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Long-term inhalation with evaluated low doses of nitric oxide for selective improvement of oxygenation in patients with adult respiratory distress syndrome

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Abstract. *Objective:* To evaluate the lowest dose of inhaled nitric oxide (NO) in patients with adult respiratory distress syndrome (ARDS), which is able to improve arterial oxygenation more than 30% compared to baseline data.
Design: Prospective, clinical study.
Setting: Anesthesiological ICU in a university hospital.
Patients: 3 consecutive patients with severe ARDS according to clinical and radiological signs.
Interventions: Pressure-controlled ventilation with positive endexpiratory pressure of 8–12 cm H_2O. Inhalation of NO was performed with a blender system and a Servo 300 ventilator. The lowest effective NO dose was defined by titrating the inspiratory NO dose until reaching a 30% improvement of PaO_2/FiO_2. This dose was used for the following continuous long-term NO inhalation; controls of efficacy by investigation of hemodynamics and blood gas exchange were performed initially and 2 times per patient after intervals of 3–5 days.
Measurements and results: Initial NO concentrations were found to be effective at 60, 100, and 230 parts per billion (ppb). In all measurements, arterial oxygenation was found to be elevated by NO inhalation with the initially evaluated dose compared to baseline data; in parallel, the venous admixture ($\dot{Q}_{va}/\dot{Q}_t$) was reduced. The O_2 delivery increased, although O_2 consumption and hemodynamics did not change. In 1 patient, interruption of NO inhalation caused remarkable increase of pulmonary resistance.
Conclusions: The improvement of oxygenation by NO inhalation in ARDS does not require reduction of pulmonary resistance and can be performed using low doses in the ppb range, which has to be considered as probably non-toxic.

Key words: Adult respiratory distress syndrome – ARDS – Nitric oxide – Endothelium-derived relaxing factor – EDRF – Inhalation

The adult respiratory distress syndrome (ARDS), a disorder described by Ashbaugh et al. with a mortality of approximately 60–70% [1], is characterized by a heterogeneous deterioration of both alveolar ventilation and pulmonary perfusion due to edema and local inflammation, associated with gas space collapse, vasoconstriction and/or vascular obliteration [2, 3]. Enhancement of intrapulmonary right-to-left shunt results in increasing requirements of ventilatory pressures, volumes, and inspiratory oxygen fractions (FiO_2), which again contribute to further impairment of the disease [4, 5]. Reduction of pulmonary vascular resistance by vasodilating drugs was shown to exert a beneficial effect in ARDS, although the intrapulmonary shunt increases by this treatment [6]. The poor prognosis, however, often demands the use of additional methods like extracorporeal respiratory support in specialized departments or hospitals [7, 8].

The vascular endothelium, which was shown to play an active role in host response [9], also contributes to the regulation of vascular resistance [10]. A factor, which is synthesized and expressed by endothelial cells and induces vasodilation, described as *e*ndothelium-*d*erived *r*elaxing *f*actor (EDRF) [11], was demonstrated to be equivalent to nitric oxide (NO), synthesized from L-arginine by the enzyme NO-synthase [12–14]. NO binds to the enzyme guanylate cyclase in smooth muscle cells, enhances synthesis of cyclic guanosine monophosphate (cGMP), and, thus, exerts a relaxing effect by the induction of dephosphorylation of myosin light chain filaments [15].

The question arose if inhaled NO might be able to induce selective vasodilation in the pulmonary vessels without influencing the systemic circulation, since binding of NO to hemoglobin inactivates the molecule within seconds. There is little evidence of toxicity of inhaled NO

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when the concentration is below 50 parts per million (ppm), whereas inhaling high concentrations can be lethal because NO causes severe acute pulmonary edema and methemoglobinemia [16]. Former toxicological studies demonstrated that animals, which had breathed the gas in concentrations up to 40 ppm for 6 days to 6 months, showed no evidence of any toxic effect [17, 18].

In recent studies, the inhalation of NO, using doses between 5 and 80 ppm, was, indeed, demonstrated to reduce pulmonary hypertension in sheep [19], adult patients [20], and newborns [21, 22]. Studies from our group showed that, in addition to a reduction of pulmonary artery pressure (PAP), inhalation of 18 or 36 ppm NO in patients with severe ARDS reduces the intrapulmonary right-to-left shunt and, hence, improves arterial oxygenation by a redistribution of pulmonary blood flow towards areas with nearly normal ventilation/perfusion ratios, probably since the gas NO reaches preferably ventilated alveoli [23]. For evaluation of the lowest effective doses of inhaled NO concerning improvement of arterial oxygenation, we performed the following study in 3 patients with severe ARDS.

