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Effect of inhaled nitroglycerine and sodium nitroprusside aerosol on hemodynamics and oxygenation in dogs with pulmonary hypertension

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Abstract

Purpose. To test the hypothesis that inhalation of aerosol of glyceryl trinitrate or sodium nitroprusside might produce selective pulmonary vasodilation, causing an improvement of oxygenation with minimal systemic hypotension as inhaled nitric oxide gas, we investigated the effect of inhaled nitroglycerine and sodium nitroprusside aerosol on hemodynamics and oxygenation in dogs with pulmonary hypertension.

Methods. Pulmonary hypertension was induced by a continuous infusion of 1.0 to 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ U-46619 in anesthetized and mechanically ventilated dogs. Aerosol preparations consisted of normal saline, 250, 500, 1000, and 2000 ppm solutions of either glyceryl trinitrate or sodium nitroprusside were administered sequentially via the breathing circuit.

Results. Inhaled nitroglycerine and sodium nitroprusside aerosol caused neither selective pulmonary vasodilation nor improved oxygenation in this pulmonary hypertension model, unlike inhaled nitric oxide gas.

Conclusion. These findings suggest that inhaled nitroglycerine and sodium nitroprusside aerosol is not effective in improving hemodynamic derangement or oxygenation in pulmonary hypertension. However, the effect of the substances in higher dose ranges remains to be defined.

Key words: Glyceryl trinitrate, Sodium nitroprusside, Aerosol, Inhalation, Pulmonary hypertension

Introduction

Over the last several years, inhaled nitric oxide (NO) gas has been used as a novel pulmonary vasodilator for a treatment of pulmonary hypertension or related pathophysiological conditions including acute respiratory distress syndrome (ARDS), experimentally and clinically [1–11]. It is assumed that NO selectively dilates the vessels of the alveoli being ventilated, causing an improvement of ventilation perfusion mismatch [9]. Previous studies showed that NO inhalation does not cause significant systemic hemodynamic alterations, probably because NO might be quickly bound by hemoglobin, forming nitrosyl hemoglobin, and then being inactivated in the pulmonary vasculature [12,13]. However, at present, the margin of safety regarding NO inhalation has not been well defined [11,14]. Clinically, NO might be used with a relatively high concentration of oxygen, since it might be applied in the patients with severe respiratory failure. NO can be easily oxidized to NO_2 in the presence of oxygen. NO_2 is a highly toxic gas, causing acute lung injury with pulmonary edema and marked methemoglobinemia [15].

Recently, it was reported that aerosolized prostacyclin, a potent vasodilatory prostanoid, might induce selective pulmonary vasodilation, resulting in improved gas exchange in patients with ARDS [16,17]. On the other hand, the common so-called nitrovasodilators such as glyceryl trinitrate, sodium nitroprusside, and isosorbide dinitrate are supposed to act by releasing NO intracellularly to simulate the effect of endogenous NO [18,19]. Although these nitrovasodilators cause potent pulmonary vasodilation, intravenous administration can result in an increase in pulmonary shunt associated with peripheral hypotension when applied to pathophysiological conditions with pulmonary vasoconstriction [20]. We hypothesized that inhalation of aerosols of these nitrovasodilators might produce selective pulmonary vasodilation to ventilated alveoli, causing an improvement of oxygenation with minimal systemic hypotension.

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Materials and methods

The protocol was approved by the Institutional Animal Research Committee at the University of Tsukuba Medical Institutions, and the care of the animals was in accordance with guidelines for ethical animal research. Glyceryl trinitrate (GTN; nitroglycerine) aqueous preparation was provided by Nippon Kayaku (Tokyo, Japan), and sodium nitroprusside (SNP) was purchased from Sigma (St. Louis, MO, USA).

Nine adult mongrel dogs of either sex, weighing 8 to 14 kg (10.4 ± 1.6 kg; mean ± SD), were randomly assigned to two groups, i.e., GTN ($n = 4$) and SNP ($n = 5$) aerosol inhalation groups. After premedication with ketamine hydrochloride (10 mg·kg^{-1}, i.m.), the animals were anesthetized with a bolus injection of pentobarbital (25 mg·kg^{-1}), followed by a continuous infusion of pentobarbital (5 to 10 mg·kg^{-1}·h^{-1}) and pancuronium (0.1 mg·kg^{-1}·h^{-1}), to institute adequate paralysis. The dogs were orotracheally intubated (Portex Blue Line Endotracheal tube, 8 mm i.d., Kent, UK), and ventilated mechanically (Model 613, Harvard Apparatus, South Natrick, MA, USA) with air (F_{IO_2} = 0.21). Respiratory rate and tidal volume were 20 breaths/min and 10 to 15 ml·kg^{-1}, respectively. The ventilatory settings were initially adjusted so that end-tidal P_{CO_2} (Capnomac Ultima, Datex Instrumentarium, Helsinki, Finland) was 30 to 35 mmHg, and were not changed until the end of the study. The dogs received a continuous infusion of lactated Ringer's solution (5 to 10 ml·kg^{-1}·h^{-1}).

