Management of Status Asthmaticus

23

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Case Presentation

A 25-year-old woman with a history of well controlled asthma presented to the emergency department with shortness of breath, wheezing, and sore throat over 4 days. Her wheezing and shortness of breath had worsened despite the use of inhaled short acting beta agonist every 1–2 h. Typically, she had been maintained on high dose inhaled corticosteroids and a long acting beta agonist with good control. She had a history of exacerbations with upper respiratory tract infections. She was evaluated in pulmonary clinic where she was noted to have tachypnea and increased work of breathing despite administration of a nebulized short acting beta agonist. She was subsequently sent to the emergency department.

In the emergency department, she was found to be in respiratory distress. Continuous albuterol and intravenous corticosteroids were administered. Arterial blood pH measured 7.5 and partial pressure of carbon dioxide and oxygen while breathing ambient air were 30 and 65, respectively. Despite the above treatment, the patient's respiratory status continued to worsen, and she required endotracheal intubation and mechanical ventilation. Initial ventilator settings were: tidal volume of 450 ml, respiratory rate of 20, fraction of inspired oxygen (FIO_2) of 0.40 and a positive end expiratory pressure (PEEP) of 5 cm of water. Peak airway pressure during a passive breath measured at 65 cm of water; with a pressure during an end expiratory hold (plateau pressure) of 15 cm of water. Continuous infusion of benzodiazepines and opiates provided sedation. She was admitted to the intensive care unit for further management.

In the evening, the intensivist received a call regarding hemodynamic instability. The patient's pulse rate was 150 beats per minute with a systolic blood pressure measuring 70 mm of Hg. Chest x-ray and thoracic ultrasound show no evidence of pneumothorax. Breath sounds were diminished but equal bilaterally with expiratory wheezing. Pressure measured at airway opening during end inspiratory and end expiratory holds are 45 and 25, respectively.

Question What is the next step in the management of this patient?

Answer Disconnect the ventilator to allow exhalation of trapped air.

The patient has life-threatening accumulation of air within the thorax, commonly referred to as "air trapping" or "auto-PEEP". Pneumothorax would have a similar presentation, but it was excluded by chest x-ray and bedside ultrasound.

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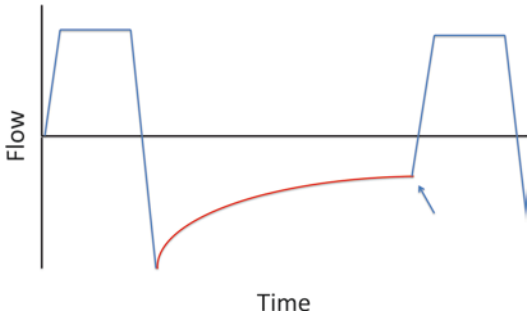

Fig. 23.1 Incomplete exhalation of delivered tidal volume. Above is a flow volume curve of an asthmatic patient on volume cycled mechanical ventilation. The patient is still exhaling the prior tidal volume at the time of the delivery of the next breath (see *arrow*). Ideally, the exhalation phase flow rate would return to 0 (complete emptying of tidal volume) prior to delivery of the next breath. The entrapped volume remains in the thorax and can accumulate and cause sequela of air trapping

Due to the patient's bronchospasm, she has an extremely prolonged expiratory phase, which leads to premature delivery of mechanical breaths prior to full exhalation of the previous breath (Fig. 23.1).

Over time, air accumulates and becomes "trapped" within the relatively fixed thoracic cage volume. Eventually, residual air increases the intrathoracic pressure (see ideal gas law below for pathophysiologic explanation).

Ideal Gas Law

$$PV = nRT$$

P = pressure, V = Volume, n = gas amount (moles), R = constant, T = temperature.

From this relationship, if the amount of gas is increased (n) in a fixed volume (V, in this case the thoracic cage) at a constant temperature, pressure will increase. If left uninterrupted, the increase in thoracic pressure will overcome the venous return pressures in the superior and inferior vena cava. Preload insufficiency and decrease in cardiac output ensue, leading to a state of obstructive shock. This trapped air cannot be discharged while mechanical breaths continue to be administered; such as in this case with the timed volume supported setting of mechanical ventilation. Thus, disconnection of the ventilator tubing from the endotracheal tube and allowing the trapped air to passively escape via an open endotracheal tube remedies this emergency.

