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Mechanical Ventilation in Severe Asthma

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Introduction

Asthma is a cause of severe morbidity and mortality in the United States. Severe acute asthma accounts for over one million emergency room visits per year *(1)*. The vast majority of patients presenting with acute asthma can be successfully managed with β_2-agonist bronchodilators, corticosteroids, and oxygen.

Despite maximal medical therapy, it is estimated that 1– 3% of patients with severe asthma may require endotracheal intubation and mechanical ventilation during their hospital course *(2,3)*. For the purposes of this chapter, severe asthma requiring mechanical ventilatory support will be referred to as status asthmaticus (SA). It appears that the number of patients progressing to SA is increasing, especially in the United States *(4,5)*.

Pathophysiology of Status Asthmaticus

The pathophysiological hallmark of asthma-related airway inflammation is infiltration of the airway wall with eosinophils and activated T-lymphocytes, in conjunction with smooth-muscle spasm, causing bronchiolar constriction and mucus plugging of the lumen *(6,7)*. Airway changes include extensive mucus plugging in the airway lumen, smooth-muscle hypertrophy, mucus-gland hyperplasia, thickening of basal membrane, and infiltration of the airway mucosa with inflammatory cells. Most deaths associated with SA are due to inspissation of the mucus in the airway, causing occlusion of as much as 50% of the cross-sectional area of the small airways 2 mm in diameter and less *(8)*. In fatal cases without significant mucus plugging the cause of respiratory failure is thought to be severe smooth-muscle spasm*(9)*.

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During an asthma attack, epithelium and adventitial layers of the airway are infiltrated with eosinophils and lymphocytes *(10).* The T-helper 2 (TH2) subtype of lymphocytes are also found in the bronchial walls, these lymphocytes can produce interkeukin (IL)-3, IL-4, IL-5, and granulocyte macrophage-colony stimulating factor (GM-CSF) *(11,12).* In SA the predominant cellular response is appears to be neutrophils *(13).*

Indications for Endotracheal Intubation and Mechanical Ventilation

The mortality associated with those who require mechanical ventilation is significant, approaching 38% *(4,14–16),* therefore, immediate, aggressive intervention is necessary to reduce morbidity and mortality in these patients. Early endotracheal intubation and mechanical ventilation in SA, when used optimally, is associated with better clinical outcome *(17).*

The majority of patients with SA have multiple indications for endotracheal intubation *(17).* It appears that older patients with severe asthma are more likely to require mechanical ventilation and other studies have suggested female patients require intubation more frequently *(15,18,19).* A history of previous intubations or mechanical ventilation increases the likelihood of subsequent intubation and mechanical ventilation *(20).*

Upper respiratory infections and medication noncompliance are important risk factors frequently identified as predisposing factors leading to endotracheal intubation *(4,15,18).* There are no clear-cut guidelines for intubation and mechanical ventilation with patients suffering from an acute attack of asthma; the decision to proceed with endotracheal intubation is largely clinical and dependent on the course of airway obstruction. Some of the indications for endotrachael intubation are listed in Table 1.

Technique of Endotracheal Intubation

Endotrachael intubation of critically ill patients in SA may involve considerable risk and has significant potential for morbidity and mortality. In general, an early controlled intubation is preferable to a late "crash" intubation of a clinically unstable patient. Two major routes for intubation exist: oral and nasal; there is no consensus on the optimal route for all patients. Blind nasal intubation for severe asthmatics, although initially attractive in that protective airway reflexes are not abolished, may precipitate laryngospasm and bronchospasm, leading

Table 1
Some Indications for Endotracheal Intubation

- Worsening respiratory distress
- Altered mental status
- Inability to speak
- Increased pulsus paradoxus
- Severe acidosis (pH <7.25)
- Hypoxemia (PaO2 <60 mm Hg and acute hypercapnia PCO_2 >42 mm Hg) in conjunction with a deteriorating clinical condition
- Respiratory or cardiac arrest

to further difficulty in airway management *(18).* The diameter of the endotrachael tube that can be successfully placed is generally smaller than the oral route. Orotracheal intubation is generally the preferred route in most circumstances,because it is associated with less trauma, sinusitis, and bleeding complications. For orotracheal intubation, the use of rapidly acting sedative and analgesic medicines will relieve the patient's anxiety, discomfort, and pain, and may facilitate intubation in a combative patient with altered mental status. The use of these drugs must be balanced against the risk of precipitating laryngospasm and an inability to successfully intubate and ventilate the patient. These patients are at high risk of requiring surgical establishment of an emergency airway.

