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Mechanical Ventilation for Severe Asthma

James Leatherman, MD

Acute exacerbations of asthma can lead to respiratory failure requiring ventilatory assistance. Noninvasive ventilation may prevent the need for endotracheal intubation in selected patients. For patients who are intubated and undergo mechanical ventilation, a strategy that prioritizes avoidance of ventilator-related complications over correction of hypercapnia was first proposed 30 years ago and has become the preferred approach. Excessive pulmonary hyperinflation is a major cause of hypotension and barotrauma. An appreciation of the key determinants of hyperinflation is essential to rational ventilator management. Standard therapy for patients with asthma undergoing mechanical ventilation consists of inhaled bronchodilators, corticosteroids, and drugs used to facilitate controlled hypoventilation. Nonconventional interventions such as heliox, general anesthesia, bronchoscopy, and extracorporeal life support have also been advocated for patients with fulminant asthma but are rarely necessary. Immediate mortality for patients who are mechanically ventilated for acute severe asthma is very low and is often associated with out-of-hospital cardiorespiratory arrest before intubation. However, patients who have been intubated for severe asthma are at increased risk for death from subsequent exacerbations and must be managed accordingly in the outpatient setting.

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ABBREVIATIONS: ECLS = extracorporeal life support; NIV = noninvasive ventilation; NMBA = neuromuscular blocking agent; PEEP = positive end-expiratory pressure; Ppk = peak airway pressure; Pplat = plateau airway pressure; V_{EI} = lung volume at end inspiration

Approximately 2% to 4% of patients who are hospitalized for an acute exacerbation of asthma will require mechanical ventilatory support.[1,2] Indications for immediate intubation include respiratory arrest, altered level of consciousness, and extreme exhaustion.[3] The majority of hypercapnic patients do not require intubation,[4] but worsening respiratory acidosis or progressive fatigue despite optimal therapy signals the need for ventilatory assistance. Intubation of the patient with asthma has been reviewed elsewhere.[5]

The role of noninvasive ventilation (NIV) in acute severe asthma is not well defined.[6-8] A review of NIV in respiratory failure found only level C evidence to support a role for NIV in asthma and recommended that its use be limited to a minority of patients who are carefully selected and monitored.[8] Nonetheless, a recent analysis of a national database documented increasing use of NIV for life-threatening asthma and a concomitant decrease in use of invasive mechanical ventilation.[9] Five studies have reported on the use of NIV for patients with asthma

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who had persistent hypercapnia or excessive work of breathing despite treatment with bronchodilators and corticosteroids. Of the 112 patients treated with NIV, only 19 (17%) ultimately required intubation.[10-14] In one of the studies, NIV was as effective as invasive mechanical ventilation in lowering the $Paco_2$ of patients with severe hypercapnia (Fig 1).[14] Although uncontrolled, these observations suggest that in the absence of contraindications such as altered consciousness, hemodynamic instability, excessive secretions, or uncooperativeness, a trial of NIV is appropriate for patients with asthma who might otherwise require intubation.

Ventilator Management

Key issues related to ventilator management of patients with acute severe asthma include: (1) methods for assessing pulmonary hyperinflation, (2) impact of ventilator settings on the severity of hyperinflation, and (3) consequences and management of hypercapnia.

Assessment of Hyperinflation

Acute severe asthma is characterized by markedly increased airway resistance and pulmonary hyperinflation. Dynamic hyperinflation is initiated when a reduction in expiratory flow leads to incomplete exhalation of delivered tidal volume. As lung volume increases with subsequent breaths, higher elastic recoil pressure and larger airway diameter augment expiratory gas flow and a new steady state is quickly reached, at which time the entire tidal volume can be exhaled (Fig 2). In a series of landmark studies, Tuxen and colleagues[3,15,16] and Williams et al[17] assessed pulmonary hyperinflation in severe asthma by measuring the volume of gas exhaled during a

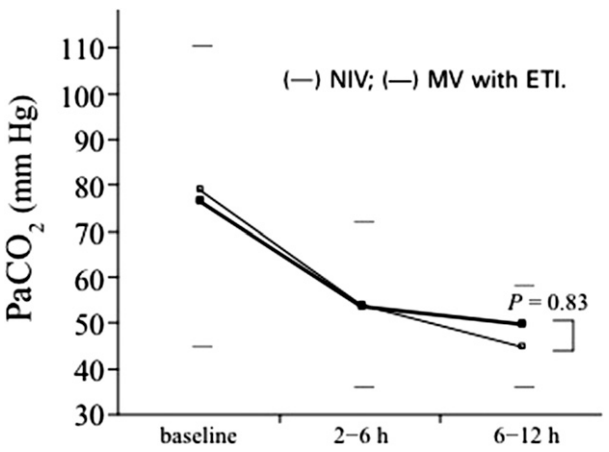

Figure 1 – *Change in $Paco_2$ with NIV and MV with ETI in patients with acute asthma and severe hypercapnia. (Observational data, patients not randomized.) ETI = endotracheal intubation; MV = mechanical ventilation; NIV = noninvasive ventilation. (Adapted with permission from Murase et al.[14])*

