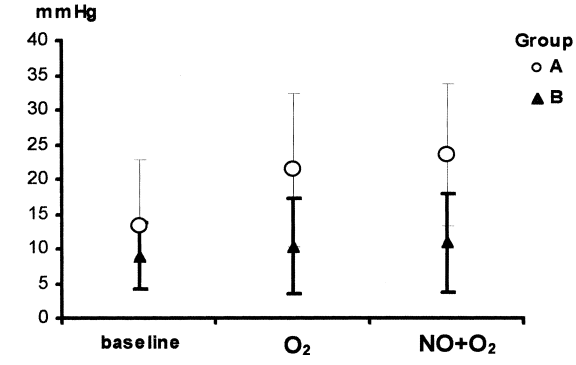

Fig. 5. Effects of oxygen (O_2) and nitric oxide in oxygen (NO + O_2) inhalation on left atrial pressure. Group A, patients without intracardiac shunt; group B, patients with intracardiac shunt.

significantly greater after NO + O_2 in comparison with O_2 ($p = 0.0049$). In group B, the decrease in PVRI was significant after O_2 and NO + O_2 ($p = 0.02$ and $p = 0.002$, respectively).

Concerning TPG, a significant reduction also occurred in values after O_2 and NO inhalation when compared with values at baseline ($p = 0.0014$ and $p = 0.0008$) (Fig. 2). In group A, the decrease in TPG was significant after O_2 and NO + O_2 ($p = 0.004$ and $p = 0.0009$, respectively). In patients with congenital heart disease, an increase occurred in pulmonary blood flow after both O_2 ($p = 0.0089$) and NO + O_2 ($p = 0.0019$) when compared with baseline values (Fig. 3). The pulmonary/systemic blood flow ratio (Q_p/Q_s) varied only after NO + O_2 ($p = 0.0017$) (Fig. 4). Mean systemic arterial pressure, mean pulmonary arterial pressure, systemic vascular resistance index, systemic cardiac index, and right atrial pressure did not change with administration of O_2 or NO + O_2.

According to the criteria of responsiveness (PVRI reduction of 20% or more), O_2 caused a positive response in 13 patients. Among the O_2 nonresponders, we identified 3 patients that responded to NO + O_2 inhalation. A positive response to NO + O_2, inhalation was seen in 15 patients. Among the 3 nonresponders to NO + O_2, 2 responded to O_2. One patient did not respond either to O_2 or NO + O_2. A significant increase occurred in left atrial pressure after O_2 and NO + O_2 ($p = 0.0018$ and $p = 0.0006$, respectively) in relation to baseline in patients in group A (Fig. 5). Three patients (ages 2, 8, and 14 years) experienced pulmonary edema after NO + O_2 inhalation. These patients had cardiomyopathy and were candidates for heart transplantation. All 3 patients developed an increase in left atrial pressure and a decrease in TPG and PVRI. At the time of the study, all patients who developed pulmonary edema were receiving furosemide, angiotensin-converting enzyme inhibitors, digoxin, and a potassium supplement. The radionuclide left ventricular ejection fractions of these patients were 18%, 18%, and 12%, respectively. Patients developed dyspnea, cool extremities, and crackles over the lungs at the end of the administration of NO + O_2 inhalation. After measurements were obtained, NO + O_2

was discontinued, and patients were successfully treated with inhalation of oxygen and intravenous furosemide and returned to the prior condition.

Among the patients with positive pulmonary vascular reactivity response, six with congenital heart disease (two patients responders to O_2 one responder to NO + O_2, and three responders to NO + O_2 and O_2) underwent cardiac surgery. One patient who did not respond to oxygen or NO + O_2 underwent a corrective intracardiac operation of congenital malformation. All seven patients had good outcome 6 months after surgery.

Among six patients referred for heart or heart–lung transplantation or lung transplantation, four had PVRI less than 6 U/m^2 (one was scheduled for orthotropic heart transplantation but died due to pulmonary thromboembolism, one patient's family refused transplantation, and two had myocarditis and underwent imunnosuppression). Two patients had PVRI > 6 U/m^2 (one was scheduled for heart–lung transplantation, and one was scheduled for lung transplantation but died waiting for a donor).

Discussion

In this study, we compared the effects of inhaled O_2 and inhaled NO + O_2 on central hemodynamics in patients with pulmonary hypertension. Inhaled NO + O_2 results in a greater decrease in PVRI than does O_2 alone. Our data demonstrated that the combination of a low dosage of NO and O_2 was a more potent pulmonary arterial vasodilator than O_2 alone in selected patients with pulmonary hypertension.

Low doses of NO have been successfully used in heart transplantation [5], cardiac surgery in adults [11], postoperative management of congenital heart disease [35], and in pulmonary arterial hypertension in newborns [30]. However, few studies have reported a short period of inhalation of low doses of NO + O_2 to test pulmonary reactivity in patients with pulmonary hypertension during routine cardiac catheterization [3, 31].

Comparison with Other Studies

We observed a significant reduction in PVRI and an increase in the pulmonary to systemic blood flow ratio, evidencing primarily an increase in pulmonary flow. Similar results have been described by other investigators but using higher doses of NO in O_2 [4, 31].

