Factors Influencing the Tracheal Fluctuation of Inhaled Nitric Oxide in Patients with Acute Lung Injury

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Background: Inhaled nitric oxide (NO) improves arterial oxygenation in patients with acute lung injury (ALI) by selectively dilating pulmonary vessels perfusing ventilated lung areas. It can be hypothesized that NO uptake from the lung decreases with increasing ventilation perfusion mismatch. This study was undertaken to determine the factors influencing the fluctuation of tracheal NO concentration over the respiratory cycle as an index of NO pulmonary uptake in patients with ALI.

Methods: By using a prototype system (Opti-NO) delivering a constant flow of NO only during the inspiratory phase, 3 and 6 ppm of NO were administered during controlled mechanical ventilation into a lung model and to 11 patients with ALI. All patients had a thoracic computed tomography (CT) scan. Based on an analysis of tomographic densities, lungs were divided into three zones: normally aerated (1,000 to −500 Hounsfield units [HU]), poorly aerated (−500 to −100 HU), and non-aerated (−100 to +100 HU), and the volume of each zone was computed. Concentrations of NO in the inspiratory limb and trachea were continuously measured by a fast-response chemiluminescence apparatus.

Results: In the lung model, tracheal NO concentration was stable with minor fluctuation. In contrast, in patients, tracheal NO concentration fluctuated widely during the respiratory cycle (55% ± 10%). Because uptake of NO from the lungs was absent in the lung model but present in the patients, this fluctuation was considered as an index of pulmonary uptake of NO. This was further substantiated by (1) the coincidence of the peak and minimum tracheal NO concentration with the end-inspiratory and end-expiratory phases, respectively, and (2) continued decrease of tracheal NO concentration during prolonged expiratory phase. In patients with ALI, the fluctuation of tracheal NO concentration expressed as the difference between inspiratory and expiratory NO concentrations divided by inspiratory NO concentration was greater at 6 ppm than at 3 ppm (P < 0.01), was linearly correlated with normally aerated lung volume, inversely correlated with alveolar dead space and with poorly aerated lung volume.

Conclusion: In patients with ALI, fluctuation of tracheal NO concentration over the respiratory cycle can be considered as an index of NO uptake from the lungs that depends on aerated lung volume and perfusion of ventilated lung areas. At bedside, it may be used to follow the evolution of ventilation-perfusion mismatch. (Key words: Nitric oxide, Mechanical ventilation, Acute lung injury.)

INHALED NO-induced vasodilation involves selective action on pulmonary vessels because after entering the pulmonary circulation, NO binds to hemoglobin and cannot dilate systemic vessels. Diffusion coefficient of NO for alveolocapillary transfer has been reported to be about 3 to 5 times that of carbon monoxide.1-4 Because alveolocapillary membrane offers little barrier to the diffusion of NO, the total alveolar surface area available for gas transfer should be one of the determinants of pulmonary NO uptake. In patients with acute lung injury (ALI), this depends on the amount of consolidated lung. Absorption of NO has been studied in isolated and perfused lungs.5-9 Less than 10% of NO has been shown to be absorbed and oxidized in rabbit lungs perfused with Ringer’s lactate solution.5 Such low absorption in isolated and perfused lungs has been attributed to...
the low solubility of NO in water. On the contrary, in a living system, despite its low solubility, absorption of NO is almost complete—80% during normal breathing and 90% during deep breathing. The difference is due to the presence of circulating hemoglobin in the latter, with which NO is known to combine strongly. Because the uptake of NO mainly depends on a mechanism related to hemoglobin, in addition to the volume of aerated lung, perfusion of the ventilated alveoli and blood hemoglobin concentration could be the other determinants of NO uptake from the diseased lungs.

