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A demand valve device decreases exhaust nitric oxide and nitrogen dioxide by nitric oxide inhalation with a nasal cannula in the human

T. SAITO, H. NINOMIYA, I. OHTSU, M. INOUE, Y. UCHIDA AND S. HASEGAWA

Department of Pulmonary Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki 305-8575, Japan

To improve patients' quality of life and decrease pollution risks to medical personnel, we tested the usefulness of a nitric oxide (NO) inhalation system consisting of a nasal cannula and a demand valve in an open circuit system. To estimate the content of NO entering the lung with the open system, concentrations of NO and nitrogen dioxide (NO_2) were measured in a mechanical lung model, and then nitrocylhaemoglobin (NO-Hb), methaemoglobin (Met-Hb), and nitrite (NO_{2-}) + nitrate (NO_{3-}) concentrations in venous blood were measured in eight healthy subjects. Exhaust NO and NO_2 in the open system were also observed in 14 healthy subjects. In the lung model, NO concentration delivered with the open system was approximately 1/11 of that in the gas tank. Increases in Met-Hb and NO_{2-} + NO_{3-} with the open system showed that the concentration of delivered NO was approximately 1/9 of that in the gas tank. The open system reduced exhaust NO to 1/10 in human subjects. These data suggest that this NO inhalation system delivers sufficient NO to spontaneously breathing patients. In addition, these findings indicate that there is little environmental toxicity associated with the open circuit system.

Key words: nitric oxide; nitrogen dioxide; nasal cannula.

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Introduction

Inhaled nitric oxide (NO) causes selective pulmonary vasodilatation in pulmonary hypertension with acute respiratory distress syndrome (ARDS) (1,2), primary pulmonary hypertension (PPH) (3,4), persistent pulmonary hypertension of the new born (5,6), chronic obstructive pulmonary disease (COPD) (7), lung fibrosis (8) and congenital heart disease (9). A long-term administration of NO to spontaneously breathing patients has many problems awaiting solution, such as restriction of activities and air pollution by exhaust NO and nitrogen dioxide (NO_2). Recently, Channick and associates reported on an open circuit NO inhalation system with a demand valve via nasal cannula to ambulatory patients with pulmonary hypertension (10). The open circuit system for pulsed delivery of NO via nasal cannula is feasible for long-term NO inhalation and leads to significant improvement in pulmonary hypertension. Katayama *et al*. have reported that NO inhaled at the beginning of the breath reduces pulmonary artery pressure and pulmonary vascular resistance (PVR) as effectively as continuous NO inhalation in pig lungs and in patients with pulmonary hypertension (11). Although these systems are useful to decrease exhaust NO and NO_2, previous reports have not described the detailed functioning of the open system. The purpose of this study was to evaluate the effect of the open circuit system on the decrease in exhaust NO and NO_2 in human subjects.

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Correspondence should be addressed to: Yoshiyuki Uchida MD, PhD, Department of Pulmonary Medicine, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan. Tel/Fax: +81-298-53-3361; E-mail: yuchida@md.tsukuba.ac.jp

Materials and methods

The study was approved by the Medical Ethics Committee of the University of Tsukuba and informed consent was obtained from each participant after a thorough explanation of the purpose of the study.

EXPERIMENT A: A MECHANICAL LUNG MODEL

To predict concentrations of NO and NO_2, a mechanical lung model was used (Fig.1). The model consisted of two anti-static latex bags inside a 15-l cylindrical plastic airtight container, which allowed free movement of the bags. The bottom of the container was made of soft rubber, which

