APPENDIX 1 (as supplied by the authors): Principles of assisted ventilation in the emergency department

Rick Hodder MSc MD, M. Diane Lougheed MD MSc, J. Mark FitzGerald MD, Brian H. Rowe MD MSc, Alan G. Kaplan MD, R. Andrew McIvor MD MSc

Introduction:

This on line supplement is provided for the interested reader who wishes additional information on assisted ventilation in general and also additional specific details of assisted ventilation for the patient with acute asthma. The main key messages and recommendations for assisted ventilation for acute asthma can be found in the Canadian Thoracic Society Guidelines published earlier in this series[1;2].

Because there is a paucity of high grade evidence to support specific approaches to this clinical problem, specialists or intensivists experienced with assisted ventilation for acute asthma may differ in the management strategies they prefer. The information in this supplement represents the consensus opinion of the authors of this section of the guidelines. We have attempted to formulate key messages and recommendations that are straight forward and pragmatic and which will be applicable to the majority of patients with acute, potentially fatal asthma who require some form of assisted ventilation.

Referral or transfer to a specialist or intensivist experienced with assisted ventilation is recommended whenever there is uncertainty about the best course of action, or whenever the patient remains unstable or is not responding to therapy.

Noninvasive ventilation for asthma

While noninvasive ventilation (NIV) for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) is now established as one of the major treatment advances in respiratory care of the last decade[3], its use in acute asthma remains controversial. There is some published anecdotal experience with this modality for acute asthma[4-10], and only two small, short duration, published randomized, controlled trials supporting its use in this setting[11;12]. Patients studied in the two randomized trials had moderately severe airflow obstruction (mean forced expiratory volume in one second [FEV_1] 30-42% predicted), but were not hypercapnic and had an oxygen saturation > 90% on room air. In one trial[11], NIV was compared to sham NIV plus usual medical care and in both groups treatment was applied for 3 hours. NIV was titrated to achieve a respiratory rate < 25 breaths/minute (inspiratory pressure range 8-15 cmH_2O, expiratory pressure range 3-5 cmH_2O). Compared to usual care, patients receiving NIV demonstrated significant improvements in hospitalization rate, (RR: 0.28; 95% CI: 0.09 to 0.84) and the number of patients discharged from the emergency department after treatment was higher in the NIV group (RR: 2.26; 95% CI: 1.03 to 4.97). Other outcomes favouring NIV included significant improvements in FEV_1, peak expiratory flow rate and respiratory rate. The other randomized controlled trial demonstrated that with NIV, FEV_1 was better at 40

From the Divisions of Pulmonary and Critical Care Medicine (Hodder), University of Ottawa, Ottawa, Ont.; the Division of Respirology, Department of Medicine (Lougheed), Queen's University, Kingston, Ont.; the Division of Respiratory Medicine (FitzGerald), University of British Columbia, Vancouver, BC; the Department of Emergency Medicine and School of Public Health (Rowe), University of Alberta, Edmonton, Alta.; the Department of Family and Community Medicine (Kaplan), University of Toronto, Toronto, Ont.; and the Firestone Institute for Respiratory Health (McIvor), McMaster University, Hamilton, Ont.

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minutes when compared to standard care[12].

No evidence-based recommendations exist for the initial set-up of NIV for acute asthma, however, the approach used in the most comprehensive randomized, controlled trial published to date[11] is a reasonable starting point. These investigators used an initial expiratory positive airway pressure (EPAP) of 3 cm H_2O and increased this by 1 cmH_2O every 15 minutes as required to a maximum of 5 cm H_2O. Their initial inspiratory positive airway pressure (IPAP) was set at 8 cm H_2O which was increased by 2 cm H_2O every 15 minutes to a maximum of 15 cm H_2O as required to achieve a reduction in the patient's respiratory rate to < 25 bpm. Additional adjustments should be made based upon the clinical response.

The duration of NIV required to treat acute asthma cannot be predicted, as it will vary with individual patients, their degrees of fatigue, the relative degrees of airway obstruction due to bronchospasm and inflammation, the time course of response to standard therapy, patient co-morbidities and the skills of the therapists involved. The skill of the therapist applying NIV for acute lung disease may be a major determinant of success or failure of this treatment modality. In addition to knowledge about selecting the best mask fit for the patient (full face masks are essential) and other technical skills, therapists must be skilled in the art of communication and emotional support for the patient. Securing the cooperation of dyspneic and often frightened patients to accept that a tight-fitting full face mask will help rather than impede breathing, is a learned skill, dependent on accumulated experience and maturity. NIV may therefore fail if attempted by inexperienced personnel who rely only on the theoretical benefits of this potentially valuable therapy[3]. For example, failure to closely observe the patient/ventilator unit during the first few minutes of application can lead to the erroneous conclusion that the patient will not tolerate NIV and should be intubated. On occasion, the patient can become acutely dyspneic if the ventilator is not responding to the patient's breathing efforts and so does not deliver adequate tidal volumes to the patient. This leads to distress and further patient/ventilator dyssynchrony. Oftentimes the problem is a poorly-fitting mask (wrong size, shape, too loose or too tight) which can result in an air leak and lost tidal volume. If this is noticed by the attentive health care professional, a simple adjustment will often solve the problem.

Bronchodilator administration during noninvasive ventilation

Bronchodilators are often administered to patients by wet nebulization or pressurized metered dose inhaler and chamber during short periods off NIV. However evidence also supports the effectiveness of interfacing either type of inhalation device into the ventilator circuit while the patient is receiving NIV[13-16]. No evidence-based guidelines exist for either the dose or frequency of bronchodilator administration during NIV for asthma. However, because of turbulent flows within the mask, if a metered dose inhaler and chamber combination is used, multiple puffs (usually 4-8) timed with the patient's inspiration, should be individually administered, similar to the technique for invasive mechanical ventilation[17-19].

