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Pharmacodynamics and pharmacokinetics of inhaled nitric oxide in dogs with septic acute respiratory distress syndrome[1]

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KEY WORDS adult respiratory distress syndrome; nitric oxide; phosphatidylcholines; pulmonary surfactants; respiratory insufficiency; respiratory therapy

ABSTRACT

AIM: To evaluate pharmacodynamics and pharmacokinetics of inhaled nitric oxide (iNO) in dogs with acute respiratory distress syndrome (ARDS). **METHODS**: ARDS, induced after iv injection of endotoxin, was evidenced by reduction of p_{aO_2}/F_{iO_2} from (62.5 ± 2.8) to (26 ± 4) kPa and dynamic lung compliance (Cdyn) from (14.8 ± 0.7) to (8.6 ± 0.6) mL·kPa^{-1}·kg^{-1}, increase of dead space (V_D/V_T) from (0.14 ± 0.06) to (0.58 ± 0.05), intrapulmonary shunting (Qs/Qt) from 4.7 % ± 1.7 % to 39 % ± 7 %, and pulmonary vascular resistance index (PVRI) from (16 ± 4) to (51 ± 8) kPa·s·L^{-1}·m^{-2} (all $P < 0.05$), along with severe intrapulmonary neutrophil recruitment and peripheral neutropenia. The animals were then treated as either a control or an NO group ($n = 6$ each, iNO 0.4 - 3.2 μmol·L^{-1}) for another 10 h. **RESULTS**: More survival was found in NO group (4/6 *vs* 0/6, $P < 0.05$). iNO at 0.8, 1.6, and 3.2 μmol·L^{-1} (20, 40, and 80 ppm) resulted in > 40 % increase of p_{aO_2}/F_{iO_2} and Cdyn, a reduction of V_D/V_T to 0.32, Qs/Qt to < 25 %, and PVRI by > 50 % (30.8 kPa·s·L^{-1}·m^{-2}) compared to the control. Optimal iNO dose was around 0.8 μmol·L^{-1} as higher methemoglobin (MetHb, > 3 %) was found at higher NO. iNO had no adverse effects on surfactant phospholipids and lung fluid balance, but attenuated expression of tumor necrosis factor α, β2 integrin CD11b, and interleukin-8 mRNA in the lungs by 22 %, 44 %, and 25 %, respectively ($P < 0.05$). **CONCLUSION**: Pharmacodynamics of iNO in this model was related to improvement in gas exchange, Cdyn, PVRI, and suppression of proinflammatory cytokine expression in the lungs, and its adverse effect was mainly confined to MetHb at higher NO dose.

INTRODUCTION

Septic acute respiratory distress syndrome (ARDS) is often encountered as a complication of various diseases, such as pneumonia, pancreatitis, trauma, burn injury, cardiovascular and gastrointestinal operations, or as a part of multiple system organ failure. Pathogenesis of acute lung injury (ALI) and ARDS in septic patients is related to intrapulmonary neutrophil accumulation and inflammatory damage of lungs. Such changes lead to impairment of lung mechanics and gas exchange, surfactant dysfunction and deficiency, pulmonary hypertension secondary to hypoxic intrapulmonary vasoconstriction, and increased vascular-to-alveolar permeability[1]. To prevent the development of ARDS from pulmonary infection and septic lung injury, inhaled nitric oxide (iNO) was introduced primarily as a selective pulmonary vasodilator[2-6], but its pharmacodynamics and pharmacokinetics in septic ARDS remain to be verified. Recent studies suggest that iNO modulates alveolar macrophage and neutrophil that mediate inflammatory processes[7] by down-regulation of expression of proinflammatory cytokines, such as β2 integrin CD11b/CD18 and P- and L-selectin of neutrophils. Interventions modulating expression and function of these cytokines should be of clinical importance. There are other concerns about the

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rationale of iNO for septic ARDS as in sepsis, there is enhanced expression of inducible nitric oxide synthase (iNOS) and increased metabolites of NO, nitrite/nitrate in circulation, and about effective dose of iNO on septic ARDS as well. In oreer to verify whether iNO is effective for septic ARDS, we developed a canine model of ARDS by a prolonged provocation with intravenous bacterial endotoxin priming and a major (bolus) administration 20 h apart, and subsequently mechanical ventilation, evaluated lung mechanics, pulmonary hemodynamics, and metabolism of iNO, and measured lung tissue TNF-α, IL-8, and CD11b mRNA expression by a reverse transcription polymerase chain reaction (RT-PCR). We also measured surfactant phospholipids in lung washes and lung fluid content to estimate any adverse effects of iNO in this model.