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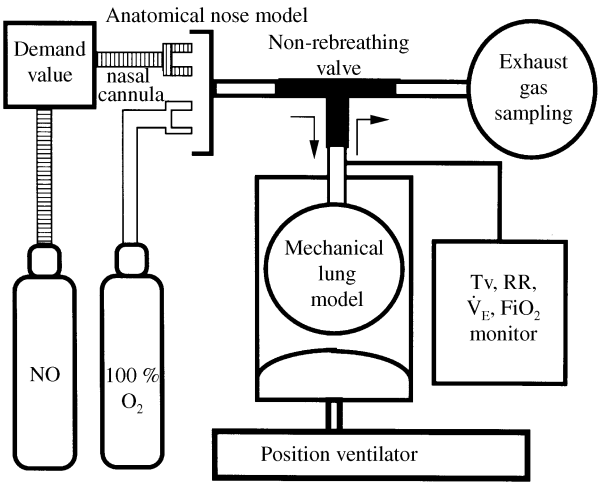

FIG. 1. The mechanical lung model. The bag-in the-container design represents the lung, thorax and diaphragm. The Piston ventilator provides negative pressure inside the container. The bags are then passively extended for the inspiration period in the mechanical lung model.

represented the diaphragm. The rubber was connected to a piston ventilator that generated negative pressure. Exhaled tidal volume (TVE), respiratory rate (RR), minute ventilation (V′E) and inspired oxygen concentration (FiO_2), were measured on a breath-by-breath basis by an Aeromonitor TM AE-280 (Minato Medical Science Co., Tokyo, Japan), consisting of a hot-wire flow meter and oxygen and carbon dioxide gas analysers. A non-rebreathing valve was mounted on the lung model, and NO and/or 100% oxygen (O_2) via a nasal cannula, together with room air, were administered from the inspired side via an anatomical nose model with two 5-mm diameter holes. A nasal cannula indicating NO gas and another nasal cannula indicating O_2 were connected to the anatomical nose model. The nasal cannula and anatomical nose are loosely connected allowing room air to circulate freely between them. Expired gas was collected in a 10-l tedlar bag. Concentrations of NO and NO_2 in the bag were then immediately measured both with and without the demand valve at a 0·5 or a 1 l min^{-1} flow rate, respectively. We observed the mechanical lung model at 10 to 30 min^{-1} of RR with 500 ml of TVE and at 200 to 500 ml of TVE with 15 min^{-1} of RR. Before the experiment, we measured the concentrations of NO and NO_2 taken from the latex bag, and the expired circuit. Because these concentrations were equal, we considered the concentration of NO and NO_2 taken from expired circuit to be equal to those in the latex bag. We measured the concentration of NO in the cylindrical plastic container during a 10 min 368 ppm NO inhalation. The concentration of NO was under 1 ppm, demonstrating that the leakage of NO from the latex bag could be ignored in this model. Concentrations of NO and NO_2 were measured on a chemiluminescence analyser CLM-500 (Simazu Co., Tokyo Japan). Concentrations of inspired NO nitrogen (N_2) balance were 0, 44, 93, 186 and 368 ppm in the tank.

EXPERIMENT B: MEASUREMENTS OF NO-HB, MET-HB, AND NO_{2^-} + NO_{3^-}

To predict NO concentration in the human lung with the open system, eight healthy non-smoking volunteers (five men and three women) with a mean age of 30·9 years (range 23–40) inhaled NO for 90 min. They inhaled NO using three different methods as follows: (i) 40 ppm NO via an airtight mask, (ii) 80 ppm NO via an airtight mask, and (iii) 368 ppm NO in the gas tank via a nasal cannula with the demand valve set equivalent to 1 l min^{-1} of continuous flow. There was an interval of at least a 1 week between each experiment. Blood and plasma samples for NO-Hb, Met-Hb, and NO_{2^-} + NO_{3^-} were obtained before the start of each NO inhalation, and at 30, 60 and 90 min during NO inhalation. Systemic blood pressure (BP), percutaneous oxygen saturation (SpO_2), pulse rate (PR), RR, TVE, V′E, and electrocardiogram were monitored throughout the experiments. For the airtight mask, NO gas was made by mixing 4000 ppm NO with N_2 and room air in a 10-l tedlar bag just prior to directly connecting a non-rebreathing valve to a detector and the airtight mask. The flow of gas was controlled by a mass flow controller (SEC Co. Ltd., Tokyo, Japan) and adjusted by measuring the concentration of NO in the inspired gas with a chemiluminescence analyser.