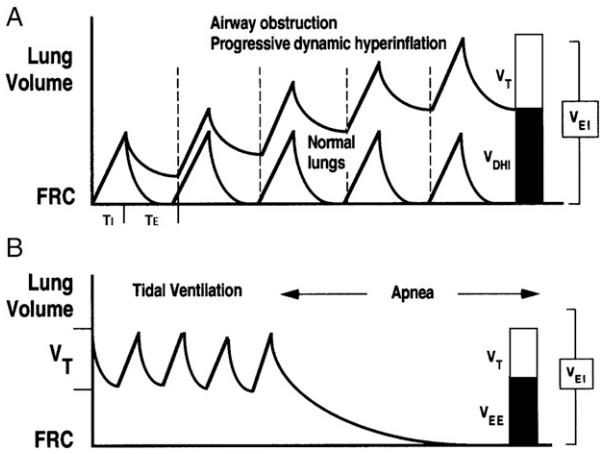

Figure 2 – *A, Dynamic hyperinflation. B, Measurement of V_{EI} and V_{EE} by use of a prolonged apnea. V_{EE} and V_{DHI} are equivalent. FRC = functional residual capacity; T_E = expiratory time; T_I = inspiratory time; V_{DHI} = volume (above FRC) caused by dynamic hyperinflation; V_{EE} = volume (above FRC) at end expiration; V_{EI} = volume (above FRC) at end inspiration; V_T = tidal volume. (Reprinted with permission from Tuxen and Lane.[15])*

prolonged apnea, defined as the lung volume at end inspiration (VEI) (Fig 2). The VEI includes the tidal volume and the additional volume of gas due to dynamic hyperinflation (Fig 2). As discussed later, VEI is influenced by both the severity of airflow obstruction and ventilator settings (Fig 3). In one study, VEI was found to be the most reliable predictor of ventilator-related complications.[17]

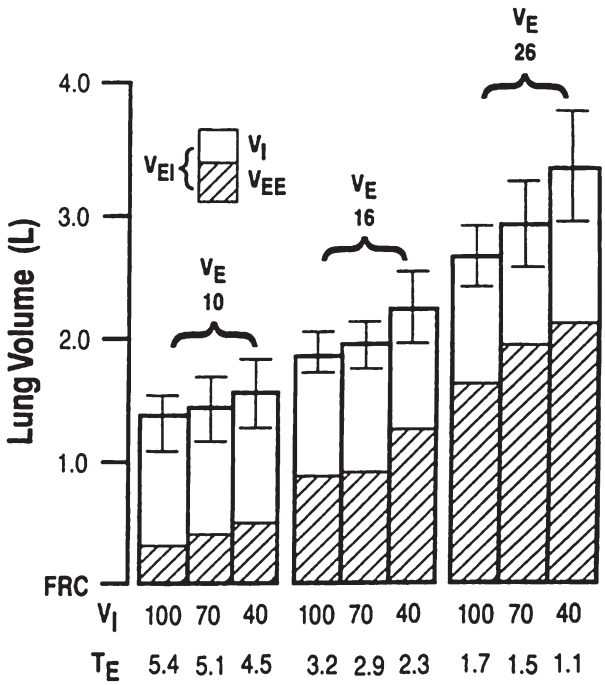

Figure 3 – *Effect of V_E and V_I on dynamic hyperinflation during mechanical ventilation for severe asthma. Note that V_I has a significant influence on dynamic hyperinflation at the two higher levels of V_E, but not at V_E of 10 L/min; see text for discussion. V_E = minute ventilation; V_I = inspiratory flow rate. See Figure 2 legend for expansion of other abbreviations. (Reprinted with permission from Tuxen and Lane.[15])*

A more common method of assessing hyperinflation is by measuring plateau airway pressure (Pplat) and auto-positive end-expiratory pressure (PEEP) during volume-cycled ventilation (Fig 4).[3,18-21] Since nonobese patients with asthma typically have near-normal respiratory system compliance, Pplat is primarily influenced by the degree of hyperinflation. In four series of mechanical ventilation for acute severe asthma, the average Pplat was 24 to 26 cm H_2O.[13,22-24] It should be appreciated that Pplat represents the average end-inspiratory alveolar pressure, and the maximal alveolar pressure in some units will be higher. An acceptable upper limit for Pplat has not been well defined, but most published algorithms have suggested a value of 30 cm H_2O.[5,18-21] One study found no relationship between Pplat and the incidence of hypotension or barotrauma,[17] but others have observed that these complications are uncommon when Pplat remains < 30 cm H_2O.[5,22] Higher levels of Pplat usually indicate excessive hyperinflation but may overestimate transpulmonary pressure and the risk of ventilator-related complications in the presence of reduced chest wall compliance due to obesity or other causes.[25]