MATERIALS AND METHODS

Animal management and inhaled NO settings Twelve healthy Beagle dogs (from Department of Experimental Animal, Fudan University) of both genders, 8.0 – 12.5 kg, were sedated with diazepam (0.5 – 1.0 $mg \cdot kg^{-1}$, im), and 15 min later anesthetized with pentobarbital (15 – 20 $mg \cdot kg^{-1}$, iv). The animals were then intratracheally intubated and mechanically ventilated with a ventilator set at a tidal volume (V_T) of 10 $mL \cdot kg^{-1}$, frequency of 15 – 20 min^{-1}, fraction of inspired oxygen (F_{iO_2}) of 0.21, to maintain p_{aCO_2} at 5 – 6 kPa, p_{aO_2} at 10 – 13 kPa, and arterial pH at 7.30 – 7.50. Additional pentobarbital (10 $g \cdot L^{-1}$) was infused at 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$, and pancuronium bromide 0.5 $mg \cdot kg^{-1}$ was given im when required. An 18 G cannula put in the right femoral artery was connected to a life sign monitor to measure mean systemic arterial pressure (SAP). Mean pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (Pcwp), and central venous pressure (CVP) were measured with a 5-F Swan-Ganz catheter. Cardiac output (CO) was measured by thermodilution technique. Pulmonary and systemic vascular resistance indices (PVRI, SVRI) were calculated using standard equations. Physiological intrapulmonary shunting (Qs/Qt, %) was also determined by standard equation. Arterial and mixed venous blood samples were drawn while F_{iO_2} was temporarily set at 1.0 for measurement of baseline values of pH, p_{aO_2}, p_{aCO_2}, p_{vO_2}, p_{vCO_2}, S_{aO_2}, and S_{vO_2} with an automatic blood gas analyzer, and for determination of nitrite/nitrate and methemoglobin (MetHb) for both endogenously produced and inhaled NO. Baseline values for V_T, dynamic compliance, (Cdyn, $mL \cdot kPa^{-1} \cdot kg^{-1}$) and resistance of the respiratory system (Rrs, kPa $\cdot s \cdot L^{-1}$) were measured with a pneumotachograph. Physiological dead space (V_D/V_T) was determined with an end-tidal CO_2 analyzer. NO gas obtained as 40 $\mu mol \cdot L^{-1}$ [1000 parts per million (ppm)] was supplied to the inspiratory limb of the ventilator and its concentration was determined as reported elsewhere[8].

Experimental protocol Approximately 30 min after induction of anesthesia, endotoxin (*Escherichia coli*, serotype 055/B5, L2637, Sigma) was given at 0.50 $mg \cdot kg^{-1}$ (iv). In order to potentiate lung injury and respiratory failure more effectively, a low dose (0.05 $mg \cdot kg^{-1}$) of the same endotoxin was given iv 20 h before the induction of anesthesia[9]. After the endotoxin infusion, the animals were ventilated with F_{iO_2} 0.6 to maintain p_{aO_2} above 7 kPa while the ventilator settings were adjusted for adequate p_{aCO_2}. Lactated Ringer's solution (pH 6.0 – 7.5) and 2.5 % bicarbonate sodium was infused iv at 8 – 10 $mL \cdot kg^{-1} \cdot h^{-1}$ to correct acidosis. Sepsis was considered when body temperature > 38 ℃ or < 36 ℃, heart rate > 90 min^{-1}, respiratory rate > 20 min^{-1}, and peripheral white blood cell counts > 12×10^9/L or < 4×10^9/L, and SAP drop more than 5 kPa of the baseline level[10]. ARDS was defined as p_{aO_2}/F_{iO_2} < 26.7 kPa (200 mmHg) and a decrease of Cdyn > 30 % of the baseline level, Qs/Qt > 25 %, and radiological evidence of bilateral infiltration of the lungs[11]. When ARDS was established, the animals were randomly assigned to groups receiving either mechanical ventilation only (Control, $n = 6$), or mechanical ventilation with iNO (NO, $n = 6$). iNO was given at 0.4, 0.8, 1.6, and 3.2 $\mu mol \cdot L^{-1}$ (10, 20, 40, and 80 ppm) each for 1 h followed by 0.4 $\mu mol \cdot L^{-1}$ for 6 h[12]. On completion of the treatment or the occurrence of early death (determined by immeasurable SAP), pentobarbital 50 $g \cdot L^{-1}$ was given iv until there was cardiac arrest. After examination of pneumothorax through a thoracotomy, the lungs were processed.

