Nitric oxide

P095

Accuracy in dosage and dose monitoring of nitric oxide in high frequency oscillatory ventilation.

P. C. Markhorst, T. Leenhoven*; A.J. van Vught*. Department of pediatrics, pediatric intensive care unit, Free University Hospital, Amsterdam, The Netherlands.

Introduction: Nitric oxide inhalation therapy requires a dosage unit, consisting of flow controllers for bias and NO flow as well as NO and NO2 monitoring devices.

Materials and methods: We compared accuracy of digital mass flow controllers for bias and NO flow as well as NO and NO2 monitoring devices.

Results: We found major influences of used flow controllers, humidification, and NO2 in clinical conditions was assessed, with NO and bias flow MFC controlled. NO and NO2 concentrations were measured using both chemiluminescence (ICL 700, EcoPhysics, Diemtigt, Switzerland) in dry gas containing 21% oxygen.

Conclusions: We conclude that a system consisting of one MFC for NO dosage, rotameter for bias flow control and electrochemical NO and NO2 analyser has adequate accuracy for clinical use during HFOV. Our electrochemical analyser uses a cell, with limited sensitivity to high oxygen levels, sample gas was dried via a permeascope tubing and pressure swings were not allowed to reach the analyser.

P096

Occupational exposure levels by nitric oxide inhalational therapy in a pediatric intensive care setting.

P. C. Markhorst, T. Leenhoven*; A.J. van Vught*. Department of pediatrics, pediatric intensive care unit, Free University Hospital, Amsterdam, The Netherlands.

Aim of the study: To determine the amount of occupational exposure of nitric oxide (NO) and nitrogen dioxide (NO2) during NO inhalational therapy.

Materials and methods: In a standard pediatric intensive care room, NO 800 parts per million (ppm) was delivered to a high frequency oscillator (3100-A, SensorMedics, Bologna, Italy). NO levels were measured with a chemiluminescence analyzer. NO flow and NO2 concentration were measured using a chemiluminescence analyzer. NO flow and NO2 concentration were measured using a chemiluminescence analyzer. NO flow and NO2 concentration were measured using a chemiluminescence analyzer. NO flow and NO2 concentration were measured using a chemiluminescence analyzer.

Results: Maximal concentrations of NO and NO2 were reached after 4 hours of NO use. Data are summarised in the table.

| Dosage accuracy | 2 MFC | 0.99 (0.863-0.99) |
|-----------------|-------|-----------------|
| Chemiluminescence | 3100 A biasflow, rotameter (NO) | 1.175 (0.793-1.74) |
| Measurement accuracy | electrochemical, dry gas | 1.017 (1.006-1.029) |
| M FC | electrochemical, humid gas | 1.131 (1.099-1.173) |
| Chemiluminescence, humid gas | 1.136 (1.126-1.145) |

Conclusions: We conclude that a system consisting of one MFC for NO dosage, rotameter for bias flow control and electrochemical NO and NO2 analyser has adequate accuracy for clinical use during HFOV. Our electrochemical analyser uses a cell, with limited sensitivity to high oxygen levels, sample gas was dried via a permeascope tubing and pressure swings were not allowed to reach the analyser.

P097

PROGNOSTIC FACTORS IN RESPONSE TO NITRIC OXIDE IN CHILDREN

Lopes-Herce J. Carrillo A, Alcaraz A, Moral R, Bustinza A, Sancho L. Pediatric Intensive Care Unit. Gregorio Marañón General University Hospital. Dr Castelo 49. 28009 Madrid, Spain.

Objective: To evaluate the prognostic factors in the response to nitric oxide (NO) in children with Acute Respiratory Distress Syndrome (ARDS) and/or pulmonary hypertension (PHM).

Materials and methods: 23 critically ill children received NO administered for ARDS and/or PHM treatment. 14 patients before and after cardiac surgery. 5 patients with bronchopneumonia, 2 multiple trauma, 1 sepsis and 1 cardiocerebral arrest. 15 patients showed ARDS and 8 PHM, in 6 with associated ARDS. We analysed age, sex, diagnosis, PaO2/FiO2, PW2, PaO2/PiO2, Oxygenation Index, PHM, shock, and sepsis as prognostic factors and response factors to NO.