Independent of its etiology, ALL results in alveolar consolidation and mismatching of perfusion. Early pulmonary thrombosis, pulmonary vasoconstriction, and late pulmonary vascular remodeling tend to alter lung perfusion and to increase alveolar dead space. According to the mechanisms of NO absorption from the lung, NO concentration in nonperfused but ventilated alveoli should be close to inspiratory concentrations, and NO concentration in the well-perfused alveoli should be close to zero because NO is totally absorbed from these alveoli if residence time is long enough. Therefore, in patients with ALL, uptake of NO from the lungs should depend on the volume of well-aerated alveoli, alveolar dead space, and blood hemoglobin level. Recently, by using a fast-response chemiluminescence apparatus in patients whose lungs were mechanically ventilated for severe ALL, we showed that tracheal NO concentration fluctuates according to the phase of respiratory cycle. Clinical experience suggests that the degree of fluctuation varies among patients with ALL. We hypothesized that the difference between inspiratory and expiratory tracheal NO concentrations could be an index of NO uptake by the lung and could correlate with alveolar dead space, volume of aerated lung tissue estimated from the thoracic computed tomography (CT) scan and blood hemoglobin concentration in patients with ALL.

**Materials and Methods**

This study was conducted in two parts. The first part was conducted in vitro in a lung model, and the second part was conducted in vivo in patients with ALL. Technique of NO administration, to be described, was similar during both the studies.

**Administration of NO**

NO was administered from cylinders containing NO in nitrogen at a concentration of 900 ppm, and the delivery was regulated by Opti-NO (Taema, Antony, France), a prototype device designed to deliver a constant flow of NO either continuously throughout the respiratory cycle (continuous mode) or only during inspiratory phase (sequential mode). This device was directly mounted on the cylinder like a pressure gauge. In sequential mode, NO is delivered throughout the inspiratory phase at a constant flow rate that is regulated by a solenoid valve synchronized with the inspiratory phase of the ventilator. NO outflow from Opti-NO was fed into the inspiratory limb of the circuit just after the Fisher Paykel humidifier. Regulation of the Opti-NO comprised of selection of the mode of administration (sequential or continuous) and setting the output pressure. By selecting the sequential mode and adjusting the output pressure with the help of a slide-rule provided by the manufacturer, it was possible to achieve a given and stable inspiratory concentration of NO for a given minute volume and an I:E ratio set on the ventilator during controlled mechanical ventilation (CMV) with a constant inspiratory flow.

Throughout the study, instantaneous NO concentrations were measured by a fast-response chemiluminescence apparatus (NOx 4000, Sère, Aix-en Provence, France), previously described, with a 95% response time of 725 ± 40 ms and a time delay of 2.4 s for the passage of the gas from the sampling site to the analyzer. NO concentrations were measured from the inspiratory limb (inspiratory NO concentrations) using a three-way swivel adaptor, from the endotracheal tube (tracheal NO concentration) using the proximal sideport of the Mallinckrodt Hilo Jet endotracheal tube (Argyle, NY) ending 6 cm from the distal tip, and during the in vitro study, from the bellows of the lung model (alveolar compartment). Percentage of fluctuation of NO concentration at any given site of monitoring was calculated as follows:

\[
\% \text{ of fluctuation} = \frac{\text{peak NO Concentration} - \text{min NO Concentration}}{\text{peak NO Concentration}} \times 100
\]

where peak and min NO concentrations are the maximum and minimum concentrations of NO measured during a respiratory cycle.

**In Vitro Study**

This part of the study was carried out on a lung model with a compliance of 50 ml/cmH₂O and a resistance of
5 cmH₂O·L⁻¹·s⁻¹ (Dual Adult TTL®, Michigan Instruments Inc., Grand Rapids, MI). The Opti-NO connected to a César ventilator (Taema, Antony, France) was set up to achieve 3 and 6 ppm of NO inside the bellows of the lung model during sequential mode with the following ventilatory settings: CMV mode using a constant inspiratory flow, a tidal volume of 600 ml, a respiratory rate of 20 breath/min, a T₁/T₉₀ of 30%, a PEEP of 10 cmH₂O, and an FiO₂ of 1. NO was delivered into the inspiratory limb of the circuit just after the humidifier. The Y-piece of the ventilator and the bellows of the lung model were connected by a Mallinckrodt Hi-lo jet® endotracheal tube to simulate the conditions in a patient. This endotracheal tube has two additional lateral openings: the distal opening at the tip of the endotracheal tube, and the proximal, 6 cm from the tip of the endotracheal tube. The concentrations of NO were measured from three different sites: alveolar site, outlet of the bellows of the lung model; tracheal site, proximal lateral port of the Mallinckrodt endotracheal tube; and inspiratory site, 60 cm from the Y-piece on the inspiratory limb and 120 cm from the site of NO administration. The chemiluminescence apparatus NOX 4000 was used to monitor the instantaneous concentrations of NO. Settings of Opti-NO to achieve 3 and 6 ppm of NO in the bellows of the lung model were noted. After the required concentrations were achieved in the bellows, instantaneous concentrations of NO from all the three sites mentioned previously were recorded on a Gould ES 1000 recorder. The airway pressure from the distal lateral opening of the endotracheal tube and the flow signal from the ventilator using a calibrated hot wire flow measuring device (Air Liquide Santé, Antony, France) were also recorded.

