Inhalation of Nitric Oxide in the Treatment of Severe Acute Respiratory Syndrome: A Rescue Trial in Beijing

Luni Chen,[1,2] Peng Liu,[3] He Gao,[2] Bing Sun,[4] Desheng Chao,[3] Fei Wang,[3] Yuanjue Zhu,[5] Göran Hedenstierna,[1] and Chen G. Wang[4]

[1]Department of Medical Sciences, Clinical Physiology, Uppsala University, Uppsala, Sweden; and [2]Air Force General Hospital, [3]Department of Intensive Care, the China-Japan Friendship Hospital, [4]Beijing Chao-yang Hospital (affiliate of Capital University of Medical Sciences), Beijing Institute of Respiratory Medicine, and [5]Department of Pulmonary Medicine, Peking Union Medical College Hospital, Beijing, China

Inhalation of nitric oxide (NO) improved arterial oxygenation and enabled the reduction of inspired oxygen therapy and airway pressure support in patients with severe acute respiratory syndrome (SARS). In addition, chest radiography showed decreased spread or density of lung infiltrates, and the physiological effects remained after termination of inhaled NO therapy. These findings suggest not only a pulmonary vasodilator effect of inhaled NO, but also an effect on SARS.

Severe acute respiratory syndrome (SARS) initially appeared in southeast China at the end of 2002 and spread rapidly to other regions inside and outside of the country [1, 2]. A coronavirus has been identified as the cause of the disease [3]. High fever, dry cough, headache, malaise, and dyspnea are associated with SARS onset. A chest radiograph shows infiltrates and widespread consolidation in severe cases. Approximately 20% of patients with SARS develop acute lung injury or acute respiratory distress syndrome, and the disease may progress, with pulmonary fibrosis. No specific treatment has been available, although antiviral drugs (e.g., ribavirin) and high doses of glucocorticoids have been given. Measures have also been taken to support vital functions. Treatment with supplemental oxygen and noninvasive ventilation (continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP] via a face mask) is regularly provided, and in most severe cases, tracheal intubation and mechanical ventilation is performed.

Inhalation of NO may improve arterial oxygenation and blunt pulmonary hypertension, an effect produced by selective dilatation of pulmonary vessels in ventilated lung parenchyma [4]. Inhaled NO trials involving patients with acute respiratory distress syndrome have confirmed the favorable effect of this treatment on arterial oxygenation, even though the mortality rate has remained high [5]. We hypothesized that inhaled NO treatment would improve arterial oxygenation and enable ventilator support to be decreased in patients with severe SARS and that the physiological effects might remain after the termination of therapy.

Methods. Our study involved 14 patients who were being treated in the intensive care units of hospitals in Beijing (Chao Yang Hospital and China-Japan Friendship Hospital) during the period of May through July 2003. There were 8 women and 6 men (age, 19–63 years), with a mean interval of 29 days between the diagnosis of SARS and the start of the study (table 1). Six patients were given inhaled NO therapy for at least 3 days. The other 8 patients served as control subjects. They were matched for age and had a similar duration and severity of the disease as and were studied simultaneously with patients in the inhaled NO group. There was no blinding of the protocol. The Chinese Food and Drug Administration approved the trial.

The inclusion criteria were as follows: (1) diagnosis of SARS based on 4 findings (all of which had to be present, according to the Ministry of Health Care of China): contact with other patients with SARS or transmission of SARS to other patients, fever and/or cough, infiltrates on a chest radiograph, and low or normal WBC counts (see also the World Health Organization criteria [6]); (2) age of $\geq$18 years; (3) >1 week duration of SARS symptoms; and (4) a value of <300 mm Hg for the arterial oxygen tension divided by inspired oxygen fraction (F_IO_2), an oxygen saturation of $\leq$93%, or an F_IO_2 of 0.5. All patients thus fulfilled the criteria of acute lung injury.

All patients received supplemental oxygen therapy. Ten patients (5 in each group) were receiving BiPAP (Vision BiPAP ventilator) or CPAP (Servo-i ventilator) via a face mask at the commencement of the study. One patient (in the inhaled NO group) underwent tracheal intubation and was mechanically ventilated (table 1).