The presence of clinically significant air trapping can be determined by measuring the pressure at airway opening (i.e. the pressure detected in the ventilator) at the end of exhalation. The total positive end expiratory pressure, or PEEP, which is composed of the PEEP set on the mechanical ventilator in combination with the pressure exerted by trapped air, or "auto-PEEP".

$$\text{Total PEEP} = \text{Ventilator PEEP} + \text{auto-PEEP}$$

Any pressure measured above the ventilator set PEEP is evidence for some degree of air trapping.

Auto peep also elevates the pressure at airway opening during an end inspiratory hold (plateau pressure) by the below formula (simplified from Truwit et al. [1]).

$$\text{Peak airway pressure} = (F \times R) + (TV / C) + \text{set PEEP} + \text{auto-PEEP}$$

Furthermore, the volume of trapped air can be directly measured and is a sensitive indicator for risk of hypotension from air trapping [2] (see section "Monitoring for Hyperinflation" and Fig. 23.2).

Air trapping can be avoided by minimizing the tidal volume and/or increasing the gas flow rate from the ventilator. Additionally, minute ventilation can be further decreased by reducing the delivered respiratory rate, which may require heavy sedation or neuromuscular blockade. Any decrease in the amount of air that needs to be exhaled, or increase in the amount of time available for exhalation, is useful. When resuming mechanical ventilation in this patient after discharge of the trapped air, she should be treated

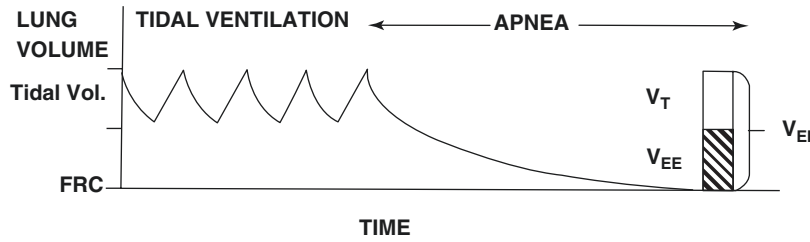

Fig. 23.2 Air trapping during mechanical ventilation in an asthmatic patient. During tidal ventilation, the lung volume never returns its physiologic starting point, the FRC. Measurement of the volume of trapped air (V_{EE}) has been studied in asthmatic patients while receiving mechanical ventilation and pharmacologic paralysis. At the end of a mechanical tidal breath, the respiratory rate is set to zero and the volume of expired air is measured until flow reaches zero. Williams and colleagues have shown that neither barotrauma nor hypotension occur when the volume of trapped air is less than 1.4 L or 15 cc/kg [2]. Note this has only been verified in the paralyzed patient. *FRC* functional residual capacity, V_{EE} end-expiratory lung volume above FRC (i.e. the volume of trapped gas), V_{EI} end inspiratory lung volume, V_T tidal volume (Reprinted with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Williams et al. [2]. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

with substantially lower minute ventilation either by a decreased respiratory rate and/or tidal volume.

Principles of Management

Inhaled Bronchodilators

Inhaled short acting bronchodilators are the mainstay of treatment of an asthma exacerbation. Most commonly, inhaled short acting beta-2 agonists such as albuterol, levalbuterol, or salbutamol are employed. These medications target the underlying physiologic cause of respiratory failure, bronchospasm. They do not, however, treat the underlying inflammatory insult which causes bronchospasm. Albuterol is the most commonly used short acting bronchodilator in the United States. In the most serious cases, it can be used as a continuous nebulized inhaled solution. No data exists in regards to withholding short acting bronchodilators during an asthma exacerbation and equipoise does not exist for such study given the presumed obvious benefit. A meta-analysis showed no advantage of continuous administration of beta agonists, as compared to intermittent administration, in acute asthma [3]. Likewise, a controlled trial in the subset of severe asthma failed to show benefit of continuous beta agonists as compared to treatments every 20 min followed by treatments every hour [4]. For the even smaller subset of life threatening asthma, no prospective data exists in adults to our knowledge.