Temperature was maintained at 37 to 38°C, using an electric heating blanket. An 18-gauge vascular catheter was inserted into a femoral artery for continuous blood pressure monitoring, and intermittent blood sampling. A 5-Fr pulmonary artery catheter (Baxter Edwards Critical-Care, Irvine, CA, USA) was inserted in a femoral vein and floated to the wedge position. EKG, arterial blood pressure (ABP), pulmonary artery pressure (PAP), central venous pressure (CVP), and airway pressure were continuously monitored and recorded using amplifier-integrated-polygraph recorder system (NEC San-ei, Tokyo, Japan). Cardiac output (CO) was determined as the mean of three measurements by thermal dilution using iced D-5W (Cardiac output computer 7350, Arrow International, Reading, PA, USA).

After 1 h of stabilization, control data including a complete set of hemodynamic variables, arterial and mixed venous blood gases (ABL3, Radiometer, Copenhagen, Denmark), and peak inspiratory pressure (PIP) were recorded (Control). Then, an infusion of the thromboxane A_2 analog, U-46619 (Sigma) was initiated at a rate of 1.0 to 4.0 μg·kg^{-1}·min^{-1} to achieve significant pulmonary hypertension, i.e., mean PAP to 30 mmHg (Baseline). First, for the purpose of a comparison between systemic administration and aerosol inhalation, GTN or SNP was infused for 5 min at a rate of 10 μg·kg^{-1}·min^{-1}, and the data were recorded (Infusion). To obtain a pulmonary vascular dose–response curve during U-46619 infusion, each animal received either series of GTN or SNP aerosol intratracheally 10 min after the infusion measurement. Aerosol preparations consisted of normal saline, 250, 500, 1000, and 2000 ppm solutions of either GTN or SNP (diluted with normal saline). Hemodynamic and other variables were recorded at 5 min after the initiation of inhalation of each aerosol, and at 10 min after the termination of each aerosol inhalation (Aft). Methemoglobin levels were measured at the control period and the end of the study (OSM-3 CO Oximeter, Radiometer). Aerosol was generated by an ultrasonic nebulizer (Omron NE-U11B, Tokyo, Japan), and was delivered intratracheally by incorporating the generating chamber into the inspiratory limb of the breathing circuit. This nebulizer has a capability of maximum output of 1.5–2.0 ml·min^{-1}, and generating particles ranging from 2.0 to 10.0 μm with a mass median diameter of 4.88 μm in size (2600C Particle Sizer, Malvern Instruments, Southborough, MA, USA). Since SNP decomposes in light [21], inspiratory limb of the breathing circuit was covered with an opaque wrapping.

All data are presented as mean ± standard error (SEM), unless otherwise mentioned. Hemodynamic parameters including pulmonary vascular resistance index (PVRI), cardiac index (CI), and pulmonary shunt (Q_s/Q_t) were calculated using standard equations [22–24]. Statistical analysis was performed by ANOVA and Fisher's protected least significant difference method, except the data regarding the dose of U-46619 which used a data analysis system (StatView, Abacus Concepts, Berkeley, CA, USA). The comparison of the dose of U-46619 between the two groups was performed by Mann-Whitney test. $P < 0.05$ was considered significant.