Sedation and Analgesia

Sedation is a critical component in the provision of mechanical ventilation in SA. Sedation provides for better patient-ventilator synchrony, decreases oxygen consumption, and may improve patient comfort. The provision of amnesia and anxiolysis is also critical to patient management. No single drug simultaneously excels in analgesia, anxiolysis, anesthesia, and amnesia, so combinations of agents are frequently employed. Sedation and amnesia may be obtained by various medication regimens including benzodiazepines, opioids, or nonopioid intravenous (IV) anesthetic agents. Benzodiazepines are excellent anxiolytic and amnesic drugs; when used in higher doses or in combination with other agents, particularly opioids, adequate levels of sedation can be achieved.

Diazepam, lorezapam, and midazolam are commonly used benzodiazepines. Midazolam, an imidazo compound with a half-life of 1–4 h has the most rapid onset of action of the benzodiazepines. Because of these pharmacodynamic properties, midazolam is commonly used for intubation and initiation of sedation. For long-term mechani-

cal ventilation, anxiolysis, amnesia, and sedation may be obtained with diazepam or lorezapam at a much lower drug-acquisition cost. Large doses or rapid infusions of benzodiazepines may cause apnea, hypotension, or prolonged sedation. Paradoxical agitation may be seen with benzodiazepine use, especially in the elderly. Sole use of a benzodiazepine produces little analgesia, so opioids are commonly used in conjunction with benzodiazepines for adequate analgesia.

Fentanyl was the first of the potent synthetic, lipid-soluble opioids; it is 100 times more potent then the morphine. Sufentanyl is 10 times more potent then fentanyl. Both of these drugs have more hemodynamic stability, absence of histamine release, and ablation of adverse reflexive sympathetic activity than morphine *(21),* rendering them an excellent choice for intubation as well as during the mechanical ventilation. Morphine is commonly used for long term mechanical ventilation.

Nonopioid IV Anesthetic Agents

Propofol is a widely used drug in anesthesia for the induction and maintenance of general anesthesia. Propofol may also be used in the intensive care unit (ICU) at lower doses for sedation of patients on mechanical ventilation *(22).* A potential advantage in the use of propofol in acute asthma is that it has mild bronchodilators properties. Many authors argue that due to short half-life and duration of action of propofol, patients on mechanical ventilation have a faster and more reliable wake-up time when compared to midazolam *(23).* Propofol is prepared in a solution of soybean oil, glycerol, and purified egg phosphate. Due to these constituents, incidences of bacterial growth with resultant sepsis and death has been reported *(24,25).*

Etomidate

Etomidate is a carboxylated imidazole, which inhibits the microsomal conversion of dehydroascorbic acid, thereby enhancing GABA receptor-mediated cell depression, its action is characterized by rapid induction and awakening. Etomidate is a widely used agent for induction of anesthesia; it is also been shown to be a safe drug for rapid sequence intubation in the emergency department (ED) *(26)*. Etomidate, when used in repeated doses, can cause adrenal suppression. There is also a dose-related association of etomidate with myoclonus (27).

Ketamine

Ketamine hydrochloride is an IV anesthetic agent with properties of analgesia as well as sedation. Ketamine is also a bronchodialator;

this effect is produced via vagolysis. There is evidence that ketamine relaxes the tracheal smooth muscle by endothelial action on the inositol, 1, 4, 5, triphosphate signaling pathway *(28).* Patients refractory to conventional bronchodilator therapy can be tried with higher doses of ketamine, as ketamine in lower doses has not been to be shown to be an effective bronchodilator. The hallucinogenic side effect of ketamine in patients may be anxiety-provoking in patients; to counter this effect, the use of concomitant benzodiazepines is recommended.

Inhalational Anesthetic Agents

Patients who remain refractory to conventional bronchodilator may respond to inhalational anesthetic agents such as halothane, enflurane, and isoflurane *(29,30).* This therapy will also provide for general anesthesia for the patient. Isoflurane has a better safety profile for cardiac arrhythmia's and hypotension; thus, it is the agent most commonly used in patients with refractory SA.

