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Unintended Inhalation of Nitric Oxide by Contamination of Compressed Air

Physiologic Effects and Interference with Intended Nitric Oxide Inhalation in Acute Lung Injury

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Background: **Compressed air from a hospital's central gas supply may contain nitric oxide as a result of air pollution. Inhaled nitric oxide may increase arterial oxygen tension and decrease pulmonary vascular resistance in patients with acute lung injury and acute respiratory distress syndrome. Therefore, the authors wanted to determine whether unintentional nitric oxide inhalation by contamination of compressed air influences arterial oxygen tension and pulmonary vascular resistance and interferes with the therapeutic use of nitric oxide.**

Methods: **Nitric oxide concentrations in the compressed air of a university hospital were measured continuously by chemiluminescence during two periods (4 and 2 weeks). The effects of unintended nitric oxide inhalation on arterial oxygen tension (n = 15) and on pulmonary vascular resistance (n = 9) were measured in patients with acute lung injury and acute respiratory distress syndrome by changing the source of compressed air of the ventilator from the hospital's central gas supply to a nitric oxide–free gas tank containing compressed air. In five of these patients, the effects of an additional inhalation of 5 ppm nitric oxide were evaluated.**

Results: **During working days, compressed air of the hospital's central gas supply contained clinically effective nitric oxide concentrations (> 80 parts per billion) during 40% of the time. Change to gas tank–supplied nitric oxide–free compressed air decreased the arterial oxygen tension by 10% and increased pulmonary vascular resistance by 13%. The addition of 5 ppm nitric oxide had a minimal effect on arterial oxygen tension and pulmonary vascular resistance when added to hospital-supplied compressed air but improved both when added to tank-supplied compressed air.**

Conclusions: **Unintended inhalation of nitric oxide increases arterial oxygen tension and decreases pulmonary vascular resistance in patients with acute lung injury and acute respiratory distress syndrome. The unintended nitric oxide inhalation interferes with the therapeutic use of nitric oxide. (Key words: Acute respiratory distress syndrome; air pollution; mechanical ventilation.)**

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INHALED nitric oxide (NO), a selective pulmonary vasodilator,[1,2] decreases pulmonary artery pressure (PAP) and increases arterial oxygen tension in patients with acute lung injury and acute respiratory distress syndrome.[3,4] Nitric oxide concentrations as low as 60 parts per billion (ppb) may increase arterial oxygen tension (Pa_{O_2}) in persons with the acute respiratory distress syndrome.[5]

Compressed air in hospitals, drawn from the local environment, may contain variable amounts of NO as a result of air pollution.[6] Combined with pure oxygen, compressed air is used for mechanical ventilation in critically ill patients. However, the effects of such unintended inhalation of NO on pulmonary gas exchange and hemodynamics in persons with acute lung injury and acute respiratory distress syndrome have not been studied.

Therefore, we wanted to determine whether contamination of compressed air by NO affects hemodynamics and gas exchange in patients with acute lung injury and acute respiratory distress syndrome, and whether the unintended NO inhalation interferes with the therapeutic use of inhaled NO.

Patients and Methods

During two periods of 4 and 2 weeks, respectively, concentrations of NO and nitric dioxide in the compressed air of the university hospital's central gas supply were monitored continuously by a chemilumi-

nescent analyzer (AL 700 MED; Eco Physics, Dürnten, Switzerland) that accurately measures NO concentrations >10 ppb (data supplied by the manufacturer). Five liter per minute of compressed air were directed to the NO analyzer. Data were stored on a personal computer every 5 min.

Environmental NO concentrations were measured by chemiluminescence at a monitoring station 300 m away from the hospital. These data were obtained from the local environmental monitoring agency (UMEG GmbH, Karlsruhe, Germany).