If the metered dose inhaler and chamber combination is used, it is most efficient when the NIV leak port is located within the mask, rather than in the circuit[14]. If the leak port is in the circuit it may be manually occluded for a few breaths to facilitate drug delivery. In general, nebulizers deliver more drug to the patient's upper airways than does the metered dose inhaler chamber combination, with the greatest amount being delivered when the noninvasive leak port is in the circuit rather than the mask[14]. Due to more efficient particle size, it is possible that multiple puffs with the metered dose inhaler chamber combination may be clinically equivalent to the nebulizer during non-invasive ventilation, but there is a paucity of controlled research on this topic[15].

Bronchodilator dosing should be empiric and titrated to simple clinical outcomes such as slower, more comfortable breathing. Just as for patients with acute asthma who are not receiving assisted ventilation, the presence or absence of wheezing has poor correlation with objectively measured airflow obstruction and so should not be used to titrate bronchodilator dosing[20]. Additional practical aspects of setting up NIV can be found in the comprehensive British Thoracic Society guidelines on this topic[3].

The main goal of NIV for acute asthma is to avoid the need for intubation and invasive ventilation by resting the patient through reducing the load on the respiratory muscles, thus buying time for the other aspects of acute asthma therapy to work. Accordingly, if patients are not visibly relaxing in response to the application of NIV within 15-30 minutes, re-assessment to ensure that NIV has been correctly applied should occur. If the set up is appropriate, but the patient is still in distress, judicious sedation with short-acting opiates and sedatives may be considered, but re-assessment for intubation and invasive

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ventilation should also occur. In general, placement of a nasogastric tube to decompress the stomach is not required during NIV, because the applied ventilating pressures from NIV do not generally exceed the pressure of the lower esophageal sphincter (about 33 mmHg).

Non-invasive ventilation for acute asthma should only be attempted in a closely monitored area or ICU by personnel skilled in its application and in intubation and invasive mechanical ventilation, should the noninvasive approach fail. In most cases of respiratory failure complicating acute asthma, the safest approach is to sedate, intubate and start invasive mechanical ventilation.

Manual ventilation by self-inflating bag and mask

Once the decision is made to intubate the patient, there is often a short period of time when manual ventilation of the patient by self-inflating bag is necessary while preparations for intubation are being made (eg. arranging for assistance; assembling and testing necessary equipment; ensuring reliable intravenous access for pre-medication, etc.). During manual ventilation, inflation from the bag is timed to occur with the patient's own inspiratory efforts (provided pharmacological paralysis has not been used), so as to provide assisted ventilation using the lowest possible airway pressure and to ensure the least discomfort for the patient[21]. Often it is prudent to delegate manual ventilation to a qualified assistant, in order to free up resources for other tasks necessary for optimum patient care.

This period of manual ventilation can also provide useful information about the patient's lung mechanics (ie. the levels of airway resistance and of lung compliance and elasticity) and the nature of the breathing problem. For example: is the patient easy to ventilate, or is considerable force necessary to generate only shallow tidal breaths? The need for high ventilating pressures indicates either obstruction to airflow (e.g., upper airway obstruction, diffuse and severe bronchospasm), or a low respiratory system compliance (e.g., pulmonary edema, extreme hyperinflation, large pneumothorax, or high intra-abdominal pressures). One major concern with bag-mask ventilation is the possibility of insufflation of air into the stomach, which increases the risk of gastric aspiration. This is particularly likely to occur in patients who require high airway pressures during assisted manual ventilation. Gastric decompression with a nasogastric tube may be required.

Intubation for acute asthma

The potential for complications associated with intubation and positive pressure ventilation for acute asthma cannot be dismissed and all efforts should be made to avoid unnecessary intubation in this setting. On rare occasions, pharmacologic paralysis and sedation for intubation can convert an alive and breathing (albeit desperately) patient into an intubated patient for whom mechanical ventilation cannot be effectively delivered because of severe degrees of hyperinflation. In this situation, fatal asphyxia or cardiac collapse may occur.

Endotracheal intubation of the agitated, unstable patient with acute asthma can potentially be difficult and should ideally be performed by experienced practitioners with knowledge of airway techniques and the potential complications associated with intubation and positive pressure mechanical ventilation. Peri-intubation complications can include hypotension and possibly a heightened risk of gastric aspiration due to pre-existing stomach distention from swallowed air, or a period of bag and mask ventilation. Therefore, for the inexperienced health care professional, if the decision to intubate has been made, expert help in the person of an anesthetist, intensivist, or other physician skilled at intubation in this setting should be called for immediately if available. There are several possible techniques for intubation in the setting of acute asthma including: awake nasotracheal intubation; awake orotracheal intubation; orotracheal intubation with sedation; orotracheal intubation with sedation and pharmacologic paralysis)[22]. Because expert help will not always be available when intubation is urgently required, we recommend a rapid sequence intubation technique as outlined in previous Canadian guidelines[23] and recently modified for the Emergency Department Asthma Care Pathway (EDACP) of the Province of Ontario's Ministry of Health and Long-Term Care's Asthma Plan of Action[1;2;24]. This rapid sequence induction or intubation scheme (see Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.080073/DCI) is based upon consensus opinion only, as there is no high grade evidence to support its use over other ways to induce relaxation and paralysis for intubation[22]. While most emergency physicians prefer full bolus dosing of ketamine or propofol in this setting, many intensivists or anesthesiologists would prefer incremental dosing of these drugs in order to minimize the possibility of provoking significant hypotension in patients with acute asthma, who may have pulmonary hypertension and who may also be intravascularly volume depleted.

