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Mechanically Ventilating the Severe Asthmatic

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Abstract

The management of the critically ill patients with asthma can be rather challenging. Potentially devastating complications relating to this presentation include hypoxemia, worsening bronchospasm, pulmonary aspiration, tension pneumothorax, dynamic hyperinflation, hypotension, dysrhythmias, and seizures. In contrast to various other pathologies requiring mechanical ventilation, acute asthma is generally associated with better outcomes. This review serves as a practical guide to the physician managing patients with severe acute asthma requiring mechanical ventilation. In addition to specifics relating to endotracheal intubation, we also discuss the interpretation of ventilator graphics, the recommended mode of ventilation, dynamic hyperinflation, permissive hypercapnia, as well as the role of extracorporeal membrane oxygenation and noninvasive mechanical ventilation.

Keywords

severe acute asthma, status asthmaticus, mechanical ventilation, acute asthma exacerbation, volume preset mode, extracorporeal membrane oxygenation, noninvasive ventilation

Introduction

In the United States, more than 2 million individuals visit emergency departments (EDs) with an acute asthmatic exacerbation on an annual basis.[1] Up to 4% of these individuals will not respond to conventional therapy and may even require intensive care unit (ICU) admission,[2] with a third of these eventually requiring endotracheal (ET) intubation and mechanical ventilation (MV).[3] Unlike most other conditions requiring MV, patients with asthma tend to have better outcomes with reported survival rates of 80% to 100%.[4,5]

Mechanical ventilation of the severe astmatic patient can be a challenging task. These patients may develop potentially serious complications such as hypotension, dysrhythmias, pulmonary barotrauma, laryngospasm, worsening bronchospasm, pulmonary aspiration, and seizures.[6,7] Risk factors for near-fatal asthma (NFA) requiring MV include a younger age at presentation, poor compliance with prescribed therapy, poor outpatient follow-up, more than 3 ED visits in the preceding year, recent hospital admission, a prior episode of NFA and prior MV.[8,9] Indications for the application of MV in patients with severe asthma include the presence of cyanosis, a partial pressure of arterial oxygenation (Pa_{O_2}) of <60 mm Hg despite the administration of high-flow oxygen, a rising Pa_{CO_2} (hypercarbia), bradycardia, persistent acidosis, diminishing levels of consciousness, signs of exhaustion, paradoxical thoracoabdominal motion, a silent chest, and respiratory arrest.[10] Since Pa_{CO_2} is expected to be low (<35 mm Hg) as a result of hyperventilation in the patient with an acute exacerbation of asthma, the presence of an elevated or even normal arterial Pa_{CO_2} is indicative of severe airway obstruction and serves as a warning sign of impending respiratory arrest.[11]

In this article, we review and discuss a practical guide as well as describe basic and advanced MV principles and techniques with regard to the management of the NFA patient.

Discussion

Endotracheal Intubation and Choice of Drugs

Endotracheal intubation, with the aid of topical anesthesia to blunt airway reflexes, should ideally be attempted by the most experienced clinician, as even minor manipulation of the airway may precipitate laryngospasm and worsen the degree of bronchospasm. Due to the strong association of asthma with nasal polyposis, the oral route is generally preferred for ET intubation over the nasotracheal route. Since resistance is inversely proportional to the radius of the ET tube to the fourth power and bronchospasm-related airway resistance is the chief pathology in asthma, consideration must be given to using the largest

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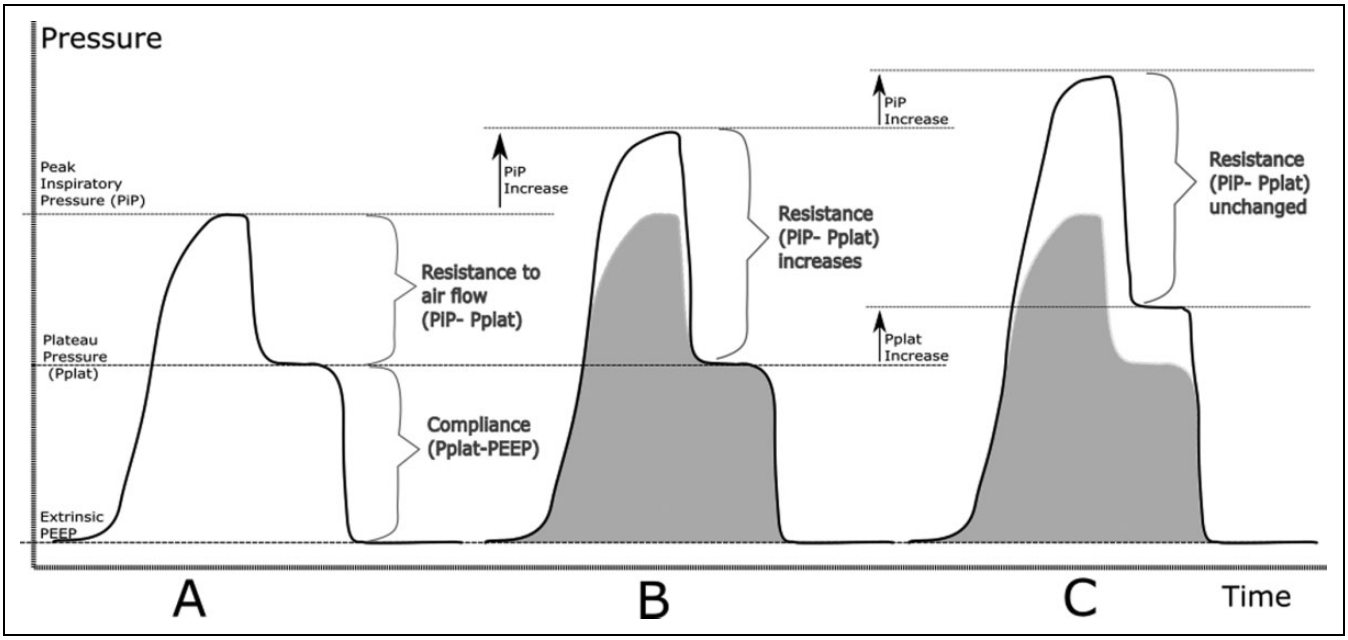

