

Effects of inhaled versus intravenous vasodilators in experimental pulmonary hypertension

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ABSTRACT: Inhaled nitric oxide (NO) causes selective pulmonary vasodilation and improves gas exchange in acute lung failure. In experimental pulmonary hypertension, we compared the influence of the aerosolized vasodilatory prostaglandins (PG) PGI₂ and PGE₁ on vascular tone and gas exchange to that of infused prostanoids (PGI₂, PGE₁) and inhaled NO.

An increase of pulmonary artery pressure (P_{pa}) from 8 to ~34 mmHg was provoked by continuous infusion of U-46619 (thromboxane A₂ (TxA₂) analogue) in blood-free perfused rabbit lungs. This was accompanied by formation of moderate lung oedema and severe ventilation-perfusion (V'/Q') mismatch, with predominance of shunt flow (>50%, assessed by the multiple inert gas elimination technique).

When standardized to reduce the P_{pa} by ~10 mmHg, inhaled NO (200 ppm), aerosolized PGI₂ (4 ng·kg⁻¹·min⁻¹) and nebulized PGE₁ (8 ng·kg⁻¹·min⁻¹) all reduced both pre- and postcapillary vascular resistance, but did not affect formation of lung oedema. All inhalative agents improved the V'/Q' mismatch and reduced shunt flow, the rank order of this capacity being NO > PGI₂ > PGE₁. In contrast, lowering of P_{pa} by intravascular administration of PGI₂ and PGE₁ did not improve gas exchange. "Supratherapeutic" doses of inhaled vasodilators in control lungs (400 ppm NO, 30 ng·kg⁻¹·min⁻¹ of PGI₂ or PGE₁) did not provoke vascular leakage or affect the physiological V'/Q' matching.

We conclude that aerosolization of prostaglandins I₂ and E₁ is as effective as inhalation of nitric oxide in relieving pulmonary hypertension. When administered via this route instead of being infused intravascularly, the prostanoids are capable of improving ventilation-perfusion matching, suggesting selective vasodilation in well-ventilated lung areas.

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Inhalation of nitric oxide (NO) has been shown to cause "selective" pulmonary vasodilation, in the absence of vasodilatory effects in the systemic circulation [1–4]. The different response of gas exchange to NO might be related to the underlying mechanism of ventilation-perfusion (V'/Q') imbalance. In patients with chronic obstructive pulmonary disease (COPD) with broad V'/Q' heterogeneity, caused by low V'/Q' ratios but negligible intrapulmonary shunt, NO may worsen gas exchange because of increased perfusion of poorly-ventilated areas [5]. By contrast, in patients with severe adult respiratory distress syndrome (ARDS), in whom shunt flow predominates, the pulmonary vasodilatory effect of inhaled NO was accompanied by an acute improvement of gas exchange [6–8]. Due to the transbronchial route, the vasodilatory property of this agent is apparently restricted to well-ventilated lung areas, effecting a redistribution of blood flow from nonventilated regions to these areas. This is considered a substantial progress compared to the intravenous use of vasodilators, such as prostaglandin (PG) I₂ and PGE₁. These prostanoids provoke nonselective vasodilation both in pulmonary and systemic vessels, and within the lung vasculature in

ventilated and nonventilated areas, with an increase in shunt flow [9, 10].

In order to circumvent these disadvantages, we employed aerosolization technology to use the transbronchial route of application for the vasodilatory prostanoid PGI₂ also. We demonstrated an improvement of arterial oxygenation due to decreased shunt flow and a selective pulmonary vasodilation in patients with severe ARDS and severe pneumonia [11, 12]. These findings are of interest, since PGI₂ is an agent that has been used for many years and has a well-known pharmacological profile [13, 14]: it does not possess the disadvantageous feature of being a free radical, such as NO, with putative side-effects on the bronchial tissue and the lung parenchyma [15, 16]. Following this line of reasoning, it may even be of interest to add PGE₁ to the list of inhalative vasodilators, since, in addition to its vasorelaxant properties, this agent has been implicated in dampening the inflammatory events in the lung alveolar, interstitial and vascular spaces [17, 18].

In the current study, in a model of pulmonary hypertension with severe disturbances of gas exchange, we directly compared lung vascular effects and the impact

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on V'/Q' matching of inhaled NO, aerosolized PGI₂ and PGE₁ to each other and to those of infused vasodilatory prostanoids. Furthermore, we wanted to determine whether high doses of the different vasodilatory agents might exert disadvantageous effects on vascular integrity and physiological V'/Q' matching when inhaled under baseline conditions.

Methods

Materials

Hydroxyethylamylpectine (molecular weight (MW) 200,000 kDa) was obtained from Fresenius (Oberursel, Germany). The thromboxane analogue, U-46619, was supplied by Sigma (Deishofen, Germany), PGI₂ (epostenol) by Wellcome (London, UK), PGE₁ (alprostadil) by Schwarz Pharma (Monheim, Germany) and NO by Messer Griesheim GmbH (Frankfurt-Griesheim, Germany).

Isolated lung model

The perfused lung model has been described previously [19]. Briefly, rabbits of either sex weighing 2.5–3.1 kg were anaesthetized with intravenous pentobarbital (60–90 mg·kg⁻¹) and anticoagulated with heparin (1,000 U·kg⁻¹). Tracheostomy was performed and the animals were ventilated with room air, using a Harvard respirator (Cat rabbit ventilator type 6025; Hugo Sachs Elektronik, March, Germany). After midsternal thoracotomy, catheters were placed into the pulmonary artery and the left atrium, and perfusion with Krebs's Henseleit buffer, containing 4% w/v hydroxyethylamylpectine, was started. Left atrial pressure (PLA) was set at 1.5 mmHg in all experiments. In parallel with the onset of artificial perfusion, room air supplemented with 4% CO₂ was used for ventilation. Tidal volume (8–14 mL·kg⁻¹) and respiratory frequency (6–10 breaths·min⁻¹) were adapted to maintain the pH of the recirculating buffer in the range 7.35–7.37. A positive end-expiratory pressure of 1 mmHg was used throughout. The organs were freely suspended from a force transducer for monitoring of organ weight. Pressures in the pulmonary artery (P_{pa}), the left atrium (PLA) and the trachea were registered (zero referenced at the hilum). Perfusate samples were taken from the arterial and venous part of the system. Gas samples were taken from the outlet of an expiration gas-mixing box. The whole system was heated to 37°C.

