Noninvasive Ventilation in Severe Acute Asthma? Still Far From the Truth

Despite the continuous improvement in the therapeutic strategy for asthma, there is still a subset of asthma exacerbations—severe acute asthma—that still requires access to the emergency department and, eventually, hospitalization.[1-3] It's estimated that approximately 5–10% of asthmatic patients experience a severe acute asthma episode in a given year, and that there are approximately 2 million emergency department visits and 500,000 hospital admissions yearly, which leads to a corresponding consumption of health-care resources.[4] Furthermore, even with the implementation of the optimized standard medical treatment (ie, medical and oxygen therapy), approximately 10% of individuals admitted to the hospital for severe acute asthma still go to the intensive care unit (ICU).[5] On the other hand, it's estimated that approximately 2–20% of medical ICU admissions are attributed to severe acute asthma.[6,7] Therefore, endotracheal intubation and conventional mechanical ventilation are deemed necessary in up to one third of the severe-acute-asthma patients admitted to the ICU (approximately 2–20 patients per year). Mortality as high as 27% has been reported in invasively ventilated patients,[6,8] given the likelihood of life-threatening intubation-associated complications in severe acute asthma (eg, barotrauma, cardiovascular collapse, cardiac arrhythmia, acute coronary syndromes, atelectasis, and pneumonia).[3,9,10]

SEE THE ORIGINAL STUDY ON PAGE 536

Within this scenario—patients arriving in the emergency department for severe acute asthma—clinicians wonder if there is a way to: accelerate the resolution of the dyspnea and bronchial obstruction; reduce the rate of hospitalization and ICU admission; and decrease the need for intubation and thus avoid its complications. In other words, the questions are: Is a therapy available, in addition to the standard medical treatment, that can prevent the quick clinical physiological deterioration that can lead to intubation in the course of the asthma attack? Maybe noninvasive ventilation (NIV)—an effective technique of ventilatory support that does not need an invasive interface (ie, endotracheal tube)—is a useful option in such kind of patients? And if it is, why, when, and where should NIV be applied in severe acute asthma?

Is There a Rationale for Noninvasive Ventilation in Severe Acute Asthma?

Since the end of the 19th century[11] a large amount of experimental data has been accumulated in favor of the use of NIV in severe acute asthma, administered with either continuous positive airway pressure (CPAP) or different inspiratory and expiratory pressures. Physiological studies have demonstrated their advantageous effects on several functional abnormalities occurring during the asthma attack: overload of respiratory muscles,[12,13] methacholine and exercise-induced bronchial hyperreactivity,[14,15] increased airway resistance,[16-20] atelectasis from mucus plugs,[21] ventilation-perfusion mismatch,[22] gas-exchange impairment,[20,23,24] and hemodynamic consequences.[25,26] It has been also shown that CPAP and/or NIV augment the response to bronchodilators, probably thanks to a better lung distribution of nebulized drugs (Table 1).[15,27,28]

Given the robust evidence for NIV to treat episodes of severe chronic obstructive pulmonary disease (COPD) decompensation leading to hypercapnic acute respiratory failure (ARF),[29] the rationale for NIV in severe acute asthma is based also on the large physiopathologic similarities between asthma attack and COPD exacerbation.[30] The major physiologic changes in severe acute asthma are associated with the onset or worsening of air-flow limitation, which results from bronchospasm, mucosal edema, and mucus hyper-production, triggered by bronchial flogosis and hyper-responsiveness. Like in COPD exacerbation, the increased airways resistance lengthens the exhalation time required to empty the lung, producing air trapping (ie, dynamic hyperinflation with intrinsic positive end-expiratory pressure) and a reduced lung elastic recoil. Furthermore, the capability of the diaphragm to generate pressure is impaired by the disadvantageous mechanical properties due to a breathing pattern shifted to higher lung volumes. Similar to a COPD exacerbation, the combination of increased work of breathing and inefficient ventilation during severe acute asthma may precipitate respiratory muscle fatigue and pump failure if these conditions persist, with the consequent need for a mechanical ventilatory support.[1,3,31]

