

A Pilot Prospective, Randomized, Placebo-Controlled Trial of Bilevel Positive Airway Pressure in Acute Asthmatic Attack*

Arie Soroksky, MD; David Stav, MD; and Isaac Shpirer, MD

Study objective: Noninvasive ventilation has been shown to be effective in patients with acute respiratory failure due to pulmonary edema and exacerbations of COPD. Its role in an acute asthmatic attack, however, is uncertain. The purpose of this pilot study was to compare conventional asthma treatment with nasal bilevel pressure ventilation (BPV) [BiPAP; Respironics; Murrysville, PA] plus conventional treatment in patients with a severe asthmatic attack admitted to the emergency department.

Design: A prospective, randomized, placebo-controlled study.

Setting: An emergency department at a university hospital.

Patients: Thirty patients with a severe asthma attack were recruited from a larger group of 124 asthmatic patients seen in the emergency department. Fifteen patients were randomly assigned to BPV plus conventional therapy and 15 patients to conventional therapy alone. The two groups had similar clinical characteristics on hospital admission. Mean (\pm SD) FEV₁ on recruitment was $37.3 \pm 10.7\%$ in the BPV group and $33.8 \pm 10.2\%$ in the control group ($p =$ not significant).

Interventions and measurements: BPV with predetermined inspiratory and expiratory pressures was applied for 3 h in the BPV group; in the control group, a similar sham device with subtherapeutic pressures was applied for 3 h. Bedside lung function test results and vital signs were obtained at baseline, and during and at the completion of the study protocol.

Results: The use of BPV significantly improved lung function test results. Eighty percents of the patients in the BPV group reached the predetermined primary end points (an increase of at least 50% in FEV₁ as compared to baseline), vs 20% of control patients ($p < 0.004$). Mean rise in FEV₁ was $53.5 \pm 23.4\%$ in the BPV group and $28.5 \pm 22.6\%$ in the conventional treatment group ($p = 0.006$). The intention-to-treat analysis of the secondary end point rate of hospitalization included 33 patients. Hospitalization was required for 3 of 17 patients (17.6%) in the BPV group, as compared with 10 of 16 patients (62.5%) in the control group ($p = 0.0134$).

Conclusion: In selected patients with a severe asthma attack, the addition of BPV to conventional treatment can improve lung function, alleviate the attack faster, and significantly reduce the need for hospitalization. (CHEST 2003; 123:1018–1025)

Key words: asthma; bilevel positive airway pressure; FEV₁

Abbreviations: BPV = bilevel pressure ventilation; CPAP = continuous positive airway pressure; NS = not significant; PEEP = positive end-expiratory pressure; PEFr = peak expiratory flow rate

Noninvasive positive pressure ventilation improves gas exchange and clinical outcome in various types of acute respiratory failure. It has been

shown to be effective in conditions such as congestive heart failure with pulmonary edema and exacerbation of COPD.^{1–7} In many ways, acute asthmatic attacks are similar to exacerbations of COPD. There is in both an increase in inspiratory and expiratory indexes of airway obstruction accompanied by a significant dynamic hyperinflation and generation of a large negative pleural pressure that is needed to overcome the increased end-expiratory intrathoracic pressure and airway resistance.^{8–11}

The progressive decline in FEV₁ during an asthmatic attack is associated with a proportional in-

*From the Pulmonary Institute, Assaf Harofeh Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. Manuscript received January 9, 2002; revision accepted October 30, 2002.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

Correspondence to: Arie Soroksky, MD, General Intensive Care Unit, Assaf Harofeh Medical Center, PO Beer Yaacov, Zerifin 70300, Israel; e-mail: ArieS@asaf.health.gov.il

crease in the inspiratory work of breathing,⁸ contributing to inspiratory muscle fatigue. Together with increased physiologic dead space and ventilation-perfusion mismatch,^{12,13} the attack may culminate in a worsening hypoxemia with hypercarbia and respiratory failure.

Continuous positive airway pressure (CPAP) has been reported to have a bronchodilatory effect in asthma,¹⁴ to unload fatigued inspiratory muscles, and to improve gas exchange.^{15,16} It also prevents methacholine- and histamine-induced asthma.^{15,17} Noninvasive ventilatory support in the form of bilevel pressure ventilation (BPV) increases tidal volume,¹⁸ and has the advantage of adding external positive end-expiratory pressure (PEEP) to offset the intrinsic PEEP that builds up during an asthmatic attack,¹⁹ thus further decreasing the work of the inspiratory muscles. The indications that BPV might be beneficial in asthma have not been supported by controlled studies; therefore, we designed a prospective, randomized, placebo-controlled study to examine whether BPV might be beneficial in selected patients with a severe attack of asthma presenting at the emergency department.