Auto-PEEP in severe asthma is often in the range of 10 to 15 cm H_2O[23,24] but may be higher. As with Pplat, the level of auto-PEEP above which risk of complications increases has not been well defined. Forced expiration can lead to significant overestimation of auto-PEEP, potentially leading to unnecessary restriction of minute ventilation.[26] Expiratory muscle activity is not always clinically apparent, especially in obese patients.[27] Repeat assessment after a brief period of neuromuscular paralysis is recommended when auto-PEEP remains markedly elevated despite sedation. On occasion, unexpectedly low values of measured auto-PEEP can be seen in patients with fulminant asthma who are ventilated at very low respiratory rates, presumably due to airway closure that prevents accurate assessment of end-expiratory alveolar pressure.[28]

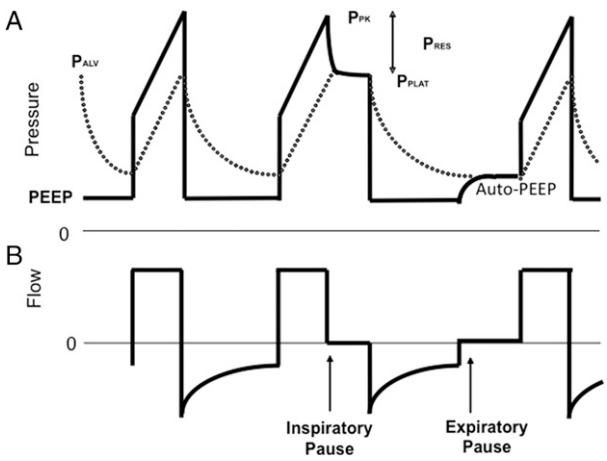

Figure 4 – *A, B, Schematic representation of airway pressure (A) and flow (B) during controlled mechanical ventilation. Note that flow persists at end-expiration, indicating that end-expiratory alveolar pressure exceeds circuit pressure (ie, auto-PEEP is present). The dotted line represents* PALV. PALV = *alveolar pressure; PEEP = positive end-expiratory pressure;* PPK = *peak airway pressure;* PPLAT = *plateau airway pressure;* PRES = *inspiratory flow-resistive pressure. (Courtesy of Robert Shapiro, MD.)*

Peak airway pressure (Ppk) has also been used to guide ventilator management. The initial description of controlled hypoventilation for severe asthma targeted a Ppk < 50 cm H_2O,[29] an approach adopted by others.[30] One limitation of this strategy is that Ppk is highly dependent on inspiratory flow-resistive properties and may not reliably reflect the degree of hyperinflation (Fig 4). Patients with asthma who are ventilated with high inspiratory flow rates often have a Ppk > 50 cm H_2O, but the latter does not necessarily predict an increased risk of barotrauma.[3,22] In addition, changes in Ppk may not consistently reflect the reduction in dynamic hyperinflation that follows prolongation of expiratory time, presumably because of an increase in airway resistance as lung volume decreases (Fig 5).[24]

Ventilator Settings

Minute ventilation is a critical determinant of hyperinflation in the setting of severe airflow obstruction. Tuxen and Lane[15] documented marked pulmonary hyperinflation when minute ventilation was increased from 10 L/min to 16 L/min and then to 26 L/min, with increased risk of hypotension and barotrauma (Fig 3).[15,17] Such high levels of minute ventilation should clearly be avoided, but extreme limitation of minute ventilation, as advocated by some authors,[31] is generally unnecessary. When

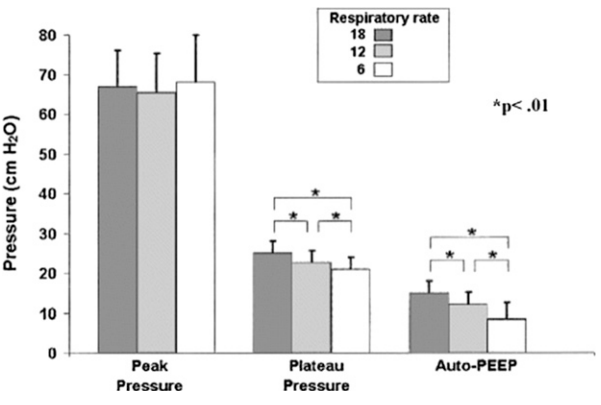

Figure 5 – *Peak pressure, plateau pressure, and auto-PEEP at respiratory rates of 18, 12, and 6 breaths/min during mechanical ventilation for severe asthma (n = 12). See Figure 4 legend for expansion of abbreviation. (Reprinted with permission from Leatherman et al.[24])*