In Vivo Study in Patients with Acute Lung Injury

After approval of the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de La Pitie Salpêtrière Hospital and after obtaining written informed consent from the next of kin, 11 patients with ALI (mean age, 61 ± 13 yr) were included in the study. Patient 11 was studied twice—once during the acute phase of ALI and again during the resolution phase characterized by an improvement in radiologic and blood gas picture. Clinical characteristics of these patients at the time of study are shown in table 1. After NO inhalation, all had either a decrease in pulmonary arterial pressure of at least 2 mmHg or an increase in PaO₂ of at least 40 mmHg using FiO₂ 1. All were being treated by inhaled NO at the time of inclusion in the study. For ethical reasons, nonresponders were excluded from the study. All patients were mechanically ventilated through a Mallinckrodt Hi-lo jet® (Argyle, NY) endotracheal tube with a César ventilator (Taema, Antony, France) and were sedated and paralyzed with fentanyl 200–400 µg/h and vecuronium 4–6 mg/h. For the purpose of the study, ventilatory parameters were set as in the lung model (CMV with constant inspiratory flow; tidal volume, 600 ml; respiratory rate, 20 breath/min; T₁/T₉₀, 30%; PEEP, 10 cmH₂O, and FiO₂ = 1). The distal side port of the endotracheal tube was used to monitor the airway pressure, whereas the proximal side port was used to sample tracheal gas for NO monitoring. NO was delivered by Opti-NO from a 900-ppm cylinder into the inspiratory limb just after the humidifier using the Opti-NO settings determined to obtain 3 and 6 ppm of NO in the bellows of the lung model in the sequential mode. Inspiratory and tracheal NO concentrations, airway pressure, ventilatory flow, and expired carbon dioxide curves obtained from a Hewlett Packard (Andover, MA) 47210 A mainstream infrared capnometer were continuously monitored and recorded on a Gould ES 1000 recorder (Gould Instruments, Cleveland, OH).

Tracheal NO concentration was also recorded during a prolonged expiratory pause obtained by clamping the connecting tube interposed between the endotracheal tube and the Y-piece for 15 s at end-expiration. The assumptions in using the same regulation of Opti-NO in the lung model and the patients with ALI were: (1) inspiratory NO concentrations should be similar between the lung model and the patients because identical ventilatory circuits were used, and (2) tracheal NO concentrations should be different between the lung model and the patients because a significant amount of inhaled NO was taken up from the patients' alveoli.

An arterial blood sample was collected at the beginning of the study to measure PaCO₂ and blood hemoglobin concentration and to calculate alveolar dead space (Vₐ/Vₜ) using the following formula:

\[ Vₐ/Vₜ = 1 - (PETCO₂/PaCO₂) \]

where PETCO₂ is the end-tidal carbon dioxide tension measured at the plateau of the expired CO₂ curve. Expired CO₂ curves were recorded at a paper speed of 10 mm/s, and only tracings demonstrating a clear end-expiratory plateau, defined as a constant CO₂ value for more than 0.5 s at end-expiration, were used to determine PETCO₂.
Table 1. Clinical Characteristics of the Patients (Respiratory Parameters Measured Using a PEEP of 10 cm H₂O and an Fo₂ of 1)

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<td>BPN</td>
<td>AP</td>
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<td>UCCL</td>
<td>BCLL</td>
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<td>BCLL</td>
<td>DPH</td>
<td>BCLL + DPH</td>
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ALI = acute lung injury; BPN = bronchopneumonia; SS = septic shock; AP = aspiration pneumonia; PC = pulmonary contusion; SAPS = simplified acute physiologic scoring; LISS = lung injury severity score; CqS = quasi-static compliance; Crs = respiratory compliance (defined as the slope of the inspiratory PV curve between 500 and 1,000 ml); VＤ/Vl = alveolar dead space; MPAP = mean pulmonary arterial pressure; BCLL = bilateral consolidation of lower lobes; UCCL = unilateral consolidation of lower lobe; DPH = diffuse patchy hyperdensities; S = survived; D = died.