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Several pharmacologic agents can be used to facilitate rapid sequence intubation for acute asthma, but because rapidity of onset is generally preferred by most emergency department practitioners, bolus dosing with ketamine or propofol followed by induced paralysis with succinylcholine or rocuronium have been recommended[25-29]. Small doses of rapid-acting narcotics such as fentanyl 25-100µg may also be helpful. Morphine is not recommended due to its relatively slow onset of action and the theoretical risk of histamine release that might aggravate bronchospasm, although the significance of this is controversial[30]. Similarly, benzodiazepines also have a relatively slow onset of action and so should not be used as the sole agents for intubation.

When giving bolus doses of medication at intubation, it is best to administer the drug by syringe as close to the patient as possible, rather than via a long length of intravenous tubing, and to flush the dose in with a flushing syringe of saline, rather than using an infusion pump. This will help avoid the situation in which slow delivery causes an initial apparent lack of drug effect leading to repeated and potentially excessive dosing that may provoke significant hypotension. Because drug-induced hypotension may occasionally complicate intubation in this setting, it is prudent to have at hand a pre-prepared syringe of a rapid-acting vasoconstrictor agent such as phenylephrine 100µg/ml for bolus dosing in 50-100µg increments (flushed in with a saline flushing syringe) as needed. An approach to other potential causes of hypotension associated with mechanical ventilation for asthma is discussed below. Following intubation, stomach decompression by nasal or orotracheal tube is a prudent practice**.**

While pharmacologic paralysis is usually required for intubation in acute asthma, if possible, it should not be continued. Pharmacologic paralysis removes the patient's ability to breathe spontaneously which is an important safety net should there be an inadvertent ventilator disconnect or accidental extubation. In addition, the concomitant use of paralytics and high dose corticosteroids in acute asthma may also predispose to the development of myopathy which can prolong weaning from mechanical ventilation and complicate recovery, although prediction of this complication is not possible based either upon duration or dosing of the drugs used[31;32]. On the other hand, in some cases, heavy sedation and short term pharmacologic paralysis are necessary in order to permit safe patient-ventilator coordination and to permit ventilator adjustments that will minimize the risk of dynamic hyperinflation and its consequences[33-37].

Basic terminology of invasive mechanical ventilation

While most physicians faced with initiating invasive ventilation for a patient with acute respiratory failure will have the assistance of a respiratory therapist or another physician knowledgeable about assisted ventilation, even those who are only infrequently faced with this task should be familiar with the basic principles involved. Such knowledge will enable the physician to verify that the ventilator setup is safe for a given patient and will help with troubleshooting the patient-ventilator system if problems arise. For the interested reader, an excellent review of the basic principles of assisted ventilation is available[38].

Mechanical ventilation can be set up to be either ***"volume-regulated"***, or ***"pressure-regulated"***. For those who are not very experienced with mechanical ventilation, the simplest type of ventilation to choose is volume-regulated ventilation, as with this technique only a few, largely intuitive parameters need be set on the ventilator interface before starting mechanical ventilation (Box 1).

i) Volume-regulated breaths

Volume-regulated ventilation signifies that the ventilator is pre-programmed, by the operator, to deliver a set volume of gas called the ***"tidal volume"***, with each machine-initiated breath. A normal tidal volume is 6-8 ml/kg body weight, and so typical set tidal volumes for adults are in the 400-800 ml range. If the ventilatory circuitry becomes disconnected (eg. a connector fails, or the patient self-extubates), an air leak occurs and the delivered tidal volume will no longer reach the patient. Because this could be dangerous, a ***"low volume", or "patient disconnect"***, or some equivalent alarm is usually pre-set on the ventilator to signal the presence of a leak. Typically this alarm is set at about 80% of the pre-set tidal volume (eg. 250-300 ml for a typical patient's pre-set tidal volume).

During inspiration, as the tidal volume is delivered by the ventilator, pressure in the patient's airways and the ventilator circuitry will rise. If the lungs are healthy, a normal delivered tidal volume will generate an inflation pressure during inhalation called the "peak inflation pressure" (PIP), of about 12-18 cm H_2O in a relaxed patient. In patients with lung disease, the airway resistance is higher (eg. asthma, COPD), or the lungs are stiffer and less compliant (eg. extreme hyperinflation, extensive pneumonia, pulmonary edema, pulmonary fibrosis, acute respiratory distress syndrome) than in health, and so the pressure generated by the ventilator in delivering even a normal tidal volume will be higher than in a healthy person.

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Box 1: Basic ventilator set-up parameters*

Volume-regulated or pressure-regulated ventilation

- Fraction of inspired oxygen (FIO_2)
- Positive end expiratory pressure (PEEP), or Continuous positive airway pressure (CPAP) level (cm H_2O)
- Ventilation mode
  - Assist-control (AC)
  - Synchronized intermittent mandatory ventilation (SIMV)
  - CPAP + Pressure support ventilation (PSV)
- Pressure support level
  - SIMV and CPAP modes + PSV
- High pressure alarm setting*
- Low volume (tidal or minute ventilation) alarm setting*
- Trigger sensitivity*

Volume-regulated ventilation

- Machine set rate (bpm)
- Machine-delivered tidal volume (ml)
- Inspiratory flow rate (litres per minute)*

Pressure-regulated ventilation

- Machine set rate (bpm)
- Inspiratory time (sec)

* These parameters are usually pre-set by the respiratory therapist as general settings, but may be modified as needed

Because very high pressures are potentially harmful to the patient, a second parameter that must be set by the operator is a ***"high pressure limit"***. This is usually set at 40-50 cmH_2O, or about 10 cmH_2O above average peak pressure of a set tidal breath. If the pressure limit is reached, an audible alarm will sound, and the ventilator will stop delivering inhaled gas, so that the delivered tidal volume will be less than the amount that was programmed at initial setup. If this continues, the non-sedated patient will sense "air hunger" and will begin to breathe with a higher spontaneous breathing rate in order to try and satisfy metabolic demands. If the patient is not able to breathe spontaneously, or cannot do so effectively because of disease, then hypoventilation will occur, leading to hypoxemia, worsening hypercapnia and acidemia.