patients with asthma with a baseline minute ventilation of approximately 10 L/min underwent a stepwise reduction in respiratory rate, both Pplat and auto-PEEP decreased as expected, but the magnitude of change was relatively modest (Fig 5).[24] The latter is explained by the very low rates of gas flow after a few seconds of expiration (Fig 6).[24] Since flow progressively decreases throughout expiration, the impact of a given prolongation of expiratory time on dynamic hyperinflation will be less at lower respiratory rates (Fig 6). In addition, a significant amount of the overall pulmonary hyperinflation in asthma may due to gas trapped behind occluded airways that is not readily amenable to ventilator manipulation.[16] In brief, there is often little to be gained by reducing the respiratory rate below 10 to 14 breaths/min when a tidal volume of 7 to 9 mL/kg is used. An exception might be when hyperinflation is marked (eg, Pplat > 30 cm H_2O) or has resulted in complications, because even a small reduction in hyperinflation could have a meaningful clinical impact.

High inspiratory flow rates (≥ 100 L/min) and a square waveform have been advocated for patients with severe airflow obstruction.[3,18,22] The rationale is to shorten inspiratory time and lengthen time for expiration, thereby reducing hyperinflation.[3] Although this approach produces a more favorable inspiratory to expiratory ratio, it results in only minor prolongation of expiratory time (Table 1). As demonstrated by Tuxen and Lane,[15] inspiratory flow rate was a major determinant of dynamic hyperinflation at high levels of minute ventilation but had minimal impact when minute ventilation was 10 L/min (Fig 3). In brief, inspiratory flow rate and waveform have minimal impact on the degree of hyperinflation once minute ventilation has already been limited (Table 1).

There are limited data regarding the use of external PEEP during controlled mechanical ventilation of patients with severe asthma.[32-34] Some patients with asthma demonstrate a biphasic response indicative of classic expiratory flow limitation, in that levels of applied PEEP up to approximately 80% of auto-PEEP will not affect lung volume or airway pressures, but both will be increased by higher levels of PEEP (Fig 7).[32] Different responses to PEEP have also been described. One prospective study of patients with asthma undergoing controlled mechanical ventilation found that applied PEEP worsened hyperinflation and had detrimental hemodynamic effects.[33] Since auto-PEEP was not recorded, it is uncertain how often adverse effects were due to levels of applied PEEP that exceeded auto-PEEP.[33] In contradistinction, it has also been reported that applied PEEP may occasionally produce paradoxical lung deflation, as evidenced by a reduction in lung volume and airway pressures (Fig 7).[34,35] Notwithstanding the latter observation, clinical experience would suggest that a beneficial response to applied PEEP during controlled mechanical ventilation of patients with asthma is unlikely, and minimal PEEP (≤ 5 cm H_2O) is recommended.[3,18-21] If a trial of stepwise increments in PEEP is undertaken, it should be terminated if Pplat increases.

Hypercapnia

Hypercapnia is common during mechanical ventilation of patients with severe asthma. One study reported an average $Paco_2$ of 68 mm Hg and pH of 7.18 despite a minute ventilation of 9 L/min.[24] In a second study, the highest $Paco_2$ on the first day of mechanical ventilation averaged 67 mm Hg and exceeded 100 mm Hg in 12% of cases.[36] The term "permissive" hypercapnia may not be entirely accurate when applied to severe asthma. Since hypercapnia is a consequence of increased dead space ventilation caused by alveolar overdistension, attempts to lower $Paco_2$ by increasing minute ventilation will result in more hyperinflation and further increase in physiologic dead space. Tuxen and colleagues[3,15] found that normocapnia often required a minute ventilation of 15 to 20 L/min, a level of ventilation often associated with potentially dangerous levels of hyperinflation.[17]

Serious adverse consequences of hypercapnia are uncommon. Effects on the central nervous and cardiovascular systems are of greatest concern. Cerebral

