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14th Colloquium of the International Society of Dermatopathology

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The Interdependence of Dermatosurgery and Dermatopathology

Dermatologic surgery and dermatologic pathology cannot be practised at a high level unless surgeons are knowledgeable about pathology and pathologists are conversant with surgery. Despite this reality, dermatopathology is not a serious component of training programs in dermatologic and plastic surgery, and dermatopathologists during their training are not imbued with principles of surgery. This colloquium seeks to help rectify these deficiencies and to educate dermatologists, pathologists and surgeons about matters of this mutual interest and concern.

Symposia

- General Principles
- Melanocytic Nevi and Malignant Melanoma
- Tumor Conference

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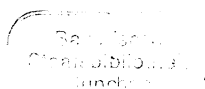
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PGI₂ Aerosol versus Nitric Oxide for Selective Pulmonary Vasodilation in Hypoxic Pulmonary Vasoconstriction

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Key Words

Prostacyclin
Aerosol
Nitric oxide
Pulmonary hypertension

.....
Abstract

Intravenous prostacyclin (PGI₂) is a potent pulmonary vasodilator in pulmonary hypertension. However, dose-dependent systemic vasodilation, an increase in intrapulmonary shunt and hypoxemia limit its clinical application. Recently, inhaled nitric oxide (NO) has been reported to elicit selective pulmonary vasodilation, but its clinical use is restricted by its potential toxicity; furthermore, the feasibility of NO application in clinical practice seems difficult. Therefore, we investigated the effects of PGI₂ aerosol on pulmonary and systemic circulation and compared the hemodynamic effects to those of inhaled NO. In 6 dogs, ventilation with a hypoxic gas mixture (FiO₂ 0.09–0.11) increased pulmonary vascular resistance (PVR) by 196% (HPV). Aerosolization of a PGI₂ solution at a concentration of 430 ng/ml reduced hypoxia-induced increase of pulmonary artery pressure by 48% and PVR by 52% within 6–10 min without systemic vasodilation. The administered dose of PGI₂ was 0.87 ± 0.26 ng/kg/min. In 2 dogs, doubling the PGI₂ concentration (860 ng/ml) did not enhance the vasodilatory effect. After termination of PGI₂ inhalation, HPV was restored within 10–15 min. Inhaled NO (50 ppm) decreased the HPV-induced increase in PAP by 76% and in PVR by 73% within 5–10 min. Clinically relevant systemic vasodilation was not observed. It is concluded that inhalation of aerosolized PGI₂ leads to selective pulmonary vasodilation in hypoxia-induced pulmonary hypertension. Aerosolized PGI₂ at a concentration of 430 ng/ml was less potent than NO (50 ppm). However, due to the lack of known toxicity and its uncomplicated mode of application, inhaled PGI₂ may be one alternative to inhaled NO in the treatment of acute pulmonary hypertension.

Prostacyclin (PGI₂), an arachidonic acid metabolite, is a potent pulmonary vasodilator [1]. It has been successfully given intravenously to decrease pulmonary artery pressure (PAP) in primary pulmonary hypertension [2], in patients with ARDS [3], and in various experimental models of acute pulmonary hypertension [4–6]. The vasodilatory effect of PGI₂ is, however, not restricted to the pulmonary circulation. When infused intravenously, PGI₂ leads to dose-dependent systemic vasodilation and hypotension. Furthermore, intrapulmonary shunt and venous admixture increase dose-dependently; consequently, arterial oxygen content decreases and the net effect of intravenous PGI₂ on oxygen delivery depends on the ability to increase cardiac output. For these reasons, the clinical use of intravenous PGI₂ to treat pulmonary hypertension is limited [1–3, 7].

Recently, inhaled gaseous nitric oxide (NO), considered to be identical with endothelial derived relaxing factor [8], has been described to act as a selective pulmonary vasodilator in pulmonary hypertension [9, 10]. In awake and spontaneously breathing lambs, inhaled NO reduced acute pulmonary hypertension induced by hypoxia or by intravenous infusion of the stable endoperoxide analogue U-46619 without being associated with systemic vasodilation. Experimental studies have demonstrated that inhaled NO improves the ventilation/perfusion mismatch in hypoxia-induced pulmonary hypertension and is efficient in reversing pulmonary hypertension due to sepsis [11, 12].

In mechanically ventilated sheep inhalation of NO (20 ppm) had no effect on pulmonary gas exchange but decreased blood flow to unventilated and poorly ventilated areas of the lung (ventilation/perfusion ratio <0.1) and consequently reduced ventilation/perfusion mismatch [11]. In addition to its effects on pulmonary circulation and arterial oxygen-

ation inhaled NO exerts dilation of the bronchial smooth muscles which might improve pulmonary ventilation/perfusion ratio [13]. Inhaled NO had no effect on pulmonary hemodynamics or gas exchange when applied during normoxia (FiO₂ 0.21) [11].

In experimental models of sepsis using infusion of endotoxin [14] or group B streptococcus [12] inhalation of NO diminished pulmonary vasoconstriction. In the latter study in ventilated piglets inhalation of 150 ppm of NO reversed pulmonary hypertension during the early (<1 h) and late phase of sepsis (2 to 6 h) whereas ventilation/perfusion mismatch was not counteracted in the late phase of sepsis [12]. More recently inhaled NO was therapeutically applied in man. In a restricted number of patients, inhaled NO proved efficient in lowering PAP; however, in contrast to intravenous PGI₂, inhaled NO caused no systemic vasodilation [7, 15, 16].

In the most recent human studies low doses of inhaled nitric oxide (20 to 80 ppm) decreased pulmonary artery pressure in hypoxia-induced pulmonary hypertension in volunteers [17], in cardiac patients before and after cardiopulmonary bypass [18] and in children with pulmonary hypertension due to congenital heart disease [19].

