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Nitric oxide inhalation increases oxygen delivery after cardiovascular surgery in adult patients whether or not they have pulmonary hypertension

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Abstract

Purpose. The purpose of this study was to quantify the increase in oxygen delivery (DO_2) produced by nitric oxide (NO) inhalation, and to clarify whether NO inhalation might be effective in adult patients after cardiovascular surgery whether or not they have pulmonary hypertension (PH).

Methods. The study was done on 26 adult patients after cardiovascular surgery. The indications for NO inhalation were postoperative hypoxic respiratory failure (POHRF) with or without PH. NO was administered via a premixing system or via a side-stream system. The dose was adjusted to between 1 and 10 (5.7 ± 2.0) (mean ± SD) ppm. Data were obtained just before and within 120 min after the initiation of NO inhalation. We initially analyzed the data from all the patients together and then compared data from two groups made up from just 22 of the 26 patients: 14 patients without PH whose PaO_2/FiO_2 before NO inhalation was less than 200 mmHg (simple POHRF group), and 8 patients who had both POHRF and PH (systolic pulmonary arterial pressure higher than 40 mmHg) (POHRF with PH group).

Results. In the original group of 26 patients, significant improvements were observed in PaO_2, PaO_2/FiO_2, CI, SPAP, CaO_2, DO_2I, and SvO_2 during NO inhalation. The increase in DO_2I was 68 $ml \cdot min^{-1} \cdot m^{-2}$ (+19.5%). PaO_2, PaO_2/FiO_2, CaO_2, DO_2I, and SvO_2 increased significantly in both groups. The increase in DO_2I was 60 $ml \cdot min^{-1} \cdot m^{-2}$ (+18.9%) in the simple POPHRF group and 79 $ml \cdot min^{-1} \cdot m^{-2}$ (+18.0%) in the POHRF with PH group.

Conclusion. NO inhalation increases DO_2 by approximately 20% in adult patients after cardiovascular surgery, irrespective of whether or not they have pulmonary hypertension.

Key words: Cardiovascular surgery, Nitric oxide inhalation, Oxygen delivery, Pulmonary hypertension, Respiratory failure

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Introduction

Inhalation of nitric oxide (NO), a selective pulmonary vasodilator [1–3], is a newly developed therapy for a variety of diseases, including hypoxic respiratory failure (HRF) [4,5], primary pulmonary hypertension of the newborn (PPHN) [6,7], postoperative pulmonary hypertension (POPH) after cardiac surgery [8–10], right ventricular dysfunction in patients with or without a left ventricular assist system (LVAS) [11], and reduced pulmonary blood flow after right ventricular bypass surgery [12]. Most of the above papers demonstrated its effectiveness by showing improvements in arterial blood oxygenation and/or reductions in pulmonary arterial pressure (PAP) or pulmonary vascular resistance. Although one of the main purposes of NO inhalation is to increase oxygen delivery, few reports have focused on this variable. Of course, it is evident that inhalation of NO should increase oxygen delivery by virtue of the improvement in arterial blood oxygenation, but little is known about the extent of the increase in oxygen delivery produced by NO inhalation. Recently, it was reported that NO inhalation increased exercise capacity in congestive heart failure [13]. An increase in oxygen delivery caused by NO inhalation might contribute to such an improvement. Further, multiple organ failures due to low cardiac output syndrome (LOS) after cardiovascular surgery result mainly from a deterioration in oxygen delivery [14], and so it is clearly very important to increase oxygen delivery in patients who have undergone cardiovascular surgery. However, it seemed doubtful whether NO inhalation would improve oxygen delivery in patients without PH. In this study, we evaluated the magnitude of the increase in oxygen delivery produced by NO inhalation and tried to determine whether it might be effective in adult patients after various types of cardiovascular surgery, irrespective of the presence or absence of PH.

Patients and methods

The study involved a total of 26 adult patients (8 women and 18 men) between 45 and 77 (67.2 ± 7.8) years of age, all of whom received NO inhalation after cardiovascular surgery (Table 1). Their underlying diseases were acquired valvular disease (AVD) in 11 patients, thoracic aneurysm of the aorta (TAA) in 11 patients, and coronary arterial obstructive disease (CAOD) in 4 patients. The indications for NO inhalation were postoperative hypoxic respiratory failure (POHRF) with or without postoperative pulmonary hypertension (PH).