The ***"inspiratory flow rate"*** at which the tidal volume is delivered by the ventilator is another parameter that can be set with volume-regulated ventilation. If the patient is sedated and not making exaggerated inspiratory efforts, inspiratory flow rates in the range of 40-60 litres per minute (lpm) are usually sufficient. On the other hand, the patient who is awake and has a very high breathing drive, may want to breathe in very quickly, so that setting a higher inspiratory flow rate (eg. 80-100 lpm) might be more appropriate in order to help avoid air hunger and distress. The higher the inspiratory flow rate, the higher will be the peak inspiratory pressure if the patient is breathing in synchrony with the ventilator. The inspiratory flow rate also indirectly controls the inspiration to expiration ratio (I:E ratio), so it is important to ensure that inspiratory times are not greater than or equal to, expiratory times.

Another parameter that must be set by the operator for volume-regulated ventilation is the ***"ventilator rate"*** in breaths per minute (bpm). Typical set rates for healthy individuals are in the range of 8-12 bpm. Patients who cannot breathe spontaneously will be totally dependent on the ventilator set rate. Most ventilators will automatically permit patient-initiated spontaneous breaths to occur in addition to the set machine rate, if the patient is awake and capable of spontaneous breathing. Most modern ventilators can also be adjusted to assist/augment the patient with these spontaneous inspiratory breaths, in order to help reduce the patient's work of breathing. Various ventilator brands label such inspiratory support differently, but a common term is called "***pressure-support"***. The level of pressure support is usually initially set from 5-20 cmH_2O (the greater the pressure set, the greater the volume delivered). Pressure support provides a inspiratory flow of gas that assists the patient's own inspiratory efforts. The term "pressure" is used to describe this inspiratory flow assist, because it is the maximum inspiratory target pressure generated that signals breath termination. Most ventilators stop delivering the pressure-supported tidal volume when the terminal inspiratory flow has fallen to about 5 lpm. Pressure support is also commonly used to counter the inspiratory resistance imposed by the endotracheal tube and therefore makes inspiration more comfortable for the spontaneously breathing, intubated patient.

ii) Pressure-regulated breaths

With pressure-regulated ventilation, instead of setting a pre-set tidal volume, the operator sets the end-inspiratory pressure (usually set to 20-35 cmH_2O). The ventilator then delivers gas flow during inspiration (up to 180 lpm) until the pre-set pressure limit has been reached. In contrast to volume-regulated ventilation in which the tidal volume is

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pre-set and fixed for all machine-initiated breaths, with pressure-regulated ventilation the delivered tidal volume is variable, and determined mainly by the state of the patient's lung mechanics (ie. airway resistance and lung compliance). The inspiratory time must also be set with pressure-regulated ventilation and for acute asthma, an inspiratory time ≤ 1–1.5 seconds is preferred in order to minimize the risks of air trapping and subsequent hyperinflation.

An important additional parameter which must also be set for both volume and pressure-regulated breaths is the ***"ventilation mode"***. The simplest mode to set is the so-called ***"assist-control" (AC)*** mode. With this mode, the ventilator not only delivers a minimum pre-set number of tidal volume breaths, but will also sense when a patient is trying to take a spontaneous breath (eg. upon awakening from sedation). These breathing efforts will trigger the ventilator to deliver a full pre-set tidal volume (volume-regulated breaths), or a variable tidal volume (pressure-regulated breaths), thus "assisting" the patient's own efforts. Another mode of ventilation that is commonly used is ***"synchronized intermittent mandatory ventilation" (SIMV).*** In this mode the ventilator is programmed to deliver the minimum pre-set number of fixed breaths, but these are timed/synchronized so as not to interfere with any spontaneous breaths the patient may take. This avoids the problem of the patient trying to breathe out while the ventilator is delivering a set inspiratory breath ("breath stacking"). In the SIMV mode, the patient is permitted to take extra breaths in addition to the pre-set machine rate and it is common to set the ventilator to assist these spontaneous breaths by employing the pressure-support function. The tidal volume of these additional spontaneous breaths in the SIMV mode is usually determined by level of pressure support, (higher the pressure support the higher the volume) and by the patient's lung mechanics. Both AC and SIMV modes are ideal for patients who are not breathing spontaneously (eg. immediately post-operative patients, heavily sedated or pharmacologically paralyzed patients), but who are expected to gradually awaken and begin spontaneous breathing efforts as drugs are weaned or discontinued.

The oxygen dose provided to the patient must also be set and is termed the ***"fraction of inspired oxygen" (FIO_2)***. For safety, the FIO_2 is usually set at 1.0 (100% oxygen) initially and then titrated down to levels sufficient to keep the oxygen saturation > 92%.

The next parameter that must be set is the applied ***"Positive End-Expiratory Pressure" (PEEP),*** or ***"Continuous Positive Airway Pressure" (CPAP)*** level. Under normal circumstances, at the end of an exhalation, the pressure in the intubated patient's airways is equal to that of the ambient atmospheric pressure, which in common parlance is defined as "Zero End-Expiratory Pressure" (ZEEP). In the presence of lung disease, especially during assisted ventilation by machine, it is generally desirable to have a small positive pressure in the airways at end exhalation to help prevent the small airways and lung units from collapsing due to forces generated by the presence of the lung disease (collapse is also referred to as "atelectasis"). This end-exhalation pressure enhances oxygenation and is done by setting the applied-PEEP or CPAP levels. PEEP and CPAP are essentially the same thing, although it is common to use the term CPAP for purely spontaneous breathing modes. Setting PEEP/CPAP is done by dialing in the desired end-expiratory pressure. Typical PEEP/CPAP settings are in the range of 5-10 cmH_2O, although for acute asthma, lower levels (eg. 2-5 cm H_2O) are generally preferred. PEEP/CPAP are often used to enhance oxygenation of the patient by helping to keep the small airways open during all phases of the breathing cycle. This will often permit reduction of the FIO_2.

