Comparison of two administration techniques of inhaled nitric oxide on nitrogen dioxide production

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The purpose of this study was to verify whether, compared with the introduction of the NO-N₂ mixture at the air inlet of the ventilator (classical method), a direct injection of NO-N₂ into the inspiratory line of the ventilator circuit with a new injection device (new method), would reduce NO₂ formation by reducing contact time between O₂ and NO. The effect of two FiO₂ (0.21 and 0.90) and NO concentrations on NO₂ production was determined. In the classical method, NO and O₂ were mixed with an air/oxygen blender before the gas mixture entered the ventilator. In the new method, NO was injected directly into the inspiratory line with the injection system. Nitric oxide and nitrogen dioxide gases were measured using a chemiluminescence analyzer. For a FiO₂ of 0.90 and 90 ppm of NO, the amount of NO₂ produced was decreased from 8.9 ± 0.8 ppm (mean ± SD) with the classical injection system to 4.4 ± 0.2 ppm with the new injection system (P = 0.0039, Mann-Whitney test), and NO₂ production was decreased from 4.5 ± 0.2 ppm to 2.1 ± 0.4 ppm (P = 0.02) at 60 ppm of NO. However, at a FiO₂ of 0.21, no difference was found in the amount of NO₂ produced. We conclude that, compared with the classical method of NO administration, the new NO injection system reduces considerably the concentration of inhaled NO₂ when a high FiO₂ and a high concentration of NO are used.

Key words

GASES: nitric oxide, nitrogen dioxide, oxygen;

TOXICITY: nitrogen dioxide;

EQUIPMENT: blenders, injection systems, ventilators.

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Cette étude avait pour but de vérifier, si, comparativement à la méthode d'introduction du mélange NO-N₂ par l'orifice d'admission d'air du ventilateur (méthode usuelle), l'injection directe du NO-N₂ dans la branche inspiratoire du circuit du ventilateur grâce à un nouveau dispositif d'injection (nouvelle méthode), réduisait la formation de NO₂ en diminuant la phase de contact entre O₂ et NO. L'influence de deux FiO₂ (0,21 et 0,90) et de différentes concentrations de NO a été établie. Dans la méthode usuelle, NO et O₂ sont réunis à l'aide d'un mélangeur d'air et d'oxygène avant leur introduction dans le ventilateur. Dans la nouvelle méthode, NO est injecté directement dans la branche inspiratoire grâce au dispositif d'injection. L'oxyde nitrique et le dioxyde d'azote ont été mesurés par chimio-luminescence. Pour une FiO₂ de 0,90 et 90 ppm de NO selon la méthode usuelle, la quantité de NO₂ produite avec le nouveau système d'injection a diminué de 8,9 ± 0,8 ppm (moyenne ± ET) à 4,4 ± 0,2 ppm (P = 0,0039, épreuve de Mann-Whitney) alors qu'à 60 ppm de NO, la production de NO₂ est passée de 4,5 ± 0,2 ppm à 2,1 ± 0,4 ppm (P = 0,02). Cependant, sous une FiO₂ de 0,21, on n'a pas trouvé de différence en rapport avec la production de NO₂. Les auteurs concluent que, comparativement à la méthode usuelle d'administration du NO, la nouvelle méthode par injection diminue considérablement la concentration inspirée de NO₂ lorsque la FiO₂ et la concentration de NO sont toutes les deux élevées.

Nitric oxide (NO) is a vasodilator released from the guanido-terminal group of L-arginine by NO synthase.¹ It has a major role in cardiovascular physiology and pharmacology.¹⁻⁴ In the lung, nitric oxide opposes hypoxic vasoconstriction,⁵ attenuates the response to vasoconstrictors⁶ and maintains the pulmonary artery pressure low at rest and during exercise.⁷ Several nitrovasodilators such as nitroglycerin and sodium nitroprusside are donors of NO,⁸ which is the active moiety of these molecules. Nitric oxide then activates intracellular guanylate cyclase which increases the intracellular level of cGMP. This latter substance is known for being a very potent vasodilator.⁹ Several new NO donors have been investigated, some of

which are already in clinical use.¹⁰ Nitric oxide can also be administered as a gas in the inspiratory line to mechanically ventilated patients.

Nitric oxide has many interesting physical properties. It is a reactive free radical and reacts readily with oxygen (O_2) to form nitrogen dioxide (NO_2). Nitrogen dioxide is a potential toxic substance, and its concentration should be kept <5 ppm as recommended by the US Occupational Safety and Health Administration.¹¹ The amount of NO_2 in the inspiratory gas depends on the cylinder concentration of NO_2 and on the production of NO_2 after the introduction of NO into the ventilator or directly into the inspiratory line. The amount of NO_2 produced is proportional to the concentration of O_2 , to the square of the concentration of NO , and the time of contact between the two gases.¹² The reaction is $2NO + O_2 = 2NO_2$.