Lung process When the chest opened, left lung hilus was ligated and a piece of tissue from the left middle lung lobe was cut and its wet/dry weight ratio (W/D) was determined as reported elsewhere[11], another piece of the lung tissue was put in liquid nitrogen for determination of proinflammatory cytokine expression.

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Broncho-alveolar lavage (BAL) of the right lung was performed with 0.9 % NaCl at 15 mL·kg^{-1} body weight and room temperature. Three such wash was performed and more than 75 % of the instilled BAL fluid (BALF) was collected and pooled from each animal. Pooled BALF was immediately centrifuged for 10 min at 200 × *g* and 4 ℃ to remove cell debris, and the supernatant was stored at − 20 ℃ for biochemical analysis. The left lung was removed and fixed for histological examination.

Biochemical analysis Disaturated phosphatidylcholine (DSPC) and total phospholipids (TPL) in BALF were determined according to the methods reported elsewhere[11]. Total proteins (TP) in BALF were measured with Lowry's method[13]. Blood and urine samples representing baseline, treatment time 0, 1, 5, and 10 h respectively, were taken for measurement of nitrite/nitrate using Griess reagent[9,11], and values are expressed as μmol·L^{-1} of total nitrite and nitrate in serum and urine. MetHb (percentage of total hemoglobin) was determined according to Hegesh *et al*[14]. Peripheral white blood cell (WBC) count was determined with an automatic blood cell analyzer.

Determination of lung cytokine mRNA expression Total RNA in lung tissue was extracted using the acid guanidinium-phenol-chloroform technique. Gibco's Super Scriptase was used for reverse trancription (RT) from targeted cytokine mRNA to cDNA according to standard procedure. Oligonucleotide primers used in amplification of cDNA of TNF-α, IL-8, and CD11b were produced by RT-PCR. Respective upstream and downstream primer sets for dog TNF-α were derived from Venta *et al* (unpublished data; Gene-specific universal mammalian sequence-tagged site for TNF-α, 1996): 5′-CTC AGC CTC TTC TCC TTC CT-3′ and 5′-ATG GGC TCA TAC CAG GGC TT-3′ (expected product size, 247 bp); that for IL-8: 5′-TGC AGT TCT GTC AAG AGT CAG-3′ and 5′-ACC TTT TGT ACC CAT TTT TCC T-3′ (477 bp); and that for CD11b: 5′-CTG GGC TGG TGG AGT CTT TCT A-3′ and 5′-CTA TGG GAG GGC CTG ATG C-3′ (588 bp, all were synthesized products by CyberSyn, Shanghai). β-Actin mRNA was used as internal reference. The PCR for these cytokines and β-actin included 35 cycles under specific conditions, and the products were identified by an automated gel-imaging analysis system.

Statistical analysis Data are presented as means and standard deviation (SD). Survival rate between groups was examined by Fisher's exact test. Wilcoxon-Mann-Whitney test was used for differences between the two groups. Within-group differences were detected with Wilcoxon signed-rank test. A P-value of < 0.05 was regarded as statistically significant.

RESULTS

General condition and treatment response of the animals Endotoxin priming resulted in body temperature at 38 − 39 ℃, increase of peripheral WBC count > 12 × 10^9/L, and weakness in most of the animals. ARDS occurred in all the animals in an average of 36 h (range 24 − 40 h) after the major (second) infusion of endotoxin and mechanical ventilation. It was evidenced by significant decrease of p_{aO_2}/F_{iO_2} from (62.5 ± 2.8) kPa (469 mmHg ± 21 mmHg, baseline) to (26 ± 4) kPa (193 mmHg ± 26 mmHg), Cdyn from (14.8 ± 0.7) to (8.5 ± 0.6) mL·kPa^{-1}·kg^{-1}, and increase of Rrs from (0.69 ± 0.21) to (0.98 ± 0.26) kPa·s·L^{-1}, V_D/V_T from (0.14 ± 0.06) to (0.58 ± 0.05), PVRI from (16 ± 4) to (51 ± 8) kPa·s·L^{-1}·m^{-2}, and Qs/Qt from 4.7 % ± 1.7 % to 39 % ± 7 % (Fig 1 A-D, $P < 0.05$; Fig 1F, $P < 0.01$, compared with the baseline values).