In disease states that compromise the patient's ability to exhale efficiently, such as asthma and COPD, air trapping occurs due to an inability to completely exhale the previous tidal volume before the next breath. This leads to a dynamic increase in end-expiratory lung volume, which is termed dynamic hyperinflation. Extreme hyperinflation generates high intrathoracic pressure, which can be measured at the end of an exhalation and is referred to as intrinsic positive end-expiratory pressure, or ***"intrinsic-PEEP"***, or occasionally, ***"auto-PEEP"***. Intrinsic-PEEP is additive to applied PEEP and can contribute to hypotension and patient and respiratory muscle fatigue because it increases the patient's work of breathing by acting as an inspiratory threshold load[39;40]. The level of intrinsic-PEEP can be measured in ventilated patients, but requires a completely relaxed patient, expertise and sophisticated equipment.

Perhaps the most comfortable and closest to natural ventilation mode for awake, spontaneously breathing patients that is commonly available on most modern ventilators is the combination of ***CPAP*** plus ***pressure support*** breathing. In this mode, all breaths are initiated by the patient, but at the same time are assisted by the ventilator. This mode is a good way to reduce the patient's inspiratory work of breathing by taking advantage of the combined benefits of CPAP to splint the airways open and prevent atelectasis, and of pressure support to provide an inspiratory "boost" to help reduce the force that must be generated by the patient to initiate and complete an inspiration. CPAP plus pressure support during invasive

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ventilation are analogous to bi-level noninvasive positive pressure ventilation (so-called "BIPAP"). With the CPAP plus pressure support mode, care must be taken that the patient has an adequate spontaneous breathing rate, and is not so sedated or fatigued that breathing efforts become too weak or too slow. If this occurs, the "**apnea alarm**" on the ventilator will sound, usually after 20 seconds, and the ventilator will begin to deliver an operator pre-programmed back up tidal volume and respiratory rate for safety. However, this situation indicates inadequate spontaneous ventilation by the patient and the need to return the patient to either the assist-control or SIMV mode. Clearly, the CPAP plus pressure support mode is suitable only for patients capable of spontaneous breathing and is never indicated for the patient who has received pharmacologic paralysis.

Initial ventilator set up for invasive mechanical ventilation for acute asthma

The goals of assisted ventilation for asthma are to oxygenate, correct extreme acidemia, and to rest the patient and the respiratory muscles. Furthermore, these goals must be accomplished safely, so that positive pressure ventilation does not worsen air trapping and its consequence of dynamic hyperinflation that is characteristic of severe acute asthma. It is therefore crucial to appreciate that mechanical ventilation is not the ideal therapy for severe, potentially fatal asthma.

Dynamic hyperinflation may be a consequence of both the disease itself and of inexperienced management of the patient and the ventilator and occurs whenever the inspiratory cycle begins before the preceding exhalation and expiratory flow have finished. Common conditions favouring the development of air trapping and dynamic hyperinflation include excessively rapid breathing rates (both spontaneous and machine rates) which lead to exhalation times that are too short to permit complete exhalation of the previous tidal volume, and the setting of too large a tidal volume on the ventilator when there is insufficient time for exhalation[41;42]. If the expiratory flow waveform can be displayed on the ventilator, the presence of dynamic hyperinflation can be inferred when expiratory flow is seen to persist right up to the onset of the next machine or spontaneous breath (Figure 1). Dynamic hyperinflation can also be suspected clinically when the clinician listens with a stethoscope over the trachea, and hears persistent exhalation sounds right up until the next inspiration[43]. Warning signs suggesting that excessive dynamic hyperinflation and intrinsic-PEEP have developed are listed in Box 2.

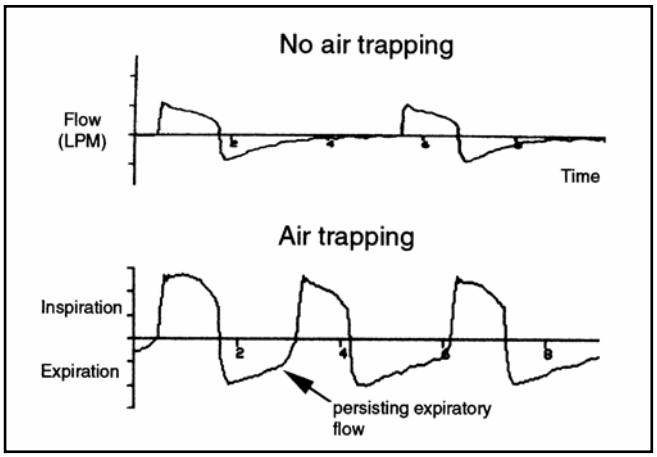

Figure 1: Ventilator flow-time tracing showing normal conditions (top) and persisting expiratory flow indicative of air-trapping and dynamic hyperinflation (bottom).