Materials and methods

The following studies were done with approval by the hospital ethics committee for human studies; informed consent was obtained from relatives after describing the nature and purpose of the study. The 3 patients were transferred from other hospitals to our unit for supportive therapy of severe ARDS, such as NO inhalation and/or extracorporeal bypass techniques, because they had not responded to conventional therapy and were thought unlikely to survive. None of the patients were treated with NO before. The catastrophic events which had led to the development of ARDS as well as additional patient data initially after transfer are shown in Table 1. Diagnosis of severe ARDS was obtained by clinical and radiological signs [1, 3]; severity scoring was performed as described by Murray et al. [24]. Mechanical ventilation was performed in the pressure-controlled mode of Servo ventilators (Types Servo 900C and Servo 300, Siemens, Lund, Sweden) via a tracheostomy tube with positive endexpiratory pressures (PEEP) in a range of 8 to 12 cm H_2O; fractions of inspired oxygen (FiO_2) were between 0.6 and 1.0. In all 3 patients, pulmonary gas exchange was supported with veno-venous extracorporeal membrane oxygenation (vv-ECMO).

For long-term inhalation of NO, a low-flow blender system was used for the first 2 patients, mixing NO at a primary dose of 2400 ppm in N_2 with pure N_2 before introduction into the gas inlet of the ventilator (Servo 900C). The third patient was continuously ventilated with a new prototype of the Servo 300 ventilator, which was equipped by the company with an inbuilt computerized NO delivery system, consisting of an additional digital-controlled NO valve. Depending on the primary NO/N_2 gas (100; 1000; 10000 ppm NO), this system was able to deliver inspiratory NO concentrations from 10 parts per billion (ppb) up to 100 ppm. This ventilator was also used in all 3 patients for the evaluation of the NO dose (see below), which was performed at FiO_2 of 1.0 in the first 12 h after transfer to our unit. In- and expiratory concentrations (in the breathing circuit, near to the patient), as well as room air NO/NO_2-concentrations were measured based on chemiluminescence (Type AL 700, ECO Physics, Duernten, Switzerland) with a sensitivity up to 1 ppb; the chemiluminometer was calibrated before and after each measurement with special calibration gases according to the highest available NIST standards (*N*ational *I*nstitute of *S*tandards), which guarantee deviations of the declared NO concentration less than 0.5%. The diluted NO mixtures (100; 1000; 10000 ppm) were produced by the delivering company by special gas blender systems based on continuous mass flow control which are calibrated with a volumetric standard according to the above mentioned NIST standard.

For the determination of the efficacy of NO in order to improve oxygenation, the NO blender system was adjusted to 0, 25, 50, 100, 250, 500 and 1000 ppb NO according to an initial calibration of the Servo 300 ventilator at the gas inlet. After 10 min for each dose, standard hemodynamics and blood gas exchanges were tested utilizing ECG, an arterial and a pulmonary artery catheter, and a new continuous intra-arterial blood gas monitoring system for pH, PaO_2, and $PaCO_2$ (Type PB 3300, Puritan-Bennett Corp., Carlsbad, CA); the system was calibrated by taking arterial blood samples before and after each measurement. The pulmonary artery catheter was used to calculate venous admixture ($\dot{Q}_{va}/\dot{Q}_t$), oxygen delivery ($\dot{D}O_2$, as a product of cardiac output and arterial oxygen content), and extrapulmonary oxygen consumption ($\dot{V}O_2$, by the reverse Fick equation, i.e. as a product of cardiac output and arteriovenous oxygen difference). Hemodynamic data such as heart rate, arterial, pulmonary and central venous pressure were also continuously monitored (CMS Patient Monitoring System, Hewlett Packard Co., Bad Homburg, Germany). Afterwards, the "lowest effective NO dose" was arbitrarily defined as the lowest NO concentration measured in the inspiratory limb, which was able to increase the PaO_2/FiO_2 at least 30% compared to the baseline data; the pulmonary artery pressure was not taken into consideration. For the following therapeutic use, inhalation was continued using the lowest effective dose which was registered by the initial study (Table 1). After 3–5 days, the efficacy of NO inhalation was controlled: NO inhalation was interrupted for 30 min to obtain new baseline data; afterwards, NO was restarted, and data were measured after another 15 min. During all measurements, ventilator settings were kept constant.

