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ORIGINAL ARTICLE

Reversal of Bronchial Obstruction with Bi-level Positive Airway Pressure and Nebulization in Patients with Acute Asthma

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Jet nebulization (JN) and non-invasive mechanical ventilation (NIMV) through bi-level pressure is commonly used in emergency and intensive care of patients experiencing an acute exacerbation of asthma. However, a scientific basis for effect of JN coupled with NIMV is unclear. **Objective.** To evaluate the effect of jet nebulization administered during spontaneous breathing with that of nebulization with NIV at two levels of inspiratory and expiratory pressures resistance in patients experiencing an acute asthmatic episode. **Methods.** A prospective, randomized controlled study of 36 patients with severe asthma (forced expiratory volume in 1 second [FEV₁] less than 60% of predicted) selected with a sample of patients who presented to the emergency department. Subjects were randomized into three groups: control group (nebulization with the use of an unpressured mask), experimental group 1 (nebulization and non-invasive positive pressure with inspiratory positive airway pressure [IPAP] = 15 cm H₂O, and expiratory positive airway pressure [EPAP] = 5 cm H₂O), and experimental group 2 (nebulization and non-invasive positive pressure with IPAP = 15 cm H₂O and EPAP = 10 cm H₂O). Bronchodilators were administered with JN for all groups. Dependent measures were recorded before and after 30 minutes of each intervention and included respiratory rate (RR), heart rate (HR), oxygen saturation (SpO₂), peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and forced expiratory flow between 25 and 75% (FEF_{25–75}). **Results.** The group E2 showed an increase of the peak expiratory flow (PEF), forced vital capacity (FVC), FEV₁ ($p < 0.03$) and FEF_{25–75} ($p < 0.000$) when compared before and 30 minutes after JN+NIMV. In group E1 the PFE ($p < 0.000$) reached a significant increase after JN+ NIMV. RR decreased before and after treatment in group E1 only ($p = 0.04$). **Conclusion.** Nebulization coupled with NIV in patients with acute asthma has the potential to reduce bronchial obstruction and symptoms secondary to augmented PEF compared with nebulization during spontaneous breathing. In reversing bronchial obstruction, this combination appears to be more efficacious when a low pressure delta is used in combination with a high positive pressure at the end of expiration.

Keywords acute asthma, aerosoltherapy, nebulization, bronchodilators, inhalation, respiratory insufficiency

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by reversible airway obstruction and presents clinically with a history recurrent episodes of wheezing, dyspnea and cough (1). Severe airway obstruction contributes to airflow resistance and reduced flow rates on expiration, premature airway closure, pulmonary hyperinflation and intrinsic positive end-expiratory pressure (i.e., auto-PEEP) and, in turn, increased work of breathing. If the symptoms are sufficiently severe, acute respiratory failure can ensue (2–4).

Inhalation therapy to administer pharmacological agents can be effective in relieving symptoms (1, 5–7). β_2 -agonists are the medications of choice to reverse bronchospasm and

improve lung function during an exacerbation and their use has been associated with reduced hospitalization (1, 3, 4). Many patients with asthma use the emergency department as the sole source of asthma care (8–9).

Other forms of treatment are being investigated to mitigate asthma symptoms. Non-invasive ventilation (NIV) has shown some promise in treating acute and chronic respiratory insufficiency (10–13). NIV is a mode of ventilatory support that does not require an artificial airway, thus, many of the complications of airway intubation can be avoided (14). In the management of acute respiratory failure, two pressure levels of NIV are typically administered (13, 15). This procedure involves two independent and adjustable levels of positive pressure, specifically, a level of inspiratory airway pressure (IPAP), and a level of expiratory positive airway pressure (EPAP) (13, 16).

The few studies in the literature investigating the use of nebulization with non-invasive positive pressure ventilation (2, 11, 12) have been controversial (13, 16, 17). In our group, França et al. (17) analyzed the deposition pattern of radioaerosol with scintigraphy during nebulization with NIV when administered to healthy volunteers. In these subjects, radioaerosol deposition was not different compared with the group that used only nebulization.

