Efficacy of Inhaled Nitric Oxide in Patients With Severe ARDS*

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Study objective: To investigate the initial and long-term effect of nitric oxide (NO) inhalation in patients with severe acute respiratory distress syndrome (ARDS).

Design: Retrospective, clinical study.

Setting: University surgical ICU.

Patients: Eighty-seven patients with severe ARDS.

Interventions and measurements: Thirty of 87 patients with ARDS inhaled low concentrations of NO for more than 48 h in addition to the standard treatment. Initial and long-term effects of NO inhalation on hemodynamics, gas exchange, and methemoglobin formation were determined. Survival of patients treated with inhaled NO was compared with survival in similar patients without NO inhalation.

Results: In 83% of the patients, NO increased the ratio of arterial PaO2 to the fraction of inspired O2 (PaO2/FiO2) by ≥10 mm Hg; in 87%, NO reduced venous admixture (Qva/Qr) by ≥10%, and in 63%, NO decreased mean pulmonary artery pressure (PAP) by ≥3 mm Hg. Daily short interruption of continuous inhalation of NO for a duration of 17 ± 2.4 days was consistently associated with a decrease in PaO2/FiO2 by 81 ± 4 mm Hg (p<0.001). Qva/Qr increased by 8.3 ± 0.4% (p<0.001) and PAP by 5.3 ± 0.3 mm Hg (p<0.001). Over time, we observed neither tachyphylaxis nor a more pronounced effect of inhaled NO. Methemoglobin increased from 0.74 ± 0.56% to 0.98 ± 0.02% (p<0.001). Survival rates in patients treated with NO did not differ from survival rates in patients not treated with NO.

Conclusion: Beneficial effects of NO inhalation can be observed in most patients with severe ARDS; in some cases, however, it may fail to improve pulmonary gas exchange or to reduce pulmonary hypertension without obvious explanation. To demonstrate a possible increase in survival associated with NO inhalation, large randomized prospective trials are required.

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ARDS=acute respiratory distress syndrome; CI=cardiac index; CPAP=continuous positive airway pressure; ECMO=extracorporeal membrane oxygenation; ED50=improvement in oxygenation with 50% maximal response; FiO2=O2 inhalation fraction; MAP=mean systemic arterial pressure; NO=nitric oxide; PaCO2=partial pressure of carbon dioxide; PaO2=partial pressure of arterial oxygen; PAP=mean pulmonary artery pressure; PEEP=positive end-expiratory pressure; Qva/Qr=venous admixture

Key words: ARDS; arterial oxygenation; methemoglobin formation; nitric oxide inhalation; pulmonary arterial hypertension; survival

Inhalation of low concentrations of the gaseous vasodilator nitric oxide (NO) has been described to cause selective pulmonary vasodilation.1,2 This phenomenon is explained on the one hand by the inhalation strategy allowing NO to dilate lung vessels and on the other hand by the immediate inactivation of NO by binding to hemoglobin as soon as NO enters the bloodstream. Moreover, in patients with severe acute respiratory distress syndrome (ARDS), inhaled NO has been shown to induce vasodilation predominantly in ventilated lung areas.3 The regional fall in vascular resistance caused by NO induces a redistribution of pulmonary blood flow away from nonventilated toward ventilated regions of the lungs, resulting in a decrease of the pulmonary right-to-left shunt and an improved arterial oxygenation.3

Recently, it has been described that in severe ARDS, NO inhalation is not always able to reduce mean pulmonary artery pressure (PAP) and to increase the arterial partial pressure of oxygen (PaO2).4 However, no study investigated how often NO fails to reduce pulmonary hypertension or to improve arterial oxygenation. Furthermore, only limited experiences exist in long-term inhalation of NO, and so far, to our knowledge, there is no information available whether NO inhalation has a positive effect on the survival rate in these patients. Controlled prospective multicenter trials, focusing on the question of whether NO inhalation will result in an increase of survival in patients with severe ARDS, will not be available within the near future. Therefore, we retrospectively studied the initial and long-term effects

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of inhaled NO on gas exchange, hemodynamics, and methemoglobin formation in patients with severe ARDS in our ICU. In addition, we made an attempt to estimate whether NO inhalation has a profound effect on mortality of our patients with ARDS.