Each patient was ventilated with a fixed tidal volume throughout the study period. NO was supplied by a cylinder containing 400 ppm NO (balance: N_2) using either a premixing system and a demand valve-type of ventilator (Servo-900C, Siemens Elema, Solna, Sweden) or a side-stream system and a constant flow-type of ventilator (Bird-8400 STi, Bird Products, Palm Springs, CA, USA). The concentration of inspiratory NO was measured by chemiluminescence, with a nitric oxide analyzer (NOA 280, Sievers Instruments, Boulder, USA) being used to analyze samples of circuit gases obtained from a T-piece connector. The flowmeter was adjusted to obtain the required inspiratory NO concentration (between 1 and 10 ppm).

Arterial blood gases and hemodynamic parameters were measured just before and within 120 min after the initiation of NO inhalation. Arterial blood gases were measured with an ABL 505 or 620 (Radiometer, Copenhagen, Denmark). Hemoglobin, methemoglobin (metHB), and arterial oxygen content (CaO_2) were measured with a cooxymeter (OSM3, Radiometer, Copenhagen, Denmark). Blood pressures were measured with a bedside monitoring system (Model 68S, Hewlett Packard, Germany). In 22 of the patients, an Oximetric Swan-Ganz catheter (7.5 Fr, Oximetrix, Abbott Laboratories, Chicago, IL, USA) was inserted, and pulmonary arterial pressure (PAP), cardiac output (CO) by the thermo-dilution method, and mixed venous oxygen saturation (SvO_2) were measured.

Oxygen delivery index (DO_2I) was calculated by a standard formula:

$$DO_2I\ (ml \cdot min^{-1} \cdot m^{-2}) = CaO_2\ (vol\%) \times CO\ (l \cdot min^{-1}) \times 10/BSA(m^2)$$

where BSA is body surface area.

Informed consent was obtained from all patients, and the study was approved by the Institutional Committee on Human Research.

We initially analyzed data from all the patients together. Then, to evaluate whether the patient's background condition influenced the effect produced by NO inhalation, we divided 22 of the patients into two groups: 14 HRF patients without PH (simple POHRF group), and eight HRF patients with PH (POHRF with PH group). The criteria for entry into this comparative analysis (for HRF and PH, respectively) were a PaO_2/FiO_2 of less than 200 mmHg just before the start of NO inhalation and a systolic pulmonary artery pressure (SPAP) higher than 40 mmHg.

All data are expressed as mean ± SD. Comparisons between data before and during NO inhalation were made by paired Student's *t*-tests, whereas comparisons between the two groups were made by unpaired *t*-tests. A *P* value less than 0.05 was considered significant.

Results

Data from all the patients are listed in Table 3. There were no significant changes in FiO_2, Hb, pH, $PaCO_2$, or base excess (BE) during NO inhalation. Both PaO_2 and PaO_2/FiO_2 increased significantly during NO inhalation. The increase in CaO_2 (+0.83 vol%) was significant. DO_2I increased significantly from 426 to

Table 1. Summary of patients' characteristics

Characteristic	Value
No. of patients	26
Sex (F/M)	8/18
Age (yr)	67.2 ± 7.8 (45–77)
Body weight (kg)	57.1 ± 9.3 (43–71.7)
Height (cm)	160.0 ± 8.8 (143–175)
Underlying disease	
AVD	11
TAA	11
CAOD	4

AVD, Acquired valvular disease; TAA, thoracic aneurysm of the aorta; CAOD, coronary arterial obstructive disease. Data are expressed as mean ± SD.

Table 2. Characteristics of patients with postoperative hypoxic respiratory failure with or without pulmonary hypertension

Characteristic	Simple POHRF	POHRF with PH
No. of patients	14	8
Sex (F/M)	4/10	3/5
Age (yr)	68.1 ± 7.8	63.5 ± 8.2
Body weight (kg)	57.7 ± 9.1	53.9 ± 8.4
Height (cm)	159 ± 7	158 ± 9
DIC (days)	16.9 ± 12.5	7.5 ± 2.7*
Outcome (died)	1	0

POHRF, Postoperative hypoxic respiratory failure with PaO_2/FiO_2 less than 200 mmHg; PH, pulmonary hypertension with systolic pulmonary arterial pressure (SPAP) higher than 40 mmHg; DIC, duration of intensive care. Data are expressed as mean ± SD. * Significant compared with simple POHRF (unpaired Student's *t*-test).

