A Prospective and Randomized Study for Improvement of Acute Asthma by Non-invasive Positive Pressure Ventilation (NPPV)

Tomoyuki Soma¹, Mitsunori Hino¹, Kozui Kida² and Shoji Kudoh²

Abstract

Objective We hypothesized that non-invasive positive pressure ventilation (NPPV) would improve an acute asthma attack in mild to moderate cases without bronchodilator therapy.

Methodology A total of 44 eligible patients with acute asthma of mild to moderate severity who had acute attacks were randomly allocated to a NPPV (n=30) or control group (n=14). Both groups received intravenous infusion of hydrocortisone prior to the study. Patients in the NPPV group were divided into two subgroups at random: a high- (n=16) and a low-pressure group (n=14). The former had a fixed expiratory positive airway pressure and inspiratory positive airway pressure of 6 cmH₂O and 8 cmH₂O, respectively, while the latter had levels of 4 cmH₂O and 6 cmH₂O, respectively. Effects on the following variables were assessed: FEV₁, oxygen saturation, heart rate, respiratory rate, scores of accessory muscle use and wheezing by auscultation, modified Borg scale score, and mean intra-airway pressure on the monitor.

Results A total of 26 patients completed the study in the NPPV group. The mean percent change in FEV₁ significantly improved after 40 minutes in the high-pressure group compared with that in the control group (p <0.0001). Similar significant improvements in modified Borg scale score and physical examination findings were observed in the high- and low-pressure groups. None of the patients required re-hospitalization or return to the emergency room in either the NPPV or control group.

Conclusion We conclude that higher inflation pressure on NPPV led to clinical improvement in patients with acute asthma attacks of mild to moderate severity.

Key words: acute severe asthma, high inspiratory positive airway pressure, NPPV, outcome measures, treatment modality

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Introduction

Acute asthma attack is a major cause of emergency room visits, focusing attention on methods to improve the treatment of it in critically ill patients (1, 2). Such patients have exaggerated bronchial responsiveness in the setting of hypoxia, hypercapnia, and acute respiratory acidosis, which can result in cardiopulmonary decompensation and asthma death (1-4). Despite the recommendation of inhaled β2-agonist therapy as initial therapy for acute asthma according to the GINA guidelines (5), approximately 30% of patients who receive such therapy exhibit insufficient effects with it (6). There are several possible explanations for the insufficient effects of inhaled β2-agonist therapy in such patients, including reduced responsiveness of β2-adrenergic receptors in airways with aging (7), and β2-adrenergic receptor dysfunction has been documented in in vitro studies of tissue obtained from patients with severe asthma (8). In addition, a number of polymorphic forms of the β2-adrenergic receptor have been described (9), and rebound hyper-responsiveness (10) as well as worsening of severity (11) are known to be
adverse effects of inhaled β2-agonist, suggesting limitations to the usefulness of inhaled β2-agonist therapy.

Non-invasive positive pressure ventilation (NPPV) has been applied in a wide variety of clinical settings (12, 13). Prospective, randomized, controlled trials have shown that this technique is efficacious in acute exacerbation of chronic obstructive pulmonary disease (COPD) (14-16), acute cardiogenic pulmonary edema (17-19), hypoxemic respiratory failure (20-22), immunocompromised patients (23), and as an adjunct to weaning in patients with COPD (24-26). Meduri et al (27) found that NPPV reduced PaCO2 in patients with status asthmaticus with hypercapnic acute respiratory failure. A few studies have shown that the combination of NPPV and conventional treatment improves lung function in patients with moderate to severe asthma attacks (28, 29), though one report indicated that refractory acute asthma improves lung function via positive expiratory pressure alone (30). However, to our knowledge, no previous study has reported adequate methods of treatment of acute attacks per se in bronchial asthma.

