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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.

References

1 Pepke-Zaba J, Higenbottam T, Dinh-Xuan A, Wallwork J: Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. Lancet 1991;338:1173–1174.

2 Frostell C, Fratacci MD, Wain J, Jones R, Zapol W: Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 1991;83: 2038–2047.

3 Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373–376.

4 Welte M, Zwissler B, Habazettl H, Messmer K: PGI_2-aerosol versus nitric oxide for selective pulmonary vasodilation in hypoxic pulmonary vasoconstriction. Eur Surg Res 1993;25:329–340.

5 Zwissler B, Welte M, Messmer K: Effects of inhaled prostacyclin as compared with inhaled nitric oxide on right ventricular performance in hypoxic pulmonary vasoconstriction. J Cardiothorac Vasc Anesth 1995;9:283–289.

6 Zwissler B, Welte M, Habler O, Kleen M, Messmer K: Effects of inhaled prostacyclin as compared with inhaled nitric oxide in a canine model of pulmonary microembolism and oleic acid edema. J Cardiothorac Vasc Anesth 1995; 9:634–640.

7 Welte M, Zwissler B, Habler O, Kleen M, Messmer K: Prostacyclin aerosol and inhaled nitric oxide fail to reverse pulmonary vasoconstriction induced by thromboxane analogue in dogs. Acta Physiol Scand 1995;154:395–405.

8 Zwissler B, Rank N, Jänicke U, Schürle B, Welte M, Reichart B, Netz H, Messmer K, Peter K: Selective pulmonary vasodilation by inhaled prostacyclin in a newborn with congenital heart disease and cardiopulmonary bypass. Anesthesiology 1995;82:1512–1516.

9 Habler O, Kleen M, Takenaka S, Leiderer R, Pusch R, Welte M, Zwissler B, Messmer K: Eight hours' inhalation of prostacyclin (PGI_2) in healthy lambs: Effects on tracheal, bronchial, and alveolar morphology. Intensive Care Med 1996;22:1232–1238.

10 Habler O, Kleen M, Zwissler B, Pusch R, Welte M, Vogelmeier C, Kempter B, Krombach F, Messmer K: Inhalation of prostacyclin (PGI_2) for 8 hours does not produce signs of acute pulmonary toxicity in healthy lambs. Intensive Care Med 1996;22:426–433.

11 Pusch R, Habler O, Kleen M, Welte M, Zwissler B, Messmer K: Inhaled sodium nitroprusside. Non-selective reduction of thromboxane analogue-induced pulmonary vasoconstriction in healthy sheep. Eur J Med Res 1995;1:149–152.

12 Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, Briegel J, Welte M, Peter K: Inhaled prostacyclin (PGI_2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 1996;154: 1671–1677.

13 Kemming GI, Kreyling W, Habler O, Merkel M, Kleen M, Welte M, Messmer K, Zwissler B: Aerosol production and aerosol droplet size distribution during mechanical ventilation (IPPV) with a new ultrasonic nebulizer. Eur J Med Res 1996;1:321–327.

14 Kemming GI, Merkel MJ, Schallerer A, Habler OP, Kleen MS, Haller M, Briegel J, Vogelmeier C, Furst H, Reichart B, Zwissler B, and Munich Lung Transplant Group: Inhaled nitric oxide (NO) for the treatment of early allograft failure after lung transplantation. Intensive Care Med 1998;24:1173–1180.

15 Kleen M, Habler O, Hofstetter C, Pusch R, Müller M, Welte M, Zwissler B: Efficacy of inhaled prostanoids in experimental pulmonary hypertension. Crit Care Med 1998;26: 1103–1109.

16 Zwissler B, Kemming G, Merkel M, Wolfram G, Kleen M, Habler O, Haller M, Briegel J: Response to inhaled nitric oxide (NO) is not associated with changes of plasma cGMP levels in patients with acute lung injury. Eur J Med Res 1999;4:463–467.

17 Kemming GI, Kisch-Wedel H, Meisner F, Flondor M, Bruhn S, Koehler K, Kuebler W, Zwissler B: Inhalation of Selective Pulmonary Vasodilators: Effects on Myocardial Contractility. Anesthesiology 2001;95:ASA 2001 Meeting Abstracts Online. www.asa-abstracts.com: P670.