Very often, a mixture of NO - N_2 delivered by an air/oxygen gas blender has been introduced into the air inlet of the mechanical ventilator.^{13,14} Some have used the cyclic flow of the nebuliser to introduce the NO - N_2 mixture at the inspiratory phase.¹⁶ As an injector specifically designed to deliver NO was not available, we designed and built a new NO injection system.

Our objective was to develop an injection system that would be simple, reliable, adaptable to any ventilator or anaesthesia machine, and which could reduce NO_2 production. We compared the measured concentration of NO_2 in the inspiratory gas when NO was added to the air inlet of the ventilator, with the concentration of NO_2 when NO was injected directly into the inspiratory line during the inspiratory phase with the new NO injection system.

Our hypothesis was that NO directly injected into the inspiratory line during the inspiratory phase by the new injector would reduce the contact time between NO and O_2 , and therefore, reduce NO_2 production.

Methods

Classical injection system

A mixture of NO and N_2 delivered from an air/ O_2 mixer (Siemens-Elcoma model 961), was added to the mechanical ventilator at the air inlet. This NO - N_2 mixture was then mixed with O_2 by the ventilator proportional solenoid valve assembly (Figure 1). Inspiratory gases were not humidified.

New injection system

A mixture of NO - N_2 was directly injected into the inspiratory line of the ventilator circuit. In this new injection system, NO injection is cyclic, occurring only during the inspiratory phase of the mechanical ventilator (Figure 2). The flow was manually adjusted using a precision flowmeter made with teflon (Cole-Parmer, Niles, Illinois).

FIGURE 1 The classical injection system. The NO cylinder was blended with a N_2 cylinder before entering the ventilator air inlet.

FIGURE 2 The new injection system. An electronic circuit (2) detects the beginning and the end of each inspiration by processing the signal coming from the 7200 AE ventilator flow sensor (1). During the inspiratory phase, the electronic circuit opens the solenoid valve, which is closed when not activated (normally closed Teflon PTFE valve, Cole-Parmer, Niles, Illinois) (3) and NO is injected into the inspiratory line 60 cm upstream of the sampling site. At the end of the inspiratory phase, the circuit closes the solenoid valve and the injection of NO is stopped. The flow was manually adjusted using a precision flowmeter (4) made with teflon (Cole-Parmer, Niles, Illinois). The concentrations of NO and NO_2 were continuously monitored using a chemiluminescence analyser (5).

Description of protocol

The ventilator used in this experiment was a Puritan-Bennett (model 7200AE, Carlsbad, California) with a disposable ventilation circuit (Puritan-Bennett #3030) and a test lung. The new injection system could also function with any ventilator or anaesthesia machine that possesses

an analogue flow signal output. All experiments were performed with a respiratory rate of 14 per minute, a tidal volume of 600 ml, an oxygen concentration of 21% or 90% (oxygen monitor, Hudson RCI #5590, Temecula, Ca), and an I/E ratio of 1/4. The NO cylinder was a NO/N₂ mixture at a concentration of 972 ppm of NO and with minimal quantity of NO₂ (<5 ppm) certified by the gas company (Air Liquide, Montreal).

The concentrations of NO and NO₂ were continuously monitored using a chemiluminescence analyser (Tecan AG model CLD 700 AL, Eco Physics, Switzerland). This analyser can measure from 1 ppb to 100 ppm, with a linearity better than 1%, at a sampling rate of 660 ml · min⁻¹, and was calibrated every day with a gas mixture consisting of 89 ppm of NO and 5 ppm of NO₂ (Air Liquide, Montreal).

The NO and NO₂ gases were measured in the inspiratory line 15 cm upstream of the Y piece. In order to avoid mixture of inspiratory gases with expiratory gases, a uni-directional valve was installed in the inspiratory line just before the Y piece.

Measurements of NO₂ were done for increasing values of NO (from 0 to 90 ppm). After completion of a set of measurements the NO was adjusted back to 0 ppm. At least five sets of measurements were done at the two FiO₂ levels (0.21 and 0.90).

Statistics

Due to the small sample size, at each point of NO administration, the different values of NO₂ production obtained by the two systems, were compared with a Mann-Whitney test (significance level $\alpha = 0.05$). Results are presented as mean $\pm$ SD of NO₂ production for each method of NO administration, at two levels of FiO₂.