METHODS

Patients

From April 1989 to August 1993, 87 patients with ARDS, aged from 1 to 62 years, without a history of previous lung disease, were referred to our hospital for treatment, including the possible application of veno-venous extracorporeal membrane oxygenation (ECMO). All patients had severe ARDS according to the lung injury scoring system of Murray et al.8 (ARDS score range, 2.5 to 4) that assesses the degree of diffuse radiographic infiltration, arterial hypoxemia, respiratory compliance, and the level of positive end-expiratory pressure (PEEP).5 Patients with pulmonary edema due to cardiac failure, immunosuppression, and advanced malignant disease were excluded. Additional organ failures were determined modifying the score described by Goris et al.6

After transfer to our ICU, all patients received standard treatment2 that consisted of pressure-controlled mechanical ventilation with 10 to 15 cmH2O PEEP and a maximum inspiratory peak pressure less than 40 cmH2O using one of two ventilators (either a Servo 900C ventilator, Siemens Elema, Lund, Sweden, or a Siemens 300 Siemens Elema, Lund, Sweden), positioning maneuvers (change of supine and prone position), adequate dehydration, if fluid overload was present, side differential ventilation in patients with unilaterally pronounced infiltrates, and acceptance of partial pressures of carbon dioxide (PaCO2) up to levels of 80 mm Hg, if pH remained above 7.25 and if no head injury was present. When patients had life-threatening hypoxemia (PaO2<50 mm Hg at an inspiratory oxygen fraction (FIO2) of 1.0 and PEEP ≥10 cmH2O for >2 h) or did not respond to the therapeutic means listed above, veno-venous ECMO with heparin-coated systems was performed as described elsewhere.8

From April 1991 to August 1993, 30 patients with PaO2/FIO2<200 mm Hg were additionally treated with NO inhalation using concentrations between 0.01 and 25 parts per million (ppm). Since only one device with a safe administration technique, including NO/nitric dioxide monitoring was available, only one patient could be treated at the same time. In patients receiving NO (NO group), NO inhalation began 7.4 ± 1.7 days (range, first and 32nd day) after the patient’s admission to our ICU. At that time, the patients had already been mechanically ventilated for an average of 20.1 ± 1.6 days.

Of the 30 patients 16 were also treated with veno-venous ECMO because pulmonary venous admixture (Qva/Qt) remained over 45% resulting in severe arterial hypoxemia. All patients were sedated with analgesics by continuous infusions of fentanyl and midazolam. Vasoactive drugs were given as necessary but neither the drugs nor the doses were changed while the effects of initial NO administration or the effects of NO withdrawal were examined.

Measurements

Routine clinical monitoring of the patients included the use of a thermodilution pulmonary artery catheter (model 95A-431-7,5F, Baxter Healthcare, Irvine, Calif) and a femoral artery catheter (model 96B-020-5F G, Baxter Healthcare). Mean systemic arterial pressure (MAP) and mean PAP were measured with disposable quartz transducers (Abbott Laboratories, Chicago) and a monitoring system (Model 66 S, Hewlett Packard, Böblingen, Germany). The supine zero reference level was the mid-axilla; vascular pressures were the average of the values taken at end-expiration from three successive respiratory cycles. Heart rate was determined from an electrocardiograph. Cardiac output was measured using thermodilution techniques (Edwards Cardiac Output Computer REF-1, Baxter Healthcare) and given as the mean value of four measurements.9 Systemic and pulmonary vascular resistance were calculated using standard formulas.

Arterial and mixed venous blood samples were collected anaerobically, placed in ice, and analyzed by measuring the partial pressure of oxygen (P02), partial pressure of carbon dioxide (PcO2), and pH using standard blood gas electrodes (ABL 300, Radiometer, Copenhagen, Denmark). Total hemoglobin, hemoglobin oxygen saturation, and methemoglobin levels of blood were obtained by spectrophotometry (OSM 3 Hemoximeter, Radiometer). Inspired gas samples were obtained from the inspiratory limb of the ventilator tubing. The ratio of PaO2/FIO2 was used as an index of arterial oxygenation throughout the study because the inspiratory admixture of nitrogen, the carrier gas for NO, induced small changes in the inspired oxygen concentration. The latter was determined by measuring the inspired P02 as well as the atmospheric pressure (ABL 300, Radiometer) and converting it to FIO2. Expired gas samples were obtained from the expiratory limb of the ventilator tubing. Arterial, mixed venous, and capillary oxygen contents were calculated and Qva/Qt was derived using the standard equation.