Substantial physiological data have shown that NIV efficiently unloads respiratory muscles in COPD exacerba-

Table 1. Favorable Physiologic Effects of Noninvasive Ventilation in Severe Acute Asthma

Abnormality	Corrective Effect	Type of NIV
↑ Work of breathing	↓ intrinsic PEEP	CPAP, NIV
	↓ resistive load	NIV
↑ Bronchial hyper-reactivity	↓ exercise-induced bronchoconstriction	PEEP
	↓ methacholine-induced bronchoconstriction	CPAP
↑ Airway resistance	↑ β_2-agonist-induced bronchodilation	PEP, CPAP, PEEP, NIV
Atelectasis from mucus plugging	Collateral re-inflation	PEEP, CPAP
Gas-exchange impairment	↓ ventilation-perfusion mismatch	PEEP
	↑ P_{aO_2}	NIV
	↓ P_{aCO_2}	
	↑ pH	
Pulsus paradoxus	↓ negative inspiratory intrathoracic pressure	CPAP

NIV = noninvasive ventilation
CPAP = continuous positive airway pressure
PEP = positive expiratory pressure therapy
PEEP = positive end-expiratory pressure

tion, by reducing the diaphragmatic effort and by counterbalancing the dynamic hyperinflation (ie, intrinsic positive end-expiratory pressure), which benefits the breathing pattern and pulmonary gas exchange.[32,33] This translates into a significant improvement in important clinical outcomes (rate of intubation and mortality, ICU and hospital stay) when NIV is applied to treat acute ventilatory failure in COPD exacerbation, thanks to the prevention of intubation-associated complications.[29,30] As a matter of fact, NIV is an effective alternative to—or even a tool to prevent—intubation in patients with severe COPD exacerbation who do not satisfactorily respond to the maximized standard medical treatment.

What Are the Goals for Noninvasive Ventilation in Severe Acute Asthma?

Time is a crucial point when the clinician has to understand the goals that may be achieved by applying NIV to acutely decompensated patients.[34] Theoretically, NIV may be applied with different aims in the time-course of an episode of acute bronchoconstriction:

- Alternative to intubation in patients with severe ARF who have failed a trial of standard medical treatment (ie, "mandatory ventilation")
- To prevent intubation in patients with mild-to-moderate ARF who do not need immediate ventilatory support (ie, "supportive ventilation")
- To prevent ARF in patients who do not have substantial impairment of gas exchange (ie, "prophylactic ventilation")
- To accelerate bronchodilation in patients who do need mechanical ventilation (ie, "inhalator ventilation") (Fig. 1)

In the *COPD exacerbation's model*, the earlier the NIV is applied, the higher the chance of success, whereas there is a greater failure rate (ie, intubation) in the later and more severe phases of the acute decompensations.[34] On the other hand, treating a milder COPD exacerbation with NIV augments the risk of useless over-treatment and unjustified consumption of resources. Moreover, patient adherence to NIV is poor in less dyspneic patients, who may do well only with the standard medical treatment.[35]

If we apply the binomial "timing-goals of NIV" to the *severe acute asthma model*, we have to consider some important differences from COPD exacerbation. Generally speaking, an asthma attack is not characterized by marked arterial desaturation or hypercapnia until very late in a life-threatening episode. In the early phases, when a mild isolated hypoxemia ensues, the compensatory hyperventilation sustains hypocapnia with respiratory alkalosis. Consequently, the finding of normocapnia in severe acute asthma should be viewed as an "alarm sign" of the impending unbalance between respiratory muscle force and mechanical load, potentially evolving to pump failure. Hypercapnia, which occurs in 10–26% of the cases presenting to the emergency department, is the expression of decompensated ventilatory failure and is associated with greater airway obstruction, higher respiratory rate, and pulsus paradoxus, compared to non-hypercapnic status. A quiet chest on auscultation, inability to talk, and cyanosis sug-

