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# Searching the Ideal Inhaled Vasodilator: From Nitric Oxide to Prostacyclin

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**Key Words**

Pulmonary hypertension · Inhaled nitric oxide and prostacyclin · Pulmonary vasodilation · Jet nebulizer

**Abstract**

Today, the technique to directly administer vasodilators via the airway to treat pulmonary hypertension and to improve pulmonary gas exchange is widely accepted among clinicians. The flood of scientific work focussing on this new therapeutic concept had been initiated by a fundamental new observation by Pepke-Zaba [1] and Frostell in 1991 [2]: Both scientists reported, that inhalation of exogenous nitric oxide (NO) gas selectively dilates pulmonary vessels without a concomittant systemic vasodilation. No more than another decade ago NO was identified as an important endogenous vasodilator [3] while having merely been regarded an environmental pollutant before that time. Although inhaled NO proved to be efficacious, alternatives were sought-after due to NO's potential side-effects. In search for the ideal inhaled vasodilator another group of endogenous mediators – the prostanoids – came into the focus of interest. The evidence for safety and efficacy of inhaled prostanoids is – among a lot of other valuable work – based on a series of experimental and clinical investigations that have been performed or designed at the Institute for Surgical Research under the guidance and mentorship of Prof. Dr. med. Dr. h.c. mult. K. Messmer [4–19]. In the following, the current and newly emerging clinical applications of inhaled prostanoids and the experimental data which they are based on, will be reviewed.



## Introduction

The treatment of pulmonary disease by inhaled agents is an attractive concept. Theoretically, this approach increases local drug efficacy while minimizing systemic side-effects. Sympathomimetics, corticosteroids, and antibiotics, among others, have been successfully administered via the tracheal route [20]. A decade ago, inhalational therapy has been extended to vasodilatory agents. The potential benefit of this approach is obvious. Inhaled vasodilators may cause dilatation of vessels within the lungs without affecting peripheral vascular tone thereby avoiding systemic hypotension ('selective pulmonary vasodilation'). It was the unwanted side effects wich made effective treatment of pulmonary hypertension difficult, such that until inhalational use of vasodilators was implemented in the 1990's the disease was regarded untreatable [21]. Ideally, inhaled vasodilators only reach ventilated areas of the lung, preserving hypoxic pulmonary vasocon-

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striction in the non-ventilated lung. Increased blood flow to the ventilated lung improves ventilation-perfusion matching ($V_A/Q$) and reduces intrapulmonary shunt. Therefore, inhaled vasodilators may, in addition to selectively dilating pulmonary vessels, increase $PaO_2$ in patients with hypoxemia due to $V_A/Q$ mismatch.

## Inhaled Nitric Oxide (iNO)

The first inhaled vasodilator investigated was nitric oxide (NO), which is gaseous under atmospheric conditions and therefore can be administered via the airway. In 1980, Furchgott and Zawadzki [3] showed that the endothelium is essential for the vasodilator action of acetylcholine. Furchgott concluded that acetylcholine stimulated the endothelial cells to release endothelium-derived relaxing factor. Moncada, Palmer and coworkers identified NO as biologically active form of EDRF [22].

*Endogenous NO: Physiologic effects in the pulmonary vasculature.* NO, which is ubiquitarious in the mammalian body, exerts multiple and diverse biological effects, the most important of which is vasodilation due to smooth muscle relaxation via the cGMP pathway. When released from endothelial cells to the pulmonary vasculature, endogeneously synthezised NO transducts signals to both, intraluminal and subendothelial effector cells. It mediates vasodilation of subendothelial smooth muscle cells. It inhibits fibroblast proliferation and synthesis of growth factors and vasoconstrictors. On the luminal side it further inhibits aggregation of bypassing platelets and endothelial adherence of neutrophils. Further NO-mediated effects include host defense and neuronal signalling. Among the multifaceted effects of NO in pulmonary vascular beds the vasodilatory action is most important for physiological and pathophysiological processes [22–24].