Technique of NO Administration

From April 1991 to August 1992, NO was delivered via the ventilator (Servo 900C, Siemens, Lund, Sweden) equipped with a modified nebulizer control box and a flowmeter (Siemens 945). The nebulizer released NO from a tank filled with nitrogen containing 400 ppm or 800 ppm NO (AGA, Bottrop, Germany) during the inspiratory cycle. The resulting bolus of NO/nitrogen mixture represented 2 to 4% of the inspiratory volume. This was confirmed by the decrease in FIO2 and increase of expired tidal volume. Inspired gas was sampled 20 cm downstream of the NO/nitrogen injection port. The NO dose was determined volumetrically and measured intermittently using chemiluminescence (CLD 700 AL, Tecan AG, Munich, Germany). From April 1992 to August 1993, NO was delivered using a new prototype of the ventilator (Servo 300, Siemens) that was equipped by the company with an inbuilt computerized NO delivery system, consisting of an additional digital-controlled NO valve. Using these delivery systems, nitric dioxide concentrations measured 20 cm before the Y-piece of the inspiratory limb always remained below 0.5 ppm.

Protocols

This investigation was performed at the Universitätsklinikum Rudolf Virchow with the approval of the institutional ethics committee. Informed consent was obtained from each patient’s family.

Effects of First Inhalation of NO

In 30 patients who inhaled NO for more than 48 h, systemic and pulmonary hemodynamics and gas exchange variables were measured immediately before and after 30 min of first inhalation of 10 to 20 ppm NO. Those patients, who demonstrated an increase of PaO2/FIO2≥10 mm Hg, were defined as responders concerning an increase in arterial oxygenation; those whose calculated Qva/Qt showed a decrease of ≥10% after 30 min of NO inhalation were considered responders with respect to an improvement in Qva/Qt; those patients presenting a decrease in PAP of ≥3 mm Hg were considered responders with regard to a reduction of pulmonary hypertension. In nonresponders, the effects of NO inhalation were reevaluated after 5 to 5 days.

The difference in PaO2/FIO2 and PAP before and during NO
inhalation was correlated with baseline pulmonary vascular resistance and QVA/Qt, respectively. Also, the change in PAP due to NO inhalation was correlated with the degree of pulmonary hypertension before NO inhalation, and the decrease in QVA/Qt after NO inhalation was correlated with QVA/Qt before NO inhalation. The changes in PaO₂/FIO₂, QVA/QT, and PAP after NO inhalation were correlated with cardiac index before NO inhalation.

Effects of Prolonged Inhalation of NO

The patients continuously inhaled NO for more than 48 h if they were either responders with respect to an improvement in arterial oxygenation or responders with respect to reduction in PAP. To determine the effect of withdrawal and resumption of NO on hemodynamics and gas exchange, the continuous inhalation of NO was stopped daily for 30 min at constant ventilator settings with an FIO₂ between 0.9 and 0.98. The NO therapy was terminated reducing the NO concentration step by step over 24 h when the PaO₂/FIO₂ had risen above 300 mm Hg during the daily tests without NO inhalation. Methemoglobin levels were analyzed before and during NO inhalation.

Analysis of Survival

We analyzed survival rates (defined as discharge from hospital) in the NO group and compared it with the survival rates of the patients not receiving NO. For this purpose, matched pairs of patients who have been treated and who have not been treated with inhaled NO were retrospectively formed if the severity of ARDS was similar. Since children younger than 10 years (n=3) were present only in the NO group, they were excluded from this part of the study. For the formation of matched pairs, the following criteria were chosen. First, patients receiving extracorporeal support were matched only with patients who had also been treated with ECMO. Moreover, they had to be equal concerning fulfilling the fast or the slow entry criteria for ECMO. Second, all other patients were allowed to have maximum differences in the PaO₂/FIO₂ ratio of 30 mm Hg and maximum differences in the lung injury score³ of 0.5. Third, due to the higher mortality in ARDS caused by pneumonia, patients with this diagnosis as underlying disease were matched only with patients also suffering from ARDS due to pneumonia. Fourth, the number of additional organ failures was not allowed to differ by more than 1.