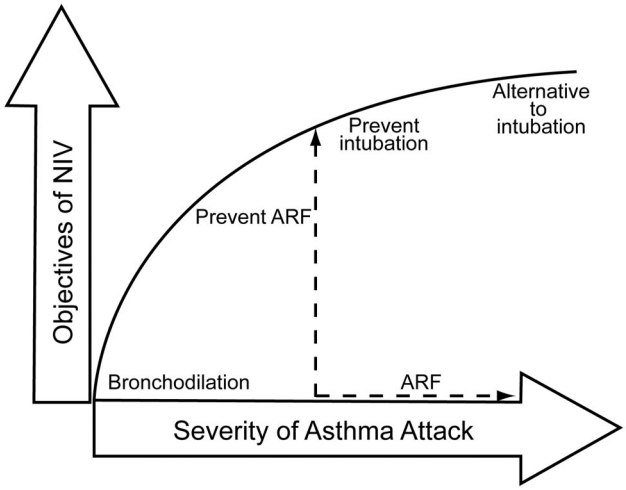

Fig. 1. Potential goals of noninvasive ventilation (NIV) in severe acute asthma. ARF = acute respiratory failure.

gest the presence of hypercapnia.[36,37] During medical therapy, the time to correct hypercapnia ranges from 30 min to 16 hours (mean 6 h), depending on pre-morbid hypercapnic drive and exacerbation duration [36]. To assess the need for mechanical ventilation, clinical physiological changes in response to the standard medical treatment appear to be as important as the absolute values of bronchial obstruction and gas-exchange impairment.[38] The reported need for mechanical ventilation (intubation or NIV) in severe-acute-asthma patients with hypercapnic ARF ranges widely (8–50%).[10,23,24,36] Importantly, the absence of hypercapnia did not exclude the need for ventilatory support in clinically deteriorating hypoxemic patients. Conversely, isolated hypercapnia is not an absolute indication for intubation if the patient is clinically improving or has not had sufficient opportunity to respond to standard medical treatment.

In this complex physiopathologic context of clinical deterioration in severe acute asthma, the large range in the need of mechanical ventilation may be also explained by the identification of at least 2 distinctive clinical-biological-functional phenotypes.[2,3,9] Type I, the most common phenotype, known as "slow-onset asthma," responsible for 80–85% of all fatal events, is characterized by an eosinophilic inflammation associated with a gradual deterioration over days or weeks, occurring in patients with severe and poorly controlled asthma. This phenotypic pattern has a slow response to standard medical treatment and is generally considered preventable. Type II, known as "rapid-onset asthma" or "asphyxic asthma," is dominated by a neutrophilic inflammation and tends to be more dangerous because it tends to be mild at baseline and the attack starts suddenly with rapidly progressive airways narrowing. Type II phenotype has both rapid onset and response to standard medical treatment. Unfortunately, as many asthmatics underestimate the duration of their symptoms, it may be difficult to distinguish between these subtypes by history alone.

However, independent of the phenotype, when the asthma attack progresses to a severe impairment of gas exchange and profound respiratory acidosis, pump failure, and life-threatening complications (hypotension, arrhythmias, decreased level of consciousness), intubation is immediately required. By that time there is limited space for a safe NIV attempt, because its "mandatory" use is likely to fail in an exhausted patient who will probably have difficulties coping with the mask.

Noninvasive Ventilation in Severe Acute Asthma: Where Are We in the Clinical Ground?

