SPECIAL REPORT

Noninvasive Positive Pressure Ventilation Treatment for Acute Respiratory Failure in SARS

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ABSTRACT

This study describes the blood gases features and short-term outcomes with noninvasive positive pressure ventilation (NPPV) treatment in the management of acute respiratory failure (ARF) during a severe acute respiratory syndrome (SARS) epidemic. Between April 22 and May 1, 2003, 120 patients meeting clinical criteria for SARS were admitted to a hospital for infectious diseases in Beijing, China. At 6 weeks after onset, 25% of patients (30/120) had experienced ARF. Of interest, 16 of these patients (53%) exhibited hypercapnia ($PaCO_2 > 45$ mm Hg), and 10 hypercapnic events occurred within 1 week of admission. The occurence of hypercapnia or CO_2 retention and was accompanied by myalgias. NPPV was instituted in 28 patients; one was intolerant of NPPV. In the remaining 27 patients, NPPV was initiated 1.2 ± 1.6 days after ARF onset. An hour of NPPV therapy led to significant increases in PaO_2 and PaO_2/FiO_2 and a decrease in respiratory rate ($p < 0.01$). Endotracheal intubation was required in one third of the patients (9 of 27) who initially had a favorable response to NPPV. Remarkable pulmonary barotrauma was noticed in 7 of all 120 patients (5.8%) and in 6 of those (22%) on NPPV. The overall fatality rate at 13 weeks was 6.7% (8/120); it was higher (26.7%) in those needing NPPV. No caregiver contracted SARS. We conclude that NPPV is a feasible and appropriate treatment for ARF occurring as a result of a SARS infection.

KEYWORDS: Noninvasive positive pressure ventilation, acute respiratory failure, acute respiratory distress syndrome

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Severe acute respiratory syndrome (SARS) is a highly infectious disease with significant morbidity and mortality. Acute lung injury (ALI), acute respiratory failure (ARF), and/or acute respiratory distress syndrome (ARDS) develops in more than 20% of cases and are risk factors for mortality.[1–4] Other factors contributing to mortality include immunosuppression due to coronavirus infection and corticosteroid use; nosocomial infections such as ventilator-associated pneumonia; and sepsis. Intubation and mechanical ventilation are reported for 13% or more of cases.[1–4] A need for intubation is a poor prognostic sign, as more than half of mechanically ventilated patients will die.[2,3] In China the survival rate in intubated SARS patients in Beijing DiTan Hospital was 10% (2/19) (Dr. L.M. Guo, personal communication). Given the strain on medical resources caused by the influx of critically ill patients during the SARS outbreak, as well as the morbidity associated with tracheal intubation, appropriately applied noninvasive positive pressure ventilation (NPPV) was considered as an alternative approach to the management of ALI in the SARS epidemic.

Use of NPPV is advocated as a first-line treatment in patients with acute hypercapnic respiratory failure caused by exacerbations of chronic obstructive pulmonary disease (COPD).[5] Recent studies also support the early application of NPPV in immunocompromised patients with hypoxemic ARF, such as hematological malignancies, AIDS, and organ transplantation.[6–8] In a prospective randomized controlled trial of NPPV support in 52 immunosuppressed patients with pulmonary infiltrates, fever, and ARF, early initiation of NPPV was associated with significant reductions in the rate of endotracheal intubation and of serious complications and an improved likelihood of survival.[9] Data on the efficacy of NPPV in SARS are limited, and whether NPPV should be administered in these patients is controversial.[10] Some have advocated an avoidance of NPPV because it might increase droplet spread of the virus.[3,11] However, NPPV with oxygen for ARF was deemed necessary because of the unexpected large influx of patients and a limited availability of positive-pressure ventilators in China.[12]

The aim of this retrospective case series study was to describe the clinical course of ARF and the short-term outcomes of NPPV treatment in a group of SARS patients with ARF. This experience may also be relevant to other current or emerging highly infectious viral respiratory illnesses in which respiratory failure is a complication.