Lungs included in the study: 1) had a homogeneous white appearance with no signs of haemostasis, oedema or atelectasis; 2) had a pulmonary artery and ventilation pressure in the normal range; and 3) were isogravimetric (lung weight gain <0.3 g·h⁻¹) during an initial steady-state period of at least 30 min. According to these criteria, 15–20% of all lung preparations were discarded before entering the study.

Gravimetric estimation of capillary filtration coefficient

Capillary filtration coefficient ($K_{f,c}$) was determined gravimetrically, employing a sudden venous pressure elevation of 10 cmH₂O for 8 min. $K_{f,c}$ was calculated by time zero extrapolation of the slope of the weight gain, using a semilogarithmic plot of the rate of lung

weight gain according to TAYLOR and GAAR [20]. The vascular compliance was determined as change in the vascular volume per change in microvascular pressure. The change of vascular volume was measured indirectly as change in lung weight over time. The initial rapid change in weight over the first 2 min was used for calculation of the compliance [19, 21].

Determination of capillary pressure

Capillary pressure (P_c) was determined by the double occlusion technique as described previously [22, 23]. Interruption of the arterial and venous flow was performed simultaneously by rapid magnetic valves during the apnoeic period between ventilation breaths, so that inhalation of vasoactive agents was not interrupted. P_{pa} and PLA pressures were digitized and sampled with an analogue-to-digital converter. P_c was calculated as the average of the mean P_{pa} and PLA during the period of 2–3 s after double occlusion. Total pulmonary vascular resistance was partitioned into arterial (R_a) (precapillary) and venous (R_v) (postcapillary) resistance as follows:

$$\begin{aligned} R_a &= (P_{pa} - P_c) / Q' \\ R_v &= (P_c - PLA) / Q' \end{aligned}$$

Inhalation and aerosolization

NO was delivered into the inspiratory gas flow by use of a precise pressure reduction valve (Messer Griesheim, Frankfurt-Griesheim, Germany), while keeping the inspiratory oxygen concentration and ventilator settings constant. The level of NO in the inspired gas was monitored by chemiluminescence (UPK 3100; UPK Bad Nauheim, Germany). PGI₂ and PGE₁ were aerosolized with a jet nebulizer (Pari, Starnberg, Germany), driven with the same gas mixture with which the lungs were ventilated, at a pressure of 125 kPa. The nebulization system and the technique for determination of particle size and lung deposition have been described previously [24, 25]. For the given ventilator setting, an absolute deposition fraction of 0.25±0.02 was determined. This deposition fraction was taken into consideration when calculating the total dose of drugs delivered to the bronchoalveolar space by aerosolization.

V'/Q' determination in isolated lungs by multiple inert gas elimination technique (MIGET)

The continuous V'/Q' distributions were determined by the multiple inert gas elimination technique (MIGET) as described by WAGNER *et al.* [26], which has been adapted to assess gas exchange of blood-free perfused rabbit lungs [27, 28]. The residual sum of squares (RSS) was the result of testing the compatibility of the inert gas data to the derived V'/Q' distribution by the least squares method. An indication of acceptable quality of the V'/Q' distributions is a RSS of 5.348 or less in half of the experimental runs (50th percentile), or 10.645 or less in 90% of the experimental runs (90th percentile) [29]. In the present study, 72% of residual sum of squares were less than 5.348 and 98% were less than 10.645.

Experimental protocols

In pilot studies, dose-effect curves for U-46619 were established. There was some variation in the responsiveness from lung to lung, and a dosage in the range 25–55 ng·kg⁻¹·min⁻¹ was found to be required for augmentation of P_{pa} to ~35 mmHg within 15 min. The individually titrated dose was then continuously infused, and stable pulmonary hypertension in the narrow range 34–35.5 mmHg was established by this technique. All pharmacological agents addressed below were then tested to find a dose which reduced the U-46619-elicited P_{pa} increase by ~10 mmHg. This was 50 ng·kg⁻¹·min⁻¹ for intravenous PGI₂, 25 ng·kg⁻¹·min⁻¹ for intravenous PGE₁, 200 ppm for inhaled NO, 4 ng·kg⁻¹·min⁻¹ for aerosolized PGI₂ and 8 ng·kg⁻¹·min⁻¹ for aerosolized PGE₁. With these doses, the definite experiments were performed.

Fifty eight isolated lung experiments were undertaken. After termination of the initial steady-state period of 30 min, duplicate samples for estimation of baseline V'/Q' relationships were drawn and time was set to zero. Further V'/Q' measurements were performed as described below for the different experimental protocols. Double clamping manoeuvres were undertaken at 0, 45, 105, 135 and 195 min. Perfusion was terminated 195 min after baseline V'/Q' determination in the U-46619 experiments, and after 180 min in the experiments with estimation of the $K_{f,c}$.

Control lungs (n=6). After termination of the steady-state period, V'/Q' measurements were performed after 15, 45, 75, 105, 135, 165 and 195 min. No interventions were undertaken.

U-46619 lungs (n=6). After termination of the steady-state period, U-46619 was continuously infused over 135 min to increase P_{pa} to ~35 mmHg. V'/Q' measurements were performed 15, 45, 75, 105 and 135 min after the beginning of the U-46619 application, and after 165 and 195 min, corresponding to 30 and 60 min after withdrawal of U46619 infusion.

Intravenous PGI₂ and PGE₁ application (n=6 each). U-46619 was administered as described. Forty five minutes after starting U-46619 infusion, PGI₂ or PGE₁ was continuously applied at a dose of 50 ng·kg⁻¹·min⁻¹ and 25 ng·kg⁻¹·min⁻¹, respectively, until termination of the experiments. V'/Q' measurements were carried out after 15, 45, 75, 105, 135, 165 and 195 min.

NO inhalation (n=6). U-46619 was correspondingly infused and, after 45 min, 200 ppm NO was admixed to the inspiration gas until termination of the experiments. V'/Q' distributions were determined at the same time-points as detailed in the preceding experiments.

