CRITICAL CARE

REVIEW

Equipment review: Pulmonary uptake and modes of administration of inhaled nitric oxide in mechanically-ventilated patients

Louis Puybasset, Jean-Jacques Rouby

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Introduction

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator which reduces pulmonary artery pressure and increases arterial oxygenation in patients with adult respiratory distress syndrome (ARDS). Despite these beneficial effects, inhaled NO has not yet been shown to improve outcome. During artificial ventilation, it can be administered in the downstream of the ventilator into the inspiratory limb of the ventilatory circuit, or can be mixed with oxygen and nitrogen in the upstream part of the system. Because of its simplicity and low cost, administration into the inspiratory limb is most commonly used in southern Europe, whereas in the United States and northern Europe, the system of administration into the upstream is more popular. Each of these systems has its own advantages and disadvantages.

Administration of inhaled NO into the upstream of the ventilator

Principle

The technique of administration of NO into the upstream of the ventilator was first developed in Scandinavia [1,2]. Mass-flow regulators are used to mix oxygen, air and NO before their entry into the low pressure inlet of the ventilator (NOMIUS system adapted to the Siemen's Servo 900 C ventilator). These flow meters are precise but expensive. They have a variability of < 1% from the set value. Each mass-flow regulator is controlled by a microprocessor in order to obtain the desired NO concentration at the point of entry into the ventilator. Most often, a system measuring the delivered NO concentration is associated.

Advantages

When NO is administered into the upstream, the interior of the ventilator serves as a mixing chamber. As a consequence, inspired NO concentration is stable in any mode of ventilation [2,3]. In this system of administration, inspired NO concentration does not depend on the pattern of the flow of gas delivered by the ventilator, the tidal volume or the I/E ratio. There is no risk of overdose due to momentary interruption of ventilation during tracheal suctioning or acute reduction of minute ventilation when the ventilator is in partial-support mode [2,3]. Similarly, an accidental interruption of the power supply to the ventilator does not result in an overdose after the restoration of power. These are the principal reasons for which this mode of administration is recommended in North America an Scandinavia [3,4].

Disadvantages

The main disadvantage of this mode of administration is the long contact time between NO and oxygen [5], resulting in the formation of nitrogen dioxide (NO_2). Nitrogen dioxide is a toxic product causing bronchoconstriction at concentrations between 0.6 and 2 ppm, and alveolo-capillary membrane damage at concentrations > 2 ppm. The quantity of NO_2 formed is proportional to the contact time between NO and O_2, the inspired oxygen fraction (FiO_2) and the square of the concentration of NO [6]. As high inspired oxygen fractions are used in acute respiratory distress syndrome (ARDS), administration of NO into the upstream of the ventilator can generate high concentrations of NO_2. For this reason, it is necessary to incorporate a sodalime canister in the inspiratory circuit to eliminate NO_2 before the inspired gas reaches the upper airways. The sodalime absorbs about 75% of the NO_2 formed but less than 10% of the NO administered. In cases of prolonged administration of NO, it is necessary to change the sodalime at regular intervals. A period of 3 days seems to be the longest

Surgical Intensive Care Unit, Department of Anesthesiology, La Pitié-Salpêtrière Hospital, 47-89, Boulevard de l'Hôpital, 75013 Paris, France

duration of utilization permissible. The different absorber systems commercially available are not equivalent in their capacity to eliminate NO_2 while allowing the passage of NO [2,7,8]. It is necessary to evaluate each system before its clinical usage and to monitor the actual concentrations of NO delivered after the absorber [9]. Another potential problem is that the passage of NO through a humidification chamber results in the dissolution of the gas in water with the formation of nitric acid (a phenomenon that does not occur with heat moisture exchangers) and in a decrease in the NO concentration actually delivered to the patient [2]. However, in case of prolonged administration, oxidation of the metallic internal components of the ventilator by NO and NO_2 does not appear to be a major risk with this kind of administration. The second disadvantage of this mode of administration is the fact that mass-flow regulators are expensive.

Administration of inhaled NO into the downstream of the ventilator

Administration of NO into the downstream of the ventilator is common practice in France and southern European countries like Spain and Italy. In this case, NO is administered into the proximal end of the inspiratory limb of the ventilator. Delivery directly into the trachea or at the level of the Y-piece of the ventilatory circuit should be avoided since high concentrations of NO and NO_2 are generated at the point of delivery, with potential toxic effects on the tracheobronchial mucosa [2]. Some plastics absorb NO, therefore, the use of teflon tubing to deliver NO from the cylinder to the point of entry into the ventilatory circuit is recommended. Such a tube should also be used for the monitoring system. It is also not advisable to administer NO at a humid site since it dissolves in water to form nitric acid [2]. This is the reason why NO should be delivered just after the humidifier when one is present.

There are two different modalities for the administration of NO after the ventilator:

1. continuous administration by a calibrated nitrogen flow meter mounted directly on the outlet of the NO cylinder, and

2.sequential administration limited to the inspiratory phase, necessitating the use of specialized equipment that recognises the different phases.

These two systems are not comparable in their performance since only sequential administration coupled with controlled mechanical ventilation assures stable inspired NO concentrations [3,10]. Continuous administration, though simple and inexpensive, does not allow homogeneous mixing of NO with the inspired gas [10]. These differences have been well evidenced by Imanaka *et al* using a test lung model [3]. As illustrated by Fig 1, these authors recorded a peak NO concentration which was 10 times greater than the target concentration when using continuous administration during volume-controlled ventilation. In contrast, using sequential administration, inspired NO was always similar to the target concentration.

Continuous administration

Principle

This method of administration consists of delivering a continuous flow of NO (regulated by a nitrogen flow meter) into the proximal end of the inspiratory limb of the ventilatory circuit. The flow is constant, varying between 50 and 2000 ml/min. The concentration in the cylinder can vary from 225-2000 ppm. Users of this system hypothesize that the NO mixes homogeneously with the inspired gases coming from the ventilator and apply the following formula to calculate the inspired concentration of NO:

$$[NOinsp] = VNO \times V^{-1} \times [NOcyl]$$

where [NOinsp] = inspired NO concentration; VNO = flow of NO delivered from the cylinder; V = minute ventilation coming from the ventilator, and [NOcyl] = NO concentration in the cylinder.

