Theoretical and experimental comparison of constant inspired concentration and pulsed delivery in NO therapy

Abstract  Objective: Inhaled NO therapy of artificially ventilated patients has been established as being based on constant inspired concentration of NO. In this study a new volumetrically controlled pulsed NO delivery mode is compared with the established concentration-based concept.

Design: To evaluate the relationship between NO delivery parameters, alveolar NO fraction, and patient uptake, a mathematical lung model was created where NO delivery can be simulated in varying ventilator settings, delivery modes, and lung properties. This model and the efficacy of pulsed delivery in inducing pulmonary capillary vasodilatation were examined experimentally.

Setting: Animal laboratory, Department of Medical Sciences, Clinical Physiology.

Subjects: The experimental study was performed with nine pigs of mixed breed weighing 25–35 kg.

Interventions: The pigs were anaesthetised and artificially ventilated. Pulmonary vasoconstriction was induced by hypoxia. NO was delivered periodically in the various delivery modes.

Measurements and results: In simulation, in all delivery modes the NO uptake was found to be dependent on the ventilator settings and the volume of the dead space. Measured from pulmonary artery pressure, the pulsed delivery was as effective in reducing the induced pulmonary vasoconstriction as the constant inspired concentration delivery. The amount of NO that could reduce the vasoconstriction back to baseline was 105 nmol · min⁻¹. By delivering in the early part of the inspiration, ambient contamination by the exhaust gas is avoided. The expired NO values obtained in the simulation and the experiments were equal. Based on the simulation, the alveolar NO fraction and the NO uptake depend on the ventilator settings and the dead space in both volumetric- and concentration-based delivery.

Conclusions: With pulsed delivery, a therapeutic effect comparable to constant inspired concentration delivery is achieved, NO gas is used more effectively, and environmental exhausts are reduced. The theoretical model shows that the NO delivery does not predict alveolar NO fraction and the NO uptake. However, it still remains an open question if the online measurement of these parameters would provide useful information, having added value in predicting and controlling the efficacy of the NO treatment.

Key words  Nitric oxide · Pulmonary vasoconstriction · Pigs · NO delivery · Hypoxia
Introduction

Nitric oxide (NO) was identified as an endothelium-derived relaxation factor in 1987 [1, 2]. The smooth muscle tone of the pulmonary vessels has been shown to be influenced by continuous release of NO from the endothelium, leading to an increase in cGMP that mediates relaxation. The NO administered by inhalation acts as replacement of the locally decreased NO production. Airing from this finding, inhaled NO has been used to reduce pulmonary hypertension [3], improve oxygenation [4, 5], and lessen the right ventricular loading [6] in patients with severe acute lung diseases.

In artificial ventilation NO has mostly been administered by constant inspired NO concentration [7, 8, 9, 10, 11, 12]. The possibility of a delivery concept based on the NO volume has also been discussed [8, 13]. However, the relation between the inspired NO concentration or amount and the alveolar NO partial pressure and the NO uptake in various ventilator settings and patient physiology has not been studied analytically before.

To exert a vasodilatory effect, the NO molecules are transported from the alveolar space into the vascular smooth muscle by diffusion. According to Fick's first law of diffusion the flux is proportional to the partial pressure gradient. Since the NO is rapidly metabolised, the blood concentration is zero. Therefore, alveolar partial pressure of NO, the NO diffusing capacity alveolar partial pressure of NO, and the NO diffusing capacity control the NO transport.

Due to high diffusing capacity, 95–100% of the NO is taken up from the alveoli [14] meaning that thus almost all the NO exhaust is coming from the dead space. NO delivery in pulses of known amounts synchronously with the inspiration makes it possible to avoid the anatomic dead space administration and reduce the environmental exhausts. Pulsed delivery mode has been used for the treatment of persistent pulmonary hypertension in spontaneously breathing patients [15, 16].

This study presents a model to predict the relationship of the administered NO to alveolar NO fraction, NO uptake and, further, to exhaled NO fraction. In an experimental part of this study a new delivery device for pulsed administration was tested. The efficacy of various pulsing schemes, including one equivalent to the constant concentration mode, was investigated. The differences in the safety aspects, including the rebound effect, between various NO administration modes will also be discussed. To confirm the theoretical model the measured exhaled NO fractions in different delivery settings will be compared to the predicted ones.

![Fig. 1 Lung model used for the simulation of the NO inhalation](image)

Methods

Theoretical study

The theoretical model consists of two elastic compartments representing perfused and non-perfused lung sections (Fig. 1). The lung volume ($V_L$) is set initially to functional residual capacity (FRC).

The elasticity is determined by compliance C. In simulation, the compliance was selected for the tidal volume to give 10–15 cmH$_2$O peak inspiratory pressure. The lung is ventilated with inspiratory flow ($V_i$) through a channel representing the anatomic dead space volume ($V_{D_{in}}$). NO is administered into the inspired flow at a rate defined by the NO delivery mode and delivery rate. NO is transported through the $V_{D_{in}}$ into the lung. The gas entering the elastic compartment is divided to flows into the parallel perfused and non-perfused lung compartments in a ratio ($V_{D_{P}} \cdot V_{L_{-1}}$) determined by the proportion of the alveolar dead space ($V_{D_{P}}$) of the $V_L$. The gas will be mixed with the gas already existing in the compartments so that the compartment mixture is always homogeneous.

The $V_i$ and lung pressure ($P_L$) during inspiration are represented by Eqs. (1) and (2). In the perfused compartment, the diffusion of NO is continuous and determined by the lung NO partial pressure, or fraction ($F_{NO}$), and diffusion constant ($D_{NO}$). The lungs are provided with NO mixed in the inspired gas in fraction ($F_{NO}$). The $F_{NO}$ for the compartments is determined by Eq. (3). In the non-perfused compartment the diffusion constant value is zero.

Expiratory gas flow ($V_e$) is determined by the $P_e$ and airway resistance (R) according to equation (4). The $V_e$ is a mixture of parallel flows derived from the perfused and non-perfused compartments in a ratio determined by the $V_{D_{P}} \cdot V_{L_{-1}}$. The corresponding decrement in the lung volume is determined by equation (5). The