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In a randomized study, Soroksky et al. (13) examined people with asthma who came to emergency rooms. Subjects who used NIV had higher forced expiratory volume in the first second (FEV_1), a lower respiratory rate, and less need for intubation compared with subjects who used conventional nebulization.

Given conflicting findings in the literature related to relieving airway resistance in patients who experience an acute asthmatic episode, this study compared the effect of jet nebulization administered during spontaneous breathing with that of nebulization with NIV at two levels of inspiratory and expiratory pressures.

METHODS

Study design and patients. We conducted a prospective randomized controlled study of 36 patients clinically diagnosed with severe asthma, between 18 and 65 years of age, with reversible bronchial obstruction established objectively with bronchodilator therapy (pre- and post- EV_1 within 10%). This study was performed in the emergency room.

Criteria for inclusion into the study were patients with an FEV_1 less than 60% of predicted, asthma history for at least one year, and current asthma crisis lasting less than 7 days. Patients were excluded from the study if they smoked, used anti-inflammatory drugs, had chronic obstructive pulmonary disease, were hemodynamically unstable (defined as having a heart rate over 150 bpm or systolic pressure below 90 mmHg), or had congestive heart failure, altered consciousness, facial deformity or were pregnant.

This study received approval from the institutional Ethics and Human Research Committee. Successive patients admitted to the emergency room were invited to participate in the study. They were informed about the study and provided signed consent.

Study protocol. A clinical assessment was performed and spirometry was conducted (Spirometer Vitalographic 2110; Kansas, USA), specifically, forced vital capacity measurement (FVC), peak expiratory flow (PEF), FEV_1 , and forced expiratory flow ($FEF_{25-75\%}$). These were expressed as a proportion of each subject's predicted values (18). In addition, respiratory rate (RR), heart rate (HR), oxygen arterial saturation (pulse Oxymeter – Morrya/model 1001; São Paulo, Brazil), and arterial blood pressure (Pressure Manometer Welchalln, DS 44-11CB, USA) were recorded.

Subjects were randomized into three groups: control group (nebulization with the use of an unpressured mask), experimental group 1 (nebulization and non-invasive positive pressure with IPAP = 15 cm H₂O and EPAP = 5 cm H₂O) and experimental group 2 (nebulization and non-invasive positive pressure with IPAP = 15 cm H₂O and EPAP = 10 cm H₂O).

The nebulization solution consisted of 2.5 mg of fenoterol bromidate, 0.25 mg of ipratropium bromide, and 4 mL of physiological saline (NaCl at 0.9%). The nebulizer used was NS ST3, of NS, (São Paulo, Brazil) with particles inhaled in the order of 0.9 microns. The subject was positioned seated upright. Inhalation was performed over 15 minutes with the use of a silicone face mask. Before the study, patients were oriented and allowed to adapt to the mask. They were instructed in standardized slow deep diaphragmatic breathing with a post-inspiratory pause.

Control group (standard nebulization). The control group consisted of 12 patients (mean age 40.7 ± 13.91 years), and 66.6% were women. The patients inhaled the aerosol through the jet nebulizer with oxygen flow at 8 L/min in the standard manner used clinically.

Experimental groups (nebulization with bi-level non-invasive ventilation). Experimental group 1 included 12 patients (mean age 33.7 ± 13.91 years) and consisted of 66.6% women. Experimental group 2 included 12 patients (mean age 41.0 ± 15.87 years) and also consisted of 66.6% women. The patients in these groups performed nebulization similar to the control group while maintaining the same particle generation flow. However, the experimental groups were nebulized while receiving NIV, specifically, the BiPAP ventilator (Model Synchrony of Respironics, Murraysville, PA). The bi-level ventilator was connected to the nebulizer through a T-tube. The selected inspiratory and expiratory airway pressures were established: 15 cm H₂O and 5 cmH₂O for experimental group 1 and 15 cm H₂O and 10 cm H₂O for experimental group 2.