In practice, the desired concentration is obtained by adjusting the flow of NO as a function of the minute ventilation of the patient and the concentration of the cylinder.

Experimental evidence for the 'bolus effect'

During continuous administration of NO in volume-controlled ventilation, a constant flow of NO mixes with a discontinuous flow of gas coming from the ventilator. During the inspiratory phase, mixing of NO, oxygen and nitrogen is homogeneous since each flow is constant. During the expiratory phase, however, the flow from the ventilator stops while the flow of NO persists. As a result, NO accumulates in the proximal part of the inspiratory limb. During the inspiratory phase of the following respiratory cycle, this 'bolus' is 'flushed' towards the upper airways of the patient without having been homogeneously mixed with the tidal volume. Using fast-response chemiluminescence apparatus, this bolus effect can be detected, and is indicated by a marked fluctuation in NO concentrations within the inspiratory limb.

It is possible to demonstrate this phenomenon in a lung model by using a long inspiratory limb and sampling the gas from sites corresponding to different multiples of tidal volume [10]. As shown in Fig 2, concentrations of NO measured from sampling sites corresponding to one and two tidal volumes are higher than those measured from sampling sites corresponding to half and one and a half tidal volumes, respectively. The explanation for this phenomenon is as follows.

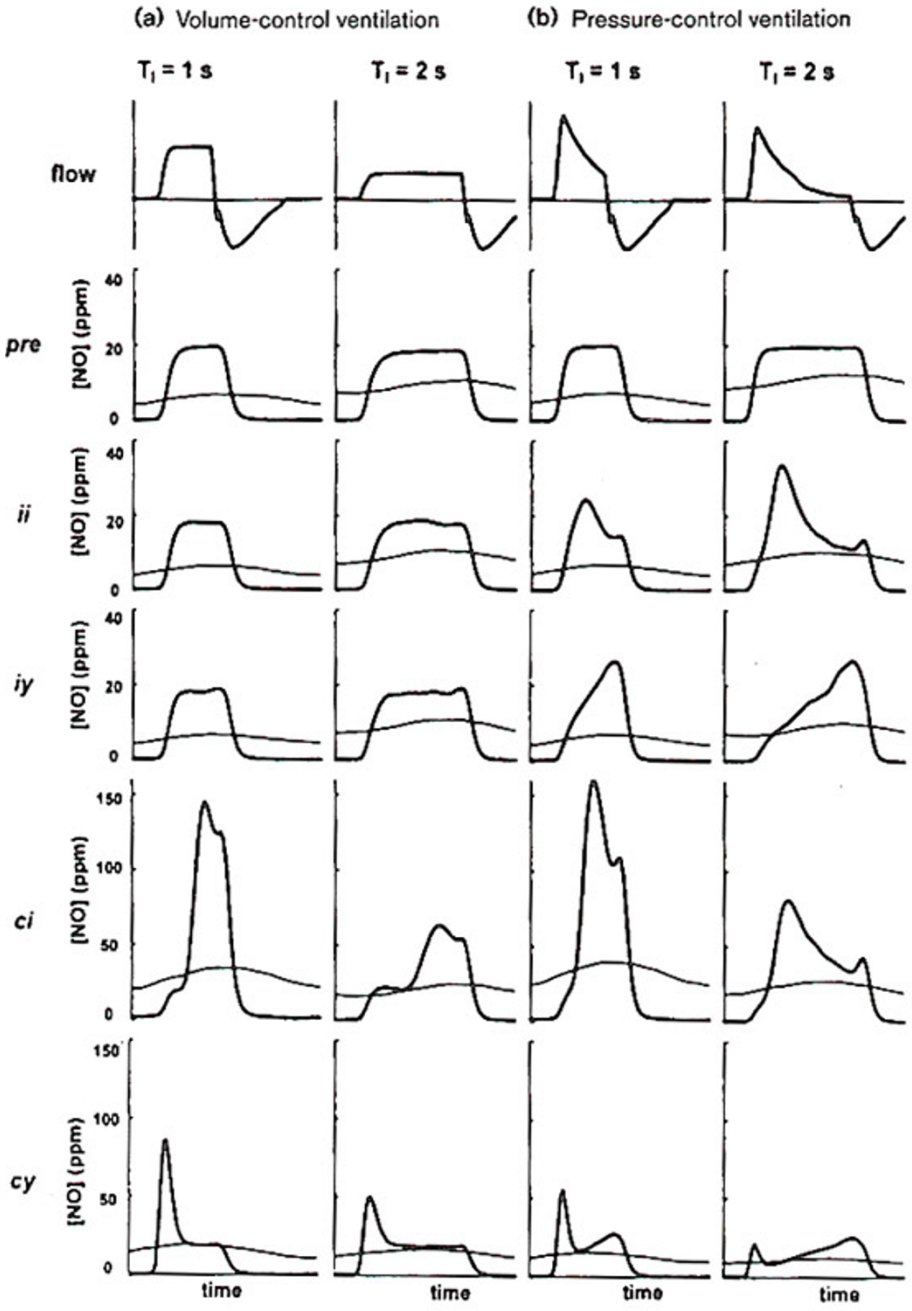

Figure 1 Nitric oxide (NO) concentrations measured in a lung model with different systems of administration during volume-control and pressure-control ventilation. The NO concentration is measured at simulated midtrachea during **(a)** volume-control and **(b)** pressure-control ventilation. The target NO concentration was 20 ppm. Thick and thin lines represent NO concentration measured using a fast and slow-response analyser, respectively. The model simulates 100% NO uptake. Different modes of administration were tested: pre = administration before the ventilator; ii = sequential administration into the inspiratory limb; iy = sequential administration into the Y-piece; ci = continuous administration into the inspiratory limb; cy = continuous administration into the Y piece. Published with permission [3].