Results

There was no significant difference in dose of U-46619 infused to achieve pulmonary hypertension of mean PAP ≥30 mmHg between the two groups; i.e., GTN: 2.25 ± 1.26 *vs* SNP: 2.00 ± 0.00 μg·kg^{-1}·min^{-1} (mean ± SD). Infusion of U-46619 caused significant increases in mean PAP in both groups during the study period, except the phases of 2000 ppm GTN inhalation and after (Fig. 1a). PVRI tended to increase both in SNP and GTN groups during the U-46619 infusion period, although the changes were statistically insignificant (Fig. 1b). There were significant decreases in CI between control and throughout the U-46619 infusion period in the GTN group. Furthermore, CI decreased signifi-

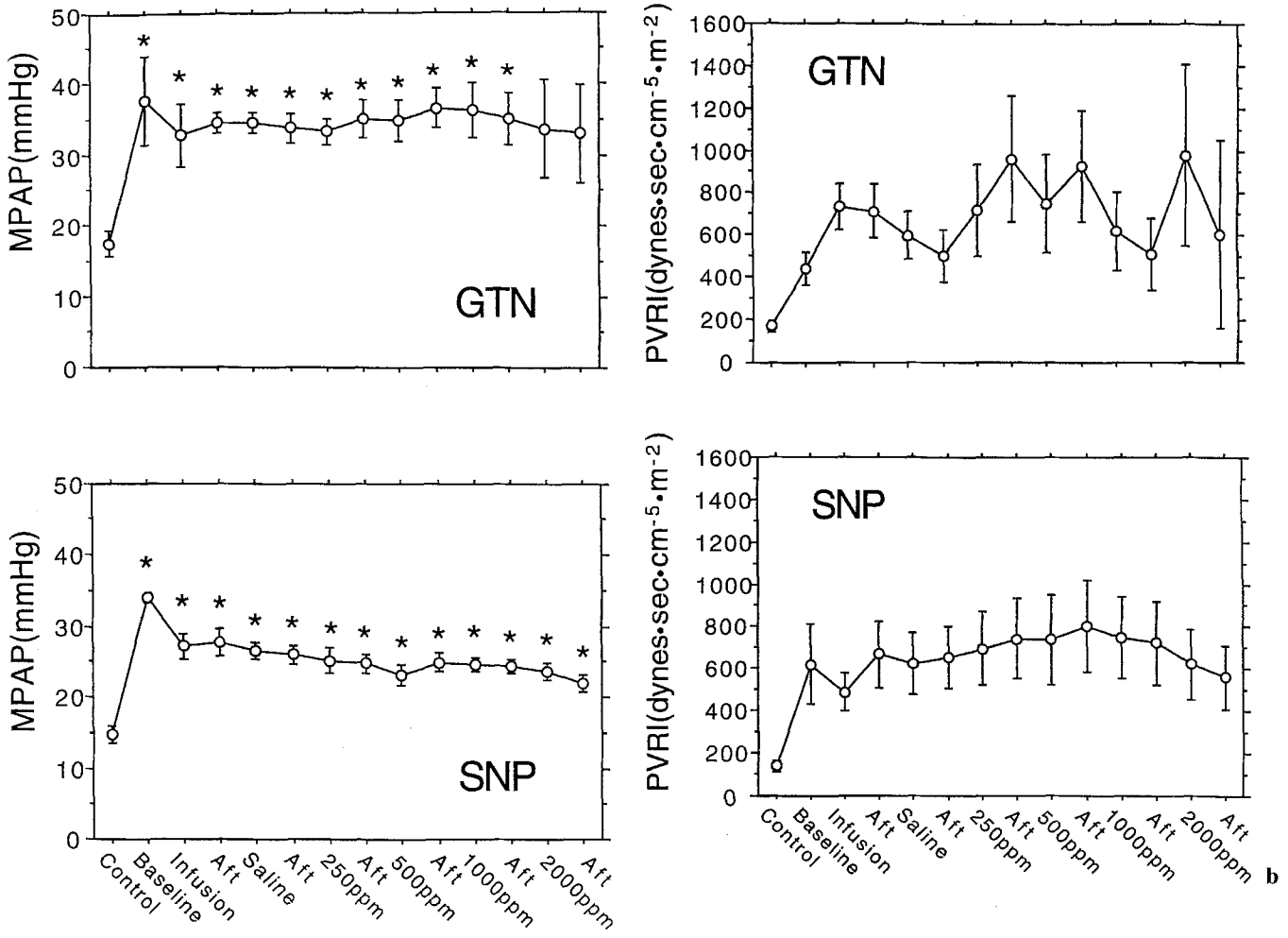

Fig. 1a,b. Changes in mean pulmonary arterial pressure (*MPAP*; **a**) and pulmonary vascular resistance index (*PVRI*; **b**) in the glyceryl trinitrate (*GTN*) aerosol inhalation group (*top*) and the sodium nitroprusside (*SNP*) aerosol inhalation group (*bottom*). *Baseline*: U-46619 infusion was established to achieve pulmonary hypertension. *Infusion*: GTN or SNP was systemically infused for 5 min at a rate of $10\,\mu g \cdot kg^{-1} \cdot min^{-1}$. *Saline*, *250ppm*, *500ppm*, *1000ppm*, and *2000ppm* indicate that aerosol preparations consisting of normal saline, 250, 500, 1000, and 2000 ppm solutions of either GTN or SNP were intratracheally administered. *Aft*: 10 min after the termination of each aerosol inhalation. See text. $^*P < 0.01$ *vs* control. Data are mean ± SEM

