

Noninvasive ventilation in life-threatening asthma: A case series

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Background: The use of noninvasive ventilation (NIV) in severe acute asthma is controversial. A pH < 7.25, PaCO₂ > 60 mmHg, and altered mental status have been described as contraindications to NIV in acute asthma. We hypothesized that NIV was safe and effective in asthma patients with a pH < 7.25 or PaCO₂ > 60 mmHg.

Methods: Following institutional review board approval, the medical records of subjects who received NIV for acute asthma in the emergency department between January 2010 and July 2012 were reviewed. Subjects were included if they had a pH < 7.25 or PCO₂ > 60 mmHg on either an arterial or venous blood gas. Primary outcome was need for endotracheal intubation.

Results: Sixty-two subjects received NIV for asthma, with 20 (mean age 42 ± 12 years, 62% male) meeting the inclusion criteria. Intubation was avoided in all 20 subjects, including nine (45%) with prior history of intubation due to asthma, eight (40%) who were obtunded, and three (15%) who were unresponsive upon arrival. Results are described as medians (ranges). Initial blood gas (80% venous) results were: pH 7.16 (6.89–7.27), PCO₂ 77 (65–144) mmHg, and HCO₃⁻ 27 (20–32) mmol/L. Repeat blood gases (45% venous) performed a median of 117 minutes later were: pH 7.31 (7.22–7.45), PCO₂ 48 (31–63) mmHg, and HCO₃⁻ 23 (19–31). Vomiting occurred in one patient; no other adverse events were noted.

Conclusion: We identified a small series of asthma patients with severe respiratory acidosis or altered mental status in whom NIV was safe and effective.

Key Words: noninvasive ventilation; asthma; status asthmaticus; NIV; respiratory acidosis; emergency department

INTRODUCTION

An estimated 2 million patients visit emergency departments (EDs) in the United States for asthma exacerbations each year [1]. Data from the National Ambulatory Care Reporting System in Canada indicate that there were 1,000 cases of severe, acute asthma required resuscitation in 2015 and 2016 (National Ambulatory Care Reporting System Quick-Stats, Accessed May 8, 2017). In the ED, asthma exacerbations are typically treated with frequent inhaled bronchodilators (beta₂-agonists and anticholinergics), systemic corticosteroids, and oxygen. Adjunctive therapies used in severe or life-threatening exacerbations include epinephrine, methylxanthines, ketamine, intravenous (IV) magnesium, heliox, and mechanical ventilation (invasive and noninvasive) [2]. There is substantial morbidity and mortality (as high as 20%) associated with invasive mechanical ventilation in asthma [3]. ED treatment is focused on maximizing therapy to avoid endotracheal intubation. Airway manipulation during attempts at endotracheal intubation in asthma patients may cause worsening bronchospasm and the subsequent increase in intrathoracic pressure post intubation can cause cardiovascular collapse, including cardiac arrest [3].

The use of noninvasive ventilation (NIV) in asthma is controversial due to lack of high-level data from randomized, controlled trials. A Cochrane review concluded that despite promising initial results, there is a lack of data to support the use of NIV in status asthmaticus [4]. A clinical practice guideline published by the Canadian Medical Association in 2011 was unable to make recommendations on NIV in asthma due to lack of data [5]. To date, no randomized trials on the use of NIV in acute asthma have enrolled patients with abnormal gas exchange. However, despite the lack of evidence from randomized trials, the use of NIV in asthma in clinical practice is increasing, with a concurrent decrease in the use of invasive mechanical ventilation [6]. For asthma patients with respiratory failure, expert reviews have recommended a pH < 7.25 [7, 8], arterial partial pressure of CO₂ (PaCO₂) > 60 mmHg [9], and altered mental status (AMS) [3, 7–10] to be contraindications to NIV. The successful use of NIV in patients with blood gas values

below these thresholds has been described, including recent reports describing successful use of NIV in an asthma patient presenting with an initial pH of 6.95 and PaCO₂ of 125 mmHg [11] and a series of 17 asthma patients who received NIV with a mean initial pH of 7.18, PaCO₂ 78 mmHg, and GCS of 14 prior to NIV. These reports have raised question regarding the limits of NIV in severe asthma exacerbations [12]. We hypothesized that NIV was safe and effective in asthma patients with a pH < 7.25 or PaCO₂ > 60 mmHg.