*11,*: Study on patient 11 at the early phase of ALI; 11,*: Repeat study on patient 11 during the course of recovery from ALI.

High Resolution and Spiral Thoracic Computed Tomography Scan

A high resolution and spiral thoracic CT scan was performed on the same day as the study. Each patient was accompanied to the Department of Radiology (Thoracic Division) by two intensivists. Lung scanning was performed from the apex to the diaphragm using a Tomoscan SR 7000 (Philips, Eindhoven, The Netherlands). All scans were performed at a PEEP of 10 cmH₂O by clamping the endotracheal tube connector at end-expiration (pulmonary volume equal to functional residual capacity after recruitment by PEEP). All images were observed and photographed at a window width of 1,600 Hounsfield units (HU) and a window level of 700 HU. An intravenous injection of 80 ml of contrast material was used to differentiate pleural fluid collections from consolidated lung parenchyma. Evaluation included thin-section CT and spiral CT in all patients. The thin-section CT examination consisted of a series of sections, 1.5-mm in thickness, with 20-mm intersection spacing selected by means of a thoracic scout view during a 25-s period of apnea. For spiral CT, contiguous axial sections of 10-mm thickness were reconstructed from the volumetric data obtained during a 15-s apnea. During the scanning, mechanical ventilation was provided by an Osiris ventilator (Taema, Antony, France) delivering 100% oxygen. Pulse oximetry, systemic arterial pressure, and electrocardiograph (ECG) were monitored by a Propaq 104 E1 monitor (Protocol System, North Chicago, IL).

Distinct tissue types can be characterized with CT scans by their Hounsfield attenuation numbers. To quantify lung density, the radiologist manually traced the right and left lung outlines with the roller ball on each spiral CT section from the apex to the diaphragm. Lung areas and mean lung density values were determined by using the region of interest function. Frequency histograms of the densities in HU were subsequently generated for each region of interest by using the analysis function. The frequency distribution of CT numbers (CT number represents the number of pixels) was computed for 50 compartments, from −1000 HU to +100 HU, examining a 22-HU segment for each compartment. The frequency distribution of CT numbers of the entire lung was then calculated by adding the absolute values of each compartment. The lung volume of
each compartment was calculated by multiplying the following: number of pixels × square pixel size × section thickness. Total lung volume was obtained by adding the lung volume of each compartment. After calibration of the CT scanner using lung phantoms, this technique of measurement of lung volumes was validated by performing the CT scans of 14 and 34 syringes (Model Series 5540, Hans Rudolph Inc., Kansas City, MO) filled with air and calculating their volumes using the CT scan density histograms. Precision of measurements was found to be ± 1%. To differentiate the lung zones with different degrees of aeration, the entire lung was divided into three zones: (1) lung zones with a density between −1000 and −500 HU were considered as normally aerated; (2) those between −500 and −100 HU as poorly aerated; and (3) those between −100 and +100 HU as nonaerated. Figure 1 shows two CT sections along with their corresponding histograms representing normally aerated and nonaerated lung.

Statistical Analysis

All data are expressed as mean ± SD. Percentages of fluctuation of tracheal NO concentration at 3 and 6 ppm were compared using a Wilcoxon test. Relationships between the percentage of fluctuation of tracheal NO concentration and (1) alveolar dead space; (2) CT measurements of the normally aerated, poorly aerated, and nonaerated lung volumes expressed in liters; and (3) blood hemoglobin concentration was assessed using linear regression analysis. A multiple regression analysis was performed to assess whether alveolar dead space, poorly aerated lung volume, and normally aerated lung volume were independent variables influencing the percentage of fluctuation of tracheal NO. A value of $P < 0.05$ was considered significant.