In adults with respiratory distress syndrome (ARDS) inhalation of NO (5 to 36 ppm) reduced pulmonary artery pressure and intrapulmonary shunting and improved arterial oxygenation for up to 53 days without tachypnoea and noticeable side effects. Though in the same study intravenous prostacyclin (4 ng/kg/min) lowered pulmonary artery pressure as well, systemic arterial pressure fell and intrapulmonary shunt increased [20].

Finally, NO (10 ppm) inhaled for 30 minutes by an infant after cardiac surgery improved gas exchange permanently while pulmonary hypertension was resolved permanently [21]. Furthermore, enhanced resolu-

tion of pneumonic infiltrates was observed upon NO inhalation [22].

Despite the convincing evidence that inhaled NO leads to selective pulmonary vasodilation and hence may be useful to treat pulmonary hypertension, it should be noted that NO itself is a radical with potential cytotoxic effects. Although severe acute lung injury and methemoglobinemia are observed after inhalation of gas mixtures containing high concentrations of NO, there is little evidence for pulmonary toxicity at low concentrations (<100 ppm) of NO inhaled for short periods of time in different species [10]. However, little is known about the toxicity of long-term breathing of NO at low concentrations and the effect of NO on lungs with pre-existing acute or chronic disease. As long as the absence of long-term toxicity of NO has not been demonstrated, its routine clinical application for selective pulmonary vasodilation is restricted [10]. Furthermore, for the application of gaseous NO, a specially designed ventilator and an expensive chemiluminescence analyzer for continuous monitoring of the inspiratory NO and NO_x concentrations are mandatory; hence it is questionable whether NO inhalation will become clinical routine.

In view of these limitations of both inhaled NO and intravenous PGI₂, the present study was designed to investigate the effect of PGI₂ inhaled as an aerosol on hypoxic pulmonary vasoconstriction in dogs. We hypothesized that inhaled PGI₂ may lead to selective pulmonary vasodilation via direct relaxation of pulmonary vascular smooth muscle cells. Vasodilatory effects on both the pulmonary and the systemic circulation were assessed. To evaluate the relative potency of inhaled PGI₂ at the concentration used, its vasodilatory effect was compared to that of inhaled NO at a concentration (50 ppm) known to cause a nearly maximal vasodilatory effect in HPV-induced pulmonary hypertension [10]. We

aimed to answer the question whether inhaled PGI₂ induces pulmonary vasodilation without causing systemic hypotension.

Methods

Animal Preparation

The studies were performed in 6 foxhounds of either sex (mean body weight 27.6 ± 1.9 kg). All animals received care in compliance with the 'Guide for the Care and Use of Laboratory Animals' [NIH Publ. No. 85-23, revised 1985]. The study was approved by the institutional animal care and use committee.

After premedication with propiomazine (1.5 mg/kg i.m., Combelen[®], Bayer AG, Leverkusen, FRG), anesthesia was induced by intravenous injection of pentobarbital (20 mg/kg, Nembutal[®], Ceva, Bad Segeberg, FRG), piritramide (0.75 mg/kg, Dipidolor[®], Janssen, Neuss, FRG) and alcuronium (0.25 mg/kg, Alloferin[®], Roche, Grenzach-Whylen, FRG), and maintained by continuous intravenous infusion of pentobarbital ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). After termination of the surgical preparation an additional infusion of piritramide ($150 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and alcuronium ($75 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was started. Fluid losses were replaced by intravenous infusion of Ringer's solution ($5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). A warming pad was used to keep core body temperature between 35.5 and 37 °C. The dogs were endotracheally intubated and mechanically ventilated at a rate of 12 cycles/min using a FiO₂ of 0.5 (Servo 900B, Siemens-Eléma, Solna, Sweden). Tidal volume (V_T) was adjusted to maintain an arterial P_{CO₂} of 35–40 mm Hg.

Fluid-filled catheters (PP270, Portex, Hythe, UK) were positioned in the descending aorta and superior caval vein via the left femoral artery and the right external jugular vein to measure mean arterial (MAP) and central venous pressure (CVP), respectively. A Swan-Ganz catheter (model 93A-431-7.5F G, Baxter Healthcare Corp., Santa Ana, Calif., USA) was inserted into the pulmonary artery via the right external jugular vein to measure mean PAP and cardiac output (CO). After median sternotomy and pericardiotomy prewarmed, precalibrated tip manometers (PC 370, Millar Instruments, Houston, Tex., USA) were inserted into the right ventricle (RV) via a stab incision at the apex of the RV and into the left ventricle (LV) via the right carotid artery. In four dogs an ultrasonic flow probe (Transonic Systems Inc., Ithaca, N.Y., USA) was placed around the pulmonary artery. At the end of the surgical preparation, the pericardium was closed with running suture to avoid constraint to the

myocardium. Thereafter, a chest tube was inserted, the thorax was closed air-tight, and the lungs were completely reinflated. Subsequently, the dogs were turned to the left lateral decubitus position.

Administration of NO

NO was obtained in 50-liter cylinders as a precise mixture of 200 ppm NO in nitrogen (Linde AG, Unterschleissheim, FRG). During inspiration the NO/N₂ mixture was introduced into the inspiratory gas using a T-tube connected to the endotracheal tube. A magnetic valve (Servo Nebulizer 945, Siemens, Erlangen, FRG) triggered by the electronic regulation system of the ventilator was used for insufflation of NO exclusively during inspiration. The inspiratory NO flow was varied using a precise pressure reduction valve (SP 750.0183.M, Kuhnke, Malente, FRG) and the NO pressure was monitored with an electronic manometer (Type 352-P, Debro GmbH, Meerbusch, FRG). The correct inspiratory NO concentration was produced by varying the NO admixture to the inspired gas mixture at constant tidal volumes (T_V). The FiO₂ was maintained constant during administration of the NO/N₂ mixture by increasing the inspiratory oxygen concentration proximal to the NO insufflation port. The inspired oxygen concentration (FiO₂) was continuously monitored distal to the NO insufflation port (Oxydig, Dräger AG, Lübeck, FRG). Expired gas was scavenged and discarded. Prior to the experiments the complete application system (ventilator, pressure reduction valve, electronic manometer) had been calibrated to achieve the desired inspiratory NO concentration at different T_V and oxygen concentrations using a chemoluminescence NO/NO_x analyzer (Beckman, Model 951 A, Beckman Instruments, Munich, FRG). The inspiratory NO concentration at a given system setting varied no more than 3% during repeated calibration measurements.