METHODS

Patients

Between April 22 and May 1, 2003, 120 clinically compatible SARS patients were admitted to four newly opened SARS wards in DiTan Hospital, a special hospital for infectious diseases in Beijing. Among them 40% (48/120) were health-care workers. All patients met a modified definition of SARS by the US Centers for Disease Control and Prevention.[13] Briefly, the case definition was fever (temperature $\geq 38^{\circ}C$), respiratory symptoms of cough or shortness of breath, new pulmonary infiltrates on chest radiography, and close contact within 10 days of onset of symptoms with a person known to have SARS. A test for the virus was not available at the time of this study.

The hospital's review board approved this retrospective analysis of the care plans and patient outcome, and each hospital that had transferred a patient to DiTan hospital approved the analysis of data collected before transfer.

Standard Treatment and Measurements

The investigations and treatments followed a consensus guideline by the Chinese Thoracic Society.[12,14]

In addition to a detailed history and physical examination, laboratory investigations including hematological tests (complete blood counts with differentials), biochemical analyses (electrolytes and liver and renal function), arterial blood gas

(ABG), and serial follow-up chest radiography were conducted at least once every 2 to 3 days within 14 days after onset of the fever in all patients. The initial chest radiograph was obtained within an average of 1.5 days (range: 0 to 5 days) after the onset of fever. Heart rate, respiratory rate, and arterial oxygen saturation (SpO_2) were monitored continuously with a bedside pulse oximeter. For patients with severe SARS, ABG and the follow-up anteroposterior chest radiographs were obtained daily, or as clinically indicated.

Initial treatment included intravenous ribavirin and roxithromycin and/or levofloxacin to cover common pathogens causing community-acquired pneumonia. Patients with persistent fever or worsening lung opacities with an increase of more than 50% in 48 hours and occurrence of evidence of ALI/ARDS were given intravenous corticosteroid therapy. In those with shortness of breath and $PaO_2 <$ 70 mm Hg or $SpO_2 < 93\%$ in room air, oxygen was given through a nasal cannula or a nasal-oral mask. The Venturi mask was not recommended for routine use. All SARS patients with respiratory distress were treated empirically with corticosteroids, ribavirin, and broad-spectrum antibiotics.

NPPV and Measurements

The criteria for consideration of NPPV treatment were as follows: respiratory failure indicated by a SpO_2 of less than 90% confirmed by $PaO_2 < 60$ mm Hg; $SpO_2 < 93\%$ and $PaO_2 < 70$ mm Hg while the patient was receiving 5 L/min of supplemental oxygen; severe dyspnea with respiratory rate exceeded 30 breaths/min at rest; occurrence of evidence of ALI/ARDS indicated by a reduced PaO_2/FiO_2 (< 300 for ALI and < 200 for ARDS) and a chest radiograph showing progressive deterioration.

ABG levels were determined before and 1 to 2 hours after institution of NPPV and on a daily basis thereafter, according to the clinical condition of the patients. NPPV was delivered to the patient through a full face or a nasal mask connected to a bilevel positive airway pressure (BiPAP) ventilator (Harmony ST, Respironics, Pittsburgh, PA, USA). Breathing-circuit filters incorporated in the exhalation limb of the ventilator were used in 13 of 27 patients on NPPV. After the mask had been secured, the level of inspiratory pressure (IPAP) was progressively increased and adjusted for each patient to improve the patient's shortness of breath or obtain a respiratory rate of fewer than 25 breaths per minute. Expiratory pressure (EPAP) was increased in increments of 1 cm H_2O repeatedly up to 10 cm H_2O until the FiO_2 requirement was 5 L/min or less. Oxygen was added to achieve a SpO_2 of $> 93\%$. Ventilator settings were adjusted on the basis of continuous monitoring of SpO_2, clinical data, and measurements of ABG. The patients were encouraged to use NPPV almost continuously in the first 24 hours with short intervals of spontaneous breathing with oxygen supplementation to allow the patients to drink and eat, while SpO_2 was continuously monitored.

NPPV was withdrawn in cases where there occurred stable improvement of blood gas values ($SpO_2 \geq 93\%$, while breathing oxygen of 1 to 2 L/min without support) along with the radiographic evidence of improvement in lung consolidation, and a stable clinical condition, as indicated by a respiratory rate of less than 23 times/min and improvement of dyspnea and the patient's comfort. Weaning was defined as complete freedom from mechanical ventilation for at least 24 hours. Two of 28 patients needed reinitiation of NPPV.

