

Evaluation of a delivery system and monitors for ventilator administration of nitric oxide

YOUNG-KYOO CHOI¹, HIDEKAZU YUKIOKA², TOKUHIRO YAMADA², MASANORI HAYASHI², and MITSUGU FUJIMORI²

¹Department of Anesthesiology, Kyung Hee University Hospital, Seoul, 130-702 Korea

²Department of Anesthesiology and Intensive Care Medicine, Osaka City University Medical School, 1-5-7 Asahimachi, Abeno-ku, Osaka, 545 Japan

Abstract: The aim of this study was to compare nitric oxide (NO) and nitrogen dioxide (NO₂) measurements obtained by chemiluminescence and electrochemical monitors using a delivery system for ventilator administration of NO. The formation of NO₂ in this system and the efficacy of a soda-lime absorber to scavenge NO₂ from inspiratory gas were also evaluated. Various concentrations of NO without and with soda lime were administered to a model lung via a Servo ventilator 900C with controlled ventilation by setting mass-flow regulators to maintain desired concentrations of NO in 80% O₂. Close correlations were found between NO concentrations, as well as NO₂ concentrations, measured using electrochemical monitors (TM100; 1002, PACII) and a chemiluminescence monitor (CLA-510SS). Soda-lime removed NO₂ almost completely during administration of 0–25 p.p.m. NO, although a high concentration of NO₂ appeared in the breathing circuit without soda lime. Four hundred grams of soda lime continued to absorb NO₂ effectively during long-term administration of inhaled NO.

These findings suggest that electrochemical monitoring is accurate and clinically useful for measurements of NO and NO₂ concentrations, and that low doses of inhaled NO can be administered safely and reliably with the NO delivery system using a soda-lime absorber and mass-flow regulators.

Key words: Inhalation, Nitric oxide, Drug delivery, Monitor, Soda-lime absorber

Introduction

Nitric oxide (NO) is of increasing clinical interest because of its potential benefits as an endogenous nitrovasodilator. When administered in gaseous form, it has selective effects on the pulmonary vasculature owing to its rapid inactivation in blood by the formation of

methemoglobin. It has the potential for wide use in intensive care units and other critical care facilities for the treatment of chronic severe pulmonary hypertension [1], adult respiratory distress syndrome (ARDS) [2], and neonatal persistent pulmonary hypertension [3,4].

However, administration of NO poses several clinical problems. It is reputed to be a toxic agent to the lungs, but the evidence for this is slim [5–7]. More importantly, it reacts with oxygen to form nitrogen dioxide (NO₂), which is eventually transformed to nitrous and nitric acids, known to damage pulmonary epithelium and to cause pulmonary edema and acid pneumonitis in animals [6,8,9]. On the other hand, animal studies have revealed no major adverse effects of administration of 10–40 p.p.m. NO for periods ranging from 5 days to 6 months [7,10], and the Occupational Safety and Health Administration of USA permits exposure to NO for 8 h daily up to 25 p.p.m. [11]. The relatively low concentrations (6–20 p.p.m.) of NO that appear to be effective in clinical studies would thus be safe in normal lungs. However, the potential for induction of pulmonary toxicity (particularly with high FIO₂) by NO in injured lungs with ongoing injury by oxidants or in newborn lung with altered oxidant defences is unknown.

Because of the potential toxicity of inhaled NO and the formation of NO₂, which is more toxic than NO, it is mandatory that if NO is used as a therapeutic agent, NO and NO₂ concentrations be monitored very carefully. Although current recommendations from the Occupational Safety and Health Administration have set the upper limit for NO₂ inhalation at 5 p.p.m. [12], Zapol et al. recommended 1 p.p.m. of NO₂ as the limit for safety for patients with pulmonary hypertension [13]. When NO is mixed with ventilator gas, which often may have an oxygen concentration above 50%, rapid oxidation of NO to NO₂ will occur, and therefore NO₂ scavengers such as soda lime may be necessary to keep concentrations of NO₂ low. However, little is known

Address correspondence to: H. Yukioka

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concerning the absorptive capacity of soda lime for NO or NO₂ [14].