MATERIALS AND METHODS

Study Design and Patient Selection

The study was approved by the Institutional Ethics Committee and by the National Helsinki committee. All patients gave written informed consent. Between November 1999 and April 2000, we screened all adults aged 18 to 50 years with an acute attack of bronchial asthma, who presented at the emergency department of Asaf Harofe Medical Center, with an asthma attack of < 7 days in duration and a history of asthma of at least 1 year.

On admission to the emergency department, all patients judged by the attending physician as having an acute attack of asthma were first treated with nebulized salbutamol, 2.5 mg, and ipratropium, 0.25 mg. Half an hour later, spirometry was performed (Spyro Analyzer ST-90; Fukuda Sangyo; Chiba, Japan). Each time, at least three readings were made. In accordance with the American Thoracic Society guidelines for reproducibility criteria,²⁰ a variance of < 0.2 L was allowed between the tests, and the best of the three results was then recorded; however, should the FEV₁ tested be < 2 L, a reproducibility variance of ≤ 10% would have been used.

In order to be eligible to enter the study, the patient had to fulfill all four of the following severity criteria: FEV₁ < 60% of predicted by age, height, and gender; respiratory rate > 30 breaths/min; history of asthma of at least 1 year; and duration of current asthma attack of < 7 days. The rationale behind the last two inclusion criteria was to include only those patients with diagnosed asthma that was well established and being treated, and to exclude patients with chronic obstructive lung diseases other than asthma. Patients with any of the following were excluded: smoking history of > 10 years, a known chronic pulmonary disease other than asthma, an emergency intubation for cardiorespiratory resuscitation, hemodynamic instability defined as heart rate > 150 beats/min, or systolic BP < 90 mm Hg, altered state of consciousness, congestive heart failure, ischemic

heart disease, upper airway obstruction, facial deformity, pregnancy, and pulmonary infiltrates consistent with pulmonary edema or pneumonia.

Of the screened patients, those who fulfilled the inclusion criteria for entering the study were randomly assigned to receive either conventional treatment combined with ventilatory support with BPV or conventional treatment plus sham BPV (control group). In both groups during the 3 h of the trial, interruption of the BPV application was allowed only for the following reasons: performance of spirometry, nebulization of aerosolized bronchodilators via a small-volume nebulizer, or clearance of secretions. Interruption of the BPV application was allowed for not > 5 min each time.

Conventional medical management in the two groups was similar and consisted of salbutamol, 2.5 mg, and ipratropium, 0.25 mg, nebulized on average once an hour, and IV corticosteroids (either methylprednisolone or hydrocortisone) at the discretion of the attending physician. In both groups, BPV was interrupted each time to deliver aerosolized bronchodilators via a separate small-volume nebulizer. Oxygen was administered as needed with the goal of keeping oxygen saturation above 95%. All patients underwent blood gas analysis (blood samples were drawn while patients were breathing room air), CBC count, determination of serum electrolytes, and chest radiograph at the outset.

After randomization, in both groups in addition to conventional medical management, BPV was applied through a nasal mask secured with head straps. In the control group, a subtherapeutic BPV (sham BPV) was applied, while in the BPV group therapeutic BPV with predetermined pressures was applied. In both groups, BPV was applied for not > 3 h.

The primary end point was improvement in lung function test results and was defined as an increase of at least 50% in FEV₁ as compared to baseline value on hospital admission or an increase in FEV₁ to > 60% of the predicted value. Primary end points were evaluated at the end of 3 h of BPV application. One hour later, primary end points were reevaluated again. The same primary end points in addition to clinical judgment were used by the attending physician as a criteria for discharge from the emergency department.

Secondary end points were the need for hospitalization and the occurrence of respiratory failure with the need for mechanical ventilation. Follow-up was 1 month following discharge from the emergency department, and readmission rate to the emergency department or to the hospital was recorded.

Conventional Treatment Group

Patients in this group were treated conventionally with nebulized salbutamol, 2.5 mg, and ipratropium, 0.25 mg, administered hourly along with IV corticosteroids as determined by the attending physician. Oxygen was given to maintain saturation at 95%. As a control group and in order to minimize the possibility of bias from the attending physicians and from the patients themselves, subtherapeutic BPV (sham BPV) was applied through a nasal mask for 3 h. Inspiratory and expiratory pressures were set at 1 cm of water. In addition, four large holes (3 mm in diameter) were made in the tube connecting the apparatus and the nasal mask. This was done in order to minimize the therapeutic effect that such low pressures could have and in order to allow unlimited flow of air to the patient. As another means of precaution, patients in this group were not instructed to breathe solely through their nasal mask, and oral breathing was allowed. This was done in order to offset any flow limitation or other side effects that a subtherapeutic nasal mask could have.

Spirometry, oxygen saturation, BP, heart rate, and respiratory rate were recorded at time zero, and 15 min, 30 min, 60 min, 2 h,

and 3 h after beginning the trial. In addition to vital signs, spirometry was performed again 1 h after the end of BPV application.

