Respiratory Physiology & Neurobiology 187 (2013) 157–163

Contents lists available at SciVerse ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Effect of nitric oxide inhalation on gas exchange in acute severe pneumonia

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ARTICLE INFO

Article history:
Accepted 9 March 2013

Keywords:
Respiratory failure
Pulmonary artery pressure
Pulmonary gas exchange
Ventilation–perfusion ratio

ABSTRACT

Inhaled nitric oxide (NO) causes selective pulmonary vasodilatation and may improve gas exchange. The study was aimed to evaluate the acute effects of inhaled NO on pulmonary gas exchange in severe unilateral pneumonia, where hypoxemia results from increased intrapulmonary shunt. We studied 8 patients without preexisting lung disease (59 ± 18 yr; 4M/4F) with early unilateral severe pneumonia and respiratory failure. Pulmonary and systemic hemodynamics and gas exchange, including ventilation–perfusion ($\dot{V}_A/\dot{Q}$) distributions, were measured at baseline and while breathing 5 and 40 parts per million (ppm) of NO. Inhaled NO caused a dose-dependent fall in pulmonary vascular resistance (by 12% and 21%, with 5 and 40 ppm, respectively; $p < 0.01$, each) and improvement of PaO_2 (by 25% and 23%; $p < 0.05$, each), owing to the reduction of intrapulmonary shunt (by 23% and 27%; $p < 0.05$, each), without changes in the amount of perfusion to low $\dot{V}_A/\dot{Q}$ ratio alveolar units. Patients with greater baseline intrapulmonary shunt exhibited greater improvement in arterial oxygenation ($r^2 = 0.55$, $p < 0.05$). We conclude that low doses of inhaled NO improve pulmonary gas exchange in acute severe pneumonia.

1. Introduction

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator that has the potential to improve pulmonary gas exchange in adults and pediatric patients with acute respiratory distress syndrome (ARDS) (American Academy of Pediatrics. Committee on Fetus and Newborn, 2000; Afshari et al., 2011; Griffiths and Evans, 2005; Rossaint et al., 1993). Randomized, multicentric, placebo-controlled studies (Dellinger et al., 1998; Lundin et al., 1999; Taylor et al., 2004) have shown that the addition of inhaled NO to conventional treatment of acute lung injury improves arterial oxygenation in about 60% of the patients, allowing to the reduction of inspired oxygen concentration and airway pressures (Dellinger et al., 1998). Nevertheless, the beneficial effect of inhaled NO usually lasts only for a short period, without affecting the high mortality rate of this condition, which in the majority of cases is due to multiple organ failure (Dellinger et al., 1998; Lundin et al., 1999; Taylor et al., 2004). Currently, inhaled NO is considered a rescue therapy to refractory acute respiratory failure, as occurs with mechanical ventilation in prone position and extracorporeal membrane oxygenation (ECMO) (Collins and Blank, 2011).

The amelioration of pulmonary gas exchange with inhaled NO in ARDS has been attributed to vasodilatation in ventilated lung areas, where exogenous NO has easy access. As a result, blood flow is redistributed from nonventilated to ventilated alveolar units, thereby reducing intrapulmonary shunt. In other respiratory disorders the effect of inhaled NO on pulmonary gas exchange remains uncertain. Based on observations made in chronic obstructive pulmonary disease patients (COPD), where inhaled NO worsens pulmonary gas exchange due to the release of hypoxic pulmonary vasoconstriction, we suggested that gas exchange effects of inhaled NO might depend on the underlying mechanism of hypoxemia (Barbera et al., 1996). Recently, we have reported that inhaled NO produces pulmonary vasodilatation without altering gas exchange in idiopathic pulmonary fibrosis (Blanco et al., 2011).

These findings suggest that inhaled NO may improve pulmonary gas exchange when arterial hypoxemia is caused predominantly by increased intrapulmonary shunt, but it may worsen it when hypoxemia is produced by $\dot{V}_A/\dot{Q}$ imbalance. Therefore, we hypothesized that inhaled NO could exert a beneficial effect on

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http://dx.doi.org/10.1016/j.resp.2013.03.006

gas exchange in acute respiratory failure associated to pneumonia, where hypoxemia is mainly due to increased intrapulmonary shunt (Gea et al., 1991). Accordingly, we investigated the acute effects of inhaled NO on pulmonary gas exchange and hemodynamics, in a group of patients without preexisting lung disease admitted in the intensive care unit because of acute respiratory failure caused by community-acquired unilateral bacterial pneumonia.