For statistical analysis, data from the end of each 15 min period were taken, and a Wilcoxon rank sum test was performed to compare the values during NO inhalation with initial baseline data; results were confirmed by a randomisation test for correlating samples after repeated measurements. p-values less than 0.01 were regarded as significant.

Table 1. Patients' data

Patient	1	2	3
Age (years)	20	35	13
Etiology of ARDS	Polytrauma	Pneumonia	Aspiration
Murray score[a]	3.5	3.0	3.75
p_aO_2/F_iO_2 (mmHg)[a]	48	84	42
Mechanical ventilation (days)	45	21	47
vv-ECMO (days)	26	9	21
NO-inhalation (days)	12	9	13
Effective NO dose (ppb)[b]	230	100	60

[a] On arrival
[b] Measured in the inspiratory limb
ARDS, Adult respiratory distress syndrome; vv-ECMO, veno-venous extracorporeal membrane oxygenation; NO, nitric oxide; ppb, part per billion

Results

Doses of NO during inhalation periods could always be held in a stable range, with deviations less than 10%, and without reducing FiO_2 more than 1.5%. The use of the new ventilator equipped with the computerized NO application system enabled us to continue inhalation even during spontaneous ventilation in a pressure supported mode without staggering inhalatory NO concentrations. Environmental NO concentrations were between 2 and 130 ppb, depending on weather conditions; no NO was detectable in the inspiratory limb of the ventilator at FiO_2 1.0 during non-inhalation periods. During and after NO inhalation, no methemoglobinemia, deterioration

of systemic circulation and organ function, or any other possible side effect could be registered.

Data from the initial NO dose evaluation are shown in Fig. 1; as demonstrated, the arbitrary limit of 30% for the relative increase in PaO_2 at FiO_2 1.0 compared to non-inhalation data was reached at blender positions of 250 (patient 1), 100 (patient 2), and 50 ppb NO (patient 3). The corresponding, measured NO concentrations in the inspiratory limb near to the patient were 230, 100, and 60 ppb NO, respectively, defined as the lowest effective NO dose for the following long-term inhalation. In all 9 determinations (3 measurements per patient, with time intervals of at least 3 days) during NO inhalation at the initially determined lowest effective dose, arterial/alveolar oxygen ratio ($a/A\text{-}O_2$) increased compared to baseline data, associated with a reduction of venous admixture ($\dot{Q}_{va}/\dot{Q}_t$) (Fig. 2); the alterations were significant. During the whole NO inhalation therapy, the effect on oxygenation had no tendency to decrease, but rather seemed to enhance, expressed as increasing differences of $a/A\text{-}O_2$ and $\dot{Q}_{va}/\dot{Q}_t$ between NO and control periods. In contrast, hemodynamic parameters such as mean systemic arterial pressure (SAP), mean pulmonary artery pressure (PAP), cardiac output (CO), and heart rate (HR) did not change significantly (Figs. 3 and 4), although the mean PAP decreased clearly, when baseline data were above 45 mmHg (Fig. 3). Calculation of oxygen parameters demonstrated that the O_2 delivery ($\dot{D}O_2$) increased significantly, whereas the calculated consumption ($\dot{V}O_2$),