Figure 1. Interpreting the pressure–time waveform on the volume preset ventilation mode in ventilated patients with asthma. A, Normal pressure–time waveform. B, Changes in the pressure–time waveform secondary to bronchospasm with no associated gas trapping. Note the increase in both the PIP and the PIP-Pplat gradient. Since Pplat remains the same as that in A, this signifies an increase in airway resistance only with no gas trapping as there is no change in the compliance from that in A. C, Changes in the pressure–time waveform secondary to the presence of either (1) bronchospasm with associated gas trapping or (2) an expanding pneumothorax. Note the similar degree of increase in both PIP and Pplat. Since the PIP-Pplat gradient remains the same as that in B, there is no further deterioration in the degree of bronchospasm (shaded area = normal pressure–time waveform). PIP indicates peak inspiratory pressure; Pplat, plateau pressure.

diameter ET tube that is able to pass through the laryngeal inlet (eg, 8- to 10-mm internal diameter ET tube in adults). Besides, a larger dimeter ET tube also facilitates suctioning of the airway as well as bronchoscopic removal of mucus plugs.[12]

Additional care should be taken in the pediatric patient. The relatively smaller diameter of the airway and ET tube coupled with a higher resting respiratory rate (RR) and increased oxygen demand ratio places them at higher risk of developing dynamic hyperinflation.[13]

Hemodynamic instability, chiefly due to more pronounced heart–lung interactions in patients with asthma, is a significant concern. A rise in intrathoracic pressure secondary to gas trapping (dynamic hyperinflation) may lead to an acute rise in pulmonary vascular resistance as well as right-sided heart pressures, thereby compromising venous return, right ventricular preload, right ventricular afterload, and therefore left ventricular end-diastolic volume and cardiac output. The already reduced circulatory return to the left heart may be further compromised by pressure-induced leftward shift of the interventricular septum (ventricular interdependence). In addition, dehydration secondary to hyperventilation-related excessive loss of water vapor, the presence of an underlying pneumothorax or systemic sepsis are other potential causes of hypotension that should be evaluated in patients with asthma, prior to atempting endotracheal intubation. Interventions to counteract the above include appropriate fluid resuscitation and consideration for the use of push-dose vasopressors during the peri-intubation period.[14,15]

With regard to selecting the appropriate induction agent, both ketamine and propofol harbor bronchodilator properties.[16,17] However, due to loss of the patient's sympathetic drive upon intravenous induction of anesthesia, coupled with propofol's vasodilatory properties, caution should be exercised with regard to the use of this and other agents that may precipitate hemodynamic instability.[18-20] Although ketamine induction should be considered the agent of choice,[21-23] etomidate, despite lacking bronchodilator properties, but due to its favorable effects on cardiovascular hemodynamics, may also be considered.[24]

Both succinylcholine and the nondepolarizing muscle relaxants have been shown to be safe in patients with asthma.[25] Although atracurium and mivacurium have been associated with dose-dependent histamine release, only minor cardiovascular effects but no significant worsening of bronchospasm have been reported.[26]

Patients with severe asthma may require ongoing paralysis and sedation due to either persistently dangerous levels of hypercarbia/arterial hypoxemia or difficult to control patient ventilator interactions (dyssynchrony). However, its duration of use must be as short as possible, as the combination of a nondepolarizing muscle relaxant coupled with a glucocorticosteroid places patients with asthma at particularly high risk of developing critical illness myopathy.[27] A study demonstrated a 30% incidence of acute myopathy in patients with asthma who had received a neuromuscular blocking agent, with an increased risk with each additional day of muscle relaxation received.[28] When selecting the appropriate drug for the maintenance of sedation, the use of