PGI₂ and PGE₁ aerosolization (n=6 each). Forty five minutes after onset of the U-46619 infusion, 4 ng·kg⁻¹·min⁻¹ PGI₂ or 8 ng·kg⁻¹·min⁻¹ PGE₁ was aerosolized over 150 min. V'/Q' measurements were performed accordingly.

Vascular permeability and gas exchange in response to high doses of inhaled vasodilators (n=4 each). In a separate set of experiments, the influence of high doses

of inhaled vasodilators on $K_{f,c}$ and gas exchange was assessed in the absence of U-46619-infusion. $K_{f,c}$ measurements and determinations of the V'/Q' distribution were performed after termination of the steady-state period (time set to zero). These manoeuvres were repeated after 90 and 180 min. NO was inhaled in a concentration of 400 ppm, and the aerosolized PGI₂ and PGE₁ dose was 30 ng·kg⁻¹·min⁻¹; each agent was started at time zero and was given throughout. Control lungs received no vasodilative drug (n=4 each experiment).

Statistical analysis

All values are presented as mean±SEM or as coefficient of variation (SD/mean, %). For analysing statistical difference, two-tailed Student's t-test for unpaired samples was performed. After Bonferroni's correction a p-value less than 0.05 was considered significant.

Results

Baseline conditions

After termination of the steady-state period, all lungs displayed P_{pa} values in the range 6–8 mmHg (initial data points in figure 1). The P_c ranged 4.2–4.5 mmHg (table 1). There was some predominance of the precapillary (R_a) over the postcapillary (R_v) vascular resistance, and the mean $K_{f,c}$ value was 8.6±2.2 mL·s⁻¹·cmH₂O·g lung wet weight ×10⁻⁵. These data correspond to previous investigations in the perfused rabbit lung [19]. Baseline V'/Q' measurements revealed unimodal, narrow distribution of perfusion and ventilation to midrange V'/Q' (0.1 < V'/Q' < 10) areas (table 2). Shunt flow (V'/Q' < 0.005) and perfusion flow to poorly-ventilated areas (0.005 < V'/Q' < 0.1) were below 3% (table 2, and initial data points for shunt flow in figs. 1a–d), and no perfusion to high V'/Q' regions (10 < V'/Q' < 100) was observed. Dead space (V'/Q' > 100) approximated 60% of ventilation.

U-46619-elicited pulmonary hypertension and gas exchange abnormalities

Infusion of 40±13.3 ng·kg⁻¹·min⁻¹ (all experiments) of the stable thromboxane analogue, U-46619, provoked an increase in P_{pa} to 34.5±1.1 mmHg within 10–15 min, with subsequent plateauing of the pulmonary hypertension upon ongoing infusion of the vasoconstrictor agent (fig. 1a). The rise in pulmonary vascular resistance was mostly due to an augmentation of R_a , with additional elevation of R_v and two- to threefold increase in P_c (table 1). The P_{pa} rise was accompanied by a delayed-onset lung weight gain and a progressive increase in shunt flow to 56±10% of the total lung perfusion after 135 min (fig. 1a). A broadening of flow dispersion in the midrange V'/Q' regions was noted under these conditions (table 2). Concomitantly, the percentage of the perfusion of areas with normal V'/Q' ratios dramatically decreased. Dead space increased by approximately