A couple of small, uncontrolled studies investigated NIV as "mandatory ventilation" in general ICUs to manage severe acute asthma leading to ARF after the failure of standard medical treatment in the emergency department. In a prospective study, Meduri et al[23] reported successful NIV in 17 severe acute asthma episodes with severe acidosis (mean pH 7.25). NIV rapidly improved physiological variables and avoided intubation in all but 2 patients. A retrospective study[24] reported favorable outcomes in 22 severe-acute-asthma patients treated with NIV due to persistent hypercapnia (mean P_{aCO_2} 63 mm Hg) and severe acidosis (mean pH 7.24), with an NIV-failure (intubation) rate of 14%.

In the first randomized controlled trial (RCT), Holley et al[39] aimed to determine whether nasal NIV, used as "supportive ventilation," would reduce the need for intubation, hospital stay, or hospital charges in patients with hypoxemic severe acute asthma. Unfortunately, this trial was stopped early because of a recognized marked bias in recruitment, which precluded its completion and validity. In the interim analysis Holley et al found only a nonsignificant trend toward less need for intubation (1 vs 2 cases) and hospital stay (median 46 h vs 42 h) in the NIV group ($n = 19$) versus the control group ($n = 16$).

A pediatric experience was reported in a prospective randomized crossover study by Thill et al,[40] who tested the hypothesis that NIV may improve respiratory function in children with lower-airway obstruction, as assessed by a Clinical Asthma Score > 3. Twenty children (mean age 48 months) were randomized to receive alternatively 2 hours of nasal NIV, followed by crossover to 2 hours of standard medical treatment. Compared to the baseline values, NIV was associated with lower respiratory rate (49.5 ± 13.9 breaths/min vs 32.0 ± 6.2 breaths/min, $P < .01$), total Clinical Asthma Score (2.1 ± 1.0 vs 5.4 ± 1.2, $P < .001$), and delivered oxygen concentration needed to maintain oxygen saturation ≥ 90% (0.57 vs 0.38, $P < .001$). Conversely, discontinuation of NIV was associated with in-

creased respiratory rate and Clinical Asthma Score. There were no significant differences in oxygen saturation or transcutaneous CO_2 measurement between the 2 groups.

So far, only one RCT[41] has evaluated NIV as "prophylactic ventilation" in milder severe acute asthma, without a substantial gas-exchange impairment ($P_{aO_2} \geq 60$ mm Hg and/or pulse-oximetry saturation $\geq 92\%$, and $P_{aCO_2} > 45$ mm Hg on room air). That study—the only one included in a recent meta-analysis[30]—was performed in an emergency department and was calibrated to analyze the impact of NIV on the speed of clinical-spirometric improvement, and the need for and duration of hospitalization. It was a single-center pilot RCT, and Soroksky et al[41] randomized 30 patients who presented at their emergency department with severe acute asthma, to either nasal NIV (mean inspiratory/expiratory pressure 14/4 cm H_2O) or sham NIV (inspiratory/expiratory pressure 1/1 cm H_2O) applied for 3 hours. The sham NIV was accomplished with a nasal mask, but with holes cut in the tubing, and patients were encouraged to breathe through the mouth. In both groups, ventilation was interrupted each time to deliver aerosolized bronchodilators from a separate small-volume nebulizer. More patients in the NIV group reached the primary end point at 4 hours of treatment (forced expiratory forced volume in the first second [FEV_1] $\geq 50\%$ of baseline or $> 60\%$ of predicted), in comparison to the control group (80% vs 20%, $P < .004$). Soroksky et al reported less need for hospital admission (17.6% vs 62.5%, $P = .01$) and more rapid improvement in percent-of-predicted FEV_1 (53.5% vs 28.5%, $P = .006$) in the patients treated with NIV, compared to the controls. As intubation was not required in either the NIV or control group, one could assume that NIV was used mainly to improve dyspnea and spirometry values rather than for ventilation in selected patients with milder severe acute asthma.