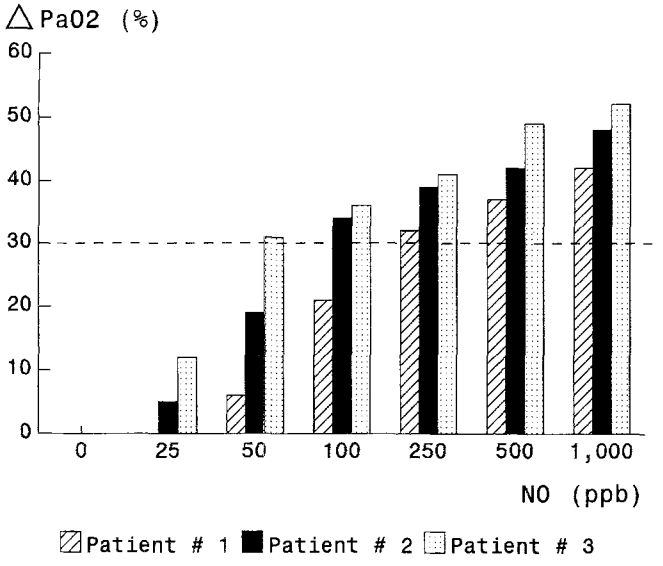

Fig. 1. Effect of inhaled nitric oxide (*x-axis*: NO dose in parts per billion (ppb) according to the blender position of the ventilator after the initial calibration) on arterial oxygenation (*y-axis*: relative increase of PaO_2, measured at $FiO_2 = 1.0$, expressed as percent increase compared to the value at 0 ppb NO) during the initial NO dose evaluation in 3 patients with severe ARDS. The *horizontal line* marks the arbitrary limit of 30% increase. As demonstrated, the 3 patients present an increase of PaO_2/FiO_2 of more than 30% at blender positions of 50 (patient #3), 100 (patient #2), and 250 ppb NO (patient #1), corresponding to measured inspiratory NO concentrations of 60, 100, and 230 ppb, respectively, which were defined as lowest effective NO dose for the following long-term inhalation therapy

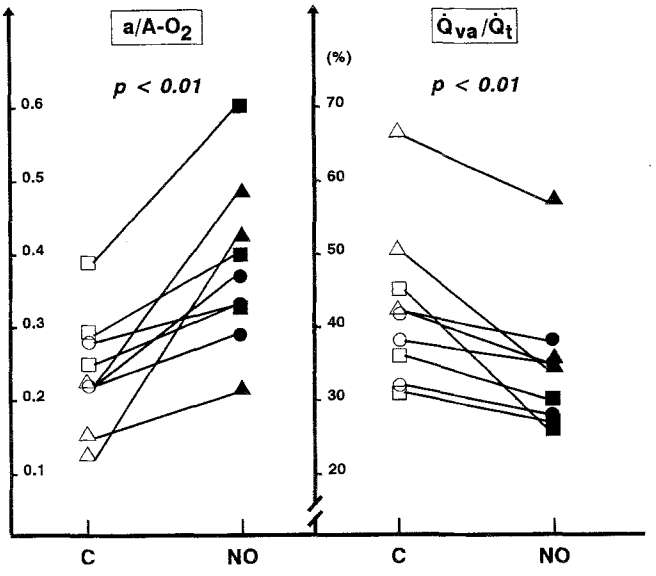

Fig. 2. Arterial/alveolar-oxygen ratio ($a/A\text{-}O_2$, *left side*) and venous admixture ($\dot{Q}_{va}/\dot{Q}_t$, *right side*) in the 3 patients with ARDS during inhalation of nitric oxide (NO, *closed symbols*) in a dose of 230 (patient 1, *circle*), 100 (patient 2, *square*), and 60 ppb (patient 3, *triangle*), measured in the inspiratory limb of the breathing circuit, near to the patient, compared to baseline data (control = *C*, *open symbols*) during non-inhalation periods. Each point represents 1 determination, 3 determinations per patient

which gives insight into the perfusion state of peripheral organs and tissues except the lung, only enhanced in 2 cases, when control data were low (Fig. 5), pointing on an insufficient tissue oxygenation during NO-free ventilation periods in these cases; the overall differences were not significant.

When, with respect to regularly performed arterial blood gas controls, FiO_2 was ready to be decreased below 0.5 during the treatment of the patients, NO inhala-

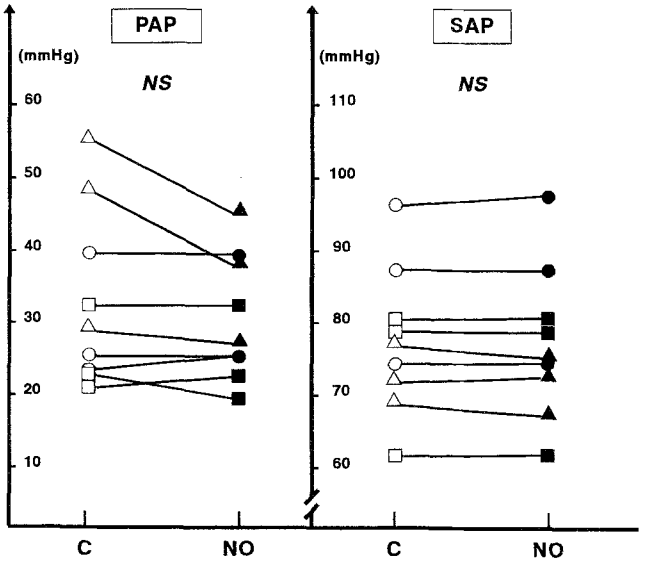

Fig. 3. Mean pulmonary artery pressure (PAP, *left side*) and mean systemic artery pressure (SAP, *right side*) during NO-inhalation and control periods (see also Fig. 2); *NS* = not significant

