A study of mixing conditions during nitric oxide administration using simultaneous fast response chemiluminescence and capnography

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Summary

We have evaluated the mixing properties of nitric oxide in inspired gases for five different administration techniques. Nitric oxide and carbon dioxide were delivered to the ventilator system before the ventilator or after the ventilator as a continuous flow, either directly into the inspiratory limb or into a mixing chamber positioned in the inspiratory limb. Both gases were delivered as above but synchronized with inspiration. Mixing conditions were evaluated using fast response chemiluminescence for nitric oxide and capnography for carbon dioxide analysis. Administration of nitric oxide and carbon dioxide directly into the inspiratory limb as a continuous flow or with a magnetic valve-controlled synchronized flow resulted in peak concentrations of 236% and 220%, respectively, of expected values. The use of a mixing chamber reduced these values to 104% and 102%, respectively. Administration of nitric oxide as a continuous flow into the tubing of an intermittent flow ventilator resulted in highly fluctuating inspiratory peak concentrations, which could be avoided with a mixing chamber. (Br. J. Anaesth. 1997; 78: 436–438).

Key words

Inhaled nitric oxide is used for the treatment of acute lung injury, persistent pulmonary hypertension of the newborn and right ventricular failure after cardiac surgery. Safe administration demands low levels of its toxic oxidation product, nitrogen dioxide. As the formation of nitrogen dioxide is proportional not only to the square of the nitric oxide concentration, but also to the contact time between nitric oxide and oxygen,1 administration of nitric oxide after the ventilator has been advocated to reduce contact time and hence nitrogen dioxide formation.2 To avoid highly fluctuating concentrations, delivery of nitric oxide into the inspiratory limb only during inspiration has been suggested. This study was designed to evaluate mixing properties of nitric oxide for five different delivery techniques.

Methods and results

A Servo 900 C ventilator (Siemens Elema, Solna, Sweden) was driven with 100% oxygen via its low pressure inlet to generate a minute volume of 9.5 litre min⁻¹, at 10 and 20 cycles min⁻¹, with inspiratory times of 25% and 33%. Nitric oxide and carbon dioxide at flow rates of 250 ml min⁻¹ for each gas were delivered to the breathing system by two mass flow regulators (Bronkhorst Hightech BV, Ruurlo, The Netherlands), the flows of which were checked with a precision gas flowmeter (ADH 3000, J &W Scientific, Fisons, Folsom, CA, USA). The gases were added either before the ventilator or as a continuous flow immediately after the ventilator into the inspiratory limb, or into a mixing chamber and soda lime absorber connected in series with the inspiratory limb. They were also delivered as above, but synchronized with inspiration via a magnetic valve-controlled Siemens Servo 945 Nebulizer (Siemens Elema, Solna, Sweden).

The inspiratory limb was connected to an “alveolar lung chamber” (1 litre) in which a continuous flow of air 3.5 litre min⁻¹ was mixed to mimic lower “end-tidal” nitric oxide/carbon dioxide concentrations. The chamber was connected to an artificial lung with a compliance of 70 ml cm⁻¹ H₂O. At the Y-piece we attached a fast response chemiluminescence (CL) analyser for nitric oxide (NOX 4000, Seres, Aix en Provence, France) with a sampling rate of 1 litre min⁻¹, and capnography for carbon dioxide (Ultima SV, Datex, Helsinki, Finland) with a sampling rate of 250 ml min⁻¹. Nitric oxide and carbon dioxide tracings were recorded on a flat bed recorder. The mixing chamber–soda lime unit comprised two 900-ml canisters of which one was filled with 450 g of soda lime (Q-sorb, Anmedic AB, Vallentuna, Sweden), exhausted for carbon dioxide before the experiments. As the primary carbon dioxide concentration was 100% and the nitric oxide concentration was 1000 parts per million (ppm) in nitrogen (AGA Gas AB, Lidingö, Sweden), the expected concentrations at the Y-piece were 2.5% for carbon dioxide and 25 ppm for nitric oxide, if complete mixing was achieved.