Results: After NO administration oxygenation did not improve in 2 patients (8.6%) and PHM did not diminish in 3 children (12%). 12 patients survived (52%). 8/15 (53.3%) with ARDS and 4/8 (50%) with PHM. The four patients with isolated PHM survived and the 5 patients with PHM and ARDS died. Patients after cardiac surgery presented less mortality (35.7%) than the rest of patients (66.2%). Patients with shock presented higher mortality (64.2%) than the rest of patients (22.2%). There are no differences in response to NO in respect of sex, age, diagnosis, shock, and sepsis. Survivors showed higher increase of PaO2/PiO2 64.3 ± 58.4 to NC of non-survivors 48.4 ± 51.1 (N.S). Patients with PHM showed higher increase in PaO2/PiO2 to NO administration (88 ± 47.1) than patients with ARDS (43.4 ± 50.8) (N.S), but patients with ARDS showed a higher increase in PaO2 15 ± 6.7, than patients with PHM 4.8 ± 4 (p < 0.05). Patients with PaO2/PiO2 < 100 showed less increase in PaO2/PiO2 to 47.8 ± 46.3, than the rest of patients 82.8 ± 65.5 (N.S).

Conclusions: 1. Mortality of isolated PHM treated with NO is less than patients with ARDS. Patients with shock and those with PHM and ARDS showed higher mortality. 2. We have not found any clinical or analytical factor to predict clinical response to NO administration.

P098

NITRIC OXIDE ADMINISTRATION IN PULMONARY HYPERTENSION AND ACUTE RESPIRATORY DISTRESS SYNDROME IN CHILDREN

López-Herce J., Vásquez P, Carrillo A, Sánchez A, Cueto E. Pediatric Intensive Care Unit, Gregorio Marañón General University Hospital. Dr Castelo 49. 28009 Madrid, Spain.

Objective: To analyze the effect of nitric oxide (NO) on pulmonary pressure and oxygenation in children with pulmonary hypertension (PHM) and/or with Acute Respiratory Distress Syndrome (ARDS). 23 critically ill children received NO administered for ARDS and/or PHM treatment. 14 patients before and after cardiac surgery. 5 patients with bronchopneumonia, 2 multiple trauma, 1 sepsis and 1 cardiocerebral arrest. 15 patients showed ARDS and 8 PHM, in 6 with associated ARDS.

Materials and methods: We administered NO inhaled between 1.5 and 45 ppm to 23 children aged between 15 days and 16 years (14 boys and 9 girls). 14 patients showed ARDS, and 9 severe PHM after cardiovascular surgery, in 5 with associated ARDS. We registered respiratory assistance, blood gases, PaO2/PiO2, the oxygenation index (OI), and mean pulmonary pressure/mean systemic pressure (PAP/BAP) before and after NO inhalation. We measured continuous concentration of NO and NO2 by electrochemical method (Nonox, Bedford, Airliquide).

Results: NO administration improved oxygenation mean PaO2 from 74 ± 17 mmHg to 119 ± 54 mmHg (p < 0.01), mean PaO2/PiO2 from 83 ± 30 to 139 ± 72 (p = 0.01) and OI from 28 ± 20 to 15 ± 12 (p < 0.01). 2 patients did not improve with NO administration. The oxygenation improved in the first five minutes and the best oxygenation was achieved with 5 - 15 ppm. There is no significant change in Pao2/PiO2, PAP/BAP diminished from 42 ± 17 to 42 ± 9 % (p < 0.05). In one patient there is no response. The NO administration was maintained between 45 minutes to 47 days. The effect of NO on pulmonary pressure and oxygenation was maintained without change during all the time it was administered. NO2 concentration were always less than 2 ppm and methemoglobinemia less than 3.5%. There are no side effects secondary to NO administration. 12 patients survived (52%).

Conclusions: NO administration improves oxygenation in children with ARDS and diminishes PHT after cardiac surgery. 2NO effect is fast and maintained during the evolution.
**P 099**

**High Frequency Oscillatory Ventilation in Combination with Inhaled Nitric Oxide**

Göteborg Sylvia, MD, Ebendörfer K E MD, PhD, Dept of Paediatric Intensive Care, Children's Hospital, S-416 85 Göteborg, Sweden

**Background:**

For many years very sick infants with congenital heart malformations or acute lung disorders have died due to pulmonary hypertension, hypoxia and multiple organ failure. Today there are several therapeutic facilities coming up for these infants. ECMO programmes have been introduced in several centres as well as improved ventilatory techniques, as high frequency oscillatory ventilation (HFOV), which provides adequate ventilation with less risk for lung injury.