The American Thoracic Society/European Respiratory Society (ATS/ERS), British Thoracic Society (BTS), and Japanese Respiratory Society guidelines demonstrate that the application of NPPV to patients with acute asthma remains controversial, though it would be suitable for severe attacks or those involving status asthmaticus (12, 13, 31). Therefore, NPPV without any bronchodilator may become other therapeutic procedure if NPPV alone improves the lung function and reduces the symptoms in patients with mild to moderate asthma attack.

The patients with acute asthma are likely to exhibit several conditions, including resistance to β2-agonist, excess administration β2-agonist, and several complications. Physicians may be faced with the situation where the medicine for acute asthma is insufficient. In particular when the effects of β2-agonists are insufficient, the current therapeutic options for acute asthma do not adequately address treatment goals for a substantial number of patients. Other types of treatment are thus still needed.

We hypothesized that NPPV is effective for acute exacerbation of asthma independent of treatment with inhaled β2-agonist. This study was undertaken in the ICU of a university hospital with careful monitoring under the supervision by pulmonary physicians.

Subjects and Methods

Subjects

Patients who presented to the Emergency Department of Nippon Medical School with acute asthma were randomly recruited. Inclusion criteria were as follows: 1) patients with acute asthma cases who had previously been diagnosed with bronchial asthma as defined by the GINA guidelines, 2) at least 18 years of age and less than 70 years of age, 3) regularly receiving inhaled corticosteroid, medication of inhaled long-acting β2-agonist as regular use and/or short-acting on demand prior to visiting the Emergency Department, 4) oxygen saturation (SpO2) above 90% on room air, and 5) able to undergo spirometry. The following were exclusion criteria: 1) obvious chronic obstructive pulmonary disease (COPD), 2) comorbidity excluding enrollment, such as congestive heart failure or arrhythmia, 3) bacterial pneumonia, 4) lung cancer, and 5) pregnancy. The diagnosis of COPD was made as suggested by the guidelines of ATS/ERS (32).

This study was approved by the Ethics Committee of Nippon Medical School, and written informed consent was obtained from all subjects who enrolled in it.

Intervention

The study design is shown in Fig. 1. All subjects underwent initial assessment, which included history taking, physical examination, biplanar chest x-ray, electrocardiogram, SpO2 on room air, and spirometry in the Emergency Department. After obtaining informed consent, eligible patients were allocated into one of three groups: a low-pressure NPPV group, a high-pressure NPPV group (see below), or a control group, in this order. For both the low- and high-pressure groups, ventilation was delivered from a BiPAP® circuit (Bi-PAP® S/T ventilator; Respironics, Inc., Oakland, CA, USA) for 60 minutes, using a softly attached nose or face mask. In the low-pressure group (NPPV-L), patients received 6 cmH2O inspiratory positive airway pressure (IPAP) and 4 cmH2O expiratory positive airway pressure (EPAP), while in the high-pressure group (NPPV-H) they received 8 cmH2O and 6 cmH2O IPAP and EPAP, respectively. All NPPV-H and -L patients were instructed to breathe through the nose during treatments, and each patient was carefully monitored for adherence. If any patient could not avoid mouth-breathing, this was considered to indicate inadequate nose mask fitting, and a face mask was promptly introduced. The mask was secured by head straps, with care taken to avoid too tight a fit. All patients in the NPPV-H and -L groups and the control group were given an intravenous infusion of hydrocortisone (5 mg per kg body weight) prior to the study.

All groups were similarly carefully monitored after intervention. After monitoring each patient’s condition for at least 20 minutes, conventional treatment according to the recommendations of GINA® was added to the control group (see Fig. 1). Study participation was discontinued for patients meeting any of the following criteria, and conventional treatment recommended by GINA® was immediately begun as required: 1) Worsening of asthma attack, defined as reduction of over 20% in FEV1 from the baseline level, 2) SpO2: or modified Borg scale deterioration compared with that prior to intervention, 3) increase in score for respiratory accessory muscle use or wheezing on auscultation compared with that prior to intervention, 4) the decision by the physician(s) of a patient that discontinuation would be required due to other medical conditions.