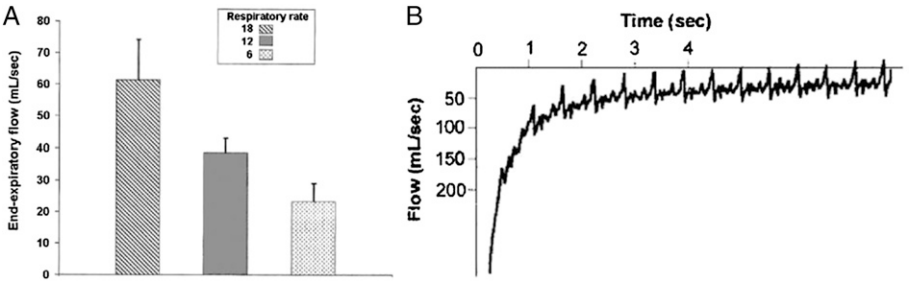

Figure 6 – *A, End-expiratory flow rates at respiratory rates of 18, 12, and 6 breaths/min during mechanical ventilation for severe asthma (n = 7). B, Expiratory flow tracing from an individual patient. (Reprinted with permission from Leatherman et al.[24])*

TABLE 1] Effect of V_I and Waveform in Severe Asthma

V_I and Waveform	T_I, s	T_E, s	I:E Ratio	ΔDHI, mL	ΔAuto-PEEP, cm H_2O
60 L/min, decelerating	1.1	3.2	1:3	…	…
120 L/min, square	0.3	4.0	1:13	Approximately −50	Approximately −1

Assume tidal volume 600 mL, respiratory rate 14 breaths/min, respiratory system compliance 60 mL/cm H_2O, and end-expiratory flow rate of 60 mL/s. DHI = dynamic hyperinflation; I:E ratio = inspiratory to expiratory timing ratio; PEEP = positive end-expiratory pressure; T_E = expiratory time; T_I = inspiratory time; V_I = inspiratory flow rate.

edema and subarachnoid hemorrhage have been attributed to hypercapnia but are rare.[37,38] Acute hypercapnia increases cerebral blood flow and intracranial pressure,[39] an effect that is of greatest concern in the setting of cerebral anoxia due to cardiorespiratory arrest prior to intubation. Cardiac effects of acute hypercapnia include a fall in intracellular pH that reduces contractility, but sympathetic activation more than compensates for this direct effect on cardiac contraction, and cardiac output is usually increased.[39] Hypercapnia-related arrhythmias are uncommon in the absence of underlying heart disease.

Alkalinizing agents may be considered when arterial pH is persistently less than 7.15 to 7.2.[3,18,22] Unfortunately, sodium bicarbonate has limitation as a treatment of respiratory acidosis. CO_2 that is produced readily crosses cell membranes and can potentially lead to a significant decrease in intracellular pH with rapid infusions.[39] Furthermore, even partial correction of severe respiratory acidosis may require several hundred milliequivalents of sodium bicarbonate.[39] If an alkalinizing agent is deemed necessary and kidney function is adequate, an alternative to sodium bicarbonate is tromethamine.[22,40,41] Tromethamine does not generate CO_2 or lead to a decrease in intracellular pH and has been shown to partially reverse the myocardial depressant effect of acute hypercapnia.[42] Absent an urgent reason to correct acidemia (eg, serious arrhythmias, hyperkalemia, unexplained hemodynamic instability), it may be reasonable to withhold alkalinizing therapy and wait for hypercapnia to resolve with lessening of airflow obstruction. Many patients show improvement in hypercapnia during the first 12 h of intubation.[43]

Nonventilator Management

Therapy of the mechanically ventilated patient with severe asthma has three essential components: inhaled bronchodilators, corticosteroids, and drugs to optimize patient-ventilator interaction. Additional nonconventional approaches, such as administration of heliox or general anesthetics, bronchoscopy, and extracorporeal