Ventilatory Support Group With BPV

In this group, BPV was applied through a nasal mask secured with head straps (BiPAP model ST; Respironics; Murrysville, PA). Inspiratory pressure was set at 8 cm H₂O and was increased gradually by 2 cm H₂O every 15 min to a maximum of 15 cm H₂O, or until a respiratory rate of < 25 breaths/min was reached, whichever came first. Expiratory pressure was set at 3 cm H₂O and was increased gradually by 1 cm H₂O every 15 min to a maximum of 5 cm H₂O. The gradual increase in both the inspiratory and expiratory pressures was aimed at increasing patient comfort and patient compliance. These values were set in a rather arbitrary manner, and were designed to provide what would be considered by most as a mild PEEP (external) and mild-to-moderate inspiratory pressure support. As opposed to the control group, breathing through the mouth was discouraged, and patients in this group were instructed to breath only through the nasal mask.

Vital signs and spirometry were performed at the same time intervals as in the control group. Bedside spirometry and vital signs were recorded also 1 h after completion of 3 h of BPV treatment. One hour after completion of the trial, patient data including spirometry results (mainly FEV₁ and peak expiratory flow rate [PEFR]) and vital signs were presented to the attending physician. The attending physician would then make a decision regarding hospitalization and/or continuation of conventional treatment based on spirometric data and clinical grounds. Criteria used by the attending physician were similar to the primary end point, *ie*, an increase of at least 50% in FEV₁ as compared to baseline value on hospital admission or an increase in FEV₁ to > 60% of the predicted value. The investigating team did not intervene in decision making regarding discharge or admission to the hospital or in the treatment plan. Neither the patient nor the attending physician knew the patient's assigned group and thus were blinded to the results of the randomization. Since respiratory pressures had to be titrated individually to each patient, knowledge of the patient's assigned group could not be concealed from the investigating team.

Statistical Analysis

The primary outcome variable was improvement in lung function test results during a short period stay in the emergency department, and the secondary end point was the need to hospitalize. Results are given as mean \pm SD, and the group means were compared by *t* test. All tests and *p* values are two-tailed. A *p* value of < 0.05 was considered statistically significant. Categorical data were analyzed using the χ^2 test. Yates correction was used for a two-by-two table.

The study population for the secondary end point analysis—the rate of hospitalization—was defined as all patients who were randomized and entered the study, either to the control group or to the BPV group. An intention-to-treat analysis was performed for this secondary variable using a two-tailed Fisher exact test. The SPSS statistical software package (SPSS; Chicago, IL) was used.

RESULTS

During the study period, a total of 124 asthmatic patients were seen at the emergency department.

Two patients had pneumonia, and 85 patients presented with an FEV₁ > 60% of predicted; therefore, these patients were excluded. Thirty-seven patients (29.8%) fulfilled the severe asthma inclusion criteria, and 4 patients refused to participate in the study. Three patients, one of them in the control group, could not tolerate the nasal mask and did not complete the 3-h protocol; they were withdrawn from the study. Altogether, 30 patients entered the study, and all completed the study protocol without any side effects. Except for the two patients with pneumonia, none of the 85 patients who did not meet the inclusion criteria for entering the study, and none of the 3 patients who were withdrawn from the study were hospitalized.

Patient characteristics in both groups were similar (Table 1). The mean FEV₁ on recruitment was similar in both groups: 37.27 \pm 10.7% of predicted in the BPV group and 33.8 \pm 10.2% in the control group. FVC was similar as well: 48.27 \pm 11.87% in the BPV group and 48.6 \pm 16.05% in the control group.

Results of blood gas analysis on hospital admission were similar: there was a mild hypocarbia in both groups (mean PaCO₂ in the BPV group, 33.59 \pm 3.48 mm Hg; control group, 34.29 \pm 5.41 mm Hg). Arterial oxygen tension was slightly decreased: 82.85 \pm 38.72 mm Hg in the BPV group and 85.82 \pm 29.6 mm Hg in the control group. Regular use of medications was similar as well, including the regular use of inhaled corticosteroids.

Patients in both groups received a similar amount of nebulizations with salbutamol and ipratropium and similar doses of IV corticosteroids (Table 2). Table 3 demonstrates the different characteristics of the patients in both groups by the end of 3 h and 4 h of treatment. The mean rise in FEV₁ in the BPV group at 3 h of treatment was 56.13 \pm 16.3%, an improvement of 51.08 \pm 19.3% as compared to an improvement of 24.08 \pm 23.6% in the control group (*p* = 0.002). By the end of 4 h of treatment, mean FEV₁ increased to 57.4 \pm 17.7% in the BPV group, an improvement of 53.53 \pm 23.4% as compared to an improvement of 28.46 \pm 22.6% in the control group (*p* = 0.006).

