

## A Prospective Randomized Controlled Trial on the Efficacy of Noninvasive Ventilation in Severe Acute Asthma

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and Digamber Behera MD

**BACKGROUND:** Noninvasive ventilation (NIV) is an emerging modality in the management of patients with acute respiratory failure. However, its role in severe acute asthma is not well defined. **OBJECTIVE:** Evaluate the efficacy of NIV in severe acute asthma. **METHODS:** Patients with severe acute asthma were randomized to receive either standard medical therapy or NIV in addition to medical therapy. The primary outcomes were improvement in forced expiratory volume in the first second (FEV<sub>1</sub>), intensive care unit (ICU) stay, and hospital stay. The secondary outcomes were rate of improvement in respiratory rate, blood pH, ratio of P<sub>aO<sub>2</sub></sub> to fraction of inspired oxygen (F<sub>IO<sub>2</sub></sub>), P<sub>aCO<sub>2</sub></sub>, requirement for inhaled medications, and failure of primary therapy. **RESULTS:** Fifty-three patients with severe acute asthma (42 females and 11 males, mean ± SD age 44 ± 15 y, FEV<sub>1</sub> < 30% of predicted) were randomized to NIV (n = 28) or standard medical therapy (n = 25). The baseline variables were similar in the 2 groups except for the mean duration of asthma, which was shorter in the standard-medical-therapy group. The median inspiratory and expiratory airway pressures applied were 12 cm H<sub>2</sub>O and 5 cm H<sub>2</sub>O, respectively. There was a significant improvement in respiratory rate, FEV<sub>1</sub>, and P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> (but not pH or P<sub>aCO<sub>2</sub></sub>) in both the groups, but no significant difference between the 2 groups. The number of patients who had a ≥ 50% improvement in FEV<sub>1</sub> at 1, 2, and 4 hours was nonsignificantly greater in the NIV arm. ICU and hospital stay was significantly shorter in the NIV group. The mean dose of inhaled bronchodilator was significantly less in the NIV group. There were 4 instances of standard-medical-therapy failure, and all those patients improved with NIV. Two patients in the NIV arm required invasive ventilation. There was no mortality in either of the arms. **CONCLUSION:** In patients with severe acute asthma, the addition of NIV to standard medical therapy probably accelerates the improvement in lung function, decreases the inhaled bronchodilator requirement, and shortens the ICU and hospital stay, but a larger study is required to settle this issue. (Clinicaltrials.gov registration NCT00510991.) *Key words:* severe acute asthma; noninvasive ventilation; NIV; medical therapy. [Respir Care 2010;55(5): 536–543. © 2010 Daedalus Enterprises]

### Introduction

Asthma is a chronic inflammatory disorder of the airways, characterized by bronchial hyper-responsiveness and reversible air-flow limitation.<sup>1</sup> The course of asthma is punctuated by exacerbations, which can range from mild to severe. Severe acute asthma is a potentially life-threatening exacerbation associated with acute respiratory failure that does not

respond to conventional therapy and generally requires hospitalization. The goals of managing severe acute asthma include correction of hypoxemia, alleviation of air-flow obstruction, and suppression of inflammation with medications. Many patients admitted to the ICU with severe acute asthma

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simply require time for the medications to act. In the past, intubation and mechanical ventilation were the mainstay of treatment for patients progressing toward acute respiratory failure from severe acute asthma. However, endotracheal intubation is associated with substantial morbid-

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ity, including upper-airway trauma, barotrauma, and pneumonia.<sup>2-4</sup>

Noninvasive ventilation (NIV) has revolutionized the management of acute respiratory failure. NIV obviates endotracheal intubation and thus decreases the risk of ventilator-induced pneumonia, shortens intensive care unit (ICU) stay, and decreases the overall cost of hospitalization.<sup>5</sup> The term NIV encompasses a range of techniques for mechanical ventilation without an artificial airway; the most commonly used modes are bi-level positive airway pressure and continuous positive airway pressure (CPAP). In acute asthma there is evidence for efficacy of CPAP, which decreases the work of breathing<sup>6,7</sup> and enhances the bronchodilator effect of inhaled albuterol.<sup>8</sup> In bi-level-positive-airway-pressure NIV, 2 different pressures are used (an inspiratory pressure and an expiratory pressure), whereas CPAP maintains one constant positive airway pressure throughout the respiratory cycle. Theoretically, NIV may have an advantage over CPAP because NIV provides additional inspiratory pressure.<sup>9,10</sup>