Blood samples were taken into 3-mm ID quartz capillary tubes and were deep-frozen in liquid nitrogen before NO-Hb analysis. NO-Hb levels were analysed by electron paramagnetic resonance (ERS) spectrometry as previous described (12). ESR spectra were recorded using an X-band spectrometer (JoeL model RE 3X) at −150°C. The ESR spectrometer settings were as follows: incident microwave power, 8 mW; modulation frequency, 100 kHz; modulation amplitude, 0·32 mT; microwave frequency, 9·1 GHz. The double-integrated area of NO-Hb agreed with that of $CuSO_4$-EDTA (13). Thus $CuSO_4$-EDTA (1 mM) was used as a standard. Blood samples were also taken into tubes containing 125 U of heparin, and Met-Hb levels were measured by light absorption using a co-oximeter (OSM3, Radiometer, Copenhagen, Denmark). NO_{2^-} + NO_{3^-} in plasma samples were analysed using a high-performance liquid chromatography technique based on the Griess reaction, as previously described (13).

EXPERIMENT C: EXHAUST CONCENTRATIONS OF NO AND NO_2

Fourteen healthy non-smoking volunteers (10 men and four women) with a mean age of 31·3 years (range 23–40) inhaled NO at 0, 44, 93, 186, and 368 ppm in a gas tank via a nasal cannula with a demand valve. The demand valve was set to generate a pulsed flow, which was equivalent to 0·5 to 2 l min^{-1} of the continuous flow. Subjects then inhaled NO in the same manner without a demand valve; these latter administrations of NO were at a continuous flow rate 0·5 to 2 l min^{-1}. The mouth and nose as well as the nasal cannula were covered with an airtight mask that was connected to a detector and a non-rebreathing valve.

The exhaust air passing through the non-rebreathing valve was collected in a 10-l tedlar bag, and the concentrations of NO and NO_2 were measured immediately. Exhaust NO and NO_2 were measured 15 min after each change of NO gas tanks and flow rates. To determine the interval time, we preliminary confirmed that concentrations of exhaust NO and NO_2 were stable for 10 to 90 min in this system.

STATISTICS

Data are expressed as mean ± SD. Statistical comparisons were performed by two-way analysis of variance (ANOVA). If a significant variance was detected, individual group differences were determined using Dunnett's test. A *P*-value of less than 0·05 was considered statistically significant.

MATERIALS

Sodium nitrite, sodium nitrate, and EDTA were purchased from Sigma (MO, U.S.A.). The NO gas in the N_2 balance, pure N_2 gas, and pure O_2 gas were purchased from Sumitomo Seika Chemicals Co., Ltd., Osaka Japan. The NO_2 concentration of each NO gas tank was below 0·05% of the NO concentration.

A demand valve device, which was modified from an inspiration-phase oxygen delivery device for home oxygen therapy, was a gift from Teijin Ltd. (Tokyo, Japan). This device detects pressure changes in excess of 0·06 cm H_2O for 0·01 sec. The demand valve senses the change from expiration to inspiration, and opens a valve to provide NO for the initial phase of the inspiration period. The opening time is determined by an internal microcomputer, which calculates the mean of the previous two inspiration periods. The opening time is approximately 30% of the inspiration period. In the continuous flow system, the gas flow during the expiration period was not inspired, and the gas flow during the later phase of the inspiration period might have stopped at the dead space and had not reached the alveoli. The demand valve is able to reduce the amount of supplied gas to a third of that used in the continuous flow system; it cut off the gas flow during the expiration period as well as during the later phase of the inspiration period. Under the above computerized settings, the demand valve generates gas flow in pulses, which is equivalent to continuous flow as regards reaching the alveolar space. Although the flow rate with the demand valve was set to be equivalent to that of continuous flow, the outflow from the tank was in fact a third that of continuous flow.