Figure 1 demonstrates the inspiratory and expiratory positive airway pressure during 3 h of treatment in the BPV group. It shows that most of the pressure increments occurred during the first 30 min to 1 h; thereafter, inspiratory and expiratory pressures did not change significantly. Although the study protocol allowed increments in inspiratory pressure of up to 15 cm H₂O, by the time inspiratory pressure of 14 cm H₂O was reached, respiratory rate has decreased in all but three patients to < 25 breaths/min. These three patients were also those patients who

Table 1—Demographic and Physiologic Parameters on Hospital Admission*

Parameters	BPV Group	Control Group	p Value
Patients, No.	15	15	
Age, yr	34.07 ± 8.55	32.53 ± 9.68	NS
Female/male gender, No.	8/7	7/8	
Mean FEV ₁ , % predicted†	37.27 ± 10.69	33.8 ± 10.18	NS
Mean FEV ₁ , L	1.26 ± 0.39	1.16 ± 0.35	NS
Mean FVC, % predicted†	48.27 ± 11.87	48.6 ± 16.05	NS
Mean FVC, L	1.94 ± 0.56	1.94 ± 0.65	NS
Mean PEF _R , % predicted†	38 ± 11.95	34 ± 11.2	NS
Duration of attack, d	2.6 ± 2.13	2.07 ± 1.71	NS
Duration of asthma, yr	12.13 ± 9.81	10.27 ± 6.33	NS
pH	7.41 ± 0.04	7.40 ± 0.02	NS
PaCO ₂ , mm Hg	33.59 ± 3.48	34.29 ± 5.41	NS
PaO ₂ , mm Hg	82.85 ± 38.72	85.82 ± 29.6	NS
Hemoglobin, g/dL	14.08 ± 2.47	14.41 ± 2.87	NS
Heart rate, beats/min	120.8 ± 19.21	109.33 ± 12.02	NS
Mean BP, mm Hg	97.32 ± 6.87	99.3 ± 8.67	NS
Respiratory rate, breaths/min	34.8 ± 1.82	33.53 ± 1.73	NS
Permanent use of inhaled corticosteroids‡	8	6	NS
Permanent use of inhaled β-agonists‡	14	13	NS
Permanent use of systemic corticosteroids‡	2	1	NS
Prior episodes of acute respiratory failure§	2	0	NS

*Data are presented as mean ± SD unless otherwise indicated; p values < 0.05 were considered statistically significant.

†Expressed as percentage of predicted for age, height, and weight.

‡No. of patients who used inhaled or systemic corticosteroids or inhaled β-agonists on a regular basis.

§No. of acute respiratory failures due to asthma that necessitated mechanical ventilation through an endotracheal tube.

were hospitalized. We did attempt to increase inspiratory pressure to a maximum of 15 cm H₂O in these three patients; however, they did not tolerate it and inspiratory pressures were decreased quite rapidly back to 14 cm H₂O in two patients and back to 12 cm H₂O in one patient. As a result, during the study none of the patients received an inspiratory pressure of > 14 cm H₂O.

Figure 2 demonstrates the increase in FEV₁ during 3 h of BPV application. The increase was steady and continued for another hour after termination of BPV. There was no statistically significant difference between the two groups in the decline of heart rate. Respiratory rate, however, decreased more in the BPV

group, 41.3 ± 12.8%, as compared to 31 ± 11.4% in the control group (p = 0.02).

The mean stay in the emergency department (Table 4) was 5.9 ± 1.3 h in the BPV group and 5.6 ± 1.3 h in the control group (p = not significant [NS]). The last 4 h of that period in both groups was devoted for the study protocol.

More patients in the BPV group reached the predetermined primary end points at 4 h of treatment (12 patients; 80%), as compared to the control group, where only 3 patients (20%) reached the primary end points (p < 0.004). With regard to the secondary end point, the rate of hospitalization, an intention-to-treat analysis was performed, comparing

Table 2—Treatment in the Emergency Department*

Parameters	BPV Group	Control Group	p Value
IV methylprednisolone†	15	12	NS
IV hydrocortisone, mg†	186.66 ± 124.6	156.66 ± 137.4	NS
Nebulizations with ipratropium and salbutamol,§ No.	11	9	NS
Inspiratory positive airway pressure	13.06 ± 0.45	1	
Expiratory positive airway pressure	4.06 ± 0.45	1	

*Data are presented as mean ± SD unless otherwise indicated.

†No. of patients receiving 125 mg of methylprednisolone. In the control group, two patients received 250 mg of methylprednisolone and one patient received none.

‡p Value < 0.05 was considered statistically significant.

§Nebulizations with ipratropium, 0.25 mg, and salbutamol, 2.5 mg, during the 3 h of the trial: BPV group, 11 patients received three nebulizations and 4 patients received two nebulizations. Control group: nine patients received three nebulizations and six patients received two nebulizations.

||Final respiratory pressures reached by the end of 3 h of treatment.