Adopting a ventilatory strategy for acute asthma that will prevent, or help reverse severe dynamic hyperinflation, may help reduce excessive morbidity and the high mortality associated with mechanical ventilation for acute asthma, although the greatest effect will be obtained not from ventilator manipulation, but from adequate treatment of the underlying airflow obstruction[34-36;41;44-49]. Ensuring an adequately long exhalation phase is an important strategy to help prevent worsening hyperinflation and this is best accomplished by maintaining relatively low breathing rates, both machine and patient rates. If expiratory flow has not stopped prior to the next inspiration in the spontaneously breathing patient, a reassessment of the adequacy of bronchodilator therapy is indicated and additional sedation may be required to slow the patient's breathing rate. If exhalation is seen to end prior to the next inspiration, inducing slower breathing rates will not further reduce the risk of hyperinflation[41;42]. The basic principles of mechanical ventilation for acute asthma and suggestions for initial ventilator setup are shown in Box 3.

As discussed earlier, there are two basic modes of mechanical ventilation: volume-regulated or pressure-regulated ventilation. With volume-regulated ventilation, dynamic hyperinflation and intrinsic-PEEP and their harmful consequences will be minimized by employing tidal volumes in the normal range of 6-8 ml/kg, relatively low total (machine plus patient) respiratory rates (8–12 bpm) and moderate-to-high inspiratory flow rates (> 60 L/min). This will permit long exhalation times and ensure a low inspiratory to expiratory ratio (I:E ratio) of 1:3, 1:4 or lower[41;42]. As mentioned earlier, success with this

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Box 2: Conditions suggesting the existence of excessive hyperinflation and intrinsic-PEEP during mechanical ventilation

- Auscultated expiratory flow does not end prior to next inspiration
- Expiratory flow on the ventilator flow-time waveform does not decrease to zero (baseline) prior to onset of inspiration
- Exhaled tidal volume indicated on the ventilator is less than the set inspiratory tidal volume
- Decreasing delivered tidal volume or minute ventilation during pressure-regulated ventilation
- Increasing peak inspiratory pressure during volume-regulated ventilation
- Unexplained increase in plateau pressure
- Unexplained hypotension
- Increasing patient distress or inspiratory effort
- Increasing chest wall girth
- Minimal movement of chest wall during breathing cycle
- Signs of pulmonary barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema)

Box 3: Principles of initial mechanical ventilation for acute, potentially fatal asthma

1. Attempt to maintain oxygen saturation ≥ 92% (FIO_2=1.0 initially)
2. Have patience with the process of reducing PCO_2
    - Keep pH >7.10 (give bicarbonate intravenously as needed)
3. Minimize dynamic hyperinflation

    i) Volume-regulated ventilation
    - Modest rate of assisted ventilation (8-12 bpm)
    - Low to normal tidal volumes (6-8 ml/kg)
    - Inspiratory flow rates > 60 L/min
    - Peak inflation pressure (PIP) < 50 cm H_2O
    - Plateau pressure < 35 cm H_2O

    ii) Pressure-regulated ventilation
    - Modest rate of assisted ventilation (8-12 bpm)
    - Aim for tidal volumes 6-8 ml/kg (dependent on lung mechanics in pressure control mode)
    - Inspiratory times ≤ 1-1.5 sec
    - Plateau pressure < 35 cm H_2O
4. Begin with low positive end-expiratory pressure initially (eg. 2 to 5 cm H_2O)
5. If necessary, use intravenous opiates to suppress breathing drive and pharmacologic paralysis to prevent dyssynchrony between patient and ventilator

manoeuvre can be confirmed by auscultation, when the sound of exhalation is heard to stop, leaving a silent gap prior to the next inhalation, when listening with the stethoscope over the trachea[43]. Adequate time for exhalation can also be confirmed from the displayed flow versus time waveform on the ventilator, by noting that expiratory flow ceases before the onset of the next spontaneous or machine breath (Figure 1). Keeping the total respiratory rate low is important and usually requires sedation and occasionally pharmacologic paralysis, at least in the initial stages of mechanical ventilation for acute asthma.

If inspiratory flow rates on the ventilator are excessive, peak inflation pressure (PIP), which mainly reflects pressure in the proximal airways and ventilator circuit, will rise. However, what constitutes a dangerous PIP is not known with precision. Because of the wide variations in lung compliance and airway resistance seen in patients with acute asthma, PIP does not correlate well with dynamic hyperinflation and barotrauma. Alveolar rupture is related primarily to peak alveolar rather than airway pressures, which are best approximated by either the mean airway pressure, or the plateau pressure, rather than the PIP as displayed on the ventilator. In general however, if PIP can be kept < 50 cm H_2O and plateau pressure < 35 cm H_2O, the risk of barotrauma should be acceptably low[50].

With pressure-regulated ventilation, the operator sets the desired end-inspiratory pressure limit (usually set to 30-40 cmH_2O). The ventilator then delivers gas during inspiration until the pre-set pressure limit has been reached. The pressure-regulated mode of ventilation is preferred by some for acute, potentially fatal asthma because it guarantees low plateau pressures, and avoids the problem of premature inspiratory time cut off when the high pressure limit is activated[33;38;51]. Furthermore, in this mode, the delivered tidal volume is determined by the state of the

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patient's lung mechanics and as such can be a helpful marker of the status of dynamic hyperinflation and airway resistance. As the asthma improves, delivered tidal volumes will increase as a sign of response to treatment. On the other hand, when airway obstruction is severe, delivered tidal volumes may be quite low with pressure-limited ventilation, and this may limit the effectiveness of aerosol bronchodilator therapy[52]. The inspiratory time must be set with pressure-regulated ventilation and a value ≤ 1–1.5 seconds is a reasonable compromise between the short inspiratory times needed to lessen air trapping and longer inspiratory times which favour optimal distribution of ventilation within the lungs.