*Inhalation of Exogenous NO*

Similar to endogenous NO, iNO causes relaxation of smooth muscle cells by stimulation of intracellular cGMP formation. After inhalation, the vasodilatory effect of iNO is restricted to the lung, because systemically absorbed, NO is rapidly (within seconds) inactivated by binding to hemoglobin; iNO does not affect basal pulmonary vascular tone [25–27] but may cause selective pulmonary vasodilation and improve gas exchange in animals or humans with pulmonary hypertension and/or hypoxemia due to VA/Q mismatch [for review see 28–32]. Species differences exist with respect to the vasodilatory potency of iNO [7, 33–35]. Except for one study [36], tachyphylaxis was not observed during iNO application [37]. Results from animal studies trying to identify the exact site of action of NO in the lungs are contradictory [38, 39]. In patients with adult respiratory distress syndrome (ARDS), predominant vasodilation occurred at pulmonary veins [40]. iNO does not affect cardiac output [41, 42] and may [43, 44] or may not improve RV function [5, 45]. Reports on inotropic effects are contradictive [17, 46]. Of note, NO has been found in exhaled air of animals [47, 48] and man [49, 50] and autoinhalation of endogenous NO has been postulated. The number of scientific publications on the actions and clinical applications of inhaled nitric oxide (iNO) is abundant and detailed reviews are available [31, 32, 51–55]. Despite the recent approval by the FDA and by the EU indicated for treatment of newborns with hypoxic respiratory failure, potential side effects of inhaled NO are still a concern.

Potential side effects include direct lung injury [56, 57], inhibition of platelet aggregation [58, 59], and methemoglobinemia [30, 60, 61]. Methemoglobin levels of 9.4 and 13.7% have been observed in patients associated with a deficiency in methemoglobin reductase [62, 63]. Methylthionine (1 mg/kg) or methylene blue (4 mg/kg) may be used for treatment [63, 64]. Whether mutagenetic or carcinogenic effects of iNO identified in vitro [65, 66] are of relevance in vivo is still uncertain [67]. Inhaled NO should be restricted to doses below 10 ppm, since efficacy has been shown for concentrations in this range [68]. Monitoring of iNO and $NO_2$ concentrations is mandatory [69, 70]. Furthermore, rebound pulmonary vasoconstriction has been observed after withdrawal of iNO resulting in hypoxemia [57] and life-threatening pulmonary hypertension [62, 71, 72]. In patients with compromised left ventricular (LV) function, iNO may result in acute LV failure and pulmonary edema [73–75], possibly caused by a deleterious increase of LV preload (due to increased pulmonary blood flow). There is a recent discussion on a possible negative inotropic effect of exogenous or endogenous NO. Endogenous NO has been reported to exert negativ inotropic effects in vitro [45]. In contrast, own experimental data do not give evidence for any negative effect of inhaled NO on myocardial contractility in vivo [17]. Inhaled NO has however been associated with an increased incidence of renal failure in ICU patients [76]. Due to these unwanted side effects of inhaled NO there have been considerable efforts to identify a vasodilator void of local and systemic toxicity, that may be inhaled via the airway and exerts selective pulmonary vasodilation.

## Inhaled Prostacyclin (PGI2)

At present, various prostanoids are under experimental and clinical investigation for inhalational use. This review will focus on pharmacology, cardiopulmonary effects, clinical administration, dosing, and potential side effects of the various analogues of prostacyclin ($PGI_2$), as there are epoprostenol (Flolan™, Glaxo-Wellcome Operations, Dartford-Kent, UK), iloprost-trometamol (Ilomedin™, Schering, Berlin, Germany), beraprost-sodium (Beraprost™, United Therapeutics, Chicago, Ill., USA) and uniprost (Remodulin™, United Therapeutics).

*Basic Pharmacology and Physiology*

Prostacyclin ($PGI_2$) is synthesized in endothelial cells from arachidonic acid and causes both potent relaxation of smooth muscle cells and inhibition of platelet aggregation [77]. These effects are elicited by a receptor-mediated increase of intracellular cAMP. The human $PGI_2$ receptor has recently been characterized [78]. Its familiar pharmacology, rapid onset of action, short half-life (2–3 min) and its lack of known toxicity make $PGI_2$ an attractive compound for inhalational therapy [79, 80].

