Contamination of anaesthetic gases with nitric oxide and its influence on oxygenation: study in patients undergoing open heart surgery

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Background. Nitric oxide is important in vasomotor regulation. Contamination of anaesthetic gases with nitric oxide could affect gas exchange.

Methods. We measured oxygenation and nitric oxide concentrations in the inspiratory and expiratory limb of the ventilator circuit in patients about to have cardiac surgery. Measurements were made before surgery when the circulation and respiratory conditions were stable. \( F_{\text{IO2}} \) was set at 0.35. The breathing circuit was supplied with a fresh gas flow greater than the minute volume so that exhaled gas was not re-used. Three gas mixtures were given in sequence to each patient: oxygen and compressed air (AIRc), oxygen and nitrous oxide, and oxygen and synthetic air (AIRs) that was free from nitric oxide. All patients were given AIRs as the second gas and the other two gas mixtures (AIRc and nitrous oxide) were given randomly as the first and third gases.

Results. During ventilation with oxygen–AIRc, the median nitric oxide concentration was 5.6 ppb, during ventilation with oxygen–nitrous oxide it was 5.0 ppb and using oxygen–AIRs it was 1.5 ppb. When AIRc and nitrous oxide were used, \( P_{\text{aO2}} \) was greater and venous admixture was less than when AIRs was used. The different gas mixtures did not affect pulmonary vascular pressures or cardiac output.

Conclusions. Compressed air and nitrous oxide contain very low concentrations of nitric oxide (<10 ppb). This can affect pulmonary oxygen transfer during anaesthesia.

Br J Anaesth 2004; 93: 629–33

Keywords: anaesthetics gases; complications, nitric oxide contamination; oxygen, inspired concentration, partial pressure

Accepted for publication: June 22, 2004

Nitric oxide is an important substance involved in many biological processes, including neurotransmission, cellular host defence and gastrointestinal motility, and is a key substance in vasomotor regulation.\(^1\)\(^2\)

Inhaled nitric oxide has been used to treat infants with pulmonary artery hypertension (PAH) and adults with acute lung injury (ALI).\(^3\) Nitric oxide concentrations of 100–2000 ppb can improve arterial oxygenation in patients with ALI,\(^4\) and concentrations of 5–40 ppm are used for treating PAH.

Compressed air (AIRc) is used in generic anaesthetic machines or ventilators. This AIRc contains variable amounts of nitric oxide as a result of air pollution,\(^5\)\(^6\) and this may affect lung function. In addition, ventilation with a mixture of nitrous oxide and oxygen is common in general anaesthesia. Little is known about the effects of contamination of nitrous oxide by nitric oxide.

We investigated pulmonary artery pressure and oxygen exchange in patients before cardiac surgery. We used a constant \( F_{\text{IO2}} \) of 0.35 and mixtures of oxygen with compressed air, nitrous oxide and synthetic air which contains less nitric oxide.

Methods

After approval from the ethics committee (Ethik-Kommission der Ärztekammer Hamburg) and with written consent,
consent we studied 37 patients (NYHA II–III) who were about to have elective cardiac surgery. We excluded patients with known lung disease or poor left ventricular function (ejection fraction <0.3).

The patients were premedicated with flunitrazepam 1–2 mg orally. An ECG lead II and a pulse oximeter probe were attached. A pulmonary artery catheter (Baxter, Irvine, CA, USA) and arterial and venous cannulae were placed before induction of anaesthesia. Anaesthesia was induced with etomidate 0.2 mg kg\(^{-1}\), fentanyl 5 \(\mu\)g kg\(^{-1}\) and pancuronium 0.1 mg kg\(^{-1}\). Anaesthesia was maintained with propofol 0.5 mg kg\(^{-1}\) i.v.

After tracheal intubation, the lungs were ventilated with a set volume (Cicero Machine, Dräger, Lübeck, Germany). The fresh gas flow was set to be greater than the respiratory minute volume to avoid rebreathing of alveolar gas. In a correctly functioning system without leaks, the fresh gas flow can be reduced to the alveolar minute volume so that only fresh and dead-space gas are present in the system at the start of the next inspiration. The respiratory minute volume was first adjusted to obtain an end-tidal carbon dioxide fraction of 3.5–4.0 vol %. Later, ventilation was adjusted to obtain an arterial pressure between 4.4 and 5.4 kPa (see Table 3 below). The inspiratory and expiratory concentrations of oxygen, nitrous oxide and end-tidal carbon dioxide were measured with an anaesthetic gas analyzer (Cardiocap, Datex, Finland).

When the circulation and respiratory state were stable, three different gas mixtures were used successively for ventilation:

(i) oxygen plus compressed air (AIRc) with \(F_{IO2}=0.35\);
(ii) oxygen plus synthetic air (AIRs) with \(F_{IO2}=0.35\);
(iii) oxygen plus nitrous oxide with \(F_{IO2}=0.35\).