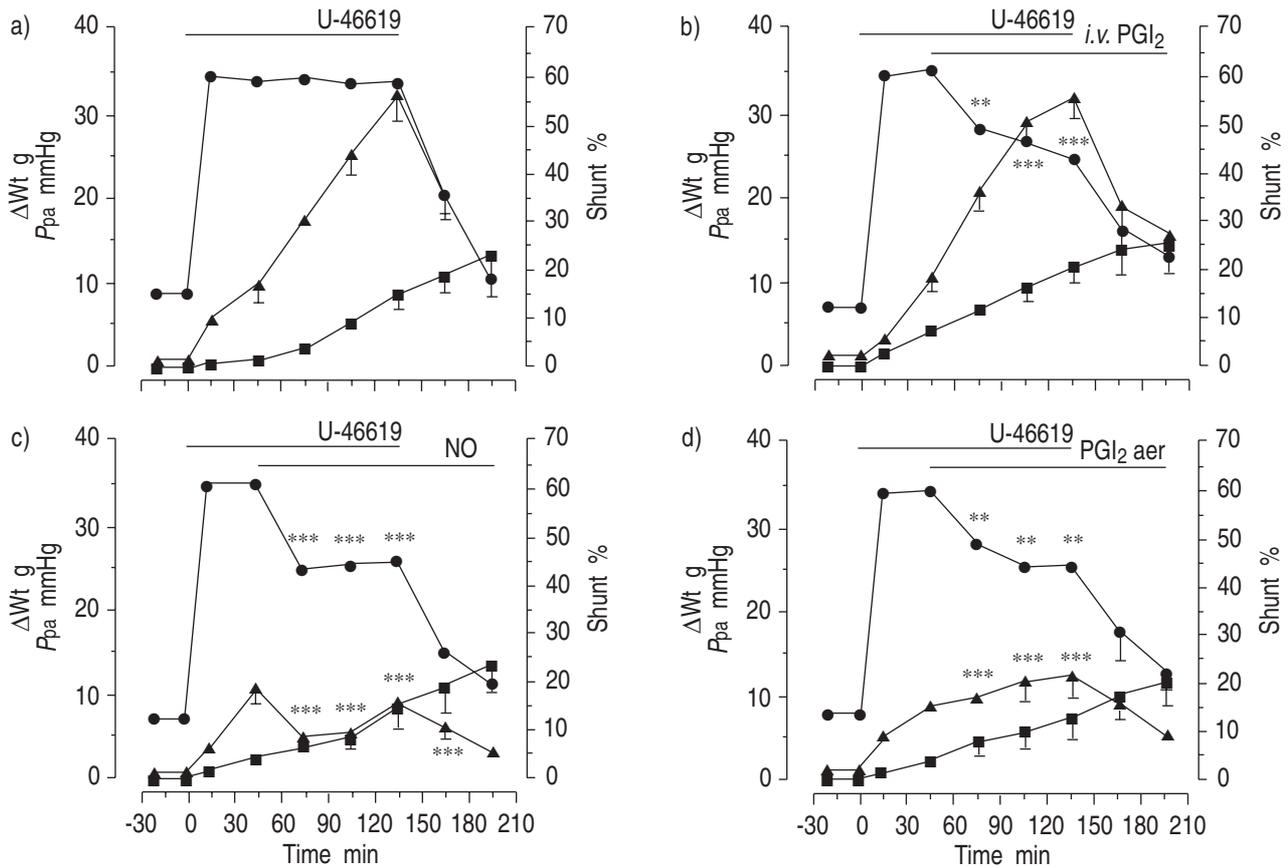


Fig. 1. – a) U-46619-elicited pulmonary hypertension; b) the influence of intravenous prostaglandin (PGI_2 ; $25 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$); c) inhaled nitric oxide (NO; 200 ppm); and d) aerosolized (aer) PGI_2 ($4 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) on U-46619-elicited pulmonary hypertension. The figures show pulmonary artery pressure (P_{pa}), lung weight gain (ΔWt), and the shunt flow (% of total perfusion). Values are presented as mean \pm SEM of six independent experiments. SEM bars are missing when falling into symbols. Horizontal bars indicate the periods of administration of the agents. In all cases U-46619 infusion was at $\approx 40 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. **: $p < 0.01$; ***: $p < 0.001$, significant changes from U-46619-infused lungs in the absence of vasodilator agent. —●—: P_{pa} ; —▲—: shunt; —■—: ΔWt . U-46619: thromboxane analogue.

Table 1. – Lung perfusion pressures and partitioning into pre- and postcapillary resistance

	Time min	Control (n=6)	U-46619 (n=6)	U-46619/ PGE_1 <i>i.v.</i> (n=6)	U-46619/ PGI_2 <i>i.v.</i> (n=6)	U-46619/ NO (n=6)	U-46619/ PGE_1 aer (n=6)	U-46619/ PGI_2 aer (n=6)
P_{pa} mmHg	0	7.5 \pm 0.2	8.0 \pm 0.4	7.0 \pm 0.5	7.1 \pm 0.4	7.1 \pm 0.2	6.8 \pm 0.2	7.7 \pm 0.2
	45	7.7 \pm 0.2	34.5 \pm 0.6***	35.3 \pm 0.5	35.0 \pm 0.4	34.8 \pm 0.2	34.5 \pm 0.3	34.0 \pm 0.6
	105	7.8 \pm 0.2	34.0 \pm 0.5***	27.5 \pm 0.4***	28.3 \pm 0.7***	24.8 \pm 0.4***	30.5 \pm 0.6***	27.7 \pm 0.7**
	135	7.4 \pm 0.2	34.3 \pm 0.4***	24.4 \pm 0.7***	24.5 \pm 0.3***	25.5 \pm 0.7***	27.0 \pm 0.5**	25.3 \pm 1.3**
	195	7.7 \pm 0.2	10.3 \pm 0.4***	12.8 \pm 0.7***	11.8 \pm 0.6***	10.8 \pm 0.7***	11.3 \pm 1.0**	12.5 \pm 2.1**
P_c mmHg	0	4.5 \pm 0.3	4.5 \pm 0.4	4.5 \pm 0.2	4.4 \pm 0.2	4.5 \pm 0.3	4.5 \pm 0.4	4.3 \pm 0.2
	45	4.7 \pm 0.3	11.3 \pm 0.5***	11.6 \pm 0.2	11.2 \pm 0.3	10.3 \pm 0.2	10.5 \pm 0.4	10.8 \pm 0.4
	105	5.1 \pm 0.4	11.0 \pm 0.3***	9.3 \pm 0.3‡	8.9 \pm 0.3‡	6.8 \pm 0.5**	8.9 \pm 0.3‡	8.0 \pm 0.4‡
	135	4.5 \pm 0.2	10.8 \pm 0.4***	8.4 \pm 0.4‡	8.2 \pm 0.4‡	7.5 \pm 0.3**	7.0 \pm 0.4‡	7.8 \pm 0.4‡
	195	4.6 \pm 0.5	6.3 \pm 0.3*	7.2 \pm 0.4	6.9 \pm 0.4	6.5 \pm 0.6	4.3 \pm 0.2**	5.0 \pm 0.4
R_a mmHg \cdot L $^{-1}$ \cdot min	0	22.5 \pm 4.2	22.5 \pm 3.2	22.3 \pm 3.6	24.3 \pm 3.7	25.0 \pm 2.5	25.0 \pm 2.5	23.4 \pm 1.76
	45	25.0 \pm 2.5	232.5 \pm 6.5***	234.9 \pm 2.3	238.0 \pm 2.6	242.5 \pm 4.2	240.0 \pm 3.5	237.5 \pm 6.5
	105	27.5 \pm 2.2	232.5 \pm 2.2***	177.2 \pm 6.4‡	190.3 \pm 6.6**	162.5 \pm 2.2***	191.3 \pm 5.7**	190.0 \pm 5.0**
	135	25.0 \pm 2.5	242.5 \pm 7.4***	161.1 \pm 5.7‡	163.6 \pm 2.6**	160.0 \pm 12.8**	182.5 \pm 6.5**	172.5 \pm 7.4**
	195	22.4 \pm 4.3	43.0 \pm 6.7*	56.2 \pm 14.4	47.4 \pm 8.6	45.0 \pm 5.6	47.5 \pm 9.6	57.5 \pm 8.2
R_v mmHg \cdot L $^{-1}$ \cdot min	0	25.1 \pm 5.6	25.0 \pm 5.6	29.5 \pm 4.9	23.6 \pm 4.7	30.0 \pm 3.5	32.5 \pm 2.2	31.3 \pm 3.2
	45	30.0 \pm 3.5	92.5 \pm 4.2***	97.7 \pm 2.0	91.9 \pm 2.6	85.0 \pm 5.6	85.0 \pm 2.5	90.0 \pm 6.1
	105	25.5 \pm 4.6	90.0 \pm 3.5***	73.3 \pm 3.9‡	68.6 \pm 1.9‡	50.0 \pm 3.5**	66.3 \pm 3.3‡	62.5 \pm 2.2**
	135	30.0 \pm 2.2	87.5 \pm 4.2***	63.7 \pm 7.1	61.4 \pm 6.4	60.0 \pm 3.5‡	52.5 \pm 7.4‡	57.5 \pm 2.3**
	195	32.5 \pm 2.2	47.5 \pm 6.5	56.7 \pm 5.0	54.2 \pm 4.8	50.0 \pm 7.9	27.5 \pm 2.2	37.5 \pm 2.4