During inspiration, the bolus passes sampling sites at a high velocity and cannot be measured adequately by the chemiluminescence apparatus despite its fast response time. In contrast, during the expiratory phase - with a duration of 2.1 s - the NO bolus can be accurately detected by the chemiluminescence apparatus. As a consequence, the fluctuation of NO concentration at sites corresponding to one and two tidal volumes is much higher than a sampling sites corresponding to half and one and a half tidal volumes. In addition, fluctuation of

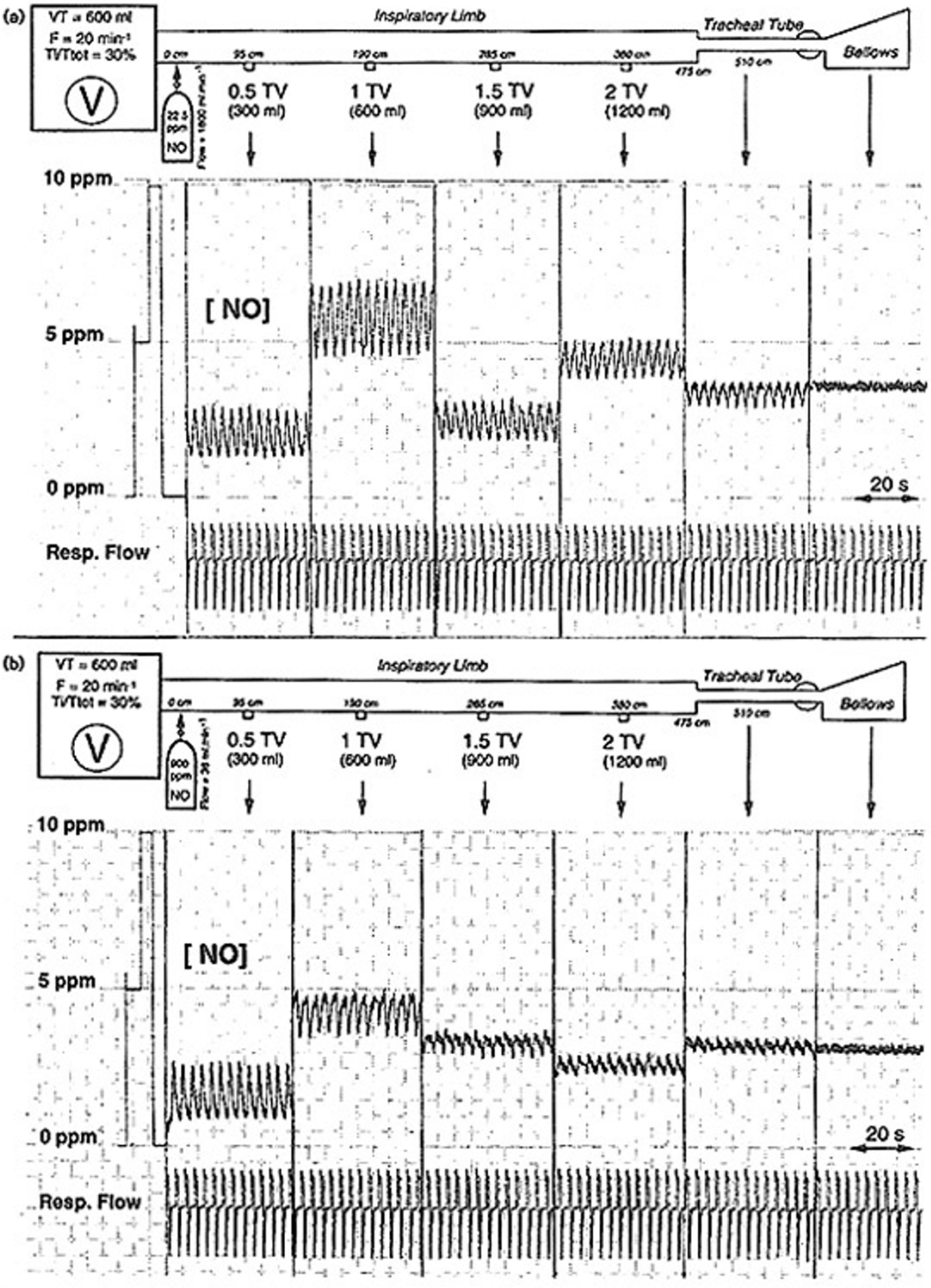

Figure 2 Evidence for variations in NO concentrations within the inspiratory limb related to the bolus effect during continuous administration in a lung model. Nitric oxide is administered into a lung model in a continuous mode after the ventilator. The inspiratory limb of the ventilator consists of a 475 cm-long tube with a provision for sampling the gas at points corresponding to 0.5 (site 1), 1.0 (site 2), 1.5 (site 3) and 2.0 (site 4) tidal volumes. **(a)** Nitric oxide is administered from a 22.5 ppm cylinder. Concentrations at sampling sites corresponding to 1 and 2 tidal volumes are higher than those from sites corresponding to 0.5 and 1.5 tidal volumes suggesting the existence of a bolus of NO moving in front of the tidal volume. **(b)** Nitric oxide is administered from a 900 ppm cylinder. The bolus effect is less pronounced than with a 22.5 ppm cylinder. There is no detectable bolus at the site corresponding to 2 tidal volumes, suggesting an early homogenization of the inspired gas. Published with permission [10].

NO concentration decreases at the most distal sampling sites suggesting homogenization of the bolus during the course of its movement down the inspiratory limb. The magnitude of the bolus effect is also inversely related to the NO concentration in the cylinder. Changing from a 22.5 ppm cylinder to a 900 ppm cylinder results in a 50-fold reduction in the volume of the bolus. Consequently, fluctuation of NO concentration is markedly attenuated in the inspiratory limb probably because the bolus is more rapidly homogenized in the tidal volume. One of the clinical implications of this observation is that utilization of cylinders with high NO concentrations minimizes the bolus effect in patients on inhaled NO therapy.