Addition of inhaled short acting anticholinergic medications to administration of short acting beta agonists improve pulmonary mechanics [5] as well as decrease admission rates [6] in patients with severe asthma, and are recommended by a panel of experts [7]. No data exists in patients receiving mechanical ventilation, though use of anticholinergic may theoretically decrease hypersecretion of mucus and mucus plugging, a finding common in fatal asthma [8].

Corticosteroids

Corticosteroids are administered during an asthma exacerbation to decrease the inflammation that leads to bronchospasm. Meta-analysis has shown a benefit of steroid therapy in adults with acute asthma [9]. No good data exist for the optimal dose of corticosteroids, but 2 mg/kg of methylprednisolone or †he equivalent is recommended by an expert panel [7]. In a randomized trial, no benefit was demonstrated with high dose (500 mg methylprednisolone) versus standard dose (100 mg methylprednisolone) corticosteroids [10].

Monitoring of Arterial Blood Gases

Arterial blood gases are monitored during status asthmaticus in the spontaneously breathing patient. In a patient with adequate respiratory reserve during an asthma exacerbation, an arterial blood gas typically shows respiratory alkalosis. A normal pH and partial pressure of carbon dioxide with a high work of breathing, respiratory acidosis, or normalization of the pH after an initial respiratory alkalosis are all harbingers of impending respiratory embarrassment, and escalation of support with adjunctive treatments and/or invasive mechanical ventilation should be initiated.

Ventilator Strategies

Strategies for asthmatic patients on mechanical ventilation hinge on the avoidance of hyperventilation, or air trapping, as illustrated in our case. Indeed, hypotensive and mechanical complications are related to the volume of gas enclosed in the thorax above functional residual capacity (FRC) at end exhalation [2] (please see section "Monitoring for Hyperinflation"). Entrapment of supra-physiologic gas volumes is best avoided by allowing for full exhalation of tidal volumes and return to FRC. Unfortunately, with severe airway obstruction the exhalation time required to fully empty the lung to FRC can be extremely prolonged. To allow full exhalation, clinicians can either decrease the tidal volume of the inspired breath, or allow additional time for exhalation. In other words, maximization of expiratory time is key. Whatever isn't inspiratory time is expiratory time.

To this end, clinicians can decrease tidal volume in order to decrease the air volume that needs to be exhaled, or decrease the respiratory rate, which increases the time of exhalation. Adjustment of the ratio of inspiratory time to expiratory time by adjusting the flow rate (i.e. 60–100 L/min) or shape (accelerating to square) also increase the amount of exhalation time, however the incremental benefit as compared to decreasing the respiratory rate is minimal at low tidal volumes [11]. Increased flows can also increase spontaneous respiratory rates in some mechanically ventilated patients, which would outweigh any incremental benefit [12]. As a starting setting, a minute ventilation of 10 L per minute or less and a respiratory rate of 10–14 breaths/minute are reasonable [13]. Vigilant monitoring for the efficacy of ventilator settings is needed and is discussed in the section "Monitoring for Hyperinflation".

$$\text{Single breath inspiratory time} = \text{Tidal volume} / \text{Ventilator flow rate}$$

$$\text{Minute ventilation} = \text{Tidal volume} \times \text{Respiratory rate}$$

Permissive Hypercapnia/Hypoventilation

During permissive hypoventilation, hypercarbia often develops as the minute ventilation provided is not adequate to eliminate the produced carbon dioxide. In a patient with spontaneous respiration on the ventilator, hypercarbia will often lead to an increased respiratory rate, which may be detrimental (see ventilator strategies). Often, deep sedation or paralysis is needed to allow for permissive hypercapnia (or permissive hypoventilation). Elevation in carbon dioxide on arterial blood gas should be tolerated; with a goal arterial blood pH above 7.15 [14]. If the pH drops below 7.15, sodium bicarbonate or THAM infusions can be utilized. Minute ventilation can be increased cautiously if there is no significant hyperinflation. If life-threatening changes in pH continue, further strategies include deeper sedation or paralysis to minimize carbon dioxide production by muscular tissues. In the rare case that these treatments are inadequate, extracorporeal life

support (ECLS) can be utilized for CO_2 removal (see evidence contour).