P_{pa} : pulmonary artery pressure; P_c : capillary pressure; R_a : arterial (precapillary) resistance; R_v : venous (postcapillary) resistance. PGE_1 and PGI_2 : prostaglandin E_1 and I_2 , respectively; U-46619: thromboxane analogue; *i.v.*: intravenous; aer: aerosolized. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$, significant differences between U-46619-infused and control. ‡: $p < 0.05$; †: $p < 0.01$; ††: $p < 0.001$, significant changes between U-46619-infused lungs in the absence and presence of vasodilator therapy.

Table 2. – Gas exchange variables in response to inhaled *versus* infused vasodilators

	Time min	Control (n=6)	U-46619 (n=6)	U-46619/ PGE ₁ <i>i.v.</i> (n=6)	U-46619/ PGI ₂ <i>i.v.</i> (n=6)	U-46619/ NO (n=6)	U-46619/ PGE ₁ aer (n=6)	U-46619/ PGI ₂ aer (n=6)
Normal	0	98.6±0.3	98.6±0.4	97.7±0.7	97.5±0.3	98.4±0.2	98.7±0.2	97.9±0.5
V'/Q' %	45	98.5±0.4	79.6±4.8*	79.8±6.9	80.0±2.7	79.7±4.6	80.0±2.9	82.9±1.5
0.1 < V'/Q' < 10	105	98.6±0.3	53.0±4.9***	57.3±8.0	46.5±3.7	89.6±3.5‡‡	69.4±3.1‡	79.1±4.6‡
	135	98.6±0.4	40.3±6.2***	53.5±9.4	42.1±4.2	80.3±5.9‡	66.5±5.8‡	75.1±4.9‡
	195	98.1±0.1	87.0±4.2*	64.5±9.8	64.5±8.2	95.0±1.5	81.5±4.3	92.2±1.9
Low	0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
V'/Q' %	45	0.1±0.2	3.0±0.5	2.6±0.8	1.6±0.7	2.0±0.6	1.8±0.6	0.4±0.9
0.005 < V'/Q' < 0.1	105	0±0	2.8±0.8	3.0±0.7	2.6±0.5	3.2±0.6	2.9±0.4	1.3±1.2
	135	0.1±0.1	5.9±1.6	6.1±0.9	5.0±0.3	4.2±1.9	2.2±0.9	1.9±0.8
	195	0±0	1.6±1.9	1.1±0.5	1.3±0.5	0.6±0.6	0.4±0.6	1.7±0.6
Dead space % V'A	0	61.7±1.8	59.9±2.7	56.2±2.2	58.5±1.1	59.5±1.2	59.8±1.4	59.0±1.8
	45	61.5±1.9	67.9±0.4*	61.0±2.5	67.1±0.9	65.6±1.1	64.1±1.1	67.8±0.9
	105	58.6±1.0	69.5±0.6***	64.8±2.1	66.4±0.7	71.6±0.9	70.4±0.8	66.4±1.4
	135	58.2±0.8	69.1±0.6***	66.6±1.6	63.7±0.4	69.6±0.9	69.4±1.5	67.4±1.1
	195	57.6±0.1	68.6±2.6*	66.7±2.5	65.1±1.8	71.4±1.4	69.7±1.6	68.3±1.4
Log sd Q'	0	0.42±0.10	0.44±0.1	0.59±0.01	0.45±0.05	0.45±0.05	0.42±0.07	0.52±0.08
	45	0.53±0.08	1.12±0.1**	1.01±0.12	0.99±0.05	1.09±0.10	0.98±0.10	0.95±0.09
	105	0.41±0.09	1.22±0.1***	1.39±0.17	1.21±0.02	1.03±0.08	1.16±0.06	1.01±0.05
	135	0.43±0.10	1.30±0.1***	1.36±0.14	1.27±0.04	1.13±0.16	1.25±0.09	0.92±0.08‡
	195	0.50±0.08	0.58±0.1	1.13±0.10‡	1.10±0.04‡	0.67±0.06	0.99±0.08‡	0.76±0.08
Log sd V'A	0	0.38±0.05	0.36±0.02	0.48±0.01	0.44±0.05	0.40±0.04	0.36±0.05	0.37±0.02
	45	0.43±0.04	1.64±0.11***	1.43±0.15	1.57±0.03	1.45±0.12	1.89±0.13	1.21±0.24
	105	0.48±0.10	1.55±0.07***	1.32±0.10	1.42±0.12	1.14±0.15	1.61±0.07	1.39±0.19
	135	0.40±0.05	1.44±0.08***	1.42±0.06	1.55±0.03	1.32±0.12	1.47±0.15	1.34±0.17
	195	0.42±0.08	0.98±0.11**	1.33±0.15	1.67±0.02‡	0.91±0.19	1.01±0.1	0.84±0.20
Mean Q'	0	1.12±0.10	1.05±0.10	1.09±0.08	1.16±0.05	1.03±0.06	1.10±0.06	1.05±0.03
	45	0.90±0.12	0.51±0.07*	0.73±0.09	0.65±0.04	0.70±0.05	0.52±0.10	0.60±0.02
	105	1.12±0.03	0.80±0.16	0.82±0.04	0.85±0.07	0.96±0.06	0.67±0.11	0.70±0.07
	135	1.09±0.09	0.71±0.43	0.77±0.07	0.78±0.06	0.83±0.05	0.75±0.05	0.75±0.10
	195	1.24±0.17	0.99±0.16	0.78±0.09	0.67±0.02	1.01±0.08	0.89±0.04	0.76±0.02
Mean V'A	0	1.26±0.04	1.22±0.1	1.43±0.1	1.44±0.1	1.20±0.1	1.28±0.1	1.10±0.1
	45	1.16±0.2	5.46±1.5***	4.63±1.1	3.45±0.1	3.51±0.5	4.38±0.8	3.76±1.4
	105	1.30±0.1	9.38±1.8***	6.76±1.8	8.67±1.7	3.44±0.6	6.41±0.5	4.73±1.5
	135	1.19±0.1	14.1±3.2***	7.81±2.2	12.7±1.8	4.65±0.9	5.95±1.1	4.10±1.5
	195	1.25±0.1	1.42±0.2	6.40±1.9‡	6.50±1.8‡	2.06±0.2	2.52±0.3	1.85±0.6