Distribution of NO concentrations

As shown in Fig 3, the concentration of NO fluctuates in the inspiratory limb. This fluctuation, which can be detected only by fast-response chemiluminescence apparatus results from the passage of the bolus past the sampling site for the inspired gas. As recently suggested, even fast-response chemiluminescence may underestimate rapid changes in NO concentrations [11]. If the NO bolus is small and moves with a high velocity, chemiluminescence apparatus with a response time between 0.5 and 1.5 s may be unable to provide accurate measurements of the true peak NO concentration. By using CO_2 as a tracer gas and infrared capnography with a response time of 350 ms, Stenqvist *et al* demonstrated that fast-response chemiluminescence (response time of 1.5 s) underestimates true peak NO concentrations when sampling at the Y piece during the inspiratory phase [11]. If this fluctuation is measured at different sites in the inspiratory limb, the peak concentration and its phase in relation to the respiratory cycle vary

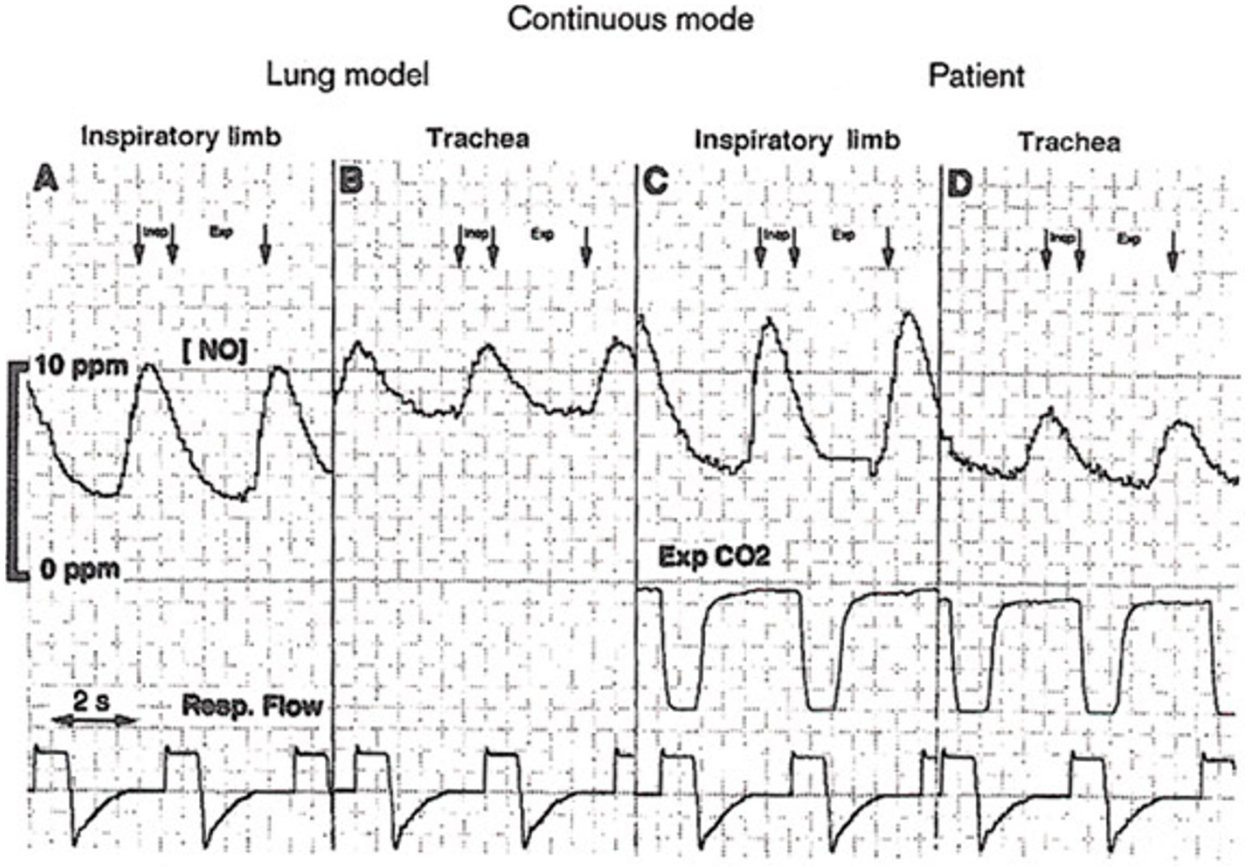

Figure 3 Nitric oxide concentrations recorded from the inspiratory limb and trachea in a lung model and a patient on artificial ventilation during continuous administration. Panel A represents the variation in NO concentration in the inspiratory limb of the lung model; panel B shows the variations in NO concentration at simulated tracheal level in the lung model; panel C shows the variations of NO concentration in the inspiratory limb in the ventilated patient; panel D shows the variations of NO concentration in the trachea of the ventilated patient. In panels A and B the lower trace represents the respiratory gas flow. In panels C and D the two lower traces represent expired CO_2 curves (end-tidal CO_2 is equal to 25 mmHg) and respiratory gas flow. Nitric oxide concentrations were measured by fast-response chemiluminescence apparatus (NOX 4000 Sérès, Aix-en-Provence, France). The time delay of the apparatus was 2.4 s. Accordingly, the beginning of inspiration and expiration (represented by arrows) is shifted 2.4 s to the right compared to the respiratory flow recording. Published with permission [10].

significantly. As previously mentioned, this is because the phase and the peak of the fluctuation are influenced by the progressive mixing of the bolus with the inspired gas, and depend on the location of the sampling site in relation to the position of the bolus at the end of inspiration. As a result of the bolus, peak concentrations of NO are created within the inspiratory circuit which can generate high levels of NO_2 [2]. It is likely that for the same mean intratracheal NO concentration, continuous administration generates higher NO_2 levels than sequential administration where the inspired NO concentrations are stable.

As shown in Fig 4, the classical formula does not allow a precise prediction of inspired NO concentrations administered to the patient. The formula underestimates the inspired concentrations delivered to the patient, thereby increasing the risk of overdose. This unpredictability of the dose received by the patient means that continuous administration can be utilized only if fast-response chemiluminescence apparatus is available for monitoring the NO concentrations. If such equipment is available, it is possible to measure the actual tracheal NO concentration during the inspiratory phase [12]. If slow-response chemiluminescence apparatus is used, only mean tracheal concentration can be measured, which underestimates the actual inspired NO concentration delivered to the patient by about 50%.

