Acute effects of nitric oxide inhalation in ARDS: A dose finding study at steady state kinetics

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Abstract

**Background:** Inhaled Nitric oxide (INO) decreases pulmonary artery pressures and improves oxygenation in patients with ARDS. **Aim:** To evaluate the dose response to 1-20 parts per million (ppm) INO in ARDS, by noting changes in oxygenation, pulmonary artery systolic pressures (PASP) and to determine optimum dose. **Methodology and Design:** Prospective study. **Setting:** 10 bed general intensive care unit. **Patients:** 13 consecutive patients with ARDS. **Interventions:** INO was given between 1-20 ppm with 15 minutes at each concentration via an insufflator from a high pressure source, to the inspiratory limb of the ventilator. Study had ascending and descending phase. **Results and Conclusions:** The optimum dose of INO to improve oxygenation was between 3 and 10 ppm. PaO₂ improvement was independent of pulmonary haemodynamic changes. The pulmonary haemodynamic changes needed higher INO initially. Once stabilized, INO could be brought down to concentrations at which maximum improvement in PaO₂ occurred. The ‘responders’ had lesser duration of pre INO ventilation and lower PaO₂/FiO₂.

Key words: ARDS, nitric oxide, acute effects

Adult respiratory distress syndrome (ARDS) is characterized by acute respiratory distress, refractory hypoxaemia and pulmonary hypertension and remains a challenging organ failure for the intensivist. Accumulating data from basic science and clinical studies have dramatically changed the understanding of the ways in which mechanical ventilation itself may interact with the acutely injured lung to further impair pulmonary function. This understanding has prompted a lung protective ventilation strategy, which in a recent clinical outcome study, was shown to improved pulmonary function and survival.[1] As an intervention- inhaled nitric oxide [INO] therapy has not been shown to improve the outcome and the optimum dose of INO in ARDS is not defined.

Our hypothesis was INO is a selective pulmonary vasodilator which redistributes the pulmonary blood flow to the ventilated parts of the lung. This reduces pulmonary vascular resistance (PVR) and improves PaO₂ by better ventilation perfusion matching. The aim of our study were to evaluate dose - response effect of INO in ARDS by noting changes in oxygenation (PaO₂/FiO₂ ratio) and pulmonary artery systolic pressure (PASP), in response to 1-20 parts per million [ppm] concentrations, to determine the optimum dose and the predictors of response to INO.

**Methodology**

We conducted a prospective non-randomized pragmatic study in a 10 bed closed intensive care unit. After obtaining approval by the regional ethics committee and informed consent from the patient or their next of kin, we included 13 consecutive patients with ARDS. INO was given between 1-20 ppm with 15 minutes at each concentration via an insufflator from a high pressure source, to the inspiratory limb of the ventilator. Study had ascending and descending phase. **Results and Conclusions:** The optimum dose of INO to improve oxygenation was between 3 and 10 ppm. PaO₂ improvement was independent of pulmonary haemodynamic changes. The pulmonary haemodynamic changes needed higher INO initially. Once stabilized, INO could be brought down to concentrations at which maximum improvement in PaO₂ occurred. The ‘responders’ had lesser duration of pre INO ventilation and lower PaO₂/FiO₂.

**Key words:** ARDS, nitric oxide, acute effects.
written consent, we studied 13 patients who satisfied the American European Consensus Criteria for the diagnosis of ALI/ARDS.\[2\] We excluded patients who were not willing to participate in study, those with an admission diagnosis of intracranial hemorrhage, those with coagulopathy and those with NYHA class III heart failure. The severity of illness was assessed using APACHE III score and MODS score. The severity of lung injury was assessed using PaO\(_2\)/FiO\(_2\) ratio and Murray scoring. Standard ICU care was continued during the study period.

Lung protective ventilatory strategy [tidal volume of 4-8 ml / kg and the mean airway pressures less than 30 cmH\(_2\)O] was used and the ventilatory parameters remained constant during the course of the study. The FiO\(_2\) was adjusted between 0.5 and 1.0 to maintain a PaO\(_2\) > 60 mmHg.

**Administration of inhaled Nitric Oxide (INO)**
INO was started when PaO\(_2\)/FiO\(_2\) ratio was less than 200. Nitric oxide was administered via an insufflator from a high pressure source, containing a concentration of 450 ppm NO in N\(_2\) fitted with OPTI NO adaptor and delivery system (ML AIR LIQUIDE, FRANCE) in the continuous mode synchronous with inspiration. The NO delivery port was connected using a non-complaint tubing distal to the humidifier near the ET tube, to minimize the O\(_2\)-INO contact time. NO was administered in the following concentration 1, 2, 3, 4, 5, 7.5, 10, 12.5, 15, 17.5, 20 ppm—‘ascending phase’ of study and decreased in the reverse order from 20 ppm—1 ppm—‘descending phase’ of study. An equilibration time of 15 minutes was given at each concentration. Once the study protocol was completed, INO levels were reduced to the lowest level at which maximum beneficial response with respect to PaO\(_2\) and pulmonary artery pressures were obtained. The concentrations of INO and INO\(_2\) were measured using chemiluminescence monitor (ML AIR LIQUIDE, FRANCE).