Currently used monitoring systems for NO and NO₂ include chemiluminescence and electrochemical detection. The chemiluminescence technique is more accurate, but the equipment required can be difficult to set up and expensive to obtain. An alternative method of measuring NO and NO₂ concentrations is electrochemical detection, the principle used in many fuel cell oxygen analyzers, although the reliability, reproducibility, and accuracy of the method in clinical studies have yet to be established [11].

The main objective of this study was to compare NO and NO₂ measurements obtained by chemiluminescence and electrochemical monitors using a system for administration of NO in breathing gas with a Servo ventilator. The formation of NO₂ in this system and the efficacy of the soda-lime absorber to scavenge NO₂ from inspiratory gas were also evaluated.

Methods

NO/NO₂ monitoring equipment

The most recent versions of three commercially available NO and NO₂ monitoring systems were obtained from their respective manufacturers: (1) the SAAN TM 100 and TM 1002 gas monitors (SAAN Laboratories, Kyoto, Japan); (2) Dräger Pac II NO and NO₂ gas monitors (Dräger AG, Lübeck, Germany); (3) the Horiba CLA-510SS NO and NO_x (NO + NO₂) gas monitor (Horiba, Osaka, Japan). The SAAN and Dräger gas monitors were used for electrochemical detection, while the Horiba gas monitor was used for chemiluminescence measurements.

The performance of each instrument was evaluated by comparing the measurements of NO and NO₂ obtained. Each instrument was maintained and calibrated in accordance with the manufacturer's specifications. Yearly maintenance was performed by a factory representative before the start of the study. Prior to use, all monitoring equipment was allowed to stabilize for a period of 1–2 h and then placed within the breathing system.

Gas delivery system

A gas delivery system was constructed with four parts: (1) one G-cylinder with an NO/N₂ gas mixture (Taiyo Sanso, Osaka, Japan); (2) three mass-flow regulators (TGB-3C, Taiyo Sanso, Osaka, Japan) for O₂, air and NO/N₂ gas delivery; (3) a Servo Ventilator 900C (Siemens-Elema AB, Solna, Sweden); (4) a breathing circuit with a model lung, humidifier with distilled

water, and three types of NO and NO₂ monitoring equipment.

Since NO is toxic at high concentrations, 800 p.p.m. NO in N₂ (NO₂ < 4 p.p.m.) was chosen for use in the gas cylinders. The NO, O₂ and air were mixed by the mass-flow regulators just in front of to the gas inlet of the ventilator. The ventilator was calibrated in accordance with the manufacturer's instructions, and fitted with a gas scavenging system. To study the efficacy of the soda-lime absorber in scavenging NO₂, a soda-lime carbon dioxide absorber (Wako Lime-A, Wako Pure Chemical Industries, Osaka, Japan) with a canister volume of 900 ml and with 400 g absorber mass was inserted in the inspiratory limb of the breathing system immediately proximal to the humidifier. Inspired gas was passed through a canister containing soda lime to absorb NO₂ or through a canister not containing soda lime, and NO and NO₂ measurements were performed in the inspiratory limb immediately proximal to the model lung using the three types of NO/NO₂ monitoring equipment simultaneously.

Experimental procedure

NO was administered via a Servo Ventilator 900C by setting three mass-flow regulators to maintain the desired concentrations of NO and O₂. In the present study, the ventilator was operated only in the volume-controlled mode. All experiments were performed with a setting of 6 l·min⁻¹ expiratory minute ventilation, since the chemiluminescence technique requires a 700 ml·min⁻¹ aspiration volume from the inspiratory tube limb to measure NO and NO₂. The ventilator was operated at 12 breaths·min⁻¹, with a peak pressure of 22.4–23.2 cmH₂O. FIO₂ was maintained at 0.8 during the experiment.

For comparison of NO and NO₂ concentrations measured by chemiluminescence and electrochemical monitors, various concentrations of NO without and with soda lime were administered at a room temperature of 24°C. Absorption rates of NO and NO₂ with soda lime were also calculated. Measurement of each concentration of NO and NO₂ was performed after a steady state had been reached (normally more than 10 min).