Statistical Analysis

All data were expressed as mean values ± SE. The initial response to NO inhalation was determined as the difference between the baseline value and the value during intervention. Effects of long-term inhalation are reported as the difference of the mean values recorded during treatment and cessation of NO inhalation. Because normal distribution could not be proved, the Wilcoxon rank sum test was used to compare values recorded during NO inhalation with those recorded without NO inhalation as well as to compare methemoglobin values before NO inhalation with the values during NO inhalation.

When a linear regression was calculated, Pearson's coefficient of correlation (r) was tested using a t distribution.

To find out differences in survival rates and sex, the χ² test was used. To analyze differences between the matched pairs, the Mann-Whitney test was used to compare patients' further characteristics. All tests of significance were two-tailed, and p values less than 0.05 were regarded as significant.

Results

Effects of First Inhalation of NO

The first inhalation of NO caused an increase in PaO₂/FIO₂ from 98±8 mm Hg to 132±12 mm Hg (p<0.001), a decrease in QVA/Qt from 47.6±3.4% to 41.6±3.3% (p<0.001), and a fall in PAP from 35±2 mm Hg to 31±2 mm Hg (p<0.001). Patients treated with ECMO showed similar responses to NO inhalation as patients not treated with ECMO: PaO₂/FIO₂ increased by 28±10 mm Hg in patients treated with ECMO and by 36±6 in patients not treated with ECMO, PAP decreased by 3±1 mm Hg and by 4±1 mm Hg, respectively, and QVA/Qt decreased by 9±2% and by 5±1% in patients treated with and without ECMO. Five patients did not show any improvement in oxygenation; four of these five had a QVA/Qt of more than 50% (Table 1). All nonresponders (except one, No. 39) became responders with regard to an improvement in oxygenation during later reevaluation of the effect of NO inhalation. However, as this patient initially showed at least a
FIGURE 1. Correlations between various physiologic parameters and the change in oxygenation index (PaO₂/FIO₂), venous admixture (QVA/QT), and pulmonary artery pressure (PAP) due to first inhalation of NO in 30 patients. Each symbol represents values of one patient. The increase in PaO₂/FIO₂ due to NO inhalation did not correlate with the pulmonary vascular resistance index (PVRI) before NO inhalation (r=0.04); furthermore, the decrease in PAP and in QVA/QT following NO inhalation was independent of QVA/QT before NO inhalation (r=0.35 and r=0.39, respectively) (a and b). There was no correlation between the effect of NO inhalation on PAP and PAP before NO inhalation (r=0.28) (c). The change in PaO₂/FIO₂, QVA/QT, and PAP due to NO inhalation did not correlate with CI before NO inhalation (r=0.22, r=0.30, and r=0.14) (d to f).
minor response to NO inhalation and was a responder concerning a reduction in QVA/QT, after 45 days of ECMO without any improvement in gas exchange, a trial with continuous NO inhalation for 35 days was performed. This patient died after 92 days of receiving ECMO due to multiple organ failure following untreatable pulmonary failure.

Four patients did not respond to the first inhalation of NO with a reduction in QVA/QT of ≥10% (Table 1). All these patients became responders during the reevaluation of the effect of NO inhalation. Initially, inhalation of NO reduced the pulmonary hypertension in 19 of 30 patients by ≥3 mm Hg (Table 1). During continuous NO inhalation, 9 of the 11 nonresponders became responders with respect to a reduction in PAP.

In NO inhalation, MAP and cardiac index (CI) remained unchanged compared with values before NO inhalation (75 ± 2 vs 76 ± 2 mm Hg [p = 0.19] and 4.0 ± 0.2 vs 3.9 ± 0.2 L/min [p = 0.11], respectively).

Norepinephrine or other cardiotonic agents that might influence the response of vessels to NO inhalation had to be infused to some responders and to some nonresponders.