METHODS

Following institutional review board approval, all adult (> 18 years of age) patients who received NIV in the ED between January 2010 and July 2012 were retrospectively identified through a search of electronic medical records as part of a larger review of NIV use in our ED. Subjects who were intubated without receiving NIV and those with abnormal gas exchange who did not receive NIV were unable to be identified. Subjects were screened for a history of asthma, as determined from physician notes, and were followed for their entire hospital stay. Subjects with chronic obstructive pulmonary disease (COPD), congestive heart failure, renal failure requiring dialysis, and suspected or known vocal cord dysfunction were excluded. Subjects were included if initial blood gas (arterial or venous) revealed they had a venous or arterial pH < 7.25 or PCO₂ > 60 mmHg. Venous blood gases are utilized routinely in our emergency department in the assessment of acid-base balance. The decision to send arterial or venous blood gases was at the discretion of the treating physician and done per departmental standards. We considered venous blood gas analysis to be an adequate surrogate for arterial blood gas analysis as a venous PCO₂ of 50 mmHg or greater has been shown to be 100% sensitive for the detection of hypercapnia (defined as a PaCO₂ > 45 mmHg) [13]. Oxygenation was measured via continuous pulse oximetry in all subjects. Mental status was determined from clinical documentation and subjects were considered to have AMS if there was any specific mention of lethargy, obtundation, or if the clinical context clearly indicated the presence of AMS.

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Subject demographics, home medication regimen, medical history, vital signs, blood gases, NIV settings, need for intubation, disposition, ED length of stay, and hospital length of stay were extracted from the medical record by the primary author (AGM) and a registered respiratory therapist (DAV). Data on epinephrine, methylxanthines, ketamine, and heliox use were not recorded. Extracted data were entered into a standardized Microsoft Excel (Seattle, WA) spreadsheet and analyzed with Graphpad statistics software. Repeated measurements of the means for pH, CO₂, HCO₃, and lactate were compared using the paired *t* test with an alpha set at 0.05.

NIV settings were titrated based on institutional protocol designed to optimize triggering, target tidal volume 4–8 mL/kg of predicted body weight, and decrease accessory muscle use while maintaining a total inspiratory pressure \leq 20 cmH₂O. NIV was delivered by critical care ventilator (Carefusion Vela) or dedicated NIV machine (Respironics Vision or V-60). Only initial NIV settings were recorded. Vital signs included heart rate, respiratory rate, blood pressure, pulse oximetry (SpO₂), and fraction of inspiratory oxygen (FiO₂). Bedside spirometry or peak expiratory flow rate were not performed in any subjects. Primary outcomes were needed for intubation at any point during their hospital stay; secondary outcomes were disposition from the ED and hospital length of stay. Disposition was determined by the attending ED physician in consultation with the admitting service. In our institution, adult asthma patients requiring continuous bronchodilator therapy or NIV are required to be admitted to the intensive care unit (ICU).

RESULTS

A total of 943 subjects received NIV in our ED during the study period. Sixty-two patients received NIV for acute asthma and 20 (median age 43 years, range 23–65 years, 65% male) met the inclusion criteria. Zero of 20 subjects required intubation during their hospital stay. Demographic variables are summarized in Table 1.