PEEP is often applied via the ventilator in order to prevent atelectasis, but there is some controversy about whether applied-PEEP should be used in acute asthma[33;51;53]. In the initial stages of mechanical ventilation for acute asthma, the patient is usually heavily sedated and may be pharmacologically paralyzed, so there are no spontaneous breathing efforts. Under these conditions, some practitioners believe that applied-PEEP may be transmitted to the alveoli and potentially worsen hyperinflation and its harmful consequences[51;53]. Others argue that applied-PEEP in low levels (less than objectively measured intrinsic-PEEP) may actually help to reduce hyperinflation by keeping airways open to assist exhalation in some patients[39;40;51]. When the patient is eventually allowed to awaken and begin spontaneous breathing, applied-PEEP may also help to reduce the work of breathing by minimizing the inspiratory threshold load imposed by intrinsic-PEEP[33]. Attempts to titrate applied-PEEP to measured intrinsic-PEEP should only be done by specialists skilled in these techniques, but in general, low levels of applied-PEEP (2-5 cmH_2O) are safe and may be beneficial.

Bronchodilator administration during mechanical ventilation

Invasive mechanical ventilation via an endotracheal tube is associated with turbulent airflow which conspires against efficient delivery of bronchodilators. Because of this, simply discharging a pressurized metered dose inhaler directly into the ventilator circuit or endotracheal tube by means of an adaptor is very inefficient and may result in virtually no bronchodilator reaching the patient[54]. The most efficient way of administering bronchodilators during invasive mechanical ventilation is to use a pressurized metered dose inhaler attached to an in-line chamber which is set close to the patient in the inspiratory limb of the ventilator circuit[17-19]. Although no high grade evidence-based guidelines exist for either the dose or frequency of bronchodilator administration during invasive mechanical ventilation for asthma or COPD, because of turbulent flows within the circuit, if a pressurized metered dose inhaler and chamber combination is used, multiple puffs (usually 4-8) timed with the patient's inspiration, should be individually administered[17-19].

Continuous or inspiration-phased wet nebulizers can also be used to deliver bronchodilators during mechanical ventilation and in non-humidified circuits, can provide larger doses to the airways than the metered dose inhaler chamber combination. However, in-line nebulizers have become less popular than in the past due to infection control concerns associated with nebulized therapy in general. When wet nebulizers are used in humidified circuits, their deposition efficiency falls and the dose delivered becomes comparable to that from a metered dose inhaler spacer combination[19].

Most often humidification is provided via an in-line heat and moisture exchanger (HME) which acts like a filter and so regardless of the inhalation device type used, care should be taken to interface the inhaler device between the HME and the patient, or to temporarily remove the HME from the circuit during bronchodilator delivery, lest the drug be trapped in the HME and not reach the patient. Bronchodilator dosing should be empiric and titrated to simple outcomes such as reduced air trapping, higher exhaled tidal volumes and in the spontaneously breathing patient, to slower, more comfortable breathing. Just as for patients with acute asthma who are not ventilated, the presence or absence of wheezing has poor correlation with objectively measured airflow obstruction and so should not be used to titrate bronchodilator dosing[22].

Potentially harmful consequences of invasive mechanical ventilation for acute asthma

Most of the morbidity and mortality occurring in ventilated asthmatic patients is due to pulmonary barotrauma, such as pneumothorax and pneumomediastinum, or to ventilator-induced hypotension and cardiovascular collapse. In one retrospective review[45], the frequencies of these complications were hypotension (20%), pulmonary barotrauma (14%) and cardiac dysrhythmias (10%), but in general this will depend on the population being treated and on the skills of the medical team. If inappropriately managed, mechanical ventilation can significantly worsen the patient's status by promoting air trapping and increased hyperinflation which raises intrathoracic pressure leading to reduced venous return to the heart, right ventricular strain and tamponade of the left ventricle by displacement

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of the interventricular septum, all of which may provoke cardio-pulmonary collapse and death. These complications are consequences of extreme degrees of dynamic hyperinflation, which can generate excessive levels of intrinsic-PEEP.

Approach to hypotension during mechanical ventilation

Hypotension is a common complication of invasive mechanical ventilation for acute asthma. It most commonly occurs shortly following intubation and may be due to a combination of relative intravascular volume depletion, sedative drugs used for intubation or to worsening of hyperinflation leading to decreased venous return to the heart. This latter phenomenon may be the consequence of too vigorous manual ventilation by self-inflating bag post intubation, or to inappropriate ventilator set up with too high tidal volumes and respiratory rates. On occasion, if hypotension due to extreme hyperinflation is suspected, temporarily disconnecting the patient from the ventilator for 30-60 seconds while continuously monitoring oxygen saturation, may allow trapped air to escape and so reduce hyperinflation and intrinsic-PEEP. If the problem is excessive hyperinflation, blood pressure will usually quickly improve as trapped air is exhaled and venous return is restored. Ventilation can then be resumed at lower tidal volumes and respiratory rates as described above. Some practitioners suggest trying to facilitate lung emptying by employing a technique called external chest compression[55] in which intermittent sustained pressure is applied to the lower chest wall or upper abdomen to assist exhalation. If blood pressure fails to improve promptly, a tension pneumothorax should be suspected.

Approach to the patient who is "fighting the ventilator"

Occasionally, patients will experience extreme discomfort or cough during invasive ventilation and this may interfere with efficient ventilation. When this happens, the ventilator high pressure and low volume alarms sound, indicating that the patient is not receiving adequate ventilation. When approaching the intubated patient who is in distress and not in synchrony with the ventilator, it is important to remember that agitation, dyspnoea, hypoxemia, and hemodynamic instability may not only be due to the patient's asthma, but also may reflect management issues such as inadequate sedation and inappropriate ventilator setup, or problems associated with the endotracheal tube or the ventilator itself (Box 4).