After approval from the local ethics committee, the effect of unintentional NO inhalation on Pa_{O_2} was evaluated in 15 patients with acute lung injury or acute respiratory distress syndrome.[7] The severity of lung injury was graded according to a lung injury score.[8] In nine of these patients with an indwelling pulmonary artery catheter, pulmonary hemodynamics and venous admixture were also determined. Table 1 lists clinical characteristics. The lungs were ventilated with pressure control (Servo 900C; Siemens-Elema, Lund, Sweden or Evita 4, Dräger, Lübeck, Germany) at a fraction of inspired oxygen (FI_{O_2}) between 0.4 and 0.7. Patients were studied on workdays between 9 A.M. and 4 P.M.. During this period, NO concentrations in the compressed air had been highest.

Inspiratory NO concentrations were measured by chemiluminescence. Pressure measurements were made at end-expiration with the patient supine using calibrated pressure transducers (Medex Novotrans II MX 860, Hilliard, OH), with zero set to ambient pressure at the midaxillary line. Pulmonary vascular resistance (PVR) and intrapulmonary venous admixture (Q_{VA}/Q_T) were calculated using standard formulas.

In the first 10 patients, the source of compressed air was changed from the central gas supply to a gas tank containing compressed air without NO (< 10 ppb) by disconnecting the tube for compressed air from the central gas supply and reconnecting it to the gas tank. This maneuver lasted <5 s. Ventilatory patterns remained unchanged. Measurements were made before, 15 min after change, and 15 min after return to baseline.

In addition, in the final five patients, the effects of 5 ppm inhaled NO were evaluated when the ventilator was connected to the central gas supply and to the gas tank. The source of compressed air and addition of NO were administered randomly. Nitric oxide was administered as described previously.[9]

Statistical Analysis

Data are expressed as the mean ± SD. Data were compared by one-way analysis of variance for repeated measurements followed by the Student–Newman–Keuls test for multiple comparisons. A P value < 0.05 was considered significant.

Results

Nitric oxide and nitric dioxide concentrations in the compressed air of the hospital's central gas supply ranged from < 10 ppb for NO and nitric dioxide to 1,270 ppb NO and 670 ppb nitric dioxide and were highest on workdays between 9 A.M. and 4 P.M. (fig. 1). During this time, NO concentrations exceeded 80 ppb 40% of the time. These concentrations were comparable to the environmental NO concentrations (fig. 1).

Replacement of the hospital-supplied compressed air by tank-supplied NO-free compressed air decreased Pa_{O_2} by 10 ± 5% (table 1), and increased PVR and Q_{VA}/Q_T by 13 ± 7% and 4 ± 3%, respectively (table 2).

Adding 5 ppm inspiratory NO to hospital-supplied compressed air did not affect Pa_{O_2}/FI_{O_2}, and PVR. In contrast, when added to gas-tank supplied NO-free compressed air, it increased Pa_{O_2}/FI_{O_2} by 16 ± 11% and decreased PVR by 14 ± 8% (table 3).

Discussion

These results show that even in nonindustrial regions such as Freiburg, Germany, compressed air contains clinically effective NO concentrations. In patients with acute lung injury and acute respiratory distress syndrome, such unintended NO inhalation may increase Pa_{O_2} and decrease PAP and PVR. The unintended NO inhalation makes the therapeutic use of inhaled NO less effective.

Nitric oxide is an air pollutant that originates from various sources. During combustion at high temperatures, such as in car engines, nitrogen is oxidized to NO. Nitric oxide is an unstable radical that is oxidized to nitric dioxide in the presence of oxygen.[10] The estimated half-life of 100 ppb NO in air is 506 h, and the estimated half-life of 500 ppb NO in air is 101 h. It is, therefore, stable enough to reach the lungs of mechanically ventilated patients *via* hospital-supplied compressed air.