To avoid oxidation of NO to NO₂, the critical contact time of NO and O₂ during inspiration [10] has been kept short by using a short inspiration time (1.65 s) and by introducing NO into the inspiratory gas mixture very close to the endotracheal tube (19 cm). The concentrations of NO₂ measured at the endotracheal tube during calibration were below 1 ppm.

Administration of PGI₂ Aerosol

For inhalation of PGI₂ as aerosol, a jet nebulizer (Servo Nebulizer 945, Siemens, FRG) was connected to a Siemens 900B ventilator. The nebulizer chamber (Intersurgical Ltd, Twickenham, UK) was located 16 cm from the endotracheal tube. The jet flow sup-

plied to the nebulizer chamber during inspiration was kept constant in all experiments at a flow rate of 14 liters/min. This high flow rate was chosen because the fraction of particles with a diameter of < 2 μm, which are likely to settle in the alveolar region of the lung, increases with flow rate. T_V and total inspiratory flow rate were maintained constant during aerosolization by decreasing the inspiratory flow from the ventilator. Total T_V was monitored (CO₂ analyzer 930, Siemens-Elerna).

PGI₂ was supplied as the sodium salt of epoprostenol (Flolan[®], Wellcome, London, UK) dissolved in glycine buffer of pH 10.5 at a concentration of 10 μg/ml; the solution was prepared on the day of the experiment and stored on ice until use. Prior to inhalation, PGI₂ was further diluted with normal saline to a concentration of 430 ng/ml and a total volume of 10 ml of this solution was filled into the nebulizer chamber. The dosage of PGI₂ was based on pilot experiments in which this concentration has proven to be effective in lowering PAP. To assess the actual amount of PGI₂ nebulized, the total volume of the PGI₂ solution in the nebulizer chamber was measured prior to and immediately after inhalation (volume nebulized × concentration/duration of inhalation).

6-keto-Prostaglandin-F_{1α} (6-keto-PGF_{1α}), the stable metabolite of PGI₂, was measured by radioimmunoassay (antibody: Pasteur Diagnostic, Marne-la-Coquette, France; ³H-PG's: Amersham Buchler, Braunschweig, FRG) in unextracted arterial plasma before and after PGI₂ inhalation in 3 dogs.

To exclude that the vasodilatory effect of PGI₂ aerosol was mediated by uptake of PGI₂ into the blood, the effects of PGI₂ infused at a rate of 1 and 2 ng/kg/min were compared to those of inhaled PGI₂ in 2 dogs.

Measurements

Hemodynamics. All measurements were performed with the dogs in left lateral position. MAP, PAP, and CVP were recorded (Astromed MT 9500, Astro-Med, Inc., West Warwick, R.I., USA) using Statham P23Db transducers (Gould-Statham, Oxnard, Calif., USA) referred to the right atrium. ECG and ventricular pressures (LVP, RVP) were sampled every 4 min, digitized in real-time (A/D converter C1000, Cosima Corp., Salem, Oreg., USA) and stored for evaluation using a PC/AT 386 computer system. Data were analyzed with interactive software ('Meduse', H. Zeintl, Neckargemünd, FRG). All parameters were evaluated at end-expiration using the average of three consecutive heart beats.

In the RV and LV, maximal (RVP_{max}, LVP_{max}) and end-diastolic pressures (RVEDP, LVEDP) were assessed. CO was obtained from triplicate thermodilution measurements at end-expiration (REF-1™, Ejection Fraction/Cardiac Output Computer, Baxter Healthcare, Santa Ana, Calif., USA).

The following parameters were calculated:

$$CI = 10 \cdot CO \cdot BW^{-0.75}$$

(according to Holt et al. [23])

$$PVR = (PAP_{\text{mea}} - LVEDP) \cdot 79.9 \cdot CO^{-1}$$

$$SVR = (MAP_{\text{mea}} - RVEDP) \cdot 79.9 \cdot CO^{-1}$$

where CI = cardiac index, CO = cardiac output, BW = body weight, PVR = pulmonary vascular resistance, LVEDP = LV end-diastolic pressure, SVR = systemic vascular resistance, RVEDP = right ventricular end-diastolic pressure, HR = heart rate.

Lung Function. P_{O₂}, P_{CO₂} and pH (ABL 300, Radiometer, Copenhagen, Denmark), as well as arterial (S_aO₂) and mixed venous oxygen saturation (S_vO₂) and arterial methemoglobin fraction (CO-Oximeter 282, Instrumentation Laboratory Inc., Lexington, Mass., USA) were analyzed. End-tidal CO₂ concentration and T_v were monitored using a CO₂ analyzer (CO₂ analyzer 930, Siemens-Elema), airway pressures (P_{peak}, P_{plat}) and total thoracic compliance (C_{tot}) were assessed (Lung Mechanics Calculator 940, Siemens-Elema).

Experimental Protocol

After termination of surgery the dogs were isovolumically hemodiluted with 6% dextran 60 (Makrodex®, 6%, Schiwa, Glandorf, FRG) to a hematocrit of 27–30% in order to achieve identical values of hematocrit and hemoglobin in all animals. The withdrawn blood was used to replace blood samples taken for laboratory analysis. Hematocrit and hemoglobin did not change significantly during the experiment.