cantly from the saline inhalation period to the end of the study compared with the baseline period in the GTN group. In the SNP group, there were also significant decreases in CI between control and the whole U-46619 infusion period, except for the baseline period. Similar to the GTN group, CI decreased significantly from saline inhalation period to the end of the study compared with the baseline period in the SNP group (Fig. 2a). ABP tended to increase following the initiation of U-46619 infusion, although the change was significant only at the baseline period of the SNP group. Subsequently, ABP decreased significantly during the infusion period and the latter half of the aerosol inhalation periods compared with the baseline period in the SNP group. In the GTN group, although the changes were statistically insignificant, ABP tended to have a similar trend as that in the SNP group (Fig. 2b). As a whole, GTN or SNP aerosol inhalation did not cause significant hemodynamic improvements of pulmonary hypertension induced by U-46619 infusion.

U-46619 infusion caused significant decreases in Pa_{O_2} throughout the study period in the GTN group. Similarly, in the SNP group, Pa_{O_2} tended to decrease while U-46619 was infused, although the changes were statistically insignificant (Fig. 3a). Changes in Qs/Qt during the study period were not significant in both groups (Fig. 3b). Thus, in both groups, no improvement in oxygenation was observed during the GTN or SNP aerosol inhalation period. Whereas U-46619 caused significant increases in PIP that persisted until the end of the study