In 1987, the endothelium derived relaxing factor was identified as nitric oxide (NO), and extensive studies have shown that inhaled NO reduces pulmonary vascular resistance and improves oxygenation in hypoxic infants with pulmonary hypertension.

**Material:**

From July 1994 to January 1996, we have treated 13 severely hypoxic children with combined HFOV-NO. Seven were newborn, 3 with CDH, one with MAS, one with BRDS, one with paediatric ARDS due to RSV infection and one with poor oxygenation after open heart surgery. 6 were between 1 month and 9 years and all had ARDS of different origin but one who was hypoxic after open heart surgery.

**Method:**

HFOV was given by means of SensorMedics 3100A oscillatory ventilator to 12 patients, and Dräger Babylight 8000 was used in one case. Mean airway pressures varied from 10-34 cm H2O. Oscillatory pressures varied from 23-45 cm H2O and ventilatory rates from 6-15 Hz. F 02 varied from 0,21 - 1.0. NO was administered by NOSPULUS classic NO and NO 2, was measured in the inspiratory limb with an electrochemical device. NO concentration varied from 2 to 20 ppm and the NO2-concentration between 0-0,2 ppm. Methemoglobin was never more than 3,7 % (average 1,7). Duration of treatment varied from 1 to 20 days.

**Results:**

Combined treatment with HFOV and inhaled NO improved oxygenation and carbon dioxide elimination in 12 out of 13 treated children. 5 patients died, 3 due to their underlying congenital heart disease, one of asphyxia due to RSV-infection and one of CDH with progressive hypoxia and multiple organ failure.

**Conclusion:**

Combined treatment with HFOV and inhaled NO may improve oxygenation in severely hypoxic children. Treatment should be started early to reduce the risk for chronic lung injury following barotrauma and high oxygen concentrations. We speculate that the combined HFOV-NO may reduce the use of ECMO, and that it may improve outcome in centres where ECMO programmes are not introduced.

---

**P 101**

**Nitric oxide (NO) in concentrations used during inhalative NO therapy and its effect upon bacterial growth**

T. Houben, J. Hübner, E. Paboura, J.U. Leitmus

Neonatal Intensive Care Unit, University Children's Hospital, Freiburg, Germany

Apart from its vasodilative properties nitric oxide appears to act also in physiologic immune defense. Intracellular concentrations of NO synthesized by macrophages are in the range of 10-9 above those produced by vascular endothelium. We investigated the bacteriostatic effect of nitric oxide at concentrations used during inhalated therapy for pulmonary vasodilatation in neonates. Ten different strains of five species were used (Staph. aureus, Staph. epidermidis, Strep. group B [GBS], E. coli and Pseudomonas aeruginosa), which are the most often tracheally isolated bacteria in mechanically ventilated premature infants and neonates. We compared bacterial growth of cultures applying three different concentrations of nitric oxide (40 ppm, 80 ppm, 120 ppm) to the growth of the same strains in room air for a duration of 24 hours.

No bacteriostatic effect was demonstrable at NO concentrations of 40 ppm. E. coli showed decreased bacterial growth at 80 ppm and 120 ppm, however without reaching statistical significance (p = 0.058). At nitric oxide concentrations of 120 ppm Staph. epidermidis and GBS grew significantly less as compared to colonies of the same strains in room air. No effects were found regarding the growth of Staph. aureus and Pseudomonas aeruginosa.

We conclude that nitric oxide has a selective bacteriostatic effect on some of the most often tracheally isolated bacteria in pressure infants and neonates. This effect appears to be dose-dependent and occurs in the upper range of dosages used with inhaled NO therapy. Further research is required in order to examine the mechanisms of action as well as specific interactions between different strains of bacteria and nitric oxide.

---

**P 102**

**Sensitivity of the Bedfont NO-Monitor to Airway Pressure and Sample Location**

H.R. van Genderinuen, D.G. Markhorst, H.N. Lafeber

The NOBox monitor (Bedfont, Kent, UK) is used to monitor nitric oxide (NO) and nitric dioxide (NO2) during NO administration in ventilated neonates. According to the manufacturer's specifications the monitor can be applied in cases where airway pressures range from 5 to 50 mbar. We investigated in-vitro the accuracy of the NO monitor in a range of ventilatory conditions.