Outcome measurements. Spirometric testing was conducted before and after nebulization with three repeated trials performed with a 1-minute interval between trials. Based on the standards of the American Thoracic Society, the inclusion criterion for an acceptable trial is less than 0.2 L difference across successive trials. The recorded value was the best of the three repeated trials.

In addition, RR, HR, and peripheral arterial oxygen saturation (based on SpO_2 estimated with pulse oximeter) were recorded before, during, and after inhalation based on three measures of each variable between 1-minute intervals.

Statistical analysis. The Kolmogorov-Smirnov test was used to analyze the distribution of the variables and the Levene test was used to evaluate the homogeneity of the data. The data were analyzed with analysis of variance (ANOVA) to compare the treatment effect among the groups, and the Tukey HSD *pos-hoc* test was selected *a priori* to analyze differences. Alpha was set at 0.05.

RESULTS

The characteristics of the patients (anthropometric and spirometric data) appear in Table 1. Experimental group 1 (assigned an IPAP of 15 cm H₂O and an EPAP of 5 cm H₂O) had a lower RR ($p = 0.04$) 30 minutes after treatment compared with before treatment. However, no differences were observed for either HR or SpO_2 (Figure 1).

In comparison of the control group and experimental group 2 (assigned an IPAP of 15 cm H₂O and an EPAP of 10 cm H₂O) no changes in HR, RR and SpO_2 were observed 30 minutes after treatment compared with before treatment.

In comparison of the effect of nebulization in the control group with the experimental groups using nebulization and NIV, experimental group 2 had a higher PEF ($p < 0.03$), FVC ($p < 0.03$), FEV_1 ($p < 0.03$) and $FEF_{25-75\%}$ ($p < 0.00$), whereas for experimental group 1, only the PEF ($p < 0.04$) was higher (Figure 2).

TABLE 1.—Baseline characteristics of patients with severe asthma.

Parameters	Control Group (n = 12)	Experimental Group 1 IPAP = 15 / EPAP = 5 cmH ₂ O (n = 12)	Experimental Group 2 IPAP = 15/ EPAP = 10 cmH ₂ O (n = 12)	p Value
Age (years)	40.75 ± 13.97	33.75 ± 13.99	41.00 ± 15.88	NS
Men/Women	4/8	4/8	4/8	
FVC(%Predicted)	41.26 ± 17.35	42.75 ± 20.48	49.99 ± 19.09	NS
FEF ₁ (%Predicted)	35.51 ± 12.26	40.65 ± 20.50	42.75 ± 21.39	NS
PEF (%Predicted)	22.37 ± 8.64	32.41 ± 16.53	34.95 ± 20.38	NS
FEV _{25–75} (%Predicted)	25.60 ± 11.55	26.03 ± 13.58	39.33 ± 19.89	NS
HR (bpm)	100.42 ± 11.72	100.17 ± 14.44	97.75 ± 16.84	NS
RR (ipm)	21.58 ± 5.71	25.58 ± 7.16	26.58 ± 7.65	NS
SpO ₂ %	91.25 ± 2.13	94.33 ± 3.91	94.00 ± 5.67	NS

Values are the mean ± SD (standard deviation).
NS = not significant.
Forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory volume in the first second (FEV₁) and forced expiratory flow (FEF_{25–75}%) Heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO₂).

DISCUSSION

Our findings support that NIV with bi-level pressure and nebulization administered to patients experiencing acute asthmatic episodes can relieve the signs of bronchial obstruction associated with respiratory distress and increased work of breathing, as evidenced by lowering RR and improving pulmonary function, i.e., greater pulmonary volumes, capacities and flows.

NIV used in the management of acute respiratory failure such as acute chronic obstructive pulmonary disease and pulmonary edema has been reported to be clinically effective (11, 12, 15, 19), but few studies have reported the use of this therapy for acute bronchospasm in patients with asthma (11, 13, 16, 20–22). The failure of inhalation therapy in the management of acute exacerbations of asthma has been attributed to inadequate deposition of medication (23).