Sequential administration

Principle

The objective of sequential administration is to limit the administration of NO to the inspiratory phase so that the bolus effect is avoided. To obtain stable and reproducible concentrations of NO in the inspiratory limb, it is necessary that the gas flows from the ventilator and the NO cylinder have the same pattern during inspiration. During sequential administration in controlled ventilatory mode with a constant inspiratory flow, a continuous flow of NO is administered only during inspiration. As shown in Fig 5, NO concentrations in the inspiratory limb are fairly stable during sequential administration both in the lung model and in patients. Since a constant inspiratory flow is delivered from both the NO cylinder and the ventilator, there is a homogenous mixing of NO with the tidal volume.

At the tracheal level, NO concentration remains constant in the lung model, whereas it fluctuates in patients [13]. Identical ventilatory and NO equipment was used in the lung model and in the patients, therefore, it can be assumed that the observed differences in tracheal NO concentrations are related to the differences in the distribution of volume or pulmonary uptake of NO.

The Opti-NO - advantages and disadvantages

The Opti-NO (Taema, Anthony, France) is a system designed for sequential administration of NO into the

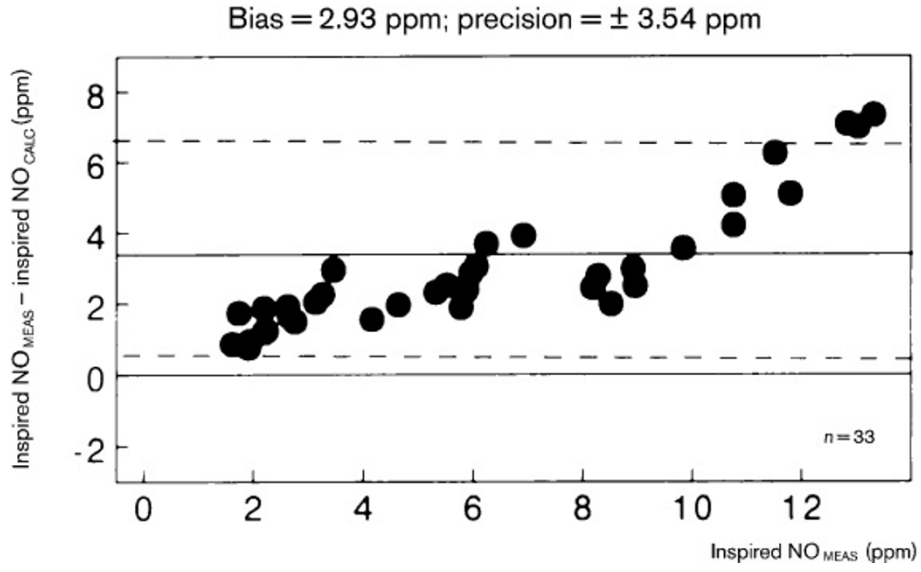

Figure 4 Correlation between measured (NO_{MEAS}) and calculated (NO_{CALC}) inspiratory tracheal concentrations of NO during continuous administration. The x-axis represents the inspiratory tracheal concentrations of NO measured by fast-response chemiluminescence apparatus. The difference between the measured and calculated inspiratory tracheal concentrations is represented on the y-axis. The dark line in the center represents the mean error. The dotted lines on either side represent the precision (± 2 SD). Calculated inspiratory tracheal NO concentrations underestimate the actual inspiratory tracheal NO concentrations delivered to the patient. Published with permission [10].

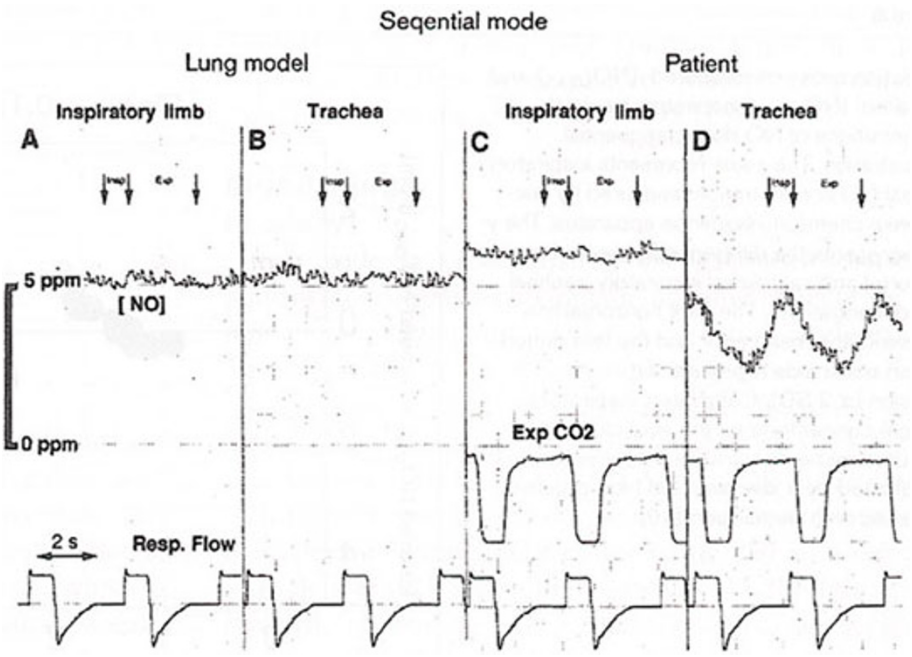

Figure 5 Nitric oxide concentrations measured from the inspiratory limb of the ventilatory circuit and the endotracheal tube in a lung model and a patient on the artificial ventilation, during sequential administration. Panel A represents the variations in NO concentration in the inspiratory limb in the lung model; panel B shows the variations in NO concentration at simulated tracheal level in the lung model; panel C shows the variations in NO concentration in the inspiratory limb in the ventilated patient; panel D shows the variations in NO concentration in the trachea of the ventilated patient. In panels A and B the lower trace represents the respiratory gas flow. In panels C and D the two lower traces represent expired CO_2 curves (end-tidal CO_2 = 25 mmHg) and respiratory gas flow. Nitric oxide concentrations were measured by fast-response chemiluminescence apparatus (NOX 4000 Sérès, Aix-en-Provence, France). The time delay of the apparatus was 2.4 s. Accordingly, the beginning of inspiration and expiration (represented by arrows) is shifted 2.4 s to the right compared to the respiratory flow recording. Published with permission [10].

downstream of the ventilator [13]. It comprises one circuit for the detection of inspiration and another for the administration of NO. The detection circuit senses the pressure increase in the inspiratory limb during inspiration and opens a solenoid valve, allowing the administration of NO more distally into the limb. The flow of NO delivered is constant throughout the length of the inspiratory phase. As shown in Fig 6, the Opti-NO delivers stable and reproducible concentrations as predicted by the formula since NO and oxygen are mixed at constant flow rates during the same period of time. To attain a similar concentration, NO flow requirement is lower during sequential mode compared to continuous mode. The Opti-NO allows a reduction in the cost of inhaled NO therapy.