In addition, whether to add other treatments for asthma
attack, and whether the patient required hospitalization for further monitoring or treatment or could return home, was determined by the physician(s) of each patient at the time of termination of the study according to changes in FEV₁ or physical status. Patients returning home were each prescribed a steroid inhaler and beta agonists as well as prednisolone (0.5 mg/kg/day) for 3-5 days.

**Assessment**

The primary endpoint was the ratio of improvement of FEV₁, defined by the formula \([\text{FEV}_1 \times 100]/\text{baseline FEV}_1\) \times 100, while the secondary endpoints were changes in SpO₂, the modified Borg dyspnea scale, score for respiratory accessory muscle use, severity of wheezing on auscultation, and adverse effects of the treatments.

The time of completion of intravenous infusion of hydrocortisone was considered time 0, and the effects of intervention by NPPV were assessed at 0, 20, 40, and 60 minutes, and 20 minutes after the conclusion of treatment of NPPV using the following items: FEV₁, FEV₁% of predicted, SpO₂, respiratory rate, heart rate, score for respiratory accessory muscle use, score for wheezing on auscultation, modified Borg scale, and intra-airway pressure, as measured by the NPPV equipment in stable condition.

The FEV₁ and FEV₁% of predicted were measured using a spirometer (Microspiro HI-198, Chest Inc., Tokyo, Japan), with reference values used according to the Japan Respiratory Society (33). Measurements were performed according to the criteria of ATS/ERS (34). The highest value of three successive maximal expiratory curves was selected. The mask was removed only during performance of spirometry, and this testing usually required less than five minutes. Dyspnea was assessed using the modified Borg scale, ranging from 0 (none at all) to 10 (maximal) (35, 36). Accessory muscle use, defined as visible retraction of the sternocleidomastoid muscles, and wheezing, defined as musical or whistling breath sounds on auscultation, were measured on a visual analog scale (VAS), using a horizontal straight line (200 mm) labeled “absent” (0 mm) at one end, and “mild” (50 mm), “moderate” (100 mm), “severe” (150 mm), and “very severe” (200 mm). Heart rate and SpO₂ were measured by pulse oximetry (PULSOX-SP, Teijin Inc., Tokyo, Japan). Inspiratory and expiratory airway pressures were continuously measured using a Bi-PAP® circuit indicator.

**Statistical analysis**

Examination of categorical variables was performed using chi-square analysis. Examination of continuous variables was performed using one-way analysis of variance (ANOVA). For the following variables, repeated-measures ANOVA was used to assess changes from the baseline among the NPPV groups and control group, and changes from the baseline for all time points within each group: per-

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<table>
<thead>
<tr>
<th>High pressure group</th>
<th>20 min</th>
<th>40 min</th>
<th>60 min</th>
<th>20 min after intervention by NPPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/kg of IV hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td>Follow up</td>
</tr>
<tr>
<td>IPAP 8 cmH₂O, EPAP 6 cmH₂O</td>
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<table>
<thead>
<tr>
<th>Low pressure group</th>
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<td>Follow up</td>
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<tr>
<td>IPAP 6 cmH₂O, EPAP 4 cmH₂O</td>
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<table>
<thead>
<tr>
<th>Control group</th>
<th>Follow up</th>
<th>Conventional treatment</th>
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<tbody>
<tr>
<td>5 mg/kg of IV hydrocortisone</td>
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*Figure 1. Design of study after random allocation with the patients divided into three groups: high pressure (NPPV-H) group, low pressure (NPPV-L) group, or control group.*
Consequent of 49 patients with acute asthma were recruited

Included (n=44)
- In acute asthma
- With current therapy of asthma
- Age: above 18, less than 70 yrs
- Received medications
  Previous medication by inhaled corticosteroid
  and inhaled β2-agonist
- SpO₂>=91% in room air
- Accepted maneuver of spirometry