Table 3—Characteristics of Patients on Hospital Admission and After 3 h and 4 h of Treatment*

Parameters	Absolute Value			Percentage Improvement		
	BPV Group	Control Group	p Value	BPV Group	Control Group	p Value
Mean FEV ₁ , % predicted						
Admission	37.3 ± 10.7	33.8 ± 10.2	NS			
3 h	56.1 ± 16.3	42.3 ± 15.9	0.03	51.1 ± 19.3	24.1 ± 23.6	0.002
4 h	57.4 ± 17.7	43.9 ± 16.7	0.04	53.5 ± 23.4	28.5 ± 22.6	0.006
PEFR, % predicted						
Admission	38 ± 11.9	34 ± 11.1	NS			
3 h	57.9 ± 20	41.9 ± 18.6	0.03	55.5 ± 43.9	21.9 ± 32.3	0.02
4 h	59.9 ± 20.4	44.1 ± 19.3	0.04	58.7 ± 34.8	29.2 ± 28.2	0.01
FVC, % predicted						
Admission	48.3 ± 11.9	48.6 ± 16	NS			
3 h	70.6 ± 13.8	56 ± 20.18	0.03	48.9 ± 20.4	15.8 ± 18.9	< 0.001
4 h	70 ± 14.3	58.1 ± 19.7	NS	47.0 ± 18.3	20.2 ± 16.2	< 0.001
Heart rate†						
Admission	120.8 ± 19.2	109.3 ± 12	NS			
3 h	104.2 ± 13.5	98.6 ± 11	NS	- 12.5 ± 11.9	- 9.4 ± 8.8	NS
4 h	103 ± 10.3	99 ± 9.4	NS	- 13.4 ± 10.6	- 8.9 ± 8.4	NS
Respiratory rate†						
Admission	34.8 ± 1.8	33.5 ± 1.7	NS			
3 h	21 ± 3.4	24.2 ± 3.7	0.02	- 39.5 ± 8.7	- 27.8 ± 8.9	0.001
4 h	20.4 ± 4.6	23.2 ± 4.4	NS	- 41.3 ± 12.8	- 31 ± 11.4	0.02

*Data are presented as mean ± SD. FEV₁, PEFR, and FVC are all expressed as percentage of predicted for age, height, and weight. p Values < 0.05 were considered statistically significant.

†A negative value was considered as improvement in heart rate and respiratory rate.

17 patients in the BPV group with 16 patients in the control group (including the 3 patients withdrawn earlier from the study). Three of 17 patients (17.6%) in the BPV group required hospitalization as compared to 10 of 16 patients (62.5%) in the control group (p = 0.0134).

A subgroup analysis of patients who were hospitalized (Table 5) shows that on hospital admission their FEV₁, FVC, PEFR, and indexes of smaller airway obstruction (data not shown) were similar. Their hospital stay, however, slightly differed and lasted 4 days in the BPV group as compared to 2.55

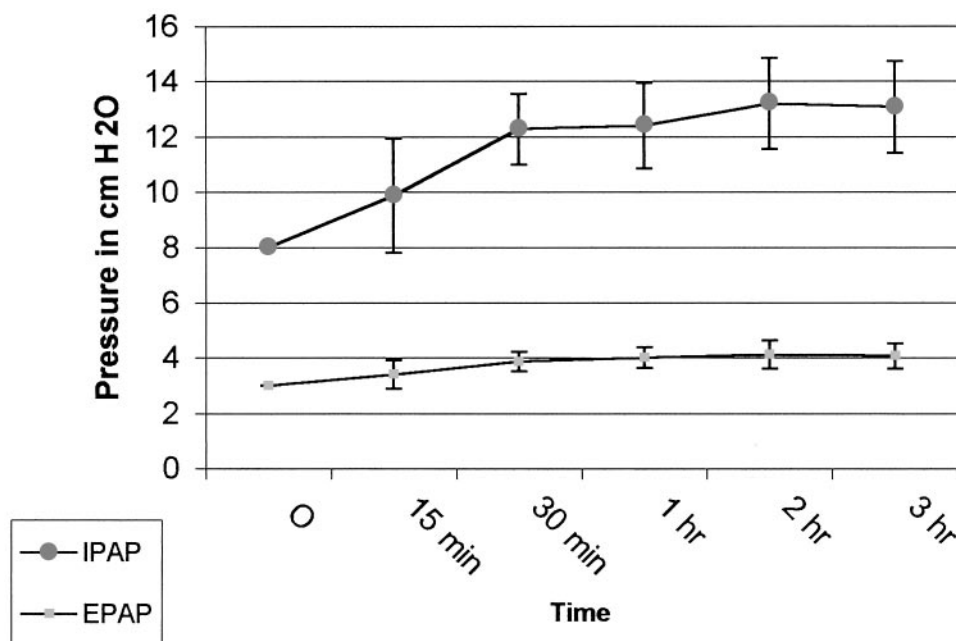


FIGURE 1. Change in inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) during 3 h of treatment in the BPV group.