Results

Computed Tomography Scan Analysis

Median duration from the onset of ALI to the study was 8.7 days, and patients had been treated by inhaled NO for 3 ± 2 days. All patients studied had unilateral or bilateral lung consolidations associated with (n = 4) or without (n = 7) diffuse patchy hyperdensities on thoracic CT scan. Lung volumes of normally aerated, poorly aerated, and nonaerated zones in each patient are given in table 2. Mean volume of normally aerated lung was 2,154 ± 1,132 ml (57 ± 20% of the total lung volume).

Distribution of NO Concentrations in the Lung Model and the Patients

To obtain 6 ppm NO concentration in the bellows of the lung model, the Opti-NO was set to an output pressure of 1.3 bar using the sequential mode. At this setting, the flow of NO delivered by the Opti-NO was 7.4 ± 1.7 ml/min, and inspiratory and tracheal NO concentrations were found stable with only a minor fluctuation (fig. 2). In the patients, using the same Opti-NO settings, peak and minimum inspiratory NO concentrations were 5.6 ± 0.2 ppm and 5.0 ± 0.7 ppm, and peak and minimum tracheal NO concentrations were 4.1 ± 0.7 ppm and 1.8 ± 0.3 ppm. As illustrated in figure 2, tracheal NO concentration was stable in the lung model, whereas in the patients, it showed a wide fluctuation. In the patients, peak tracheal NO concentration coincided with the end of the inspiratory flow, and minimum tracheal NO concentration coincided with the end of the expiratory flow. Figure 3 shows the tracheal NO concentration during a prolonged end-expiratory pause. There was a uniform decline of tracheal NO concentration over the 15-s period of clamping, suggesting a continued uptake of NO from the lungs during this period. Similar results were observed for NO at 3 ppm (data not shown).

Factors Influencing the Percentage of Fluctuation of Tracheal NO Concentration in Patients with Acute Lung Injury

When inspiratory NO concentration was increased from 3 to 6 ppm, percentage of fluctuation of tracheal NO concentration significantly decreased from 61 ± 8% to 57 ± 10% ($P < 0.01$). As shown in figures 4-6, for both inspiratory NO concentrations, there was a significant inverse correlation between the percentage of fluctuation of tracheal NO concentration and $V_{pO}/V_{T}$ and poorly aerated lung volume and a significant direct correlation between the percentage of fluctuation of tracheal NO concentration and normally aerated lung volume. Using multiple regression analysis, $V_{pO}/V_{T}$ was identified as the only independent factor influencing the fluctuation of tracheal NO concentration ($V_{pO}/V_{T}$, $P = 0.05$; normally aerated lung volume, $P = 0.2$; poorly aerated lung volume, $P = 0.08$), whereas normally and poorly aerated lung volumes appeared linked, inversely related to each other ($y = -0.9x + 76$; $r = 0.8$; $P < 0.001$). In addition, no correlation was found between the fluctuation of tracheal NO concentration and nonaerated lung volume (NO 3 ppm: $y = -4.5x$)

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Fig. 1. Thoracic computed tomography (CT) sections of two patients representing normally aerated and nonaerated lung parenchyma along with their corresponding density histograms. The CT section on the left side shows normally aerated left lung of patient 11. The corresponding histogram located under the CT section demonstrates that the majority of the lung volume has a density $< -500$ HU. The CT section on the right side shows nonaerated lower lobes along with normally aerated upper lobes in patient 6. Under the CT section, the corresponding histogram demonstrates tomographic densities concentrated at either end of the density spectrum representing the normally aerated and nonaerated lung areas. On CT sections, the limits of lung parenchyma and main fissura manually traced by the radiologist using the roller ball of the CT scan are represented. Dashed areas represent pleural effusion.

+ 62, $r = 0.01$; NO 6 ppm: $y = 1.8x + 55$, $r = 0.01$) and between the fluctuation of tracheal NO concentration and blood hemoglobin concentration.