AMS was present in nine (45%) subjects. Of these, eight (40% of all subjects) were noted to be lethargic or obtunded, including three (15%) who were unresponsive, and one (5%) who had significant agitation. Glasgow coma scale was documented to be 8 in one unresponsive subject; specific measures of responsiveness were not documented in the

TABLE 1
Subject demographics

Demographic	No. (%) [*]
Median (range) age in years	43 (23–65)
Male	13 (65)
History	
Intubation	8 (40)
ICU admission	10 (50)
NIV	7 (35)
No hx of intubation, ICU admission, or NIV	10 (50)
Home medications	
Rescue only	10 (50)
ICS + rescue	0 (0)
ICS + LABA + rescue	8 (40)
None	2 (10)
Arrived via EMS	17 (85)
Cause of exacerbation	
Noncompliance	3 (15)
Polysubstance abuse	3 (15)
Weather change	2 (10)
Allergies	2 (10)
Viral infection	1 (5)
Tobacco abuse	1 (5)
Tracheobronchitis	1 (5)
Environmental exposure	1 (5)
Other	4 (20)

Note: ICU, intensive care unit; NIV, noninvasive ventilation; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; EMS, emergency medical services.

^{*}Unless otherwise specified.

other subjects. Two (10%) subjects received bag valve mask ventilation via emergency medical services personnel during transport to the ED.

Blood gas results and NIV settings for all subjects are summarized in Table 2. Results for lethargic/obtunded subjects are summarized in Table 3. Venous blood gases were obtained initially in 16 (80%) subjects, repeat blood gases were performed in 18 subjects and of these, 11 (55%) were arterial blood gases. Eighteen (90%) subjects received continuous albuterol (50% at 40 mg/h, 39% at 20 mg/h, and 11% at 30 mg/h), 19 (95%) received IV magnesium, 19 (95%) received IV corticosteroids, and 5 (25%) received benzodiazepines.

Pre-NIV vitals are summarized in Table 2. Six (30%) subjects were admitted to the ICU, 12 (60%) to a regular bed, one (5%) was discharged home, and one (5%) signed out against medical advice. Of the eight obtunded patients, three (38%) were admitted to the ICU, four (50%) to the floor, and one (13%) signed out against medical advice. Total time spent in the ED was 327 (97–1400) minutes for all subjects and 269 (118–1400) minutes for obtunded subjects. The median (range) hospital length of stay was 2 (0–4) days and 1.5 (0–4) days for obtunded subjects, with all 20 subjects being discharged to home. Vomiting occurred in one patient with no concern for acute aspiration. No other complications (including pneumothoraces) related to NIV were noted.

DISCUSSION

In our series, no subjects required endotracheal intubation, including those presenting with AMS. To our knowledge, this is the first case series of NIV in the emergency setting in acute asthma that included severe acidosis, hypercapnia, and AMS as entry criteria. Previous reviews have included severe acidosis and AMS to be contraindications to NIV in acute asthma; however, our results indicate NIV was safe and efficacious in our cohort as indicated by no significant adverse events, rapid improvement in blood gas values, low rate of ICU admission, and short hospital stay [3, 7–10].

There have been a few small case series (enrolling between 17 and 22 subjects) on the use of NIV in asthma patients with respiratory acidosis. These studies have been done in the ICU, not the ED [12, 14, 15]. Studies done in the ED environment have enrolled patients with normal gas exchange [16–21]. Meduri et al. [14] reported a case series of 17 (mean pH 7.25, PaCO₂ 65 mmHg) subjects treated with NIV in their ICU with a subsequent intubation rate of 12%. Fernandez et al. [15] reported the use of NIV in 22 subjects with a pre-NIV pH of 7.28 and PaCO₂ 63 mmHg who failed to respond to aggressive initial management in the ED. Their blood gases worsened prior to NIV initiation (mean pH decreased from 7.26 to 7.24 and PaCO₂ increased from 53 to 63 mmHg) but improved within 6 hours of NIV initiation to a mean pH of 7.32 with a PaCO₂ 51 mmHg following NIV. Three (14%) patients were intubated, two due to AMS and one due to mask intolerance [15]. Our study adds to these prior studies as the accumulation of data from different centers demonstrates the use of NIV in acute asthma and respiratory acidosis is a safe practice that is associated with low intubation rates.