Patients in whom standard treatment and NPPV were not successful underwent endotracheal intubation and received invasive mechanical ventilation. Endotracheal intubation is indicated to protect the airways, for sedation due to agitation that precluded effective care, for severe hemodynamic instability, for deterioration of blood gas despite NPPV with oxygen saturation less than 90% while receiving oxygen at 5 L/min, and for intolerance to NPPV.

Outcomes

The outcome variables were as follows: breathing rate and ABG levels during hospital stay, including

before, 1 hour after institution of NPPV, and after weaning from NPPV; new onset of radiographic evidence of pulmonary barotrauma including pneumothorax, pneumomediastinum, pneumopericardium, and subcutaneous emphysema; the duration of NPPV ventilatory assistance; the need for endotracheal intubation and mechanical ventilation at any time during the study; hospital death rate; the numbers of front-line health-care workers who were affected with SARS during the NPPV use.

Data Collection and Analysis

The information retrieved included the following: age, sex, occupation, medical history, daily changes in symptoms, the physical examination, laboratory tests, and diagnostic and therapeutic procedures. Onset of disease was defined as the first day of fever. All the patients' records were reviewed using a standard data collection form. For patients transferred from other hospitals, data before admission to DiTan Hospital were also retrieved and analyzed. Specialist radiologists and respiratory physicians jointly reviewed the chest radiographs for this retrospective analysis.

Data are presented as mean ± SD. Comparisons between the mean values of measurements taken before or after ventilatory support and during NPPV treatment were made using paired *t*-tests. Comparisons between groups were made using unpaired *t*-tests. Comparisons of nonparametric data were made using chi-square tests. Difference was considered significant at a p value of less than 0.05.

RESULTS

Demographic Features

To the time of data analysis (June 1, 2003, at least 40 days after the onset of SARS in all patients), there were 34 patients among the 120 SARS cases who met criteria for consideration for NPPV; 28 were eligible. Thirty cases (25%) including the 28 who would receive NPPV met the criteria for either ALI or ARDS during the course of the illness. Among these 30 patients, 16 were men and 14 women with a mean age of 41 ± 13 years (range: 24 to 74). Nine patients were 50 years or older. Seventeen patients with ARF were health-care workers. Five patients had pre-existing comorbidity, including one with diabetes and coronary heart disease, one with hypertension, and one each with hypertension and coronary heart disease, with chronic bronchitis, or with lung abscess.

Blood Gases Characteristics

These 30 patients developed ARF 10.7 ± 3.8 (range 5 to 21) days after the onset of SARS. All of them had a PaO_2/FiO_2 ratio of less than 300 mm Hg, with a mean of 161.9 ± 43.4 mm Hg (range 74 to 263) when the ARF occurred. ABG showed a PaO_2 of 7.9 ± 2.2 kPa (range 4.05 to 12.49) at 4.5 ± 2 L/min oxygen inhalation (range 0 to 10), and pH of 7.40 ± 0.05 (range 7.31 to 7.5).

The mean $PaCO_2$ level was 5.2 ± 0.82 kPa (range 3.62 to 7.35), and hypocapnia with a $PaCO_2$ of less than 35 mm Hg was present in only 3 patients (10%) at the time of diagnosis of respiratory failure. In contrast, 16 patients (53%) had hypercapnia, as defined by a $PaCO_2$ of more than 45 mm Hg, during the course of SARS. The CO_2 retention generally lasted for 2 to 3 days, and only one patient had persistent hypoventilation from the fourth day after SARS onset until intubation, but this disappeared after withdrawal from NPPV.