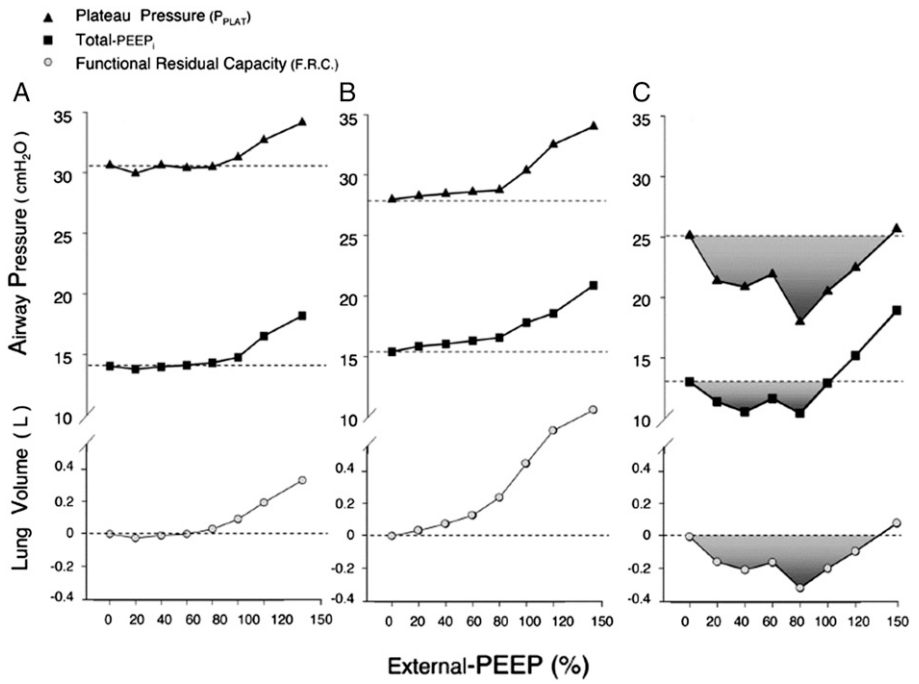

Figure 7 – *Effect of a stepwise increase in external PEEP (as percentage of auto-PEEP) on lung volume, P_{PLAT}, and total PEEP (defined as the measured end-expiratory occlusion pressure) in patients with severe airflow obstruction: three possible responses. A, Biphasic response indicating expiratory flow limitation (no change P_{PLAT}, total PEEP, or lung volume until external PEEP exceeds auto-PEEP, after which all increase); B, Overinflation (increase in lung volume P_{PLAT}, and total PEEP at levels of external PEEP less than auto-PEEP); C, "Paradoxical" deflation (reduction in P_{PLAT}, total PEEP and lung volume). See Figure 4 legend for expansion of abbreviations. (Adapted with permission from Caramez et al.[34])*

life support (ECLS), may be considered in selected cases but are seldom necessary.

Standard Therapy

Either a metered-dose inhaler or nebulizer can be used to administer bronchodilators. When delivery is optimal, the recommended dose of albuterol is four to six puffs by metered-dose inhaler or 2.5 mg by nebulization.[44] Continuous albuterol has not been studied during mechanical ventilation for severe asthma, but the evidence in nonintubated patients suggests it offers no advantage over intermittent therapy.[45] With very high doses of albuterol there is increased potential for side effects. In particular, albuterol-related lactic acidosis may be a serious concern for patients with asthma who already have respiratory acidosis.[46] Combination therapy with ipratropium should be considered.[47] Corticosteroids have a beneficial antiinflammatory effect that may become evident within 6 to 12 h of administration and are an essential component of therapy for acute severe asthma. The optimal dose of corticosteroids for patients with asthma who require mechanical ventilation has not been established, but 2 mg/kg/d of methylprednisolone or equivalent is probably adequate.[47]

Deep sedation is often necessary to prevent patient-ventilator dyssynchrony and enforce controlled hypoventilation. A combination of propofol (or a benzodiazepine) and fentanyl is optimal, and high doses may be required.[12] Since patients may have substantial improvement in airflow obstruction within 24 to 48 h,[22,43] avoidance of residual sedation that unnecessarily delays extubation is desirable. A major advantage of propofol over benzodiazepines is that it permits deep sedation with rapid awakening when discontinued. Patients who require more prolonged ventilatory support may benefit from daily awakening with physical therapy to lessen the risk of ICU-acquired weakness,[48] provided that weaning of sedation is not accompanied by excessive agitation or a marked increase in airway pressures.

Administration of a neuromuscular blocking agent (NMBA) is sometimes necessary. It is preferable to give the NMBA by intermittent boluses rather continuous infusion, because intermittent dosing permits serial assessment of the adequacy of the sedation and may lessen the risk of myopathy associated with prolonged paralysis (see later discussion).[49] When sedative and opioid agents are used liberally, supplemented by intermittent boluses of an NMBA if needed, relatively few patients will require prolonged, continuous neuromuscular paralysis.[50]

Nonconventional Interventions

Heliox is a mixture of helium and oxygen whose density is less than air. Heliox reduces frictional resistance when gas flow is turbulent and, by lowering the Reynolds number, encourages laminar flow.[51] Since the benefit of heliox depends on the percentage of helium, potential candidates for its use should require an $F_{IO_2} \leq 0.4$.[51] Although heliox has been used in the treatment of asthma for >80 years, relatively few studies have described its use during mechanical ventilation.[51] Two early reports noted a decrease in P_{aCO_2} when heliox was administered to patients with asthma, but in one study ventilator settings were continually adjusted, and the other included mostly nonintubated patients.[52,53] Subsequent studies that ensured a constant tidal volume and respiratory rate found that P_{aCO_2} was unaffected by heliox.[51,54] Heliox has been reported to lessen dynamic hyperinflation. Two studies that evaluated its use in mechanically ventilated patients with COPD found that auto-PEEP decreased by an average of 4 and 8 cm H_2O, respectively.[55,56] In contrast, we administered 70:30 heliox to nine mechanically ventilated patients with asthma or COPD and could not document a single instance in which heliox led to a meaningful reduction in indices of hyperinflation (Pplat, auto-PEEP) or P_{aCO_2}.[57] The reason for the variable response to heliox in different studies is unclear. Any benefit from heliox should be seen almost immediately, and changes that occur much later should not be attributed to its use. A brief (15-30 min) therapeutic trial in which indices of hyperinflation and P_{aCO_2} are measured before and after its administration, without other interventions, will suffice to test its efficacy. Prior to using heliox, it is essential to understand how it influences ventilator operation.[58]