Echeverria reported an unusual case of SA whose severe bronchospasm was unresponsive to enflurane inhalational anesthesia, who then responded to halothane (*31*). Patients on prolonged halothane anesthesia can develop increased serum level of bromide, which can cause encephlopathy. Blood levels of bromide may be followed as a level of serum bromide of >12.5 correlates with neurological symptoms *(31).*

Neuromuscular Blocking Agents (Muscle Relaxants)

In order to provide for mechanical ventilation and employ long expiratory times, neuromuscular blockade may be required. The potential benefits of this therapy must be weighed against the risks of prolonged muscular weakness. Two major classes of neuromuscular blocking (NMB) agents are used for pharmacologic paralysis, depolarizing agents, and nondepolarizing agents.

Depolarizing NMB agents produce prolonged depolarization of the motor end-plate; this causes an initial fasciculation in skeletal muscles, followed by a rapid onset of relaxation and paralysis.

Succinylcholine is the prototype of the depolarizing muscle relaxants; the widespread use of this drug for endotracheal intubation is due to its reliable and rapid onset of muscle relaxation. Succinylcholine complications include transient elevation of potassium, myalgias, increase in intraocular, intracerebral, and intragastric pressure. Succinylcholine is also related with a potentially fatal but rare complication, malignant hyperthermia, with an incidence of 1 in 50,000 adults and 1 in 15,000 children.

Nondepolarizing NMB agents

Nondepolarizing muscle relaxants act as competitive inhibitors of acetylcholine at the motor end-plate. Pancuronium, Atracurium, Cisatracurium, Vecuronium, and Rocuronium are classified as either long-acting, intermediate-acting, or short-acting according to the duration of action. It has been shown that in near-fatal asthma requiring intubation and prolonged use of NMB, there is a higher incidence of acute myopathy. The incidence of myopathy increases with concomitant use of corticosteroids and each additional day of muscle relaxation *(32).* The use of nondepolarizing NMB agents in critically ill patients has led to prolonged muscle paralysis; this complication usually involves the proximal as well as the distal muscle groups. The cause of prolonged paralysis has been attributed to a myopathy produced by the nondepolarizing relaxants. In case of Vecuronium, it can also be a result of the slowly excreted metabolite, 3-desacetylvecuronium *(33).* Muscle paralysis is not only has been reported with amino steroid-based NMB (Pancuronium and Vecuronium) but also benzylisoquinolinium NMB agents (Atracurium). The pathogenesis of this process is unclear; there is some evidence from animal studies that an interaction between NMB agents and corticosteroids can lead to a corticosteroid-induced myopathy.

The need for the use of prolonged paralysis of a patient with asthma in ICU must be carefully considered; the lowest dose and shortest duration of NMB should be selected and the need for continued paralysis continuously reassessed. The use of a peripheral nerve stimulator with regular monitoring of the train of four stimulation is highly recommended.

Respiratory Mechanics in SA

Patients with acute asthma or other causes of obstructive lung disease display a number of dynamic changes in the respiratory mechanics. These changes include an increase in inspiratory and expiratory resistance; the expiratory flow in the patient is too slow to fully reach relaxation volume (V_{rel}). The alveoli are then not fully evacuated before the next breath is initiated, producing an increase in the functional residual capacity (FRC), and leading to the development of dynamic hyperinflation or intrinsic positive end expiratory pressure (PEEPi) *(16,34).* Jain et al. has described the predictors of dynamic hyperinflation in patients with asthma and obstructive lung disease; these include: elevated intrinsic PEEP, elevated plateau pressure, and elevated volume at end-inspiration *(35).*

Elevated PEEPi

In normal individuals at rest, the end expiratory lung volumes correspond closely with the elastic equilibrium volume or the relaxation volume of the respiratory system. In obstructive lung diseases, the rate of alveolar emptying is impaired due to increasing airways resistance. This produces hyperinflation, thus there is a positive end expiratory elastic recoil pressure, which is termed as intrinsic PEEP or (PEEPi). In asthmatic patients on mechanical ventilation, PEEPi can be measured by monitoring the expiratory limb of flow volume curve; this provides an estimate of PEEPi. Patients with high PEEPi may be unable to trigger the ventilator to deliver a breath. If the ventilator is set to trigger breaths via changes in airway pressure, patients have to overcome the intrinsic PEEP present and then generate further negative pressure before they can trigger the next breath. Patients with high blood pressure may have increased respiratory muscle fatigue due to the increased work of breathing to overcome this pressure. The use of flow triggering reduces this problem.