During the use of each gas mixture we measured the inspiratory (NOinsp) and expiratory (NOexp) concentrations of nitric oxide 20 cm away from the Y-piece in the inspiratory and expiratory limbs of the breathing circuit. We used a chemiluminescent analyzer (TE24C-Chemiluminescens-NO-NO\(_2\)-NOx-Analysator, Thermo Instruments GmbH, Dortmund, Germany). This device measures nitric oxide concentrations down to 0.4 ppb and is linear to within 1% over the range 0.4 ppb to 100 ppb. We calibrated the analyzer periodically using three calibrating gases: pure nitrogen, nitrogen containing 180 ppb nitric oxide and nitrogen containing 320 ppb nitric oxide.

During ventilation with each gas mixture, we measured the following: inspiratory and expiratory oxygen concentration, inspiratory and expiratory nitrous oxide concentration, end-tidal carbon dioxide concentration, heart rate, mean arterial pressure, mean central venous pressure, mean pulmonary arterial pressure, mean pulmonary artery wedge pressure, cardiac output (thermodilution method), and arterial and mixed venous blood gases.

The pulmonary vascular resistance and the total peripheral resistance were calculated using standard formulae. The alveolar–arterial oxygen partial pressure difference \(P(A-a)_{o2}\) was calculated using the alveolar air equation:

\[
P_{AO2} = F_{IO2}(P_{bar}-P_{H2O})-P_{ACO2}/R + [(P_{ACO2}/R) \times (F_{IO2}1-R)]
\]

where \(R\) is the respiratory quotient. Values of \(P_{bar}=101.08\) kPa, \(P_{H2O}=6.25\) kPa and \(R=0.8\) were assumed. The shunt fraction \(Q/Q_i\) was calculated using the equation:

\[
Q_s/Q_i=(C_cO_2-C_{aO2})/(C_cO_2-C_{vO2})
\]

Arterial, venous and capillary oxygen saturation were obtained from line charts representing the oxyhaemoglobin dissociation curve (Kelman and Nunn) after correction of saturation for pH using the nomogram given by Kelman and Nunn.\(^8\)

The oxygen content \(C_{o2}\) was calculated using the formula:

\[
C_{O2}=Hb\times1.37So2+Po2\alpha
\]

where \(\alpha\) is the solubility coefficient (Bunsen) and has a value of 0.0228 ml dl\(^{-1}\) kPa\(^{-1}\) for oxygen, and each gram of haemoglobin can bind 1.37 ml of oxygen. The oxygen content of end-capillary blood was calculated from the ideal alveolar \(P_{O2}\).

After the study was completed, anaesthesia appropriate for the subsequent surgery was started.

Statistical analysis

Data are expressed as the median with the (25, 75) quartile or as the mean and standard deviation (SD). The data distributions are displayed using box and whisker plots of the inspiratory and expiratory nitric oxide concentrations. Histograms of the AIRc and nitrous oxide–nitric oxide values were used to determine whether the distribution of the measured concentrations was normal.

Comparisons of values obtained during AIRs–oxygen ventilation with those obtained in the other two periods were made using the Wilcoxon test.

Results

We studied 37 patients (13 male, 24 female) with a mean age of 66 yr (range 41–80), a mean height of 169 (SD 9) cm and a mean weight of 78 (13) kg. Coronary bypass grafts were planned in 29 patients, aortic valve replacements in three patients, mitral valve replacements in three patients, and aortic and mitral valve replacements in two patients.

The nitric oxide concentrations of the inspired and exhaled gases in the three measurement periods are given in Table 1 as median and quartile values and are shown graphically as box and whisker plots in Figure 1. Differences between oxygen–AIRs and the other gas mixtures are all significant (\(P<0.0001\)). Figure 2 shows the distribution of nitric oxide values in the oxygen–AIRc and oxygen–nitrous oxide mixtures. In the oxygen–AIRc mixture the nitric oxide values are nearly normally distributed, but in the
The oxygen–nitrous oxide mixture the values for two patients fall outside the normal distribution curve.

Figure 3 shows the individual values of the arterial $P_{O_2}$ during ventilation with compressed air, synthetic air and the nitrous oxide mixture. Lines link values for the same patient. The dotted line indicates that the gas mixture was given first (AIRc, $n=20$; nitrous oxide, $n=17$); the solid line indicates that the gas mixture was given last.

Table 2 presents the oxygenation data as medians and quartile values. Measures of oxygenation were significantly different during ventilation with AIRc and nitrous oxide mixtures: $P_{aO_2}$ was greater and $P(a-a)_{O_2}$ and $Q_s/Q_T$ were less with the nitrous oxide mixture than with AIRs. The mixed venous oxygen partial pressure was significantly greater during ventilation with AIRc than with AIRs, but the difference was not significant during ventilation with nitrous oxide.

The haemodynamic values obtained during the study are listed in Table 3. The heart rate, the cardiac output and the arterial, atrial and pulmonary pressures did not differ significantly in the three study periods.