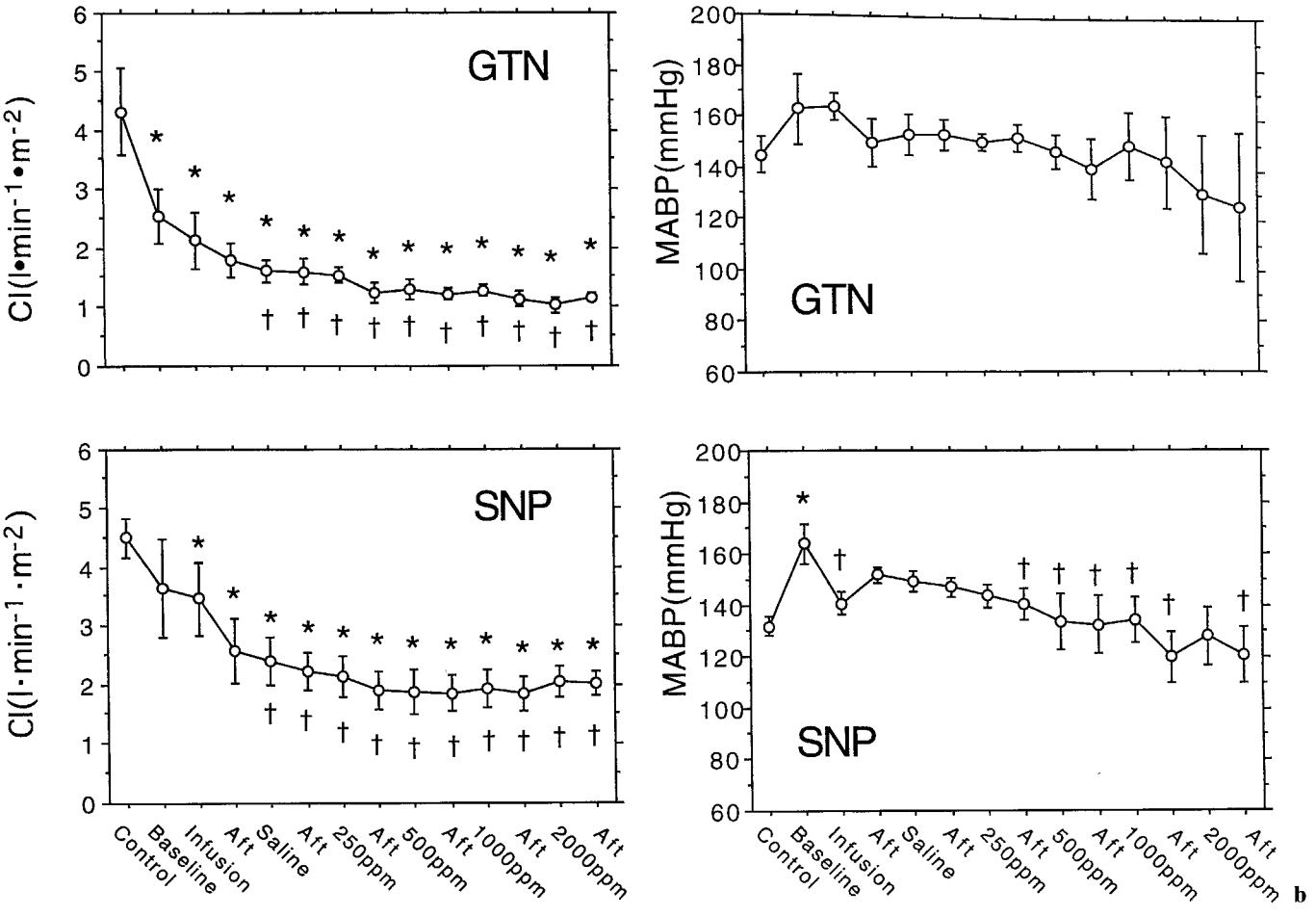

Fig. 2a,b. Changes in cardiac index (*CI*; **a**) and mean arterial blood pressure (*MABP*; **b**) in the glyceryl trinitrate (*GTN*) aerosol inhalation group (*top*) and the sodium nitroprusside (*SNP*) aerosol inhalation group (*bottom*). *Baseline*: U-46619 infusion was established to achieve pulmonary hypertension. *Infusion*: GTN or SNP was systemically infused for 5 min at a rate of 10 μg·kg^{-1}·min^{-1}. *Saline*, *250ppm*, *500ppm*, *1000ppm*, and *2000ppm* indicate that aerosol preparations consisting of normal saline, 250, 500, 1000, and 2000 ppm solutions of either GTN or SNP were intratracheally administered. *Aft*: 10 min after the termination of each aerosol inhalation. See text. $*P < 0.01$ *vs* control; $\dagger P < 0.05$ *vs* baseline. Data are mean ± SEM

in both groups, GTN or SNP aerosol inhalation did not affect PIP (Fig. 4). Changes in methemoglobin level between the control period and at the end of the study were insignificant in each group; methemoglobin levels at the control period compared with those at the end of the study in GTN and SNP groups were 0.87% ± 0.12% vs 0.53% ± 0.17%, and 0.86% ± 0.17% *vs* 1.02% ± 0.22%, respectively.

Discussion

This study showed that GTN or SNP aerosol generated by an ultrasonic nebulizer using 250 to 2000 ppm solutions did not improve hemodynamic derangements nor oxygenation in canine pulmonary hypertension induced by U-46619 infusion, unlike NO gas [2]. The causes of this ineffectiveness might be speculated as follows. First, the potency of GTN or SNP aerosol in dilating pulmonary vessels might be weaker than that of NO, because GTN or SNP aerosol inhalation did not cause a significant decrease in PAP or PVRI in the present study. However, it was not delineated precisely in this study, because no NO gas inhalation group was assigned. Second, species and dose of U-46619 infusion in our study were obviously different from the previous study [2]. Frostell and co-workers [2] showed that NO inhalation at 40 ppm or more reversed acute vasoconstriction caused by U-46619 infusion using an awake lamb model. They were able to produce a similar level