During the treatment period, all the animals in the control group died (2 after 3 h, 4 after 4 h). In contrast, 4 animals in the NO group survived for 10 h but 2 died after 8 h of treatment ($P < 0.05$) despite deteriorations in both groups. In the NO group, marked improvements in p_{aO_2}/F_{iO_2}, Cdyn, V_D/V_T, PVRI, and Qs/Qt were seen. iNO at 0.8 − 3.2 μmol·L^{-1} (20 − 80 ppm) resulted in > 40 % increase of mean p_{aO_2}/F_{iO_2} and Cdyn compared with the controls, a reduction of V_D/V_T to 0.32, PVRI by more than 50 % (to 30.8 kPa·s·L^{-1}·m^{-2}), and $Qs/Qt \leqslant 25$ %. The optimal dose response was at 0.8 μmol·L^{-1} (20 ppm, Fig 1A-D, F), even if compared with the corresponding values at the time 0 h (ARDS, $P < 0.05$). When iNO was reduced from 3.2 μmol·L^{-1} (80 ppm) to 0.4 μmol·L^{-1} (10 ppm), there was a modest rebound of p_{aO_2}/F_{iO_2}, Cdyn, V_D/V_T, PVRI, and Qs/Qt. In the NO group at the end period of the experiment, there was deterioration mainly due to hypotension, acidosis, and cardiac depression. In the NO group, SVRI varied highly but its average level remained unchanged (Fig 1E).