Box 4: Possible causes of dyssynchrony between patient and ventilator

Patient Causes

- Airway
  - Bronchospasm, obstruction, excessive secretions, coughing
- Lung parenchyma
  - Hyperinflation, atelectasis, pneumothorax
- Altered drive to breathe
  - Pain, anxiety, fear, dyspnea, delerium, metabolic or drug-related causes
  - Inadequate sedation or analgesia
- Cardiac
  - Myocardial ischemia, pulmonary edema, heart failure, pulmonary embolism

Endotracheal tube causes

- Right main stem bronchus intubation
- Esophageal intubation
- Self-extubation to larynx
- Obstruction
- Kinking
- Biting endotracheal tube
- Ruptured cuff

Ventilator Causes

- Inappropriate ventilator set-up parameters
  - Set tidal volume too large or too low
  - Ventilator set rate too high or too low
  - Pressure support level too low
  - Inappropriate inspiratory trigger sensitivity
  - Inspiratory flow rate set too low or too high
  - Positive end-expiratory level set too low or too high

Miscellaneous

- Ventilator disconnect
- Humidifier problems

The easiest way to begin to sort through all the potential causes of a patient's distress during invasive ventilation is to disconnect the patient from the ventilator and begin manual ventilation via the endotracheal tube with a self-inflating bag and supplemental oxygen[21]. If the patient is easy to ventilate manually and begins to relax and improve along with a rising oxygen saturation, it is likely that the problem was poor sedation leading to air hunger and panic, or inappropriate ventilator setup, or a mechanical problem with the ventilator itself. Great care must be taken not to worsen hyperinflation with too vigorous manual ventilation by bag and mask. If manual ventilation is difficult and the patient's distress continues or escalates, potential problems include an obstructed

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endotracheal tube, right main stem intubation, worsening bronchospasm or hyperinflation, or a complication such as a pneumothorax, or mucus plugging, or significant atelectasis. If significant atelectasis is suspected and confirmed by a chest radiograph, an urgent bronchoscopy to remove a large mucous plug may be necessary. As mentioned above, on occasion, extreme degrees of hyperinflation may occur, effectively ceasing adequate ventilation and causing patient distress (if awake) from air hunger and hypotension. If hypotension due to extreme hyperinflation is suspected, temporarily disconnecting the patient from the ventilator to allow trapped air to escape and so reduce critical hyperinflation may be necessary.

A potentially fatal but correctible complication in this circumstance is obstructive shock due to a tension pneumothorax. Although physical examination will usually reveal significant asymmetry in breath sounds and percussion note and so suggest the diagnosis and location, this is not always the case. On occasion, severe dynamic hyperinflation will obscure the clinical diagnosis of a tension pneumothorax and the only signs may be rapidly progressive hypotension and falling oxygen saturation. If the situation is desperate, as it might be in acute, potentially fatal asthma, there may be no time for a confirmatory chest radiograph. In such circumstances, large bore needles (eg. 12-14 gauge) should be empirically inserted into the pleural space through the 2nd intercostal space anteriorly, and followed by a chest tube. It is important to recognize that on occasion, bilateral pneumothoraces may occur in this setting.

Inability to ventilate the intubated asthmatic

In the sickest asthmatic patients, hyperinflation and intrinsic-PEEP may become so extreme that it is physically impossible to get any more air into the lungs. Although rare, in this situation, effective ventilation ceases and fatal asphyxia soon follows. In these desperate circumstances the ventilator high pressure and low volume alarms are usually sounding and the patient's oxygenation and hemodynamic status are deteriorating rapidly. On occasion, patients who are not pharmacologically paralyzed may be tensing their abdominal and chest wall muscles and so interfering with machine ventilation, and this may not be readily apparent at the bedside. In this situation rapid induction of pharmacologic paralysis may restore the ability to ventilate the patient safely. However, if it is still extremely difficult to ventilate the patient and cardiopulmonary collapse has not yet occurred, the situation is desperate and calls for unconventional interventions.

It is unlikely that administration of intravenous bronchodilators such as salbutamol[56;57], epinephrine[58], or magnesium sulphate[59] will be dramatically effective in such dire circumstances, but this can be tried, although concern about side effects of epinephrine have been raised[58]. A few reports have documented successful augmentation of bronchodilation with intravenous ketamine infusions[27;60-62] and inhalational anesthetics[63-74] for such patients. Attempts to reduce turbulent airflow and facilitate lung emptying with helium-oxygen[75-78], and other strategies such as external chest compression[55;79], bronchoscopy[80], and extracorporeal assist[81-85] have also been described as rescue therapies in critical situations. Many of these approaches require specialized equipment and should only be carried out by specialists familiar with these techniques. These therapies may carry significant risk, and so their use must only be considered on a case by case basis[33].

Liberation from mechanical ventilation ("weaning") in acute asthma

In general, once the patient is improving, paralytic drugs should first be stopped and sedation slowly decreased to permit increased spontaneous breathing efforts. At this point, many patients can be quickly awakened and extubated promptly. If ventilation has been prolonged, or the patient is weak, liberation from the ventilator may take longer. In this case, any of several ventilation modes may be employed to assist spontaneous breathing in preparation for extubation. Many practitioners prefer the continuous positive airway pressure (CPAP) plus pressure support mode, feeling that this mode will be more comfortable for the patient and will help to avoid the problem of fighting the ventilator as the patient awakens. Some clinicians find that NIV may be helpful in supporting the extubated but still fatigued patient with asthma until unassisted breathing becomes possible[10;86;87].

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Correspondence to: Dr. Rick Hodder, Divisions of Pulmonary and Critical Care Medicine, The Ottawa Hospital—Civic Campus, Ottawa ON K1Y 4E9;
rhodder@ottawahospital.on.ca
Fax: 613 761-4152

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