In addition, in order to determine the maximum recommended dose of inhaled NO in the NO delivery system, the relationship between NO and NO₂ concentrations was studied using soda lime, since Zapol et al. [13] and the Occupational Safety and Health Administration [12] recommended 1 p.p.m. and 5 p.p.m. of NO₂, respectively, as safety limits.

The capacity of the absorber to scavenge NO₂ was tested for 4 and 7 days with NO (25 and 15 p.p.m., respectively) in 80% oxygen at the same ventilatory settings.

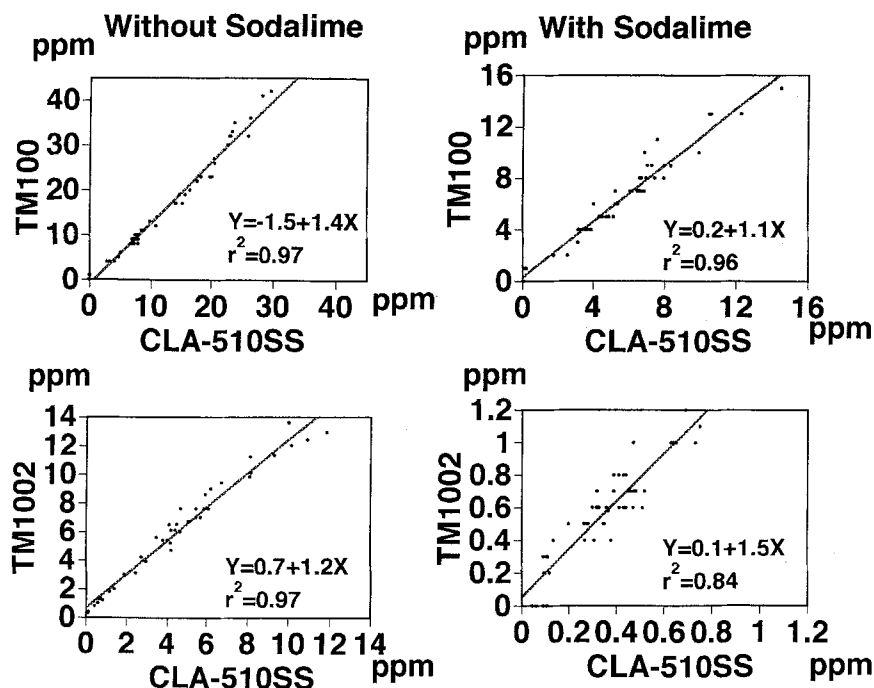


Fig. 1. Regression analysis of NO (*upper*) and NO₂ (*lower*) concentrations measured using the TM 100 or TM 1002 (electrochemical monitor) and the CLA-510SS (chemiluminescence monitor) without soda lime (*left*) or with soda lime (*right*)

Statistical analysis

All values are expressed as means \pm SD. Statistical analyses were performed by analysis of linear regression using the least-squares method, and analysis of variance was performed on a Macintosh IIfx computer using Statview 4.0 (FPU) software (Abacus Concepts, CA, USA). Probability values less than 0.05 were considered to indicate statistical significance.

Results

In the studies without and with soda lime, a close correlation was found between NO concentrations measured using the TM 100 (electrochemical monitor) and the CLA-510SS (chemiluminescence monitor) (without soda lime, $r^2 = 0.97$; with soda lime, $r^2 = 0.96$). A close correlation was also found between NO₂ concentrations measured using the TM 1002 (electrochemical monitor) and the CLA-510SS (without soda lime, $r^2 = 0.97$; with soda lime, $r^2 = 0.84$) (Fig. 1).

In measurements of NO and NO₂ concentrations obtained using another electrochemical monitor (Dräger Pac II), close correlations were found between measurements obtained with the Pac II and CLA-510SS (NO and NO₂ concentrations measured without soda lime, $r^2 = 1.00$, $r^2 = 0.99$; NO and NO₂ concentrations measured with soda lime, $r^2 = 0.98$, $r^2 = 0.79$) (Fig. 2).