Nitrogen dioxide in the ventilator circuit was < 0.12

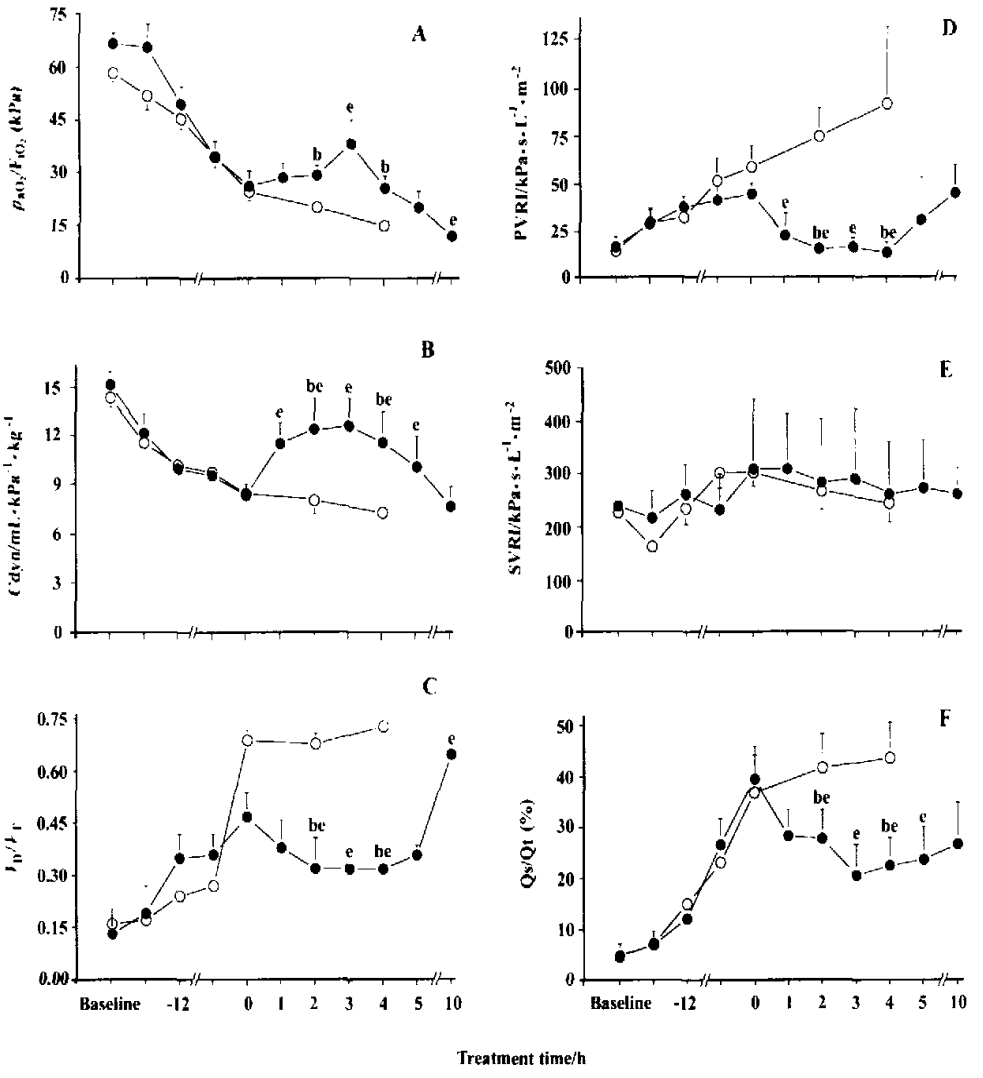

Fig 1. Lung mechanics (A-C) and pulmonary and systemic hemodynamic properties (D-F) of dogs with ARDS. Empty circle is Control and filled circle is inhaled nitric oxide (NO) group. Baseline is the moment before induction of sepsis was initiated by major dose of endotoxin. Treatment time 0 is the moment ARDS was established. Treatment time at 1, 2, 3, 4, 5, and 10 h corresponding to iNO at 0.4, 0.8, 1.6, and 3.2 μmol·L^{-1}(10, 20, 40, and 80 ppm) each for 1 h, and 0.4 μmol·L^{-1}(10 ppm) for 1 and 6 h, respectively. Treatment time at - 12 h corresponding to 12 h before ARDS was established. n = 4-6, including those of early death. $\bar{x} \pm s$. $^bP < 0.05$ *vs* Control. $^eP < 0.05$ *vs* the time point of 0 h (ARDS, within-group comparison).

μmol·L^{-1}(3 ppm) during treatment. Nitrite/nitrate levels in serum, urine, and MetHb were presented in Fig 2. Endotoxin priming and major infusion induced modest increase of nitrite/nitrate production in serum and urine of the animals, but iNO resulted in a steady increment of nitrite/nitrate in serum and urine concomitantly and an increase of MetHb. For the NO group, these levels were not significantly different from those at the time 0 h (ARDS) until 1.6 - 3.2 μmol·L^{-1} (40 - 80 ppm) of NO were applied, and MetHb level > 3 % was also revealed at higher iNO. These values decreased when iNO was reduced from 3.2 μmol·L^{-1} to 0.4 μmol·L^{-1}.

Biochemical analysis Values for TPL, DSPC/

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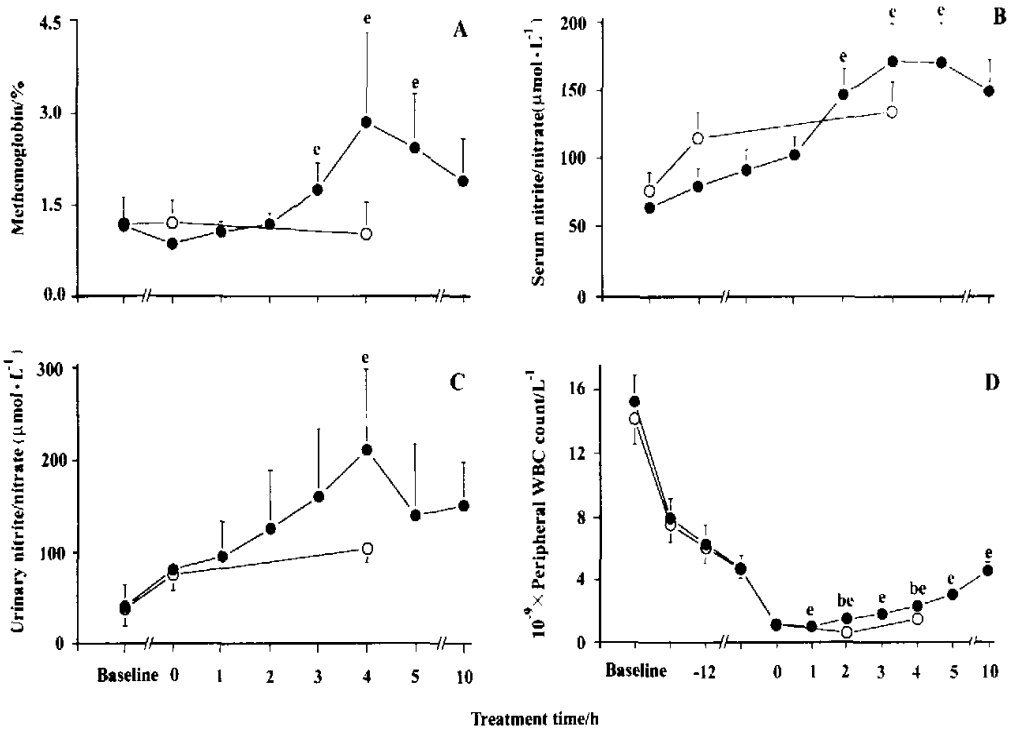