The study enrolling subjects most similar to ours was that of Murase et al. [12], who reported the use of NIV in 17 asthma subjects treated in their ICU following the introduction of NIV into their clinical practice. They included patients who were confused in whom mental status rapidly normalized, except for one patient who required intubation. Their cohort who received NIV had a mean pre-NIV pH of 7.18 with a PaCO₂ of 77 mmHg and found an intubation rate of 12%. One patient was intubated due to mask intolerance and the other after 72 hours of NIV due to worsening blood gases [12]. Compared with our cohort, the patients in their study were older (55 vs 42 years of age), more likely to be female (82% vs 38%) and had a longer hospital length of stay (8.4 vs 2 days). They did not report the amount or frequency of bronchodilator treatments, making comparison difficult. Both of these studies indicate NIV can be safely delivered to patients with AMS, provided they are in a closely monitored area with a team experienced in providing NIV. In patients with mask intolerance, we administer low dose benzodiazepines to reduce anxiety and allow improved treatment tolerance.

TABLE 2
Blood gas results and NIV settings for all 20 subjects

	Initial NIV settings				Pre-NIV vital signs		
	Mean	Median	Range		Mean	Median	Range
IPAP cm H ₂ O	13.4 ± 2.6	12	10–18	Heart rate	115 ± 20	116	75–156
EPAP cm H ₂ O	6.7 ± 2.0	7	3–10	RR	29 ± 8.3	28	17–146
FiO ₂	0.53 ± 0.22	0.40	0.30–1	Systolic BP	173 ± 32	172	93–234
Respiratory rate	32 ± 9	32	16–50	Diastolic BP	100 ± 22	103	60–139
				SpO ₂	97 ± 4.2	97	88–100
Time on NIV minutes*	163 ± 75	156	45–259				

	Blood gas results prior to NIV initiation			Blood gas results post-NIV initiation			p
	Mean	Median	Range	Mean	Median	Range	
Time between blood gases	n/a	n/a	n/a	135 ± 83	117	44–350	n/a
pH	7.13 ± 0.10	7.16	6.89–7.27	7.31 ± 0.07	7.31	7.22–7.45	<0.001
PCO ₂ (mmHg)	82 ± 18	77	65–144	48 ± 9.6	48	31–63	<0.001
HCO ₃ ⁻ (mmol/L)	27 ± 2.8	27	20–32	24 ± 2.9	23	19–31	<0.001
Lactate [†] (mmol/L)	2.9 ± 2.3	1.9	0.9–9.3	2.1 ± 1.2	2.1	0.7–4.4	0.18

NIV, noninvasive ventilation; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; RR, XXXXX; BP, blood pressure.

*Available for 6 subjects.

†Available for 19 subjects.

TABLE 3
Lethargic or obtunded subjects, n = 8

	Initial blood gas			Repeat blood gas			p
	Mean	Median	Range	Mean	Median	Range	
Time between blood gases, minutes	n/a	n/a	n/a	142 ± 85	119	44–350	
pH	7.05 ± 0.10	7.07	6.89–7.16	7.29 ± 0.06	7.30	7.22–7.36	<0.001
PCO ₂ (mmHg)	94 ± 22	91	73–144	50 ± 9.7	49	38–63	<0.001
HCO ₃ ⁻ (mmol/L)	26 ± 2.3	26	22–29	24 ± 2.9	24	19–27	0.02
Lactate* (mmol/L)	4.2 ± 2.9	3.9	0.9–9.3	1.5 ± 0.9	1.5	0.7–2.4	0.09

Note: Paired t-test performed to compare means, arterial, and venous blood gas results combined for analysis.

*Available for eight subjects, repeat measurement available for three subjects.

Our results indicate venous blood gases may have a potential role in the assessment of acute asthma, either as a screening tool or as the primary assessment of acid–base status. Venous blood gases can easily be obtained using existing IV lines or upon IV placement. Investigation into the role of venous blood gases in acute asthma is warranted. Aggressive therapy focused on the maximization of bronchodilation through the use of continuous bronchodilator therapy and IV magnesium may also have played a role in our success, as both therapies have been shown to improve airflow in severe asthma [22, 23].