The increase in PaO2/FIO2 due to NO inhalation did not correlate with the pulmonary vascular resistance index before NO inhalation (r = 0.04); furthermore, the decrease in PAP and in QVA/QT following NO inhalation was independent of QVA/QT before NO inhalation (r = 0.35 and r = 0.39, respectively) (Figure 1, a and b). There was no correlation between the effect of NO inhalation on PAP and PAP before NO inhalation (r = 0.28) (Fig 1, c). The change in PaO2/FIO2, QVA/QT, and PAP due to NO inhalation did not correlate with CI before NO inhalation (r = 0.22, r = 0.30, and r = 0.14) (Fig 1, d through f).

**Effects of Prolonged Inhalation of NO**

Nitric oxide was inhaled by 30 patients for 17 ± 2.4 days (range, 2 to 53 days). The average concentration used was 11.5 ± 1.4 ppm (range, 0.01 to 25 ppm). During brief daily interruptions of NO inhalation, PaO2/FIO2 consistently decreased by 81 ± 4 mm Hg (p < 0.001), QVA/QT increased by 8.3 ± 0.4% (p < 0.001), and PAP increased by 5.3 ± 0.3 mm Hg (p < 0.001). Over time, we observed neither tachyphylaxis nor a more pronounced effect of inhaled NO. Methemoglobin increased from 0.74 ± 0.56% to 0.98 ± 0.02% (p < 0.001) (Fig 2).

**Analysis of Survival**

Using the defined criteria for matching pairs, 26 pairs consisting of patients receiving NO and patients not receiving NO could be formed. These patients were comparable concerning the severity of ARDS (Table 2). A retrospective analysis of survival in these patients demonstrated no difference in survival between the NO group and the non-NO group (69 vs 68%). In addition to three children out of the NO group, one patient of this group suffering from ARDS following pneumonia had to be excluded from this part of the study, as no patient could be found in the non-NO group who fulfilled the matching criteria.

**DISCUSSION**

The present study investigates the efficacy of NO inhalation in 30 patients with severe ARDS and basically confirms the findings of our earlier study3 that inhaled NO causes vasodilation predominantly in ventilated lung areas and, thereby, improves arterial oxygenation and reduces pulmonary hypertension in patients with severe ARDS. In addition, we demonstrated that in some patients, NO inhalation may fail to develop its beneficial effects and that adding NO inhalation to our standard treatment had no detectable influence on survival rate in our patients with severe ARDS.

Analyzing the effect of first-time NO inhalation using a concentration of 10 to 20 ppm, in general, we found an increase in arterial oxygenation, a decrease in QVA/QT, and a decrease in PAP, even if NO inhalation was not always associated with relevant changes in pulmonary gas exchange and pulmonary hypertension. Although the criteria to define relevant changes or so-called responders with respect to arterial oxygenation, QVA/QT and PAP were chosen arbitrarily, they reflect our idea of clinical important changes in this group of patients. In 5 of 30 patients, NO inhalation failed to improve arterial oxygenation, an observation that has been described earlier by Ricou and Suter.4 These authors could not identify any cause for the failure of inhaled NO to

![Figure 2. Methemoglobin levels during the first 3 weeks of NO inhalation measured in 30 patients inhaling 11.5 ± 1.4 ppm NO for 17 ± 2.4 days (mean ± SE).](image-url)
improve pulmonary gas exchange and to reduce pulmonary hypertension. We also can only speculate on the cause for the nonresponsiveness to inhaled NO in our patients. One reason might be that four of these five had QvA/Qr of more than 50% (Table 1). This could have reduced the selective vasodilatory activity of NO to such a small lung area that global beneficial effects did not result. However, this hypothesis is in contrast to the finding that, in our study, four patients with QvA/Qr of more than 50% were among the responders. Recently, Putensen et al. described the association of an improvement in the ventilation/perfusion mismatch due to inhaled NO with the recruitment of lung units with the use of PEEP. These authors administered an inhalation gas mixture containing 40 ppm NO to dogs with acute lung injury using ambient airway pressure or continuous positive airway pressure (CPAP). In both groups, inhaled NO caused selective pulmonary vasodilation. However, NO inhalation decreased only the intrapulmonary shunt and improved pulmonary gas exchange, when simultaneously lung units were recruited with CPAP. Although in the present study all patients were ventilated using PEEP between 10 and 15 cm H2O, it cannot be excluded that the PEEP level may have been insufficient to recruit enough alveoli for a redistribution of blood flow from nonventilated toward ventilated lung units after NO inhalation. However, since PEEP may cause overexpansion of healthy lung areas, the resulting mechanical compression on the pulmonary blood vessels may limit the vasodilatory effect of inhaled NO. Interestingly, four of the five initial PaO2 nonresponders became responders when reevaluating inhaled NO routinely 3 to 5 days later. In these patients, the PEEP level was unchanged; however, it might be that owing to a change in the patients’ conditions at the time of reevaluation, this PEEP was more appropriate to recruit or to avoid overdistention of lung units.