Elevated Plateau Pressure (P_{plat})

Plateau pressure may be a better indicator of dynamic hyperinflation than peak airway pressure. Although elevated volume at end expiration (V_{EI}) has been shown to more accurately correlate with various complications, however, the patient needs to be heavily sedated and paralyzed to accurately measure this value. P_{plat}, therefore, is a more practical parameter to follow in patients on the mechanical ventilation. Elevated peak inspiratory pressure (PIP) during volume cycle mode often precedes and does not have any consistent relationship with the development of barotrauma *(36).* High PIP has not been shown conclusively to be related to increased barotrauma, some studies have identified peak airway pressures less than 50 cm H_2O as safe, in one study none of the patients on mechanical ventilation with peak airway pressures less than 50 cm H_2O suffered barotrauma (37).

Elevated Volume at End-Inspiration (V_{EI}):

This volume can be measured by applying a period of apnea after disconnecting the ventilator in a patient on NMB agents and measuring the total volume exhaled. V_{EI} has been shown to correlate with hypotension and barotrauma better than standard ventilatory airway pressure monitoring in patients with severe asthma *(38).* A V_{EI} of less than 20 mL/kg is associated with lower morbidity and mortality in patients with severe asthma and on mechanical ventilation. A target

minute ventilation of <20mL/kg is achieved by adjusting tidal volumes, inspiratory time, and respiratory rate. The patient may require sedation and neuromuscular blockade to achieve these goals *(16)*.

Complications Associated with Dynamic Hyperinflation (DHI)

Patients with increased dynamic hyperinflation are at a high risk for complications of barotrauma. The chances of barotrauma increase when the transalveolar pressure becomes excessive relative to the structural integrity of the alveolus, leading to rupture of the alveoli. This air then dissects along the intralobular septa producing pneumothorax, subcutaneous (SC) emphysema, and pneumomediastinum. Some of the other complications of barotrauma include bronchopleural fistula, tension lung cysts, systemic gas embolism, and subpleural air cysts. The hemodynamic complications that occur as a result of dynamic hyperinflation caused by PEEPi, applied PEEP, or tension pneumothorax include decreases in venous return. This may lead to severe systemic hypotension, shock, and electromechanical dissociation. Other hemodynamic complications include compression of the pulmonary vascular bed, increases in the pulmonary vascular resistance, producing decreases in the right ventricular output, and impaired left ventricular filling due to shifts in the interventricular septum. Various cardiac arrhythmias have been reported to be associated with the barotrauma, including sinus tachycardia and supraventricular tachycardia (SVT) *(16)*.

Modes and Strategies for Mechanical Ventilation in Acute Asthma

To reduce the morbidity and mortality in a patient with acute severe asthma, the goal of the ventilator strategy should be to decrease DHI. Thus to achieve this low tidal volumes of 5–7 mL/kg, inspiratory flow V_I of 80–100 and respiratory rate (R) 11–14 breaths/min should be employed to achieve an initial minute ventilation of <115 mL/kg/min. V_{EI} and P_{plat} should then be checked. If V_{EI} is >20 mL/kg, the target <20 V_{EI} mL/kg can often be achieved by reducing the respiratory rate. The target for the P_{plat} should be <30. DHI can also be reduced with further reductions in respiratory rate and/or tidal volume. If intrinsic peep is significant the patient may have difficulty triggering the ventilator as a negative inspiratory pressure equal to PEEPi plus the ventilator sensitivity must be generatedby the patient in order to obtain a breath. The use of spontaneous ventilator modes such as pressure or volume support, if possible, may be better tolerated by the patient in these situations. This problem can be overcome by increasing the applied PEEP to

just slightly beneath the measured PEEPi (so-called bias PEEP) or changing the level to flow triggering. In the extreme cases of excessive PEEPi, the patient may suddenly develop cardiovascular collapse; in this situation, removing the patient from the ventilator to let the gases exhale may be a life-saving act.