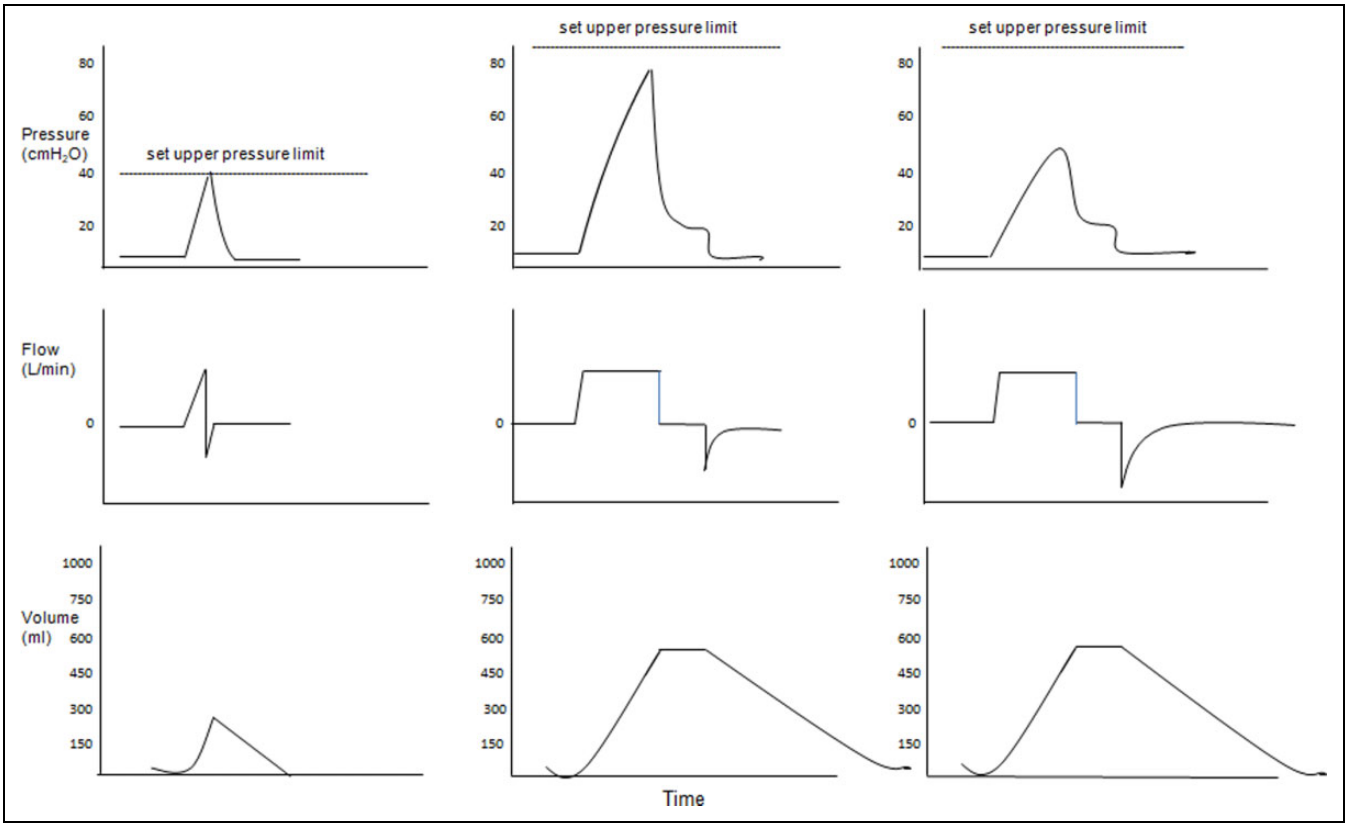

Figure 2. Ventilating patients with asthma using the volume preset ventilation mode (recommended). Left: Patient with severe bronchospasm and PIP of 80 cm H_2O. The upper pressure limit has been set too low at 40 cm H_2O; therefore, the inspiratory breath is prematurely terminated. Note the low tidal volume of 270 mL resulting in alveoli hypoventilation. Middle: The same patient with severe bronchospasm and PIP of 80 cm H_2O. The upper pressure limit is now correctly set at >80 cm H_2O with the patient now receiving an adequate tidal volume of >450 mL. Note that despite the high PIP (80 cm H_2O), the plateau pressure is 20 cm H_2O, which is within recommended safe pressure limits. Right: The same patient with a sudden improvement in bronchospasm (PIP = 50 cm H_2O). Despite the upper pressure limit remaining unchanged at >80 cm H_2O, the delivered tidal volume and plateau pressure remain the same at >450 mL and 20 cm H_2O, respectively. PIP indicates peak inspiratory pressure.

dexmedetomidine, propofol, or remifantanyl has been associated with a shorter length of ICU stay, shorter duration of MV, and improved long-term neurocognitive outcomes when compared to the benzodiazepine class of drugs.[29-31]

Selecting the Appropriate Mode of Ventilation

When selecting the mode of ventilation in the asthmatic patient, consideration must be given to the degree of underlying airway resistance and the presence of gas trapping, alveolar hyperinflation and permissive hypercapnia. An elevated peak inspiratory pressure (PIP) together with an increase in the PIP to plateau pressure (Pplat) gradient on ventilator waveform analysis is indicative of the presence of airflow resistance.[32] A PIP >80 to 100 cm H_2O is not an unusual finding in mechanically ventilated patients with severe asthma. Since the pathophysiology of asthma does not directly involve the alveoli, Pplat (which is a reflection of lung compliance or alveolar pressure) is expected to be within normal limits (<20 cm H_2O). Therefore, an increase in Pplat would suggest the presence of either worsening bronchospasm with associated gas trapping or an expanding pneumothorax.[33,34] This is described in Figure 1.

Although there has been no overall outcome differences between the volume preset versus the pressure preset mode of ventilation,[7] the volume preset mode is preferred in patients with asthma as both PIP and Pplat can be directly monitored in this mode but not the pressure preset mode. It must be remembered, so long as the Pplat is maintained below 30 cm H_2O, even extremely high levels of PIP (which is a hallmark of asthma) will not result in injury to the alveoli (barotrauma).