Using a Dräger Babylight 8000 we ventilated an artificial lung. NO was administered (800 ppm NO in 100% nitrogen) with a mass flow controller to the inspiratory tube, at a distance of 20 cm from the Y-piece. The NO target value was set to 10 ppm. The ventilator was operated in both CPAP and IPPV modes at different settings. The NO sampling tube was placed on two different locations: in the inspiratory tube close to the Y-piece and the ventilator.

The NO-monitor was calibrated with 84 ppm NO at 30 mbar. At nitric oxide concentrations of 120 ppm Staph. epidermidis and GBS grew significantly less as compared to colonies of the same strains in room air. No effects were found regarding the growth of Staph. aureus and Pseudomonas aeruginosa.

We conclude that the accuracy of the Bedfont NO-monitor is dependent upon airway pressure and sample location, which are in the range of 10 above those produced by vascular endothelium. We investigated the bacteriostatic effect of nitric oxide at concentrations used during inhalated therapy for pulmonary vasodilatation in neonates. Ten different strains of five species were used (Staph. aureus, Staph. epidermidis, Strep. group B [GBS], E. coli and Pseudomonas aeruginosa), which are the most often tracheally isolated bacteria in mechanically ventilated premature infants and neonates. We compared bacterial growth of cultures applying three different concentrations of nitric oxide (40 ppm, 80 ppm, 120 ppm) to the growth of the same strains in room air for a duration of 24 hours.

No bacteriostatic effect was demonstrable at NO concentrations of 40 ppm. E. coli showed decreased bacterial growth at 80 ppm and 120 ppm, however without reaching statistical significance (p = 0.058). At nitric oxide concentrations of 120 ppm Staph. epidermidis and GBS grew significantly less as compared to colonies of the same strains in room air. No effects were found regarding the growth of Staph. aureus and Pseudomonas aeruginosa.

We conclude that nitric oxide has a selective bacteriostatic effect on some of the most often tracheally isolated bacteria in pressure infants and neonates. This effect appears to be dose-dependent and occurs in the upper range of dosages used with inhaled NO therapy. Further research is required in order to examine the mechanisms of action as well as specific interactions between different strains of bacteria and nitric oxide.
Availability of Nitric Oxide Inhalation Therapy Reduces Use of Extracorporeal Membrane Oxygenation (ECMO) as Therapy for Severe Neonatal Respiratory Failure

Ross GA MD; Hoffman, GM, MD; Nelin, LD, MD; Havens, PL, MD
Children's Hospital of Wisconsin, Milwaukee, Wisconsin, 53201

Hypothesis: Availability of therapy with inhaled nitric oxide (iNO) decreases ECMO use in patients referred to a tertiary care hospital for treatment of respiratory failure unresponsive to conventional therapies.

Background: At Children's Hospital of Wisconsin (CHW) treatment for patients who have failed conventional treatment for respiratory failure, sometimes called "rescue" therapy, has included ECMO since 1986 and high frequency oscillatory ventilation since 1992. iNO has been in experimental use at CHW since May of 1994 and has resulted in the perception of a decreased need for ECMO therapy in those patients referred for rescue therapy. This study was designed to test the validity of that perception.

Study Type: Retrospective cohort.

Methods: The medical records of all 105 patients referred to CHW from 1/1/93 to 4/1/95 for rescue therapy for severe respiratory failure were included in the chart review. Data were collected regarding diagnoses, illness severity, hospital course including interventions and complications, and outcomes. Exclusion criteria were the finding of structural heart disease or congenital diaphragmatic hernia as the basis for hypoxemia. Qualification for iNO treatment included an A-aDo2 > 600 or Os2 > 40 for two hours or > 25 for twelve hours and echocardiographic demonstration of persistent pulmonary hypertension of the newborn. Patients were classified into two groups based on the availability of iNO at the time of their hospitalization.

Results: In the time period of the study, 105 patients were referred for possible ECMO therapy. Twelve patients greater than 4 weeks old, 31 with congenital diaphragmatic hernia and 12 with congenital heart disease were excluded from this analysis, leaving 50 patients for study. iNO availability reduced ECMO use from 16 of 34 (47%) patients in the "NO unavailable" group to 2 out of 16 (12.5%) patients in the "NO available" group, p=0.026 by Fisher's exact test. The fact that the two groups were composed of patients of similar severity of illness is reflected by comparable rates of ECMO and iNO rescue therapy (47% vs. 56%).

Conclusion: By providing an alternative rescue therapy, iNO has reduced the need for ECMO in this group of neonates referred for respiratory failure.