Table 3. Changes in various values induced by nitric oxide (NO) inhalation in all patients

Value	Before NO inhalation	During NO inhalation	% change
NO (ppm)	—	5.7 ± 2.0	
FiO_2	0.72 ± 0.17	0.70 ± 0.17	
pH	7.441 ± 0.066	7.443 ± 0.062	
$PaCO_2$ (mmHg)	40.8 ± 4.9	39.7 ± 3.9	
PaO_2 (mmHg)	93.6 ± 43.3	146.3 ± 65.7*	+62.6 ± 50.1
PaO_2/FiO_2 (mmHg)	140.3 ± 88.6	223.4 ± 109.0*	+70.6 ± 60.4
Hb ($g \cdot dl^{-1}$)	11.1 ± 1.6	11.3 ± 1.4	
CaO_2 (vol%)	14.6 ± 2.3	15.4 ± 2.0*	+6.3 ± 6.2
DO_2I ($ml \cdot min^{-1} \cdot m^{-2}$)	426 ± 107	494 ± 95*	+19.5 ± 22.0
SvO_2 (%)	64.0 ± 11.3	70.3 ± 7.1*	+11.6 ± 13.4
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.93 ± 0.74	3.20 ± 0.68*	+11.8 ± 18.1
SPAP (mmHg)	37.8 ± 11.4	31.5 ± 9.0*	−14.9 ± 13.6
RAP (mmHg)	10.7 ± 3.2	10.0 ± 2.4	
metHB (%)	—	0.89 ± 0.19	

FiO_2, Fraction of oxygen in inspired air; CaO_2, oxygen content in arterial blood; DO_2I, oxygen delivery index; SvO_2, oxygen saturation of mixed venous blood; CI, cardiac index; SPAP, systolic pulmonary arterial pressure; RAP, right atrial pressure; metHB, methemoglobin. Data are expressed as mean ± SD. *Significant compared with the data before NO inhalation (paired Student's *t*-test).

Table 4. Results of the comparative analysis

	Simple POHRF		POHRF with PH	
Value	Before NO inhalation	During NO inhalation	Before NO inhalation	During NO inhalation
NO (ppm)	—	5.4 ± 1.6	—	6.3 ± 1.6
FiO_2	0.71 ± 0.15	0.69 ± 0.17	0.84 ± 0.16*	0.81 ± 0.13
pH	7.460 ± 0.067	7.461 ± 0.065	7.417 ± 0.028*	7.413 ± 0.043
BE	4.7 ± 4.0	4.0 ± 4.4	1.6 ± 2.6*	1.4 ± 2.9
$PaCO_2$ (mmHg)	40.7 ± 5.0	39.1 ± 3.9	40.7 ± 3.5	40.9 ± 4.8
PaO_2 (mmHg)	75.2 ± 14.6	115.4 ± 32.9†	94.0 ± 40.6	179.0 ± 96.0†
PaO_2/FiO_2 (mmHg)	111.5 ± 33.5	175.4 ± 57.5†	112.6 ± 42.5	225.3 ± 115.8†
Hb ($g \cdot dl^{-1}$)	11.2 ± 1.5	11.3 ± 1.4	10.8 ± 1.8	11.0 ± 1.6
CaO_2 (vol%)	14.4 ± 2.0	15.2 ± 1.9†	14.5 ± 2.6	15.5 ± 2.2†
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.80 ± 0.61	3.02 ± 0.39	3.29 ± 0.96	3.58 ± 1.07†
DO_2I ($ml \cdot min^{-1} \cdot m^{-2}$)	417 ± 98	477 ± 67†	440 ± 115	519 ± 139†
SvO_2 (%)	64.2 ± 13.6	69.4 ± 8.8†	63.5 ± 10.5	72.5 ± 4.9†
SPAP (mmHg)	28.3 ± 4.3	26.3 ± 5.4†	48.3 ± 7.2*	39.5 ± 8.8†
RAP (mmHg)	10.4 ± 1.9	9.9 ± 1.8	11.9 ± 4.7	10.3 ± 2.8
metHB (%)	—	0.89 ± 0.20	—	0.83 ± 0.18

POHRF, Postoperative hypoxic respiratory failure with PaO_2/FiO_2 less than 200 mmHg; PH, pulmonary hypertension with systolic pulmonary arterial pressure (SPAP) higher than 40 mmHg. Data are expressed as mean ± SD. *Significant compared with simple POHRF (unpaired Student's *t*-test). †Significant compared with the data before NO inhalation (paired Student's *t*-test).

494 $ml \cdot min^{-1} \cdot m^{-2}$ (+19.5%). SvO_2 also increased significantly. Of the hemodynamic parameters, CI and SPAP showed significant changes during NO inhalation. The level of metHB measured during the study period was 0.89 ± 0.19%.