For data analysis, absorption rates were stratified into five groups based on concentration of NO administered (0–5, 5–10, 10–15, 15–20, and 20–25 p.p.m.). High con-

centrations of NO₂ (5–13 p.p.m.) appeared in the breathing circuit without soda lime during administration of 10–25 p.p.m. NO (Table 1). The absorption rate of NO (30%–55%) with the soda-lime absorber increased depending on the NO concentration administered, ranging from 0 to 25 p.p.m.. The rates of absorption of NO₂ with the soda-lime absorber were higher than 87% in all five groups (Table 1, Fig. 3).

The relationship between NO and NO₂ concentrations during use of soda lime is illustrated in Fig. 4. A close correlation was found between NO and NO₂ concentrations ($r^2 = 0.89$), and NO₂ concentrations did not exceed 1.5 p.p.m. during inhalational administration of 0–30 p.p.m. NO.

During long-term administration of NO (25 p.p.m. for 4 days and 15 p.p.m. for 7 days), 400 g soda lime removed NO₂ effectively, and NO₂ concentrations were maintained below 1 p.p.m..

Discussion

Despite the growing clinical use of NO inhalation, its potential toxicity should not be underestimated. Since NO and higher oxides such as NO₂ are highly toxic in high doses [15,16], it is of vital importance to ensure safe and precise delivery of NO while delivering as little NO₂ as possible. In maximizing safety, the first precaution is use of a primary NO concentration in the gas cylinders which would not pose a severe risk for the patient even if administered undiluted. In the present study, we used mass-flow regulators and a gas cylinder that contained

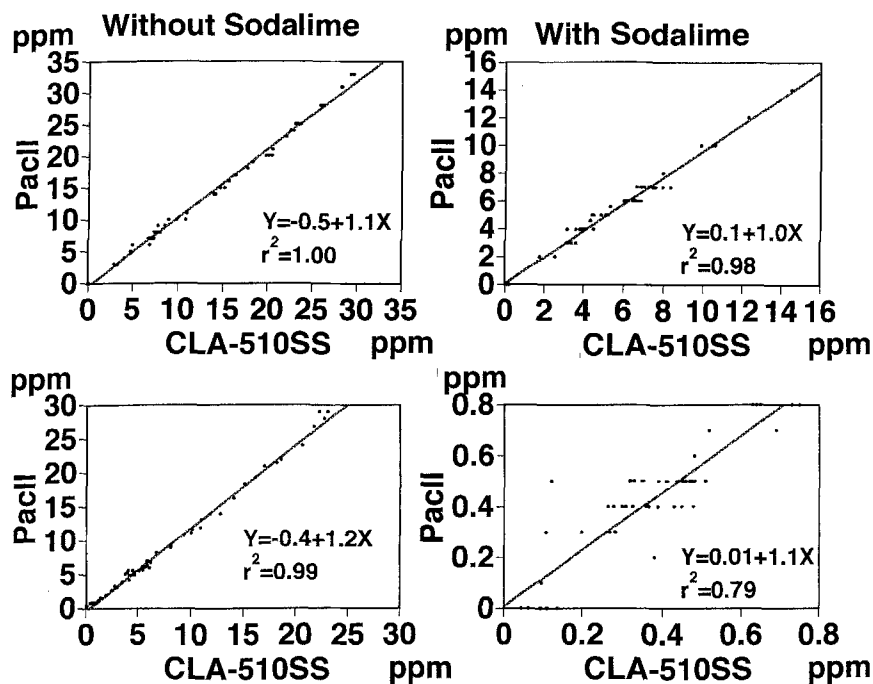


Fig. 2. Regression analysis of NO (upper) and NO₂ (lower) concentrations measured using the Pac II (electrochemical monitor) and the CLA-510SS (chemiluminescence monitor) without soda lime (left) or with soda lime (right)