Antiviral therapy (ribavirin, 0.5–1.0 g/day) and steroid treatment (methylprednisolone, 40–160 mg/day) was started when the diagnosis of severe SARS was established. Antibiotic or antifungal therapy was given in cases in which concomitant bac-

Received 24 February 2004; accepted 28 June 2004; electronically published 22 October 2004.

Reprints or correspondence: Dr. G. Hedenstierna, Dept. of Clinical Physiology, University Hospital, SE-751 85 Uppsala, Sweden (goran.hedenstierna@medsci.uu.se). Cocorrespondence inside China: Dr. Yuanjue Zhu, Dept. of Pulmonary Medicine, Peking Union Medical College Hospital, Beijing 100730, China, CPUMC (Zhuyi@pumch.ac.cn).

Clinical Infectious Diseases 2004;39:1531–5

1058-4838/2004/3910-0022$15.00

Table 1. Characteristics of patients with severe acute respiratory syndrome (SARS) who did or did not receive inhaled NO (INO) therapy.

Characteristic	INO group ($n = 6$)	Control group ($n = 8$)
Male sex/female sex	4/2	5/3
Age, mean years ± SD	45 ± 16	47 ± 10
Duration of SARS symptoms, mean days ± SD	32 ± 12	25 ± 9
Duration of INO treatment, mean days ± SD	4.3 ± 1.7	0
Use of ventilatory support[a]		
Before INO treatment	5	6
After INO treatment	1[b]	5
Changes in overall lung appearance on chest radiograph 2–3 days after initiation of INO treatment		
Improved	5[b]	2
No change	1	3
Worsened	0	3
Outcome		
Death	1	2
Hospital discharge	5[c]	6[d]

NOTE. Data are no. of subjects, unless otherwise indicated.

[a] Includes continuous positive airway pressure, bilevel positive airway pressure, and mechanical ventilation.

[b] Significantly different from the number of patients who received support before INO treatment ($P < .05$, by the Wilcoxon signed ranks test).

[c] Mean time, 4.4 weeks.

[d] Mean time, 6.2 weeks.

terial or fungal infection was diagnosed (3 patients in the inhaled NO group and 5 in the control group) [7].

Medicinal NO (INOmax; INO Therapeutics) was delivered with INOvent delivery systems (Datex-Ohmeda). Inhaled NO therapy was given for ⩾3 days (30 ppm on the first day, followed by 20 and 10 ppm on the second and third days, respectively). On day 4, the NO concentration was reduced stepwise to 0 ppm. Inhaled NO treatment (10 ppm) was resumed if arterial oxygenation deteriorated during weaning. New attempts to wean the patients from NO treatment were done daily until such therapy was successfully discontinued.

Arterial oxygen saturation (SpO_2) was continuously monitored by pulse oximetry (Hewlett-Packard). In 4 patients in the inhaled NO group and 5 in the control group, arterial blood gas levels were measured intermittently. F_IO_2 was measured by means of the O_2 monitor in the ventilator. The heart rate was measured by means of electrocardiography, and the respiratory rate was determined by observation of breathing patterns.

Chest radiography was performed on the basis of clinical indications and shortly before the onset and after the termination of inhaled NO therapy. Similarly, radiography was performed for control patients at corresponding times.

Results. During a 1–2-day period before commencement of NO inhalation therapy, oxygen saturation remained stable or worsened, and the F_IO_2 value was, on average, kept constant. Respiratory and heart rates were also stable. Mean data values are shown in figure 1.