Results

EXPERIMENT A: A MECHANICAL LUNG MODEL

To estimate the effect of the demand valve, we compared the NO concentration in the mechanical lung model both with a demand valve and without a demand valve (constant flow system). In both systems, the NO concentration increased in proportion to increases in NO concentration in the tank and flow rate (Fig. 2). In the case of the 0·5 l min^{-1} flow rate, the NO concentration with a demand valve was slightly less than that without a demand valve [Fig. 2(a)]. In the case of the 0·5 l min^{-1} flow rate with a demand valve, the NO concentration in the lung model was approximately 1/40 of that in the gas tank. There was no difference in NO concentration between inhalation with or without a demand valve and at the 1 l min^{-1} flow rate [Fig. 2(b)]. In the case of the 1 l min^{-1} flow rate, the NO concentration in the lung model was approximately 1/11 of that in the gas tank. In the case of the 2 l min^{-1} flow rate, there was greater NO concentration with than without a demand valve [Fig. 2(c)]. The NO concentration varied

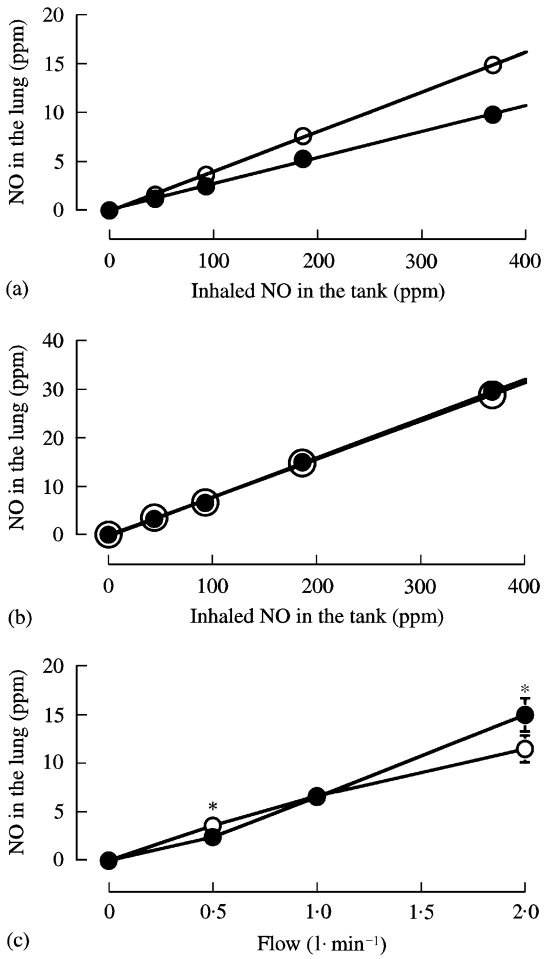

FIG. 2. Concentration- and flow-response curves of NO in the lung model during NO inhalation via a nasal cannula with (●) or without (○) the demand valve: (a) the flow rate is 0·5 l min^{-1}; (b) the flow rate is 1 l min^{-1}; (c) inhaled NO concentration is 93 ppm in the gas tank. The tidal volume is 500 ml and respiratory rate is 20 min^{-1}. Data are expressed as mean ± SD ($n = 5$). (*)shows significant differences between measurements with and without the demand valve ($P < 0·05$).

inversely with both TVE and RR (Fig. 3). The NO_2 concentration was under 0·05 ppm throughout all experiments.

To evaluate the effect of the increase in FiO_2 on concentrations of NO and NO_2, O_2 (1–5 lmin^{-1}) was inhaled with NO (93 ppm in the gas tank) via a nasal cannula with a demand valve. There were no changes in the concentration of NO and NO_2, regardless of increases in FiO_2 (data not shown).