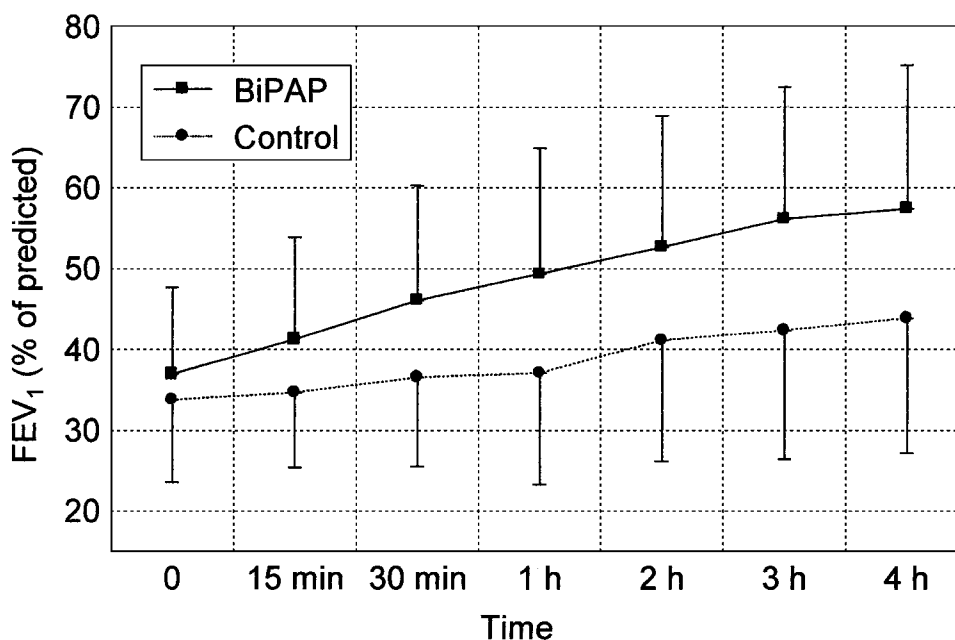


FIGURE 2. Change in FEV₁ in BPV group (BiPAP) and control group during 4 h.

days in the control group (Table 5). There was no variance for independent sample *t* test analysis; therefore, *p* value could not be calculated for this parameter. During a follow-up of 1 month after discharge from the emergency department, only one patient in each group was readmitted to the emergency department. Both were discharged after a short treatment in the emergency department and were not hospitalized.

DISCUSSION

This study shows that the use of noninvasive ventilatory support in the form of BPV in selected

patients with a severe attack of asthma can alleviate the attack faster, improve lung function test results more completely—namely FEV₁, FVC, and PEFR—and prevent hospitalizations. Although the use of noninvasive ventilation in treating respiratory failure in cardiogenic pulmonary edema and COPD has been shown to be effective,¹⁻⁷ its role in asthma has not been established.

Table 4—Characteristics of the Discharged Patients

Parameters	BPV Group	Control Group	<i>p</i> Value
Patients discharged,* No.	12	5	0.02
Stay in the emergency department, h†	5.9 ± 1.3	5.6 ± 1.3	NS
FEV ₁ on discharge‡	63.1 ± 13.4	60.8 ± 12.4	NS
PEFR on discharge‡	66.66 ± 15.8	57.4 ± 13.4	NS
FVC on discharge‡	75.4 ± 11.5	75.8 ± 16.4	NS

*After 4 h of treatment in the emergency department; *p* < 0.5 was considered statistically significant. Fisher exact test was used.

†Mean stay in the emergency department ± SD in hours; the last 4 h of that period was devoted for the study protocol.

‡Expressed as percentage of predicted (mean ± SD) for age, height, and weight.

Table 5—Characteristics of the Hospitalized Patients*

Parameters	BPV Group	Control Group	<i>p</i> Value
Patients who reached primary end points, † No.	12	3	< 0.004
Patients hospitalized, ‡ No./total	3/17	10/16	0.013
Days of hospitalization§	4 ± 0	2.5 ± 1.4	
FEV ₁ on hospital admission	24.67 ± 9.5	28.4 ± 7.63	NS
PEFR on hospital admission	22.33 ± 1.53	31.4 ± 12.9	0.057
FVC on hospital admission	35.67 ± 7.02	40 ± 10.6	NS

*Data are presented as mean ± SD unless otherwise indicated. The improvement in percentage was not significant in any of the values, hence not presented; *p* values of < 0.05 were considered statistically significant.

†Primary end point was defined as increase in FEV₁ to > 60% of predicted or an increase of at least 50% as compared to baseline value on hospital admission.

‡Three of 17 in the BPV group and 10 of 16 in the control group were analyzed with an intention to treat.

§There was no variance for independent sample *t* test in the No. of days of hospitalization; hence, a *p* value was not calculated.

||After 4 h of treatment in the emergency department.