18 Kisch-Wedel H, Meisner F, Kemming G, Flondor M, Bruhn S, Koehler K, Kuebler W, Zwissler B: The increased left ventricular contractility by the prostacyclin analogue epoprostenol is mediated by cyclic adenosine monophosphate (cAMP). Anesthesiology 2001;95:ASA 2001 Meeting Abstracts Online. www.asa-abstracts.com: P614.

19 Kisch-Wedel H, Kemming G, Meisner F, Bruhn S, Koehler K, Flondor M, Kuebler W, Zwissler B: Intravenous Infusion of Prostacyclin (PGI_2) Increases Left Ventricular Contractility in vivo. Eur Surg Res 2001;33:173–173.

20 Manthous CA, Hall JB: Administration of therapeutic aerosols to mechanically ventilated patients. Chest 1994;106:560–571.

21 Higenbottam T, Siddons T: Trials of inhaled iloprost and other new vasodilating prostaglandins. Eur Respir J 2001;17:6–7.

22 Moncada S, Palmer RM, Higgs EA: Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43:109–141.

23 Moncada S: The 1991 Ulf von Euler Lecture. The L-arginine:nitric oxide pathway. Acta Physiol Scand 1992;145:201–227.

24 Leeman M: Effects of endogenous nitric oxide on the pulmonary circulation; in Vincent JL (ed): Yearbook of Intensive Care and Emergency Medicine 1994. Berlin, Springer, 1994, pp 101–107.

25 Winberg P, Lundell BP, Gustafsson LE: Effect of inhaled nitric oxide on raised pulmonary vascular resistance in children with congenital heart disease. Br Heart J 1994;71:282–286.

26 Finer NN, Etches PC, Kamstra B, Tierney AJ, Peliowski A, Ryan CA: Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: Dose response. J Pediatr 1994; 124:302–308.

27 Rich GF, Lowson SM, Johns RA, Daugherty MO, Uncles DR: Inhaled nitric oxide selectively decreases pulmonary vascular resistance without impairing oxygenation during one-lung ventilation in patients undergoing cardiac surgery. Anesthesiology 1994;80:57–62.

28 Zapol WM, Rimar S, Gillis N, Marletta M, Bosken CH: Nitric oxide and the lung. Am J Respir Crit Care Med 1994;149:1375–1380.

29 Puybasset L, Rouby JJ: Inhaled nitric oxide in acute respiratory failure; in Vincent JL (ed): Yearbook of Intensive Care and Emergency Medicine 1995. Berlin, Springer, 1995, pp 331–355.

30 Lunn RJ: Inhaled nitric oxide therapy. Mayo Clin Proc 1995;70:247–255.

31 Zwissler B, Welte M, Messmer K: Inhalation of vasodilatory drugs or gases: Curr Opin Anaesth 1995;8:557–564.

32 Haddad E, Lowson SM, Johns JA, Rich GF: Use of inhaled nitric oxide perioperatively and in intensive care patients. Anesthesiology 2000;92:1821–1825.

33 Tod ML, O'Donnell DC, Gordon JB: Sites of inhaled NO-induced vasodilation during hypoxia and U-46619 infusion in isolated lamb lungs. Am J Physiol 1995;268:1422–1427.

34 Romand JA, Pinsky MR, Firestone L, Zar HA, Lancaster JR: Inhaled nitric oxide partially reverses hypoxic pulmonary vasoconstriction in the dog. J Appl Physiol 1994;76:1350–1355.

35 Tönz M, von Segesser L, Schilling J, Lüscher TF, Noll G, Leskosek B, Turina MI: Treatment of acute pulmonary hypertension with inhaled nitric oxide. Ann Thorac Surg 1994;58:1031–1035.

36 Shah N, Jacob T, Exler R, Morrow S, Ford H, Albanese C, Wiener E, Rowe M, Billiar T, Simmons R, Motoyama E, Nakayama D: Inhaled nitric oxide in congenital diaphragmatic hernia. J Pediatr Surg 1994;29:1010–1015.