Consistent with prior reports, the use of NIV in acute asthma appears to be a safe practice that can be used even in patients who present with severe respiratory failure and AMS. NIV in this type of patient should only be initiated by experienced teams in well-monitored areas in which practitioners and equipment needed for emergency intubation are available. In our facility, the RT does not leave the bedside of patients with AMS receiving NIV. The feasibility of performing a randomized trial in asthma patients presenting respiratory failure is questionable, as many clinicians may feel withholding NIV would be unethical, and consenting subjects with AMS would be extremely challenging given the window between identification and initiation of some form of respiratory support. Any future trial of NIV in asthma should be multi-center with a well-defined protocol for NIV settings/titration, continuous bronchodilator therapy delivered via vibrating mesh nebulizer, IV magnesium, and strict criteria for NIV failure. While intubation is a logical primary outcome, studies should also examine the effect of NIV on need for ICU admission, hospital/ED length of stay, or time to clinical improvement.

The use of NIV in patients with AMS is controversial; however, the successful use of NIV in hypercapnic encephalopathy due to COPD has been described when delivered by an experienced team in a closely monitored environment where invasive mechanical ventilation was

readily available [24–26]. Of the eight obtunded patients in our series, none required endotracheal intubation and only 38% required ICU admission. Given the rapid resolution of acidosis in our study, a trial of NIV in severe asthma may be warranted, as long as the patient is in a well-monitored environment. When a patient with AMS was placed on NIV during the study period, an RT stayed at the bedside with the patient until their mental status improved. Rapid-sequence induction medications and intubation equipment were also kept readily at the bedside.

The role of external PEEP in acute asthma is unclear; however, its use may facilitate bronchodilation, improve gas exchange, and improve ventilation/perfusion mismatching [8, 9, 27]. The optimal method to determine expiratory positive airway pressure (EPAP)/PEEP during NIV in acute asthma is unknown. Our results indicate that a moderate amount (median 6.7 cm H₂O) of EPAP was not associated with adverse effects. The NIV settings were adjusted via institutional protocol to target a tidal volume 4–8 mL/kg/pbw, maintain synchrony, and reduce work of breathing. Given the relatively low level of pressure support used in our study, it is likely there was some bronchodilation resulting from positive pressure ventilation.

LIMITATIONS

There are many limitations in our study. The nature of the study limited us to data available in the electronic medical record. Changes to our electronic medical record resulted in a shortened timeframe as we were no longer able to reliably track subject location. There was no control group and we were unable to identify asthma patients who were intubated without a trial of NIV or patients with severe acidosis who did not require NIV. The terms lethargic and obtunded were not explicitly defined and relied on clinical documentation. The decision to place a subject on

NIV, NIV settings, medication administration, and disposition were not based on standardized criteria. It is possible that our results are attributable to selective application of NIV to patients who are likely to succeed. Likewise, the initial decision to place a patient on NIV may have biased clinicians against intubating patients or admitting to ICU settings (incorporation bias). The higher proportion of arterial blood gases in repeat analysis may have overestimated the improvement in gas exchange. Venous blood gases have not been validated in patients with asthma. Disposition was determined by the treating physician in consultation with the inpatient team without formal criteria for ICU admission. The lack of a control group makes any reduction in endotracheal intubation rate highly speculative; however, it is likely many of our subjects would have required intubation without NIV. It is unlikely that subjects with this degree of illness will be enrolled in randomized controlled trials in the future as their illness severity makes it unlikely informed consent could be obtained from the patient or legal representative before treatment is initiated. Thus, case series and observational data remain, for now, the best source of evidence for NIV in severe acute asthma with respiratory acidosis.

CONCLUSION

In conclusion, we identified a series of patients presenting to our ED with severe asthma exacerbations as measured by severe respiratory acidosis or altered mental status in whom NIV was safe and effective.

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