Safety

In order to know how well the solenoid mechanism and the electronic circuit perform over time, the injection system was tested for six weeks in the biomedical engineering laboratory. After that, the system was used in experiments using pigs (30) for >6 months. The injection system is CSA (Canadian Standard Association) approved. Also the injector is being used in a clinical trial, and up to now 15 patients have been treated with the system for a total of 3000 hr without any technical problems.

The NO-N₂ gas pressure, in the injection circuit, was set to one third of the maximum working pressure of the solenoid valve as recommended by the manufacturer (at 10 lbs · in⁻²). Under these conditions, the solenoid valve lifespan should be at least 30 days of continuous operation.

The injection device has two alarms, the first is triggered by an injection time of >7 sec and the second

FIGURE 3 Gas mixing diagram for the classical and the new injection systems. With the classical system, NO and O₂ interact after the solenoid valve assembly up to the sampling site in the inspiratory line of the ventilator circuit (approximately 2755 ml). With the new injection system, NO and O₂ interact only from the injection site to the sampling site.

if the time between injections is >30 sec. If the injection system fails an emergency kit is available for immediate installation and for continuous injection of NO in the inspiratory line.

Contact time between NO and O₂

The contact time between NO and O₂ was estimated and measured.

With the classical system, NO and O₂ are in contact between the ventilator solenoid valve assembly, where normally O₂ and air are mixed, and the sampling site in the inspiratory line of the ventilator circuit (Figure 3). From the solenoid valve assembly a 10 cm tube (35 ml) leaves the ventilator, then the inspiratory gas passes through a bacterial filter (approx. 400 ml) and a 60 ml

tube between the filter and the humidification cascade (1700 ml), and then to the inspiratory line (560 ml) of the ventilator circuit. The total volume in which NO and O₂ can interact is approximately 2755 ml. With the ventilator settings used (14 breaths per minute, tidal volume of 600 ml and an I/E ratio of 1/4), a time of approximately 21.5 sec, for the inspiratory gas to flow from the outlet of the ventilator to the sampling site, was anticipated for the classical injection system: it would take five breaths before NO reaches the sampling site.

To verify this the time for NO to reach the outlet of the ventilator just before the bacteria filter (after turning the blender knob from 21% to 30%), and the time for NO to disappear completely from the outlet (after turning the blender knob back to 21%) were measured. Also, the time for NO to reach the sampling site, and the time for NO to disappear completely from the sampling site was measured. For this purpose we used the Sievers NOA 270B nitric oxide analyzer, with a response time of 200 msec for 90% of fullscale.

Results

Both nitric oxide delivery systems were able to deliver concentrations of NO from 0 to 100 ppm. The adjustment was more difficult with the classical system, because no precise blender for NO/N₂ exists. As expected, the increased concentration of NO and O₂ delivered into the circuit induced an increase in the production of NO₂. The total number of measurements at a FiO₂ of 0.90 were 44 for the classical system and 36 for the new injection system. At a FiO₂ of 0.21, the total number of measurements were 37 for the classical system and 73 for the new injection system.

As seen on the curve of best fit (Figure 4) and on the bar graph (Figure 5), for a FiO₂ of 0.90 and 60 ppm of NO, the amount of NO₂ produced was decreased from 4.5 ± 0.2 to 2.1 ± 0.4 ppm with the new injection system ($P = 0.02$). The difference was also statistically significant ($P = 0.0495$) with a NO concentration of 80 ppm. At 90 ppm of NO, the amount of NO₂ produced was decreased from 8.9 ± 0.8 with the classical injection system to 4.4 ± 0.2 ppm with the new injection system ($P = 0.0039$). The lowest concentration of NO for which there was a difference in the quantity of NO₂ produced was 60 ppm.

No difference in NO₂ production was found between the two NO delivery systems at a FiO₂ of 0.21 (Figures 6 and 7), except with a NO concentration of 50 ppm ($P = 0.02$). This difference does not correlate with the other values obtained at a FiO₂ of 0.21, and may be due to the small sample size.

With the classical system, the fresh NO-N₂ gas mixture from the blender took 6.6 ± 0.5 sec ($n = 5$) to reach

FIGURE 4 Curve of best fit of the nitrogen dioxide concentration as a function of the nitric oxide concentration for the classical (●) and the new injection (○) systems, with FiO₂ of 0.90.

FIGURE 5 Bar graph of the nitrogen dioxide concentration as a function of the nitric oxide concentration for the classical and the new injection systems, with FiO₂ of 0.90. ** $P < 0.05$.

the outlet of the ventilator, and 12.6 ± 0.8 sec to reach the sampling site. The real contact time between NO and O₂ was therefore 6.0 ± 1.3 sec. If the humidification cascade was removed, the contact time was reduced to 4.0 ± 1.0 sec.