Our results showed higher PEFs in the experimental groups using nebulization and NIV compared with conventional nebulization used by the control group. For other spirometric values, greater values were observed for FVC, FEV₁ and FEF_{25–75} in experimental group 2 that used NIV with IPAP

= 15 cm H₂O and EPAP = 10 cm H₂O. Our results compare with those reported by Pollack et al. (16) who studied 100 patients with acute bronchospasm and a history of asthma in an emergency room setting. They observed greater PEFs in experimental group 1 that used NIV with IPAP = 10 cm H₂O and EPAP = 5 cm H₂O) with nebulization of adrenergic-β₂ agonists. However, these investigators did not establish whether the improved PEF resulted from the NIV support pressure, the drug distribution, a drug-NIV interaction, or some combination.

Fauroux et al. (23) studied ventilation in children with cystic fibrosis. They analyzed scintigraphy to determine the extent of aerosol deposition associated with pressure support ventilation (PSV) and positive end expiration pressure (PEEP) with a PSV of 8 to 10 cm H₂O. They reported an increase of 30% in aerosol deposition in the lungs with PSV and PEEP with no deposited particles in the proximal airways.

In a randomized study, Soroksky et al. (13) compared two groups of patients with acute severe asthma in the emergency room. One group used only NIV up to 4 hours and the other group underwent the conventional treatment (nebulization

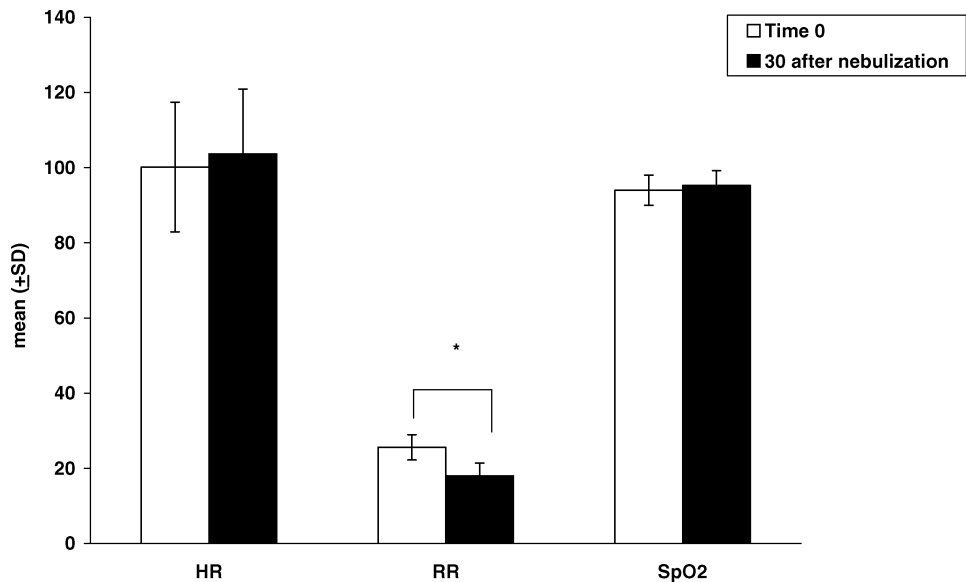


FIGURE 1.—Comparison (mean±SD) of the heart rate (HR), respiratory rate (RR), and SpO₂ in the experimental group 1 before and after 30 minutes nebulization and noninvasive ventilation NIV (**p* = 0.04).