All the study patients had a radial artery catheter and a PA-catheter in situ, during the course of the study. Monitoring of hemodynamic variables was using Mennen Medical Inc. Monitor Horizon 2000. Hemodynamic and oxygenation variables were measured at end expiration, every 15 minutes before changing the INO concentration. For the pulmonary mechanics ventilator, display was noted. For blood gas analysis, AVL 998 monitor was used. One point calibration was done every 30 minutes and two point calibrations were done every 8 hours. The ‘responders/response to treatment’ were defined by the following criteria: PaO\(_2\)/FiO\(_2\) ratio increase was more than 15% of base line and/or PSAP fall was more than 15% of base line value in three consecutive concentrations.

**Analysis**
Data analysis was performed using BMDP Dynamic Release 7.0. Distribution of data was tested for normality. Parametric data are presented, as are presented as mean ± SD. ANOVA for repeated measures and Bonferroni t-test for multiple comparisons were used to analyze the dose-response to INO. The risk factors for ARDS and ‘responders’ were analysed using Yates corrected chi-square test and Fisher exact (two tail) test.

**Results**
The mean (SD) age of our patients was 50 (15.3) yrs, with a mean (SD) Apache III score of 53.7 (13.3). The mean (SD) MODS and Murray score were 7.2 (1.4) and 2.8 (0.5), respectively.

On analysis of risk factors for ARDS present at admission, 12 patients had pneumonia which was statistically significant (P=0.002), 3 patients had laparotomy evidence of peritonitis which was statistically significant (P=0.04) and one patient each had eclampsia, pancreatitis and polytrauma with fat embolism.

The baseline respiratory characteristics of the patient are presented in Table 1.

The baseline mean PaO\(_2\)/FiO\(_2\) ratio was 129.1 (44.2). The maximum improvement of 160.3 (80) was observed at 4 ppm, which was 24% above baseline. The mean values at 3 ppm to 7.5 ppm and 15 ppm to 20 ppm, showed an increase of greater than 15% above baseline values, by our definition ‘Response to treatment/Responder status’. However, there was no statistically significant improvement in PaO\(_2\)/FiO\(_2\) ratio at any INO concentrations [Figures 1a and 1b].

**Table 1: Baseline respiratory characteristics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>PaO(_2)/FiO(_2)</td>
<td>123.3 (43.2)</td>
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<tr>
<td>FiO(_2)</td>
<td>0.75 (0.2)</td>
</tr>
<tr>
<td>PEEP cmH(_2)O</td>
<td>6.5 (3.1)</td>
</tr>
<tr>
<td>VT mls</td>
<td>473 (165.3)</td>
</tr>
<tr>
<td>Peak inspiratory pressure cmH(_2)O</td>
<td>32.6 (6.9)</td>
</tr>
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</table>
Baseline mean (SD) PASP was 37.5 (12.1) mmHg. Statistically significant reduction in PASP was observed at INO concentrations of 20 ppm in the ‘ascending phase’ of the study and at 2 ppm and 3 ppm in the ‘descending phase’ of the study. \( (P=0.013) \) [Figures 2a and 2b].

The hemodynamic parameters i.e., the heart rate, blood pressure, central venous pressure, pulmonary artery wedge pressure and peak inspiratory pressure showed no statistically significant improvement. The baseline mean (SD) cardiac output (CO) was 7.3 (0.7) L/min, which increased to 7.7 (0.06) L/min at 20 ppm NO.

There were 8 responders in the study- 4 by increase in \( \text{PaO}_2/\text{FiO}_2 \) ratio and 4 by decrease in PSAP without corresponding increase in \( \text{PaO}_2/\text{FiO}_2 \) ratio. Seven of the eight responders had pneumonia. Responders had significantly lower \( \text{PaO}_2/\text{FiO}_2 \) ratio (96.7 ± 26.6 vs 135.2 ± 45 mmHg) \( (P=0.032) \), were ventilated for significantly shorter period before INO treatment than non responders (103.5 ± 82.43 vs 394.89 ± 479.87 hrs) \( (P=0.037) \) and had a higher hematocrit (28.2 ± 5.94 vs 22.3 ± 2.06). 8 out of 13 patients enrolled into the study, did not survive.