In patient 11, in whom the study was conducted twice—once during the acute phase of ALI and again during the resolution phase—percentage of fluctuation of tracheal NO concentration was 59% (6 ppm) and 62% (3 ppm) during the acute phase and 71% (6 ppm) and 68% (3 ppm) during the resolution phase. Corresponding values of $V_{DA}/V_t$, normally aerated lung volume, poorly aerated lung volume, and non-aerated lung volume are indicated in table 2.
Table 2. Tracheal NO Concentrations, Hemoglobin (Hb), Alveolar Dead Space (V\(_{\text{DL}}/V_{T}\)), and CT Lung Volumes of the Patients

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<th>Patient No.</th>
<th>Peak (ppm)</th>
<th>Min (ppm)</th>
<th>Fluctuation [% (3 ppm)]</th>
<th>Fluctuation [% (6 ppm)]</th>
<th>Hb (g/dl)</th>
<th>V(<em>{\text{DL}}/V</em>{T}) (%)</th>
<th>Normally Aerated [ml (%)]</th>
<th>Poorly Aerated [ml (%)]</th>
<th>Non-aerated [ml (%)]</th>
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<td>677 (36)</td>
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<td>14</td>
<td>4,372 (82)</td>
<td>322 (10)</td>
<td>462 (9)</td>
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*11\(_{1}\): Study on patient 11 during the acute phase of ALI; 11\(_{2}\): Repeat study on patient 11 during the course of recovery from ALI.

Discussion

In this study, we attempted to define an index of NO uptake from the lungs based on monitored NO concentrations and to investigate the determinants of that index in patients with ALI. Our results suggest that the percentage of fluctuation of tracheal NO concentration (1) is an index of the pulmonary uptake of NO, (2) is inversely correlated with alveolar dead space, (3) is linearly correlated with normally aerated lung volume, and (4) is inversely correlated with poorly aerated lung volume as estimated by the thoracic CT scan. Pulmonary uptake of NO in ALI depends on the amount of ventilated and perfused lung.

Fluctuation of Tracheal NO Concentration as an Index of Pulmonary Uptake of NO

To be able to measure tracheal fluctuation of the NO concentration, a chemiluminescence apparatus with a response time of 725 ms was used. According to the ventilatory settings used, the duration of inspiration was 900 ms, a period of time long enough to accurately measure inspiratory NO concentration.\(^{11}\) Therefore, even if, very likely, some damping of the NO tracing was present, the fluctuation could be measured precisely.

When Opti-NO settings similar to those used in lung model were used to deliver NO to the patients, it was presumed that the alveolar concentrations in the patients should be different from those observed in the lung model because of pulmonary uptake of NO. When recordings from the lung model were compared with those from the patients, it was evident that the tracheal site recordings showed a stable NO concentration in the lung model, whereas the recordings from the patients showed a marked fluctuation of the concentration, the peak tracheal NO concentration coinciding with the end of inspiratory flow, and minimum tracheal NO concentration coinciding with the end of the expiratory flow. When a prolonged end-expiratory pause was produced, there was a continued steady decrease in the tracheal NO concentration, suggesting a time-dependent uptake of NO from the lungs. These results strongly suggesting that the fluctuation of tracheal NO concentration was an index of the pulmonary uptake of NO, we attempted to investigate its determinants and found that it correlated well with the volume of normally and poorly aerated lung and alveolar dead space.

Estimation of Aerated Lung Volume

In this study, thoracic CT scan was used to measure the lung volumes because it is accurate and clinically more feasible than other methods like nitrogen washout technique and body plethysmography. Morphologic and tomensitometric features of CT scan in ALI have been described previously.\(^{15,16}\) In these studies, lung weight and regional distribution of air and tissue have been estimated in normal and injured lungs from 1–3 CT scan sections supposed to be representative of the entire lung. In the present study, multiple and contiguous CT scan sections were performed, allowing the
Fig. 2. Tracheal NO concentrations in the lung model and the patient during NO inhalation. The recording on the left shows tracheal NO concentration (TRACH-NO) in the lung model. The recording on the right shows TRACH-NO in patient 3. The two lower traces represent expired CO₂ curves and respiratory gas flow. NO concentrations were measured by a fast-response chemiluminescence apparatus (NOX 4000 Sérès, Aix-en-Provence, France). Time delay of the apparatus was 2.4 s, and the response time was 725 ± 40 ms. Accordingly, the beginnings of inspiration and expiration (represented by arrows) were shifted 2.4 s rightward compared with the respiratory flow recording. TRACH-NO was stable in the lung model, whereas it fluctuated widely in the patient. In the patient, peak TRACH-NO coincided with the end of the inspiratory flow, and the minimum TRACH-NO coincided with the end of the expiratory flow.

