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Evaluation of Mapleson systems for administration of inhaled nitric oxide

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Abstract: To assess the safety of nitric oxide (NO) inhalation during manual-controlled ventilation using Mapleson A, D, and F systems, we examined nitrogen dioxide (NO_2) production using a chemiluminescence analyzer. The NO concentration was changed from 0 to 19 parts per million (ppm), and at each level of NO the oxygen (O_2) concentration was changed from 21% to 100%. The NO_2 concentration was observed to increase when either the O_2 or NO concentration was increased. The maximum NO_2 concentrations (mean ± standard deviation) of the Mapleson A, D, and F systems were 0.20 ± 0.03, 0.15 ± 0.03, and 0.17 ± 0.02 ppm, respectively, when the concentrations of NO and O_2 were 19 ppm and 100%, respectively. The NO_2 concentrations of the Mapleson A system were significantly higher than those of either the Mapleson D or F system at 4, 8, and 12 ppm NO and 100% O_2, and than that of the Mapleson D system at 19 ppm NO and 100% O_2. From the viewpoint of NO_2 production, we suggest that the Mapleson D and F systems are safer than the Mapleson A system when manual-controlled ventilation is required.

Key words: Nitric oxide, Nitrogen dioxide, Mapleson system

Introduction

Nitric oxide (NO) is an endogenous vasodilator mediated by stimulation of the soluble guanylate cyclase [1–3], and the addition of low-dose NO to inspired gas has been shown not only potentially to provide selective pulmonary vasodilation in patients with pulmonary hypertension [4,5], but also to improve the ventilation/perfusion mismatching in patients with respiratory failure [6–9]. However, NO is a potentially toxic molecule and easily reacts with oxygen (O_2) to form nitrogen dioxide (NO_2). The toxic effects to the lungs of NO_2 at high concentrations are well known [10–12], and lower concentrations of NO_2 may produce NO_2-induced lung injuries [10,13]. The NO_2 concentrations of inspired gas should thus be kept as low as possible.

Mapleson systems are partial rebreathing methods which can allow patients manual ventilation [14]. The advantages of these systems for NO inhalation are their simplicity and ease of use [15]. Among the Mapleson A–F systems, the A, D, and F systems are the circuits most frequently used today [16]. Each system is distinguished on the basis of its fresh gas inflow and overflow valve relative to the patient connection [14]. The present study was designed to evaluate NO_2 production in the Mapleson A, D, and F systems for assessment of the safety of NO inhalation during manual-controlled ventilation.

Materials and methods

NO was obtained from Nihon Sanso (Oyama, Japan) as a mixture of 793 ppm NO in pure nitrogen gas. Measurement with an infrared analyzer (270–30, Hitachi, Tokyo, Japan) indicated the presence of less than 5 parts per million (ppm) NO_2 in the NO stock gas.

Each A, D, and F Mapleson system is composed of fresh gas inflow and overflow valves, an 80-ml section of corrugated tubing, and a 600-ml reservoir bag (2-A, Igarashi-Ika, Tokyo, Japan), and each was connected to a 70-ml test lung (Fig. 1). Each system was modified by altering the combination of these components. NO gas was regulated by a precise flowmeter (RK-1200, Kojima, Tokyo, Japan) and administered via a Y-piece into a 10 $l \cdot min^{-1}$ continuous stream of fresh gas flow just proximal to the gas inlet of each system. The flow rate and O_2 concentration of fresh gas were regulated by a flowmeter (Siemens-Elema, Stockholm, Sweden) and an O_2–air mixer (961, Siemens-Elema), respectively. The test lung was manually ventilated at the rate of

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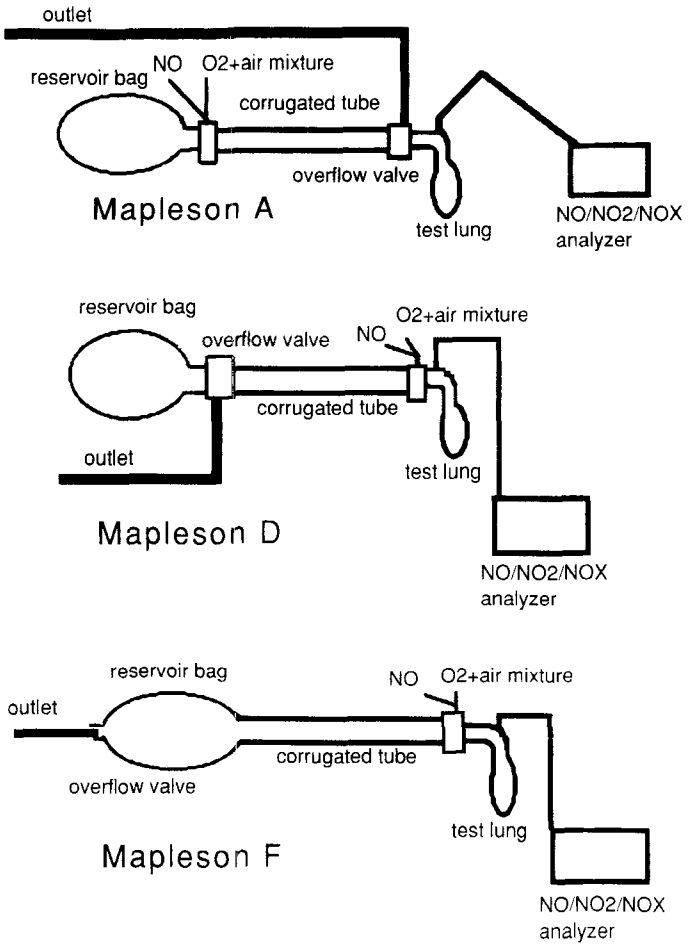