37 Rossaint R, Gerlach H, Schmidt-Ruhnke H, Pappert D, Lewandowski K, Steudel W, Falke K: Efficacy of inhaled nitric oxide in patients with severe ARDS. Chest 1995;107:1107–1115.

38 Lindeborg DM, Kavanagh BP, Van Meurs K, Pearl RG: Inhaled nitric oxide does not alter the longitudinal distribution of pulmonary vascular resistance. J Appl Physiol 1995;78:341–348.

39 Koizumi T, Gupta R, Banerjee M, Newman JH: Changes in pulmonary vascular tone during exercise. Effects of nitric oxide (NO) synthase inhibition, L-arginine infusion, and NO inhalation. J Clin Invest 1994;94:2275–2282.

40 Benzing A, Geiger K: Inhaled nitric oxide lowers pulmonary capillary pressure and changes longitudinal distribution of pulmonary vascular resistance in patients with acute lung injury. Acta Anaesthesiol Scand 1994;38:640–645.

41 Rich GF, Murphy GD, Jr, Roos CM, Johns RA: Inhaled nitric oxide: Selective pulmonary vasodilation in cardiac surgical patients. Anesthesiology 1993;78:1028–1035.
42 Sitbon O, Brenot F, Denjean A, Bergeron A, Parent F, Azarian R, Herve P, Raffestin B, Simonneau G: Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension: A dose-response study and comparison with prostacyclin. Am J Respir Crit Care Med 1995;151:384–389.
43 Rossaint R, Slama K, Steudel W, Gerlach H, Pappert D, Veit S, Falke K: Effects of inhaled nitric oxide on right ventricular function in severe acute respiratory distress syndrome. Intensive Care Med 1995;21:197–203.
44 Gatecel C, Mebazaa A, Kong R, Guinard N, Kermarrec N, Matéo J, Payen D: Inhaled nitric oxide improves hepatic tissue oxygenation in right ventricular failure: Value of hepatic venous oxygen saturation monitoring. Anesthesiology 1995;82:588–590.
45 Snow DJ, Gray SJ, Ghosh S, Foubert L, Oduro A, Higenbottam TW, Wells FC, Latimer RD: Inhaled nitric oxide in patients with normal and increase pulmonary vascular resistance after cardiac surgery. Br J Anaesth 1994;72:185–189.
46 Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL: Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 1992;257:387–389.
47 Persson MG, Lönnqvist PA, Gustafsson LE: Positive end-expiratory pressure ventilation elicits increases in endogenously formed nitric oxide as detected in air exhaled by rabbits. Anesthesiology 1995;82:969–974.
48 Stewart TE, Valenza F, Ribeiro SP, Wener AD, Volgyesi G, Mullen JB, Slutsky AS: Increased nitric oxide in exhaled gas as an early marker of lung inflammation in a model of sepsis. Am J Respir Crit Care Med 1995;151:713–718.
49 Gerlach H, Rossaint R, Pappert D, Knorr M, Falke KJ: Autoinhalation of nitric oxide after endogenous synthesis in nasopharynx. Lancet 1994;343:518–519.
50 Trolin G, Andén T, Hedenstierna G: Nitric oxide (NO) in expired air at rest and during exercise. Acta Physiol Scand 1994;151:159–163.
51 Zapol WM, Hurford WE: Inhaled nitric oxide: State of the art; in Vincent JL (ed): Yearbook of Intensive Care and Emergency Medicine 1995. Berlin, Springer, 1995, pp 323–330.
52 Fratacci MD, Frostell CG, Chen TY, Wain JC, Robinson DR, Zapol WM: Inhaled Nitric oxide. Anesthesiology 1991;75:990–999.
53 Eisenmenger A, Lorber C, Roder G, Klimscha W, Germann P: Inhaled nitric oxide (NO): A concise review. Acta Anaesthesiol Scand Suppl 1998;42:240–243.
54 Frostell CG, Zapol WM: Inhaled nitric oxide, clinical rationale and applications. Adv Pharmacol 1995;341:439–456.
55 Zapol WM: Inhaled nitric oxide. Acta Anaesthesiol Scand Suppl 1996;109:81–93.
56 Gaston B, Drazen JM, Loscalzo J, Stamler JS: The biology of nitrogen oxides in the airways. Am J Respir Crit Care Med 1994;149:538–551.
57 Frostell CG: Acute lung injury and inhaled NO. The reduction of pulmonary capillary pressure has implications for lung fluid balance. Acta Anaesthesiol Scand 1994;38:623–624.
58 Högman M, Frostell C, Arnberg H, Hedenstierna G: Bleeding time prolongation and NO inhalation. Lancet 1993;341:1664–1665.
59 Högman M, Frostell C, Arnberg H, Sandhagen B, Hedenstierna G: Prolonged bleeding time during nitric oxide inhalation in the rabbit. Acta Physiol Scand 1994;151:125–129.
60 Wessel DL, Adatia I, Thompson JE, Hickey PR: Delivery and monitoring of inhaled nitric oxide in patients with pulmonary hypertension. Crit Care Med 1994;22:930–938.