In exacerbations of chronic obstructive pulmonary disease (COPD), NIV is associated with less need for endotracheal intubation, shorter hospitalization, and lower mortality, and NIV has become the standard of care in that setting.<sup>11-14</sup> Although severe acute asthma demonstrates many pathophysiologic abnormalities akin to COPD exacerbation, the role of NIV in the management of severe acute asthma is still unclear. Preliminary data suggest that NIV could be beneficial in carefully selected and monitored patients with severe acute asthma.<sup>15,2</sup>

NIV is known to decrease the work of breathing, and NIV enhanced the efficacy of inhaled drugs in experimental studies of acute asthma, which might improve clinical outcomes in routine clinical practice. We hypothesized that in patients with severe acute asthma, NIV would quickly improve lung function and shorten stay. The aim of this study was to evaluate the efficacy of NIV in patients with severe acute asthma.

## Methods

This was a prospective randomized controlled trial (RCT) conducted in our respiratory ICU. The study was cleared by our institute's ethics committee, and written consent

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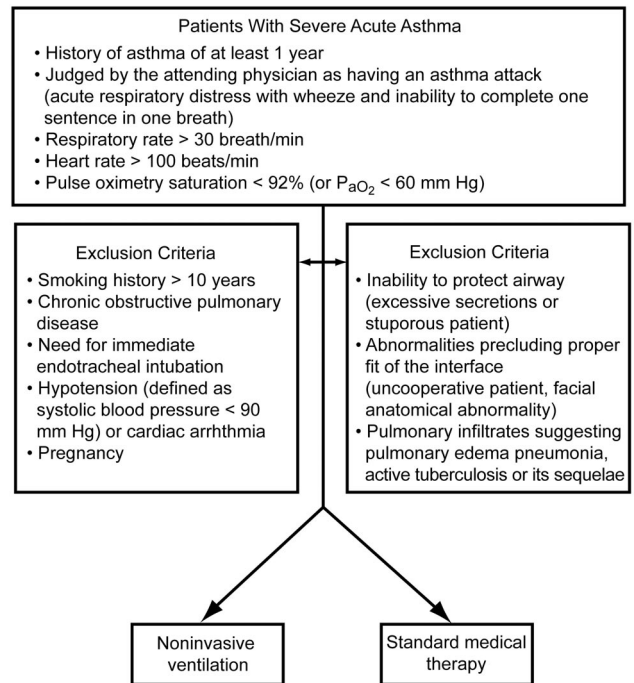


Fig. 1. Flowchart of inclusion and exclusion process.

was obtained from all patients or the next of kin. All patients admitted to the respiratory ICU for severe acute asthma between July 2006 and December 2007 were enrolled. The respiratory ICU has 8 beds, 8 pulmonary fellows (5 posted each day), 5 consultants, and a nurse/patient ratio of 2/1. The unit has been using NIV since the year 2000, and has considerable expertise with the management of NIV. The entire faculty and all the fellows are internists and during residency are well trained in intubation and invasive ventilation.

## Patients

Patients with severe acute asthma who met the inclusion criteria (Fig. 1) were randomly assigned to either standard medical therapy or NIV.<sup>1</sup> The randomization sequence was generated with statistics software (StatsDirect version 2.6.2, StatsDirect, Cheshire, United Kingdom). The assignments were placed in sealed opaque envelopes and each patient's assignment was made by the attending physician, on admission to the respiratory ICU. Blinding of treatment allocation was not possible.

## Study Procedure

All subjects received, in the first hour in the respiratory ICU, 3 doses of nebulized albuterol (2.5 mg every 20 min), one dose of nebulized ipratropium bromide (0.25 mg), intravenous hydrocortisone (100 mg) or equivalent dose of methylprednisolone, and intravenous magnesium sulfate

(2 g, slowly, over 10 min), and were randomized to receive either conventional treatment alone or conventional treatment combined with NIV. Both the groups received oxygen therapy to maintain blood oxygen saturation (measured via pulse oximetry [ $S_{pO_2}$ ] > 92%). Additional medical management in both the groups included nebulized albuterol (2.5 mg hourly for the first 6 h, then every 4 h and as needed), ipratropium (0.25 mg, every 6 h and as needed), and intravenous hydrocortisone (100 mg every 8 h).