2. Materials and methods

2.1. Subjects

Eight patients (age, 59 ± 7 yr; 4 women) with unilateral bacterial pneumonia and severe arterial hypoxemia (PaO_2/F_IO_2 at hospital admission, 188 ± 19 mm Hg) were studied (Table 1). Patients were selected according to the following criteria: (a) community-acquired pneumonia, diagnosed on the basis of unilateral alveolar opacities on the chest radiograph with two or more of the following signs: fever (>38 °C), purulent sputum, localized rales and/or bronchial sounds on auscultation, and leukocytosis ($\geq 12 \times 10^9$/L); (b) respiratory failure, defined by a PaO_2/F_IO_2 less than 250 mm Hg, fulfilling the criteria of severe community-acquired pneumonia (Mandell et al., 2007); and (c) absence of preexisting lung disease.

We paid careful attention to study only patients with unilateral radiological abnormalities in order to exclude those cases with pneumonia-associated ARDS. Four patients required mechanical ventilation, while the other four were studied breathing spontaneously. Two patients were cigarette smokers, but none of them had previous knowledge of chronic pulmonary disease. Subjects were studied within the first days from hospital admission (median, 37 h; range, 23–105 h) as soon they were under stable conditions without changes in F_IO_2, ventilator settings or hemodynamics for at least 12 h. The study was approved by the Ethics Committee on Human Research of our institution (CEIC-211195), and informed consent was obtained from each patient or his/her relatives, after the purpose and potential risks of the investigation were explained and understood.

2.2. Measurements

A transvenous balloon-tipped Swan-Ganz® catheter (Edwards Laboratories) was placed into the pulmonary artery under pressure wave monitoring, and a polyethylene catheter was inserted in the radial artery. Intravascular pressures were continuously monitored and registered (7754B; Hewlett-Packard, Germany). External zero reference level was positioned at midchest. Two measurements were made under each study condition and the mean value was reported as the final result. Measurements of pulmonary artery pressure were taken at the end of expiration. Cardiac output was determined by the thermodilution technique (M1012A; Hewlett-Packard, Germany) and it was expressed as the mean of three measurements.

Minute ventilation and respiratory rate were recorded minute by minute using a calibrated Wright spirometer (MK8, BOC-Medical, Essex, UK). A heated-mixing box was used to collect the expired gas. It was attached to the expiration port of a low dead space, low resistance, non-rebreathing valve (Hans Rudolph, Kansas City, MO) in spontaneously breathing patients, or placed between the endotracheal tube and the expiration inlet of the ventilator, in mechanically ventilated patients. Oxygen uptake and CO_2 production were calculated from mixed expired O_2 and CO_2 concentrations (CPX System, Medical Graphics, St. Paul, MN). Arterial and mixed venous PO_2, PCO_2 and pH were analyzed in duplicate using standard electrodes, together with hemoglobin and methemoglobin concentrations (860 System, Ciba-Corning, Medfield, MA).

Table 1
Characteristics of the patients and outcome.

N	Gender	Age, years	Lung infiltrates (etiology)	MV	F_IO_2	PEEP, cmH_2O	PaO_2, mm Hg	PaO_2/F_IO_2, mm Hg	$PaCO_2$, mm Hg	Shunt, % of Q_T	Log SDQ	MAP, mm Hg	PVR, dyn s cm^{-5}	Outcome
1	M	17	ULL, LLL (unknown)	Yes	0.91	12	82	90	49	31	0.85	58	300	Septic shock, dead
2	F	69	LRL (pneumococcus)	Yes	0.44	3	91	206	29	20	0.76	74	163	MOF, dead
3	F	66	URL (unknown)	No	0.33	SB	82	248	37	13	0.76	68	161	Discharged
4	M	59	URL, MRL (unknown)	Yes	0.44	4	97	219	37	17	1.17	88	214	Septic shock, dead
5	M	60	LRL, MRL (pneumococcus)	Yes	0.66	0	81	122	44	23	1.27	69	195	Discharged
6	F	74	LLL (unknown)	No	0.26	SB	60	234	38	7	1.64	100	284	Discharged
7	F	63	LRL, MRL (pneumococcus)	No	0.60	SB	73	121	37	23	0.35	79	173	Discharged
8	M	60	LRL (aspiration pneumonia)	No	0.40	SB	94	234	38	8	1.62	86	375	Discharged

Definition of abbreviations: MV: mechanical ventilation; F_IO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; SB: spontaneous breathing; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; Shunt: fraction of cardiac output perfusing lung units with $\dot{V}_A/\dot{Q}$ ratio <0.005; Q_T: cardiac output; Log SDQ: dispersion of blood flow distribution; MAP: mean arterial pressure; PVR: pulmonary vascular resistance; ULL: upper left lobe; LLL: lower left lobe; URL: upper right lobe; LRL: lower right lobe; MRL: mid right lobe; MOF: multiple organ failure.