

Failure of noninvasive ventilation in adult patients with acute asthma exacerbation

Mabrouk Bahloul¹, Kamilia Chtara¹, Rahma Gargouri¹, Ali Majdoub², Anis Chaari¹, Mounir Bouaziz¹

¹Service de Réanimation médicale, CHU Habib Bourguiba, 3029 Sfax, Tunisie; ²Hospital Tahar Sfar de Mahdia, Service Anesthésie Réanimation Chirurgicale, Mahdia, Tunisie

Correspondence to: Mabrouk Bahloul, MD. Professeur En Réanimation Médicale, Service de Réanimation médicale, Hôpital Habib Bourguiba, Route el Ain Km 1, 3029 Sfax, Tunisie. Email: bahloulmab@yahoo.fr.

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We read with interest the article entitled “Use of noninvasive ventilation in adult patients with acute asthma exacerbation” by Ganesh *et al.* (1). The authors have concluded that non-invasive ventilation (NIV) can be used initially in patients with acute asthma exacerbation, as it was associated with shorter duration of hospital stay and can prevent the morbidity of mechanical intubation. In this regard I would like to make the following observations.

In their study, Ganesh *et al.* (1) found that NIV failed only in 19% of all included patients (n=98). Patients who failed NIV were found to have longer duration of hospital stay (6.8 *vs.* 3.9 days, P=0.016) and longer intensive care unit stay (4 *vs.* 0.9 days, P=0.002). Use of inhalers and other medications was not found to significantly affect the rate of failure of NIV. However, the analysis of the included population leads to the following remarks.

First, the included population seems more likely a COPD than asthmatic population. In fact all clinical and biological characteristics: age of the included patients (48 *vs.* 50 years; P=0.58), history of smoking (78.5 *vs.* 78.9 pack-year), use of inhaled corticosteroids (50.6% *vs.* 42.1%), history of intubation and invasive mechanical ventilation (46.8 *vs.* 42.1) and bicarbonate serum level (27.3 *vs.* 28.3 mmol/L) were more suggestive of COPD rather than asthma. In this specific condition (COPD patients) noninvasive positive-pressure ventilation (here after, noninvasive ventilation) reduces the need for endotracheal intubation and mortality among patients with acute exacerbations of chronic obstructive pulmonary disease (2). The physiological effects of noninvasive ventilation consist on decreasing the load of work for breathing as well as

improving gas exchange (2). Second, in successful NIV group, the FiO₂ used was 20.42%; standard deviation (SD); lower and upper value; and median value were not mentioned. I would ask Ganesh *et al.* (1) why they used low FiO₂ in order to treat a group of patient with respiratory failure requiring NIV (considered as asthma exacerbation). In fact, the included population was characterized by a severe impairment of gas exchange with a severe hypercapnia (54.4 mmHg) meaning that these patients had severe asthma attack (3). In fact, an asthma attack is usually characterized by compensatory hyperventilation inducing hypocapnia with respiratory alkalosis. Marked hypercapnia is synonym of severe asthma attack with respiratory failure requiring mechanical ventilation (3). Third, we would ask Ganesh *et al.* (1) what was the objective of NIV in their study? Is it mandatory ventilation? Supportive ventilation? prophylactic ventilation? or inhalator ventilation?

NIV has proven benefits in preventing invasive mechanical ventilation in acute exacerbation of COPD, acute pulmonary edema, as well as preventing reintubation of extubated COPD patients (2,4). However, its use during asthma attack is also controversial.

Asthma and COPD are the most prominent obstructive lung diseases and affect millions of people with an increasing incidence (5). However, there is some difference between COPD and asthma. In COPD disease, both the distal airways and lung parenchyma are affected by the disease and airflow limitation is progressive (5). However, in asthma only the airways are affected and, the remodeling process involves the whole bronchial tree, from large to small conductive airways (5).

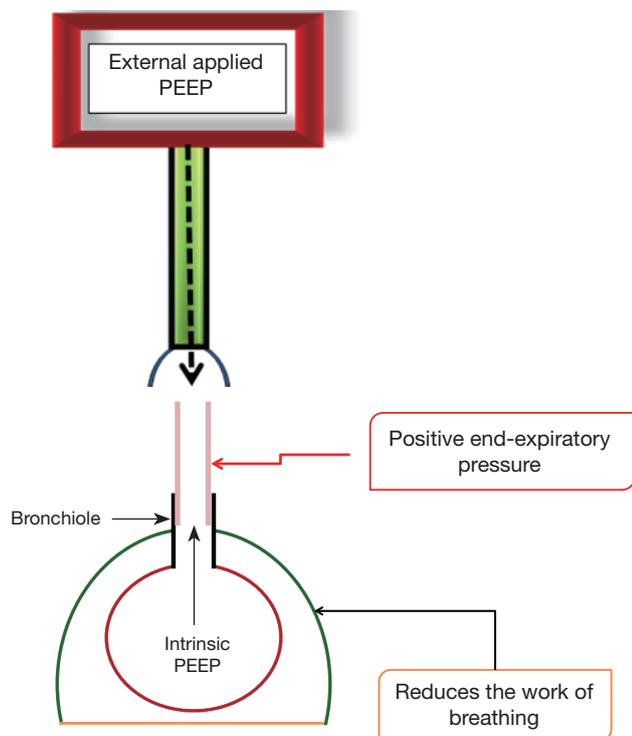


Figure 1 Positive effects of NIV in COPD. External PEEP prevents lung collapse (bronchioles and alveolar collapse) and can counterbalance intrinsic PEEP. Moreover, externally applied PEEP and inspiratory positive airway pressure reduce the work of breathing. PEEP, positive end expiratory pressure; NIV, non-invasive ventilation; COPD, chronic obstructive pulmonary disease.