Despite its promising positive results, some limitations of this pilot study should be underlined: the limited sample size (underpowered?), the potential harmful effects of mouth leaks during nasal sham ventilation (airways-dryness-induced bronchial hyper-reactivity?), the need of withdrawing NIV for administering the inhaled therapy (treatment too short?). Last but not least, the benefits of NIV may have been overestimated because the researchers did not standardize and/or maximize standard medical treatment with systemic steroids before the randomization.

In an RCT in this issue of RESPIRATORY CARE,[7] Gupta et al randomized 53 patients admitted in their respiratory ICU for hypoxemic severe acute asthma to either NIV via full-face mask (median inspiratory/expiratory pressure 12/5 cm H_2O, $n = 28$) or to standard medical treatment ($n = 25$). Gupta et al found a significant improvement in respiratory rate, FEV_1, and ratio of P_{aO_2} to fraction of inspired oxygen (F_{IO_2}) (but not pH or P_{aCO_2}) in both groups, but no significant differences between the 2 groups. Concerning the primary end points, the NIV group had a nonsignificant trend toward a quicker reversal of bronchial obstruction (ie, 50% improvement in FEV_1) at 4 hours of treatment (64% vs 86%), significantly shorter ICU stay (median 10 h vs 24 h, $P = .01$) and hospital stay (median 38 h vs 54 h, $P = .01$), significantly smaller mean cumulative doses of inhaled albuterol (31.2 mg vs 42.8 mg, $P = .008$) and ipratropium (5.2 mg vs 7.6 mg, $P = .007$), and quicker disappearance of accessory muscle use (2.3 h vs 3.2 h, $P = .06$). There were 4 instances of standard-medical-treatment failure, and all those patients improved with NIV and avoided intubation. Conversely, 2 patients assigned to NIV required intubation because of clinical-physiological deterioration associated with mask intolerance. There was no mortality in either group.

To my knowledge, the Gupta et al study is the largest RCT to date on NIV as a "supportive ventilation" in patients with severe acute asthma and at a risk of intubation.[7] The severity of the asthma attacks in this study is shown by the high degree of bronchial obstruction (mean FEV_1 23% of predicted); hypoxemia (mean $P_{aO_2}/F_{IO_2} < 300$ mm Hg), which required oxygen therapy; and normocapnia, an index of impeding pump failure. One must appreciate the efforts of Gupta et al in recruiting patients with severe acute asthma, as a mean of 8 out of 10 of the Global Initiative for Asthma (GINA) asthma severity criteria[2] were satisfied in both the NIV and control group.

In contrast to the previous RCT,[41] Gupta et al[7] found that NIV was of similar efficacy to standard medical treatment in improving respiratory rate, FEV_1, and P_{aO_2}/F_{IO_2} in severe acute asthma. However, the effects of NIV on bronchial obstruction were achieved with lower doses of inhaled bronchodilator and shorter ICU and hospital stay, compared to the standard medical treatment. Furthermore, NIV as a rescue therapy in patients who fail standard medical treatment is likely to have caused under-estimation of the differences in the need for intubation between the 2 groups. In fact, it's reasonable to believe that the 4 patients who failed standard medical treatment may have been intubated if they had not been offered NIV.

It has to be highlighted also the different setting (ie, respiratory ICU) where Gupta et al[7] treated their severe-acute-asthma patients. The management of severe acute asthma by pulmonologists in a specialized high level of care unit, such as a respiratory ICU,[42] where all the staff are very familiar with NIV, may constitute an advantage, compared to an emergency department where the evidence supporting NIV in ARF is not as well recognized. Gupta et al opportunely emphasized the importance of closely monitoring patients with severe acute asthma, because their condition may worsen abruptly, and Gupta et al strongly suggest promptly recognizing NIV failure and having facilities for immediate intubation. In this context, the pulmonologists' skills in a respiratory ICU to manage the

airways with expertise (ie, perform intubation) may be an advantage.[43] On the other hand, the costs associated with admission to the respiratory ICU, even for a short time, should be borne in mind, especially for milder severe acute asthma.