Table 1. Actual concentrations of NO and NO₂ without or with soda lime and absorption rates of NO and NO₂ with soda lime (mean ± SD)

		Ranges of NO (p.p.m.)				
		0-5 (n = 5)	5-10 (n = 10)	10-15 (n = 10)	15-20 (n = 10)	20-25 (n = 10)
Without soda lime	Actual concentration of NO (p.p.m.)	3.84 ± 0.84	6.52 ± 0.94	12.71 ± 1.82	17.86 ± 1.75	22.28 ± 1.38
	Actual concentration of NO ₂ (p.p.m.)	1.75 ± 0.57	3.19 ± 1.31	5.93 ± 1.09	8.90 ± 2.04	12.61 ± 3.45
With soda lime	Actual concentration of NO (p.p.m.)	2.66 ± 0.64	4.14 ± 0.66	7.45 ± 2.12	9.85 ± 2.51	10.56 ± 4.39
	Actual concentration of NO ₂ (p.p.m.)	0.15 ± 0.11	0.36 ± 0.16	0.62 ± 0.21	0.71 ± 0.40	1.26 ± 0.48
	Absorption rate of NO (%)	30.7 ± 7.7	35.7 ± 10.5	41.9 ± 11.7	45.1 ± 11.6	52.6 ± 19.0
	Absorption rate of NO ₂ (%)	91.5 ± 5.3	87.6 ± 6.8	89.4 ± 3.8	91.6 ± 4.6	89.2 ± 4.0

800 p.p.m. NO in N₂ for safe and precise delivery of NO [12].

Since the most likely therapeutic level for inhaled NO is probably around 20 p.p.m. [17], and high FIO₂ is required for patients with severe respiratory failure, and the rate of formation of NO₂ from O₂ and NO depends on the concentration of O₂ and the square of the NO concentration, close monitoring of NO, NO₂, and FIO₂ is essential. They should be monitored close to the patient in the breathing circuit. However, relatively few monitors can be used clinically for measurements of NO and NO₂ in a ventilatory circuit. The ideal monitor is

small and quiet and provides precise, continuous real-time analysis with minimal sampling volumes. The monitor should be unaffected by water vapor, FIO₂, CO₂, or other compounds excreted by the lungs; it should function reliably, require minimal maintenance, and be easily calibrated and inexpensive, and it should monitor both NO and NO₂ with a digital readout and have adjustable alarms that announce when safety limits have been exceeded [11].

The chemiluminescence device used was designed for industrial use in measuring atmospheric pollutants. It is extremely precise. However, in its current configura-

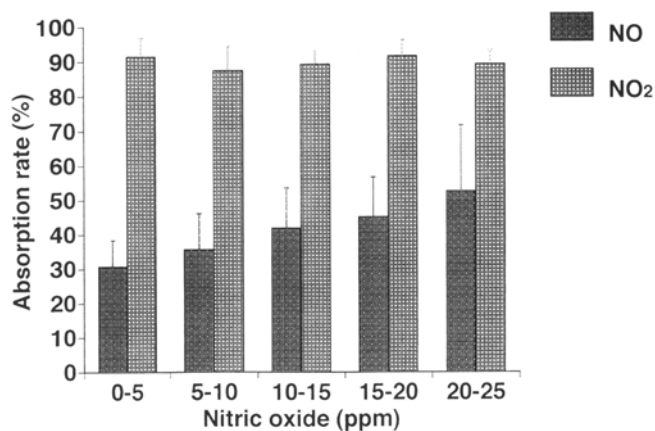


Fig. 3. Rates of absorption of NO and NO₂ following inhalation of NO ranging from 0 p.p.m. to 25 p.p.m. with a soda-lime absorber. Mean \pm SD