All data were obtained by multiple inert gas elimination technique (MIGET). V'A: alveolar ventilation; V'/Q' : ventilation/perfusion; PGE₁ and PGI₂: prostaglandin E₁ and I₂, respectively; Log sd Q': dispersion of perfusion distribution; Log sd V'A: dispersion of ventilation distribution; U-46619: thromboxane analogue; aer: aerosolized; *i.v.*: intravenous. *: p<0.05; **: p<0.01; ***: p<0.001, significant differences between U-46619-infused and control. ‡: p<0.05; ‡‡: p<0.01; ‡‡‡: p<0.001, significant changes between U-46619-infused lungs in the absence and presence of vasodilator therapy.

10%. After withdrawal of the U-46619 infusion, P_{pa} and P_c returned to near baseline values, whereas the lung weight displayed progressive increase, resulting in a total weight gain of 13±5.2 g at the end of experiments. In contrast to the formation of ongoing oedema, shunt flow declined to 18±6%, and the increase in log sd Q' and log sd V' was largely reversible.

Influence of intravenous PGI₂ and PGE₁ on U-46619-elicited pulmonary hypertension and gas exchange abnormalities

The infusion of PGI₂ (fig. 1b) and PGE₁ reduced the U46619-provoked increase in P_{pa} by ~10 mmHg. There was a decrease both of R_a and R_v , and the P_c values declined slightly (table 1). During the intravenous vasodilator therapy, the shunt flow increased to 56±8% (PGI₂) and to 48±14% (PGE₁): these data were not significantly different from the shunt fraction observed during U-46619 challenge in the absence of vasodilator infusion. The time course and extent of lung oedema

formation and the decline of P_{pa} and shunt fraction after cessation of U-46619 infusion did not substantially differ between the presence and absence of intravenous prostanoïd administration (fig. 1b).

Influence of NO inhalation and PGI₂ and PGE₁ aerosolization on U-46619-elicited pulmonary hypertension and gas exchange abnormalities

All three inhalative vasodilator regimens reduced the increase in P_{pa} values in response to U-46619 infusion by ~10 mmHg (figs. 1c and 1d). There was a decrease of R_a and R_v and the P_c values declined slightly, with no substantial difference between the three inhaled vasodilator agents (table 1). All transbronchially-applied drugs caused a marked and significant reduction in the U-46619-elicited augmentation of shunt flow: as compared to 56±10% in response to mono-U-46619, the maximum shunt fractions were only 16±5% (NO), 21±9% (aerosolized PGI₂) and 31±8% (aerosolized PGE₁). The higher efficacy of NO in suppressing shunt

Table 3. – Gas exchange, vascular pressure and lung weight in response to high doses of inhaled vasodilators

	Time min	Shunt % Q'	Normal V'/Q'	Log sd Q'	Log sd V_A	P_{pa} mmHg	Compliance $mL \cdot cmH_2O^{-1}$	ΔWt g
Control (n=4)	10	1.67±0.14	98.3±0.16	0.40±0.06	0.38±0.05	7.40±0.22	0.35±0.03	0.87±0.27
	100	1.52±0.22	98.4±0.20	0.49±0.04	0.45±0.04	7.50±0.18	0.34±0.04	1.05±0.17
	190	1.45±0.18	98.3±0.23	0.50±0.02	0.30±0.09	7.60±0.19	0.36±0.04	0.86±0.20
NO (400 ppm) (n=4)	10	1.70±0.22	98.3±0.20	0.39±0.06	0.36±0.05	7.75±0.22	0.29±0.02	0.82±0.26
	100	1.25±0.10	98.6±0.14	0.49±0.06	0.43±0.04	7.75±0.41	0.36±0.01	1.26±0.23
	190	1.07±0.17	98.8±0.11	0.47±0.02	0.30±0.09	7.75±0.22	0.34±0.02	1.50±0.17
PGI ₂ aer (30 ng·kg ⁻¹ ·min ⁻¹) (n=4)	10	4.82±1.03	95.2±1.04	0.43±0.03	0.41±0.03	7.50±0.25	0.30±0.02	0.99±0.11
	100	2.37±0.71	97.5±0.67	0.42±0.04	0.36±0.01	7.75±0.54	0.33±0.02	1.41±0.13
	190	1.92±0.49	98.0±0.44	0.39±0.03	0.26±0.08	7.75±0.22	0.34±0.01	1.33±0.08
PGE ₁ aer (30 ng·kg ⁻¹ ·min ⁻¹) (n=4)	10	3.12±0.54	96.8±0.54	0.34±0.04	0.36±0.04	7.50±0.25	0.27±0.04	0.97±0.19
	100	1.17±0.30	98.9±0.20	0.44±0.05	0.37±0.02	7.50±0.43	0.30±0.04	1.10±0.17
	190	2.35±1.63	97.1±1.86	0.66±0.22	0.23±0.07	7.75±0.22	0.32±0.04	1.02±0.29

Values are presented as mean±SEM. Gas exchange was assessed by the multiple inert gas elimination technique (MIGET). ΔWt : change in lung weight imposed by a single manoeuvre of venous pressure elevation for determination of the capillary filtration coefficient ($K_{f,c}$); Q' : perfusion; P_{pa} : pulmonary artery pressure. For further definitions see legend to table 2.

was also evident from the fact that the ongoing rise in the shunt fraction in response to U-46619 was not only retarded, but also partially reversed after onset of NO inhalation. As a result of this differential impact on the gas exchange abnormalities, the perfusion of normal V'/Q' areas ($0.1 < V'/Q' < 10$) was best maintained under NO application > PGI₂ aerosolization > PGE₁ aerosolization. In contrast, the progressive formation of lung oedema was not influenced by either agent.