Unfortunately, the study by Gupta et al[7] had some limitations, most of them correctly reported by the authors:

- The small sample size precludes the reliability of their results, which creates a risk of type 2 error.
- They used subjective criteria for respiratory ICU discharge, which could have biased the ICU-stay values.
- They had heterogeneous criteria for defining standard medical treatment and NIV failure, which creates a risk of bias in the between-groups treatment-failure comparison.
- The ipratropium doses were lower than recommended and may have been inadequate.
- They did not evaluate the effects of the first trial of standard medical treatment before randomization; some patients might have quickly improved without NIV. That creates a risk of selection bias.

Very recently, 2 short-term physiological RCTs suggested the possibility of using NIV not as a ventilatory support but as bronchodilator therapy in patients who presented in the emergency department for milder asthma exacerbations and who did not require hospitalization or ventilatory support. In such patients NIV may resolve the bronchial obstruction, either alone or in combination with inhaled bronchodilators.

To study whether NIV would help independent of treatment with inhaled β_2 agonists, Soma et al[19] randomized 44 patients with mild to moderate asthma exacerbations and who had previously received only systemic corticosteroid, to either NIV via a nasal or face mask ($n = 30$) or to controlled observation ($n = 14$). Patients who received NIV were furthermore randomly divided into 2 subgroups: 16 patients who received inspiratory/expiratory pressure of 8/6 cm H_2O, and 14 patients who received inspiratory/expiratory pressure of 6/4 cm H_2O, both groups for 60 min. Twenty-six of the 30 patients who were initially assigned to the NIV group completed the study; 2 were excluded because of mask discomfort, and 2 because of inadequate spirometry recording. There was a significant FEV_1 improvement (approximately 20% of the absolute value and approximately 6% compared to the baseline value 20 min after the intervention) only in the higher-pressure NIV group. Similar improvements in dyspnea and in wheezing were observed 20 min after the start of the intervention in both the higher-pressure and lower-pressure NIV groups. Soma et al suggested that NIV, even if delivered at lower pressures than those usually recommended to support ARF patients, may help acute asthma attacks without inhaled bronchodilators, and hypothesized that there is a direct bronchodilation induced by mechanical effects. However, the very low pressure support (2 cm H_2O) they used is physiologically closer to CPAP than to NIV.

In a subsequent RCT with 36 patients with acute asthma, Brandão et al[28] evaluated the effects of bronchodilators administered via jet nebulization during either spontaneous breathing or NIV at inspiratory/expiratory pressure of 15/5 cm H_2O or 15/10 cm H_2O. In comparison to the control group, the improvement in peak expiratory flow, FEV_1, and forced vital capacity, 30 min after nebulization, was greater with the NIV with the smaller difference between the inspiratory and expiratory pressure. Brandão et al speculated that this synergistic effect of NIV in adjunct to the nebulized bronchodilator may be due to better drug penetration into the peripheral airways[44] (probably due to a shift from turbulent to laminar bronchial flow) and to improved alveolar recruitment due to the augmented collateral pulmonary ventilation in obstructed pulmonary regions.[21]

Even if these findings open the possibilities of useful application of NIV as bronchodilator therapy in less severe asthma attacks, the implications of a time-consuming (nurse and physiotherapist workload) and expensive (machine and equipment) treatment should be carefully considered. Furthermore, there were important design weakness in these trials; the Soma et al study[19] lacked a second controlled arm (that would have received conventional inhaled bronchodilators), and Brandão et al[28] did not offer systemic steroids.

Drawbacks of Noninvasive Ventilation in Severe Acute Asthma

Despite several physiopathologic similarities to COPD exacerbation, there is a paucity of RCT data on NIV in severe acute asthma.[7,19,28,39-41] Consistently, a recent Cochrane analysis[30] concluded that evidence for NIV in severe acute asthma was "promising" but so far "controversial" (Table 2).

