Effects of inhaled nitric oxide on oxygenation and haemodynamic performance during one-lung ventilation in pigs

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Abstract

Objective: To study the effects of 20 ppm inhaled nitric oxide (iNO) on haemodynamics and systemic oxygenation during one-lung ventilation (OLV) in vivo. **Design:** Prospective animal study with a cross-over design. **Setting:** Animal laboratory of a university hospital. **Subjects:** Eight female pigs. **Outcome measures:** The pigs were anaesthetized, tracheally intubated, and mechanically ventilated. Following placement of femoral arterial and pulmonary artery catheters, a left-sided double-lumen tube (DLT) was placed via tracheotomy. After DLT placement, in each animal OLV was performed during intravenous anaesthesia in a cross-over design with and without iNO (20ppm) in 100% oxygen. After haemodynamic stabilization, haemodynamic measurements and blood gas analyses were made, in addition we measured differential lung perfusion with colored microspheres in three animals. **Results and Conclusions:** iNO did not improve oxygenation nor did iNO reduce pulmonary arterial pressure in our animal model. Mixed venous PvO_2 and cardiac output were comparable during the study periods.

Key words: Thoracic anaesthesia; One-lung ventilation; Nitric oxide; Oxygenation

Introduction

One-lung ventilation (OLV) is frequently required for lung, mediastinal, esophageal or aortic surgery. Although OLV is not always mandatory for such procedures, it improves access to the operative field and expedites the surgery. The most important problem that occurs during OLV is hypoxemia. The incidence of hypoxaemia during OLV is 5-10%, even if 100% oxygen is used for ventilation.[1-4] The reason for this is that the non-ventilated lung remains perfused during the procedure, increasing the transpulmonary shunt fraction. Increasing the perfusion of the ventilated lung by drugs may be a possible strategy to improve oxygenation during OLV without inflating the non-dependent lung. One possible agent for this purpose is the endothelial dependent vasorelaxing factor nitric oxide (NO). In theory inhaled nitric oxide (iNO) could increase oxygenation by selectively decreasing pulmonary resistance and increasing blood flow to the ventilated lung. To investigate the effects of iNO on oxygenation and haemodynamics during OLV in vivo, we performed an animal study in pigs.

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Methods

With approval of the local animal protection committee, 8 female pigs (German land race, 32± 1kg) were studied. The animals were premedicated with ketamine (500mg intramuscularly) to allow placement of an intravenous catheter in an auricular vein, and to initiate ECG and pulse oximetry monitoring. Anaesthesia was induced with propofol (2-3mg/kg intravenously), muscle relaxation was achieved with pancuronium (0.2mg/kg intravenously), and the trachea of the animal was orally intubated with a 7.5ID tracheal tube. Ventilation was adjusted to maintain arterial CO_2 tension ($PaCO_2$) at approximately 35-40mmHg. During preparation

anaesthesia was maintained with a 1:1 mixture of nitrous oxide (N_2O) and oxygen (O_2) and a continuous infusion of propofol (20-35mg·kg^{-1}·h^{-1}), remifentanil (10-20µg·kg^{-1}·h^{-1}) and pancuronium (0.15-0.2mg·kg^{-1}·h^{-1}). Using a sterile technique, an arterial catheter was placed in the left femoral artery and a central venous catheter was placed via the right internal jugular vein, to measure arterial and central venous blood pressure, respectively. A flow-directed thermodilution pulmonary artery catheter was passed through the right external jugular vein to measure cardiac output and pulmonary artery pressure. We positioned the tip of the pulmonary artery catheter just beyond the pulmonary valve to ensure placement in the main pulmonary artery (i.e. the catheter was not advanced to the wedge-position). The catheter was connected to a cardiac output (CO) device. CO measurements were performed in triplicate, using an injectate of 10ml cold saline (1-5°C), and averaged for each time point.

Tracheostomy was performed and the orotracheal tube replaced using Fibreoptic control by a left-sided, specially designed 39Ch double-lumen tube. This DLT ensured that the right upper bronchus (which, according to the pig's anatomy originates from the trachea) could also be ventilated or accessed through the tracheal limb. After DLT placement, the animals were positioned in the right lateral decubitus position, and an 8.5F tracheal tube was passed through a left-sided mini-thoracotomy into the left pleural space. Ventilation to the left lung was then discontinued and lung collapse was verified by Fibreoptic observation of the left pleural space. OLV of the right lung was maintained during the whole study and correct DLT placement was verified by continuous dual capnography, Fibreoptic bronchoscopy, and by thoracoscopy at the end of both study periods.[5]

After these measures, remifentanil and N_2O were discontinued, and intravenous anaesthesia was continued with propofol without changing the infusion rate throughout the experiment.