NIV was administered with the noninvasive module of a critical care ventilator (Servo-i, Maquet, Germany). All NIV patients used an oronasal mask as the interface. We explained the detailed procedure of NIV to the patient, to improve patient adherence to therapy. NIV was delivered while the patient was in bed, with the head of the bed at an angle of 30–45°. The fraction of inspired oxygen ( $F_{IO_2}$ ) was titrated to maintain  $S_{pO_2}$  > 92%. The patient was started on a inspiratory/expiratory pressure of 8/4 cm  $H_2O$ . The inspiratory and expiratory pressure were titrated in increments of 2 cm  $H_2O$ , based on continuous pulse oximetry, arterial blood gas values (at 1, 2, and 4 h, and periodically thereafter, as clinically indicated), alleviation of dyspnea, decrease in respiratory rate, and patient-ventilator synchrony. The maximum allowed inspiratory pressure was 20 cm  $H_2O$ . The maximum allowed expiratory pressure was 10 cm  $H_2O$ . Instead of titrating the pressure to the expiratory tidal volume (which is recommended), we titrated the pressure according to clinical criteria, blood gas values, and patient comfort (which is our respiratory ICU policy). We frequently checked for air leaks, and the patient was constantly encouraged and reassured. NIV was applied continuously for as long as possible, and interruption of NIV was allowed only for spirometry or secretion clearance, and for no more than 5 min. Inhaled bronchodilators were given via T-piece in the ventilator circuit, with the ventilator's built-in ultrasonic nebulizer, without discontinuing the circuit. Per our respiratory ICU policy, with patients in acute respiratory distress we use only nebulizer, not metered-dose inhaler (MDI) with spacer, although nebulizer and MDI are equally effective. Once the patient is stable, we shift to MDI with spacer or another device. The role of inhaled steroids in severe acute asthma is still controversial, and we start inhaled steroids only when planning the patient's discharge from the respiratory ICU.

Weaning from NIV was begun when there was clinical improvement of the severe acute asthma, respiratory rate was < 25 breaths/min, and  $P_{aO_2}$  was > 60 mm Hg. Patients who failed an NIV trial underwent endotracheal intubation and mechanical ventilation, and patients who failed standard medical therapy were crossed over to receive NIV, followed by invasive ventilation. The primary decision-making responsibility was left to the respiratory ICU

physician, and none of the investigators had any primary role in care of the patients.

### Outcomes and Definitions

We collected detailed clinical history and physical examination, including age, sex, duration of asthma, and duration of exacerbation. All patients had a complete blood count, determination of serum electrolytes, and chest radiograph at the outset. Arterial blood samples, via radial arterial catheter, were taken at baseline, 1, 2, and 4 h. Spirometry (PIKO-I, Ferraris Respiratory Europe, Hertford, United Kingdom) was performed at admission, and repeated at 1, 2, and 4 h. At least 3 spirometry readings were taken. In accordance with the American Thoracic Society guidelines for spirometry reproducibility we required that at least 2 of the volumes differed by no more than 0.2 L, unless the forced expiratory volume in the first second ( $FEV_1$ ) was less than 0.2 L, in which case we required a difference of < 10%. We recorded the best of the 3 spirometry results. The predicted  $FEV_1$  values were generated with previously defined prediction equations.<sup>16</sup>

The primary outcomes were improvement in lung function (defined as an  $FEV_1$  increase of at least 50%, compared to the hospital-admission  $FEV_1$ ), ICU stay, and hospital stay. The secondary outcomes were: improvement in clinical status (with respect to respiratory rate and disappearance of use of accessory muscles of respiration); improvement in arterial blood gas values (pH,  $P_{aO_2}$ ,  $P_{aCO_2}$ ,  $P_{aO_2}/F_{IO_2}$ ) from baseline at 1, 2, and 4 h; requirements for inhaled albuterol and ipratropium; and failure of primary therapy (need for NIV in the standard-medical-therapy arm, and endotracheal intubation and mechanical ventilation in the NIV arm).