Why do we still not have a clear demonstration of the utility of NIV in severe acute asthma? First of all, the assessment of severity of an asthma attack suggested by the literature (eg, in GINA)[2] (Table 3) may be misleading for several reasons. Unpredictably, many patients, particularly those with a history of severe acute asthma, have an impaired perception of dyspnea and may underestimate the severity of their attacks. Although wheezing may be severe, the chest becomes silent as air flow decreases with the onset of ARF. Furthermore, in critically ill patients, spirometry should be deferred because it may provoke bronchospasm and because severely dyspneic patients may not be cooperative. Pulsus paradoxus may be absent if the patient develops respiratory muscle fatigue and cannot gen-

Table 2. Randomized Controlled Trials on Noninvasive Ventilation in Severe Acute Asthma

First Author	Year	Patients	Severity of Asthma Attack (GINA criteria)	NIV Purpose	Setting	NIV Setup	Key Results	Study Weaknesses
Holley[39]	2001	19 NIV 16 controls	5 pre-defined criteria Found only 1 in controls (tachycardia) ABGs not impaired	Supportive ventilation (?)	Emergency department	Nasal mask IPAP 10 cm H_2O EPAP 5 cm H_2O 4–18 h/day	Trend towards less endotracheal intubation and shorter hospital stay with NIV	Small sample size Study terminated early due to recruitment bias (physicians had ethical concerns about "withholding" NIV from controls) No blinding Suboptimal initial bronchodilator therapy
Soroksky[41]	2003	15 NIV 15 controls	2 criteria FEV_1 % predicted 37% in NIV group, 34% in controls ABGs not impaired	Prophylactic ventilation	Emergency department	Nasal mask IPAP 14 cm H_2O EPAP 4 cm H_2O Sham NIV in controls 3 h	Greater FEV_1 increase and less need for hospitalization with NIV No need for endotracheal intubation	Small sample size NIV stopped to administer nebulized medications No evidence that sham NIV not worse for patients than nebulizer alone (mouth breathing: discomfort? bronchial hyper-reactivity?) Suboptimal initial standard medical therapy (systemic steroids)
Soma[19]	2008	16 higher-pressure NIV 14 lower-pressure NIV 14 controls 4 dropped out in NIV arm	2 criteria FEV_1 % predicted 34% in higher-pressure NIV group, 30% in lower-pressure NIV group, 42% in controls ABGs not impaired	Bronchodilator delivery	Emergency department	Nasal/Full-face mask High: IPAP 8 cm H_2O EPAP 6 cm H_2O Low: IPAP 6 cm H_2O EPAP 4 cm H_2O 1 h	Greater improvements in FEV_1 with the higher-pressure NIV, and in dyspnea and wheezing with higher or lower pressure NIV No need for endotracheal intubation	Small sample size Mild asthmatic attacks Suboptimal pressures, similar to CPAP Bronchodilators not given (lack of a second control arm receiving bronchodilators)
Brandão[28]	2009	12 higher-pressure NIV 12 lower-pressure NIV 12 controls	1 criterion (dyspnea)? FEV_1 % predicted 41% in higher-pressure NIV group, 43% in lower-pressure NIV group, 36% in controls ABGs not impaired	Inhalator ventilation	Emergency department	Full-face mask High: IPAP 15 cm H_2O EPAP 5 cm H_2O Low: IPAP 15 cm H_2O EPAP 10 cm H_2O 15 min	Greater improvement in peak expiratory flow, FEV_1, and forced vital capacity (with the lower-pressure NIV) No need for endotracheal intubation	Small sample size Mild asthma attacks Suboptimal initial standard medical therapy (systemic steroids)
Gupta[7]	2010	28 NIV 25 controls	8 pre-defined criteria FEV_1 % predicted 22% in NIV group, 24% in controls P_{aO_2}/F_{IO_2} < 300 mm Hg No hypercapnia	Supportive ventilation	Respiratory ICU	Full-face mask IPAP 12 cm H_2O EPAP 5 cm H_2O 4 h	Trend towards faster FEV_1 and clinical improvement with NIV Shorter hospital and respiratory ICU stay Smaller total doses of bronchodilator No differences in endotracheal intubation	Underpowered NIV as rescue therapy for controls Subjective criteria for respiratory ICU discharge Inadequate ipratropium dose No evaluation of standard medical therapy before randomization

