Inhaled nitric oxide in acute respiratory failure: dose-response curves


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Abstract. Objective: To determine the dose-response curve of inhaled nitric oxide (NO) in terms of pulmonary vasodilation and improvement in PaO2 in adults with severe acute respiratory failure.

Design: Prospective randomized study.

Setting: A 14-bed ICU in a teaching hospital.

Patients: 6 critically ill patients with severe acute respiratory failure (lung injury severity score ≥ 2.5) and pulmonary hypertension.

Interventions: 8 concentrations of inhaled NO were administered at random: 100, 400, 700, 1000, 1300, 1600, 1900 and 5000 parts per billion (ppb). Control measurements were performed before NO inhalation and after the last concentration administered. After an NO exposure of 15–20 min, hemodynamic parameters obtained from a fiberoptic Swan-Ganz catheter, blood gases, methemoglobin blood concentrations and intratracheal NO and nitrogen dioxide (NO2) concentrations, continuously monitored using a bedside chemiluminescence apparatus, were recorded on a Gould ES 1000 recorder. In 2 patients end-tidal CO2 was also recorded.

Results: The administration of 100–2000 ppb of inhaled NO induced: i) a dose-dependent decrease in pulmonary artery pressure and in pulmonary vascular resistance (maximum decrease - 25%); ii) a dose-dependent increase in PaO2 via a dose-dependent reduction in pulmonary shunt; iii) a slight but significant decrease in PaCO2 via a reduction in alveolar dead space; iv) a dose-dependent increase in mixed venous oxygen saturation (SVO2). Systemic hemodynamic variables and methemoglobin blood concentrations did not change. Maximum NO2 concentrations never exceeded 165 ppb. In 2 patients, 91% and 74% of the pulmonary vasodilation was obtained for inhaled NO concentrations of 100 ppb.

Conclusion: In hypoxemic patients with pulmonary hypertension and severe acute respiratory failure, therapeutic inhaled NO concentrations are in the range 100–2000 ppb. The risk of toxicity related to NO inhalation is therefore markedly reduced. Continuous SVO2 monitoring appears useful at the bedside for determining optimum therapeutic inhaled NO concentrations in a given patient.

Key words: Acute respiratory failure – Mechanical ventilation – Nitric oxide (inhaled)

Inhaled nitric oxide (NO) vasodilates preconstricted human pulmonary arteries without causing systemic vasodilation [1, 2]. Because pulmonary hypertension is a common feature observed in various forms of acute lung diseases, inhaled NO in concentrations of 18 or 36 parts per million (ppm) has been shown to reduce pulmonary arterial hypertension observed in critically ill patients with severe Adult Respiratory Distress Syndrome [3]. By redistributing pulmonary blood flow away from under-ventilated towards normally ventilated lung areas, inhaled NO in concentrations as low as 50 parts per billion (ppb) might improve arterial oxygenation in hypoxemic patients with acute respiratory failure [4, 5]. Pulmonary vasodilator dose-response curves of inhaled NO have been found within limits of 5–180 ppm in unanesthetized sheep [6, 7]. In healthy humans, a study recently suggested that the maximum effect of inhaled NO on the pulmonary circulation was reached for concentrations of 10 ppm [8]. In patients treated with extracorporeal membrane oxygenation for a severe acute respiratory failure, a dose-dependent pulmonary vasodilator effect of inhaled NO has been shown for concentrations ranging from 1 to 100 ppm [9]. Because of its potential toxicity, inhaled NO should be administered at the lowest concentration required to obtain the maximum effect on the pulmonary circulation and the optimal gas exchange improvement [5]. The aim of this prospective study was to determine the pulmonary dose-response curve of inhaled NO administered to critically ill patients with acute respiratory failure and pulmonary hypertension treated with conventional mechanical ventilation.
Methods