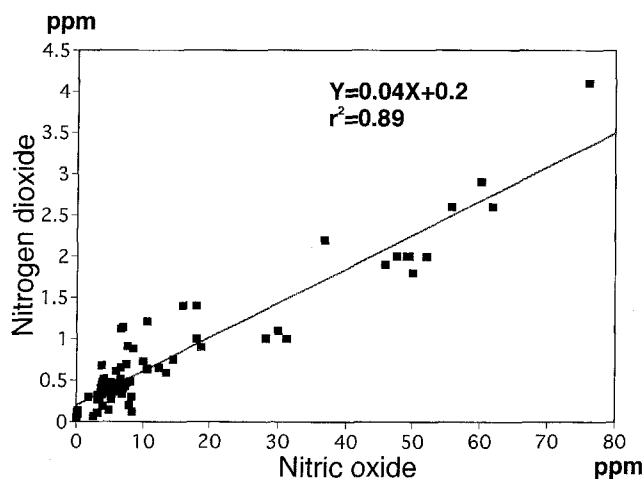


Fig. 4. Relationship between NO and NO₂ concentrations following inhalation of various concentrations of NO using a soda-lime absorber

tion, it is not ideally suited for bedside use. The large aspirating volumes (0.71-min^{-1}) of this chemiluminescence device are associated with noisy aspirating pumps and loss of positive end-expiratory pressure. The water-vapor filters that are inserted in the aspirating line of the device need to be replaced frequently unless sampling and monitoring are performed intermittently (e.g., hourly) rather than continuously. Quenching effects related to variable FIO₂ necessitate accurate calibration data. In addition, the size of the device is relatively large [11].

Smaller, less expensive electrochemical monitoring devices which are free of the problems associated with large aspirating volumes are available. Although a separate device is needed for NO and NO₂ measurements, and calibration is subject to drift and must be checked against a chemiluminescence measurement before use, the monitors, which are fitted with alarms, are less

cumbersome and are minimally affected by humidification of the inspired gas, may be more practical in a clinical setting. Measurements obtained with two electrochemical detectors, the Polytron (Dräger AG, Lübeck, Germany) and the NO Sensor Stik (Enviroconics Cerebus Ltd., Oldham, UK) have recently been compared with those obtained with a chemiluminescence monitor and found to be accurate [18,19]. In the present study, two electrochemical monitors (TM100, TM1002 and Pac II) were compared using the chemiluminescence monitor as a reference. NO and NO₂ concentrations measured by electrochemical monitors were closely correlated with those measured by chemiluminescence, indicating that the electrochemical monitors are clinically useful.

In the present study, we attempted to evaluate the effects of a soda-lime absorber on removal of NO and NO₂ during delivery of different NO concentrations (0–25 p.p.m.) in an FIO₂ of 0.8. Soda lime removed NO₂ almost completely during administration of 0–25 p.p.m. NO, and also removed between 30% and 55% of NO depending on the NO concentrations administered, although high concentrations of NO₂ appeared in the breathing circuit without soda lime. Because Zapol et al. [13] and the Occupational Safety and Health Administration [12] recommended 1 p.p.m. and 5 p.p.m. of NO₂, respectively, as safety limits, we determined the relationships between NO and NO₂ concentrations following administration of various concentrations of NO using soda lime. NO₂ concentrations did not exceed 1.5 p.p.m. during administration of inhaled 0–30 p.p.m. NO. In contrast, according to Pickett et al. [14], soda lime cannot be recommended for use as a NO₂ scavenger during administration of inhaled NO. However, Kain [20] reported that 5–10 mesh soda lime with a green-to-brown color change (indicator = sodium manganate) was able to absorb higher oxides of N₂ from a flowing gas stream. He calculated that each gram of soda lime was able to absorb 1.1 ml of the higher oxides. The reason for the difference between the findings of our own study and those of the earlier one [14] is unclear.

In the present study, 400 g soda lime continued to absorb NO₂ almost completely during long-term administration of inhaled NO (15–25 p.p.m.). These findings indicate that the NO delivery system is suitable for long-term administration of inhaled NO. However, the corrosion by NO of some plastics and metals in the ventilator might be of concern.

We conclude that electrochemical monitoring is accurate and useful for measurements of NO and NO₂ concentrations, and that low doses of inhaled NO can be administered safely using a delivery system for Servo ventilator administration of NO with soda-lime and mass-flow regulators.

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