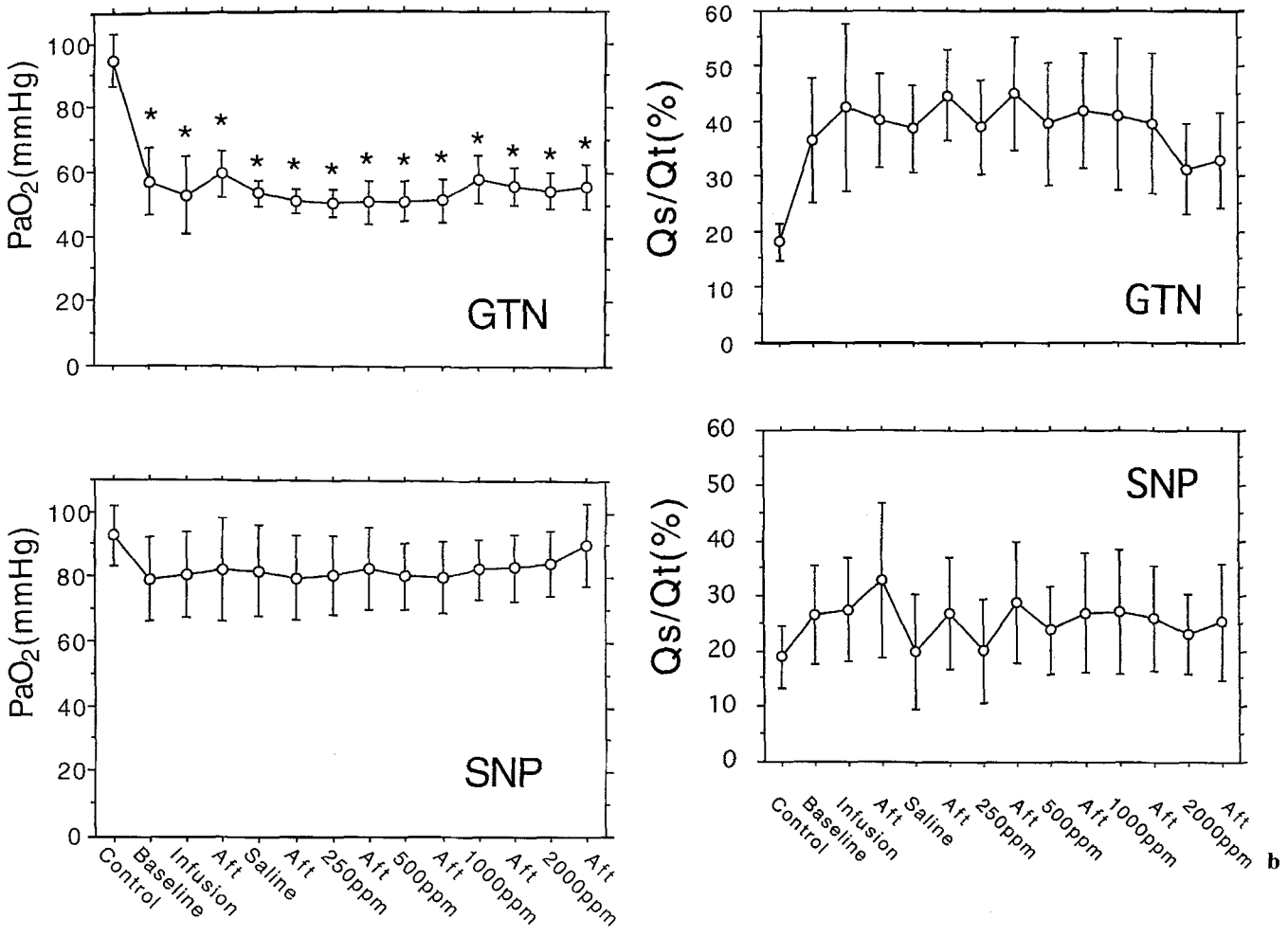

Fig. 3a,b. Changes in Pao_2 (**a**) and pulmonary shunt fraction (*Qs/Qt*; **b**) in the glyceryl trinitrate (*GTN*) aerosol inhalation group (*top*) and the sodium nitroprusside (*SNP*) aerosol inhalation group (*bottom*). *Baseline*: U-46619 infusion was established to achieve pulmonary hypertension. *Infusion*: GTN or SNP was systemically infused for 5 min at a rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. *Saline*, *250ppm*, *500ppm*, *1000ppm*, and *2000ppm* indicate that aerosol preparations consisting of normal saline, 250, 500, 1000, and 2000 ppm solutions of either GTN or SNP were intratracheally administered. *Aft*: 10 min after the termination of each aerosol inhalation. See text. $^*P < 0.01$ *vs* control. Data are mean ± SEM