GINA = Global Initiative for Asthma
NIV = noninvasive ventilation
ABGs = arterial blood gas values
FEV_1 = forced expiratory volume in the first second
ICU = intensive care unit
F_{IO_2} = fraction of inspired oxygen

erate sufficiently large intrathoracic pressure swings. According to GINA,[2] several, but not necessarily all, the suggested criteria are required to assess the severity of an asthma attack, so an asthma exacerbation could be classified as severe even without impairment of blood gas values or clinical signs of respiratory muscle fatigue. This makes it difficult to compare the published studies, which probably had different objectives for NIV: was NIV used as ventilation or as nebulization device? Was the NIV "mandatory," "supportive," or "prophylactic"?

Second, as previously highlighted, unfortunately, the few published RCTs have had limitations that preclude making clear recommendations about NIV in severe acute asthma.

Third, compared to COPD exacerbation, severe acute asthma has a shorter safe time-window for trying NIV, so it seems reasonable to think that NIV has to be applied earlier in the course of severe acute asthma (ie, "supportive ventilation"). On the other hand, because an asthma attack usual has a speedy reversal under standard medical

Table 3. Criteria for Defining Severe Acute Asthma

Clinical Signs
Breathless at rest
Wheezing. Life-threatening respiratory arrest is imminent if chest silent.
Use of accessory respiratory muscles. Life-threatening respiratory arrest is imminent if paradoxical thoraco-abdominal movement.
Limited ability to talk
Agitation. Life-threatening respiratory arrest is imminent if confusion or coma.
Physiological Signs
Respiratory rate > 30 breaths/min
Heart rate > 120 beats/min. Life-threatening respiratory arrest is imminent if bradycardia.
Pulsus paradoxus > 25 mm Hg. Life-threatening respiratory arrest is imminent if pulsus paradoxus absent.
Post-bronchodilator peak expiratory flow < 60% of patient's best or predicted, or < 100 L/min
FEV_1 < 30% of patient's best or predicted
S_{pO_2} < 90% on room air
P_{aO_2} < 60 mm Hg on room air
P_{aCO_2} > 45 mm Hg

FEV_1 = forced expiratory volume in the first second
S_{pO_2} = oxygen saturation measured via pulse oximetry

treatment, it's difficult to design a study that would clearly demonstrate that the addition of NIV—a sophisticated and time-consuming technological support—provides any advantage over standard medical treatment.

Fourth, during an asthma attack the patient may have difficulty coping with NIV, for several reasons: these patients are usually tachypneic and might struggle 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 exacerbate sputum retention; and bronchial hyper-reactivity may be increased by the high inspiratory flow and airway dryness associated with NIV.

Fifth, technical issues of NIV in severe acute asthma have not been clarified. Is NIV surely better than CPAP, which is easier and cheaper? If NIV is chosen, what inspiratory and expiratory pressure should be applied? Do we need to apply sham ventilation to the controls?

Finally, it's not clear where NIV should be delivered (emergency department, respiratory ICU, other ICUs?) from the perspective of a cost-utility analysis.

In conclusion, even if the study by Gupta et al[7] did not add a point in favor of NIV in severe acute asthma, the existence of a strong physiopathologic rationale should keep open a "window" for the use of NIV in severe acute asthma. Further larger RCTs in selected subsets of patients with acute asthma are urgently needed to clarify when, where, and why a trial of NIV may be justified in severe acute asthma.

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