Nitric oxide concentrations were highest on workdays, which is probably related to car traffic. Although

Table 1. Clinical Characteristics of Patients and Pulmonary Gas Exchange

Patient No.	Age (yr)/ Sex	Underlying Disease	Mechanical Ventilation at Time of Study (days)	LIS†	$F_{I_{O_2}}$	NO in Compressed Air of Central GS (ppb)	NO_{insp} (ppb) with the Ventilator Connected to: Central GS	Gas Tank	Central GS	$Pa_{O_2}/F_{I_{O_2}}$ (mmHg) with the Ventilator Connected to: Central GS	Gas Tank	Central GS	Survival
1*	66/M	Multiple trauma	3	3.25	0.7	1080	376	1	431	101.1	92.0	107.6	No
2	44/M	Pneumonia	22	1.75	0.4	161	107	2	111	191.0	172.8	183.0	Yes
3	26/M	Pneumonia	2	2	0.4	220	168	1	164	169.5	158.3	171.8	Yes
4	45/M	Pneumonia	28	2.5	0.5	160	128	3	124	194.0	182.2	184.0	Yes
5	55/M	Peritonitis	8	3.25	0.4	383	208	2	193	115.0	89.8	111.2	No
6*	48/M	Peritonitis	4	2.75	0.4	115	100	3	92	163.0	152.0	159.8	No
7*	89/M	Peritonitis	2	1.75	0.4	175	102	2	129	225.0	208.5	229.0	Yes
8	25/F	Malaria tropica	20	3.25	0.5	161	142	5	97	127.0	120.0	128.2	Yes
9*	76/M	Cardiac surgery	1	1.25	0.4	80	63	3	57	262.5	240.0	242.8	Yes
10*	77/M	Post–liver resection	2	1.5	0.4	111	100	1	87	296.8	248.5	271.0	Yes
11*	75/M	Peritonitis	4	2.0	0.4	273	190	6	470	216.8	174.5	216.0	No
12*	38/F	Peritonitis	7	1.5	0.4	124	78	6	123	249.0	231.8	237.3	Yes
13	24/F	Multiple trauma	16	2.5	0.5	101	74	6	60	181.8	153.2	182.0	Yes
14*	44/M	Pneumonia	4	3.5	0.4	97	65	4	62	148.3	140.3	147.8	Yes
15*	50/M	Peritonitis	5	3.0	0.65	401	171	3	82	107.7	95.7	98.6	No
Mean ± SD			10 ± 9	2.4 ± 0.8	0.47 ± 0.1	243 ± 252	138 ± 80	3 ± 2‡	152 ± 127	183 ± 59	164 ± 52‡	178 ± 53	

LIS = lung injury score; GS = gas supply; NO_{insp} = inspiratory nitric oxide concentration.

* Patients with an indwelling pulmonary artery catheter.

† The lung injury score[8] is calculated from a chest roentgenogram score, a hypoxemia score, a positive end-expiratory pressure score, and a respiratory system compliance score. The range of the lung injury score is 0–4. A score of 0 indicates no lung injury, a score between 0.1 and 2.5 indicates mild-to-moderate lung injury, and a score between 2.5 and 4 indicates severe lung injury.

‡ $P < 0.05$ *vs.* central gas supply.