*Experimental Data*

Selective pulmonary vasodilation upon nebulization of $PGI_2$ in the experimental setup was first demonstrated in 1993 by our group in a model of hypoxic pulmonary vasoconstriction [4, 5] and confirmed by a case report in 3 ARDS patients in the same year [81]. Since then, pulmonary vasodilation, improved RV function, and/or an improvement of gas exchange have been reported after inhalation of $PGI_2$ in various experimental models [82] including chronic hypoxic pulmonary vasoconstriction [83]. Similar to iNO, no or not much of a pulmonary vasodilation has been observed with inhaled $PGI_2$ in pulmonary hypertension induced by pulmonary microembolism [6] or the thromboxane analogue U46619 [7]. Formerly, the improvement of RV function had been attributed to a reduction in RV afterload. New data from our group suggest an intrinsic load-independent positive inotropic effect of the $PGI_2$ analogues epoprostenol and iloprost following intravenous administration [18, 19] and following inhalation, as well [17]. Effects are assumed to be mediated via an increase in cyclic adenosine monophosphate levels [18]. In combination with inhaled NO synergistic effects on pulmonary hemodynamics were observed [84], as well as in combination with phosphodiesterase inhibitors [85, 86]. In contrast to inhaled NO, selectivity of inhaled $PGI_2$ for ventilated lung regions could however not be increased by intravenous almitrine [87].

*Clinical Applications*

There have been several initial case reports on the efficacy of inhaled $PGI_2$ in three patients with ARDS, where a decrease of PAP and intrapulmonary shunt, and an increase of $PaO_2$ were observed [81], and others (mainly infants) which displayed either selective pulmonary vasodilation and/or improved gas exchange during inhalation of $PGI_2$ [88–91]. More recent reports give evidence for the efficacy of $PGI_2$ in cardiac surgical patients with postoperative sepsis [92], with intraoperative right heart failure, with pneumonia in absence of preexisting lung disease [93], in children with secondary pulmonary hypertension due to congenital heart disease [94], and in lung transplant recipients with allograft failure where $PGI_2$ aerosol was given instead of inhaled NO [95]. If both substances are combined during the lung transplant procedure, synergistic effects may be observed [96]. Like reported in experimental studies, combination of $PGI_2$ with the phosphodiesterase inhibitor sildenafil also was associated with a more pronounced effect than $PGI_2$ alone [97]. Effects of $PGI_2$ in pneumonia seem to be related to coexisting interstitial lung disease [93]. Effects in ARDS may relate to the fact, if ARDS is consequence to a primary or secondary lung damage [98].

*Administration and Dosing*

$PGI_2$ has to be aerosolized prior to administration. Both, jet nebulizers [81, 93] and ultrasonic nebulizers [13, 90, 91] have been used for this purpose. Jet nebulizers are driven by a supplementary gas supply, which must be considered when setting the respiratory minute volume on the ventilator. Especially in pressure-controlled ventilation modes which may often be indicated in neonates or ARDS patients this may require a considerable reduction of ventilator pressure to maintain inspiratory pressure unchanged. Sometimes only the standard nebulizing device of a normal ventilator will be available [99]. Ultrasonic nebulizers tend to be bulky and more expensive than jet nebulizers [100]. However, they showed to deliver aerosols which are assumed to reach the alveolar region after inhalation [13] even with pressure-controlled mode and infant ventilator settings. Nebulization time even may be reduced due to a more effective areosol production [101]. This is underlined by the fact that no additional gas flow that would increase inspiratory pressure is needed to drive the nebulizer. Thus, ultrasound nebulization may be assumed the technique of choice for safety

and efficacy reasons. Dosing of aerosolized drugs is in principle difficult, because the amount of aerosol actually reaching alveoli depends on both the underlying pathology of the lung and the ventilatory setup [100] and may vary considerably between 0.7% and 15% [100, 102–104]. A considerable amount of aerosol is trapped in the ventilator tubing [13]. Administered $PGI_2$ aerosol doses have to be calculated (1) from the aerosol production rate per time which has to be measured for any specific combination of nebulizer and ventilator [13] and (2) from the concentration of the aerolized $PGI_2$ solution. Administered doses range from 2 to 50 ng/kg/min epoprostenol and from 10 to 300 μg iloprost daily. Definite alveolar deposition only can be verified using fluorescent or radioactive tracers which is not done at the bedside.