Monitoring for Hyperinflation

A thorough understanding of respiratory pressures generated during mechanical ventilation is requisite to understand the pathophysiology of asthma during mechanical ventilation. Peak airway pressure is the combination of several components, as discussed below. These pressures can **ONLY** be measured in a mode with constant tidal volumes (i.e. not a pressure mode).

Respiratory causes of death from status asthmaticus often stem from circulatory collapse or mechanical complications of invasive mechanical ventilation, which are typically caused by air trapping and pneumothorax respectively. Avoidance of these complications requires monitoring for hyperinflation. Indeed, the volume of trapped air above functional residual capacity (FRC) at end exhalation correlates with risk for pneumothorax and hypotension (see Fig. 23.1) [2]. However, measuring this volume in clinical practice is difficult due to lack of familiarity with the technique needed (see Fig. 23.2 for full discussion).

Plateau pressure, Auto-PEEP, and analysis of flow volume curves are used as surrogates to directly measuring the entrapped air volume above FRC. Interestingly, plateau pressure and Auto-

Determination of Components of Peak and Plateau Airway Pressure in the Absence of Patient Effort [1]

$$\text{Peak pressure} = \text{Pressure to overcome airways resistance} + \text{Pressure to inflate lungs} + \text{total PEEP}$$

Ohm's law, or Pressure needed to overcome airways resistance

$$P_{\text{resistace}} = \text{Flow} \times \text{Resistance of airways}$$

$$\text{Compliance}\left(\text{definition}\right) = \text{Volume} / \text{Pressure}$$

(Note compliance is of respiratory system, which includes the lungs as well as external compliance from abdomen and chest wall)

$$P_{\text{compliance}} = \text{Tidal volume} / \text{Compliance}_{(\text{lugs} + \text{soft tissues})}$$

From previous PEEP discussion

$$\text{Total PEEP} = \text{Set PEEP} + \text{ Auto-PEEP}$$

$$\text{Peak airway pressure} = \left(\text{F} \times \text{R}\right) + \left(\text{TV} / \text{C}\right) + \text{set PEEP} + \text{ auto-PEEP } *$$

Plateau Pressures

During an inspiratory hold at the end of a full tidal volume (plateau pressure), the flow is zero, eliminating the first term in the equation so

$$\text{Plateau pressure} = \text{TV} / \text{C} + \text{set PEEP} + \text{ auto-PEEP } **$$

Thus

Peak airway pressure – Plateau pressure = pressure needed to overcome airways resistance; and plateau pressure is an indicator of compliance and total PEEP

PEEP did not correlate with barotrauma or hypotensive complications in a single study of mechanically ventilated asthmatic patients [2], despite having some correlation with end inspiratory lung volume (VEi) [15]. However, monitoring of these parameters is advocated by experts as a surrogate for direct measurement of trapped air volume, with goals being auto-PEEP as low as possible and plateau pressures less than 30 cm H_2O [11, 16].

Plateau pressure is reflective of the pressure "seen", collectively as an average, by the alveoli and it is this increased pressure that causes alveolar rupture and pneumothorax. In pure asthma in the non-obese patient, lung and thoracic cage compliance is normal; therefore if plateau pressure is elevated it is likely secondary to air trapping and auto-PEEP or pneumothorax.

Auto-PEEP is the difference of the measured end-expiratory pressure and the set PEEP on the ventilator, which is measured with an end expiratory hold. Exhalation is usually passive, although a mechanically ventilated patient with asthma who is not paralyzed may attempt active exhalation and thereby falsely elevate auto-PEEP. If there is air trapped within the thorax, it will increase pressure due to the increased amount of gas within a fixed thoracic cage (see previous discussion of ideal gas law in case answer). Should this complication develop and cause hemodynamic deterioration, the best solution is transient disconnection of the mechanical ventilator to eliminate further inspired air and allow for full exhalation of the trapped air. Alternatively, these emergent complications are avoided by permissive hypoventilation and diligent monitoring for air trapping by regularly measurement of auto-PEEP and plateau pressures. Air trapping can be seen on a breath to breath basis when a mechanical breath is delivered without the expiratory flow returning to zero on a flow time curve (Fig. 23.1).