Based on the occurrence time of hypercapnia, these patients may be divided into two groups (Fig. 1). CO_2 retention started within 1 week (3 to 8 days) of SARS onset in 10 patients. All reported severe myalgias and eight had normal or only mild radiograph changes. PaO_2/FiO_2 was 502 ± 107 mm Hg (range 364 to 635); hypoxemia was corrected easily by only oxygen supply. NPPV was administered in only two for progressive chest radiograph deterioration and ALI, as indicated by

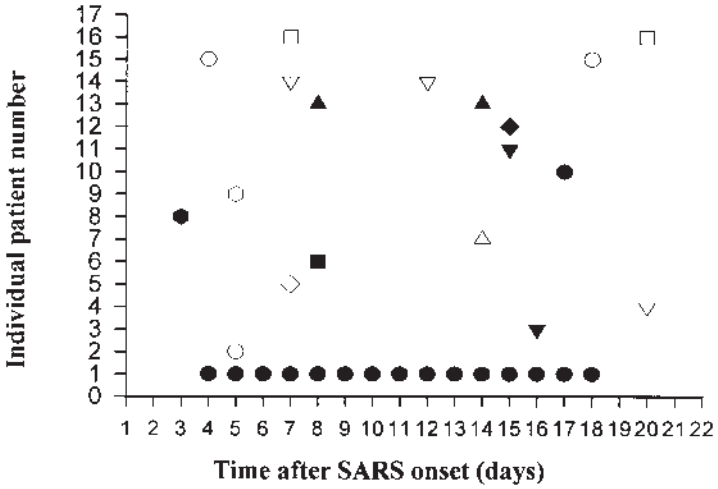

Figure 1 The time of occurrence of hypercapnia in 16 patients. CO_2 retention started within 1 week (3 to 8 days) of SARS onset in 10 patients. Eleven cases with hypercapnia occurred between 11 to 20 days, including six new occurrences, four recurrences (nos. 13–16), and one with persistent hypercapnia (no. 1). Each symbol represents a different patient. SARS, severe acute respiratory syndrome.

PaO_2/FiO_2 of 206 and 293 mm Hg, respectively. Eleven patients had hypercapnia, including six new occurrences, four recurrences, and one with persistent hypercapnia, between 11 to 20 days after SARS onset. In 10 of these 11 patients CO_2 retention occurred with a PaO_2/FiO_2 of 174.7 ± 55.9 mm Hg (range 96.6 to 248.5); one patient had hypercapnia noted after the withdrawal of NPPV; the PaO_2/FiO_2 was 363 mm Hg. All of these 11 patients had chest radiographic changes of pulmonary infiltrates progression in multiple areas of both lungs.

NPPV Usage and Its Effect on Blood Gases and Breathing Rate

Two of the 30 patients considered for NPPV did not receive NPPV therapy, as their respiratory failure was corrected easily by oxygen and standard treatment. One was intolerant of NPPV treatment and was promptly intubated. In the remaining 27 patients, NPPV was initiated 1.2 ± 1.6 days (range 0 to 10) after onset of respiratory failure. The mean IPAP used was 11.9 ± 3.0 cm H_2O (range 8 to 18) and mean EPAP utilized was 5.9 ± 1.6 cm H_2O (range 4 to 10). The arterial blood gases and respiratory rate responses to approximately 1 hour of NPPV treatment are shown in Figure 2. The FiO_2 level before and during NPPV use showed no significant differences (4.5 ± 2.0 vs. 4.3 ± 1.1; $p = 0.67$). An hour of NPPV therapy led to significant increases in PaO_2, SpO_2, and PaO_2/FiO_2 ratio, and decrease in respiratory rate (all $p < 0.01$). However, the changes of pH and $PaCO_2$ levels were not statistically significant.

Eighteen of the 27 patients demonstrating sustained improvement in blood gases and clinical status were weaned successfully from NPPV. In these patients the mean duration of NPPV use was 9.9 ± 6.1 days (range 5 to 30). The arterial blood gases and respiratory rate after stopping NPPV use are shown in Figure 2. Mean flow of 1.9 ± 1.3 L/min oxygen supplementation could achieve a mean PaO_2 of 16.8 ± 6.4 kPa (range 9.5 to 27.5) and a mean SpO_2 of $97.9 \pm 1.2\%$ (range 93 to 100%).Only one patient needed a FiO_2 level of 5 L/min to maintain a SpO_2 over 93%.