The decision to move a patient to the next level (standard medical therapy to NIV to invasive ventilation) was based on the following criteria: failure to improve clinical variables and gas exchange at 1 h; development of alteration in sensorium; hemodynamic instability; and inability to tolerate face mask. However, the final decision was left to the intensivist's clinical judgment.

### Statistical Analysis

Statistical analysis was performed with statistics software (SPSS 10, SPSS, Chicago, Illinois). The analysis was based on intention to treat. Statistical significance was assumed at a  $P$  value of < .05. Results are presented in a descriptive fashion as number (percentage), mean  $\pm$  SD, or median and interquartile range if not normally distributed. The normalcy of distribution was evaluated with the Kolmogorov-Smirnov test. The differences between continuous variables were analyzed with the Mann-Whitney  $U$  test if not normally distributed, or with Student's  $t$  test

Table 1. Baseline Characteristics

	Standard Medical Treatment ( <i>n</i> = 25)	NIV ( <i>n</i> = 28)	All Subjects ( <i>n</i> = 53)	<i>P</i>
Age (mean ± SD y)	41.6 ± 12.5	46.2 ± 16.2	44.1 ± 14.6	.26
Female ( <i>n</i> , %)	20 (80)	22 (78.6)	42 (79.2)	.91
Body mass index (mean ± SD kg/m <sup>2</sup> )	24.3 ± 4.3	22.9 ± 3.3	23.6 ± 3.8	.19
Duration of asthma (median and IQR y)	6 (4–10)	10 (3.5–20)	8 (4–15)	.03
Duration of exacerbation (mean ± SD d)	3.2 ± 2.2	3.4 ± 2.2	3.3 ± 2.2	.91
Respiratory rate (median and IQR breaths/min)	38 (32–42)	36 (32–40)	36 (32–41)	.60
Heart rate (mean ± SD beats/min)	117.1 ± 13.7	120.7 ± 12.8	119 ± 13.3	.58
Systolic blood pressure (median and IQR mm Hg)	140 (126–165)	130 (124.5–140)	130 (126–150)	.09
Diastolic blood pressure (median and IQR mm Hg)	90 (80–98)	84 (80–90)	86 (80–90)	.26
Pulsus paradoxus (mean ± SD mm Hg)	21.9 ± 11.1	19.6 ± 5.3	20.7 ± 8.5	.33
FEV <sub>1</sub> (mean ± SD L)	0.56 ± 0.3	0.48 ± 0.2	0.51 ± 0.3	.25
FEV <sub>1</sub> (mean ± SD % predicted)	24.4 ± 12.3	21.6 ± 10.3	22.9 ± 11.3	.67
pH (mean ± SD)	7.43 ± 0.04	7.42 ± 0.06	7.43 ± 0.05	.70
P <sub>aO<sub>2</sub></sub> /F <sub>IO<sub>2</sub></sub> (mean ± SD mm Hg)	298 ± 63	281 ± 65	289 ± 64	.33
P <sub>aCO<sub>2</sub></sub> (mean ± SD mm Hg)	35.1 ± 8.8	37 ± 7.9	36.1 ± 8.3	.41
Number of GINA criteria (median and IQR)*	8 (7–9)	8 (8–9)	8 (7–9)	.64

\* The Global Initiative for Asthma (GINA) criteria are: breathlessness at rest, can speak only in short sentences, respiratory rate > 30 breaths/min, use of accessory muscles of respiration, loud wheeze, heart rate > 120 beats/minute, pulsus paradoxus > 25 mm Hg, peak expiratory flow < 60% of predicted or < 100 L/min, P<sub>aO<sub>2</sub></sub> < 60 mm Hg.

IQR = interquartile range

FEV<sub>1</sub> = forced expiratory volume in the first second

F<sub>IO<sub>2</sub></sub> = fraction of inspired oxygen

if normally distributed. The differences between categorical variables were analyzed with Fisher's exact test. Improvements in respiratory rate, heart rate, pH, P<sub>aO<sub>2</sub></sub>, and P<sub>aCO<sub>2</sub></sub> were analyzed with repeated-measures analysis of variance. The within-groups factor was time (0, 1, 2, and 4 h), and the between-groups factor was the experimental group (NIV vs standard medical therapy). We constructed Kaplan-Meier curves to study NIV's effect on ICU and hospital stay. Differences between the 2 curves were analyzed with the log-rank test.