When ventilating patients with asthma, it is essential to reset the upper pressure limit to a value above the patient's intrinsic PIP. Failure of which may result in fatal alveolar hypoventilation secondary to premature termination of volume delivery. This is better understood by way of the following example. If the upper pressure limit is set to 40 cm H_2O in a patient with asthma having severe bronchospasm and an underlying PIP of 80 cm H_2O, volume delivery will be terminated once a pressure of 40 cm H_2O is reached. Since anatomical dead space volume (volume that does not participate in gaseous exchange) makes up one-third (approximately 150 mL in an adult) of the normal

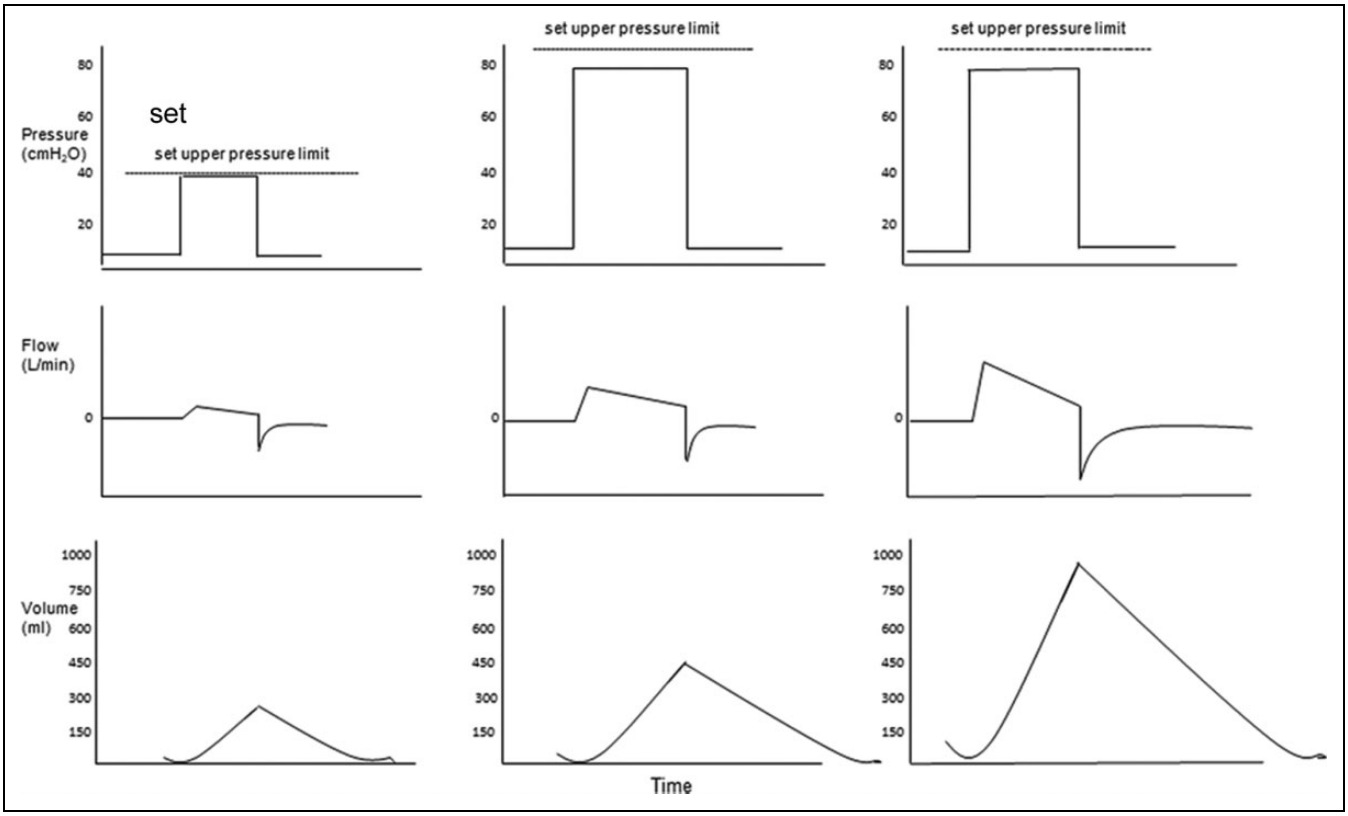

Figure 3. Ventilating patients with asthma using the pressure preset ventilation mode (not recommended). Left: Patient with severe bronchospasm and PIP of 80 cm H_2O. The upper pressure limit has been set too low at 40 cm H_2O, which only allows for a delivered tidal volume of 270 mL resulting in alveoli hypoventilation. Middle: The same patient with severe bronchospasm and PIP of 80 cm H_2O. In order to achieve an adequate tidal volume of >450 mL, the pressure control has been set at 80 cm H_2O and the upper pressure limit adjusted to >80 cm H_2O. Note that with this mode, the plateau pressure cannot be determined; hence, potential causes of high plateau pressures in the patient with asthma (pneumothorax or gas trapping) cannot be easily suspected with this mode. Right: The same patient with a sudden improvement in bronchospasm (PIP = 50 cm H_2O) and set pressure control of >80 cm H_2O. Due to the sudden decrease in airway pressure, the delivered tidal volume (driven by the set pressure control of 80 cm H_2O) is now dangerously high (1000 mL), thereby increasing the risk of pulmonary barotrauma and development of a pneumothorax. PIP denotes peak inspiratory pressure.

tidal volume (6 mL/kg), alveolar hypoventilation may ensue as a result of the delivered tidal volume being well below the set tidal volume. Therefore, the upper pressure limit must be set to a level above the PIP (>80 cm H_2O in this hypothetical scenario) to prevent fatal alveolar hypoventilation. With a sudden improvement in bronchospasm (and drop in PIP), the patient will continue to receive the set tidal volume with no increase in alveolar pressure (Figure 2).