However, this prototype device has some limitations. Although in sequential mode it is capable of delivering steady inspired concentrations during controlled mechanical ventilation with constant ventilatory settings, it is not capable of maintaining a stable inspiratory NO concentration in the face of decelerating inspiratory flow, changing tidal volumes and I/E ratios such as occurs during pressure support ventilation, intermittent mandatory ventilation, airway pressure release ventilation and pressure-controlled ventilation [3]. Its use in pressure-support ventilation, characterized by a decelerating inspiratory flow, results in a non-homogenous mixing of NO during the inspiratory phase and a significant fluctuation of inspiratory NO concentration. As shown in Fig 7, any change in the patient's inspiratory drive resulting in variations in tidal volume, inspiratory flow and duration induced fluctuation in inspiratory NO concentrations since the NO flow delivered by the Opti-NO remained constant. Therefore, the sequential mode provided by the Opti-NO can be used only in association with controlled and assisted-controlled mechanical ventilation with constant inspiratory flow, but not with pressure-controlled modes of ventilation. Furthermore, in patients on controlled ventilation, any change in ventilatory settings requires a corresponding change in Opti-NO settings in order to maintain a constant inspiratory NO concentration. This can be achieved using the slide-rule provided with the Opti-NO which indicates the inspiratory NO concentration predicted from the classical formula.

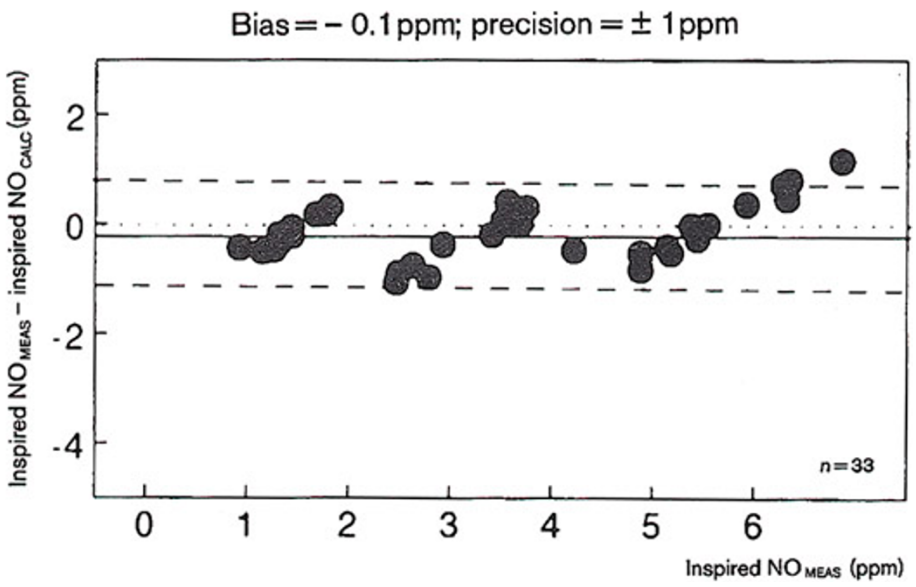

Figure 6 Correlation between measured (NO_{MEAS}) and calculated (NO_{CALC}) inspiratory tracheal concentrations of NO during sequential administration. The x-axis represents inspiratory tracheal NO concentration measured by fast-response chemiluminescence apparatus. The y-axis represents the difference between the measured and calculated inspiratory tracheal NO concentrations. The dark horizontal line represent the mean error and the two dotted lines on either side represent the precision (± 2 SD). Calculated inspiratory tracheal concentrations are very close to the measured inspiratory tracheal concentrations as indicated by a low bias and high precision. Published with permission [10].

From the above comments, it follows that an ideal system for delivering NO into the downstream of the ventilator should have the following characteristics:

1. it should be a sequential system delivering NO only during the inspiratory phase of the ventilator with the flow of NO synchronized with the flow signal of the ventilator, and

2. the flow of NO should be regulated by a proportional valve with a fast response time which, at any given setting, maintains a constant ratio between the flow of NO and ventilatory gas.

Such a set-up, which remains to be manufactured, would ensure steady and predictable inspired NO concentrations and would represent an alternative to the present systems of administration into the upstream of the ventilator. It would also offer the advantage of not generating high concentrations of NO_2 and obviate the need for sodalime.

Factors influencing the pulmonary uptake of inhaled NO in ARDS

Experimental data

The diffusion coefficient of NO for the alveolo-capillary membrane is 3-5 times higher than that of carbon monoxide [14]. Paradoxically, experimental evidence demonstrates that in isolated animal lungs perfused with Ringer's lactate, the uptake of NO is only 10% [15]. Such a low pulmonary uptake, despite a high diffusion coefficient, results from its poor solubility in water. When the isolated lung is perfused with blood instead of Ringer's lactate, more than 90% of the inhaled NO is taken up [16]. The difference between the two experimental models lies in the presence of circulating hemoglobin in the lungs perfused with blood. Because of the high affinity of NO for the heme moiety of hemoglobin, blood plays a key role in the clearance of NO as it crosses the alveolo-capillary membrane.

From these experimental data it can be theoretically assumed that the factors which influence pulmonary uptake of NO are:

1. alveolar surface available for gas exchange;
2. perfusion of this alveolar surface, and
3. quantity of circulating hemoglobin.