## Results

During the study period there were 337 respiratory ICU admissions. 162 patients received invasive ventilation, 108 received NIV, and 67 received oxygen therapy and ICU care, for various indications. Sixty-two patients were admitted with a diagnosis of acute asthma. Of those 62 patients, 7 had cyanosis and altered sensorium at presentation and were intubated and mechanically ventilated. Two patients who were initially enrolled as having acute asthma were subsequently found to have COPD (one patient) and allergic bronchopulmonary aspergillosis (the other patient), and those 2 patients were excluded. Fifty-three patients met the inclusion criteria and were enrolled. There were 42 females and 11 males, and their mean ± SD age was 44 ± 15 y. Twenty-eight patients were randomized to the

NIV arm and 25 to the standard-medical-therapy group. Table 1 shows the baseline characteristics. All the patients were breathless at rest, could speak only in short sentences, and were using the accessory muscles of respiration. The mean peak expiratory flow and FEV<sub>1</sub> were less than 30% of predicted at baseline in all the patients. There was no history of tobacco smoking in any patient. Twenty-nine of the 53 patients met 8 of the 10 Global Initiative for Asthma (GINA) criteria for acute asthma.<sup>1</sup> There were no significant differences between the 2 groups except for the duration of asthma, which was significantly shorter in the standard-medical-therapy arm (see Table 1). In the NIV arm the mean ± SD inspiratory and expiratory pressures administered were 11.5 ± 3 cm H<sub>2</sub>O, and 4.6 ± 1 cm of H<sub>2</sub>O, respectively, and NIV was administered for a mean ± SD duration of 9 ± 5 h. NIV was well tolerated and there were no serious adverse effects, such as nasal-bridge skin necrosis, severe headache, claustrophobia, or gastric distention. A frequent complaint was pain in the nasal bridge area, which was alleviated by placing a gauze piece over that region.

Table 2 shows the values for respiratory rate, FEV<sub>1</sub>, pH, P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub>, and P<sub>aCO<sub>2</sub></sub>. In both the groups there was a significant improvement in respiratory rate, FEV<sub>1</sub>, and P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> at 1, 2, and 4 h. However, there was no significant difference in improvement between the 2 groups. There was no significant difference in pH or P<sub>aCO<sub>2</sub></sub> within or between the groups, in any time period (see Table 2).

## NONINVASIVE VENTILATION IN SEVERE ACUTE ASTHMA

Table 2. Clinical and Arterial Blood Gas Variables

	Standard Medical Therapy				NIV			
	0 h	1 h	2 h	4 h	0 h	1 h	2 h	4 h
Respiratory rate (mean ± SD breaths/min)	37.7 ± 7.2	32.1 ± 5.4 <sup>*a</sup>	28.3 ± 3.8 <sup>†a</sup>	23.3 ± 4.8 <sup>‡a</sup>	36.8 ± 6.8	31.3 ± 5.9 <sup>*a</sup>	27.1 ± 4.5 <sup>†a</sup>	21.7 ± 2.8 <sup>‡a</sup>
FEV <sub>1</sub> (mean ± SD L)	0.56 ± 0.3	0.86 ± 0.49 <sup>*a</sup>	0.94 ± 0.41 <sup>†a</sup>	1.14 ± 0.56 <sup>‡a</sup>	0.48 ± 0.2	0.67 ± 0.29 <sup>*a</sup>	0.81 ± 0.35 <sup>†a</sup>	1.02 ± 0.38 <sup>‡a</sup>
pH (mean ± SD)	7.43 ± 0.04	7.41 ± 0.06	7.43 ± 0.03	7.43 ± 0.03	7.42 ± 0.06	7.43 ± 0.05	7.41 ± 0.06	7.42 ± 0.05
P <sub>aO<sub>2</sub></sub> /F <sub>IO<sub>2</sub></sub> (mean ± SD mm Hg)	298 ± 62	345 ± 67 <sup>*a</sup>	348 ± 61 <sup>†b</sup>	371 ± 55 <sup>‡b</sup>	281 ± 63	296 ± 72 <sup>*a</sup>	321 ± 63 <sup>†b</sup>	329 ± 60 <sup>‡b</sup>
P <sub>aCO<sub>2</sub></sub> (mean ± SD mm Hg)	35.1 ± 5.2	34.9 ± 4.7	33.9 ± 4.1	34.8 ± 4.4	37 ± 7.9	35.1 ± 6.8	34.1 ± 8.8	35.3 ± 7.7