FiO_2 was adjusted at 1.0. We set the ventilation pressure at 25cmH_2O, expiratory pressure (PEEP) at 5cmH_2O, and varied the respiratory frequency to achieve an end-tidal CO_2 at 33-38mmHg.

We used a modified ICU respirator including a NO delivery device (Evita 2 NODOMO). The NODOMO adjusts NO flow proportionally to the flow of the respirator to maintain a stable NO concentration. In addition it reliably measures NO concentrations in the inspiratory limb of the respiratory circuit. Each animal underwent in randomized order, two study phases, i.e. OLV with and without iNO 20ppm. Data were recorded in each study period after equilibration times of at least 30 minutes with variations of blood pressure, heart rate and end-tidal CO_2 of no more than 10%. We noted cardiorespiratory parameters and obtained blood gas analysis. In three animals colored microspheres (see below) were administered through a central venous line for measurement of pulmonary perfusion in each study phase.

Microsphere technique: Application and methodological consideration of microsphere measurements have been presented in detail elsewhere.[6] In summary, for measurements of regional pulmonary perfusion, 1.2·10^6 colored microspheres with a nominal diameter of 15µm were injected slowly over 2min via the central venous catheter into the superior vena cava. Microsphere injections were performed at the end of the two experimental phases, using different colored microspheres in random sequence. At the end of the experiment the right and the left lungs were removed, dissected, and digested separately by placing them in a 4N concentrated solution of KOH. To obtain the microspheres, the digested samples were filtered through 8µm pore polyester membranes filters. The colored microspheres were quantified by their dye content. The dye was removed from the microspheres by adding 150µl dimethylformamide as a solvent. The photometric absorption of each dye solution was determined using a spectrophotometer at wave lengths 190-820mm. The number of microspheres was calculated using the specific absorbance value of the different dyes. Percentage of the right lung perfusion was calculated as the proportion of the microsphere number obtained from right lung on total number of microspheres.

Throughout the experiment the animals were kept in the right lateral decubitus position. The pigs received 10 ml/kg of body-warm balanced electrolyte solutions during the study period. At the end of the experiment the pigs were euthanized with a lethal dose of potassium chloride.

The data was statistically analyzed with the computing program SPSS, using Wilcoxon's signed rank test. A p value of <0.05 was considered statistically significant. No statistical test was used to compare lung perfusion data because these data were only obtained in three animals.

Results

Oxygenation during OLV with application of 20ppm nitric iNO was not improved as compared with oxygenation during OLV without iNO. In addition, all haemodynamic parameters in both study periods, including pulmonary arterial pressure, were comparable with and without the application of NO (Table 1). Perfusion of the ventilated lung seems to remain unchanged during application of iNO (Perfusion of the right lung during OLV measured in three animals with the microsphere technique: 89±14% with iNO vs. 88±11% without iNO).

Table 1: The effects of nitric oxide on haemodynamic variables and oxygenation during one-lung ventilation

	OLV with iNO	*OLV without iNO*
PaO_2 (mm Hg)	347±124	353±110
$PaCO_2$ (mm Hg)	43±9	44±10
$etCO_2$ (mm Hg)	40±7	38±6
PvO_2 (mm Hg)	48±6	50±6
SvO_2 (%)	82±4	82±5
SpO_2 (%)	99±1	99±1
HR (/min)	86±18	86±19
PAP (mm Hg)	20±4	21±4
MAP (mm Hg)	91±21	81±18
CVP (mm Hg)	8±2	9±2
CO (L/min)	3.8±1	3.8±1.2
Vt (ml)	345±80	357±75
RR (/min)	22±7	20±7
PAW (cm H_2O)	25±1	25±1

Means ± SD; No significant differences between OLV with and without iNO for all variables.
PAP = mean pulmonary artery pressure; MAP = mean systemic arterial pressure; CVP= central venous pressure; CO = cardiac output; Vt = tidal volume; RR = Respiratory rate; $etCO_2$ = endtidal CO_2; PAW = peak airway pressure.