Inhaled NO therapy (initially administered at 30 ppm and then reduced stepwise over the subsequent days) improved SpO_2 from 93% to a mean level of 99% ($P < .05$). Moreover, the amount of O_2 delivered was reduced from a mean of 6 L/min to 2 L/min (decrease in the F_IO_2, 0.7 to 0.4; $P < .05$) while the SpO_2 was maintained at 99%. The ratio of PaO_2 to F_IO_2 increased from 97 mm Hg on the day before the initiation of inhaled NO therapy to 260 mm Hg during the final day of inhaled NO therapy in the 4 patients who underwent blood gas testing. Also, CPAP and BiPAP ventilation was reduced and even discontinued in all 4 patients who received this support ($P < .05$ for both), with no decrease in SpO_2, unlike a similar attempt to lower airway pressure before receipt of inhaled NO treatment. In several patients, pneumothorax was diagnosed before the initiation of inhaled NO treatment, and 2 patients also had emphysematous bullae in both lungs. There was a gradual decrease in respiratory and heart rates during inhaled NO treatment ($P < .05$ for both).

In 3 patients, inhaled NO treatment was discontinued after 3 days without any worsening of the arterial oxygenation. In the other 3 patients, inhaled NO treatment lasted for 4, 6, and 7 days before weaning trials were successful. SpO_2 then remained elevated, compared with the period before initiation of

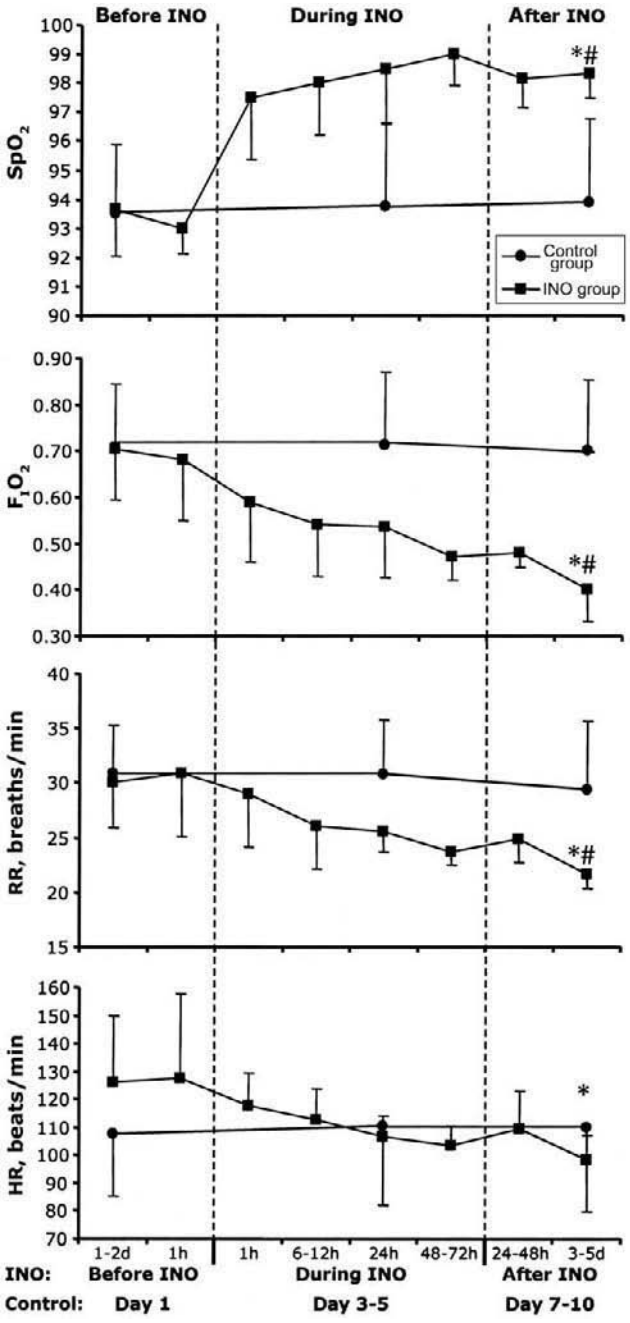

Figure 1. Mean and standard deviation of oxygen saturation (SpO_2), inspired oxygen fraction (F_IO_2), heart rate (HR), and respiratory rate (RR) before, during, and after inhaled NO (INO) treatment in the INO group and the control group. *Significant difference between the periods before and after INO treatment ($P < .05$, by the Wilcoxon signed rank test). #Significant difference between the INO group and the control group ($P < .05$).