of pulmonary hypertension (mean PAP to 30 mmHg) as in the present study by infusing U-46619 at a rate of 0.4 to 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The dose of U-46619 was about one-fifth to one-third of those in our study. This might be attributable to species difference and/or use of anesthetics. Also, in the present study, pulmonary hypertension was associated with a significant reduction in cardiac output. Hence, it is likely that pathophysiology or severity of the animal in our model was different from the lamb preparation which Frostell et al. used. Romand et al. [25,26] reported that inhaled NO only partially reversed pulmonary vasoconstriction induced by hypoxia, but did not change pulmonary vascular tone in oleic acid-induced acute lung injury in a mechanically ventilated dog model. Similarly, in a canine pulmonary hypertension model induced by a thromboxane analog with fixed cardiac output using total right heart bypass, inhalation of 10 and 40 ppm NO reversed pulmonary vasoconstriction only partially [27]. Therefore, it is likely that the effect of inhaled NO on pulmonary vasoconstriction depends to some extent on species and experimental conditions. Although these models were relatively similar to our model, it remains to be answered whether or not NO might be effective in reversing the pulmonary vasoconstriction of the same model as our study.

In human physiological airways, about 20% to 30% of airborne particles in the diameter range of 4.0 to 5.0 μm deposit in the lower respiratory tract [28]. During positive pressure ventilation, the aerosol fraction de-

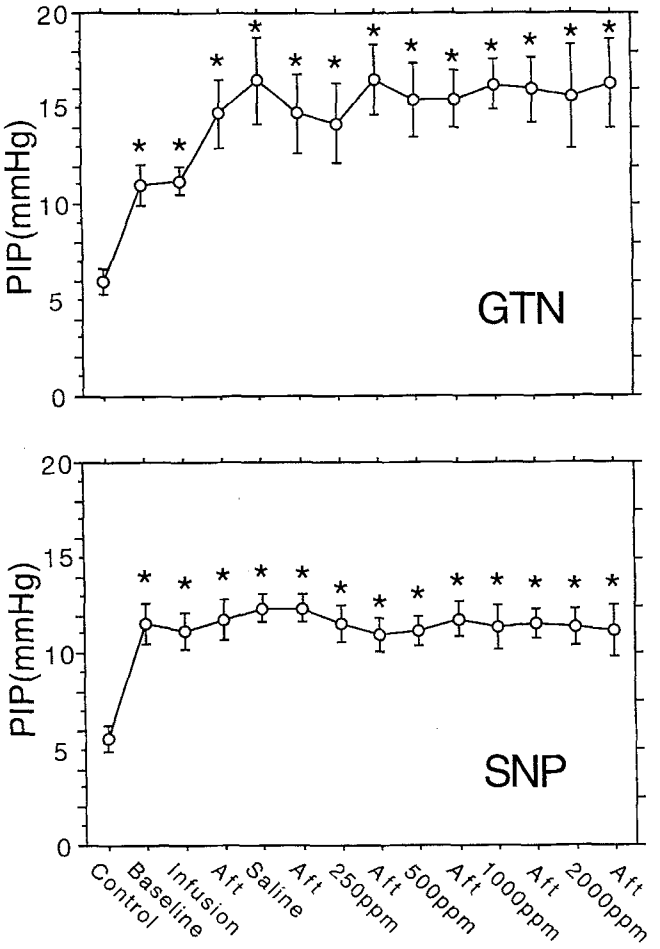

Fig. 4. Changes in peak inspiratory pressure (*PIP*) in the glyceryl trinitrate (*GTN*) aerosol inhalation group (*top*) and the sodium nitroprusside (*SNP*) aerosol inhalation group (*bottom*). *Baseline*: U-46619 infusion was established to achieve pulmonary hypertension. *Infusion*: GTN or SNP was systemically infused for 5 min at a rate of $10\,\mu g \cdot kg^{-1} \cdot min^{-1}$. *Saline*, *250ppm*, *500ppm*, *1000ppm*, and *2000ppm* indicate that aerosol preparations consisting of normal saline, 250, 500, 1000, and 2000 ppm solutions of either GTN or SNP were intratracheally administered. *Aft*: 10 min after the termination of each aerosol inhalation. See text. * $P < 0.01$ *vs* control. Data are mean ± SEM

posited in the airway varies according to several factors such as the volume of nebulizer solution, the size of aerosol storage chamber, the size of the tracheal tube, and inspiratory time [29]. We have no direct evidence indicating that a substantial amount was delivered to bronchiolar and alveolar space in this study. However, we have used the same nebulizer in several studies regarding airway responsiveness [30]. In these studies, airway responsiveness was assessed by measuring specific airway resistance as a function of increasing concentration of histamine aerosol generated by the same nebulizer. In these study methods, the primary site of the action of the inhaled aerosol is assumed to be the smaller airways, including the bronchiole. Extrapolating from these observations, the assumption that a substantial amount of GTN or SNP aerosol was delivered to the bronchiolar and alveolar space might be likely. However, there remains some uncertainty as to the actual amount of GTN or SNP that deposited on the alveoli. Several drugs, such as antibiotics and bronchodilators, can be changed or destroyed chemically [31]. Although we have no data regarding the effect of an ultrasonic nebulizer on the chemical structure of GTN or SNP, it is unlikely that a substantial change in chemical structure can occur, because the operating time of the nebulizer for each solution was only 5 min in duration.