Peak airway pressures are often extremely elevated in patients with asthma during mechanical ventilation due to the resistive force of constricted airways (Ohm's law: Pressure = Flow × Resistance). If increased flows are used to extend exhalation time, this will likewise raise peak airway pressure (see equation above).

However, this pressure is merely the pressure needed to overcome the airway resistance and is **NOT** transmitted to the alveolus. It is the plateau pressure, not the peak airway pressure, that is a marker of alveolar pressure and hence an indicator of risk for pneumothorax. Note that elevated plateau pressure will, by default, cause an elevated peak airway pressure. An elevated peak airway pressure with a normal plateau pressure in a patient with asthma is not worrisome and does not require specific intervention.

Recognizing Barotrauma

Pneumothorax can occur and will create similar hemodynamic instability and increased plateau airway pressures as an air trapping emergency such as seen in the clinical case above. A low threshold is needed for investigation or treatment of pneumothorax especially in an abrupt decline in clinical status or exam signs of pneumothorax (crepitus, deviated trachea, asymmetric breath sounds) develop. Pleural ultrasound can yield rapid bedside evaluation of suspected pneumothorax. Lung sliding, when seen at all intercostal spaces examined, essentially rules out pneumothorax [17]. Absence of lung sliding, while consistent with pneumothorax, is only 78 % specific for pneumothorax due to multiple false positives [17]. When seen, lung point is nearly 100 % specific, and therefore the most reliable confirmatory ultrasonographic sign for pneumothorax [17] (Video 23.1).

At the beginning of the video lung sliding is seen. When lung sliding is visualized, it rules out pneumothorax at the interspace examined. Absence of lung sliding does not confirm pneumothorax with acceptable specificity for intervention. Midway through the video, sliding can be seen to continue on the left-most part of the screen where it vanishes on the right of the screen. The point of transition of normal sliding lung (normal pleura opposing chest well) to that of no lung sliding (lack of pleural contact with chest wall) is referred to as a "lung point". This ultrasonographic sign, when seen, is nearly

100 % specific [17] and a reliable bedside sign to justify tube thoracostomy if indicated.

Evidence Contour

Adjuvant Pharmacologic Treatments

Adjuvant pharmacologic treatments are used to stave off mechanical ventilation or salvage someone failing ventilator support such that they cannot be successfully oxygenated or hypercapnic acidosis has become profound.

Magnesium

Intravenous magnesium sulfate has been promoted for patients with life-threatening asthma. Meta-analyses have demonstrated an improvement in air flow [19, 20] and hospitalization rates in adults with acute asthma [19]. A recent randomized controlled trial in the subset of severe, acute asthma showed no significant clinical benefit for magnesium sulfate infusion or nebulized inhalation [21]. Trials for the even smaller subset of life threatening asthma or impending respiratory failure do not exist. It is noted nearly all trials involve a single administered dose in the emergency room. We advocate for the adjunctive use of intravenous infusion of 2 g magnesium sulfate given the supportive meta-analyses of airflow improvement in patients with impending or current respiratory failure because even small improvements in airflow can improve air-trapping and respiratory reserve in patients with extremely impaired obstructive physiology.

Intravenous Bronchodilators

Terbutaline and isoproterenol can be used as infusions for refractory asthma unresponsive to typical measures, if tolerated by the heart rate. Limited data exists for the use of these agents [22].

Lactic Acidosis from Beta Agonist

Type B lactic acidosis from inhaled beta agonists does occur, is common, and is related to serum albuterol level, and is **NOT** a predictor of worse clinical outcomes [23, 24]

Due to their efficacy, in patients with life-threatening asthma beta agonist medications cannot be avoided and the lactic acidosis this is simply tolerated.

Heliox

Helium decreases viscosity of air allowing it to travel more efficiently through small, constricted airways [25]. Heliox is a mixture of helium and oxygen which can be inhaled as a salvage maneuver for impending respiratory failure to prevent intubation as a temporizing measure. Routine use in adult asthma exacerbations is not supported by meta-analysis [26, 27]. In the subset of patients with status asthmatics, heliox has been shown to improve oxygenation presumably by improved V/Q matching [28], It is noted if there is concomitant hypoxemia such as from pneumonia, there is a limitation in the amount fraction of inspired oxygen (FiO_2) which can be provided as the remaining fraction is needed for helium to exert is effect on the viscosity of ambient air. In a patient with impending respiratory failure, a short trial of heliox with frequent clinical monitoring can be attempted given the difficulties and potential complications of asthmatic patients during mechanical ventilation.