Need for Endotracheal Intubation and Invasive Mechanical Ventilation

In addition to one patient who was intolerable to NPPV treatment, intubation was required in nine other patients who initially had a favorable response to NPPV. Thus, intubation was required in 10 of the 30 patients (33%) with ARF, representing 8.3% of the SARS cohort in this study. Nine were intubated and mechanical ventilation was administered, and one declined intubation and remained on

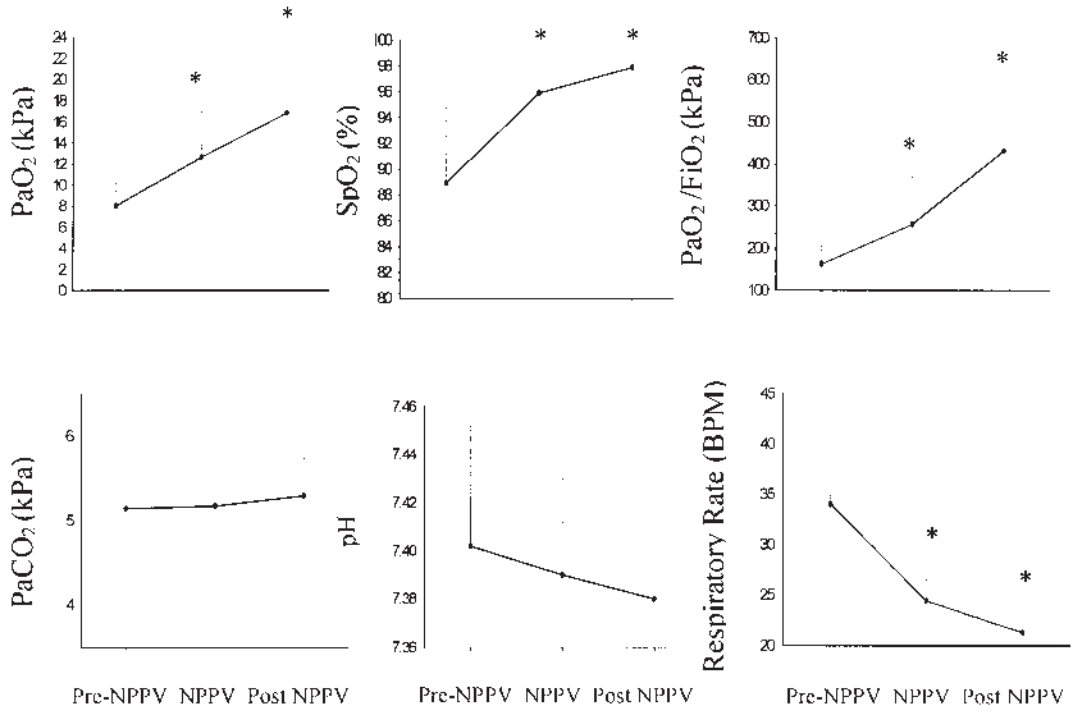

Figure 2 Changes in arterial blood gases and respiratory rate in the patients during the first hour of NPPV use and after withdrawal of NPPV. *, compared with pre-NPPV treatment, $p < 0.05$; NPPV, noninvasive positive pressure ventilation.

NPPV until death. The interval between institution of NPPV and intubation was 8.3 ± 2.9 days (range 5 to 13). The major reason for intubation was the deterioration in clinical condition, chest radiographs, and ABG tensions. Respiratory secretion was not noted as a factor in NPPV failure. To the time of this writing (July 20, 2003, at least 90 days after the onset of SARS in all patients), two of nine on invasive ventilation were withdrawn completely from mechanical ventilation, and seven have died.

Pulmonary Barotrauma

Pulmonary barotrauma was noticed in 7 of the 120 patients (5.8%) with SARS, including 5 with pneumomediastinum and subcutaneous emphysema; 1 with bilateral pneumothorax, pneumomediastinum, and subcutaneous emphysema; and 1 with right pneumothorax and pneumomediastinum. In 6 instances (22% of cases on NPPV) barotrauma was recognized 5.6 ± 2.2 days (range 2 to 9) after the institution of NPPV. No barotrauma was present in the patients without ARF/ALI.

Barotrauma on NPPV presented as acute, life-threatening hypoxemia, indicated by a mean PaO_2 of 7.6 ± 1.8 kPa (range 5.5 to 10.8) while breathing oxygen of 5 L/min. This event resulted in the need for intubation in five of the six patients while on NPPV, and subcutaneous emphysema worsened during subsequent invasive ventilation. No further treatment except a careful lung protective strategy for pulmonary barotrauma was needed. Tube thoracostomy drainage and high-frequency oscillatory ventilation was administered to one patient who developed barotrauma after intubation.