Another maneuver to reduce dynamic hyperinflation is to reduce the inspiratory time and prolong the expiratory time enough to permit adequate lung emptying *(34).* With reduced tidal volumes and decreased inspiratory time leading to prolonged expiratory time and decreased set rate on the ventilator, there is a possibility of the patient developing hypercapnia. This hypercapnea is secondary to the priority for these patients to decrease the dynamic hyperinflation while keeping adequate oxygenation. This maneuver is often employed via permissive hypercapnea (*see* below).

Permissive Hypercapnia

Permissive hypercapnia is an approach to critically ill ventilated patients with dynamic hyperinflation. It allows for acceptable gas exchange while minimizing the increased risk of barotrauma or volutrauma to the patient. Contraindications for permissive hypercapnia include intracraneal hypertension, hypovolumia, or hyperkalemia. The negative inotropic effect of hypercapnia can aggravate the cardiovascular effects of asthma; correction of pH above 7.15 can be corrected via metabolic means, although clear-cut guidelines do not exist *(39).* Correction of the respiratory acidosis may be achieved using Carbicarb with sodium load 15 mEq or with Bicarbonate with sodium load of 30 mEq.

If low sodium and low volume is a priority to correct the acidosis, Tris (hydroxymethyl)aminometane (THAM) can be used; it is an amine buffer that does not generate CO_2. The deleterious effects of THAM include hypotension, hypoglycemia, and shift of oxy hemoglobin dissociation curve to the left.

Intratracheal insufflation is another possibility to increase CO_2 excretion without increasing the airway pressure in the ventilated patients. This technique is still in the experimental stages and is not widely available.

Noninvasive Mechanical Ventilation

There is a lot of interest in noninvasive mechanical ventilation in the patients with hypercapnic or hypoxic respiratory failure, including asthma, COPD, and congestive heart failure. In one study where patients were randomized into closely matched groups, noninvasive

mechanical ventilation was found to be effective as conventional ventilation in improving gas exchange in patients with acute hypoxemic respiratory failure. The risk of ventilator-associated pneumonia was less in the group receiving noninvasive ventilation *(38)*. Few studies have examined noninvasive mechanical ventilation in SA. The inability to use NMBs and the tenuousness to the airway must be balanced against the attractiveness of this modality of ventilation before it can be recommended for routine use. The personnel and economic resources needed for the first 48 h of mechanical ventilation in patients with obstructive disease are similar between invasive and noninvasive mechanical ventilation. The long-term economical impact of noninvasive ventilation is yet to be determined (40).

Delivery of Bronchodilators Therapy in Patients Receiving Mechanical Ventilation:

The aggressive use of inhaled bronchodilators is an important part of the of the management of acute asthma exacerbation. In various large studies, the use of β-agonists has consistently been shown to be superior, through inhalation rather than IV routes, but there is no consensus in the optimal aerosol delivery method of bronchodilators in the patients on mechanical ventilation.

In one study, metered dose inhaler (MDI) plus aerosol-holding chamber delivered a nearly fivefold greater dose of drug as compared with a jet nebulizer in patients on mechanical ventilation *(40)*. The advantages of MDI with aerosol chamber include: ease of use, reliable dosing, lower cost, and higher deposition of the drug in the lungs *(41)*. Other studies fail to reproduce this difference and suggest that there is no significant difference between the delivery of bronchodilators via jet nebulizer or MDI.

Conclusion

Patients with SA, usually respond well to intensive therapy with β-agonist and systemic steroids with improvement in symptoms. If the patient's condition does not respond to the conventional medical therapy and continues to deteriorate to the point where the respiratory failure is imminent, rapid recognition of the urgency of the situation is important because it can be life-saving. The morbidity and mortality of asthma remains high; a 6-yr posthospitalized patient follow-up study found mortality of 22.6% *(47)*. Once mechanical ventilation has been instituted, it is important to recognize the importance of various strategies to achieve ventilatory goals for these patients. Initial ventilatory goals include avoidance of hyperinflation by decreasing patient's V_{EI} to

less than 20 mL/kg while keeping P_{plat} less than 30 cmm/H_2O. If these ventilator strategies are used correctly, the morbidity and mortality in patients with SA can be reduced *(42)*. The physician should also recognize the importance of the detrimental effects of PEEPi, and use the various strategies to reduce the hyperinflation. The physician should also be aware of the use of sedation, as well as the use and potential complications of NMBs.

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