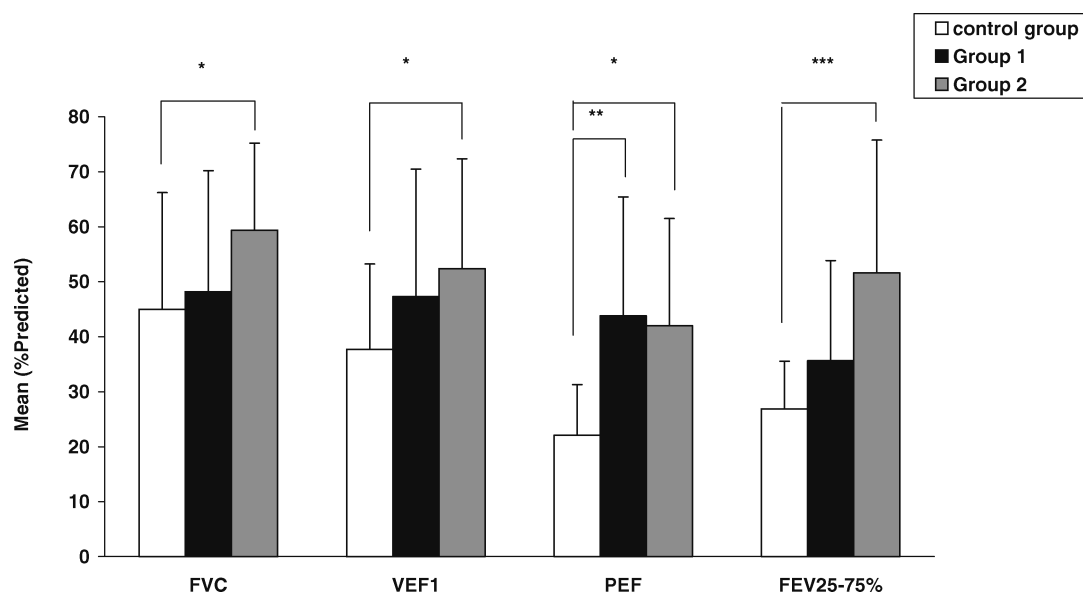


FIGURE 2.—Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), peak expiratory flow (PEF), and forced expiratory volume in 25–75% ($FEV_{25-75\%}$) between the control group and experimental group 1 (IPAP = 15 cm H_2O and EPAP = 5 cm H_2O) and experimental group 2 (IPAP = 15 cm H_2O and EPAP = 10 cm H_2O); (* p = 0.03, ** p = 0.04, *** p = 0.0001).

with bronchodilators). Pulmonary function was reported to improve, specifically, greater FVC and FEV_1 , relief of respiratory discomfort, and less need for hospitalization in patients using NIV. These results were attributed to effective direct bronchodilation, intrinsic PEEP compensation, recruitment of collapsed alveoli, and improved ventilation perfusion matching and lower respiratory work associated with bi-level ventilation.

In addition to the hypothesis proposed by Pollack et al. (16), we propose that pulmonary volumes and capacities are improved in the group using nebulization with NIV and an IPAP = 15 cm H_2O and an EPAP = 10 cm H_2O , as a result of improved alveolar recruitment, which may reflect improved PEEP and patency of peripheral airways. In turn, this could augment collateral pulmonary ventilation in obstructed pulmonary regions (24). In addition, the lower pressure delta in this group, i.e., ΔP = 5 cm H_2O (pressure difference between IPAP and EPAP), likely favored laminar air flow and greater drug deposition by sedimentation in peripheral airways.

In experimental group 1 that used nebulization with NIV with an IPAP = 15 cm H_2O and an EPAP of 5 cm H_2O we did not observe improved FVC, FEV_1 , and $F_{25-75\%}$. These results may be explained by the lower EPAP and reduced collateral ventilation. The higher pressure delta, i.e., ΔP = 10 cm H_2O , may also have favored turbulent air flow and particle deposition in the oropharynx, trachea, and large upper airways, which leads to less drug deposition within the affected airways.

Not only PEF, but FEV_1 as well, are useful standard measures of pulmonary function (10, 25). Although FEV_1 did not change, greater PEF was observed. PEF is more effort dependent than FEV_1 and for this reason serves as a good indicator of patient cooperation in the final phase of expiration. Because of this, the degree of airway obstruction may be overestimated.

Collateral ventilation may augment pulmonary volumes as well as function as a mechanism for mucociliary clearance (21, 26, 27) and hence, promote secretion clearance toward the central bronchioles (21, 28). Maintenance of airway patency may be explained by positive NIV pressure as suggested by Soroksky et al. (13). The association of these two factors could account for augmented pulmonary function in experimental group 2. However, other studies are needed to examine specific changes in mucociliary clearance.