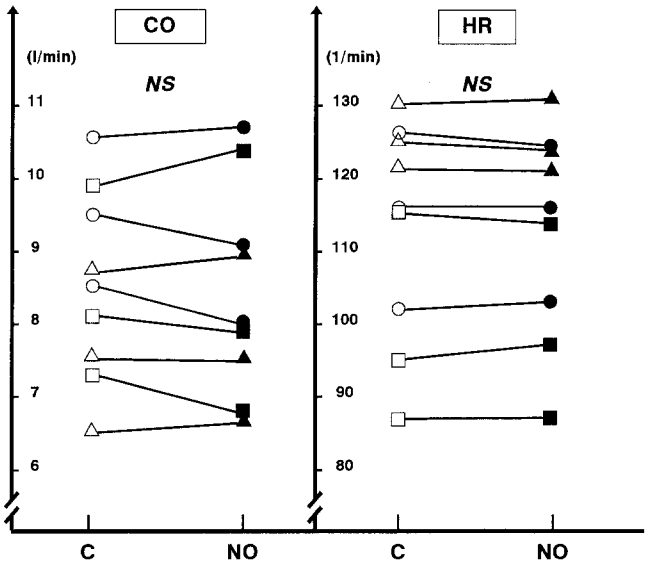

Fig. 4. Cardiac output (*CO, left side*) and heart rate (*HR, right side*) during NO-inhalation and control periods (see also Fig. 2); *NS* = not significant

tion was planned to be terminated. In all 3 patients, however, it was found that NO inhalation could not be stopped without clinically relevant decreases of PaO_2. In 1 patient, this phenomenon went parallel with marked increases of the PAP in the 2 control measurements during NO inhalation treatment (Fig. 3, left part, upper 2 data pairs); effects on other hemodynamic parameters were not registered (Fig. 3, right part; Fig. 4). As demonstrated by continuous monitoring, the increase of PAP after interruption of NO inhalation sometimes presented an initial peak before stabilizing at a constant level (Fig. 6). These rebound effects for systemic oxygenation and PAP were attenuated by systemic weaning-off procedures in all 3 patients by stepwise reduction of inhalatory NO doses

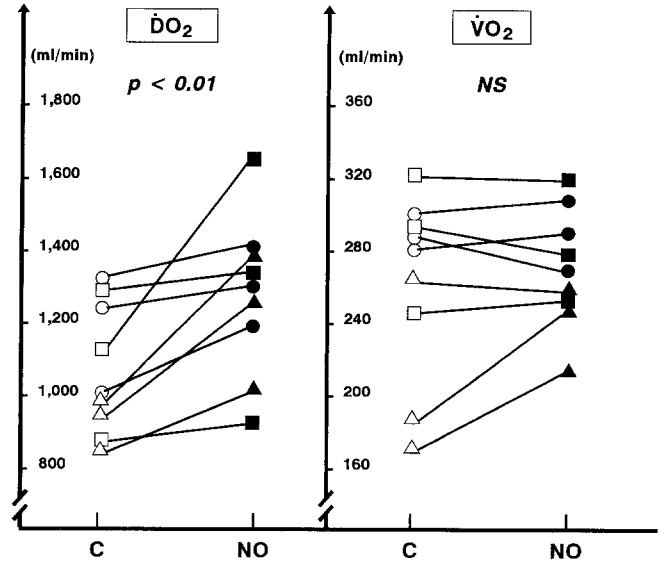

Fig. 5. Calculated oxygen delivery ($\dot{D}O_2$, *left side*) and calculated extrapulmonary oxygen consumption ($\dot{V}O_2$, *right side*) during NO-inhalation and control periods (see also Fig. 2); *NS* = not significant