accurate determination of the lung volume within a given density range by counting the total number of pixels in that density range. This technique of volume measurement was validated by using lung phantoms and calibrated syringes. The entire lung was divided into three zones based on the tomographic densities: normally aerated, poorly aerated, and nonaerated lung areas. By this classification the volume of normally ventilated lung, which is exposed to inhaled NO, was quantified.

Estimation of Alveolar Dead Space
Alveolar perfusion being an important determinant of the pulmonary uptake of any inhaled agent, ventilation-perfusion mismatch might play an important role in the uptake of inhaled NO in patients with ALI. In this study, we tried to assess the effect of alveolar dead space on the pulmonary uptake of NO. The choice of alveolar dead space to assess ventilation-perfusion mismatch was based on the following rationale. Alterations of the pulmonary circulation together with loss of aerated lung volume are the characteristic features of ALI. In lung areas remaining well aerated, some of the regions might be underperfused or nonperfused, constituting alveolar dead space where CO₂ elimination cannot occur. Anatomical dead space, comprising of tracheobronchial tree and respiratory tubings distal to the Y-piece, and alveolar dead space together form the classical physiologic dead space that can be calculated from the Bohr equation. Alveolar dead space can be considered as an index of the extension of the pulmonary vascular lesions characterizing ALI, whereas anatomic dead space is more related to patient’s morphology. As a consequence, in patients with different heights and weights, alveolar dead space is a better index of decreased lung perfusion in the well-aerated lung areas than physiologic dead space calculated by the Bohr equation, which considers the anatomic dead space. Because we tested the hypothesis that pulmonary uptake of NO cannot occur in ventilated and nonperfused lung areas, alveolar dead space was measured in the present study and correlated with fluctuations of tracheal NO concentrations.

Determinants of the Fluctuation of Tracheal NO Concentration
The percentage of fluctuation of tracheal NO concentration correlated linearly with the CT estimates of the volume of normally aerated lung and inversely with alveolar dead space and poorly aerated lung volume. Using a multiple regression analysis, alveolar dead space only appeared as an independent factor influencing fluctuation of tracheal NO. Normally aerated lung volume, which was inversely correlated with poorly aerated lung volume, was not identified as an independent factor. Loss of aerated lung volume and increased alveolar dead space are two important hallmarks of pulmonary pathology in ALI. A decrease in the volume of aerated lung decreases the number of alveoli accessible to NO. An increase in the alveolar dead space (decrease in the perfusion of ventilated alveoli) might further limit the uptake.
of NO in the ventilated lung regions. In patients with ALI, Stenqvist et al.16, assuming a NO concentration of zero in ventilated and perfused alveoli and a NO concentration equal to inspiratory NO concentrations in ventilated but nonperfused alveoli, calculated that 33% of the total amount of NO administered, 67% of the NO reaching the alveoli, and 99% of the NO reaching the perfused alveoli might be taken up by the lungs. On the contrary, the same group found that in healthy volunteers, about 55% of the total amount of NO administered and 90% of the NO reaching alveoli was taken up by the lungs.17 This difference between the volunteers and the patients suggests a definite role played by alveolar consolidation and dead space in the pulmonary uptake of inhaled NO. In concurrence with this hypothesis, the pulmonary uptake of NO, as assessed by the fluctuation of tracheal NO concentration, correlated well with the volume of poorly aerated lung and alveolar dead space in our patients.

Because hemoglobin has a major role in the metabolic pathway of NO, we expected a correlation between the fluctuation of tracheal NO and blood hemoglobin concentration, but we could not demonstrate any such correlation in our patients. Several reasons might explain this negative result. First, the ability of hemoglobin to bind NO is important and was likely not saturated when using NO concentrations as low as 3 and 6 ppm. Second, the turnover of nitrosyl-hemoglobin appears to be exceedingly rapid, and methemoglobin concentration does not increase for NO concentrations < 10 ppm.11,18 Third, in the present study, a small dispersion of blood hemoglobin concentrations was observed, values ranging between 8.1 and 12.2 g/dl.