Human data

As shown in Fig 5, when a sequential system of administration such as the Opti-NO is used in combination with controlled ventilation at a constant inspiratory flow, NO concentrations are stable in the inspiratory limb, whereas they fluctuate in the trachea. This fluctuation, which is not seen in the lung model, reflects the pulmonary uptake of NO. As shown in Figs 8 and 9, the percentage fluctuation of tracheal NO concentration (the difference between the inspired and expired NO concentrations divided by the inspired concentration) is inversely proportional to the alveolar dead space and directly proportional to the volume of normally aerated pulmonary parenchyma in ARDS [13]. This is due to

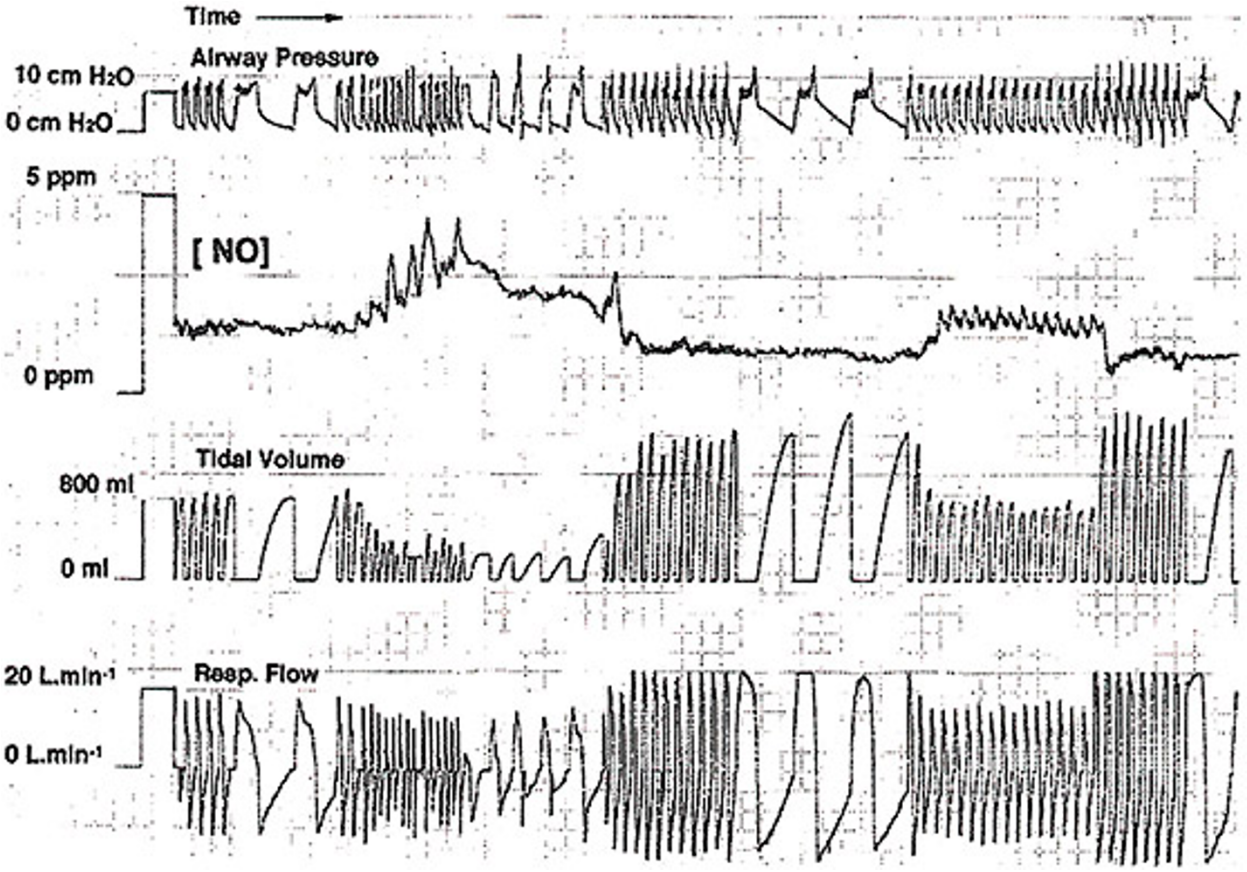

Figure 7 Variations in NO concentration in the inspiratory limb with a healthy volunteer on pressure support ventilation receiving NO by sequential method. The subject breathed from the ventilator through an air-tight mask. Nitric oxide was administered in sequential mode by the Opti-NO (Taema, Anthony, France). The Opti-NO settings corresponding to 3 ppm in the bellows of the lung model and a pressure support of 10 cmH_2O were utilized. Inspiratory NO concentrations were measured by fast-response chemiluminescence apparatus having a time delay of 2.4 s. The scale at the top of the recording indicates time (interval between two consecutive bars represents 1 s). From top to bottom, the traces correspond to airway pressure, inspired NO concentration, expired tidal volume and respiratory flow. With the level of pressure support and the settings of the Opti-NO remaining constant, inspired NO concentration varied by more than 200% as a function of varying tidal volume and inspiratory time. A decrease in the tidal volume or an increase in the inspiratory time was associated with an increase in the inspired NO concentration. Published with permission [10].

the fact that only the perfused part of the ventilated lung parenchyma takes part in the pulmonary uptake of NO [13]. It follows that the fluctuation of tracheal NO concentration can serve as an index of the extent of alveolar disease as well as the severity of pulmonary hypoperfusion. Continuous monitoring of the fluctuation of tracheal NO concentrations in a given patient could thus be a reliable 'marker' of pulmonary function during the course of ARDS [13].

Monitoring

Necessity

Nitric oxide is a potentially toxic gas. In humans, the plateau concentration to obtain maximal effects on pulmonary circulation and arterial oxygenation rarely exceeds 5 ppm [12,17-20]. In 90% of adult cases, maximal effect is obtained with inspired concentrations between 3 and 5 ppm. Concentrations of NO >10 ppm in 100% oxygen result in toxic levels of NO_2 [12]. Since peak concentrations well above 10 ppm occur during continuous administration, it is recommended to use either sequential administration or to deliver NO before the ventilator [13,21]. Despite the low risk of overdose with these systems, an accidental increase in the inspired NO and NO_2 concentrations must be detected, justifying the use of ventilator monitoring as an indispensable complement to the administration of NO.

Which type of monitor?