Noninvasive Positive Pressure Ventilation (NIV)

Noninvasive positive pressure ventilation in an asthmatic patient at risk of intubation may be useful to allow acute pharmacologic therapies to take effect, although data for this approach is limited [29]. Any asthma patient on NIV should be monitored in the intensive care unit with close clinical monitoring including serial measures of arterial blood gases. Trials of NIV should be short (1–2 h)

and a low threshold for endotracheal intubation and mechanical ventilation is needed among patients who deteriorate or fail to improve.

Avoidance of mechanical ventilation, while desirable, must be balanced with the risk of waiting too long and developing an emergent airway, which ultimately may be more dangerous for the patient.

Anesthetics

Some inhaled and infusion anesthetics, such as halothane, isoflurane, enflurane, and sevoflurane, have bronchodilatory properties and have been used in refractory status asthmaticus [30, 31]. Intravenous ketamine may be useful if the patient is also mechanically ventilated as it can be used concomitantly as a sedative [32–34]. Familiarization with the contraindications and side effects of these medications are required if the Intensivist intends to use this medication, and may require local credentialing.

Inhaled anesthetics can be used as a salvage technique; however, the logistics needed for continuous delivery are not trivial; though in refractory cases this may be preferable to extracorporeal life-support (ECLS) especially if this technology is not available at the treating center. Consultation with an anesthesia provider is requisite if inhaled anesthetics are utilized in the ICU.

Bronchoscopy

Plugging of airways by mucus and cellular debris is a common finding in autopsy of fatal asthma [8]. Use of bronchoscopy for refractory asthma patients receiving mechanical ventilation has been described in case reports with favorable outcomes [35]. Creation of a one-way valve by mucus, such as a check valve phenomenon that can be seen in COPD, to our knowledge has not been reported in asthma. One case of unilateral asthma has been described, however it was not felt to be due to check valve mechanism [36]. Regardless, if regional air trapping is seen on a radiograph (such as seen in Fig. 23.3) bronchoscopy is indicated for secretion clearance.

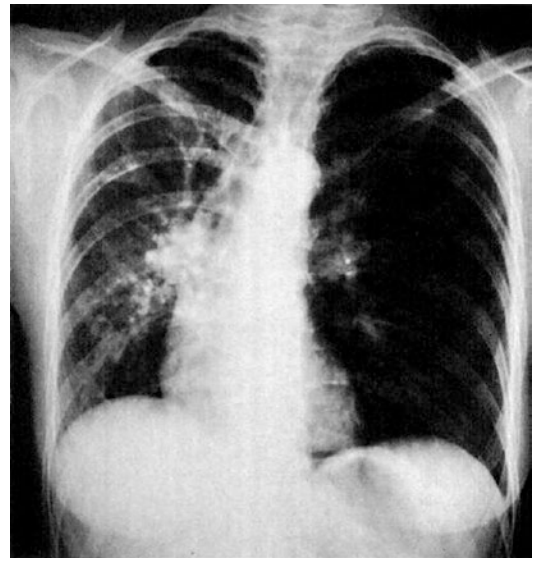

Fig. 23.3 Unilateral left lung asthma. If regional asthma or air trapping is seen, such as on the above radiograph, bronchoscopy is indicated for secretion clearance (From DiFrancia et al. [36]. Reprinted with permission from Elsevier Limited)

Extracorporeal Life Support (ECLS)

ECLS efficiently eliminates carbon dioxide from the blood. In patients failing mechanical ventilation with hypercarbia, ECLS can be a salvage technique for asthmatic patients with life threatening hypercarbia [37, 38]. Given the efficiency of extracorporeal carbon dioxide removal, new pumpless techniques of gas elimination have been developed [39] and have been used successfully in status asthmaticus [40, 41].

A myriad of complications can develop during ECLS and avoidance, if possible, is advised by maximizing adjuvant pharmacological treatments and ventilator strategies.

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