Patients

Six consecutive patients with ARDS diagnosed after admission to the Surgical Intensive Care Unit (SICU) of La Pitié Hospital in Paris were included in the study after informed consent was obtained from each patient’s next of kin. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de La Pitié-Salpêtrière Hospital and promoted by l’Assistance Publique Hopitaux de Paris. Inclusion criteria were: i) lung injury severity score [10] \( \geq 2.5; \) ii) bilateral and extensive hyperdensities on a high resolution thoracic CT scan; iii) a positive test to inhaled NO at a concentration of 10 ppm, defined as a decrease in mean pulmonary artery pressure of at least 2 mmHg and an increase in PaO\(_2\) (FiO\(_2\) 1) of at least 50 mmHg. Exclusion criteria were: i) pulmonary edema of cardiac origin; ii) circulatory shock and/or dependence on exogenous catecholamines; iii) cardiac arrhythmias; iv) mean pulmonary arterial pressure (MPAP) \(< 22\) mmHg; iv) pulmonary vascular resistance (PVRI) \(\leq 250\) dynes\(\cdot\)s\(\cdot\)cm\(^{-5}\)\(\cdot\)m\(^{-2}\).

These exclusion criteria were intended to exclude patients with cardiovascular instability and those in whom inhaled NO induced either no response (non-responders) or a response the magnitude of which was insufficient to determine the dose-response curve. No patient received high dose steroids before, during or after the study. All patients were sedated and paralyzed with a continuous intravenous infusion of fentanyl, flunitrazepam and vecuronium and ventilated using a Cesar ventilator (Taema, France). A positive end-expiratory pressure (PEEP) of 10 cm H\(_2\)O was used in patients 2, 3, 4 and 5 in whom lung recruitment was demonstrated on the thoracic CT scan. In order to detect changes in FiO\(_2\) induced by the inhalation of various concentrations of NO, FIO\(_2\) was continuously monitored using an O\(_2\) analyzer (SERES 2000, precision \(\pm 0.5\%)\). All patients were monitored using a fiberoptic thermomodulation pulmonary artery catheter (Oximetrix Opticath, Abbott Critical Care Systems) and a radial or femoral arterial catheter.

In two patients, a second arterial catheter was inserted in a femoral artery in order to continuously monitor PaO\(_2\) using a Continucath 1000\(^\text{TM}\) oxygen system (Pfizer). This intravascular oxygen sensor, the accuracy of which was previously evaluated [11], has a precision of \(\pm 2\) mmHg in the range 0–150 mmHg and a precision of \(\pm 9\) mmHg in the range 150–400 mmHg.

Before the study, each patient was transported to the Department of Radiology where lung scanning was performed using a Tomoscan SR 7000 (Philips, Heindoven). Evaluation included thin section CT (1.5-mm thick sections with 20-mm intersection spacing) and spiral CT (contiguous axial sections 10-mm thick reconstructed from the volumetric data) obtained during a 25-s period of apnea (pulmonary volume equal to anatomic functional residual capacity). PEEP of 10 cm H\(_2\)O was then applied for 10 min and the same CT scan protocol was repeated after clamping the inspiratory circuit at end-expiration (pulmonary volume equal to functional residual capacity after PEEP recruitment). Lung volume recruitment was visually assessed by comparing slices with and without PEEP.

Measurements

Throughout the study period, systolic and diastolic arterial pressures (SAP, DAP) and systolic and diastolic pulmonary arterial pressures (PAPs and PAPD), which were measured using 2 calibrated pressure transducers (91 DPT-308 Mallinkrodt) positioned at the midaxillary line, were continuously recorded on a Gould ES 1000 recorder at a speed of 1 mm/s simultaneously with tidal volume measured using a pneumotachograph and airway pressure measured through the distal port of the endotracheal tube.

In each phase (see experimental protocol), after a leveling of the pulmonary arterial pressure was achieved, SAP, DAP, PAPs, PAPD, PWP andRAP were recorded at a recorder speed of 50 mm/s. Mean arterial pressure (MAP) was calculated as 1/3 SAP + 2/3 DAP. MPAP was measured by planimetry as the mean of 4 measurements performed at end expiration. SAP, DAP, PAPs, PAPD, PWP and RAP were also measured at end expiration. Cardiac output was measured using the thermodilution technique and a bedside computer allowing the recording of each thermodilution curve (Oximetry 3 SO\(_2\)/CO Computer). Four serial injections of 10 ml of 5% dextrose solution at room temperature were performed at random during the respiratory cycle in order to average the variations in cardiac output related to mechanical ventilation. Heart rate (HR) was measured from the recorded ECG. Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 1 min following the measurements of cardiac output. Arterial pH, PaO\(_2\), PaCO\(_2\) and PaCO\(_3\) were measured using an IL BGE blood gas analyzer. Hemoglobin concentration, methemoglobin concentration, oxygen saturations (SaO\(_2\) and SvO\(_2\)) were measured using a calibrated OSM3 Hemoximeter. Standard formulae were used to calculate cardiac index (CI), pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), true pulmonary shunt (Qs/Qt), oxygen delivery (DO\(_2\)), and oxygen consumption (VO\(_2\)).