Furthermore, the lack in response to NO inhalation could be caused by an ineffective concentration of NO. Dose-response studies showed that, in general, the effect of NO on PaO2 was significant at 0.1 ppm, whereas the effect of NO on PAP was significant only with concentrations of 1 ppm and more. The idealized dose-response curves for PaO2 and PAP showed different patterns: the improvement in oxygenation with 50% maximal response (ED50) at about 0.1 ppm had a maximum at 10 ppm NO and, at the highest tested concentration (100 ppm), drifted back toward the baseline data, whereas PAP presented a continuous, dose-dependent downwards tendency with an ED50 of approximately 2 to 3 ppm NO. This may be based on a diffusion of NO at high concentrations not only to ventilated but also to nonventilated lung areas. Thereby, the intrapulmonary shunt may increase and the arterial oxygenation may deteriorate. Whereas these were general observations, this study by Gerlach et al. revealed, in addition, the individually different pattern of response to increasing concentrations of inhaled NO. Since in the present study we used only one concentration for the analysis of the first inhalation of NO (10 to 20 ppm), we cannot exclude that this concentration was individually too high or too low to cause the desired effects on pulmonary gas exchange and hemodynamics. Therefore, for future studies, we propose individual repetitive dose-response analysis to exclude false-negative responses concerning an improvement in arterial oxygenation and a reduction in pulmonary hypertension due to inadequate concentrations of inhaled NO.
Trying to find factors influencing the effect of inhaled NO, we analyzed the correlation between several parameters. However, the increase in PaO₂/FI0₂ due to NO inhalation did not correlate with the pulmonary vascular resistance index; also, the decrease in PAP following NO inhalation was not dependent on QVA/Qt before NO inhalation. In contrast to Bigatello et al., who demonstrated in seven patients with ARDS that the magnitude of the vasodilator response during NO inhalation correlated with the degree of vasoconstriction when stopping NO inhalation, we found no correlation between the effect of NO inhalation on PAP and PAP before NO inhalation. Furthermore, also in contrast to these authors, we could not demonstrate that the decrease in QVA/Qt due to NO inhalation correlated with QVA/Qt before NO inhalation. Moreover, we were not able to demonstrate that the effect of NO inhalation correlated with CI. In addition, we observed responders and nonresponders independent of the necessity for ECMO or intravenous catecholamine infusions. We conclude that, at present, the efficacy of inhaled NO in patients with such severe ARDS cannot be predicted.

In accordance with our previous study and also in this study, continuous inhalation of low concentrations of NO remained effective for 17 ± 2.4 days in improving pulmonary gas exchange and reducing pulmonary hypertension. Also, we could not observe tachyphylaxis or a more pronounced effect of NO inhalation over time, i.e., that the effect of inhaled NO on PaO₂/FI0₂ and PAP determined with the brief daily periods when NO inhalation was discontinued was similar both at the end of treatment and at the beginning. So, adding NO to the inhaled gas facilitated a reduction of FI0₂, which minimizes the exposure to high inhaled oxygen concentrations and may reduce pulmonary oxygen toxic reactions. Although inhaling NO did not reduce the PAP to a normal value, it lowered PAP to the same level obtained by infusions of vasodilators like prostacyclin or nitroprusside in ARDS without reducing the MAP. However, whether a reduction in PAP from 35 ± 2 mm Hg to 31 ± 2 mm Hg causes a reduction in extravascular lung water, as it has been shown in experimental pulmonary edema, remains speculative. Furthermore, as this small reduction in PAP due to inhaled NO has been shown to induce only a 10% increase in right ventricular ejection fraction assessed by the thermodilution technique, the capability of inhaled NO to prevent right ventricular dysfunction, which might occur in severe ARDS, is not clear.