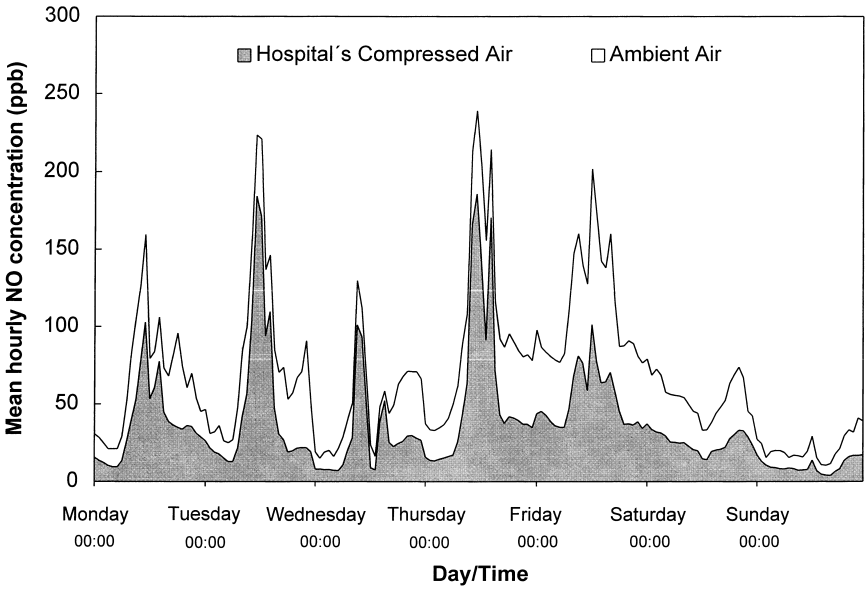

Fig. 1. Mean hourly nitric oxide (NO) concentrations in the hospital's compressed air and in ambient air at each weekday. Environmental NO concentrations were measured at a monitoring station located 300 m away from the hospital. Although NO concentrations in the compressed air were less than the environmental NO concentrations, the time courses of the NO concentrations were comparable.

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Table 2. Effect of Contamination of Hospital's Compressed Air by Nitric Oxide on Gas Exchange and Hemodynamics in Nine Patients with ALI and ARDS

Source of Compressed Air	Central GS	Gas Tank	Central GS
NO_{insp} (ppb)	138 ± 99	3 ± 2*	170 ± 161
Pa_{O_2}/FI_{O_2} (mmHg)	197 ± 70	176 ± 60*	190 ± 63
Sa_{O_2}	0.95 ± 0.02	0.94 ± 0.03*	0.95 ± 0.02
Pa_{CO_2} (mmHg)	44 ± 5	44 ± 5	43 ± 4
Pv_{O_2} (mmHg)	40 ± 5	40 ± 5	40 ± 5
Sv_{O_2}	0.72 ± 0.07	0.72 ± 0.07	0.73 ± 0.06
Q_{VA}/Q_T (%)	30 ± 15	34 ± 17*	31 ± 16
MAP (mmHg)	77 ± 19	76 ± 18	77 ± 16
PAP (mmHg)	34 ± 5	36 ± 5*	34 ± 5
PCWP (mmHg)	14 ± 4	14 ± 3	14 ± 3
CO (1 min)	7.3 ± 1.3	6.9 ± 1.4	7.4 ± 1.7
PVR (dyn · s · cm^{-5})	234 ± 105	267 ± 133*	235 ± 122
CVP (mmHg)	18 ± 5	19 ± 5	18 ± 65
HR (beats/min)	105 ± 20	104 ± 22	104 ± 21

Data are means ± SD.

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; GS = gas supply; NO_{insp} = inspiratory concentration of nitric oxide; Pa_{O_2} = arterial oxygen tension; FI_{O_2} = fraction of inspired oxygen; Sa_{O_2} = arterial oxygen saturation; Pa_{CO_2} = arterial carbon dioxide tension; Pv_{O_2} = mixed venous oxygen tension; Sv_{O_2} = mixed venous oxygen saturation; Q_{VA}/Q_T = venous admixture; MAP = mean arterial pressure; PAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance; CVP = central venous pressure; HR = heart rate.

* $P < 0.05$ *vs.* central gas supply.