Control measurements were performed 30 min after termination of surgery under stable hemodynamic conditions (control). Thereafter, hypoxia was induced by decreasing the FiO₂ to 0.09–0.11 to achieve a PaO₂ of near 40 mm Hg. The inspired FiO₂ was monitored and PaCO₂ was maintained constant by adjusting V_T. Following a period of stable hemodynamics, baseline recordings were obtained during hypoxia (HPV). Subsequently, either NO at a concentration of 50 ppm or PGI₂ at a concentration of 430 ng/ml were administered in random order. Measurements were obtained after 10 min of NO or PGI₂ application, respectively (NO, PGI). Subsequently, the administration of either NO or PGI₂ was terminated and a further measurement under hypoxic conditions was performed (post-NO, post-PGI) 10–15 min thereafter.

Statistical Analysis

Data are reported as mean ± SD. Statistical analysis was performed using a repeated measures analysis of variance (rANOVA). If the f value was significant (p < 0.05), the following time points were compared by paired t test: control vs. HPV, HPV vs. NO, HPV vs. PGI₂ as well as the difference between HPV and NO versus the difference between HPV and PGI₂. Bonferroni correction was applied as appropriate. Differences were considered significant for p < 0.05.

Results

Hemodynamics

The effects of NO and PGI₂ on hypoxia-induced changes in pulmonary and systemic hemodynamics are summarized in figure 1. Aerosolization of the solvent (glycine buffer, pH 10.3) and normal saline did not exert effects on systemic or pulmonary hemodynamics.

Hypoxia. Ventilation with a hypoxic gas mixture (FiO₂ 0.09–0.11) produced a significant increase in PAP (+57%, p < 0.001), PVR (+196%, p < 0.001), heart rate (control 99 ± 11, HPV 135 ± 30, p < 0.01) and CI (control 2.3 ± 0.3, HPV 3.0 ± 0.5, p < 0.05) as well as a reduction in SVR (–26%, p < 0.05) in all dogs (fig. 1). The degree of hypoxic pulmonary vasoconstriction as assessed by PVR remained constant during basic HPV, post-NO and post-PGI. Right and left ventricular preload (RVEDP, LVEDP) remained constant.

Nitric Oxide. When NO was added to the hypoxic gas mixture, PAP was significantly reduced in all dogs (–28%, p < 0.001 vs. HPV) but did not reach baseline levels (FiO₂ 0.5). NO attenuated the HPV-induced increase in PAP and PVR by 76 and 73%, respectively (fig. 1). A minor reduction in MAP (–5%, p < 0.05 vs. HPV) was observed, however, there was no change in calculated SVR (fig. 1). The maximal pulmonary vasodilating effect of NO occurred within 7 ± 1.3 min (fig. 2). After termination of NO inhalation, all hemody-

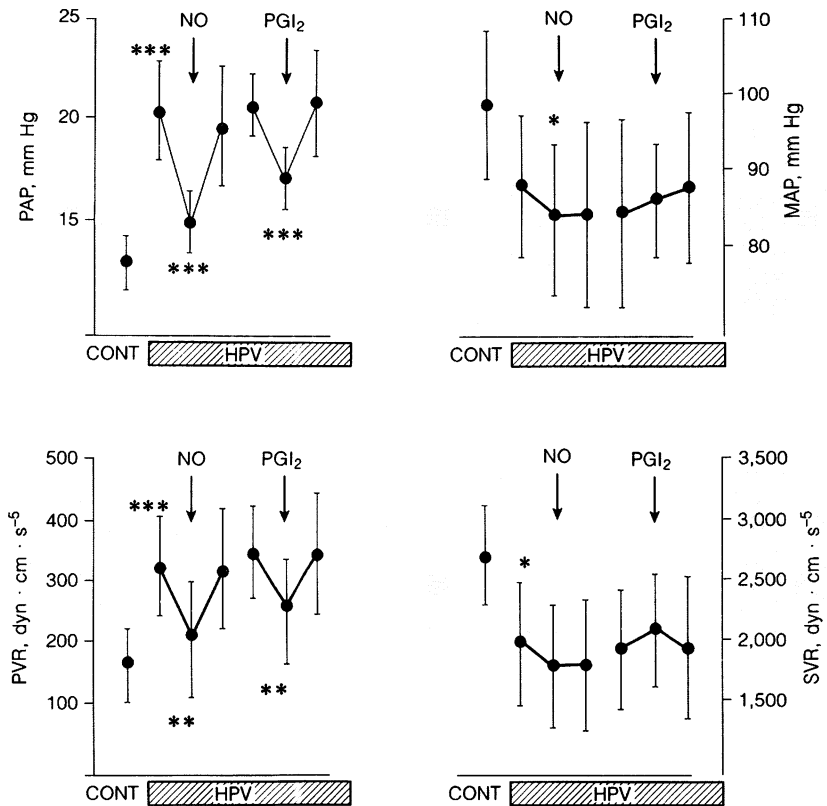


Fig. 1. Effects of inhalation of NO (n = 6) and PGI₂ (n = 6) during hypoxia on PAP, MAP, PVR and SVR. Inhalation of NO and PGI₂ decreased PAP and PVR reversibly while MAP and SVR remained unchanged. Data are given as mean \pm SD. CONT = Control before hypoxia. * p < 0.05; ** p < 0.01; *** p < 0.001 versus preceding measurement.

dynamic variables returned to pre-NO values. During inhalation of NO, HR, CI, LVEDP and RVEDP remained unchanged.

Mean methemoglobin levels increased from 0.8 ± 0.2 to $1.2 \pm 0.3\%$ after NO inhalation (p < 0.05) and returned to baseline values after termination of NO application.

Prostacyclin. Inhalation of PGI₂ aerosol during HPV decreased PAP and PVR by 17 and 32%, respectively (fig. 1). The hypoxia-induced increase in PAP was reduced by 48% and the increase in PVR by 52%. No signifi-

cant changes occurred in MAP (-2 ± 5 mm Hg), SVR ($+83 \pm 124$ dyn·cm·s⁻⁵) (fig. 1), CI (-0.25 ± 0.27 liter/min) and RVEDP. During PGI₂ inhalation, HR was slightly reduced (HPV 139 ± 27 , PGI 127 ± 27 , p < 0.05). The maximal pulmonary vasodilating effect of PGI₂ was achieved within 8 ± 1 min (fig. 2). The decrease in PAP induced by PGI₂ was smaller compared to the effect of NO in all dogs (p < 0.02). After termination of PGI₂ administration, hypoxic pulmonary vasoconstriction was restored within 10–15 min.