The difference between the means was analyzed with repeated-measures analysis of variance. The within-groups factor was time (baseline, 1, 2, and 4 h). The between-groups factor was the 2 groups (standard medical therapy vs noninvasive ventilation [NIV]). There was a significant improvement in respiratory rate, forced expiratory volume in the first second (FEV<sub>1</sub>) and the ratio of P<sub>aO<sub>2</sub></sub> to fraction of inspired oxygen (F<sub>IO<sub>2</sub></sub>) in both the groups, but there was no difference in improvement between the groups. There was no improvement in pH or P<sub>aCO<sub>2</sub></sub> within or between the groups.

\* Value at 1 h significantly different from that at baseline within the groups.

† Value at 2 h significantly different from that at 1 h within the groups.

‡ Value at 4 h significantly different from that at 2 h within the groups.

<sup>a</sup> P value < .001

<sup>b</sup> P value < .05

Table 3. Outcomes

	Standard Medical Therapy (n = 25)	NIV (n = 28)	P
<b>Primary Outcomes</b>			
≥ 50% improvement in FEV <sub>1</sub> over baseline (n, %)			
At 1 h	11 (44)	10 (36)	.62
At 2 h	12 (48)	15 (54)	.70
At 4 h	16 (64)	24 (86)	.08
ICU stay (median and IQR h)	24 (18–36)	10 (8–20)	.01
Hospital stay (median and IQR h)	54 (48–72)	38 (24–48)	.01
<b>Secondary Outcomes</b>			
Time to disappearance of accessory muscle use (mean ± SD h)	3.2 ± 1.7	2.3 ± 1.4	.06
Dose of inhaled salbutamol (mean ± SD mg)	42.8 ± 10.4	31.2 ± 14.5	.008
Dose of inhaled ipratropium (mean ± SD mg)	7.6 ± 2.2	5.2 ± 2.8	.007
Failure of primary therapy (n, %)	4 (16)	2 (7)	.35

FEV<sub>1</sub> = forced expiratory volume in the first second

IQR = interquartile range

### Primary Outcomes

Sixteen of the 25 patients in the standard-medical-therapy arm, and 24 of the 28 patients in the NIV arm, had a ≥ 50% improvement in FEV<sub>1</sub> at 4 h, and there was a nonsignificant trend toward better outcomes in the NIV group (Table 3). Figure 2 shows the Kaplan-Meier curves for ICU and hospital stay. The median ICU and hospital stay were significantly shorter in the NIV group (P = .01 via log-rank test for both ICU and hospital stay) (see Table 3).

### Secondary Outcomes

The time to disappearance of accessory muscle use was statistically similar in the 2 groups, albeit with a trend

toward quicker improvement in the NIV group (see Table 3). The total doses of inhaled albuterol and ipratropium required during hospitalization were significantly less in the NIV group (see Table 3). Four patients in the standard-medical-therapy arm did not improve and were crossed over to the NIV arm, and they improved. Two patients in the NIV arm did not tolerate NIV and consequently required endotracheal intubation and mechanical ventilation (one patient required intubation after 1 h, and the other after 2 h of NIV trial) due to respiratory fatigue, hypoxia, and agitation. There was no mortality in any group.

### Discussion

Our results suggest that NIV is similar in efficacy to standard medical therapy in improving respiratory rate,