In patients 4 and 6, expired CO\(_2\) concentrations were continuously measured using a non-invasive calibrated 47210A infrared capnometer (Hewlett-Packard) positioned between the proximal tip of the endotracheal tube and the Y piece of the ventilator. Expired CO\(_2\) curves were continuously recorded at a speed recorder of 1 mm/s. After simultaneously drawing an arterial blood sample, alveolar dead space (V\(_{DA}\)) was calculated as:

\[
V_{DA} = VT \left(1 - \frac{\text{PetCO}_2}{\text{PaCO}_2}\right)
\]

where PetCO\(_2\) is end-tidal CO\(_2\) measured at the plateau using the capnographic method and VT is tidal volume. In all patients, respiratory minute volume curves were measured using a 1-L syringe. Afterwards, the patient was disconnected from the ventilator to allow functional residual capacity to be reached; then, slow injections of O\(_2\) were given 1.5-s pauses in 50 ml increments with a simultaneous recording of tracheal pressure measured through the distal port of the endotracheal tube. Static respiratory compliance (Crs) was considered as the slope of the pressure-volume curve between 500–1000 ml.

NO administration

Inhaled NO was released from a tank of nitrogen that had a NO concentration of 2235 ppm and a N\(_2\)O concentration of 10 ppm (Air Liquide, France). NO was delivered within the inspiratory limb of the ventilator, before the Y piece, via an injection prototype device (CFFP, France) connected to the nebulizer of the ventilator allowing NO administration only during inspiration. Nebulization resulted in an increase in inspiratory flow of 1 l/min and administration of NO was performed by adding to the inspiratory flow 10–15 ml/min of nitrogen. With the aid of the calibrated and heated pneumotachograph (Model Series 3500B, Hans Rudolph Inc., Kansas City, MO) attached to the proximal tip of the endotracheal tube, minute ventilation was adjusted to compensate for the added volume of inhaled NO (nebulization plus nitrogen flow) so that tidal volume and minute ventilation delivered to the patient were kept constant. Endotracheal concentrations of NO and N\(_2\)O were continuously measured using a chemiluminescence apparatus (NOX 2000\(^\text{TM}\), SERES, Aix-en-Provence, France), calibrated in the range 0–5000 parts per billion (ppb) using a tank of nitrogen containing 900 ppb of NO and 30 ppb of N\(_2\)O (Air Liquide, France). NO concentrations were measured using a continuous aspiration of tracheal gases (150 ml/min) through the proximal side port of the Mallinkrodt endotracheal tube, i.e. 52 cm from the site of NO administration. The precision and the response time of the NOX 2000 were respectively of \(\pm 5\) ppb and 40 s. This technique of NO administration (high NO concentration tank, NO administration limited to the inspiratory phase) was intended to avoid any significant decrease in FIO\(_2\). In order to detect significant NO adsorption on the different plastic components of the respiratory circuits, NO concentrations were measured using chemiluminescence at 7 different sites: Y piece, connecting tube, proximal tip, middle and distal tip of the endotracheal tube, 5 and 10 cm below the distal tip of the endotracheal tube. Because NO concentrations

\[
\text{MPAP} = \frac{1}{3} \text{SAP} + \frac{2}{3} \text{DAP}
\]

where PetCO\(_2\) is end-tidal CO\(_2\) measured at the plateau using the capnographic method and VT is tidal volume. In all patients, respiratory minute volume curves were measured using a 1-L syringe. Afterwards, the patient was disconnected from the ventilator to allow functional residual capacity to be reached; then, slow injections of O\(_2\) were given 1.5-s pauses in 50 ml increments with a simultaneous recording of tracheal pressure measured through the distal port of the endotracheal tube. Static respiratory compliance (Crs) was considered as the slope of the pressure-volume curve between 500–1000 ml.