Fig. 1. Schematic illustrations of the manual ventilation circuits for NO inhalation using the Mapleson A, D, and F systems and $NO/NO_2/NO_x$ chemiluminescence analysis

30 cycles·min^{-1} and tidal volume of about 100 ml during the study. The tidal volume was monitored by a respirometer (HC4748, Medishield, Windlesham, UK) connected just above the test lung. The exhaled gases from the overflow valves were released into the outdoor air.

NO and NO_2 measurements were performed between the respirometer and the test lung. NO and NO_2 concentrations were measured by a chemiluminescence analyzer using a molybdenum converter [12] (Model 42, Thermo Environmental Instruments, Franklin, MA, USA) instead of a stainless steel converter to minimize the underestimation of NO_2 concentration at high oxygen concentrations [17]. The minimum detection limit of this analyzer is 0.5 parts per billion (ppb). The chemiluminescence analyzer was calibrated before each measurement.

NO_2 concentrations were measured at NO concentrations of 0, 4, 8, 12, 16, and 19 ppm with each of the A, D, and F Mapleson systems. At each NO concentration, the O_2 concentration of the continuous gas flow was changed from 21% to 40%, 60%, 80%, and 100%. Measurements were repeated seven times on different days.

All values are expressed as mean ± standard deviation (SD). Statistical analyses of differences within a system or among systems were performed using a one-way analysis of variance with repeated measures. Scheffe's test was used for internal comparisons within each system and for external comparisons between systems. A P value of less than 0.05 was considered to be significant.

Results

The mean values of NO_2 concentrations at each combination of inhaled NO and O_2 concentrations for the A, D, and F Mapleson systems are shown in Tables 1, 2, and 3, respectively. In each system, as the concentration of NO increased, the concentration of NO_2 produced also increased. Likewise, as the concentration of O_2 administered was increased, the concentration of NO_2 produced increased. The maximum NO_2 concentration for each system was observed when the NO and O_2 concentrations were 19 ppm and 100%, respectively. The maximum concentrations of NO_2 for the Mapleson A, D, and F systems were 0.20 ± 0.03, 0.15 ± 0.03, and 0.17 ± 0.02 ppm, respectively.

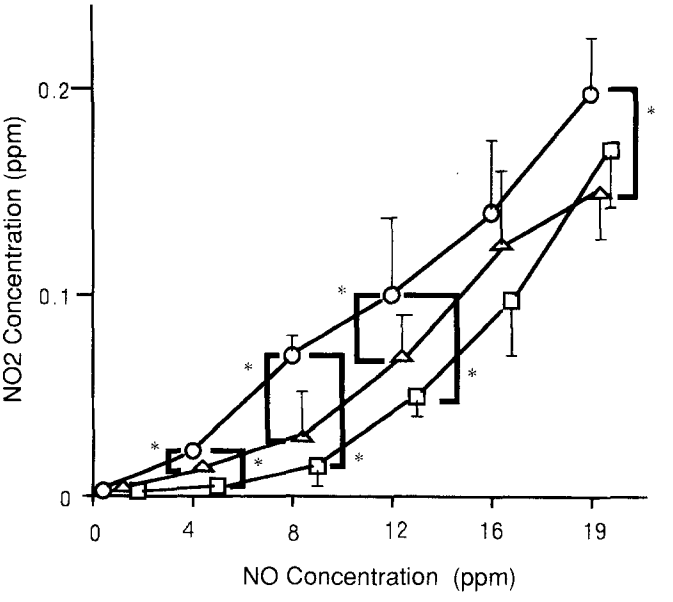

Fig. 2. Comparison among the Mapleson A, D, and F systems of NO_2 concentrations under 100% oxygen inhalation at inhaled NO concentrations ranging from 0 to 19 ppm. *$P < 0.05$, between systems. *Open circles*, Mapleson A; *open triangles*, Mapleson D; *open squares*, Mapleson F