NO inhalation ($P < .05$) (figure 1). Respiratory and heart rates remained lower than the rates before inhaled NO treatment was started ($P < .05$) (figure 1). Chest radiography showed decreased spread or decreased density of the lung infiltrates in 5 of the 6 patients (table 1). An example of the changes in the radiograph findings is given in figure 2. In the most severely ill patient, who was intubated and receiving mechanical ventilation, arterial oxygenation improved temporarily. He died 5 weeks later, whereas the other 5 patients continued to improve and left the hospital within 6 weeks after NO treatment (table 1). No influence of additional antibiotic therapy on the duration or outcome of inhaled NO treatment could be distinguished in this small group of patients.

In the control group, the initial SpO_2 and F_IO_2 values were similar to those of the inhaled NO group (figure 1). No improvement in SpO_2 or PaO_2 was seen, and BiPAP or CPAP was discontinued in only 1 of 6 control patients during the ~7-day study period. Respiratory and heart rates did not change (figure 1). SpO_2 was thus significantly lower and F_IO_2 was significantly higher at the end of the study period, compared with such values in the inhaled NO group ($P < .05$). Four control patients had emphysematous changes or a pneumothorax. The condition of 2 control patients worsened, and treatment was switched to controlled mechanical ventilation via a tracheal tube. Both individuals died, whereas the other 6 control patients recovered and left the hospital within 8 weeks after the study period (table 1).

Discussion. The improvement of arterial oxygenation by inhaled NO treatment was as good as or better than that seen in previous reports on acute respiratory distress syndrome [4, 5]. The ratio of PaO_2 to F_IO_2 more than doubled after initiation of inhaled NO treatment. Moreover, the possibility of eliminating the use of pressure support during NO inhalation without a decrease in SpO_2 may reduce the risk for lung damage. Several patients had emphysematous bullae or a pneumothorax, indicating lung tissue damage by the disease, or hyperinflation damage caused by the ventilator treatment. Avoidance of CPAP and BiPAP may also reduce the risk of exposing the nursing staff to the SARS coronavirus. It has even been recommended that noninvasive ventilation be discontinued in the treatment of patients with SARS in some hospitals.

The increased oxygen saturation remained after discontinuation of inhaled NO treatment and improvement of chest radiograph findings. This can hardly be explained by the vasorelaxant properties of inhaled NO. NO is also a potent antimicrobial agent and exerts an inhibitory effect on several viruses [8, 9]. A recent study on clinical isolates of coronavirus showed that glycyrrhizin (from the liquorice root) inhibited the replication of the SARS-associated virus [10]. This effect was presumably mediated via NO release [11]. We have recently shown that the NO donor S-nitroso-N-acetylpenicillamine greatly increased the survival rate of SARS coronavirus–infected Vero E6 cells [12]. It is thus tempting to attribute our results to inhaled NO treatment. However, the number of patients we treated was small. Readers therefore need to be cautious when interpreting our results.