The arterial carbon dioxide pressure was 4.7 (0.4) during ventilation with AIRc, 4.6 (0.5) during ventilation with AIRs and 4.6 (0.5) during ventilation with nitrous oxide. The pulmonary vascular resistance and total peripheral resistance did not change substantially with any of the different gas mixtures.
Discussion

Compressed air and nitrous oxide are used commonly in combination with oxygen to ventilate patients during general anaesthesia. We found that both gases contained low concentrations of nitric oxide. The contamination of compressed air with nitric oxide is well known. Low concentrations of nitric oxide in compressed air can improve arterial oxygenation in adult and paediatric ICU patients.\textsuperscript{67,9}

The mean nitric oxide concentrations used in those studies (70–140 ppb) were greater than in the present study (median 5.6 ppb). We checked our measurement device by measuring nitric oxide concentrations at a control point for air pollution near the hospital on the same day (median 4.0 (3.2–7.8) ppb). The lower level of air pollution is due to the location of Hamburg near the North Sea.

We found that the concentration of nitric oxide in nitrous oxide was similar to that in compressed air. Nitrous oxide is produced by heating ammonium nitrate to 240°C. After cleaning, it is liquefied under pressure. Overheating can result in contamination with nitric oxide and nitrogen dioxide. German standards require that nitric oxide contamination of nitrous oxide must not exceed 1 ppm. The concentrations we found were much less than this value (the highest concentration was 22.3 ppb).

The inspiratory nitric oxide values in nitrous oxide were not normally distributed. In our hospital nitrous oxide is stored in large tanks. When a tank is empty, nitrous oxide is taken from the next tank. The tanks do not contain supplies from the same batch. In contrast, synthetic air is obtained from small tanks, and this gas is highly purified for analytical use.

Surprisingly, these very low concentrations of nitric oxide in AIRc and nitrous oxide had significant effects on oxygenation in intubated and ventilated patients. Physiologically, nitric oxide is produced in the respiratory tract, with the largest contribution coming from the upper airways.\textsuperscript{10–12} Intubation deprives the inspired gas of its natural source of nitric oxide. Ventilation with nitric oxide free AIRs significantly affected oxygenation. We did not find a correlation between concentrations of nitric oxide in the inspiratory gas mixture and the effects on oxygenation. This supports previous findings.\textsuperscript{67}

The increase in arterial \( P_{A\text{\textsubscript{\text{O}}}_2} \) and the decrease in \( P(\text{\textsubscript{\text{a}}A\text{\textsubscript{\text{O}}}_2}) \), and the venous admixture during ventilation with nitrous oxide, relative to the values obtained during ventilation with AIRs, were obviously more pronounced than those during ventilation with AIRc. Nitrous oxide can
cause vasoconstriction.\textsuperscript{13–15} In combination with nitric oxide this effect of nitrous oxide could reduce shunt, as has been shown with the vasoconstrictor almitrine. We should also consider the second-gas effect.\textsuperscript{16} At the onset of ventilation with nitrous oxide, this gas is absorbed from the alveoli into the blood more rapidly than nitrogen diffuses from blood to the alveoli. This increases the alveolar partial pressures of oxygen and nitric oxide. When nitrogen is washed out and the body is saturated with nitrous oxide the second-gas effect ceases. This process takes about 10 min. We did not start our measurements until the expiratory nitrous oxide concentration had reached the inspiratory value. Thus it is unlikely that the second-gas effect was important. Further study would be needed to determine whether nitrous oxide has an additional effect on oxygenation and matching of ventilation and perfusion.

We measured the nitric oxide concentration in both the inspiratory and the expiratory limbs of the ventilation circuit. The concentration of exhaled nitric oxide should correspond to the production of nitric oxide in the lower airways when ventilated with AIRs. It was between 1.5 and 2.8 ppb. Some of the nitric oxide inspired with AIRQ and nitrous oxide was taken up. Assuming an endogenous production of 2.8 ppb, the share of exhaled nitric oxide was calculated as 26\% during ventilation with AIRQ. Therminarias and colleagues\textsuperscript{17} found that about a third of the inspired nitric oxide was re-exhaled. During ventilation with nitrous oxide the calculated uptake of nitric oxide was greater and the percentage of exhaled nitric oxide was only 7\%. This could be caused by the second-gas effect.

In summary, our data demonstrate the following. Intubation deprives the patient, at least partially, of the natural source of nitric oxide during inspiration. Nitric oxide free synthetic air impairs pulmonary oxygen exchange. Compressed air and nitrous oxide often contain very low concentrations of nitric oxide (<10 ppb). However, these concentrations can increase oxygenation. There is no correlation between the concentration of nitric oxide and the decrease in $P_{O_2}$($\lambda$-a). An individual value between 3 and 5 ppb nitric oxide is probably necessary to obtain physiological matching of ventilation with perfusion.

In our study we found that the nitric oxide concentrations in nitrous oxide were similar to those found in compressed air.

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