In contrast, PIP and Pplat cannot be monitored on the pressure preset mode of ventilation. The patient will hence only receive adequate tidal volumes with this mode if the pressure limit as well as set pressure support is adjusted above the intrinsic airway resistance/pressure. With fluctuations in the degree of bronchospasm and its associated change in peak airway pressure which may be sudden, there runs the risk of either delivering extremely high and injurious or unacceptably low tidal volumes which may go unnoticed if alarm limits are not meticulously set and the patient not closely monitored.[35] For example, if in the above patient with severe bronchospasm and an underlying PIP (airway pressure) of 80 cm H_2O, the patient will only receive adequate tidal volumes if the upper pressure limit as well as the pressure control/pressure support level has been set >80 cm H_2O. In the event of worsening bronchospasm, in which case the PIP increases (eg, 90 cm H_2O), the patient will receive suboptimal tidal volumes, whereas with a sudden improvement in bronchospasm (and drop in PIP), the patient is at risk of receiving extremely high and injurious tidal volumes if not closely monitored (Figure 3).

Dynamic Hyperinflation

Gas trapping (Figure 4), also described as intrinsic positive end-expiratory pressure (PEEP) (PEEPi), auto-PEEP, dynamic hyperinflation, or expiratory airflow obstruction, may be quantified by measuring the total volume of exhaled gas during a 20- to 40-second period of apnea (end-inspiratory lung volume [VEI).[7,36] A VEI greater than 20 mL/kg has been associated with barotrauma as well as adverse heart–lung interactions. Since this technique requires complete patient paralysis and is not easy to perform, its use is not routine.[25]

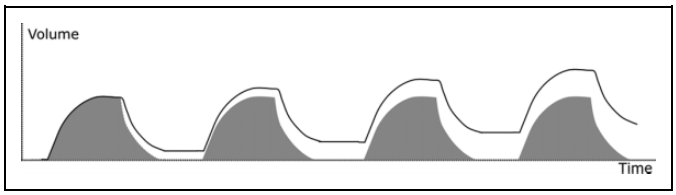

Figure 4. Gas trapping with dynamic hyperinflation (shaded area = normal breathing).

The presence of PEEPi is more easily determined by real-time analysis of ventilator waveform graphics. There are 2 ways of determining PEEPi on analyzing the pressure/time waveform in the volume preset mode: (1) observing for an increase in pressure above the set PEEP after initiating an end-expiratory hold maneuver with the patient paralyzed. The difference between this and the set PEEP (if any) is the PEEPi (Figure 5). (2) Observing for an increase in both Pplat and PIP with no change in the PIP to Pplat gradient. An expanding pneumothorax must also be considered as part of the differential diagnosis with this change (Figures 1C and 6 [top graph]).

The presence of PEEPi can also be determined on the flow/time waveform in the volume preset mode as a failure of the expiratory flow to return back to its baseline prior to initiation of the next inspiration (Figure 6 [middle graph]). When analyzing the volume/time waveform, (1) failure of the expiratory (descending) arm of the waveform to return to its baseline or (2) a difference between the inspiratory and expiratory volumes are both indicative of the presence of PEEPi (the presence of a leak in the ventilator circuit or around the ET tube must also be considered with these graphical changes) (Figure 6 [bottom graph]).[33,35]

Since bronchospasm is associated with slow emptying of the alveoli and prolongation of the alveoli time constant, adjusting the ventilator settings to allow for a longer expiratory time forms the bases of minimizing the buildup of PEEPi. Interventions aimed at achieving these goals include: (1) lowering the RR to 6 to 10 breaths per minute, (2) decreasing the inhalation:exhalation ratio (eg, 1:4 or 1:5), (3) increasing the inspiratory flow rate (eg, 80-100 L/min), (4) decreasing the inspiratory time, (5) decreasing the inspiratory pause time, and (6) administering lower tidal volumes of 4 to 6 mL/kg.[25,32,37,38] The above maneuvers are at the expense of worsening hypercapnia (see section on "Permissive Hypercapnia" below). Recommended initial ventilator settings are described in Table 1.

Significant gas trapping may yet develop despite implementation of the above precautions. In which case, the "trapped gas" may be manually decompressed by disconnecting the ventilator from the ET tube for a period of 20 to 30 seconds, while the clinician simultaneously decompresses the chest wall by placing his/her hands around the patients axilla and squeezing inward.[39]

In the mechanically ventilated patient who is spontaneously triggering the ventilator (not paralyzed), low levels of extrinsic positive end-expiratory pressure (PEEPe), just sufficient to counterbalance PEEPi, is believed to stent the airways open.