As a result, applying external positive end expiratory pressure (PEEP) to offset intrinsic PEEP might be of value in patients with COPD exacerbation. In fact, PEEP may improve ventilation/perfusion mismatch and gas exchange abnormalities, recruit collapsed alveoli, and reduce the work of breathing. Moreover, Respiratory and/or limb muscle dysfunction, which are frequently observed in chronic obstructive pulmonary disease (COPD) patients, contribute to their disease prognosis irrespective of the lung function (6,7). As consequence, pressure support on ICU ventilators or its equivalent inspiratory positive airway pressure (IPAP) on an external noninvasive positive pressure ventilation (NPPV) circuit has an additional advantage of reducing the respiratory load of work and lowering muscle fatigue (*Figure 1*).

In asthma, the remodeling process involves the whole bronchial tree, from large to small conductive airways. In severe asthma, airway wall thickness

was increased by between 50% and 230% (6). These changes result from airway inflammation with epithelial cell alterations, subepithelial fibrosis, submucosal gland hyperplasia, increased airway smooth muscle mass, and increased airway vascularization (8). These changes contribute to thickening airway walls and, consequently, airway narrowing, bronchial hyper-responsiveness, airway edema and mucous hypersecretion (8). Additionally, in acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly and increases airway obstruction. As consequence, during an asthma attack the patient may have difficulty coping with NIV, for several reasons.

First, severely dyspneic patients may not be cooperative, might resist to coordinate their breathing with the NIV machine and might therefore find NIV uncomfortable. Mucus production is a feature of severe acute asthma, and NIV can intensify sputum retention; and bronchial hyper-reactivity may be increased by the high inspiratory flow and airway dryness associated with NIV (*Figure 2*).

Second, the use of positive pressure in asthmatic patients can be associated with increased risk of barotraumas (9). Third, application of extrinsic PEEP in severe asthma could contribute to further dynamic hyperinflation. The combination of relative hypovolemia and excessively applied extrinsic PEEP may decrease venous return and expose the patient to the risk of hemodynamic compromise. Fourth, technical issues of NIV in severe acute asthma have not been clarified (bi-level pressure ventilation or continuous positive airway pressure?).

Fifth, asthma is characterized by reversible airway obstruction. In most patients, control of disease activity is easily achieved and in a small minority of patients, asthma may be fatal and/or requiring mechanical ventilation (10). Finally, there is limited evidence to recommend use of noninvasive positive-pressure ventilation in patients with respiratory failure from severe asthma exacerbations. In fact, only five randomized controlled trial (RCT) (11-15) including only a total of 206 patients were published and were subsequently analyzed in a recent meta-analysis (16). The review of these trials highlighted the paucity of data that exist to support the use of NIV status asthmaticus patients. In fact, no benefit was found when examining the primary outcomes—mortality and intubation rates—in patients who received NPPV. Regarding endotracheal intubation as primary outcome, there were two studies (14,15) that contributed data: two intubations were

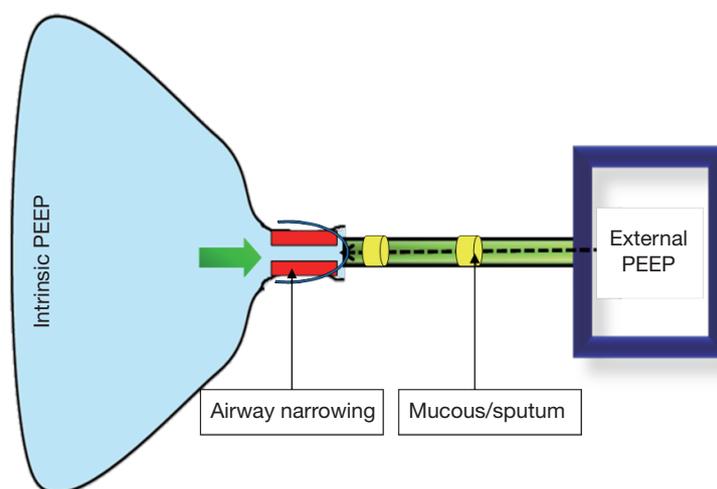


Figure 2 Effects of NIV in severe asthma. Remodeling changes contribute to thickening of airway walls and, consequently, lead to airway narrowing, bronchial hyper-responsiveness, airway edema and mucous hypersecretion. Additionally, in acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly and increases airway obstruction. Finally, NIV can intensify sputum retention, and bronchial hyper-reactivity may be increased by the high inspiratory flow. PEEP, positive end expiratory pressure; NIV, non-invasive ventilation.

needed in 45 participants on NPPV and no intubations in 41 control patients with no evidence of an effect between groups [risk ratio (RR), 4.48; 95% CI, 0.23–89.13]. There were no deaths in either of these studies. Length of hospital stay was reported in two studies. Though meta-analysis was not possible. Hospitalization was reported in one small study (15), in which there were three admissions out of 17 on NPPV and 10 admissions out of 16 in control patients (RR, 0.28, 95% CI, 0.09–0.84). However, in this last study (15), although the study was blinded to the patients, a limitation of the study was that investigators did not succeed in blinding it from the investigating team. Regarding, the treatment failure, two studies reported on treatment failure (14,15) with 45 participants in the intervention group and 41 in the control. Overall, no statistically significant benefit was identified for this outcome on meta-analysis (RR, 0.73; 95%, CI 0.21–2.53).

We concluded that, there is limited evidence to recommend use of noninvasive positive-pressure ventilation in patients with respiratory failure from severe asthma exacerbation. Hence, this treatment remains controversial despite its continued use in current clinical practice. Larger, prospective RCTs of rigorous methodological design is needed to clarify when, where and why a trial of NIV may be attempted in severe asthma attack.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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