Inhalational anesthetics have been administered to patients with asthma who were refractory to conventional bronchodilator therapy.[59-61] In the only study, to our knowledge, that assessed lung mechanics, isoflurane led to a decrease in airway resistance and auto-PEEP in three patients with severe asthma.[60] Use of an anesthesia conserving device allows inhalational anesthetics to be administered in the ICU. Inhalational anesthetics may cause hypotension due to decreased arterial and venous tone, requiring additional fluid loading and sometimes vasopressors.[61] As with heliox, a positive response to inhaled anesthetics should be evident within a short period of time, and continued administration in the absence of a clinically meaningful reduction in hyperinflation or hypercapnia is unwarranted.

Ketamine is an IV dissociative anesthetic with bronchodilator properties. Its use in asthma has been primarily

in nonintubated patients, with mixed results.[62] Most of the published experience with ketamine during mechanical ventilation has involved children, but there have been anecdotal reports of benefit in adults.[63] One prospective study of 11 mechanically ventilated adults with severe asthma found that an infusion of ketamine (1 mg/kg load, then 1 mg/kg/h for 2 h) was associated with a decrease in Ppk and $Paco_2$.[64] Although usually given for only a few hours, prolonged use of ketamine by continuous infusion has been reported.[62]

Bronchoscopic removal of impacted mucus has been anecdotally reported to lower airway pressures and improve gas exchange in patients with severe asthma.[65,66] A study of children with asthma who were mechanically ventilated compared the outcomes of 29 patients who underwent bronchoscopy with 15 patients who did not.[67] Bronchoscopy was associated with a significantly shorter duration of mechanical ventilation and was without complications, but given the retrospective nature of the study it is uncertain if the two groups were comparable.[67] Although probably safe in most instances, there is a potential for worsening bronchospasm. Of note, excellent outcomes without use of bronchoscopy have been reported.[23,68] Patients who fail to improve after several days of mechanical ventilation might be considered for diagnostic bronchoscopy to inspect the airways for mucus plugs that could be extracted, the goal being to reduce the duration of ventilator support. Administration of *N*-acetylcysteine during bronchoscopy or rhDNase intratracheally have been reported to enhance clearance of impacted mucus.[65,69]

ECLS has also been used for severe asthma.[70] Data from the international ECLS registry revealed that status asthmaticus was the primary indication for extracorporeal support in 24 cases, with a survival of 83%.[70] Venovenous ECLS has been used most often, but extracorporeal CO_2 removal has also been achieved with a pumpless arteriovenous circuit.[71] Since acute severe asthma is fully reversible and is rarely associated with nonpulmonary organ failure, fulminant asthma would seem to be an ideal indication for ECLS. However, large series have reported excellent outcomes without using extracorporeal support, indicating that the latter is rarely necessary.[23,68] One scenario in which ECLS would be appropriate would be the combination of profound respiratory acidosis and extreme hyperinflation that had resulted in significant barotrauma or hemodynamic instability. One potential benefit of ECLS is that it could provide a period of stability during which bronchoscopy could be used to remove impacted mucus.[72]

Outcomes

Important outcomes for the patient with severe asthma who is mechanically ventilated include mortality, nonfatal complications, and posthospitalization prognosis.

Mortality

The risk of death for patients who underwent mechanical ventilation for severe asthma was analyzed in four large databases, with reported mortality rates ranging from 6.5% to 10.3%.[1,2,73,74] A literature review of single-center studies published between 1977and 2003 reported an average mortality of 8%, with a range of 0% to 38%.[75] The reason for the wide variation in reported mortality is not clear. Two centers with extensive experience in managing patients with asthma who are mechanically ventilated have reported mortality rates of 2.5% (4 of 162) and 0.6% (1 of 139), respectively.[23,68]