Excluded (n=5)
- COPD (n=3)
- Inadequate cases and medical contraindications identified by physicians (n=2)

Figure 2. Flow chart of the study in which 49 patients with acute asthma were recruited. Finally, a total of 44 patients fulfilled the inclusion criteria.

cent change from baseline in FEV₁, change from baseline in FEV₁% of predicted, modified Borg scale score (dyspnea), accessory muscle use and wheezing, heart rate, respiratory rate, and inspiratory and expiratory airway pressures. If differences were significant (p<0.05), the above values were compared using Dunnett’s test (37). We considered a 20% difference in percent change in FEV₁ between the control and NPPV groups to be clinically important in this study. The study was designed to recruit 15 patients with 80% power to detect a 25% difference in percent change in FEV₁ at an α of 0.05, given an SD of 25% (data not shown). All tests and p values are two-tailed. A p value of <0.05 was considered to indicate significance. Statistical analyses were performed with SPSS Version 11.5 for Windows (Chicago, USA).

Results

Of the 49 patients who were initially screened for inclusion in the study, a total of 44 patients were included in the NPPV and control groups. Figure 2 shows the patient flow chart for the study. Among a total of 44 eligible patients, 30
Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-pressure group (n=14)</th>
<th>Low-pressure group (n=12)</th>
<th>Control Group (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>37.4 ± 19.8</td>
<td>46.3 ± 13.6</td>
<td>44.1 ± 13.0</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>8 / 6</td>
<td>4 / 8</td>
<td>4 / 10</td>
</tr>
<tr>
<td>Pulse, beats/min</td>
<td>84 ± 15</td>
<td>83 ± 17</td>
<td>93 ± 18</td>
</tr>
<tr>
<td>Respiration, breaths/min</td>
<td>22 ± 6</td>
<td>18 ± 6</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>Accessory muscle use, cm</td>
<td>2.8 ± 2.8</td>
<td>5.1 ± 5.5</td>
<td>1.8 ± 2.9</td>
</tr>
<tr>
<td>Wheezing*, cm</td>
<td>8.1 ± 4.0</td>
<td>9.4 ± 5.9†</td>
<td>3.8 ± 3.1</td>
</tr>
<tr>
<td>Borg scale†, points</td>
<td>4.5 ± 5.3</td>
<td>5.3 ± 1.8§</td>
<td>3.0 ± 2.3</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>94.6 ± 1.6</td>
<td>93.6 ± 2.1</td>
<td>95.3 ± 1.9</td>
</tr>
<tr>
<td>FEV₁, L/min</td>
<td>1.022 ± 0.439</td>
<td>0.798 ± 0.435</td>
<td>1.113 ± 0.462</td>
</tr>
<tr>
<td>FEV₁% of predicted‡, %</td>
<td>33.6 ± 12.8</td>
<td>30.0 ± 11.8§</td>
<td>42.2 ± 12.8</td>
</tr>
</tbody>
</table>

Values are the mean ± SD, unless otherwise indicated.

Low-pressure: IPAP = 6 cmH₂O, EPAP = 4 cmH₂O. High-pressure: IPAP = 8 cmH₂O, EPAP = 6 cmH₂O.

* p = 0.006, † p = 0.034, § p < 0.05 compared among all groups using one-way ANOVA.

Both wheezing and accessory muscle use were significantly decreased in the NPPV groups. The mean change over time in wheezing was significantly larger in the NPPV-H group compared to the control group. The FEV₁% of predicted in the NPPV-H group was increased significantly after 40 minutes, compared to the pretreatment value (2.83±3.29% at 40 minutes; p=0.012, 4.97±4.24 at 60 minutes; p <0.0001, 6.24±3.28 at 20 minutes after intervention; p <0.0001), but notably increased in neither the NPPV-L group nor the control group.
Figure 3. Changes of FEV₁ along with the time course (mean ± SD). Values were compared to those of the control group using repeated-measures analysis of variance with Dunnet’s test. There was a significant difference between NPPV-H and control group (*: p=0.009). NPPV-H: High pressure group, NPPV-L: Low pressure group.