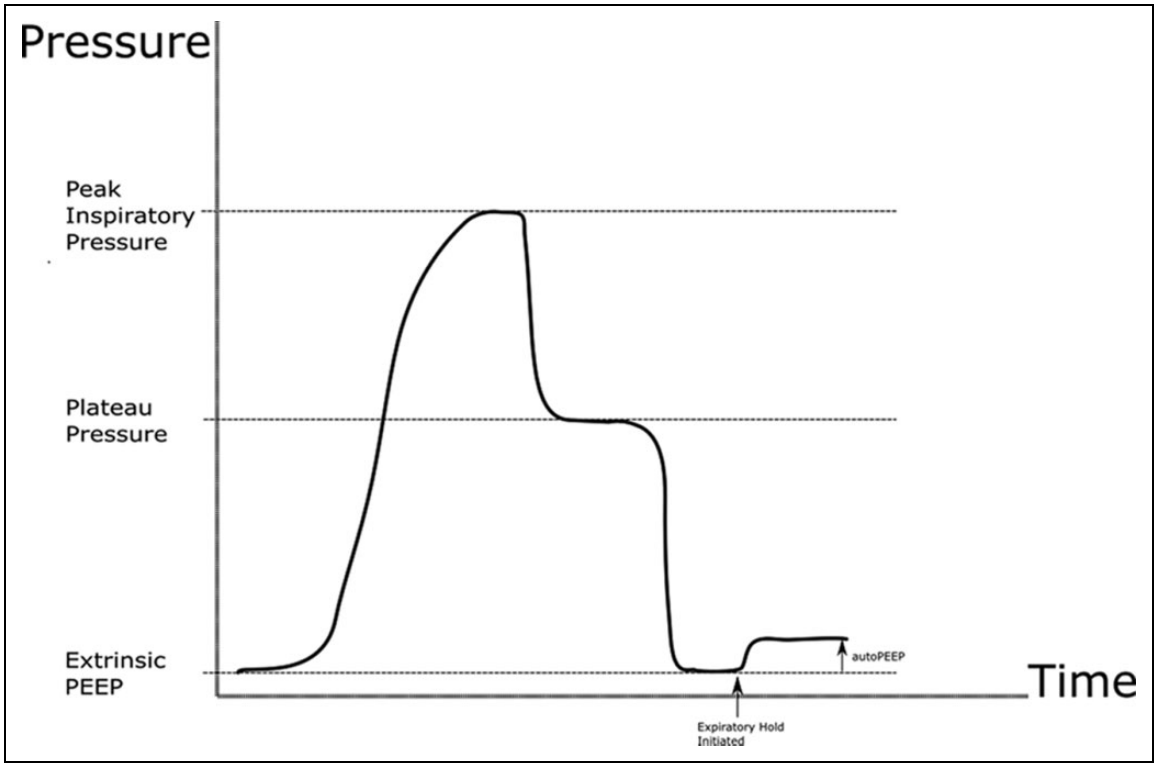

Figure 5. Determining the level of auto-PEEP on the pressure–time waveform in the volume preset ventilation mode by initiating an expiratory hold maneuver with the patient paralyzed. PEEP denotes positive end-expiratory pressure

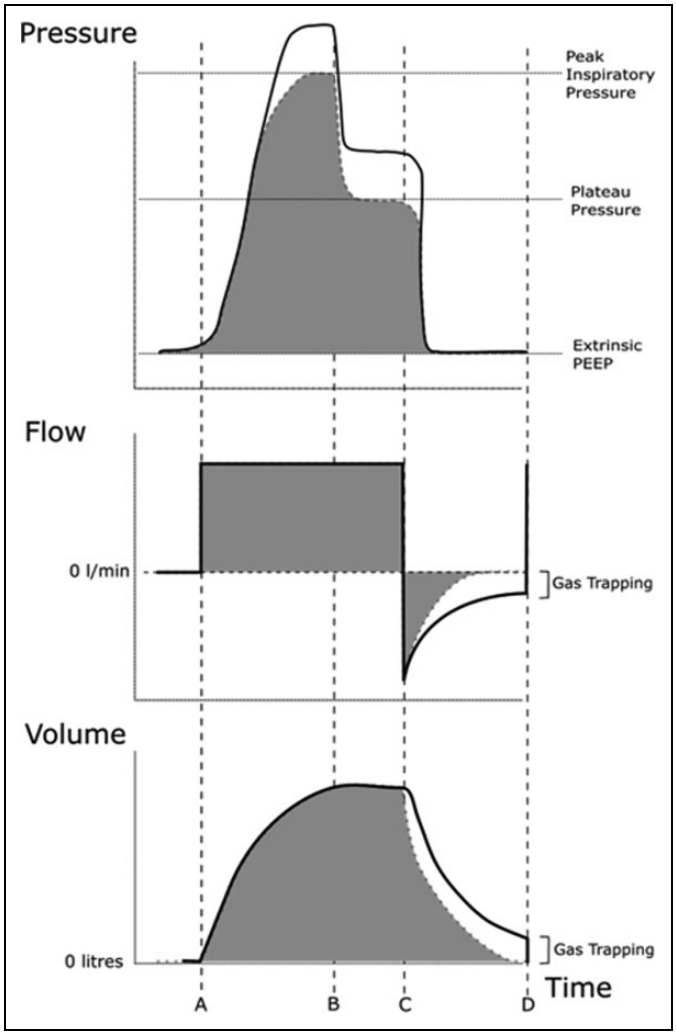

Figure 6. Identifying auto-PEEP (gas trapping) on the volume preset ventilator mode using ventilator graphics. Top: Pressure–time waveform: Note the increase in PIP and Pplat with no change in the PIP-Pplat gradient. This change is also noted with the presence of a pneumothorax. Middle: Flow–time waveform: Note the prolonged expiratory phase with failure of air flow to return to baseline before the next breath is initiated. Bottom: Volume–time waveform: Note the prolonged expiratory phase with gas trapping manifesting as the failure of the expiratory volume to return to baseline (shaded area = normal expiration). PEEP denotes positive end-expiratory pressure; PIP, peak inspiratory pressure; Pplat, plateau pressure.

Addition of PEEPe in these patients has been shown to reduce the mechanical work of breathing as well as improve respiratory effort, lung mechanics, ventilator triggering sensitivity, ventilation/perfusion mismatch, and gaseous exchange. Furthermore, there is no significant associated deterioration in pulmonary hyperinflation.[40-42] However, during controlled MV of the paralyzed asthmatic patient, there is no benefit with regard to the work of breathing by the addition of PEEPe, since there is no need for patient effort. In fact, since obstruction to airflow in the paralyzed severe asthmatic patient is more diffuse and involves both central noncollapsible and distal airways, the addition of PEEPe may actually worsen gas trapping. Therefore, consideration should be given for PEEPe to be set at zero (zero end-expiratory pressure (ZEEP)) in these patients.[35]

Table 1. Recommended Initial Ventilator Settings in Patients With Asthma. PEEPi denotes intrinsic positive end-expiratory pressure; I:E, inspiration to expiration ratio.