When delineated, the immediate cause of death has been attributed to a variety of complications, including sepsis with multiorgan failure, pulmonary embolism, myocardial infarction, tension pneumothorax, and unplanned extubation. In many instances, a fatal outcome is due to cerebral anoxia due to out-of-hospital cardiorespiratory arrest rather than to complications that arise in the ICU.[3,23,73,76] An analysis of > 1,200 patients who underwent mechanical ventilation for severe asthma found that in-hospital deaths were often preceded by cardiorespiratory arrest before admission to the ICU.[73] Prehospital cardiac arrest with cerebral anoxia was the leading cause of death in the large experience reported by Tuxen et al.[3] An analysis of 162 episodes of mechanical ventilation found that each of the four fatalities was due to cerebral anoxia from out-of-hospital cardiorespiratory arrest.[23]

Complications

Patients with severe asthma may experience complications common to other critical illnesses, including ventilator-associated pneumonia, sepsis, or VTE. Additional important complications include barotrauma, hypotension, CNS injury, and myopathy.

The incidence of pneumothorax during mechanical ventilation for severe asthma in three large series ranged from 3% to 6%.[23,36,68] The risk of pneumothorax increases with marked hyperinflation and in one study was limited to patients whose V_{EI} exceeded 20 mL/kg.[17] Even a small pneumothorax may be catastrophic in patients with asthma, because hyperinflated lungs that resist collapse permit a rapid increase in intrapleural pressure

with sudden clinical deterioration and sometimes death. For this reason, pneumothoraces must be identified and treated promptly. Unfortunately, clinical diagnosis of tension pneumothorax in patients with severe asthma may be challenging.[3] Thoracic ultrasonography may aid in bedside diagnosis.[77] Unless a chest radiograph has confirmed a large pneumothorax, chest tubes should ideally be placed by blunt dissection rather than by trocar or the Seldinger technique to avoid piercing the hyperinflated lungs.[3]

The risk of hypotension during mechanical ventilation for severe asthma is also related to the degree of pulmonary hyperinflation.[17] The primary mechanism through which excessive pulmonary hyperinflation causes hypotension is by decreasing venous return, but an increase in right ventricular afterload may also be important. Rarely, extreme hyperinflation can lead to circulatory arrest.[78] When a ventilated patient with severe airflow obstruction develops unexplained hypotension, a 30- to 60-s apnea trial is recommended.[3] If the apnea trial and a rapid infusion of fluid do not restore BP, other causes of hypotension such as pneumothorax and myocardial depression must be considered. Rarely, hypotension in status asthmaticus can be due to stress cardiomyopathy, most likely as a consequence of massive sympathetic activation.[79]

The most devastating complication of status asthmaticus is irreversible damage to the CNS. In the vast majority of cases, the mechanism is cerebral anoxia due to cardiorespiratory arrest prior to intubation. In the absence of cardiac arrest, it is rare for patients with status asthmaticus to suffer permanent cerebral injury. Severe hypercapnia may cause coma, but long-term neurologic sequelae are rare, even when carbon dioxide levels are markedly elevated.[39]

Approximately 15% of patients who undergo mechanical ventilation for severe asthma develop muscle weakness due to an acute myopathy.[50] Affected patients typically have severe generalized weakness that is apparent only after sedation is discontinued. As a rule, the diaphragm is relatively spared, and acute myopathy by itself seldom causes delays in extubation once airflow obstruction has resolved.[49] The pathogenesis of acute myopathy in severe asthma is not well understood but has been attributed to the combined effects of glucocorticoids and prolonged neuromuscular paralysis.[49] However, patients with asthma who undergo prolonged mechanical ventilation under deep sedation with minimal or no paralysis can also develop severe myopathy.[50] Patients who develop severe myopathy have undergone mechanical ventilation for persistent airflow obstruction for a minimum of 5 to 7 days, with an average of duration of 12 days in several series.[49,50,80,81] It is likely that prolonged near-total muscle inactivity, whether induced by neuromuscular paralysis or by deep sedation, is a critical factor in development of acute myopathy. Although physical therapy is sometimes needed for $\geq$ 2 weeks, patients invariably make a complete recovery.

Postdischarge Prognosis

Although mechanical ventilation for severe asthma is associated with low immediate mortality, patients are at increased risk for recurrent fatal attacks over the subsequent decade.[82] Indeed, prior intubation has been identified as the strongest risk factor for death from asthma.[1] These data emphasize the critical importance of outpatient management following hospital discharge, including avoidance of known triggers, regular use of controller medications, and early use of oral corticosteroids for exacerbations. Patients must also be educated about the importance of activating the emergency medical system without delay when experiencing severe symptoms. Excellent outcomes are the rule even for those patients who are intubated when unconscious or moribund, as long as they are not pulseless. In contrast, the majority of patients with asthma who have an out-of-hospital cardiac arrest die or suffer devastating neurologic sequelae. For patients experiencing a potentially life-threatening exacerbation of asthma, every minute counts.

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