Table 1. NO_2 concentrations in the Mapleson A system

NO concentrations (ppm)	O_2 concentrations (%)*				
	21	40	60	80	100
19†	0.05 ± 0.01[a]	0.10 ± 0.02[abcd]	0.15 ± 0.03[abcdeA]	0.15 ± 0.04[abcdAB]	0.20 ± 0.03[abcdeAB]
16†	0.05 ± 0.01[a]	0.08 ± 0.02[abc]	0.10 ± 0.02[abcA]	0.11 ± 0.02[abcAB]	0.14 ± 0.04[abcABC]
12†	0.05 ± 0.01[a]	0.06 ± 0.01[a]	0.08 ± 0.02[ab]	0.08 ± 0.03[a]	0.10 ± 0.04[abAB]
8†	0.04 ± 0.02[a]	0.04 ± 0.01[a]	0.05 ± 0.01[a]	0.06 ± 0.02[aA]	0.07 ± 0.01[aAB]
4	0.04 ± 0.01[a]	0.04 ± 0.01[a]	0.05 ± 0.01[a]	0.04 ± 0.02	0.04 ± 0.02
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

*$P < 0.05$ among groups under different NO concentrations; †$P < 0.05$ among groups under different O_2 concentrations.
a, $P < 0.05$ *vs* 0 ppm NO; b, $P < 0.05$ *vs* 4 ppm NO; c, $P < 0.05$ *vs* 8 ppm NO; d, $P < 0.05$ *vs* 12 ppm NO; e, $P < 0.05$ *vs* 16 ppm NO.
A, $P < 0.05$ *vs* 21% O_2; B, $P < 0.05$ *vs* 40% O_2; C, $P < 0.05$ *vs* 60% O_2; D, $P < 0.05$ *vs* 80% O_2.

Table 2. NO_2 concentrations in the Mapleson D system

NO concentrations (ppm)	O_2 concentrations (%)*				
	21	40	60	80	100
19†	0.03 ± 0.02[a]	0.05 ± 0.04[abc]	0.12 ± 0.05[abcdeAB]	0.14 ± 0.03[abcdeAB]	0.15 ± 0.03[abcdAB]
16†	0.02 ± 0.02	0.04 ± 0.02[a]	0.05 ± 0.02[a]	0.09 ± 0.03[abcAB]	0.13 ± 0.04[abcdABC]
12†	0.01 ± 0.01	0.02 ± 0.02	0.02 ± 0.01	0.05 ± 0.03[a]	0.07 ± 0.02[abcABC]
8	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.02	0.01 ± 0.01	0.03 ± 0.03
4†	0.00 ± 0.01	0.00 ± 0.00	0.01 ± 0.02	0.00 ± 0.01	0.02 ± 0.01
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

*$P < 0.05$ among groups under different NO concentrations; †$P < 0.05$ among groups under different O_2 concentrations.
a, $P < 0.05$ *vs* 0 ppm NO; b, $P < 0.05$ *vs* 4 ppm NO; c, $P < 0.05$ *vs* 8 ppm NO; d, $P < 0.05$ *vs* 12 ppm NO; e, $P < 0.05$ *vs* 16 ppm NO.
A, $P < 0.05$ *vs* 21% O_2; B, $P < 0.05$ *vs* 40% O_2; C, $P < 0.05$ *vs* 60% O_2; D, $P < 0.05$ *vs* 80% O_2.

Table 3. NO_2 concentrations in the Mapleson F system

NO concentrations (ppm)	O_2 concentrations (%)*				
	21	40	60	80	100
19†	0.02 ± 0.01[abc]	0.06 ± 0.03[abcde]	0.09 ± 0.04[abcdA]	0.14 ± 0.02[abcdeABC]	0.17 ± 0.02[abcdeABC]
16†	0.02 ± 0.01[a]	0.01 ± 0.02	0.06 ± 0.02[abcAB]	0.09 ± 0.03[abcdAB]	0.10 ± 0.03[abcdABC]
12†	0.01 ± 0.01	0.01 ± 0.02	0.03 ± 0.01	0.06 ± 0.02[abcABC]	0.05 ± 0.01[abAB]
8†	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01[AB]	0.02 ± 0.01
4	0.00 ± 0.01	0.00 ± 0.00	0.00 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

*$P < 0.05$ among groups under different NO concentrations; †$P < 0.05$ among groups under different O_2 concentrations.
a, $P < 0.05$ *vs* 0 ppm NO; b, $P < 0.05$ *vs* 4 ppm NO; c, $P < 0.05$ *vs* 8 ppm NO; d, $P < 0.05$ *vs* 12 ppm NO; e, $P < 0.05$ *vs* 16 ppm NO.
A, $P < 0.05$ *vs* 21% O_2; B, $P < 0.05$ *vs* 40% O_2; C, $P < 0.05$ *vs* 60% O_2; D, $P < 0.05$ *vs* 80% O_2.