Parameter	Setting
Mode	Volume preset
Fraction of inspired oxygen	Adjust to SaO_2 >94%
Peak inspiratory pressure (PIP) limit	Adjust to level above peak airway pressure
Plateau pressure (Pplat)	Monitor to keep <20 to 30 cm H_2O
Positive end-expiratory pressure	0 cm H_2O if paralyzed and sedated, can use low levels to balance the PEEPi in the nonparalyzed patient
Tidal volume	4 to 6 mL/kg
Peak inspiratory flow	80 to 100 L/min
Respiratory rate	6 to 10 breaths/min
I:E ratio	1:4 or 1:5
Expiratory time	4 to 5 seconds

Troubleshooting the High Pressure Alarm

Although worsening bronchospasm is the most likely reason for a sudden increase in airway pressure in ventilated patients with asthma, consideration must also be given to other causes.[43] Firstly, it must be determined whether the sudden increase in pressure is secondary to a rise in airway resistance or to deterioration of pulmonary compliance (Figure 1). Figure 7 describes a practical approach to this.

Permissive Hypercapnia

In patients with severe asthma, retention of carbon dioxide is a direct consequence of the vicious cycle of worsening airflow obstruction and increase in gas trapping (alveolar dead space). The overall deterioration in alveolar ventilation is unable to overcome CO_2 production, thereby resulting in hypercarbia.[44] This is explained by the alveolar ventilation equation, where $Paco_2$ levels are inversely proportional to alveolar ventilation (alveolar ventilation = [tidal volume (Vt) − dead space volume (Vd)] × RR). Based on this equation, an increase in the RR should result in a reciprocal decrease in $Paco_2$. However, in patients with asthma, an increase in the RR leads to a decrease in the overall expiratory time and worsening of dynamic hyperinflation (and physiologic dead space volume), resulting in a worsening of hypercarbia ($Paco_2$) as well as an increase in intrathoracic pressure with its potential adverse consequences (hypotension, pneumothorax formation, and pulmonary barotrauma).

To balance the risks associated with ventilating patients with asthma, a strategy of permissive hypercapnia that allows for higher levels of $Paco_2$, on condition that the pH is

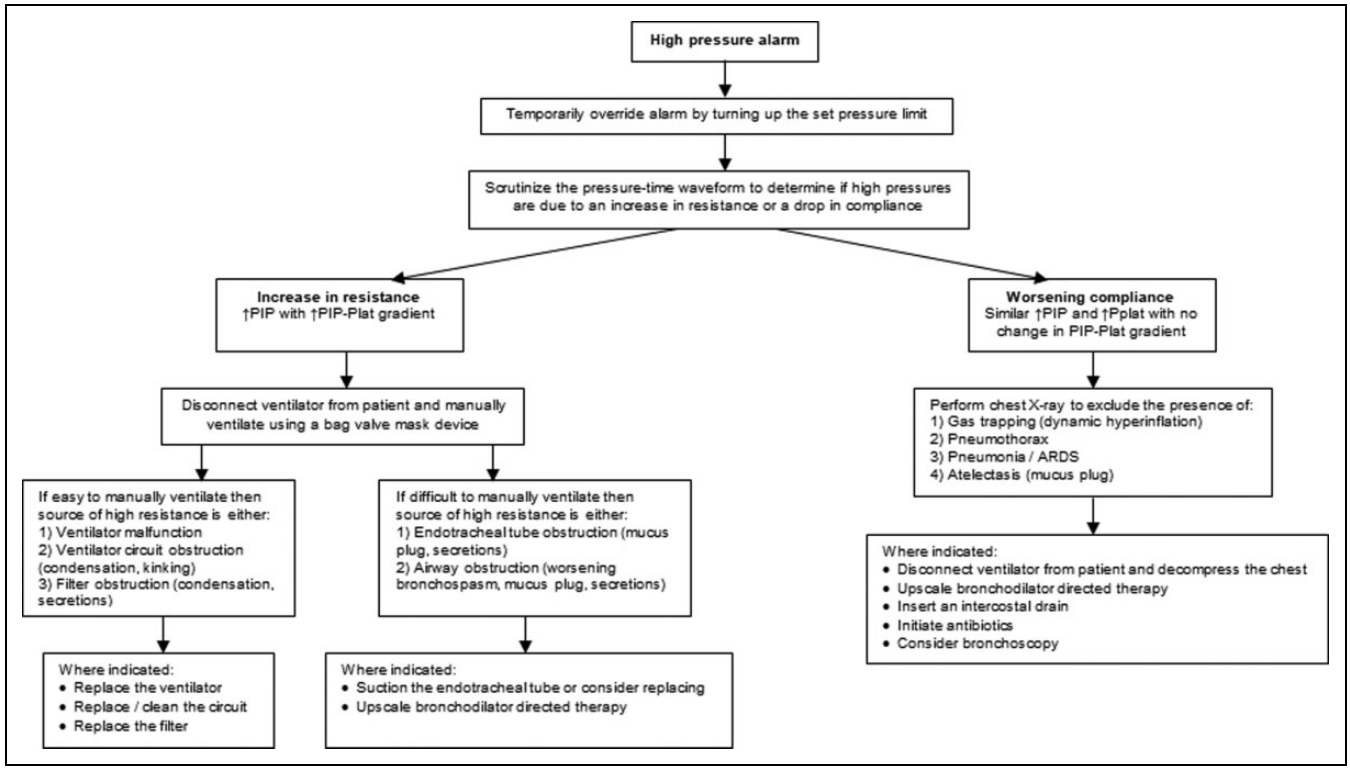

Figure 7. Troubleshooting high ventilator pressures in patients with asthma.