We also observed that after turning off the NO supply (from 30% to 21% on the blender), it took 58.4 ± 2.1 sec to flush the ventilator circuit completely (2755 ml) with NO-free gas, and that the contact time between NO and O₂ could be as long as one minute.

FIGURE 6 Curve of the best fit of nitrogen dioxide concentration as a function of nitric oxide concentration for the classical (●) and the new injection (○) systems, with FIO_2 of 0.21.

FIGURE 7 Bar graph of nitrogen dioxide concentration as a function of nitric oxide concentration for the classical and the new injection systems, with FIO_2 of 0.21.

With the new injection system, NO concentration increased during inspiration, and decreased to zero at the end of inspiration. The contact time between NO and O_2 was therefore the inspiration time (0.86 sec).

Discussion

The main finding of this study is that the new injection system reduces considerably the concentration of inhaled NO_2 , and can effectively deliver any concentration of NO, when compared with the classical injection system. The

contact time between NO and O_2 can be reduced by directly injecting NO into the inspiratory line during the inspiratory phase, instead of adding NO/ N_2 at the air entry of the mechanical ventilator.

During any therapy using inhaled NO, NO_2 concentration must be kept as low as possible.¹² The amount of NO_2 delivered to the patient depends on the concentration of NO_2 in the NO- N_2 cylinder, the square of the concentration of NO, the concentration of O_2 , and the contact time between O_2 and NO. Currently, nitric oxide cylinders are not medical grade and are not standardized particularly with respect to the presence of NO_2 in the gas mixtures itself; hence, monitoring of the NO_2 level is required to prevent toxic administration, even though the contact time between NO and O_2 is very short.

It has been shown that NO_2 in the inspiratory gas can be reduced by using soda lime or soda lime dye.¹⁵ However, Pickett *et al.*¹⁷ showed that soda lime with either potassium permanganate, kenazol yellow, or ethyl violet as indicator cannot be recommended for use as a nitrogen dioxide scavenger during administration of inhaled nitric oxide. Moreover, NO_2 absorption is not selective because NO is also partially absorbed.¹⁸ Consequently, the use of soda lime as a NO_2 scavenger is still controversial.

In the classical injection system, the discrepancy between the anticipated (21.5 sec) and the measured (6.0 sec) contact time of NO with O_2 , was due to the mixing (convection and diffusion) of the fresh gas with the gas present in the circuit. This mixing phenomenon could also explain why the complete elimination time of NO from the circuit is approximately one minute. It is therefore surprising that Channick *et al.*¹³ observed no NO_2 production with a prolonged contact time. We also disagree with Wessel *et al.*¹⁴ that the classical injection system minimizes the exposure of NO and O_2 . However, our results are in agreement with Stenqvist *et al.*¹⁵ and Wessel *et al.*¹⁴ who measured significant NO_2 production.

With the new injection system, the contact time was equal to the inspiratory time which causes a reduction in NO_2 production. Moreover, the direct injection of NO into the inspiratory line by the NO injector solves many problems encountered in the classical method of NO administration.

Mechanical ventilators use gas flow to activate certain pneumatic mechanisms (for example the 7200AE ventilator regulator consumption is 1 to 3.6 L · min⁻¹). Consequently, the introduction of NO into the air inlet will increase operational costs and contribute to unnecessary pollution levels.

There is no specific NO/ N_2 mixer available. The standard air/ O_2 mixers most often in use are not accurate, despite the conclusions of Channick *et al.*¹³ and Wessel *et al.*¹⁴ Adjustment of precise NO concentrations is more

difficult with these mixers, than with the new injection system.

As the NO/N₂ mixture is introduced into the air inlet of the ventilator, there is a risk of administering an anoxic gas to the patient. If an FiO₂ of 0.21 is chosen on the ventilator, then the gases present in the inspiratory line will be exclusively N₂ mixed with a few ppm of NO. The new injection system cannot give an anoxic gas mixture although the injection process will reduce the oxygen concentration. However, with both injection systems an oxygen analyser with alarms should be added in the inspiratory line in order to readjust correctly the O₂ concentration.

Finally, the effect of NO and NO₂ on different ventilator components in the classical injection system may lead to premature oxidation and could fail during a patient's treatment. We question the conclusion by Channick *et al.*¹³ and Wessel *et al.*¹⁴ that inhaled NO can be reliably delivered through a ventilator. No specific long-term studies were done on the oxidation process, although Wessel *et al.*¹⁴ indicated no problems were seen with intermittent operation, over a period of 20 months. Further studies should be performed to assess the oxidation phenomenon on ventilator components.

We conclude that the new injection system considerably reduces the concentration of inhaled NO₂ compared with the classical injection method.

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