Prior reports indicate that noninvasive ventilatory support may have a role in asthma as well. CPAP has been shown to avert bronchoconstriction in asthma induced by methacholine or histamine,^{14,15} and reduce dyspnea in acute asthmatic attacks.²¹ Patients with severe asthma attacks probably have intrinsic PEEP causing an increased work of breathing.^{19,22} The application of externally applied PEEP to offset this effect might be of value in an asthmatic attack. Wilson and coworkers²³ demonstrated that externally applied PEEP prevents exercise-induced asthma. Externally applied PEEP may also improve ventilation-perfusion mismatch and gas exchange.²⁴ Pollack and coworkers²⁵ demonstrated the superiority of administering aerosolized albuterol through a BPV circuit using a small-volume nebulizer to improve PEFr. Delivering nebulized bronchodilator with externally applied PEEP showed similar improvement in peak flow.^{26,27} Finally, Meduri and coworkers²⁸ demonstrated the efficacy of noninvasive positive pressure ventilation in improving gas exchange in asthmatic patients with acute respiratory failure.

We did not choose CPAP in our study, which is in essence a positive pressure that is applied at the same magnitude during both expiration and inspiration, and is used mainly for the purpose of improving oxygenation, which was not a significant problem in our asthmatic patients. However, during BPV application, two different levels of positive airway pressures are applied. The difference between the inspiratory and the expiratory pressures is thought to offer some advantage over a simple CPAP device; namely, it may increase tidal volume,¹⁸ decrease work of breathing, and be more comfortable for the patient. Perhaps adding another CPAP intervention arm in the study and performing a head-to-head comparison with the BPV group could have been informative with regard to preference and a better efficacy of either one modality over the other.

Our study was designed to test the hypothesis that applying BPV in addition to conventional treatment for a period of 3 h in the emergency department to patients with a severe asthmatic attack will improve lung function and prevent hospitalization. Most patients with asthma attacks presenting to the emergency department have mild disease. Only a minority of the patients have an attack severe enough to require hospitalization. Our enrollment criteria were designed to select patients with a severe attack who did not improve after initial treatment in the emergency department, and most likely would need hospitalization. Indeed, 29% of the patients who presented to the emergency department fulfilled the inclusion criteria with a mean FEV₁ of < 40%. Although four patients, two in each group, presented

with an FEV₁ of < 20%, none deteriorated to the point needing mechanical ventilation.

More patients in the BPV group reached the predetermined primary end points, and avoided secondary end points. We found a significant improvement in the BPV group in FEV₁, PEFr, and FVC, and a significant reduction in respiratory rate as compared with the control group. This effect lasted for at least an hour after the end of BPV application. The highly significant improvement in FEV₁, PEFr, and FVC that almost doubled as compared to the control group during a short treatment period of 3 h in the emergency department could not be attributed to drug treatment or patient characteristics on hospital admission; these parameters were similar in both groups. This difference can only be attributed to the addition of BPV to conventional treatment in the study group. As can be seen in Figure 2, FEV₁ improved steadily during the 3 h of treatment. This steady improvement did not coincide with the pressure increments during the 3 h of the study. As shown in Figure 1, most of the pressure increments in respiratory pressures were done during the first 30 min to 1 h; thereafter, while FEV₁ continued to improve, respiratory pressure did not change significantly. Although the investigating team could not be blinded to the randomization, the patients and the attending physicians were unaware of whether BPV or the placebo ventilation was used, adding validity to our findings.

The mechanism whereby externally applied positive pressure ventilation, in our case BPV, exerts its benefit is not fully understood. Prior studies reported improved FEV₁ and PEFr when aerosolized bronchodilators were delivered through a CPAP or BPV circuit,^{26,27} postulating that perhaps positive airway pressure could disperse the bronchodilators to more peripheral airways. Since in our study BPV application was interrupted each time to deliver aerosolized bronchodilators via a small-volume nebulizer, the larger bronchodilation achieved by adding BPV was independent of better drug dispersion.

We postulate that the favorable effect of BPV on patients with a severe asthma attack is exerted through several mechanisms. By unloading fatigued inspiratory muscles, patients may be able to reach their total lung capacity more effectively; as a consequence, the larger FEV₁ may be a reflection of starting the forced expiration at a higher lung volume than the control patients. We did not test this possibility because of the extreme difficulty in measuring total lung capacity in patients with severe obstruction, and also because the expected changes in total lung capacity would be small. Other possible mechanisms include a direct bronchodilating effect, offsetting intrinsic PEEP, recruiting collapsed alve-

oli, improving ventilation-perfusion mismatch, and reducing the work of breathing.

Although the study was blinded to the patients and the attending physicians and was placebo controlled, a limitation of the study was that we did not succeed in blinding it from the investigating team. In conclusion, noninvasive ventilatory support in the form of BPV may provide an adjuvant therapy in selected patients with a severe asthma attack, alleviate the attack faster, improve lung function and, consequently, might prevent hospitalization.