61 Edwards AD: The pharmacology of inhaled nitric oxide. Arch Dis Child: Fetal and Neonatal Edition 1995;72:F127–F130.
62 Adatia I, Lillehei C, Arnold JH, Thompson JE, Palazzo R, Fackler JC, Wessel DL: Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. Ann Thorac Surg 1994;57:1311–1318.
63 Lönnqvist PA, Winberg P, Lundell B, Selldén H, Olsson GL: Inhaled nitric oxide in neonates and children with pulmonary hypertension. Acta Paediatr 1994;83:1132–1136.
64 Young JD, Dyar OJ, Xiong L, Zhang J, Gavaghan D: Effect of methylene blue on the vasodilator action of inhaled nitric oxide in hypoxic sheep. Br J Anaesth 1994;73:511–516.
65 Nguyen T, Brunson D, Crespi CL, Penman BW, Wishnok JS, Tannenbaum SR: DNA damage and mutation in human cells exposed to nitric oxide in vitro. Proc Natl Acad Sci USA 1992;89:3030–3034.
66 Routledge MN, Wink DA, Keefer LK, Dipple A: Mutations induced by saturated aqueous nitric oxide in the pSP189 supF gene in human Ad293 and E coli MBM7070 cells. Carcinogenesis 1993;14:1251–1254.
67 Ichinose F, Adrie C, Hurford WE, Zapol WM: Prolonged pulmonary vasodilator action of inhaled nitric oxide by Zaprinast in awake lambs. J Appl Physiol 1995;78:1288–1295.
68 Gerlach H, Rossaint R, Pappert D, Falke KJ: Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Eur J Clin Invest 1993;23:499–502.
69 Francoe M, Troncy E, Blaise G: Inhaled nitric oxide: Technical aspects of administration and monitoring. Crit Care Med 1998;26:782–796.
70 Miller OI, Celermajer DS, Deanfield JE, Macrae DJ: Guidelines for the safe administration of inhaled nitric oxide. Arch Dis Child 1994;70:F47–F49.
71 Ivy DD, Wiggins JW, Badesch DB, Kinsella JP, Kelminson LL, Abman SH: Nitric oxide and prostacyclin treatment of an infant with primary pulmonary hypertension. Am J Cardiol 1994;74:414–416.
72 Beghetti M, Habre W, Friedli B, Berner M: Continuous low dose inhaled nitric oxide for treatment of severe pulmonary hypertension after cardiac surgery in paediatric patients. Br Heart J 1995;73:65–68.
73 Loh E, Stamler JS, Hare JM, Loscalzo J, Colucci WS: Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. Circulation 1994;90:2780–2785.
74 Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW, Fifer MA: Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24:982–988.
75 Bocchi EA, Bacal F, Auler JOC, Jr, De Carvalho Carmone MJ, Bellotti G, Pileggi F: Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. Am J Cardiol 1994;74:70–72.
76 Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, Davis K, Hyers TM, Papadakos P: Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26:15–23.
77 Vane JR, Botting RM: Pharmacodynamic profile of prostacyclin. Am J Cardiol 1995;75:3A–10A.
78 Katsuyama M, Sugimoto Y, Namba T, Irie A, Negeshi M, Narumiya S, Ichikawa A: Cloning and expression of a cDNA for the human prostacyclin receptor. FEBS Lett 1994;344:74–78.
79 Royston D: Inhalational agents for pulmonary hypertension. Lancet 1993;342:941–942.
80 Wetzel RC: Aerosolized prostacyclin. In search of the ideal pulmonary vasodilator. Anesthesiology 1995;82:1315–1317.
81 Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W: Aerosolised prostacyclin in adult respiratory distress syndrome. Lancet 1993;342:961–962.
82 Zobel G, Dacar D, Rödl S, Friehs I: Inhaled nitric oxide (NO) versus inhaled prostacyclin (PGI_2) in acute respiratory failure with pulmonary hypertension in piglets. Clinical Intensive Care 1995;6:18–18.
83 Abe Y, Tatsumi K, Sugito K, Ikeda Y, Kimura H, Kuriyama T: Effects of inhaled prostacyclin analogue on chronic hypoxic pulmonary hypertension. J Cardiovasc Pharmacol 2001;37:239–251.
84 Hill LL, Pearl RG: Combined inhaled nitric oxide and inhaled prostacyclin during experimental chronic pulmonary hypertension. J Appl Physiol 1999;86:1160–1164.
85 Schermuly RT, Ghofrani HA, Enke B, Weissmann N, Grimminger F, Seeger W, Schudt C, Walmrath D: Low-dose systemic phosphodiesterase inhibitors amplify the pulmonary vasodilatory response to inhaled prostacyclin in experimental pulmonary hypertension. Am J Respir Crit Care Med 1999;160:1500–1506.