The results of the comparative analysis are listed in Table 4. PaO_2, PaO_2/FiO_2, CaO_2, DO_2I, and SvO_2 increased significantly in both groups following NO inhalation. The increase in PaO_2/FiO_2 was 64 mmHg (+75.4%) in the simple POHRF group and 113 mmHg (+125%) in the POHRF with PH group. The increase in CaO_2 was 0.88 vol% in simple POHRF and 0.98 vol% in POHRF with PH. The increase in DO_2I was 60 $ml \cdot min^{-1} \cdot m^{-2}$ (+18.9%) in simple POHRF and 79 $ml \cdot min^{-1} \cdot m^{-2}$ (+18.0%) in POHRF with PH. The increase in CI was significant in both simple POHRF and POHRF with PH. One patient in the simple POHRF group died of multiple organ failure.

Discussion

Our study demonstrated that a low dose of inhaled NO significantly increased oxygen delivery in adult patients after cardiovascular surgery. Marked improvements in PaO_2/FiO_2 were also obtained with NO inhalation, as also reported elsewhere [4–10]. The improvements were accompanied by increases in CaO_2 of nearly 1 vol% (Tables 3 and 4), which is the equivalent of one-quarter of the normal oxygen difference between arterial and mixed venous blood ($CaO_2 - CvO_2$). CI increased significantly (by 11.8 %) in all patients, as a result of the increase in pulmonary blood flow caused by the inhaled NO and the consequent augmentation of the preload for the left ventricle.

The increases in CaO_2 and CI caused by inhaled NO should both lead to an improvement in oxygen delivery in POHRF and POPH patients. To judge from our results, oxygen delivery can be expected to increase by approximately 20% during NO inhalation in adult patients after cardiovascular surgery. Such an increase in oxygen delivery would be expected to improve tissue oxygenation, and this seemed to be confirmed by the increase in SvO_2 seen in this study. This should help to prevent the organ dysfunction that can be caused by the deterioration in tissue oxygenation that occurs in POHRF and POPH.

Although inhaled NO is known effectively to counteract POPH in patients with or without respiratory failure [8–10], it seemed doubtful whether inhaled NO would be effective in patients with postoperative hypoxic respiratory failure without PH. However, the data obtained in this study suggest that it should also be effective for POHRF without PH, though there was a small decrease in SPAP (2 mmHg) in such patients. It is known that pulmonary vasoconstriction occurs in LOS after cardiac surgery [15]. Usually, release of the pulmonary vasoconstriction is accompanied by an increase in intrapulmonary shunt flow, resulting in a reduction in oxygenation. However, it is likely that NO treatment in patients suffering from POHRF without PH is effective, because rather than a dilatation of resistance vessels, there is a pulmonary vasodilatation redistributing regional pulmonary blood flow and leading to an improvement in the ventilation/perfusion mismatch seen after cardiovascular surgery.

In the present study, the concentration of inhaled NO was between 1 and 10 ppm and the average was 5.7 ppm. In the current study we did not attempt to obtain a dose-effect relationship for inhaled NO. The low doses were comparable to the initial doses commonly used in clinical settings and were effective in almost all the patients. Inaccuracies in the inhaled NO dose [16] might be one of the limitations of our study. However, in the premixing system the NO concentration, measured by an analyzer with a very rapid response, was constant. Although some fluctuations in NO concentration were observed when using the side-stream system, as reported elsewhere [16], the flowmeter was adjusted to keep the NO concentration at a constant maximum level during the inspiratory phase. For this reason, we feel that the measurements of the NO doses when we used the side-stream system were not so inaccurate as to affect the results of this study. Another limitation of this study was that we did not measure any indicators of tissue hypoxia. However, the blood levels of methemoglobin, a molecule that cannot carry oxygen [3], were within the normal range in all patients throughout the study period, indicating that no adverse effects on tissue oxygenation occurred because of changes in this variable during NO inhalation.

There were no significant differences before NO inhalation between the simple POHRF group and POPHRF with PH group, except in FiO_2, pH, BE, and SPAP (Table 4). However, simple POHRF required a more prolonged period of intensive care, and one patient in this group died, whereas all the patients in the POHRF with PH group survived (Table 2). The reasons for this are unclear. However, our speculation is that the main mechanisms responsible for the deteriorated oxygenation in POPHRF with PH led to an accumulation of extravascular lung water concomitant with hypoxic pulmonary vasoconstriction, symptoms that were treated without much difficulty by eliminating the extravascular lung water and by NO inhalation. In contrast, the etiologies of simple POHRF might be more complicated.

In conclusion, inhaled NO increases oxygen delivery by approximately 20% in adult patients after cardiovascular surgery. This may lead to improved tissue oxygenation. These effects should be obtainable in patients suffering from postoperative hypoxic respiratory failure, irrespective of whether or not they have pulmonary hypertension.

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