REFERENCES

- 1 Bott J, Carrol MP, Conway JH, et al. Randomized controlled trial of nasal ventilation in acute ventilation failure due to chronic obstructive airway disease. *Lancet* 1993; 341:1555-1557
- 2 Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333:817-822
- 3 Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; 339:429-435
- 4 Bersten AD, Holt AW, Vedig AE, et al. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *N Engl J Med* 1991; 325:1825-1830
- 5 Meduri GU, Turner RE, Abou-Shala N, et al. Noninvasive positive pressure ventilation via facemask: first-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest* 1996; 109:179-193
- 6 Keenan SP, Kernerman PD, Cook DJ, et al. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. *Crit Care Med* 1997; 25:1685-1692
- 7 Rasanen J, Heikkila J, Downs J, et al. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Am J Cardiol* 1985; 55:296-300
- 8 Martin JG, Shore SA, Engel LA. Mechanical load and inspiratory muscle action during induced asthma. *Am Rev Respir Dis* 1983; 128:455-460
- 9 Cormier Y, Lecours R, Legris C. Mechanisms of hyperinflation in asthma. *Eur Respir J* 1990; 3:619-624
- 10 Martin J, Powell E, Shore S, et al. The role of respiratory muscles in the hyperinflation of bronchial asthma. *Am Rev Respir Dis* 1980; 121:441-447
- 11 Buda AJ, Pinsky MR, Ingels NB Jr, et al. Effect of intrathoracic pressure on left ventricular performance. *N Engl J Med* 1979; 301:453-459
- 12 Wagner PD, Hedenstierna G, Bylin G. Ventilation-perfusion inequality in chronic asthma. *Am Rev Respir Dis* 1987; 136:605-612
- 13 Ferrer A, Roca J, Wagner PD, et al. Airway obstruction and ventilation-perfusion relationships in acute severe asthma. *Am Rev Respir Dis* 1993; 147:579-584
- 14 Wang CH, Lin HC, Huang TJ, et al. Differential effects of nasal continuous positive airway pressure on reversible or fixed upper and lower airway obstruction. *Eur Respir J* 1996; 9:952-959
- 15 Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am Rev Respir Dis* 1982; 126:812-817
- 16 Shivaram U, Donath J, Khan FA, et al. Effects of continuous positive airway pressure in acute asthma. *Respiration* 1987; 52:157-162
- 17 Lin HC, Wang CH, Yang CT, et al. Effect of nasal continuous positive airway pressure on methacholine-induced bronchoconstriction. *Respir Med* 1995; 89:121-128
- 18 Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994; 120:760-770
- 19 Aldrich TK, Hendler JM, Vizioli LD, et al. Intrinsic positive end-expiratory pressure in ambulatory patients with airways obstruction. *Am Rev Respir Dis* 1993; 147:845-849
- 20 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152:1107-1136
- 21 Shivaram U, Miro AM, Cash ME, et al. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. *J Crit Care* 1993; 8:87-92
- 22 Leatherman JW, Ravenscraft SA. Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. *Crit Care Med* 1996; 24:541-546
- 23 Wilson BA, Jackson PJ, Evans J. Effects of positive end-expiratory pressure breathing on exercise-induced asthma. *Int J Sports Med* 1981; 2:27-30
- 24 Broux R, Foidart G, Mendes P, et al. Use of PEEP in management of life-threatening status asthmaticus: a method for the recovery of appropriate ventilation-perfusion ratio. *Appl Cardiopulm Pathophysiol* 1991; 4:79-83
- 25 Pollack CV Jr, Fleisch KB, Dowsey K. Treatment of acute bronchospasm with beta-adrenergic agonist aerosols delivered by a nasal BiPAP circuit. *Ann Emerg Med* 1995; 26:552-557
- 26 Andersen JB, Klausen NO. A new mode of administration of nebulized bronchodilator in severe bronchospasm. *Eur J Respir Dis Suppl* 1982; 119:97-100
- 27 Frischknecht-Christensen E, Norregaard O, Dahl R. Treatment of bronchial asthma with terbutaline inhaled by cone spacer combined with positive expiratory pressure mask. *Chest* 1991; 100:317-321
- 28 Meduri GU, Cook TR, Turner RE, et al. Noninvasive positive pressure ventilation in status asthmaticus. *Chest* 1996; 110:767-774

A Pilot Prospective, Randomized, Placebo-Controlled Trial of Bilevel Positive Airway Pressure in Acute Asthmatic Attack

Arie Soroksky, David Stav and Isaac Shpirer

Chest 2003;123;1018-1025

DOI 10.1378/chest.123.4.1018

This information is current as of May 7, 2007

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://chestjournals.org/cgi/content/full/123/4/1018
References	This article cites 28 articles, 10 of which you can access for free at: http://chestjournals.org/cgi/content/full/123/4/1018#BIBL
Citations	This article has been cited by 8 HighWire-hosted articles: http://chestjournals.org/cgi/content/full/123/4/1018
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournals.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://chestjournals.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]