Vascular integrity and gas exchange in response to high doses of inhaled vasodilators in control lungs

When administered in the absence of U-46619, neither high-dose NO (400 ppm) nor large quantities of aerosolized vasodilator prostanoids (30 ng·kg⁻¹ × min⁻¹ of PGI₂ and PGE₁) affected the baseline P_{pa} (table 3), including the distribution of R_a and R_v (data not given). $K_{f,c}$ values (fig. 2) and vascular compliance were not changed, and the same was true for the venous challenge-related increase in lung weight. Moreover, detailed analysis of the V'/Q' matching revealed no impact of the inhaled vasodilators under baseline conditions.

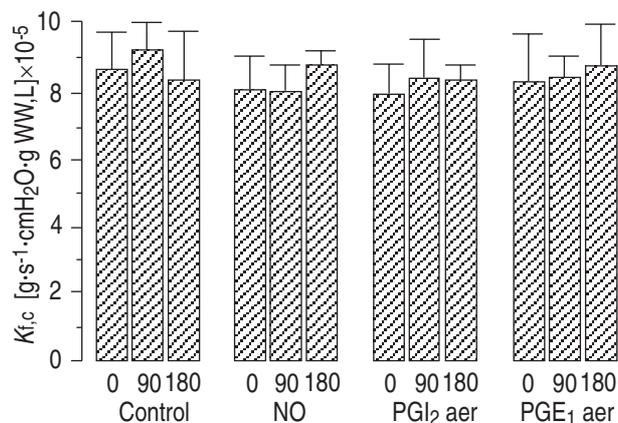


Fig. 2. – The capillary filtration coefficient ($K_{f,c}$) in response to high doses of inhaled vasodilators. $K_{f,c}$ was determined in control lungs, and in lungs treated with 400 ppm nitric oxide (NO), 30 ng·kg⁻¹·min⁻¹ aerosolized prostaglandin I₂ (PGI₂) or 30 ng·kg⁻¹·min⁻¹ aerosolized prostaglandin E₁ (PGE₁). Values are presented as mean±SEM of four independent experiments each. WW.L: lung wet weight.

Ventilation pressures

Peak airway pressure during constant volume ventilation did not significantly change in any of the experimental groups (data not given in detail).

Discussion

The model of U-46619-elicited stable pulmonary hypertension in perfused lungs has been employed repeatedly to test the effects of pharmacological agents on pulmonary haemodynamics [23, 30, 31]. It was found that the stable thromboxane analogue is operative largely *via* precapillary vasoconstriction, in addition to some postcapillary pressor effect, with concomitant moderate augmentation of P_c [23, 31]. This profile of efficacy on the longitudinal distribution of pulmonary vascular resistance was corroborated in the present study.

NO has previously been demonstrated to reduce P_{pa} in U-46619-precontracted lungs [23, 30, 32]. In the current study, 200 ppm NO possessed equivalent potency in relieving the pulmonary hypertension as the continuous infusion of 25 and 50 ng·kg⁻¹·min⁻¹ PGE₁ and PGI₂, a dose range corresponding to clinical studies employing intravenous vasodilators for reduction of pulmonary hypertension in ARDS [9, 10]. The concentration of inhaled NO necessary for effecting pulmonary vasodilation differs considerably among different species, including humans, and has different underlying vasoconstrictor mechanisms. In U-46619-elicited hypertension in rabbit lungs, gaseous NO has been used in the range 20–240 ppm [23, 30–32], and the current dosage employed to achieve substantial pressure reduction is well within this range.

Concerning the longitudinal distribution of vascular resistance in U-46619-elicited pulmonary hypertension, inhaled NO was recently shown to cause a substantial reduction in R_a , but it also relieves the R_v [23, 31]. These studies suggested that inhaled NO is able to diffuse from the alveoli to all significant resistance vessels of the lung, known to be located in direct contact with the alveoli [33]. This finding is confirmed by the present study, and, in addition, we have shown that the same profile of vasodilatory efficacy is encountered upon

inhalation of the aerosolized prostanoids PGI₂ and PGE₁. In other words, the different inhalative vasodilators did not exert a differential impact on the longitudinal distribution of pulmonary vascular resistance, but when standardized to achieve a comparable overall vasodilatory effect, all agents decreased the capillary pressure to a similar extent. Interestingly, to achieve the preset level of P_{pa} reduction, low quantities of PGI₂ (4 ng·kg⁻¹·min⁻¹) and PGE₁ (8 ng·kg⁻¹·min⁻¹) had to be employed for the transbronchial route of application. This finding is even more impressive when considering the fact that not all of the aerosolized dose will be trapped in the alveolar compartment, but some substantial fraction will be deposited on the mucosal surface of the conducting bronchi.

The U-46619-elicited pulmonary hypertension was accompanied by severe gas exchange abnormalities. The predominant abnormalities were a dramatic increase in shunt flow to >50%, and a broadening of both perfusion and ventilation dispersion in the midrange V'/Q' areas, which signalled marked V'/Q' mismatch. This profile of gas exchange disturbances is reminiscent of that encountered under the clinical conditions of the most severe ARDS [6, 34]. Initially, the U-46619-elicited oedema formation may be assumed to be solely responsible for the the predominant shunt flow. Several of the present observations do, however, place doubt on such a simplified assumption. The total amount of oedema formation was still moderate (~10 g when shunt already approached 50%), in comparison to >50 g in states of frank alveolar oedema filling. Shunt flow started before any significant increase in lung weight became evident and, moreover, it declined to <20% after offset of U-6619 infusion, although oedema formation progressed further.