Fig 2. *Nitrite/nitrate in methemoglobin content* (**A**), *serum* (**B**), *urine* (**C**), *and peripheral WBC counts* (**D**) *in dogs.* **Definition of treatment time see Fig 1.** $n=6$. $\bar{x}\pm s$. $^bP<0.05$ *vs* **Control.** $^eP<0.05$ *vs* **the time point of 0 h (ARDS, within-group comparison).**

TPL, TP, and DSPC/TP in BALF are presented in Tab 1. DSPC/TPL and DSPC/TP were higher and W/D was lower in the NO group than that of the control group. Peripheral WBC counts were reduced from 14.2×10^9/L at baseline to $<1.2\times10^9$/L when ARDS was established. It did not recover in the control group during the treatment period. In the NO group there was a moderate increment of peripheral WBC counts to slightly above 4×10^9/L (Fig 2).

Tab 1. Biochemical analysis of bronchoalveolar lavage fluid and wet-to-dry weight ratio of the lungs (W/D) from the ARDS dogs after inhaled nitric oxide (NO) treatment. $n=6$. $\bar{x}\pm s$. $^bP<0.05$ *vs* **Control.**

Group	TPL ($mg\cdot kg^{-1}$)	DSPC/TPL(%)	TP ($mg\cdot kg^{-1}$)	DSPC/TP ($mg\cdot g^{-1}$)	W/D
Control	6.2±0.9	26.6±1.7	117±15	14±3	4.9±0.5
NO	7.3±2.7	33±4^b	125±39	18.7±2.3^b	3.4±1.2^b

TPL, total phospholipids; DSPC, disaturated phosphatidylcholine; TP, total proteins.

Cytokine expression Values for expression of TNF-α, IL-8, and CD11b mRNA in the lungs were measured by RT-PCR. iNO resulted in reduction of the cytokine expression by 22 %, 44 %, and 25 %, respectively. However, these changes were not closely correlated to the changes of oxygenation, pulmonary hemodynamics, and peripheral WBC counts (Tab 2).

Tab 2. Contents of TNF-α, IL-8, and CD-11b mRNA in the ARDS dog lungs after inhaled nitric oxide (NO) treatment. $n=6$. $\bar{x}\pm s$. $^bP<0.05$ *vs* **Control.**

Group	TNF-α	IL-8	CD11b
Control	53±17	63±17	61±16
NO	41±13^b	35±14^b	46±17^b

DISCUSSION

In this study, we established a septic ARDS model and the randomized treatment initiated at peak of septic ARDS, therefore the observed response of iNO should be relevant for pharmacodynamic and pharmacokinetic

study. The effects of iNO were supported by improved survival time, lung mechanics, gas exchange, pulmonary hemodynamics, and ameliorated expression of pro-inflammatory cytokines. It took an average of 36 h (ranging 24 – 40 h) to induce septic ARDS during mechanical ventilation following the major endotoxin infusion, which mimics a clinical course of ARDS, and development of persistent inflammatory lung injury in all the animals. As iNO was intervened at the peak of ARDS, treatment effect of iNO should be reliable. Recent clinical trials of iNO in ARDS, with or without sepsis, generally showed transient improvement in gas exchange but no effect on mortality reduction[2-6]. It is generally accepted that, in the early stage of ARDS (ie, ALI), proinflammatory cytokines, such as TNF-α, integrin, intercellular adhesion molecule-1, IL-1, -6, and -8, are mainly involved in the initiation of inflammation and provocation of a series of intracellular signal transduction and intercellular response[15]. This pivotal process is important to local immune defence, but its overreaction may cause damage of the tissue cells and alter organ system function. IL-8 is a chemotactic factor for neutrophils in ALI and an important marker for ARDS. The β-2 integrin CD11b is also an important indicator for neutrophil activity in the lungs of ARDS. Our findings revealed that there were moderate suppression of TNF-α, IL-8, and CD11b mRNA expression by iNO. In our previous rabbit models using either surfactant-depletion-[8], oleic acid-[11,16] or endotoxin-induced ALI/ARDS[9], iNO alone at 0.8 $\mu mol \cdot L^{-1}$ (20 ppm) only exerted vasodilating activity, but did not show directly protective role towards lung injury, unless exogenous surfactant was applied. It again suggests that more effective intervention to prevent lung injury should be adopted when iNO is considered.