EXPERIMENT B: MEASUREMENTS OF NO-HB, MET-HB, AND NO_{2^-} + NO_{3^-}

When NO was administered to subjects via an airtight mask for 90 min, Met-Hb and $NO_{2^-} + NO_{3^-}$ concentrations increased in a time- and a dose-dependent manner (Fig. 4). Met-Hb and $NO_{2^-} + NO_{3^-}$ concentrations in response to 40 ppm NO administered via an airtight mask were similar to those in response to 368 ppm NO in the gas tank

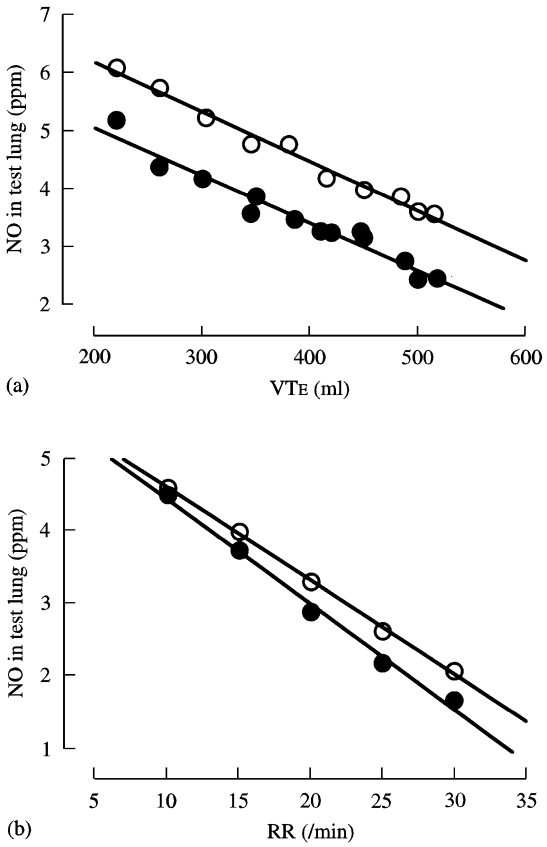

FIG. 3. Effects of changes of tidal volume (TVE) and respiratory rate (RR) on expired NO during NO inhalation via a nasal cannula with (●) or without (○) the demand valve in the lung model. The concentration of inspired NO is 93 ppm in the gas tank and the flow rate is 0·5 lmin^{-1}: (a) the effect of changes of TVE with 15/min of RR; (b) The effect of changes of RR with 500 ml of TVE.

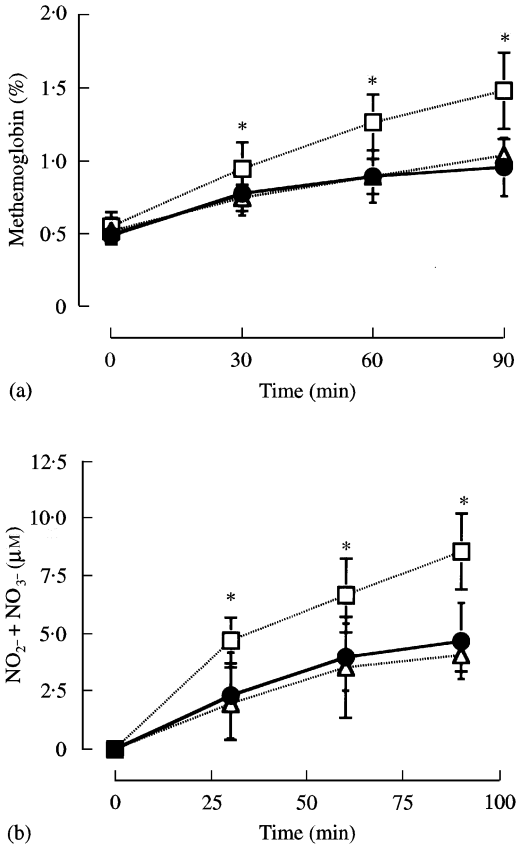

FIG. 4. Time-relation curves of (a) Met-Hb and (b) nitrite and nitrate in response to NO inhalation for 90 min by healthy subjects. The concentrations during 368 ppm in the gas tank of NO inhalation via a nasal cannula with the demand valve with setting, which is equivalent to a 1 l.min^{-1} flow rate of constant flow (●), during 40 ppm in the closed circuit of NO inhalation via an airtight mask (△), and during 80 ppm in the closed circuit of NO inhalation via an airtight mask (□) are shown. Data are expressed as mean ± SD ($n = 8$). (*)shows significant differences between 80 ppm NO and others ($P < 0·05$).