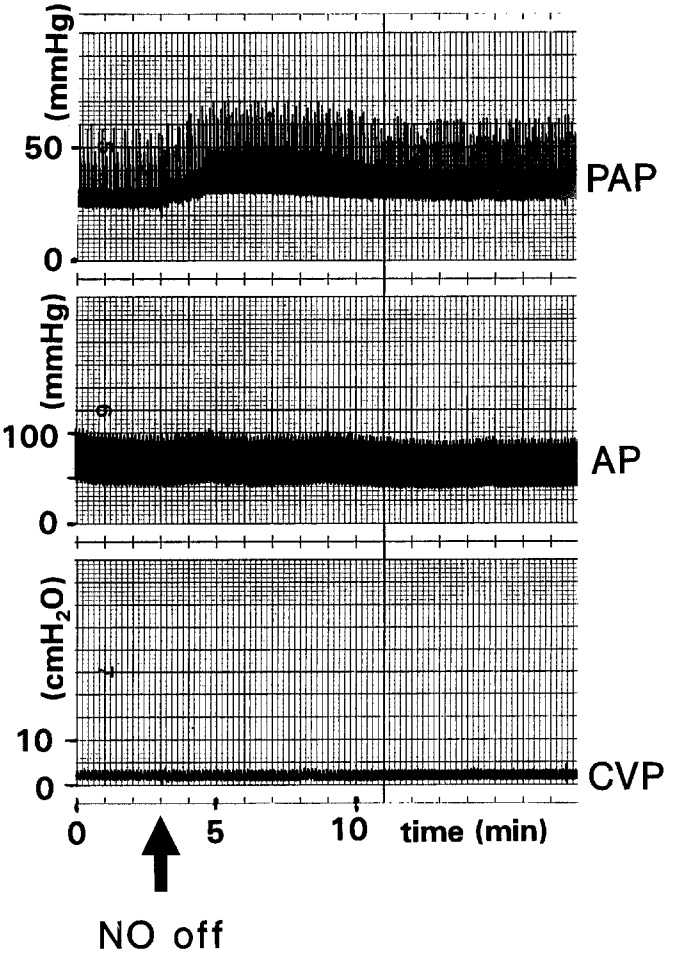

Fig. 6. Representative example for a continuous registration of pulmonary artery pressure (*PAP, upper panel*), systemic artery pressure (*AP, central panel*), and central venous pressure (*CVP, lower panel*) during shut-off period of NO-inhalation after long-term inhalation. Ranges are indicated at the *left side*, the time at the *horizontal line*. Note the rebound effect on the PAP after interruption of NO-inhalation

down to 10–70 ppb before the final shut-off. Interestingly, even lower doses of NO compared to the initially evaluated "lowest effective doses", e.g. down to 25 ppb, were demonstrated to be effective during these weaning-off procedures.

All 3 patients were successfully weaned from vv-ECMO after 9 to 26 days as well as from ventilatory support. They were re-transferred to the original hospital or to special rehabilitation units, and recovered well.

Discussion

Recent publications demonstrating a positive effect of NO inhalation in patients with primary pulmonary hypertension presumed that improved systemic oxygenation can not be achieved with inhalatory NO concentrations below 20–80 ppm and is mainly based on a general pulmonary vasodilation, associated with enhanced perfusion [21, 22]. Our patients were suffering from severe ARDS, in which the increased pulmonary resistance also plays an important role for the lung fluid balance and the right

ventricular function [25, 26]. Several reports already demonstrated that, in severe ARDS, vasodilating agents, which reduce PAP and pulmonary capillary pressure, exert a beneficial effect by reducing pulmonary edema and right ventricular stroke work, although the ventilation-perfusion distribution is worsened by these drugs [6, 27–29]. As shown by studies from our group [23], NO inhalation in patients with severe ARDS induces a redistribution of pulmonary perfusion in favor of ventilated areas without a significant change of cardiac output, associated with a decreased PAP, a reduced intrapulmonary right-to-left shunt, and an improvement of PaO_2, probably because the inhaled NO predominantly dilates vessels of ventilated areas. The 2 NO doses (18 and 36 ppm NO), however, which were used in this study, had no significant differences concerning these effects, i.e. there was no dose-dependence, which is untypical for biological processes, unless a "plateau" of the response has already been reached.

The new data presented here demonstrate that significant improvement of PaO_2 is already induced by doses of NO (60–230 ppb), which are much lower than those used in the cited studies [19–23], exert a dose-response (Fig. 1), and are similar to those measured in the free atmosphere (2–130 ppb). Oxygen and air for the ventilators derived from the central gas supply of the hospital were found to contain no NO (O_2) or not more than 4 ppb NO (air), probably due to the production procedure or to the conversion of NO to NO_2 by compression of the gases in the tanks. Hence, adding these low doses of NO to the inspiratory gas mixture, at least in patients 2 and 3, is not different to breathing room air relative to the NO content, i.e. the NO inhalation might be not more than a replacement of missing NO – a provocative hypothesis not only for future therapy, but also for theories about the pathophysiology of ARDS (ventilation as a form of NO deprivation?).