In this study, there exist several limitations. First, we could not answer the question whether even much higher dosages of GTN or SNP are able to influence pulmonary and systemic circulation. We chose the highest concentration of 2000 ppm, because it was the highest possible concentration of water-soluble GTN preparation available. Thus, there remains the possibility that much higher dosages of SNP or GTN, if available, can influence pulmonary and/or systemic circulation. In addition, it is also unclear whether GTN or SNP aerosol acts as does NO in the alveoli, if they affect pulmonary circulation. Second, mean ABP did not change during GTN infusion in comparison with the baseline period, whereas mean ABP decreased in response to SNP infusion. Although we chose the same dose ($10\,\mu g \cdot kg^{-1} \cdot min^{-1}$) to infuse GTN or SNP, the potency of SNP is greater than GTN in terms of arterial vasodilating activity [32]. Therefore, GTN might be virtually ineffective in reducing MABP under the influence of a potent vasoconstrictor, U-46619. Third, the hemodynamics of the animals might be rather deteriorated progressively during the study, in terms of cardiac index. The cause of this hemodynamic deterioration might be attributable to prolonged use of the potent thromboxane A_2 analog, U-46619. Since the primary aim of the study was to examine the changes in pulmonary hemodynamics in response to GTN or SNP aerosol inhalation, we could not use catecholamines to maintain cardiac output. From our observation, however, the effect of GTN or SNP aerosol inhalation on pulmonary hemodynamics might be delineated. Fourth, Pao_2 did not decrease significantly in the GTN group after U-46619 infusion was initiated, whereas it did in the SNP group. Although the precise mechanism of this phenomenon is unclear, one can recognize that inhalation of both agents did not improve oxygenation. Fifth, in this study, the numbers of animals were small. However, it is unlikely that basic results would differ if the numbers of animals were larger.

In this study, U-46619 infusion caused significant increases in airway pressure. This agent is a stable

thromboxane A_2 analog which is well known as a highly potent constrictor of airway smooth muscles [33]. A previous study showed that NO has a bronchodilating effect in guinea pig preparation [34]. This might also contribute to improving ventilation perfusion mismatching. It was demonstrated that GTN as well as SNP has a bronchodilating action clinically or experimentally [35,36]. However, their bronchodilating action is relatively weak in potency compared with isoproterenol [37]. In this study, no change in PIP, which was elevated by U-46619 infusion, was observed during GTN or SNP aerosol inhalation. Therefore, it is likely that the bronchoconstriction caused by U-46619 at this dose range was so intense that GTN or SNP aerosol used in this study could not reverse the process.

It was reported that aerosolized prostacyclin was effective in improving gas exchange in pediatric and adult patients with ARDS resulting from selective pulmonary vasodilation [16,17]. In this study, we chose GTN and SNP as the representative agents of so-called nitrovasodilators, because they are supposed to be clinically important and to have higher potency among these groups of drugs [20]. If we can obtain any other highly potent vasodilating agent which is nontoxic, short-acting, and easy to generate as an aerosol, it might be a probable substitute for NO gas. Among them, we tested isosorbide dinitrate (ISDN) solution in the preliminary study. It seemed that ISDN was less effective than GTN or SNP, at least up to 500 ppm solution. Other candidates to be tested might be a new class of NO-based vasodilators, i.e., NO/nucleophile complexes [38], a newly developed pirsidomine derivative [39], and water-soluble, short-acting calcium antagonists such as nicardipine [20].

In conclusion, the present study indicates that an intratracheal administration of GTN or SNP aerosol causes neither selective pulmonary vasodilation nor improved oxygenation in the canine pulmonary hypertension model, unlike inhaled NO gas. The effect of GTN or SNP aerosol in other models, such as the lamb, with pulmonary hypertension or in higher dose ranges, remains to be defined.

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