administered via a nasal cannula with the demand valve at a flow rate of 1 lmin^{-1}. The NO-Hb signal was not detected by ESR spectrometry in any of the blood samples, although a $CuSO_4$–EDTA signal was detectable. BP, PR, RR, and the electrocardiogram were unchanged during the experiments. Adverse effects of NO were not seen, expect for one complaint of mild nasal congestion in a subject using a nasal cannula. Observation with a rhinoscope showed normal nasal mucosa after the experiment.

EXPERIMENT C: EXHAUST CONCENTRATIONS OF NO AND NO_2

Without a demand valve at a flow rate of 0.5 lmin^{-1}, the exhaust NO concentration increased in proportion to

the inhaled NO concentration in the gas tank. However, the exhaust NO concentrations did not increase in the same manner when the demand valve was set equivalent to 0·5 l min^{-1} of the continuous flow [Fig. 5(a)]. To determine the efficacy of NO reduction with the demand valve, the on/off ratio of the demand valve (exhaust NO concentration with the demand valve/exhaust NO concentration without the demand valve) was calculated. The efficacy of reduction achieved by the demand valve was approximately 1/10; similar results were obtained regardless of the change in inhaled NO concentration in the gas tank [Fig. 5(b)]. BP, PR, and RR did not change, and the subjects did not complain of discomfort.

The concentration of exhaust NO also increased in proportion to the flow rate of NO inhaled without a demand valve. However, the exhaust NO concentrations were not similarly increased with a demand valve [Fig. 6(a)]. The efficacy of reduction with the demand valve was decreased in comparison with the increase in the flow rate [Fig. 6(b)]. The exhaust NO_2 concentration with the demand valve was less than 0·1 ppm throughout each of the

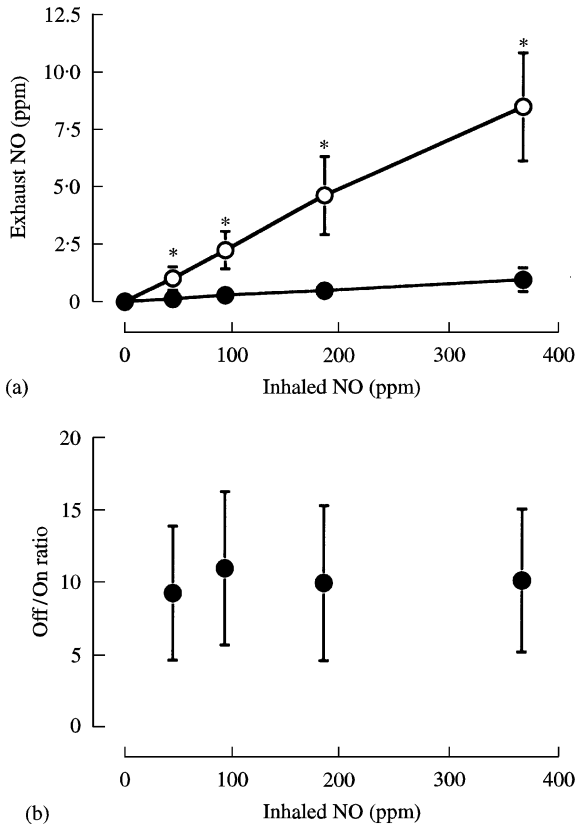

FIG. 5. (a) Exhaust NO concentrations in response to inhaled NO concentration in the gas tank with (●) or without (○) the demand valve (the flow rate is 0·5 l min^{-1}). (*)shows significant differences between measurements with and without the demand valve ($P<0·05$). (b) On/off ratios of the demand valve are shown (on/off ratio is calculated by the formula shown in the text). Data are expressed as mean ± SD ($n=14$).