When carbon dioxide was administered before the
ventilator or after the ventilator into the mixing chamber, whether as continuous or synchronized flow, final concentrations varied between 2.35% and 2.60%, with a clear plateau phase for each administration technique (Table 1). For nitric oxide, this resulted in concentrations of 22–28 ppm, with only a flattened peak and no plateau phase. Continuous administration of both gases directly into the inspiratory tubing resulted in inspiratory carbon dioxide concentrations of 220 and 28% of expected values. Recently, methaemoglobin concentrations in this patient. For carbon dioxide, a peak of 236% and a minimum of 34% of the expected value was measured, whereas for nitric oxide values varied between 160 and 60%. This also shows that the fast response CL analyser cannot detect these rapid fluctuations and considerably underestimates peak and overestimates minimum concentrations. With a continuous flow, nitric oxide supplied from a concentrated cylinder (usually approximately 1000 ppm) accumulates at the entry point in the inspiratory limb during expiration and forms a nitric oxide plug. The latter moves nearly undiluted to the patient during the next inspiration. Although we have no flow data and consequently no idea of the volume of gas with the high concentration, we expect that the first part of the tidal volume would preferentially reach alveoli with a low time constant, exposing them and their bronchiolar structures to high nitric oxide concentrations. This may result not only in nitric oxide related toxicity, but also in inhomogeneous distribution of nitric oxide in the lungs. In view of our data, dose–response curves in studies where nitric oxide was delivered as a continuous flow into the inspiratory limb may have to be reconsidered, as it is not clear if nitric oxide is mixed completely with the tidal volume when entering the lungs. Furthermore, the equipment used to monitor nitric oxide and nitrogen dioxide concentrations was probably not sophisticated enough to detect these peak concentrations. Synchronizing nitric oxide flow with inspiration with a magnetic valve clearly does not solve the problem of inhomogeneous mixing. A pressure increase upstream of the synchronizing unit during expiration probably results in bolus injection as soon as it opens during inspiration, as suggested by carbon dioxide concentrations between 220 and 28% of expected values. Recently, methaemoglobin concentrations of 67% were reported in a patient receiving nitric oxide 8–45 ppm, as measured with a CL analyser. Nitric oxide was delivered in the inspiratory limb with a flow synchronized to ventilator flow. Our data support the authors’ speculation that the CL analyser underestimated real inspiratory peak concentrations. The latter were probably responsible for the extremely high methaemoglobin concentrations in this patient.

In our experiments a mixing chamber–soda lime
canister provided effective mixing of the gases, as evidenced by a plateau phase in the carbon dioxide curves, but increased residence time of the gases in the system. Our data provide no conclusive information on nitrogen dioxide production for two reasons: soda lime was exhausted for carbon dioxide and may not have had its full capacity to scavenge nitrogen dioxide, and the CL analyser was not fast enough to detect rapid changes in nitric oxide concentrations and therefore was unable to measure corresponding nitrogen dioxide concentrations correctly, as the latter are measured indirectly via nitric oxide. It might be interesting to evaluate our system with a smaller mixing chamber or with a single soda lime canister serving both as a mixing chamber and nitrogen dioxide scavenger.

A mixing chamber in the system does not necessarily increase nitrogen dioxide production dramatically, provided that adequate mixing is achieved. As nitric oxide oxidation is proportional not only to the contact time with oxygen, but also to the square of its own concentration, even a short peak in nitric oxide may result in considerable nitrogen dioxide production. Consequently, nitric oxide delivery systems using more sophisticated technology such as NODOMO (Drager, Germany), Pulmonox (Messer Griesheim, Austria), the new Ohmeda device (Ohmeda, USA) and the system described by Young, may synchronize nitric oxide flow correctly and generate less nitrogen dioxide. However, these systems require expensive technology such as a mass flow controller and a pneumotachograph or a very fast electronic mixer as in the NODOMO. The latter also has a humidifier in the system which acts as a mixing chamber. The Pulmonox and Ohmeda device measure inspiratory flow and deliver nitric oxide into the inspiratory limb proportional to the latter.

The performance of systems which deliver nitric oxide into the inspiratory limb depend on the accuracy of measuring the ventilator flow pattern (inspiratory time 0.75–1.5 s) and the delay in matching nitric oxide flow (5–20 ml per breath) with the latter. Impaired matching or any mechanical delay in nitric oxide delivery inevitably results in inhomogeneous distribution of concentrated nitric oxide in the inspiratory gases.

In summary, continuous administration of nitric oxide into the tubing of an intermittent flow ventilator resulted in a very fluctuating inspired nitric oxide fraction. Interposition of a mixing chamber may avoid this problem.

References