Figure 4. Changes in the Borg scale along with the time course (mean ± SD). Values were compared to those of the control group using repeated-measures analysis of variance with Dunnet’s test. There were significant differences between NPPV-L and control group (**: p<0.001), and between NPPV-H and control group (*: p=0.023). NPPV-H: High pressure group, NPPV-L: Low pressure group.

and 2.0±2.6, respectively. The mean change over time in accessory-muscle use score was significantly greater in the NPPV-L group (p=0.035), but not in the NPPV-H group, compared to the control group.

Neither heart nor respiratory rate differed among the two intervention subgroups and the control group. Changes in both inspiratory and expiratory airway pressure are shown in Table 2. There was little change in inspiratory or expiratory pressure in the NPPV-H and -L groups.

Discussion

Several previous studies (28, 29) reported the efficacy of NPPV for acute asthma attacks. Pollack et al (28) conducted a study involving two groups with acute asthma of moderate severity, comparing inhalation of β₂-adrenergic agonists...
Table 2. Changes in Inspiratory and Expiratory Airway Pressure* with Time

<table>
<thead>
<tr>
<th>Time after intervention (min)</th>
<th>20</th>
<th>40</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-pressure group</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Inspiratory airway pressure</td>
<td>7.6 ± 0.9</td>
<td>7.7 ± 0.9</td>
<td>7.9 ± 0.9</td>
</tr>
<tr>
<td>Expiratory airway pressure</td>
<td>5.4 ± 1.2</td>
<td>5.4 ± 1.3</td>
<td>5.4 ± 1.2</td>
</tr>
<tr>
<td><strong>Low-pressure group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspiratory airway pressure</td>
<td>6.0 ± 0.0</td>
<td>6.2 ± 0.4</td>
<td>6.2 ± 0.4</td>
</tr>
<tr>
<td>Expiratory airway pressure</td>
<td>3.5 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>3.6 ± 0.5</td>
</tr>
</tbody>
</table>

* All measurements are the mean ± SD, cmH2O, unless otherwise indicated.

alone with that of β2-adrenergic agonists plus NPPV. Findings indicated that combined treatment with β2-adrenergic agonists plus NPPV was more effective in improving lung function (28). A study by Soroksky et al (29) focused on acute asthma with severe attacks, comparing NPPV with a sham condition, with the two groups receiving inhalation of β2-adrenergic agonists and an anti-cholinergic regimen in similar fashion. The findings indicated a better outcome for the NPPV group. However, these studies differed from the present one, since they used NPPV as well as inhalation therapy; it was thus difficult to assess the effectiveness of NPPV alone with them. An investigation performed by Meduri et al (27) indicated the effectiveness of NPPV for gas exchange; however, that study used NPPV as ventilatory support, unlike the present study.

The findings of the present study indicated that acute asthma of mild to moderate severity was improved by NPPV with IPAP and EPAP of 6 cmH2O and 4 cmH2O, with further improvement obtained with higher pressures of 8 cmH2O and 6 cmH2O, respectively. An earlier study by Barach and Swenson (38) found that CPAP (7 cmH2O) increased the diameter of small bronchi by 1 mm and moderate-sized bronchi by 2 mm in 7 patients with acute asthma. These findings strongly suggest that NPPV therapy achieves bronchial dilation by mechanical effects. They also strongly justify the pressures applied in the present study. The official guidelines of the ATS/ERS and BTS (12, 13) recommend pressure levels of IPAP and EPAP of 12-15 cmH2O and 4-5 cmH2O, respectively, which are higher than those used in the present study. Our findings suggest that lower pressure settings than appear in the guidelines could be clinically sufficient for recovery from acute asthma attack, and might be beneficial for avoiding adverse effects such as pneumothorax. Although the present study was terminated at 60 minutes after intervention, the study by Soroksky et al (29) involved NPPV for 180 minutes. Determination of appropriate settings including EPAP and IPAP and duration of treatment will clearly require further study.