All the patients on NPPV had severe cough when barotrauma occurred, and the IPAP and EPAP used then were 11.1 ± 3.2 cm H_2O (range 8 to 16) and 5.4 ± 1.5 cm H_2O, (range 4 to 8) respectively. Both IPAP and EPAP did not differ from that used by patients without barotrauma ($p = 0.459$ for IPAP and 0.342 for EPAP), which were 12.2 ± 2.9 (range 8 to 18) and 6.1 ± 1.6, (range

4 to 10) respectively. Radiography of pulmonary infiltrates progression in multiple areas of both lungs were present in all patients.

Death Rate

By the writing of this paper (July 20 at least 90 days after the onset of SARS in all patients), eight patients had died, including three who were health-care workers. The fatality rate was 6.7% (8/120) in the patient cohort, and 26.7% (8/30) in the ALI/ARDS patients. One patient who died could not tolerate NPPV and was promptly intubated and one patient who failed NPPV refused intubation and remained on NPPV until death. The mean age of the eight patients was 53.1 ± 11.8 years (32 to 74); all were over 50 except one who was 32 years old. Three had pre-existing comorbidity. Three died of intractable hypoxia, and 4 died of multi-organ failure.

SARS Infection Related to the Care of NPPV Patients

None of the health-care workers contracted SARS during the care of patients receiving NPPV treatment.

DISCUSSION

In this article, we describe indications and outcomes for NPPV treatment in a group of SARS patients. The major findings are that: (1) at 6 weeks of SARS onset, 25% of patients (30/120) had respiratory failure with ALI/ARDS. Of these patients 16 (53%) had hypercapnia ($PaCO_2 > 45$ mm Hg) during the course of SARS; (2) NPPV therapy led to significant increases in PaO_2, SpO_2, and PaO_2/FiO_2 ratio and to decrease in respiratory rate. Intubation was avoided in two thirds of patients with respiratory failure; (3) no caregiver-SARS related to the use of NPPV occurred. The fatality rates were 6.7% in the cohort and 26.7% in the ALI/ARDS patients.

We identified that 25% of patients in this cohort with probable SARS developed respiratory failure with ALI/ARDS. This is consistent with the overall rate in the whole hospital (22%, 71/329) as well as with the reports in Hong Kong, Canada, and Singapore[1–4] ($p > 0.05$).

Based on the presentation of tachypnea and chest radiographic changes of pulmonary infiltrates progression in multiple areas of both lungs, it is reasonable to predict that a severe SARS patient with ALI/ARDS has hypoxic hypocapnic respiratory failure. However, careful review of the blood gases in this study did not reveal hypocapnia in most of the patients when ARF occurred. In contrast, a high proportion of these patients had hypercapnia during the disease course. Autopsy in some serologically confirmed cases also demonstrated that disease of less than 10 days' duration may not reflect pronounced diffuse alveolar damage,[15] so that other causes for respiratory failure, such as muscle weakness, are possible. The mechanisms of CO_2 retention in our case series can be reasoned as follows. These were previously healthy people, making it difficult to attribute hypercapnia to pre-existing respiratory or neuromuscular disease. While a high oxygen supplement could depress ventilation-perfusion matching or inhibit breathing, this is considered less likely than acute neuromuscular disease. In our series, maximum inspiration and expiration pressure tests were not conducted, but some patients reported difficulty in movement and breathing when severe myalgias occurred. Indeed, others have reported evidence for muscle involvement including myalgias and increases in lactic dehydrogenase (LDH) and creatine phosphokinase (CPK) patients with SARS.[16] Hence, muscle involvement may play a role in those patients with early appearances of hypercapnia. In those whose hypercapnia developed later, in addition to respiratory muscle damage and deterioration of lung function, the demands on the respiratory muscles became excessive, causing fatigue and eventually the retention of CO_2.