In summary, inhaled NO treatment for severely sick patients

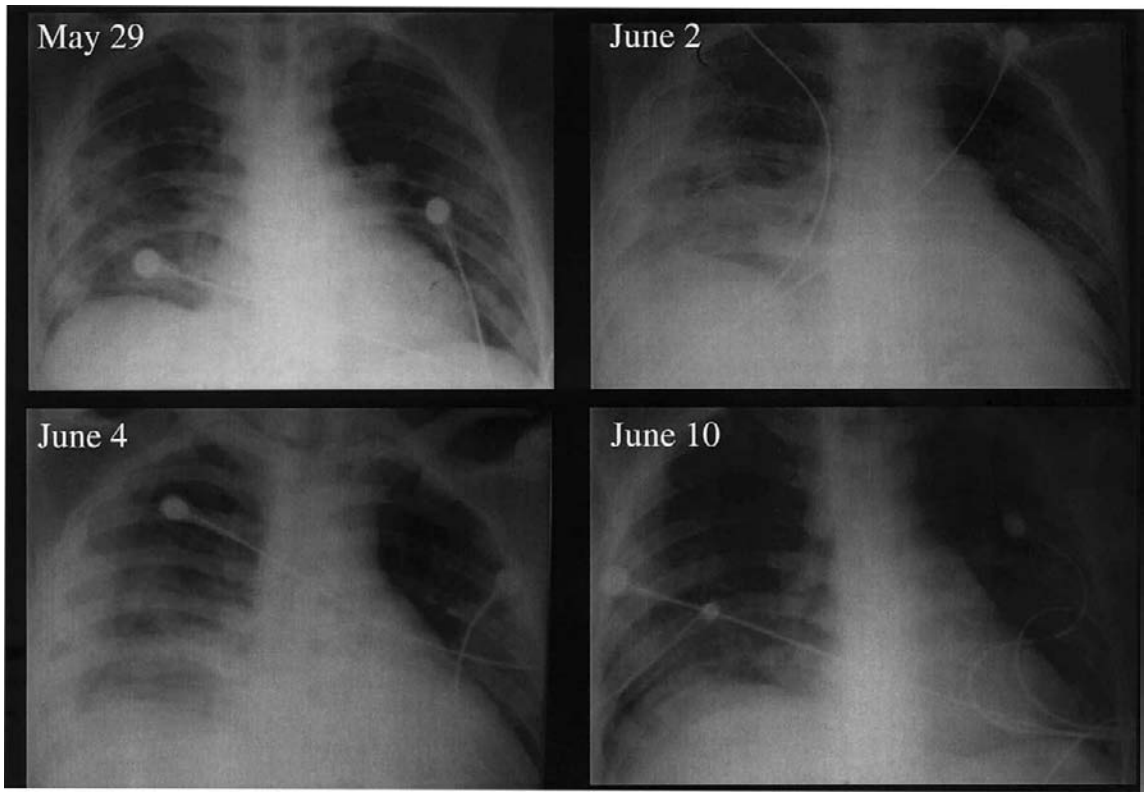

Figure 2. Chest radiographs from one patient showing the progression of pneumonia (*top left* and *right,* 29 May and 2 June, respectively), the effect of 8 h of inhaled NO therapy (*lower left,* 4 June), and the effect after 1 week of treatment, with a decrease in the pneumonia infiltrates (*lower right,* 10 June). *Top left,* Shadows with blurred margins bilaterally and a normal heart size; *top right,* shadows have increased in extent and density (pleural effusion can be seen on the right side), and there is marked bulging of the pulmonary artery segment (suggestive of pulmonary hypertension) and an increased heart size; *lower left,* extension and density of shadows are similar to those in the radiograph from 2 June; however, the pulmonary artery segment has become flatter, indicating a reduction in pulmonary artery pressure during the inhaled NO treatment; *lower right,* densities are reduced bilaterally, and the heart size is almost normal.

with SARS resulted in improvement of arterial oxygenation and allowed noninvasive pressure support to be discontinued. Moreover, the positive effects remained after the termination of NO inhalation. The findings may suggest not only a vasodilator effect of inhaled NO treatment, but also an effect on the disease.

Acknowledgments

Professor Uwe Ewald (Uppsala University, Sweden) made great contributions to this study by advising us in the clinical support of the patients and in the administration of inhaled NO therapy; Dr. Limin Zhang (Beijing Chao-yang Hospital, China) helped us with the design of the study protocol; Dr. Antonio Vena (Bari University, Italy) helped us on technical matters associated with the manuscript; INO Therapeutics AB (a subsidiary of AGA-Linde Health Care, belonging to the Linde-Group) generously donated equipment for delivering and monitoring NO gas, as well as medicinal-grade NO gas; and Maquet Critical Care generously provided ventilators.

Financial support. Ministry of Science and Technology of China (International Collaborative Research Project for SARS), Ministries of Education and of Health Care of China, Uppsala University, and Swedish Medical Research Council (grant 5315).

Potential conflicts of interest. G.H. and L.C. have interests in 2 patent applications on inhaled NO treatment; G.H. also serves as a consultant for Maquet Critical Care, has received recent research funding from Maquet Critical Care, and is a board member of the GEMI fund (founded by AGA-Linde Healthcare to promote research on medical cases). All other authors: No conflict.

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