Discussion

The main result of our animal study is in accordance with the results of most clinical studies during OLV in patients, where oxygenation was not improved by using iNO in concentrations of 20-40ppm.[3,7-9] Only Rocca demonstrated in a clinical study in 30 patients a small benefit of iNO in high-risk patients with a severe ventilation-perfusion mismatch.[10]

In 2002 Sticher published data of an animal study in pigs, using different concentrations of iNO (4, 8, 16, 32ppm) during one-lung ventilation.[11] Oxygenation during OLV with iNO was improved in a dose-dependent manner, in the course of which iNO at 4ppm improved oxygenation to a greater extent than 8, 16 or 32ppm. The improvement in oxygenation was due to a reduction in intrapulmonary shunt flow, measured with the multiple inert gas elimination technique. The authors hypothesized that iNO at larger doses may spill over into the systemic circulation, thus attenuating the hypoxic pulmonary vasoconstriction effect of the upper lung which decreases PaO_2.

The improvement of oxygenation during OLV with iNO in the study of Sticher may be as a result of the fact that Sticher ventilated the smaller left lung of the animal using a FiO_2 of 0.8 compared with the setting in our study (ventilation of the larger right lung with a FiO_2 of 1.0). One may assume that the positive effect of iNO could be seen more easily during the use of a lower PaO_2. One reason why iNO could not divert blood from the non-ventilated to the ventilated lung in our experiment could be that the blood flow to the ventilated right lung in our experiment was already very high (88% of the total blood flow) without application of iNO, just as a result of the lateral decubitus position and of the maximum effect of hypoxic pulmonary vasoconstriction, which is not impaired by propofol.[12] In this situation, a further dilatation of the pulmonary vessels in the ventilated lung is probably not possible.

Conclusion

20ppm inhaled nitric oxide failed to improve oxygenation in our study in pigs during OLV in the right lateral decubitus position with total intravenous anaesthesia.

References

1. *Guenoun T, Journois D, Silleran-Chassany J, Frappier J, D'attellis N, Salem A, et al, Prediction of arterial oxygen tension during one-lung ventilation: Analysis of preoperative and intraoperative variables. J Cardiothorac Vasc Anesth 2002; 16 (2):199-203.*
2. *Hurford WE, Alfille PH. A quality improvement study of the placement and complications of double-lumen endobronchial tubes. J Cardiothoracic Vasc Anesth 1993; 7(5):517-520.*
3. *Schwarzkopf K, Klein U, Schreiber T, Preussler N, Bloos F, Helfritsch H, et al. Oxygenation during one-lung ventilation: effects of inhaled nitric oxide and increasing levels of inspired fraction of oxygen. Anesth Analg 2002; 92(4):842-847.*
4. *Slinger P, Suissa S, Triolet W. Predicting arterial oxygenation during one-lung anaesthesia. Can J Anaesth 1992; 39(10):1030-1035.*
5. *Shafieha MJ, Sit J, Kartha R, Sabnis L, Halianpour B, Pappas AL, et al. End-tidal CO2 analyzers in proper positioning of the double-lumen tubes. Anesthesiology 1986; 64(6):844-845.*
6. *Walter B, Bauer R, Gaser E, Zwiener U. Validation of the multiple colored microsphere technique for regional blood flow measurements in newborn piglets. Basic Res Cardiol 1997; 92(3):191-200.*
7. *Fradj K, Samain E, Delefosse D, Farah E, Marty J. Placebo-controlled study of inhaled nitric oxide to treat hypoxaemia during one-lung ventilation. Br J Anaesth 1999; 82(2):208-212.*
8. *Moutafis M, Liu N, Dalibon N, Kuhlman G, Ducros L, Castelain MH, et al. The effects of inhaled nitric oxide and its combination with intravenous almitrine on PaO2 during one-lung ventilation in patients undergoing thoracoscopic procedures. Anesth Analg 1997; 85(5):1130-1135.*
9. *Wilson WC, Kapelanski DP, Benumof JL, Newhart 2nd JW, Johnson FW, Channick RN. Inhaled nitric oxide (40ppm) during one-lung ventilation, in the lateral decubitus position, does not decrease pulmonary vascular resistance or improve oxygenation in normal patients. J Cardiothorac Vasc Anesth 1997; 11(7):172-176.*
10. *Rocca GD, Passariello M, Coccia C, Costa MG, Di Marco P, Venuta F, et al. Inhaled nitric oxide administration during one-lung ventilation in patients undergoing thoracic surgery. J Cardiothorac Vasc Anesth 2001; 15(2):218-222.*
11. *Sticher J, Scholz S, Boening O, Schermuly RT, Schmacher C, Walmrath D, et al. Small-dose nitric oxide improves oxygenation during one-lung ventilation: an experimental study. Anesth Analg 2002; 95(6):1557-1562.*
12. *Nakayama M, Murray PA. Ketamine preserves and propofol potentiates hypoxic pulmonary vasoconstriction compared with conscious state in chronically instrumented dogs. Anesthesiology 1999; 91(3):760-771.*