Figure 2 shows the NO_2 concentrations for the three systems when 100% oxygen was administered and the NO concentration was varied from 0 to 19 ppm. Significant differences were observed between the Mapleson A system and the other two systems for NO_2 concentrations at 4, 8, 12 and 19 ppm NO concentrations. The NO_2 concentrations of the Mapleson A system were significantly higher than those of either the Mapleson D or F system at 4, 8, and 12 ppm NO and than that of the Mapleson D system at 19 ppm NO. No significant differences in NO_2 concentrations were observed between the Mapleson D and F systems.

Discussion

Attention has increasingly been focused on NO inhalation therapies [4–9]. Although inhaled NO may be effective in patients with pulmonary hypertension [4,5] and respiratory failure [6–9], the sudden

discontinuation of inhaled NO may produce severe arterial desaturation and pulmonary hypertension [7,8,18]. For the safe use of inhaled NO, it is essential to prepare an NO breathing system that allows manual ventilation of patients during and just after tracheal suctioning and during an episode of ventilator malfunction.

The Mapleson A, D, and F systems are frequently used manual ventilation circuits [16]. Each system has specific rebreathing characteristics depending on the location of the fresh gas inflow and overflow valves, the fresh gas flow rate, the ventilatory rate and tidal volume, and the mode of ventilation [14,19,20]. The magnitude of NO_2 production varies with the concentrations of NO and O_2 administered, and with the retention time of NO within the lungs and the breathing circuits in each system [21]. NO_2 production may increase when higher concentrations of NO or O_2 are administered [21]. In the present study, a higher concentration of NO_2 was produced when a higher concentration of NO or O_2 was administered. These findings are consistent with those reported by Nishimura et al. [22]. In addition, the longer the retention time of NO in the circuit, the higher may be the concentration of NO_2 produced. The greater the rebreathing, the longer the retention time of NO in the circuit. In the Mapleson A, D, and F systems, the mean values of the inspired maximum concentrations of NO_2 were consistently low (about 0.2 ppm or less), even under the administration of 19 ppm NO and 100% O_2. The findings suggest that the extent of rebreathing in all three systems would be very low when an infant with a very small lung volume (about 70 ml) is manually ventilated by the Mapleson A, D, or F system at respiratory rates of 30 cycles·min^{-1} and a tidal volume of about 100 ml under a fresh gas flow rate of 10 l·min^{-1}. However, the retention time of NO in the Mapleson systems may increase with decreased fresh gas flow rate, decreased minute-volume and increased lung volumes, resulting in production of high concentration of NO_2 [14,19,20,22].

The concentrations of NO_2 in the Mapleson D and F systems were significantly lower than those in the Mapleson A system. Based on studies of carbon dioxide elimination in Mapleson systems, the extent of rebreathing in the Mapleson A system has been suggested to be greater than that in either of the other two systems during controlled ventilation [14]. The greater the rebreathing in the Mapleson A system, the higher the concentration of NO_2 which may be produced.

There is no firm agreement regarding the safety levels of NO_2 during NO inhalation. Recommendations for occupational health and safety have set the upper limit for NO_2 exposure at 5 ppm for a 15-min period and at 3 ppm for an 8-h period [23]. However, these recommendations are intended for healthy workers and not for children or adults with pulmonary diseases. Lower concentrations of NO_2 have been shown potentially to produce lung injuries [10,13]. In addition, inhaled NO therapy must frequently be continued for prolonged periods, ranging from several hours to several days [8,24,25]. The National Air Quality Standard for NO_2 in the United States has been set at 0.05 ppm. To minimize NO_2-induced lung injuries, the inhaled NO concentrations should be kept as low as possible. Our results suggest that the Mapleson D and F systems are safer than the Mapleson A system during controlled ventilation.

In conclusion, the present study demonstrated that NO_2 production during manual-controlled ventilation using the Mapleson A, D, and F systems is very low, even under the administration of 19 ppm NO and 100% O_2, when respiratory rates, tidal volume, and fresh gas flow are set at 30 cycles·min^{-1}, 100 ml, and 10 l·min^{-1}, respectively. The systems are very simple and easy to use, even in emergency situations. These systems may be used during transportation if the NO and NO_2 of the exhaled gases can be collected by soda lime [26] or activated charcoal. We suggest that from the viewpoint of NO_2 production, the Mapleson D and F systems are safer than the Mapleson A system when manual-controlled ventilation is required.

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