To find out whether NO inhalation results only in cosmetic corrections of some blood gas and hemodynamic parameters or whether this new therapy also increases survival, outcome studies are required. So far, it has not been demonstrated that an increase in PaO₂ or a decrease in PAP necessarily results in an improved survival. Montgomery et al. pointed out that only 16% of deaths in patients with ARDS were from irreversible respiratory failure with hypoxemia. Using ECMO in patients with QVA/Qt > 45% and without any sign of recovery, in our study, only one of the patients (treated with ECMO, but without inhaled NO) died due to hypoxemia. Therefore, adding NO inhalation to the standard treatment indeed enabled a reduction in FI0₂ and thereby in oxygen toxicity, but, in general, was not needed to avoid hypoxemia. Since prospective randomized multicenter trials focusing on the question of whether NO inhalation will result in an increase of survival in patients with severe ARDS will not be available within the near future, we decided to analyze retrospectively the outcome in our patients. Interestingly, despite the observed beneficial effects on arterial oxygenation and pulmonary hemodynamics, this retrospective analysis did not show any change in survival adding NO inhalation to the standard treatment. Although, in general, a retrospective approach gives less evidence compared with a prospective study, forming matched pairs increased the reliability of this comparison. For this approach, we used criteria that should identify patients with similar severity of their disease. This concept enabled us to identify two groups of patients that were similar in all included parameters but sex, which is unknown to influence outcome in ARDS.

We do not believe that the survival in patients treated with NO was influenced by the possible toxicity of NO itself. Although inhaling high concentrations of NO can be lethal because it causes severe acute pulmonary edema and methemoglobinemia, there is little evidence of toxicity when the concentration is as low as in our study. Animals have breathed the gas in concentrations of 10 to 40 ppm for 6 days to 6 months without evidence of such toxic reactions. In our study, we did not observe a sudden intensification of the pulmonary edema or methemoglobin levels above 1.5%, which might have indicated toxic effects of inhaled NO. Furthermore, our NO delivery systems also limited the oxidation of NO to nitric dioxide. This is of importance since nitric dioxide, which is a strong oxidizing gas, initiates lipid peroxidation resulting in cell injury or cell death. Acute effects inducing pulmonary edema could be observed during exposure to nitric dioxide in concentrations above 50 ppm, and delayed effects have been described after prolonged exposure to such low concentrations as 2.3 ppm nitric dioxide. Since the maximum concentration of nitric dioxide measured in this study was below 0.5 ppm,
we do not believe that nitric dioxide formation influenced survival in our patients.

Therefore, we believe that the observed identical survival rate in both groups allows three statements. First, if low concentrations of NO as well as appropriate delivery and monitoring systems are used, NO inhalation appears to be safe. Second, NO inhalation has no striking effect on outcome in patients with severe ARDS; hence, at present, the treatment of severe ARDS with NO inhalation cannot be considered mandatory, which might be suggested by the presented data regarding the effect of NO inhalation on arterial oxygenation and pulmonary hypertension. Third, the identical survival rate of both groups implies the need for controlled randomized clinical trials to answer the question of whether NO inhalation will result in an increase of survival in patients with ARDS. However, the difficulty of such outcome studies is that patients with ARDS demonstrate multifactorially determined problems, which make it difficult to identify outcome changes due to a specific intervention. Although a one-center trial such as ours may have the advantage that at least the routine therapeutic approach can be standardized easily, a controlled randomized one-center trial is unlikely to demonstrate an improved outcome following a new therapy, if only a limited number of patients can be included and if the new therapy will not dramatically improve survival. Therefore, a controlled randomized multicenter trial is required, even if multicenter studies will have the problem that the routine treatment of patients with ARDS consisting of a variety of therapeutic means will vary in many details among the centers. Consequently, multicenter studies most probably will have to enroll a huge number of patients.

In conclusion, the present study demonstrated that although we observed the beneficial effects of NO on PaO2 and PAP in most patients, NO inhalation may fail to improve pulmonary gas exchange or to reduce pulmonary hypertension in patients with severe ARDS. At present, no parameter or condition in patients with severe ARDS has been shown that may allow us to predict the efficacy of inhaled NO. To demonstrate any increase in survival adding NO inhalation to the standard treatment, large controlled randomized trials are both justified and required.

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