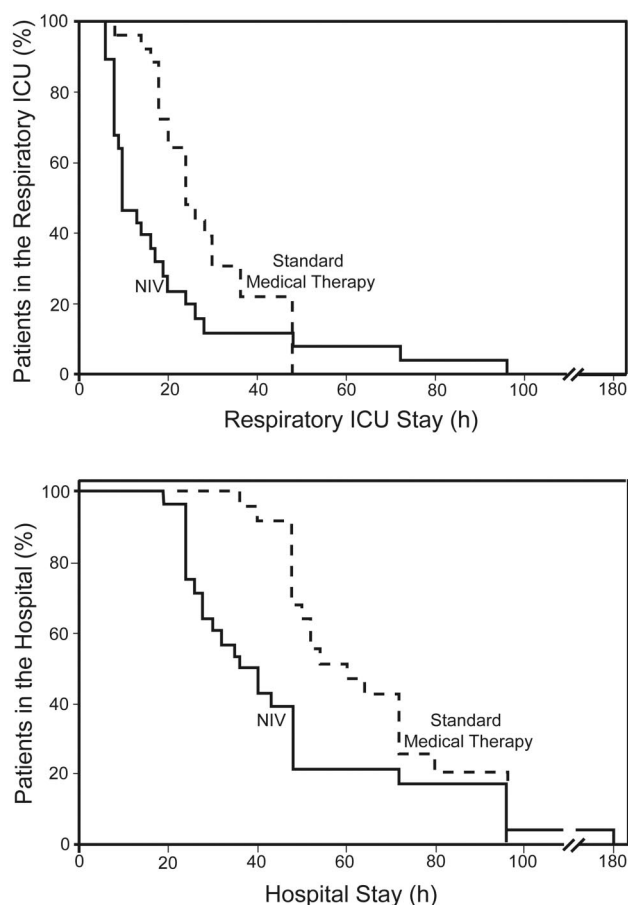


Fig. 2. Kaplan-Meier curves of the probability of discharge from the respiratory intensive care unit (ICU) and the hospital. ICU and hospital stay were significantly shorter in the noninvasive ventilation (NIV) group than in the standard-medical-therapy group.

FEV<sub>1</sub>, pH, P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub>, and P<sub>aCO<sub>2</sub></sub> in patients with severe acute asthma. However, NIV was associated with a trend of improved lung function in a larger number of patients, shorter ICU and hospital stay, a trend toward quicker clinical improvement, and less requirement for inhaled bronchodilators.

There is strong experimental evidence that NIV may be effective in patients with acute asthma. Mask CPAP decreases airway resistance by direct bronchodilation,<sup>17</sup> and improves the response to bronchodilators in methacholine-induced bronchial constriction.<sup>8</sup> Nasal CPAP also improves respiratory mechanics in histamine-induced bronchoconstriction<sup>6</sup> and improves clinical variables in acute asthma.<sup>7,18</sup> Mask CPAP also helps re-expand atelectatic lung regions, by increasing collateral flow through collateral lung channels to atelectatic lung segments; this can improve the secretion drainage by increasing pressure beyond the collapsed segment and moving the secretions to larger bronchi.<sup>19</sup> Applied positive end-expiratory pressure (PEEP) also offsets intrinsic PEEP and may improve ven-

tilation-perfusion mismatch.<sup>20</sup> Nasal CPAP also offsets intrinsic PEEP,<sup>21,22</sup> but CPAP alone does not improve P<sub>aO<sub>2</sub></sub> or P<sub>aCO<sub>2</sub></sub> in patients with COPD or asthma exacerbation.<sup>7,21-23</sup> NIV provides the additional inspiratory pressure that improves gas exchange both in COPD and asthma exacerbations.<sup>21-24</sup> With aerosolized medication from a small-volume nebulizer, delivering the aerosol via the NIV circuit improves peak expiratory flow better than via small-volume nebulizer alone.<sup>25</sup>

Two observational studies (one prospective and one retrospective) reported suitable outcomes in patients with acute asthma managed with NIV.<sup>24</sup> Both studies reported that NIV effectively corrected gas-exchange abnormalities and might decrease the need for endotracheal intubation.<sup>24,26</sup> In our study NIV effectively corrected respiratory rate, FEV<sub>1</sub>, and oxygenation but provided no added advantage over standard medical therapy in the initial hours. The findings of other RCTs are, however, conflicting. In a study of 35 patients with severe acute asthma, NIV (versus standard medical therapy) neither decreased intubation rate nor significantly improved clinical, spirometric, or blood-gas variables.<sup>27</sup> In another RCT, with 30 patients with severe acute asthma, the addition of NIV to standard medical therapy improved spirometry values and decreased the need for hospitalization.<sup>28</sup> However, neither of those RCTs used suitable statistical methods for analyzing the repeated measurements of clinical, spirometric, and blood-gas values in the 2 groups. Both the studies divided the repeated measurements from the 2 groups into different pairs and used Student's *t* test for different pairs, which increases the chance of a type 1 error. The ideal method for this situation is repeated-measures analysis of variance, which we used.<sup>29</sup>