It is highly likely that fluctuation of tracheal NO concentration is also depending on ventilatory settings: an increase in respiratory rate and I:E ratio should decrease the percentage of fluctuation via an increase in inspiratory tracheal NO concentration. The effects of changing inspiratory flow waveform will depend on the NO delivery system: if the waveform of the NO flow exactly follows the waveform of the inspiratory flow, then inspiratory NO concentration will remain constant, and fluctuation of tracheal NO concentration will not be affected. If the waveform of the NO flow is different from the waveform of the inspiratory flow, then NO will not be homogeneously mixed in the tidal volume, resulting in a “fluctuating NO concentration” and the administration of “a bolus” in the airways. In the present study, ventilatory settings were kept constant and had no influence on the fluctuation of tracheal NO concentration, whereas the NO delivery system provided homogeneous mixing conditions.12 Inspiratory NO concentration also influences the fluctuation of tracheal NO, although it does not change the correlations between the percentage of fluctuation and alveolar dead space, volume of poorly aerated lung, and volume of normally aerated lung. In the present study, increasing the inspiratory NO concentration from 3 to 6 ppm induced an
Fig. 4. Correlation between alveolar dead space expressed in percentage of tidal volume and the percentage of fluctuation of tracheal NO concentration (TRACH-NO) during the administration of NO at 3 and 6 ppm in 11 patients with acute lung injury. At both inspiratory NO concentrations, there is an inverse correlation between the two values, suggesting that the absorption of NO from the lungs decreases with an increase in the alveolar dead space. The small numbers identify patient 11 who was studied twice, during the acute phase (1) and the recovery phase (2) of acute lung injury.

Fig. 5. Correlation between the volume of normally aerated lung parenchyma, expressed in liters, and the percentage of fluctuation of tracheal NO concentration (TRACH-NO) during the administration of NO at 3 and 6 ppm in 11 patients with acute lung injury. At both inspiratory NO concentrations, there is a significant correlation between the two values, suggesting that the uptake of NO from the lungs decreases with a decrease in the volume of normally aerated lung. The small numbers identify patient 11 who was studied twice, during the acute phase (1) and the recovery phase (2) of acute lung injury.
UPTAKE OF INHALED NO IN ACUTE LUNG INJURY

Fig. 6. Correlation between the volume of poorly aerated lung parenchyma, expressed in liters, and the percentage of fluctuation of tracheal NO concentration (TRACH NO) during the administration of NO at 3 and 6 ppm in 11 patients with acute lung injury. At both inspiratory NO concentrations, there is a significant inverse correlation between the two values, suggesting that the uptake of NO from the lungs decreases with an increase in the volume of poorly aerated lung. The small numbers identify patient 11 who was studied twice, during the acute phase (1) and the recovery phase (2) of acute lung injury.

8% decrease in the percentage of fluctuation of tracheal NO concentration.

An important corollary of the previous observations is that any decrease in the pulmonary uptake of NO, due either to an increase in the poorly aerated lung volume or to an increase in the alveolar dead space, should decrease the fluctuation of tracheal NO concentration if ventilatory settings and inspiratory NO concentrations are kept constant. A decrease in the fluctuation of tracheal NO concentration indicates a more severe degree of ventilation perfusion mismatch and vice versa. Thus, the fluctuation of tracheal NO concentration over the respiratory cycle may be used at bedside to follow the evolution of ventilation perfusion mismatch in acute lung injury.

The authors thank Dr. Ola Stenqvist, Department of Anaesthesia and Intensive Care, Sahlgrenska University Hospital, Göteborg, Sweden for the fruitful discussions that were useful in carrying out this study; Dr. Liliane Bodin, Dr. Pascale Poire, and Dr. Pierre Kalkon for their contributions to the study; the nurses of the Surgical Intensive Care Unit, and the technicians of the Department of Radiology for their active participation; and Véronique Connan for her secretarial assistance.

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