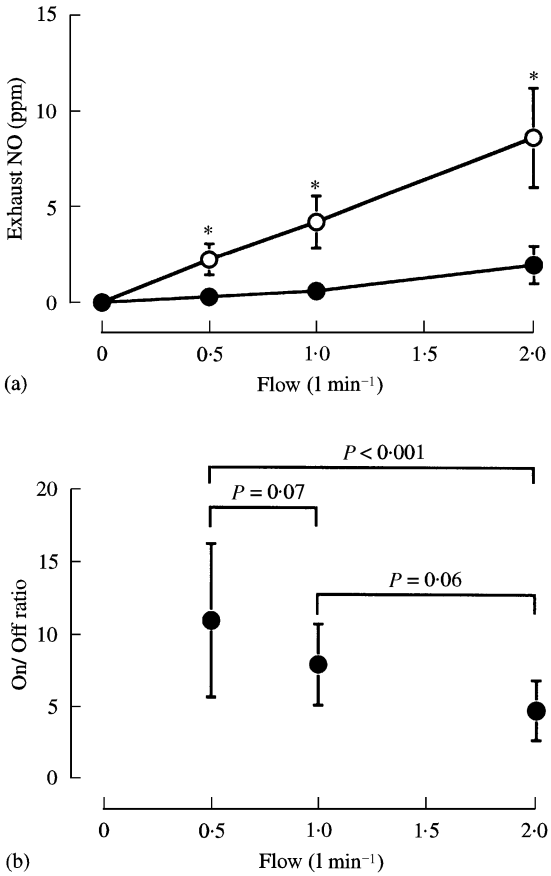

FIG. 6. (a) Exhaust NO concentrations in response to flow rate setting with (●) or without (○) the demand valve (inhaled NO concentration is 93 ppm in the gas tank). (*)shows significant differences between measurements with and without the demand valve ($P<0·05$). (b) On/off ratios of the demand valve are shown (on/off ratio is calculated by the formula shown in the text). Data are expressed as mean ± SD ($n=14$).

experiments. Increases in concentrations of exhaust NO and NO_2 were calculated over a 1-h period in a standard room (31·11m^3) at Tsukuba University Hospital. Concentrations of exhaust NO and NO_2 were under 3 ppb and 0·1 ppb, respectively, when 44 ppm of NO in the tank was inhaled for 1 h via a nasal cannula with the demand valve setting at equivalent to 0·5 l min^{-1} of the continuous flow.

Discussion

Recently, several investigators have reported that the initial phase of NO inhalation during the inspiration period is effective in reducing pulmonary artery pressure. Katayama *et al.* demonstrated 'spiked' 100 ppm NO during early inspiration and found this to be as effective as administering 40 ppm of continuous NO to pig and patients with pulmonary hypertension (11). Channick *et al.* have shown a significant decrease in pulmonary artery pressure and PVR

during pulsed delivery of NO (80 ppm) inhalation in patients with pulmonary hypertension (10). In this study, we used a similar system and demonstrated that little NO and NO_2 exhaust is produced in an open NO inhalation system employing a nasal cannula with a demand valve that supplied NO to spontaneously breathing subjects. Concentrations of NO and NO_2 in the mechanical lung model and measurements of Met-Hb and $NO_{2^-} + NO_{3^-}$ in healthy subjects both suggest that a sufficient amount of NO is supplied with this system.