86 Schermuly RT, Roehl A, Weissmann N, Ghofrani HA, Schudt C, Tenor H, Grimminger F, Seeger W, Walmrath D: Subthreshold doses of specific phosphodiesterase type 3 and 4 inhibitors enhance the pulmonary vasodilatory response to nebulized prostacyclin with improvement in gas exchange. J Pharmacol Exp Ther 2000;292:512–520.
87 Dembinski R, Max M, Lopez F, Kuhlen R, Kurth R, Rossaint R: Effect of inhaled prostacyclin in combination with almitrine on ventilation-perfusion distributions in experimental lung injury. Anesthesiology 2001;94:461–467.
88 Bindl L, Fahnenstich H, Peukert U: Aerosolised prostacyclin for pulmonary hypertension in neonates. Arch Dis Child: Fetal and Neonatal Edition 1994;71:F214–F216.
89 Bein T, Pfeifer M, Riegger GAJ, Taeger K: Continuous intraarterial measurement of oxygenation during aerosolized prostacyclin administration in severe respiratory failure. N Engl J Med 1994;331:335–336.
90 Santak B, Schreiber M, Kuen P, Lang D, Radermacher P: Prostacyclin aerosol in an infant with pulmonary hypertension. Eur J Pediatr 1995;154:233–235.
91 Pappert D, Busch T, Gerlach H, Lewandowski K, Radermacher P, Rossaint R: Aerosolized prostacyclin versus inhaled nitric oxide in children with severe acute respiratory distress syndrome. Anesthesiology 1995;82:1507–1511.
92 Marggraf G, Balzereit A, Schönfelder B, Doetsch N, Zerkowski HR, Reidemeister JC: Hämodynamische Effekte von Epoprostenol als Aerosol zur selektiven pulmonalen Vasodilatation versus intravenöser Applikation nach kardiochirurgischer Intervention. Anaesthesist 1994;43 (suppl 1):209–209.
93 Walmrath D, Schneider T, Pilch J, Schermuly R, Grimminger F, Seeger W: Effects of aerosolized prostacyclin in severe pneumonia: Impact of fibrosis. Am J Respir Crit Care Med 1995; 151:724–730.
94 Rimensberger PC, Spahr-Schopfer I, Berner M, Jaeggi E, Kalangos A, Friedli B, Beghetti M: Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: Vasodilator capacity and cellular mechanisms. Circulation 2001;103:544–548.
95 Fiser SM, Cope JT, Kron IL, Kaza AK, Long SM, Kern JA, Tribble CG: Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide for patients with reperfusion injury after lung transplantation. J Thorac Cardiovasc Surg 2001;121:981–982.
96 Rocca GD, Coccia C, Pompei L, Ruberto F, Venuta F, De-Giacomo T, Pietropaoli P: Hemodynamic and oxygenation changes of combined therapy with inhaled nitric oxide and inhaled aerosolized prostacyclin. J Cardiothorac Vasc Anesth 2001;15:224–227.
97 Wilkens H, Guth A, Konig J, Forestier N, Cremers B, Hennen B, Bohm M, Sybrecht GW: Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. Circulation 2001;104:1218–1222.
98 Domenighetti G, Stricker H, Waldispuehl B: Nebulized prostacyclin (PGI2) in acute respiratory distress syndrome: Impact of primary (pulmonary injury) and secondary (extrapulmonary injury) disease on gas exchange response. Crit Care Med 2001;29:57–62.