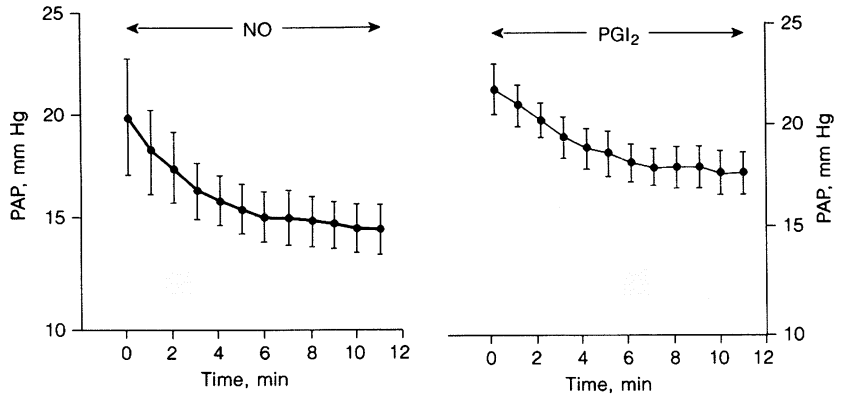


Fig. 2. Sequential changes of PAP during inhalation of NO ($n = 6$) and PGI₂ ($n = 5$). NO and PGI₂ led to an immediate decrease of PAP that reached its maximum within 10 min with both substances; the magnitude of PAP and PVR change was greater during NO than during PGI₂ inhalation ($p < 0.05$). Data are given as mean \pm SD.

Table 1. Blood gas and respiratory parameters at control, at baseline HPV and during NO and PGI₂ inhalation

| Variables | Control | HPV | HPV + NO | Post-NO | HPV | HPV + PGI ₂ | Post-PGI ₂ |
|-----------------------------|-----------------|-----------------------------|-----------------|-----------------|-----------------|------------------------------|-----------------------|
| PaO ₂ , mm Hg | 186 \pm 65 | 41 \pm 9.6 ^a | 42.4 \pm 9.2 | 41.1 \pm 9.6 | 40.8 \pm 9.7 | 45.1 \pm 13.1 ^c | 39.6 \pm 5.2 |
| PvO ₂ , mm Hg | 46.1 \pm 3.0 | 27.6 \pm 5.3 ^b | 28.4 \pm 5.0 | 27.8 \pm 5.2 | 27.1 \pm 5.2 | 29.0 \pm 5.4 ^c | 26.6 \pm 3.5 |
| PaCO ₂ , mm Hg | 38.9 \pm 2.0 | 37.6 \pm 2.8 | 37.2 \pm 2.1 | 35.3 \pm 2.9 | 36.3 \pm 2.9 | 33.5 \pm 4.5 | 36.5 \pm 6.6 |
| pH art | 7.36 \pm 0.06 | 7.36 \pm 0.03 | 7.36 \pm 0.03 | 7.37 \pm 0.04 | 7.38 \pm 0.04 | 7.39 \pm 0.05 | 7.36 \pm 0.05 |
| COM, ml/cm H ₂ O | 59.5 \pm 18.4 | 52.8 \pm 14.3 | 53.5 \pm 15.0 | 50.8 \pm 13.5 | 50.3 \pm 14.8 | 51.0 \pm 12.2 | 50.7 \pm 14.1 |
| AWP _{plat} , mbar | 12.0 \pm 2.2 | 11.7 \pm 2.7 | 11.0 \pm 1.7 | 12.2 \pm 2.6 | 12.5 \pm 3.0 | 11.7 \pm 1.8 | 11.8 \pm 3.1 |

Data are given as mean \pm SD. PaO₂ = Arterial O₂ tension; PvO₂ = mixed venous O₂ tension; PaCO₂ = arterial CO₂ tension; pH art = arterial pH; COM = total compliance of lung and thoracic wall; AWP_{plat} = plateau airway pressure at end inspiration.

^a $p < 0.05$; ^b $p < 0.01$ HPV vs. control; ^c $p < 0.05$ PGI₂ vs. HPV.

The mean effective dose of PGI₂ administered to the lungs was 0.87 ± 0.26 ng/kg/min. Intravenous infusion of PGI₂ at comparable infusion rates (1 and 2 ng/kg/min) in 2 dogs had neither effects on pulmonary nor systemic hemodynamics (data not shown).

Plasma concentrations of 6-keto-PGF_{1 α} measured in 3 dogs before, during and after

PGI₂ inhalation remained unchanged (HPV 94 ± 50 pg/ml, PGI 112 ± 20 pg/ml, post-PGI 103 ± 9 pg/ml).

Lung Function

Blood gas parameters and lung mechanics are summarized in table 1. Ventilation with the hypoxic gas mixture (FiO₂ 0.09–0.11) re-

sulted in a decrease of mean arterial P_{O_2} from 186 ± 65 mm Hg and mean PvO_2 from 46.1 ± 3.0 to 41 ± 9.6 mm Hg and 27.6 ± 5.3 mm Hg, respectively. Arterial and mixed venous P_{O_2} remained constant during ventilation with the hypoxic gas mixture. There was no significant change in arterial P_{CO_2} throughout the experiments. Mean arterial pH was maintained between 7.36 and 7.39. PaO_2 and PvO_2 increased slightly and reversibly only during PGI_2 inhalation. There was no change in airway pressures (P_{peak} , P_{plat}). Total thoracic compliance slightly decreased after induction of hypoxia, but remained constant during NO and PGI_2 administration.

Discussion

The main finding of this study was that inhaled PGI_2 selectively attenuated hypoxia-induced pulmonary hypertension without causing systemic vasodilation. Both PGI_2 aerosol and NO gas reduced hypoxia-induced increase in PVR within minutes without affecting systemic vascular resistance or CI; the effects on the pulmonary vessels were reversible upon termination of either drug within 10–15 min.