Other studies do not support these findings. Dollovich et al. (29) studied nine individuals with stable chronic bronchitis and observed that breathing using intermittent positive pressure (Bird Mark 10 with an inspiratory pressure of 15 cm H_2O) and nebulization did not result in greater deposition of radioaerosol throughout the lungs. This was attributed to the flow rate at the onset of inspiration that strongly affects the deposition of aerosol particles in the oropharynx, trachea, and large airways. In turn, this would reduce bronchodilator efficacy in relieving bronchial obstruction.

In another recent study by our group, França et al. (17) examined pulmonary radioaerosol particles in the lungs with scintigraphy in 13 healthy subjects. The effect of jet nebulization during spontaneous breathing was compared with nebulization and NIV. Substantial aerosol deposition in the lungs was observed in subject using nebulization without NIV. The high inspiratory flow associated with bi-level ventilation produced a large deposition of particles in the upper airways.

Comparison of our results with those of Dollovich (29) and França et al. (17) who reported that the combination of nebulization with NIV was less effective is not viable because the groups studied by these investigators did not have asthma. In the study by Dollovich et al. (29), patients were screened based on spirometry with less reversal of bronchial

obstruction compared with acute asthma. In addition, the ventilator mode used by Dollovitch et al. (29) was intermittent positive pressure breathing (IPPB), which is not as comfortable as the PSV mode used in the bi-level ventilation, and lastly, IPPB exerts pressure only in the inspiratory phase of respiration.

In the lungs of people with asthma, this would depend on the difference of the inspiratory flow through the airway, as well as, the different degrees of obstruction. Thus, this factor may contribute to heterogeneity in drugs deposition and concentrate in areas that less affected by the disease. In general, patients with extreme bronchoconstriction, drugs are deposited predominately in the central airways during nebulization with spontaneous respiration. When associated with NIV, nebulization appears to open airways and in turn areas of atelectasis. Consequently, the peripheral airways have improved aerosol deposition.

In our study, nebulization and NIV lead to a lower RR compared with standard nebulization (spontaneous breathing), which may have contributed to greater inspiratory flow provided by bi-level NIV. Thus, RR was substantially lower in experimental group 1, which was exposed to a large delta pressure and consequently a higher inspiratory flow. However, the tendency toward a lower RR in experimental group 2 may be explained by the inspiratory flow that resulted from a lower pressure delta required to perform NIV.

In addition, when comparing HR across the three groups no differences were observed, which is consistent with the findings of Soroksky et al. (13).

Numerous benefits related to use of non-invasive ventilation have been reported and these include improved exercise and physiotherapy tolerance, a decrease in PaCO_2 , a reduction in the rate and severity of respiratory exacerbations, and attenuated decline of lung function. Some centers report improved quality of sleep, quality of life, and survival (30).

NIV has been compelling clinically because of its relative ease of use and minimal side effects compared with invasive ventilation modes. However, potential problems related to the clinical use of NIV have focused on individual tolerance to this ventilatory mode and interface with the patient. Abdominal distension and barotraumas have also been reported (30). On balance, it appears that NIV should be exploited wherever possible when mechanical ventilation is indicated.

Although the risks of NIV are minimal, we took special precautions in our study. First, the examiner held the mask such that it was maximally comfortable but secure for each subject during the procedure. In addition, the patient was cued to breathe through the nose to minimize abdominal distension. Finally, consistent with guidelines in the literature our pressures were well within the limits that have been reported in cases of barotraumas.

With respect to the potential for barotrauma, there is no literature to the best of our knowledge related to the occurrence of barotraumas in people with asthma who were receiving NIV. The limit of a plateau pressure of 30 cm H_2O has been recommended to avoid barotrauma. In our study, IPAP was set at a maximum of 15 cm H_2O , which is our view effectively minimized any risk to the patient (31).

In conclusion, nebulization coupled with NIV in patients with acute asthma has the potential to reduce bronchial obstruction and symptoms secondary to augmented PEF compared with nebulization during spontaneous breathing. In reversing bronchial obstruction, this combination appears to be more efficacious when a low pressure delta is used in combination with a high positive pressure at the end of expiration, given both pulmonary volumes and capacities were increased in this condition.

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