**Discussion**

The ventilatory strategy used in our study is similar to the treatment group data provided by the acute respiratory distress syndrome network.\(^1\)\(^2\)

The following studies formed the basis for the INO concentrations in our study. Bigatellow \textit{et al}\(^4\) and Rossaint \textit{et al}\(^5\) have showed that INO of 5-20 ppm are sufficient to elicit a significant increase in \( \text{PaO}_2 \) and that toxicity is immeasurable at these concentrations. Gerlach
et al\textsuperscript{[6,7]} showed that INO of 10 ppb to 100 ppb is required to improve oxygenation and INO of 1-10 ppm, to improve pulmonary hypertension in ARDS.

The variability in response to INO prompted us to study the same concentrations in the reverse order to note consistency in response. The repeat dose testing to see the consistency in response, was also done by Lundin \textit{et al}\textsuperscript{[8]} and Treggiary Venzi \textit{et al}.\textsuperscript{[9]} The consistency in response (± 10% of corresponding values) to INO was not seen in our study, which corresponded with the results of these authors.

Equilibration time of inhaled and alveolar concentrations has been reported as 10 to 20 minutes. This prompted us to use INO for 15 minutes at each concentration.

The observed change in the PaO$_2$/FiO$_2$ ratio in our study was a non dose dependent, non linear increase. The non dose-dependent change in oxygenation parameters in our study was similar to Johannigam \textit{et al}.\textsuperscript{[10]} but the data from Bigatellow \textit{et al}.\textsuperscript{[4]} showed a dose dependent increase in PaO$_2$/FiO$_2$.

Treggiari-Venzi\textsuperscript{[9]} \textit{et al} and Lowson \textit{et al}\textsuperscript{[11]} found a maximum increase in PaO$_2$/FiO$_2$ ratio at 10 ppm INO, with a range of 1-20 ppm INO. However, in our study, the INO concentration at which maximum response observed was 3-10 ppm, which we attribute to optimal lung recruitment.

The observed change in PASP was non dose dependent, non linear and unrelated to the change in oxygenation. From our data, it was observed that the reduction in PAP is related to the duration of INO treatment, as the PASP was lower in the descending phase of study, than the ascending phase for the same INO concentration.

Reviewing the literature, we have found contradictory reports. Rossetti \textit{et al}\textsuperscript{[12]} described a significant fall in pulmonary artery pressures (PAP) at 15 and 25 ppm INO ($P=0.001$). Lowson \textit{et al}\textsuperscript{[11]} showed non dose dependent fall in mean PAP ($P<0.022$) at 10 ppm INO. Iotti \textit{et al}\textsuperscript{[13]} described a dose dependent fall in mean PAP from 0.5-5 ppm, while Puybasset \textit{et al}\textsuperscript{[14]} described a dose dependent fall in mean PAP with INO of 0.1-2 ppm. However, Luyt \textit{et al}\textsuperscript{[15]} and Lundin \textit{et al}\textsuperscript{[16]} showed that INO had no effect on PAP.

In our study, we had 21 concentrations of INO. Due to extreme variability in response to INO, we defined responders as those who had either persistent increase in PaO$_2$/FiO$_2$ of 15% or more, or decrease in PASP of 15%. Of the 13 patients studied, 8 patients were responders by the above criteria i.e., 62% which corresponds with the data by Manketelow \textit{et al}.$^{[17]}$

A marked variation was observed during our study in the hemodynamic and oxygenation effects of INO. The reasons for the variability include preexisting pulmonary disease, infusions of vasoactive drugs, ventilation associated lung injury and pulmonary vascular remodeling in ARDS. The “Responders” had maximum increase in PaO$_2$/FiO$_2$ at concentrations between 3 and 10 ppm. Once maximum increase was reached, further increase in INO did not increase PaO$_2$ or reduce PASP significantly. Patients who were “Responders” by PAP criteria, were non-responders by PaO$_2$/FiO$_2$ criteria, thereby showing that changes in PAP were independent of PaO$_2$ changes, which was similar to the data from Lundin \textit{et al}.\textsuperscript{[9]} From our study, it was clear that the “Responders” had significantly lower PaO$_2$/FiO$_2$ ratio similar to data from Treggiari-venzi\textsuperscript{[9]} and Dupont \textit{et al}.\textsuperscript{[18]} the duration of ventilation before INO treatment as a marker of response to INO was lesser, which has not been shown before and that we feel probably reserves the place for INO treatment in early severe ARDS.

From the concentrations, we studied that the optimum dose to improve oxygenation was between 3 ppm and 10 ppm. Neither oxygenation nor the pulmonary hypertension in ARDS showed dose dependent change. Concentrations of inhaled NO above 10 ppm do not produce any further benefit. We could not identify a uniform predictor of response to INO treatment, however low baseline PaO$_2$/FiO$_2$ ratio and shorter duration of ventilation prior to INO treatment appears to be best predictive markers of beneficial response to INO.

\textbf{Conflict of interests: None}

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References