PGI_2 is the main metabolite of arachidonic acid produced by endothelial cells in different species. It is a potent dilator of both arteries and veins [24]. The vasodilatory effect is endothelium independent and is mediated by stimulation of specific receptors on membranes of vascular smooth muscle cells [25]. Intracellular PGI_2 acts by increasing the concentration of cyclic adenosine monophosphate (cAMP) [25]. PGI_2 has a rapid onset of action and a short half-life (2–3 min) when infused intravenously. Due to the lack of a carrier mechanism to transfer PGI_2 across the cell membrane, it is, unlike most other prostaglandins, not metabolized by the lung and

retains its pulmonary vasodilatory properties [26]. Therefore, and because of its lack of known toxicity, PGI_2 aerosol was chosen for inhalation.

Since the first description of the dilating effects on pulmonary and systemic vessels of intravenous PGI_2 in dogs [1], it has been successfully applied as pulmonary vasodilator in animal models of acute pulmonary hypertension [4, 5, 27, 28] and in patients with pulmonary hypertension of various etiologies [2, 29]. At doses effective in reducing PVR, intravenous PGI_2 did, however, induce systemic vasodilation and an increase in cardiac output. In addition, intravenous PGI_2 was shown to attenuate HPV and to increase venous admixture; consequently, arterial oxygen content decreases and the net effect of intravenous PGI_2 on oxygen delivery depends on the ability to increase cardiac output [4, 30].

In this study, the inhalation of PGI_2 aerosol reduced the hypoxia-induced increase in PAP and PVR without eliciting systemic vasodilation or changes of CI. The finding that inhaled PGI_2 did not completely reverse HPV is in agreement with the results of previous studies, in which PGI_2 given intravenously also failed to completely abolish the hypoxia-induced increase in PVR [5, 28].

In contrast to intravenous PGI_2 , PGI_2 aerosol did not increase cardiac output. Therefore, the calculated PVR, which was used in this study to assess pulmonary vascular tone and that is influenced by changes of cardiac output, may truly reflect PVR changes.

In contrast to the decrease in PaO_2 occurring during intravenous infusion of PGI_2 , the inhalation of PGI_2 produced a small and reversible increase in PaO_2 and PvO_2 . This finding cannot be easily explained from our data. One may speculate that PGI_2 inhalation led to a reduction in V_a/Q mismatches as it has been described during NO inhalation in

patients with ARDS [7]. However, in this study, NO did not affect either arterial or mixed venous oxygenation during inhalation. The effect of inhaled PGI₂ on pulmonary ventilation/perfusion ratio has to be assessed in further studies using more appropriate techniques (e.g. multiple inert gas elimination technique).

The mean dose of PGI₂ aerosolized was 0.87 ± 0.26 mg/kg/min. Doubling the concentration of the PGI₂ solution (860 ng/ml) at constant inspiratory flow, and hence presumably doubling the dose administered, did not enhance the effect on pulmonary or systemic hemodynamics. So far, we have not yet established the minimal effective dosage of inhaled PGI₂, therefore we cannot exclude that a higher concentration of the PGI₂ solution might have a more pronounced effect. Furthermore, it cannot be excluded that inhalation of PGI₂ at higher concentrations might affect systemic hemodynamics. In patients with bronchial asthma, systemic vasodilation has been reported following the short-time inhalation (maximal time of inhalation 3 min) of considerably higher doses of PGI₂ (200–400 µg) [31].

It should be noted that the dose of PGI₂ administered was assessed by measuring the volume of the PGI₂ solution in the nebulizer chamber before and after inhalation; this dose may, however, not reflect the actual amount of PGI₂ inhaled as it does not account for losses in the nebulizer, the ventilator tubing, the endotracheal tube and the extrapulmonary airways. Using radiolabeled aerosol, it has been demonstrated that during mechanical ventilation only a small fraction of a given dose of aerosol (0.37–3.68%) is actually deposited in the lung [32]. Therefore, the effective dose of inhaled PGI₂ may be considerably lower than calculated. Furthermore, it must be emphasized that the actual output of nebulizers is influenced by the type of nebulizer

used, by the volume initially placed in the nebulizer and by the ventilator setting [33].

Still, the dose of PGI₂ aerosol effective in reducing HPV in this study is considerably lower than the dose of intravenously given PGI₂ necessary to lower PAP in different models of experimental pulmonary hypertension (249 ± 69 ng/kg/min [4], 79 ± 5 µg/kg/min [5]) or in patients with pulmonary hypertension of various origin (7.1–35.0 ng/kg/min [3, 29]. In 2 dogs the intravenous infusion of PGI₂ at a rate of 1 and 2 ng/kg/min – comparably to the inhaled dose – neither caused pulmonary nor systemic vasodilation and had no effect on CO (data not shown).

Our findings indicate that aerosolized PGI₂ at the concentration used in this study acts predominantly on smooth muscle cells in the lung vessels and does not reach the systemic circulation in efficient amounts. This view is supported by the fact that the arterial concentration of 6-keto-PGF_{1α}, the main metabolite of PGI₂, did not increase during inhalation of prostacyclin. From our data, however, we cannot decide whether the selective pulmonary dilation was due to the low concentration of inhaled PGI₂ or whether it is exclusively the route of administration that prevents systemic effects of the drug.

A reduction in PAP and PVR has previously been reported upon inhalation of aerosolized arachidonic acid in dogs [34]. The pulmonary changes were, however, accompanied by systemic vasodilation and by bronchoconstriction indicating that prostaglandin precursors were absorbed and metabolized into different prostanoids in lung tissue. In contrast, prostacyclin administered as aerosol is neither transformed into an active form nor metabolized by the lung [26]. Although we did not measure dynamic compliance and airway resistance, we observed no change in total static compliance and in plateau airway pressure during PGI₂ inhalation. Hence, PGI₂

aerosolized at low concentrations appears to act as pulmonary vasodilator without causing side effects (e.g. bronchoconstriction) attributable to other arachidonic acid metabolites or to systemic absorption.