To prevent injury to medical personnel involved in patient care, concentrations of exhaust NO-related products, especially NO_2, must be decreased to the lowest possible levels. Although the Occupational Safety and Health Administration has set the 8 h maximal working-exposure level at 3 ppm of NO_2 (14), recent studies have demonstrated that 1·5 ppm NO_2 may cause injury to the lungs over time (15,16). In our NO inhalation system, exhaust NO and NO_2 concentrations remained low while the demand valve was in use; this was true at all flow rates and source tank concentrations. With 44 ppm NO at a flow rate of 0·5 $l min^{-1}$, exhaust NO and NO_2 were 0·13 ppm and 0·06 ppm, respectively, and NO and NO_2 per hour in a standard room at Tsukuba University Hospital were calculated as under 3 ppb and 0·1 ppb, respectively. These measurements are lower than the environmental standard for NO_2 in Japan (0·06 ppm). Since the rate of conversion to NO_2 from NO is increased in the presence of O_2 (17), we examined the effects of an increase in FiO_2 on the production of NO_2. An increase in NO_2 was not observed in the mechanical lung model within the FiO_2 range of 0·20 to 0·32; these findings suggest that inhalation of NO and O_2 together is safe within this FiO_2 range.

There are two reasons for decreased NO and NO_2 exhaust with the use of the demand valve. First, the demand valve system is designed to reduce the supplied gas volume to 1/3 of that used in a constant flow system; this is because the gas is inhaled only during the inspiration period. Second, as inhaled NO gas reaches the alveolar space, it is inactivated by rapid absorption and combination with haemoglobin. Since the demand valve supplies NO in the initial phase of the inspiration period, subsequent inspired air pushes NO already in the airway into the alveolar space.

It is difficult to measure the concentration of NO in the human lung directly. Several studies have demonstrated that the levels of blood Met-Hb and $NO_{2^-} + NO_{3^-}$ increase according to inhaled NO (18,19,20). Therefore, we measured these products in the blood. Our results indicated that NO at 368 ppm in the gas tank with 1 $l min^{-1}$ of flow rate, inhaled via a nasal cannula, supplied the same concentration of NO to the body that was supplied by an airtight mask via closed circuit NO at 40 ppm. This conversion rate (9:1) was similar to the data obtained in the mechanical lung model (11:1). It is important to predict concentrations of delivered NO, because the correct inhaled concentration could not be measured with this system and the haemodynamic changes in response to NO inhalation are different in each patient.

We could not detect NO-Hb in the blood in this study. Although NO-Hb has been detected in rats and mice (12,21), it has not been detected in pigs, piglets and dogs (18,19,22). *In vitro* formation of NO-Hb occurs only with deoxyhaemoglobin in the complete absence of O_2 and not with oxyhaemoglobin (23). NO-Hb itself converts to Met-Hb in the presence of O_2, limiting NO-Hb accumulation (24). Production of NO-Hb may therefore be extremely limited, when most haemoglobin is saturated in healthy subjects.

In this system, inhaled NO concentrations vary according to TVE and RR. To decrease the influence of this problem, a minimal dose, e.g., less than 40 ppm in the gas tank, should be delivered via this system. When the NO level is 40 ppm in the gas tank and is flowing at a 0·5 $l min^{-1}$ via a nasal cannula (corresponding to 1 ppm in the closed circuit NO system delivered via an airtight mask), the variation of NO concentration in the human lung might be within 1–3 ppm. Recent data suggest that under 1·5 ppm of NO is effective for achieving an improvement in pulmonary circulation and gas exchange in patients with ARDS (25,26). This system is not only simple, easy, and safe; it also can supply such low concentrations of NO.

A large study of NO inhalation in ARDS suggested that 30 days NO inhalation does not alter mortality although it does reduce the frequency of severe respiratory failure (27). The effect of long-term NO inhalation in patients with respiratory failure, in addition to ARDS, must be examined further. This system may be useful for the long-term supply of NO in these patients. Katayama *et al*. reported that NO inhalation worsens gas exchange in patients with COPD (28). In COPD patients, it is necessary to inhale NO and oxygen simultaneously. The open NO inhalation system employing a nasal cannula can be easily added to a home oxygen therapy system.

In summary, an open NO inhalation system consisting of a nasal cannula and a demand valve significantly decreased the exhaust NO and NO_2 in spontaneously breathing healthy subjects. This system may be useful for improving the pathophysiological condition of ambulatory patients with pulmonary hypertension.

Acknowledgement

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