Altered lung function may be associated with impairment of the pulmonary surfactant system and lung fluid clearance in septic ARDS[9]. In our study, there was a decrease of both TPL and DSPC/TPL in BALF for both groups exposed to endotoxin, which is in accordance to endotoxin induced suppression of SP-A mRNA expression[9]. It implies that the impairment of the lungs was at alveolar level[1], and iNO seemed to have modest effect on production of DSPC. The same is probably true for fluid removal from the lungs as W/D was significantly lower in the NO group. Improved pulmonary blood perfusion may be beneficial for lung fluid absorption. Although W/D was low in the NO group, there was no evidence of capillary leak by the content of total proteins in BALF at the end of the experiment. Bjertnaes *et al*[17] reported that iNO at 1.5 $\mu mol \cdot L^{-1}$ (37.6 ppm) effectively reduced lung fluid filtration in sheeps by decreasing micro-vascular pressure and permeability in endotoxic respiratory distress. Whether such a high concentration of iNO requirement for the lung fluid clearance affects structural and functional changes in alveolar epithelial cell remains to be verified. The adverse effect of iNO at 1.6 – 3.2 $\mu mol \cdot L^{-1}$ (40 – 80 ppm) was the significantly elevated MetHb (> 3 %).

Optimal concentration of iNO for septic ARDS is a balance between response and tolerance. Earlier study by Krafft *et al*[2] revealed that only a subgroup of septic ARDS responded to iNO at 0.72 and 1.45 $\mu mol \cdot L^{-1}$ (18 and 36 ppm). In this study, the response to iNO was immediate and maximized at 0.8 – 1.6 $\mu mol \cdot L^{-1}$ (20 – 40 ppm) after a short period of inhalation (more than 50 % gain in p_{aO_2}/F_{iO_2}), with no additional improvement at 3.2 $\mu mol \cdot L^{-1}$ (80 ppm). The effects tended to diminish with decreasing iNO from 3.2 to 0.4 $\mu mol \cdot L^{-1}$ (10 ppm). The transiently improved blood oxygenation and selective pulmonary vasodilatation by iNO were accompanied by a suppressed expression of TNF-α, IL-8, and CD11b mRNA. The measured levels of nitrite/nitrate in serum were modestly elevated after endotoxin challenge, whereas iNO at 0.4 – 3.2 $\mu mol \cdot L^{-1}$ (10 – 80 ppm) was accompanied by a concomitant elevation of nitrite/nitrate levels in serum and urine, and blood MetHb. It suggests that the animals with ARDS responded the iNO treatment although there had been a modest elevation of endogenous NO production, that an optimal effective dose of iNO, presumably at 0.8 $\mu mol \cdot L^{-1}$ (20 ppm) or less, should be required for the initial treatment while high levels of nitrite/nitrate and MetHb due to cumulated NO exposure can be avoided. More studies will be focused on the mechanism of iNO on modulation of pulmonary and systemic white blood cell behavior during endotoxic attack, and therapeutic potential of iNO in septic ARDS.

REFERENCES

1 Pugin J, Verghese G, Widmer MC, Matthay MA. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 1999; 27: 304 – 12.

2 Krafft P, Fridrich P, Fitzgerald FD, Koc D, Steltzer H. Effectiveness of nitric oxide inhalation in septic ARDS. Chest 1996; 109: 486 – 93.

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E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