In this study, we compared PGI₂ aerosol to NO in order to assess the maximal dilation of pulmonary vessels that can be pharmacologically achieved during HPV without systemic side effects. We chose an inspiratory concentration of 50 ppm NO, because it has been demonstrated that a further increase of the inspiratory NO concentration produces virtually no additional vasodilatory effect [10]. In this study, the inhalation of NO at a concentration of 50 ppm produced a reduction of hypoxia-induced increases in PAP by 76% and in PVR by 73% accompanied by a slight decrease in arterial pressure (fig. 1) and no change in cardiac output. A complete reversal of hypoxic pulmonary vasoconstriction, as demonstrated in spontaneously breathing sheep at a NO concentration of 40 ppm [10], was not achieved in ventilated dogs in this study. The failure of NO to reverse HPV completely may be partially explained by species differences or by positive pressure ventilation producing a more heterogeneous distribution of pulmonary ventilation and blood flow. The slight systemic vasodilation observed was not reported in other studies [9, 10].

At the concentrations used, the magnitude of pulmonary vasodilation was more pronounced during NO than during PGI₂ inhalation. However, PGI₂ infused intravenously did not fully reverse HPV [5, 28]. Thus, inhaled NO may be the more potent pulmonary vasodilator when compared to prostacyclin at both routes of administration.

It must be noted that NO is a radical ($\cdot\text{N} = \text{O}$) with the potential for cytotoxicity. Superoxide (O_2^-) and NO, which both are generated by endothelial cells, macrophages and neutrophils, combine to form peroxynitrite an-

ion (ONOO^-). Peroxynitrite decomposition products are nitrogen dioxide and hydroxyl radical which exert cytotoxic effects by initiating lipid peroxidation of cell membranes [35]. In the presence of molecular oxygen, NO reacts in a concentration- and FiO_2 -dependent manner to form nitrogen dioxide (NO_2), which is subsequently transformed to nitric and nitrous acid. Severe damage to the lung and airways may result. NO binds avidly to hemoglobin to form nitrosylhemoglobin (Hb-NO) which is subsequently oxidized to methemoglobin (Met-Hb). Reduction of Met-Hb occurs, however, much slower than Met-Hb formation from Hb-NO and the rate of Met-Hb reduction is decreased by increasing NO concentrations [36]. Although Met-Hb plasma concentrations at doses of NO inhaled for pulmonary vasodilation remain low (<1–2%), methemoglobinemia following inadvertent overdosage of NO may lead to critical reduction of oxygen transport. Oxidative cross-linking of membrane proteins of erythrocytes exposed to NO may impair their rheological properties [36]. Although there is little evidence for severe toxicity at low concentrations (<100 ppm) of NO inhaled for short time periods in different species, little is known about the toxicity of long-term breathing of NO at low concentrations and the effect of NO on lungs with pre-existing acute or chronic disease [10].

The feasibility of NO inhalation in clinical routine seems cumbersome: due to its potential toxicity, the application of gaseous NO requires specially designed respirators which permit exact adjustment and long-term constancy of the inspired NO concentration. Expensive chemiluminescence analyzers for continuous monitoring of the inspired NO concentration and for detection of NO oxidation products (NO_2) are mandatory and finally, NO gas has not been approved for medical purposes so far.

Thus, the clinical application of inhaled NO as a selective pulmonary vasodilator appears limited by the lack of data on long-term toxicity and effects on preinjured lungs, but also due to the necessity of complicated and expensive techniques to safely allow and control NO administration.

In contrast to the potential toxicity of NO, no severe toxic side effects of PGI₂ have been reported. Furthermore, PGI₂ can be administered as aerosol using a standard jet nebulizer and no sophisticated system to monitor the inspired PGI₂ concentration is required. In further studies the dose-response relationship for inhaled PGI₂ has to be established, the pulmonary vasodilatory effects have to be as-

sessed in different models of pulmonary hypertension and the effects of long-term inhalation have to be investigated. Finally, due to the different mechanisms of action, the combination of inhaled NO and aerosolized PGI₂ may have additive pulmonary vasodilatory effects. Upon clarification of these open questions, PGI₂ aerosol may become an attractive alternative to the inhalation of NO in the treatment of acute pulmonary hypertension.