99 Bein T, Metz C, Keyl C, Sendtner E, Pfeifer M: Cardiovascular and pulmonary effects of aerosolized prostacyclin administration in severe respiratory failure using a ventilator nebulization system. J Cardiovasc Pharmacol 1996;27:583–586.
100 Lloyd TC, Cooper JA: Effect of diaphragm contraction on canine heart and pericardium. J Appl Physiol 1983;54:1261–1268.
101 Gessler T, Schmehl T, Hoeper MM, Rose F, Ghofrani HA, Olschewski H, Grimminger F, Seeger W: Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur Respir J 2001;17:14–19.
102 Thomas SHL, O'Doherty MJ, Fidler HM, Page CJ, Treacher DF, O'Nunan T: Pulmonary deposition of a nebulised aerosol during mechanical ventilation. Thorax 1993;48: 154–159.
103 Thomas SHL, Harvey C, Page CJ, Treacher DF, O'Doherty MJ: Aerosol deposition in mechanically ventilated patients. Am J Respir Crit Care Med 1994;150:1474–1475.
104 O'Riordan TG, Palmer LB, Smaldone GC: Aerosol deposition in mechanically ventilated patients. Optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149:214–219.
105 Szczeklik A, Gryglewski RJ, Nizankowska E, Nizankowski R, Musial J: Pulmonary and anti-platelet effects of intravenous and inhaled prostacyclin in man. Prostaglandins 1978;16:651–660.
106 van Heerden P, Gibbs NM, Michalopoulos N: Effect of low concentrations of prostacyclin on platelet function in vitro. Anaesth Intensive Care 1997;25:343–346.
107 van Heerden PV: Systemic levels of 6-keto-prostaglandin F-1 alpha following administration of inhaled aerosolized prostacyclin. Anaesth Intensive Care 1997;25:701–703.
108 Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, Hamm M, Fabel H: Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med 2000;342:1866–1870.
109 Machherndl S, Kneussl M, Baumgartner H, Schneider B, Petkov V, Schenk P, Lang IM: Long-term treatment of pulmonary hypertension with aerosolized iloprost. Eur Respir J 2001;17:8–13.
110 Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jöbsis MM, Blackburn SD, Jr, Shortino D, Crow JW: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996; 334:296–301.
111 Schenk P, Petkov V, Madl C, Kramer L, Kneussl M, Ziesche R, Lang I: Aerosolized iloprost therapy could not replace long-term IV epoprostenol (prostacyclin) administration in severe pulmonary hypertension. Chest 2001;119:296–300.
112 Machherndl S, Kneussl M, Baumgartner H, Schneider B, Petkov V, Schenk P, Lang IM: Long-term treatment of pulmonary hypertension with aerosolized iloprost. Eur Respir J 2001;17:8–13.
113 Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, Seeger W: [Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to pulmonary fibrosis]. Pneumologie 2000;54:133–142.
114 Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J: [Long-term treatment of primary pulmonary hypertension with inhaled iloprost]. Pneumologie 2001;55:38–43.