3 Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, *et al*. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Crit Care Med 1998; 26:15-23.
4 Troncy EC, Collet JP, Shapiro S, Guimong JG, Blair L, Ducruet T, *et al*. Inhaled nitric oxide in acute respiratory distress syndrome. A pilot randomised controlled study. Am J Respir Crit Care Med 1998; 157 (5 Pt 1):1483-8.
5 Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. Intensive Care Med 1999; 25: 911-9.
6 Chollet-Martin S, Gatecel C, Kermarrec N, Gougerot-Pocidalo MA, Payen DM. Alveolar neutrophil function and cytokine levels in patients with adult respiratory distress syndrome during nitric oxide inhalation. Am J Respir Crit Care Med 1996; 153:985-90.
7 Sato Y, Walley KR, Klut ME, English D, D'Yachkova Y, Hogg JC, *et al*. Nitric oxide reduces the sequestration of polymorphonuclear leukocytes in lung by changing deformability and CD18 expression. Am J Respir Crit Care Med 1999; 159 (5 Pt 1):1469-76.
8 Zhou BH, Sun B, Zhou ZH, Zhu LW, Fan SZ, Lindwall R. Comparison of effects of surfactant and inhaled nitric oxide in rabbits with surfactant-depleted respiratory failure. Acta Pharmacol Sin 1999; 20: 691-5.
9 Zhao DH, Sun B, Wu ZH, Lindwall R, Robertson B. Mitigation of endotoxin-induced acute lung injury in ventilated rabbits by surfactant and inhaled nitric oxide. Intensive Care Med 2000; 26: 229-38.
10 Bone R, Balk R, Fein AM, Perl TM, Wenzel R, Reines HD, *et al*. A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: results of a prospective, multicenter, randomized, controlled trial. Crit Care Med 1995; 23: 994-1006.
11 Zhu GF, Sun B, Niu SF, Cai YY, Lin K, Lindwall R, *et al*. Combined surfactant therapy and inhaled nitric oxide in rabbits with oleic acid-induced acute respiratory distress syndrome. Am J Respir Crit Care Med 1998; 158: 437-43.
12 Romand JA, Pinsky MR, Firestone L, Zar HA, Lancaster Jr JR. Effect of inhaled nitric oxide on pulmonary hemodynamics after acute lung injury in dogs. J Appl Physiol 1994; 76:1356-62.
13 Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951; 193: 265-75.
14 Hegesh E, Gruener N, Cohen S, Bochkovsky R, Shuval HI. A sensitive micromethod for the determination of methemoglobin in blood. Clin Chim Acta 1970; 30: 679-82.
15 Donnelly SC, Streiter RM, Kunkel SL, Walz A, Robertson CR, Grant IS, *et al*. Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet 1993; 341: 643-7.
16 Zhou ZH, Sun B, Lin K, Zhu LW. Prevention of rabbit acute lung injury by surfactant, inhaled nitric oxide and pressure support ventilation. Am J Respir Crit Care Med 2000; 161 (2 Pt 1): 581-8.
17 Bjertnaes LJ, Koizumi T, Newman JH. Inhaled nitric oxide reduces lung fluid filtration after endotoxin in awake sheep. Am J Respir Crit Care Med 1998; 158 (5 Pt 1): 1416-23.

吸入一氧化氮对内毒素诱发犬急性呼吸窘迫综合征的药效和药代动力学特性[1]

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关键词 成人型呼吸窘迫综合征；一氧化氮；磷脂酰胆碱类；肺表面活性剂；呼吸功能不全；呼吸疗法

目的：研究犬败血症急性呼吸窘迫综合征时吸入一氧化氮(NO)的药效和药代动力学特点。**方法**：12只成年犬静脉注射内毒素导致败血症性急性呼吸窘迫综合征，表现为 p_{aO_2}/F_{IO_2} 由基线水平(62.5±2.8) kPa下降为(26±4) kPa，动态顺应性(Cdyn)由(14.8±0.7)下降为(8.6±0.6) mL·kPa^{-1}·kg^{-1}。气道死腔由(0.14±0.06)增加到(0.58±0.05)，肺内分流由4.7 %±1.7 %增加到39 %±7 %，肺血管阻力指数由(16±4)增加至(51±8) kPa·s·L^{-1}·m^{-2} ($P<0.05$)，并伴随大量白细胞肺内集聚和外周循环白细胞减少。动物随机分组给予单纯机械通气或机械通气加吸入NO 0.4-3.2 μmol·L^{-1} (10-80 ppm)治疗10 h。**结果**：NO治疗组比对照组生存率高(4/6比0/6，$P<0.05$)。吸入NO迅速提高血氧分压，降低肺血管阻力，以0.8 μmol·L^{-1} (20 ppm)为理想浓度。吸入NO可降低细胞促炎症介质(TNFα，IL-8，CD11b)基因表达，且不对肺表面活性物质和肺液吸收产生不良影响。**结论**：吸入NO对于犬感染性急性肺损伤具有调节肺血管张力和抑制细胞炎症介质表达的双重作用，吸入高浓度NO可导致高铁血红蛋白血症。

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