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References

- 1 Kadowitz PJ, Chapnik BM, Feigen LP, Hyman AL, Nelson PK, Spannhake EW: Pulmonary and vasodilator effects of the newly discovered prostaglandin, PGI₂. *J Appl Physiol* 1978;45:408-413.
- 2 Rubin LJ, Growes BM, Reeves JT, Frosolono M, Handel F, Cato AE: Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. *Circulation* 1982;66:334-338.
- 3 Radermacher P, Santak B, Wust HJ, Tarnow J, Falke KJ: Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: Effects on pulmonary capillary pressure and ventilation-perfusion distributions. *Anesthesiology* 1990;72:238-244.
- 4 Prielipp RC, McLean R, Rosenthal MH, Pearl RG: Hemodynamic profiles of prostaglandin E₁, isoproterenol, prostacyclin, and nifedipine in experimental porcine pulmonary hypertension. *Crit Care Med* 1991; 19:60-67.
- 5 Owall A, Davilen J, Sollevi A: Influence of adenosine and prostacyclin on hypoxia-induced pulmonary hypertension in the anaesthetized pig. *Acta Anaesthesiol Scand* 1991; 35:350-354.
- 6 Devitt HH, Burka JF, Jones R, Amy RW, King EG: Hemodynamic and pathologic effects of prostacyclin on oleic acid-induced pulmonary injury. *Surgery* 1988;103:213-220.
- 7 Falke KJ, Rossaint R, Pison U: Inhaled nitric oxide selectively reduces pulmonary hypertension in severe ARDS and improves gas exchange as well as right heart ejection fraction - A case report. *Am Rev Respir Dis* 1991;143(suppl):A248.
- 8 Palmer RMJ, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;327:524-526.
- 9 Fratacci M-D, Frostell CG, Chen T-Y, Wain JC, Robinson DR, Zapol WM: Inhaled nitric oxide - A selective pulmonary vasodilator of heparin-protamine vasoconstriction in sheep. *Anesthesiology* 1991;75: 990-999.
- 10 Frostell C, Fratacci M-D, Wain JC, Jones R, Zapol WM: Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991;83:2038-2047.
- 11 Pison U, López FA, Heideimeyer CF, Rossaint R, Falke KJ: Inhaled nitric oxide reverses hypoxic pulmonary vasoconstriction without impairing gas exchange. *J Appl Physiol* 1993;74:1287-1292.
- 12 Berger JI, Gibson RL, Redding GJ, Standaert TA, Clarke WR, Truog WE: Effect of inhaled nitric oxide during group B streptococcal sepsis in piglets. *Am Rev Respir Dis* 1993; 147:1080-1086.
- 13 Dupuy PM, Shore SA, Drazen JM, Frostell C, Hill WA, Zapol WM: Bronchodilator action of inhaled nitric oxide in guinea pigs. *J Clin Invest* 1992;90:421-428.
- 14 Weitzberg E, Rudehill A, Alving K, Lundberg JM: Nitric oxide inhalation selectively attenuates pulmonary hypertension and arterial hypoxia in porcine endotoxin shock. *Acta Physiol Scand* 1991;143:451-452.

- 15 Frostell C, Blomqvist H, Lundberg J, Hedenstierna G, Zapol WM: Inhaled nitric oxide dilates human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. *Anesthesiology* 1991;75:A989.
- 16 Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Wallwork J: Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. *Lancet* 1991;338:1173-1174.
- 17 Frostell CG, Blomqvist H, Hedenstierna G, Lundberg J, Zapol WM: Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. *Anesthesiology* 1993;78:427-435.
- 18 Rich GF, Murphy GD, Roos CM, Johns RA: Inhaled nitric oxide - Selective pulmonary vasodilation in cardiac surgical patients. *Anesthesiology* 1993;78:1028-1035.
- 19 Roberts JD Jr, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM: Inhaled nitric oxide in congenital heart disease. *Circulation* 1993;87:447-453.
- 20 Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM: Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399-405.
- 21 Sellén H, Winberg P, Gustafsson LE, Lundell B, Böök K, Frostell CG: Inhalation of nitric oxide reduced pulmonary hypertension after cardiac surgery in a 3.2-kg infant. *Anesthesiology* 1993;78:577-580.
- 22 Blomqvist H, Wickerts CJ, Andreen M, Ullberg U, Örtqvist Å, Frostell C: Enhanced pneumonia resolution by inhalation of nitric oxide. *Acta Anaesthesiol Scand* 1993;37:110-114.
- 23 Holt JP, Rhode EA, Kines H: Ventricular volumes and body weight in mammals. *Am J Physiol* 1968;215:704-715.
- 24 Moncada S, Vane JR: Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A₂, and prostacyclin. *Pharmacol Rev* 1979;30:293-332.
- 25 Nicosia S, Oliva D, Bernini F, Fumagalli R: Prostacyclin-sensitive adenylate cyclase and prostacyclin binding sites in platelets and smooth muscle cells. *Adv Cyclic Nucleotide Protein Phosphorylation Res* 1984;17:593-599.
- 26 Bahkle YS, Ferreira SH: Lung metabolism of eicosanoids: Prostaglandins, prostacyclin, thromboxane, and leukotrienes; in Fishman AP, Fisher AB (eds): *Handbook of Physiology, Section 3: The Respiratory System*. Bethesda, American Physiological Society, 1985, pp 365-386.
- 27 Lock JE, Olley PM, Coceani F: Direct pulmonary vascular responses to prostaglandins in the conscious newborn lamb. *Am J Physiol* 1980;238:H631-H638.
- 28 Archer SL, Chesler E, Cohn JN, Weir EK: ZH 36-374, a stable analog of prostacyclin, prevents acute hypoxic pulmonary hypertension in the dog. *J Am Coll Cardiol* 1986;8:1189-1194.
- 29 Rubin LJ, Mendoza J, Hood M, McGoan M, Barst R, Williams WB, Diehl JH, Crow J, Long W: Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med* 1990;112:485-491.
- 30 Sprague RS, Stephenson AH, Lonigro AJ: Prostaglandin I₂ supports blood flow to hypoxic alveoli in anesthetized dogs. *J Appl Physiol* 1984;56:1246-1251.
- 31 Szczeklick A, Gryglewski RJ, Nizankowska E, Nizankowska R, Musial J: Pulmonary and anti-platelet effects of intravenous and inhaled prostacyclin in man. *Prostaglandins* 1978;16:651-660.
- 32 Fuller HD, Dolovich MB, Posmituck G, Wong Pack W, Newhouse MT: Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients - Comparison of dose to the lungs. *Am Rev Respir Dis* 1990;141:444.
- 33 O'Riordan TG, Greco MJ, Perry MJ, Smaldone GC: Nebulizer function during mechanical ventilation. *Am Rev Respir Dis* 1992;145:1117-1122.
- 34 Spannhake EW, Hyman AL, Kadowitz PJ: Dependence of the airway and pulmonary vascular effects of arachidonic acid upon route and rate of administration. *J Pharmacol Exp Ther* 1980;212:584-590.
- 35 Radi R, Beckman JS, Bush KM, Freeman BA: Peroxynitrite-induced membrane lipid peroxidation: The cytotoxic potential of superoxide and nitric oxide. *Arch Biochem Biophys* 1991;288:481-487.
- 36 Maeda N, Imaizumi K, Kon K, Shiga T: A kinetic study on functional impairment of nitric oxide-exposed rat erythrocytes. *Environ Health Perspect* 1987;73:171-177.