Several European cities have reported environmental NO concentrations as high as 991 ppb (Copenhagen, Denmark),[11] 1,045 ppb (Düsseldorf, Germany),[12] 600 ppb (Berlin, Germany),[13] and 498 ppb (Innsbruck, Austria).[14] Nitric oxide concentrations correlated with car traffic and working days and correlated inversely with wind intensity.[14]

In our study, NO concentrations in compressed air exceeded 80 ppb on weekdays between 9 A.M. and 4 P.M. nearly half of the time. At an FI_{O_2} of 0.4, 80 ppb NO in compressed air results in an inspired NO concentration of 60 ppb. Nitric oxide may improve oxygenation and decrease PVR at concentrations as low as 50 to 150 ppb.[5,15–17] In one of our patients, withdrawal of just 63 ppb NO decreased Pa_{O_2}. In a study of the effects of unintended NO inhalation in 11 patients after cardiac surgery and in one patient after renal transplantation, the Pa_{O_2} decreased by 10.5 ± 7.8% when the compressed air was substituted for by a mixture of pure nitrogen and oxygen with a similar FI_{O_2}.[18] However, maintaining an identical FI_{O_2} in this way may be difficult. Changing the source of compressed air of the ventilator as we did reliably prevents any change in FI_{O_2}.

In our patients, withdrawal of the unintended NO inhalation increased PAP and PVR, in contrast to a previous study that showed no effect on PAP.[18] However, baseline PAP was less than in our patients (25 ± 8 mmHg *vs.* 34 ± 5 mmHg). The NO-induced decreases in PAP and PVR are more pronounced when baseline PAP and PVR are high.[4,17,19,20]

Table 3. Interaction of Unintended and Intended Nitric Oxide Inhalation in Five Patients with ALI and ARDS

Source of Compressed Air	Central GS 1	Gas Tank	Gas Tank +5 ppm NO	Central GS +5 ppm NO	Central GS 2
NO_{insp} (ppb)	116 ± 60†	5 ± 1*	5118 ± 112†	5046 ± 59*	159 ± 175†
Pa_{O_2}/FI_{O_2} (mmHg)	181 ± 56†	159 ± 50*	183 ± 57†	187 ± 50†	176 ± 55†
PVR (dyn · s · cm^{-5})	183 ± 41†	204 ± 45*	174 ± 32†	170 ± 46†	187 ± 50†

Data are means ± SD.

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; GS = gas supply; NO_{insp} = inspiratory nitric oxide; Pa_{O_2} = arterial oxygen tension; FI_{O_2} = fraction of inspired oxygen; PVR = pulmonary vascular resistance.

* $P < 0.05$ *vs.* central gas supply.

† $P < 0.05$ *vs.* gas tank.

Contamination of compressed air in a hospital's central gas supply in industrial regions is more pronounced than in our hospital. Nitric oxide concentrations up to 6.5 ppm NO have been measured in compressed air of other hospitals.[6] In industrial regions, critically ill patients possibly inhale NO during longer periods and at higher concentrations than in our hospital.

We found minimal effects of intentional inhalation of 5 ppm NO on oxygenation and pulmonary hemodynamics when added to hospital-supplied compressed air, but significant effects when added to tank-supplied NO-free compressed air. This is consistent with previous reports showing that patients responding positively to low inhaled concentrations of NO (*i.e.*, 50–250 ppb) show little further improvement with higher concentrations.[5,15] Similarly, the response to NO is more favorable during severe than during less severe hypoxemia.[21] Because severe hypoxemia requires a high FI_{O_2}, inspired gas contains little or no compressed air and, therefore, little or no NO. In this situation, the response to an intentional NO inhalation may be favorable because there was no preceding unintended inhalation of NO. Because measurement of low NO concentrations requires chemiluminescence and is not possible by electrochemical cells, unintended NO inhalation may not be detected readily in studies using electrochemical cells to measure NO.

Different responses to inhaled NO at different days,[21,22] and seemingly contradictory findings regarding the incidence of rebound phenomena after the sudden withdrawal of therapeutic NO inhalation,[23–26] may be related in part to varying NO concentrations in the compressed air.

Our findings may have implications for prospective randomized studies on the effects of inhaled NO in patients with acute lung injury and acute respiratory distress syndrome. In such studies, care must be taken that patients in the control group are not exposed to inhaled NO by contamination of the hospital's compressed air.

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