These data strongly suggest that oedema formation *per se* is not sufficient to result in significant shunt flow in the present model, but marked elevation of pulmonary artery pressure is a prerequisite of this event. This may then force perfusion redistribution to oedema-filled regions or otherwise nonventilated areas, putatively distributed in a patchy pattern, which are spared from perfusion by hypoxic vasoconstriction at normal pulmonary artery pressures. When the pulmonary hypertension is relieved, due to discontinuation of the vasoconstrictor agent, the normal local compensatory reflexes in the vasculature can direct flow away from these injured areas. However, the observation that shunt flow further increased with the U-46619 infusion contrasts with the common belief that increases in pulmonary artery pressure are usually associated with an improvement in V'/Q' matching. In patients with ARDS, it was recently shown that combining the inhaled vasodilator NO with the intravenously applied vasoconstrictor, almitrine, potentiated an improvement in gas exchange and reduction of shunt flow, as with either NO or almitrine applications [35]. Because almitrine selectively constricts pulmonary arteries and not pulmonary veins [36], it is unlikely that almitrine increases the hydrostatic capillary pressure, but this might be responsible for the U-46619-induced shunt flow, probably as a result of a greater proportion of the lungs in zone 3. In addition, almitrine mimics, by an unknown mechanism, hypoxic pulmonary vasoconstriction [36], which is not evident for the U-46619-provoked

vasoconstriction. Moreover, the marked rise in pulmonary artery pressure caused by U-46619 might inhibit a pre-existing hypoxic vasoconstriction and could thus contribute to further shunt flow.

In contrast, the relief of pulmonary hypertension upon intravascular use of PGI₂ and PGE₁ was not accompanied by a substantial alteration in gas exchange abnormalities, including shunt flow. The most reasonable explanation for this "discrepancy", improvement of gas exchange upon cessation of the infused vasoconstrictor but not infusion of a vasodilator, is the fact that the intravascularly applied vasodilators are distributed non-selectively to nonventilated regions also: they thereby counteract not only the U-46619-elicited "excess" vasoconstriction, but also the normal regulatory local vasoconstrictor mechanisms. The current study, thus, supports previous clinical observations that intravenous use of PGE₁ and PGI₂ in ARDS causes pulmonary vasodilation, but without benefit for, or even at the expense of, V'/Q' matching [9, 10]. In contrast, inhaled NO was impressively efficient in improving V'/Q' matching in the midrange V'/Q' areas, and, in particular, in decreasing shunt-flow. This observation supports the concept that the transbronchial route of administration allows targeting of the vasorelaxant properties to lung vessels in well-ventilated areas, thereby decreasing local vascular resistance and effecting redistribution of perfusion from nonventilated to gas-accessible regions, synonymous with an improvement of matching V'/Q' . This advantageous effect of NO on perfusion distribution occurred in the absence of any change in ventilation pressure, suggesting the absence of major alterations of gas flow distribution. Notably, the experiments were performed in the absence of blood, which has been suggested to be essential for a complete restriction of the vasodilatory effect of NO to the local pulmonary vasculature, due to instantaneous binding of haemoglobin and inactivation upon entrance into the vascular space [30]. Thus, even in the absence of such haemoglobin inactivation, the concentration gradient of the short-lived NO between aerated and nonaerated regions appears to be operative in effecting selective vasodilation in well-ventilated lung areas, with subsequent redistribution of perfusion.

The same mechanisms must be assumed to underlie the beneficial effect of aerosolized PGI₂ and PGE₁ on V'/Q' matching, including a reduction of shunt flow. In contrast to the intravascular route of administration, the application *via* gas flow evidently allows targeting of the vasodilatory properties to well-ventilated areas for these agents also. There was, however, a clear rank order in the ability to improve gas exchange: PGI₂ was nearly as effective as NO, whereas PGE₁ was clearly less efficient in this respect. At present, we can only speculate which pharmacological or pharmacokinetic differences may underlie such differential impact on V'/Q' matching. At physiological pH, PGI₂ possesses a half-life of approximately 2–3 min [37], which may be sufficiently short to establish an effective gradient of active agent between well-ventilated and nonventilated regions. PGE₁ is a stable compound at neutral pH, is rapidly metabolized to the inactive 13,14-dihydro-15-keto-PGE₁ upon contact with the pulmonary endothelium [38], but may then be reduced back to the

13, 14-dihydro-PGE₁ (PGE₀), which again possesses full vasodilatory potency [39, 40]. Differences in the conversion from the active agent to inactive metabolites, and possibly also differences in the diffusion characteristics, may thus underlie the superiority of PGI₂ over PGE₁ in optimizing V'/Q' matching. Further studies, e.g. addressing the entrance of the active agent into the vascular space upon aerosol delivery into the alveolar compartment, will be necessary to elucidate this difference.

All three inhaled agents were additionally applied in "supratherapeutic" doses in control lungs to question possible disadvantageous effects on lung barrier properties. However, no change in the K_{f,c} values and no lung weight gain was noted, suggesting, at least, an absence of major short-term injury to the endothelial barrier function. Interestingly, no impact of either agent on V'/Q' matching was noted in these experiments. This finding may be interpreted to suggest that under the conditions of low baseline pulmonary artery pressure, the efficacy of the local regulatory mechanisms in optimizing V'/Q' matching may not be further improved, but are also not disturbed by this approach of inhalative vasodilator administration.

In conclusion, the current study shows that aerosolization of prostaglandins I₂ and E₁ is as effective as inhalation of gaseous nitric oxide and as intravascular infusion of prostanoids in reducing pulmonary hypertension. All agents exerted comparable effects on the longitudinal distribution of pulmonary vascular resistance, with reduction both of its pre- and postcapillary component. The improvement of ventilation-perfusion matching upon transbronchial administration of all three agents further supports the concept that inhalative vasodilator application is effective to target vasorelaxant properties of well-ventilated lung areas. Pharmacological and pharmacokinetic differences may underlie the rank order in the ability to improve gas exchange (nitric oxide > aerosolized prostaglandin I₂ > aerosolized prostaglandin E₁) between the different gas-borne agents. The extension of the concept of inhalative vasodilator therapy to prostanoids may be attractive, in view of the fact that non-vasomotor events, such as impact on inflammation, mesenchymal proliferation and fibrosis, and host-defence mechanisms in the lung, may be differentially influenced by nitric oxide and E- and I-type prostanoids.

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