*Potential Side Effects*

Endogenous $PGI_2$ has no known toxic effect or toxic metabolites. However, experience with $PGI_2$ as an inhalational agent is limited and few toxicologic data exist. Potential side effects of $PGI_2$ have been reviewed [80] and include coughing, facial flushing, headache, and an increase of airway resistance. Most of these effects are transient and may be negligible in ventilated and sedated patients. However, preceeding clinical evaluation of $PGI_2$ inhalation in humans, experimental evaluation of side-effects of prolonged $PGI_2$ administration was indispensible. Habler and coworkers did not observe cause signs of acute lung toxicity after prolonged inhalation (8 h) of epoprostenol in sheep [9, 10]. Systemic absorption of inhaled $PGI_2$ may occur at high doses and cause a reversible drop of blood pressure [81, 93]. Women may be – at identical doses – more susceptible to systemic hypotension than men [105]. Bleeding due to inhibition of platelet aggregation has not been reported. However, there has been described a platelet aggregation defect following platelet exposition to low $PGI_2$ concentrations in vitro [106] and in vivo [107]. Other authors report a mild jaw pain [108]. However, at present at least three uncontrolled long-term trials have been published, in which iloprost has been repeatedly administered up to more than one year without obvious adverse effects [109].

*Long-Term Effects and Outcome Studies*

Such studies have been performed with intravenous and inhaled analogues of $PGI_2$ predominantly in patients with pulmonary hypertension. Barst and coworkers [110] were the first to report improved survival after intravenous epoprostenol as compared to a conventional therapy for primary pulmonary hypertension in a controlled study. In contrast, two uncontrolled studies in patients observed a lack of efficacy of inhaled iloprost. Schenk and coworkers [111] tried to replace i.v. epoprostenol in 3 patients (NYHA II after 4 years of continuous application) by inhaled iloprost. Even though short-term hemodynamic effects were observed, all patients developed right heart failure and i.v. epoprostenol had to be continued, which could be done successfully. Machherndl and coworkers [112] observed neither an improvement of exercise capacity nor improved pulmonary hemodynamics after an observation period of 10 ± 5 months. In contrast to the above mentioned results there are – however also uncontrolled – clinical trials that show positive long-term effects of oral and inhaled analogues. Olschewski and coworkers [113] investigated 19 patients with progressive right heart failure under maximum conventional therapy. With inhaled iloprost (50–200 μg daily), 15 of 19 survived after 3 months, 8 of which improved according to NHYA class and 7 remained unchanged. In 12 patients data were available after the 3-month observation time and showed significant improvement in hemodynamics and exercise capacity. Similar improvements were reported in patients with pulmonary hypertension secondary to pulmonary fibrosis. [113] Hoeper and coworkers [114] report in 24 patients with primary pulmonary hypertension improvements in pulmonary hemodynamics and exercise capacity after a daily dose of 100–150 μg inhaled Iloprost over a period of at least one year.

## Conclusion

There is convincing evidence that inhaled vasodilators are effective in selectively dilating pulmonary vessels and improving gas exchange with low risk of deleterious side-effects in patients with pulmonary pathology. In this regard, inhaled vasodilators are clearly superior to systemic vasodilators. NO has been approved for treatment of newborns with hypoxic respiratory failure. $PGI_2$ might improve survival and quality of life in primary pulmonary hypertension. A controlled multicenter outcome study to evaluate the clinical benefit of inhaled $PGI_2$ in patients with pulmonary hypertension is under way and preliminary data suggest that patients may significantly benefit from this treatment. Inhaled prostanoids are an excellent example, how a therapeutic concept, which originally was developed and tested in the animal laboratory setting, may finally reach clinical application and improve patient care.

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