maintained above 7.2, has been advocated.[35,45-47] Except in patients with raised intracranial pressure, hypercapnic acidosis is generally well tolerated, and furthermore, its inflammatory blunting effects may be associated with additional benefit.[48] Alkalizing agents should only be considered in cases where the pH is consistently below 7.2. However, sodium bicarbonate must be avoided as the CO_2 produced from its metabolism readily crosses the cell membrane, thereby worsening intracellular acidosis.[45,49] Tris(hydroxymethyl) aminomethane (THAM), a weak base that is not metabolized into CO_2, has been shown to be effective in the management of hypercapnic acidemia.[48,50,51]

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is an invasive therapy with known complications. Although its exact indications have not been well defined, it is generally recommended in the setting of potentially reversible cardiopulmonary failure that is poorly responsive to maximal conventional medical therapy.[52,53] The literature is rather scarce with regard to the role of ECMO in the setting of status asthmaticus.[54,55] A review of the multicenter International Extracorporeal Life Support Organization registry by Mikkelsen and colleagues documented that status asthmaticus was the primary indication for ECMO in 24 of 1257 adult patients included in the registry. A total of 20 (83.3%) patients with asthma survived to hospital discharge, whereas only 50.8% of patients with other causes of respiratory failure (odds ratio = 4.86) survived.[56] This is not surprising, considering that the pathophysiology associated with acute asthma is fully reversible. The early use of ECMO, especially in the setting of refractory hypoxemia or severe hypercarbia (pH <7.2), is aimed at minimizing the adverse effects of MV, such as dynamic hyperinflation, pulmonary barotrauma, and hemodynamic instability.

Since hypercarbia rather than hypoxemia is the primary abnormality in status asthmaticus, the use of modified ECMO techniques such as extracorporeal carbon dioxide removal ($ECCO_2$ R) must also be given consideration. Extracorporeal carbon dioxide removal when compared to ECMO requires a much lower blood flow rate, is less invasive (requiring just a single venous catheter), and is less labor intensive.[57] Brenner and colleagues reported the successful use of $ECCO_2$ R in 2 cases of refractory status asthmaticus.[58] In patients with asthma, transfer to an ECMO/$ECCO_2$ R facility may be considered in the setting of severe refractory hypercarbia with persistent acidosis (pH < 7.2), when extremely high airway pressures limit the delivery of adequate tidal volumes to the alveoli or when hemodynamic instability is persistent.

Noninvasive MV

Although the utility of noninvasive positive pressure ventilation (NIPPV) is controversial and not well established in the management of patients with acute asthma,[59] there are increasing number of studies demonstrating potential benefit.[60-63] However, appropriately powered trials proving its efficacy in patients with asthma are currently lacking. In a

retrospective study comparing the pre- and post-introduction of NIPPV eras, Murase and colleagues reported a reduction in ET intubation rates in individuals with severe asthma who had been initiated on NIPPV.[64] Fernández and colleagues also documented a decrease in the need for ET intubation but reported no differences in the length of ICU stay, hospital stay, or mortality.[65] Other smaller studies documented an improvement in oxygenation, decrease in carbon dioxide retention,[66] improvement in airflow obstruction (FEV_1)[67,68] and a reduction in in-hospital mortality.[69] One study reported a prolongation of hospital stay though.[70]

Continuing Asthma-Directed Therapy

Continuous combination inhaled bronchodilator therapy (β_2-agonist and anticholinergic class agents) must continue to be administered via the in-line nebulization unit of the ventilator and not directly from the wall oxygen supply.[71,72] Since the degree of bronchospasm is intense in most of these patients, the likelihood of inhaled therapy effectively reaching its target receptor is suboptimal. Hence, other routes of drug delivery such as intravenous infusion of salbutamol or subcutaneous adrenaline/terbutaline must be considered in the poorly responsive patient.[73] The benefits of adjuvant systemic corticosteroid therapy and intravenous magnesium sulfate (2 g every 30 minutes to a maximum of 10 g) has been well documented.[35] However, magnesium must be used with caution in the setting of renal dysfunction and other magnesium accumulation states.[74] In hospitalized patients, a 7- to 14-day course of an intravenous corticosteroid (eg, hydrocortisone 100-200 mg or equivalent, 6 hourly) is recommended.[27,75]

Heliox in a 70:30 helium to oxygen ratio, which although sharing the same viscosity, is less dense than ambient air. The decreased density leads to a lower Reynolds number with a higher predisposition to laminar rather than turbulent flow and has been shown to improve nebulized drug delivery in refractory cases.[76,77] There are also case reports suggesting benefit with the use of inhalational anesthetic agents in severe refractory asthma.[78,79]

Mechanical ventilation and the increased likelihood of hemodynamic instability, coupled with the use of corticosteroids and paralyzing agents, places patients with asthma at higher risk of both gastrointestinal stress ulceration and venous thromboembolism. Hence, standard doses of stress ulcer prophylaxis as well as anticoagulation therapy must also be administered in this setting.[80,81]

Conclusion

Appropriate and timely management of patients with severe asthma requiring MV is a rewarding exercise in the hands of the knowledgeable and experienced clinician. Clinician understanding of the underlying pathophysiology and correct interpretation of ventilator graphics forms the foundation and basis to correctly and safely managing these patients.

Authors' Note

Abdullah Ebrahim Laher contributed to literature search and review, drafting of manuscript, and final editing. Buchanan K. Sean assisted with literature search and review, initial draft, drawing of figures, and editing.

Declaration of Conflicting Interests

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