Slow-response systems

Systems with a response time of >10 s are not suitable for monitoring ventilatory fluctuations of NO

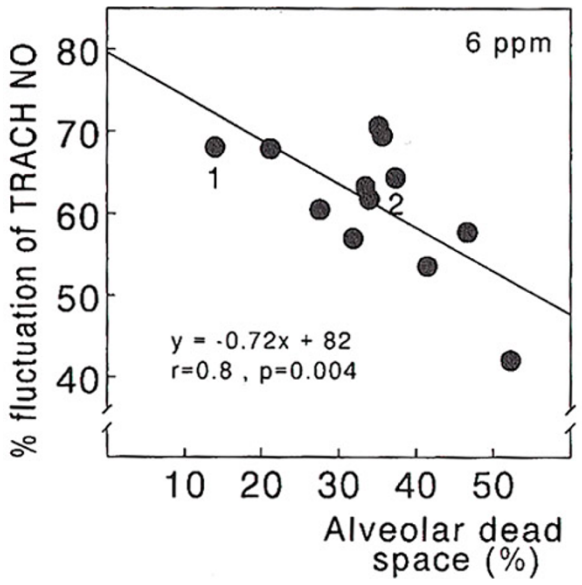

Figure 8 Correlation between the alveolar deadspace and the percentage of fluctuation of tracheal NO concentration (TRACH-NO) while administering 6 ppm of NO to 11 patients with ARDS. There is an inverse correlation between the two values suggesting that the pulmonary uptake of NO decrease with an increase in the alveolar dead space. Points 1 and 2 relate to one of the patients who was studied twice: during the acute phase of ARDS (point 2 corresponding to an alveolar dead space of 37%) and during the phase of recovery from ARDS (point 1 corresponding to an alvealor dead space of 14%). Published with permission [13].

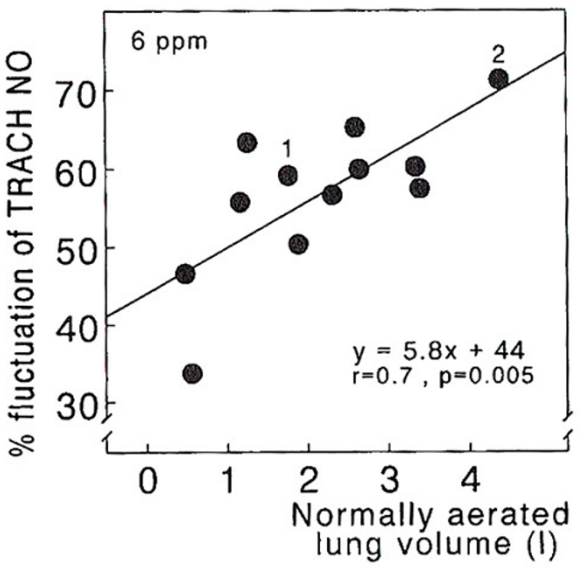

Figure 9 Correlation between the volume of normally-aerated pulmonary parenchyma, expressed as a percentage of the total lung volume and the percentage of fluctuation of tracheal NO concentration (TRACH-NO) while administering 6 ppm of NO to 11 patients with ARDS. There is a significant correlation between the two values suggesting that the pulmonary uptake of NO decreases with a reduction of aerated lung volume. Points 1 and 2 relate to one of the patients who was studied twice: during the acute phase of ARDS (point 1 corresponding to a normally aerated lung volume of 52%) and during the recovery phase of ARDS (point 2 corresponding to a normally aerated lung volume of 82%). Published with permission [13].

concentrations [3,12]. Electrochemical monitors and the first generations [3,12]. Electrochemical monitors and the first generation chemiluminescence monitors such as the NOX 2000 (Ecophysics, Aix-en-Provence, France) are examples of slow-response monitors. They can be used during sequential administration to monitor NO concentrations in the inspiratory limb since it is stable [10]. During continuous administration they do not permit measurement of the fluctuations in concentration in the inspiratory limb or in the trachea and hence should not be used in this setting. Electrochemical monitors are less expensive than chemiluminescence systems and with regular calibration, their precision is good (within 1 ppm) [22].

Fast-response systems

An accurate assessment of the mixing of NO in the different parts of the ventilatory circuit requires fast-response chemiluminescence apparatus [3,23]. Only second generation chemiluminescence equipment, specifically designed for medical usage, have a response time sufficiently rapid to permit measurement of inspired and expired tracheal NO concentrations [12]. It is necessary to differentiate the response time of the apparatus from the transit time for the gas to move from the sampling site to the measuring chamber. As an example, NOX 4000 (Sérès, Aix-en-Provence, France) has a response time of 735 ms. When the equipment aspirates the gas sample at a flow rate of 1 l/min, the transit time is 2.4 s. The NO signal is then displaced by 2.4 s in relation to the flow signal (Fig 5). A display of tracheal NO concentration on the monitor screen is available on the latest chemiluminescence apparatus (EVA 4000, Sérès, Aix-en-Provence, France) giving the possibility of continuously monitoring the fluctuations in tracheal NO concentration as an index of 'pulmonary function' during the course of ARDS [13].

Conclusion

In 1998, inhaled NO should be administered in such a way that stable and predictable concentrations in the inspiratory limb are obtained. This can be performed by administering NO either in the upstream of the ventilator or directly into the proximal end of the inspiratory circuit using a sequential system. In the former case, NO concentrations will remain constant in any ventilatory setting whereas in the latter, any change in ventilatory parameter will impose corresponding changes in

the NO flow. In the future, this drawback will be corrected by the use of fast-response time valves, administering NO with a flow perfectly proportional to the one delivered by the ventilator. Although constant NO concentrations are obtained in the inspiratory limb in both modes of administration, fluctuations in NO concentration are observed at the tracheal site. This fluctuation is due to the uptake of NO by the lung and is directly correlated to the volume of normally aerated lung and inversely proportional to the alveolar deadspace. It can, therefore, be considered as an index of ventilatory perfusion ratio mismatch, and can be continuously monitored in ARDS. In contrast, the continuous delivery of NO in the inspiratory limb leads to unpredictable and fluctuating concentrations of NO and must be considered as an unsafe mode of administration, unless fast-response chemiluminescence apparatus is used for monitoring.

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