A recent study [26] reported that inhaled NO at a concentration of 20 ppm was the lowest mean dose to cause a maximum reduction in PVRI in patients with heart failure and pulmonary hypertension, even though a few patients required 40 ppm. In our study, a positive reactive pulmonary territory response was obtained in all pediatric heart transplant recipients using 20 ppm NO with FiO_2 at 0.4.

The absence of changes in systemic arterial pressure in our investigation was similar to that in other trials [3, 31]. Therefore, the association of NO + O_2 seems to be more appropriate when systemic hypotension must be avoided in patients with pulmonary hypertension.

The presence of some responders to O_2, but not to NO + O_2, and a greater pulmonary vasodilation response to the association of NO + O_2 compared with O_2 alone were consistent with those observations described by Atz and collegues [4]. Nevertheless, these authors used higher doses of NO + O_2. These findings suggest that the mechanisms involved may not be identical, and that the individual dose–response could be quite different. Nitric oxide causes vasorelaxation through a cyclic guanosine monophosphate-mediated pathway. The mechanism of vasorelaxation caused by O_2 is not known [15].

Side Effects of NO + O_2

Our results show that in patients with congenital heart disease, acute pulmonary vasodilation with inhalation of NO + O_2 was obtained without any adverse side effects. Otherwise, this mixture in pediatric candidates for heart transplantation may cause relief of pulmonary vasoconstriction and determine pulmonary edema. Pulmonary edema was observed during the acute vasodilator test mainly in those patients with severe left ventricular dysfunction. Despite the low dosage of NO in our study—lower than the dosage described by Bocchi et al. [8] (40 and 80 ppm), who reported pulmonary edema in an adult population—three children in our study developed this complication. A decrease in PVRI and an increase in pulmonary wedge pressure observed in our study were previously reported in the evaluation of pulmonary hypertension using NO [8, 9, 23, 26, 27, 32] in adult candidates for heart transplantation. In the clinical trials [3, 4, 31] of the inhalation of NO + O_2, pulmonary edema has not been reported. The mechanism of pulmonary edema in patients with severe ventricular dysfunction and pulmonary hypertension is unknown and speculative. Loh et al. [27] suggest that NO induces an increase in left ventricular filling pressure due to a small increase in left ventricular volume that occurred secondary to an increase in pulmonary venous return flow. For a given pulmonary artery pressure, a decrease in pulmonary vascular resistance will result in an increase in the net driving force for left ventricular fill-

ing. Although an increase in left ventricular volume would increase ejection fraction and stroke volume in a normal left ventricle, in the presence of depressed contractility the ventricle may not respond to the acute preload increase. Another hypothesis is that inhaled NO could exert a direct negative inotropic effect on the heart [17], resulting in a primary increase in left ventricular filling pressure. The passive pulmonary vasodilation might occur because of recruitment of precapillary vessels [20]. However, this hypothesis is less likely because NO is rapidly inactivated by hemoglobin [29] and might not reach the coronary circulation. However, counter suggestion has been made that NO binds avidly with heme proteins and sulfhydryl-containing groups [33], and the half-life of these active intermediates may extend to 15 to 30 seconds [25]—long enough to reach the coronary circulation and endocardium and potentially modulate ventricular function.

Hayward et al. [22] reported an increase in pulmonary capillary wedge pressure in patients with dilated cardiomyopathy and normal pulmonary vascular resistance during inhaled NO. They concluded that 20 ppm NO does not affect left ventricular function. They believe that elevation in left ventricular filling pressure during inhaled NO is probably due to intrathoracic volume shifts in the context of reversible pulmonary hypertension, as suggested by modeling studies [16] in patients with severe heart failure and pulmonary hypertension.

$NO + O_2$ Toxicity

It has been reported that NO in combination with O_2 may generate toxic compounds, notably NO_2 [19]. This process can be reduced by limiting the concentration of NO used and minimizing the time of contact between NO and O_2 prior to and during administration. In our study, NO_2 was always below the toxicity level, probably because the NO protocol was limited to 20 minutes combined with the low dosage of NO and O_2 and the NO inflow was near the patient's airway. In addition, the reduction of NO_2 content may also be explained by the presence of soda lime before inhalation [19].

Limitations and Clinical Implications

This report shows that low doses of NO in O_2 *at cardiac catheterization in patients with pulmonary hypertension may be efficient despite differences in the causes of pulmonary hypertension in the study population.*

Our results demonstrate that the combination of low-dose inhaled NO and O_2 may cause a potent selective pulmonary vasodilation, with no changes in systemic arterial pressure. It appears that the combination of a low dosage of NO and O_2 fulfills many of the ideal characteristics required to test the responsiveness of the vascular bed in patients with pulmonary hypertension during diagnostic cardiac catheterization. However, it is important to be aware of the potencial hazards of the combination of NO + O_2. Large studies on the effects of low NO + O_2 are required to prove the beneficial effect of testing pulmonary vascular reactivity in children with severe left ventricular dysfunction, mainly in those nonresponders to pure O_2. In fact, the combination of NO + O_2 even at low doses may cause undesired side effects, such as pulmonary edema, which could have a detrimental effect on clinical outcome.

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