The improvement in the modified Borg scale in our study was similar to those in several studies which found that breathlessness decreased with each increment in medical therapy for acute asthma patients (36, 39, 40). Moy et al (36) found that a serial decrease in intensity of dyspnea was obtained in acutely ill asthmatic individuals with administration of a β-adrenergic agonist. Improvement of breathlessness with the use of CPAP in the setting of acute asthma has also been reported, and the findings of the present study suggest that CPAP can be expected to benefit inspiratory muscles (41). Because CPAP reduces the inspiratory work of breathing (27), NPPV, which functions like CPAP, lets the diaphragm and inspiratory muscles result, and thereby decreases the intensity of dyspnea. In the present study, the improvement of wheezing and accessory-muscle use was similar to that in the modified Borg scale. In assessing treatment for acute asthma, subjective as well as objective measurements are important. The goal in the treatment of exacerbation of asthma is improvement of asthma symptoms resulting from reversal of airflow limitation. Our findings indicate that NPPV has the advantage of rapidly improving the patient’s condition, and that the level of BiPAP should be set to 6 cmH2O IPAP and 4 cmH2O EPAP or higher.

Recently, NPPV has been used to improve acute or chronic respiratory failure in various diseases. Though several studies have shown that combined treatment with NPPV and conventional therapy for status asthmaticus is effective in improving pulmonary function and gas exchange, and for reducing hospitalization rate, the current strategies conclude that NPPV should not be used routinely in acute asthma. However, our results support those of the previous studies, especially in terms of the benefit of the combination therapy of NPPV and conventional therapy for acute asthma. This may thus permit earlier use of NPPV, which may in turn prevent worsening of the clinical condition of patients if NPPV combined with conventional therapy is performed at a minimum. The benefit of NPPV is supported by the efficacy of NPPV including a direct bronchodilating effect, offsetting intrinsic PEEP, recruiting collapsed alveoli, improving ventilation-perfusion mismatch, and reducing the work...
of breathing.

However, the present study has certain limitations in design. First, we did not set the minimum values of lung function tests in the inclusion criteria, suggesting the possibility that relatively severe cases were included, which might have affected findings concerning the improvement of FEV1, in this study. Second, the present study did not include a sham group for NPPV, which might have resulted in “noise” affecting examiners and examinees engaged in this study. Third, the small population in this study weakened its statistical power, so that it might have been unable to detect differences among subpopulations of patients. Finally, although the present study suggested the effectiveness of NPPV in acute asthma, we did not compare results with those obtained with conventional treatment alone (6). However, the speculated reasons, including based on patient selection, prior management to the study, and ethnic differences, clearly need further study.

Patients with acute asthma having a variety of historical factors visit the hospital, including those who regularly use β2-agonist and have inhaled β2-agonist excessively before seeing physicians, who are complicated by cardiac disease, and who are unable to receive drugs by a nebulizer well because of coughing, hypersensitivity to nebulizer liquid and increasing inspiratory workload, and other reasons. Though the mainstays of treatment in the emergency room are inhaled β2-adrenergic agonists, up to 30% of patients with acute asthma fail to respond adequately to them (6). NPPV without a bronchodilator may be useful for such patients. In addition, NPPV might become an emergency procedure in selective situations, for example the place where the medicine for acute asthma is insufficient. For the clinical application of the present study results, as NPPV equipment is a compact size NPPV may be applied during the emergency transportation of patients with severe asthma attacks. This can also be expected as additional or alternative therapy.

In conclusion, the present findings suggest that NPPV without bronchodilators can improve acute asthma attacks, and thus suggest an additional useful application of NPPV. Without bronchodilators, the initial treatment with NPPV may improve pulmonary function and physical status with sustained efficacy, making it an additional therapeutic option for acute asthma in the emergency or outpatient department.

References

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