The reduction of PAP is obviously not necessary to improve systemic oxygenation during inhalation of NO, i.e. that, as considered by our previous studies [23], the redistribution, not the enhancement of pulmonary perfusion causes the increasing PaO_2. However, when the baseline value of PAP was above 45 mmHg, NO clearly reduced PAP without change of cardiac output, i.e. that the increased PAP was obviously not due to an irreversible macro- and microvascular occlusion as a typical feature of ARDS, but was at least partially based on an active pulmonary vasoconstriction, possibly by humoral factors like cytokines or by an absolute or relative deficiency of NO synthesis. Furthermore, it was found that, even using NO doses in the ppb range, termination of NO inhalation treatment requires a stepwise weaning-off procedure, since a sudden withdrawal of NO after prolonged inhalation may result in a marked deterioration of $\dot{Q}_{va}/\dot{Q}_t$ and PaO_2, and, as registered in one case, in a relevant enhancement of pulmonary vascular resistance. This effect might be due to a feed-back inhibition of the endothelial NO-synthase by the exogeneously supplied NO; thus, vasoconstriction in the ventilated areas may reoccur after shut-off of NO. These findings, combined with other studies showing that the absolute level of PAP is a marker for the severity of pulmonary microvascular injury in ARDS [35], and that pulmonary hypertension is associated with impaired NO production [36], confirm the hypothesis that even low doses of NO might reduce PAP in most severe cases of ARDS as presented here since the endogen NO production by the pulmonary vascular endothelium is considerably impaired under these circumstances. This was underlined by the observation, that intravenous application of N^G-monomethyl-l-arginine (l-NMMA), an inhibitor of endogeneous NO synthesis, which was shown to increase systemic and pulmonary artery resistance [37], had no effect in our ARDS patients during NO inhalation (data not shown). Further investigations might give more information about this aspect.

Systemic arterial pressure, heart rate and cardiac output did not change by the low dose NO treatment; the same results were found in previous studies from our group [23]. Hence, the significant increase of oxygen delivery ($\dot{D}O_2$) by NO inhalation is mainly based on an improved arterial oxygenation. The results for the oxygen consumption ($\dot{V}O_2$), which present no alterations by NO inhalation except when the baseline data were low, demonstrate that the oxygenation of the peripheral tissues (except the lung) mostly was in a saturated state. The validity of $\dot{D}O_2$ and $\dot{V}O_2$ as prognostic indices is doubted, especially in cases of ARDS [38, 39], because the oxygen consumption of the altered pulmonary parenchyma is not involved. However, there are several studies showing that the $\dot{V}O_2$, either calculated as presented or measured noninvasively as oxygen uptake [40], is useful for evaluation of tissue oxygenation in patients with ARDS [40, 41]. Hence, we think that both $\dot{D}O_2$ and $\dot{V}O_2$ give additional information especially for demonstrating short-term effects of NO inhalation in individual patients as presented, although statements about the long-term effect or prognostic value of NO inhalation should not be made.

As demonstrated, the use of low doses of inhalatory NO enables to continue ventilation treatment of ARDS patients with lower FiO_2, thus decreasing the risk of further tissue damage. The question, however, which dose finally should be recommended in patients with ARDS in order to improve the overall prognosis, can not be answered by these findings. It still has to be considered if the reducing effect of NO on the pulmonary artery pressure is a useful tool and should always be applied, since pulmonary hypertension promotes the accumulation of extravascular lung water by increasing the microvascular filtration pressure [2, 25, 30], and causes right ventricular dysfunction [26]. On the other hand, possible side effects of long-term inhalation with NO like methemoglobinemia [31], or interferences with other target functions of NO as an endogeneous mediator like neurological, platelet, or leukocyte functions [32–34] still have to be considered carefully. Controlled, randomized, prospective studies in the future are necessary to answer these questions.

In conclusion, we believe that NO inhalation in patients with ARDS in order to improve arterial oxygenation can be performed using concentrations in the ppb range which have to be regarded as non-toxic, although any possible risks still should be considered carefully.

Dose-response studies for the evaluation of the optimal dose in order to increase oxygenation and/or to reduce pulmonary resistance for each individual patient are recommended urgently, and NO inhalation should be terminated by a stepwise reduction of inhalatory NO doses. Finally, experimental and clinical studies concerning regulatory mechanisms on the sensitivity for externally applicated NO in volunteers and patients in the future might also deliver new aspects for the pathophysiology of ARDS and, thus, merit further attention.

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Announcements

Intensive Care Medicine

2nd Congress of the European Society of Anaesthesiologists

This congress will be held from February 9–12, 1994 at the Brussels Congress Centre, Brussels, Belgium. *For further information and registration please contact:* ESA Secretarial Office, Department of Anaesthesiology, CUB Erasme, Route de Lennik 808, B-1070 Brussels, Belgium. Tel.: 32-2-5554733; Fax: 32-2-5554335.