Institution of NPPV therapy rapidly and significantly improved oxygenation and clinical conditions in SARS patients with ARF. Although the cohort ALI/ARDS rate was the same, the intubation rate and the fatality rate at 13 weeks in both the patient cohort and the respiratory failure group were somewhat lower than that reported[1–4] in other major areas with SARS outbreak ($p < 0.05$). A self-limiting clinical course might also exist in some cases, as occurred in two patients here and as reported in the literature.[2] Because CPAP can also improve oxygenation and reduce the work of breathing effectively, there is the possibility that this simpler and less expensive method could be used as a first-line therapeutic choice.[10,12] As bilevel NPPV is considered to be advantageous over CPAP in improving CO_2 retention and may be more comfortable and acceptable, we prefer the routine use of bilevel pressure when available.

Use of NPPV is theoretically proposed to increase the risk of droplet transmission of virus.[11] With foreknowledge of risk and implementation of rigorous protective measures, nosocomial SARS infection in health-care workers appears unlikely. A similar finding was reported if care is taken during intubation and invasive mechanical ventilation.[2] As early aggressive intervention may cause better outcomes in patients with ARDS,[9,17] we suggest, as others have, early implementation of ventilatory support to prevent respiratory failure from progressing in patients with SARS and ARF.[18]

Pulmonary barotrauma occurred with the use of NPPV. The mechanisms of this phenomenon remain to be determined. A high rate of pneumomediastinum and pulmonary barotrauma during invasive mechanical ventilation is reported.[1,3,10] Correlation between the radiographic changes and the occurrence of barotrauma supports the idea that air leaks occur in patients with more severe lung lesions. Dynamic hyperinflation and auto-PEEP was not noticed in SARS-related ARDS,[2] suggesting that intrinsic high pressures are not the sole cause of air leaks. No computed tomography[19] or autopsy[15] evidence of blebs on the lungs surface are reported although it is proposed that adhesions and cyst formation might occur at the interface between the mediastinal pleura and the pulmonary pleura.[1] Pulmonary barotrauma is rarely reported in viral pneumonia,[20,21] but spontaneous pneumothorax is common in AIDS patients with *Pneumocystis carinii*.[22,23] Whether SARS coronavius infection itself plays a role similar to that of *P. carinii* in a predisposition to development of air leaks is not known. Our experience with several hundreds of patients with sleep apnea and/or COPD does not include a case of pulmonary barotrauma related to NPPV use. There are four cases reported in the literature of pneumothorax complicating NPPV therapy in a patient with COPD,[24] with AIDS,[25] with neuromuscular disease,[26] and following coronary artery bypass graft surgery.[27] Greater PEEP (EPAP) increases the risk of barotrauma during conventional mechanical ventilation. However, pressures in this study were not high and did not differ between the patients with and without barotrauma. Another factor may be the timing of positive pressure swings, especially during a cough. All the patients on NPPV had severe cough when barotrauma occurred. Antitussives are reported to decrease the incidence of barotrauma in SARS patients on CPAP to a lower level (6.7% of the patients treated with CPAP)[10] than reported in the our study. The length of time on NPPV may be important as pulmonary interstitial emphysema is reported to occur following positive pressure ventilation in neonate and older patients with respiratory distress syndrome.[28,29] We suspect that NPPV, like invasive ventilation, produces barotrauma due to the interactions of lung injury and pressure swings; however, the use of NPPV is not accompanied by a negligible risk of barotrauma injury.

This study has several limitations. First, the size of the population was limited and there was lack of a control group. We point out that the proportion of patients with ALI/ARDS is very similar to the reported incidence in the literature.[1–3] This was a sporadic outbreak and, moreover, it would be difficult to illustrate the natural history of $PaCO_2$ changes because of indications for medical

interventions. Second, the diagnosis was based on clinical features; we have no evidence that the patients had been infected with the same causative agent. Third, we were unable to precisely identify all variables that may influence the hypercapnia or the outcomes of NPPV therapy.

In conclusion, this study confirms reports that SARS patients with ALI/ARDS may experience CO_2 retention, which might be related to the impairment of respiratory muscles. NPPV is useful for improving hypoxia in SARS patients who were at high risk of intubation-related complications. Further support for applying NPPV is the finding that rigorous protective measures could prevent nosocomial SARS infection in health-care workers. Although pulmonary barotrauma unrelated to NPPV use might occur, a careful lung protective strategy is necessary during the administration of NPPV as well as during invasive mechanical ventilation.

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