Our study also differs from those other 2 RCTs in that all the patients were in the respiratory ICU, in contrast to the emergency department in the other 2 studies. Our emergency department is organized in a manner that makes aggressive therapy impossible in the vast majority of patients, because all patients with severe respiratory distress are sent to the ICU as soon as possible. Hence, almost all patients with severe asthma are treated in the respiratory ICU, because of the key role of pulmonologists in our hospital in the management of critically ill respiratory patients. Although, we have not specifically calculated the economic implications, the cost at any point is likely to be higher in the ICU, given the higher cost of ICU care.

In the present study there was a nonsignificant trend toward better spirometry values in the NIV group in the initial hours, but ICU and hospital stay were significantly shorter in the NIV group, which suggests a delayed improvement with NIV. This is further corroborated by the finding of a lower inhaled bronchodilator dosage requirement, which suggests superiority of NIV over standard medical therapy.<sup>25</sup> There was also a trend toward quicker

improvement in accessory muscle function in the NIV group. Overall, the results of the study suggest that NIV may be helpful in the routine management of patients with severe acute asthma.

### Limitations

The study was unblinded, and the possibility of bias among the attending physicians cannot be excluded. We did not use any sham NIV, as was done in a previous study.<sup>28</sup> However the use of a sham device can only make a difference in subjective sense of improvement, not in objective measurements of clinical, spirometric, or gas-exchange variables. Moreover, sham NIV does not guarantee absolute blinding.<sup>28</sup>

Another limitation was our sample size. We would require 166 patients in each group to detect a 25% improvement in outcomes from baseline in the control group and a 40% improvement in the NIV group (confidence level  $[1 - \alpha]$  95%, power level  $[1 - \beta]$  80%).

Another possible limitation is the lower doses of ipratropium we used. The Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma recommends 500  $\mu\text{g}$  of ipratropium.<sup>30</sup> We used doses of only 250  $\mu\text{g}$ , although we also gave inhaled ipratropium as-needed in addition to the routine doses.

Our patient-discharge policies were not standardized, and the discharge decision was left to the discretion of the managing physician, because there are no definite discharge criteria for severe acute asthma. Clinical assessment plays a major role in this decision, so physician bias could have affected our results. In general, patients were considered fit to be discharged from the respiratory ICU if they met most of the following criteria: dyspnea improvement, respiratory rate  $< 25$  breaths/min, minimal wheeze on auscultation, and able to walk comfortably for approximately 30 m. However, the lack of precise discharge criteria is a major limitation in this and other studies on NIV in respiratory distress. The absence of blinding and lack of predefined discharge criteria may have caused the observed difference in stay between the 2 groups.

Finally, the step-by-step management (from standard medical therapy to NIV to invasive ventilation) might not have allowed for a reliable comparison of the 2 groups. One might guess that the severity of illness of the 4 patients in the standard-medical-therapy group who improved after being switched to NIV was lower than that of the 2 patients in the NIV group who were intubated, but the ultimate decision for moving to the next level of care was left to the ICU physician instead of being based on specific predefined criteria that would make the decision more precise and transparent but would also decrease the real-life simulation. If NIV were not available, the 4 patients who failed standard medical therapy would have required invasive ventilation.

### Conclusions

What is the current role of NIV in severe acute asthma? Our results do not suggest that the addition of NIV to standard medical therapy has clear advantages over standard medical therapy alone in the routine management of patients with severe acute asthma. However, as NIV may improve lung function quicker and therefore prevent clinical deterioration, a trial of NIV may be justified in carefully selected and monitored patients with severe acute asthma, if performed by a team with a great experience in NIV. Moreover, as the condition of an asthmatic patient may worsen abruptly, extreme caution is advisable to recognize NIV failure, and there should be readily available facilities for immediate endotracheal intubation and invasive ventilation.<sup>31</sup>

Within its limitations, this study suggests that adding NIV to medical therapy may be superior to standard medical therapy alone in shortening the time to resolution of a severe asthmatic attack in the respiratory ICU. However, because of the limitations associated with the small sample size, our results require confirmation in a larger study.

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