2nd European Consensus Conference in Intensive Care Medicine (ECCICM) – "Predicting outcome in ICU patients"

This conference will be held from December 9–10, 1993 in Paris, France. *For further information and registration please contact:* Dr. J. Carlet, Service de Réanimation Polyvalente, Hôpital Saint-Joseph, 7, rue Pierre Larousse, F-75014 Paris, France. Phone: (33-1)-44.12.34.15; Fax: (33-1)-44.12.32.92.

11th Workshop on Neurocritical Care (ANIM)

This meeting will be held from 13–15 January 1994 at Heidelberg, Germany, at the Congress Center "Stadthalle" and "Kopfklinikum". Invited are doctors, especially neurologists and neurosurgeons, anesthesiologists, internists, physiotherapists and nurses. *Topics include:* Stroke management and revascularization, inflammations of the CNS, infection control. Tutorials and workshops deal with elevated intracranial pressure, neuroradiology, and artificial ventilation. *For further information please contact:* ANIM, PD Dr. V. Schuchardt, Neurologische Universitätsklinik, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany. Tel.: (06221) 568211; Fax: (06221) 565348 or 563161.

5th International Steglitz Symposium – Sepsis

This scientific programme which will be held in Berlin, Germany, from February 9–12, 1994, is designed for anaesthesists, intensive care physicians, emergency room physicians, internists and surgeons who care for patients suffering from sepsis. *Topics include:* definition – do we need new definitions?, pathogenesis and pathophysiology, prophylaxis and therapy, therapy and monitoring and new therapeutic perspectives. *For further information please contact:* Mrs. Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, D-12203 Berlin, Germany. Phone: (030) 7982732; Fax: (030) 8347407.

3rd International Symposium on Cardiothoracic Critical Care

This symposium will be held on Febaruary 11–12, 1994 in Jakarta, Indonesia. *For further information please contact:* Iqbal Mustafa, MD, National Cardiac Centre, Jalan Letjen S. Parman kav. 87, Slipi, Jakarta 11420, Indonesia. Phone: 62-21-5684085, ext. 2242/3737; Fax: 62-21-568-4130.

3rd International Congress on the Immune Consequences of Trauma, Shock and Sepsis – Mechanisms and Therapeutic Approaches

This congress will be held from March 2–5, 1994 in Munich, Germany. Deadline for abstracts is October 30, 1993. *For further information please contact:* Dr. E. Faist, Ludwig-Maximilians-Universität München, Klinikum Grosshadern, Department of Surgery, Marchioninistrasse 15, D-81377 München, Germany. Phone: (089)-7095-3441/3436; Fax: (089)-7095-2460.

14th International Symposium on Intensive Care and Emergency Medicine

This symposium will be held from March 15–18, 1994, in Brussels, Belgium. *For further information please contact:* Prof. J.L. Vincent, Department of Intensive Care,, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Phone: 32.2555.3215; Fax: 32.2555.4555.

Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists

This meeting will be held from April 30–May 5, 1994 at Launceston, Tasmania, Australia. *For further information please contact:* Convention Secretariat, Jetset Groups & Conventions (Tas), P.O. Box 206, Launceston, Tasmania 7250, Australia. Phone: 008-03-0566; Fax: 003-34-2969.

7th European Congress on Intensive Care Medicine

This congress will be held from June 14–17, 1994 in Innsbruck, Austria and will be organized by the European Society of Intensive Care Medicine (ESICM). *For further information please contact:* Peter Schwab, Mensch & Arbeit Veranstaltungsorganisation GmbH, Keltenweg 22, A-5020 Salzburg, Austria. Phone: +43662436215; Fax: +43662436716.

10th European Congress of Neurosurgery

This congress will be held from May 7–12, 1995 in Berlin, Germany. All major topics of neurosurgery will be covered. Highlights will be: spinal neurosurgery, minimally invasive neurosurgery, neuronavigation, interventional procedures, neurooncology, pediatric neurosurgery, functional neurosurgery and neurotraumatology. Lunch seminars will be held daily by outstanding experts and will cover topics of practical interest. There will be an extensive social program. The organizers are making an effort to keep the fees as low as possible. *For further information please contact:* Prof. Dr. M. Brock, Congress President, Department of Neurosurgery, Universitätsklinikum Steglitz, Hindenburgdamm 30, D-12203 Berlin, Germany. Fax: 0049-30-798-3569.