Chapter 4

Mechanical Ventilation

Thomas Johnson and Joann Bennett

Learning Objectives

1. Describe the indications for mechanical ventilation.
2. Understand the fundamental physics behind mechanical ventilation.
3. Develop a basic understanding of the function of positive pressure mechanical ventilation.
4. Describe the basic settings of mechanical ventilation and the impact on development of patient care plans.
5. Determine appropriate approaches to medication delivery related to the mechanical ventilator.

INTRODUCTION

Mechanical ventilation is a basic therapeutic and supportive intervention used in the critically ill patient. While pharmacists do not spend significant time working directly with the mechanical ventilator, a basic understanding of the settings used in and the function of mechanical ventilation is very helpful in the development of patient care plans. For example, sedation and analgesia regimens must take into account current ventilator settings, and nutrition regimens can impact or be impacted by mechanical ventilation. Complications, or avoiding complications, related to mechanical ventilation can be a significant component of developing patient care plans.

Understanding mechanical ventilation will also allow the pharmacist to better interpret medical literature and participate in interdisciplinary rounds. This chapter will cover the basics of mechanical ventilation with a focus on the impact on medication use.

History of Mechanical Ventilation

The history of mechanical ventilation dates at least as far back to a 1555 description of a tracheotomy and ventilation procedure, and initial work can be traced back at least one thousand years earlier.[1,2] However, the first workable negative pressure ventilator, the iron lung, was developed and produced by Drinker and Shaw in the late 1920s.[2,3] Positive pressure ventilation came of age during the polio epidemics of the 1950s with the large scale production of portable positive pressure mechanical ventilators.[1–4] Over the next 50 years, various modes and techniques of positive pressure ventilation have been attempted, revised, refined, abandoned, and revived. Current ventilators are capable of perhaps hundreds of combinations of settings and airflow patterns, but the fundamental principle of mechanical ventilation remains the same: moving air in and out of a patient's lungs.

Indications for Mechanical Ventilation

Mechanical ventilation is indicated in the patient requiring support to maintain oxygenation or eliminate carbon dioxide.[1,5–7] Mechanical ventilation may also be initiated for airway protection in an unresponsive or incoherent patient. A summary of the generally accepted indications and objectives for mechanical ventilation is listed in Table 4–1.

Table 4–1 Indications for and Objectives of Mechanical Ventilation[5–7]

Indications:	Reduce or change the work of breathing
Acute Respiratory Failure/Apnea	Reverse hypoxemia
Coma/Inability to protect airway	Reverse acute respiratory acidosis
Acute exacerbation of COPD	Relieve respiratory distress
Ventilatory dysfunction secondary to neuromuscular disorders	Prevent or correct atelectasis
Objectives:	Reverse or minimize ventilatory muscle fatigue
Alveolar ventilation	Permit sedation or neuromuscular blockade
Arterial oxygenation	Decrease systemic or myocardial oxygen consumption
Increase lung volume	Stabilize the chest wall

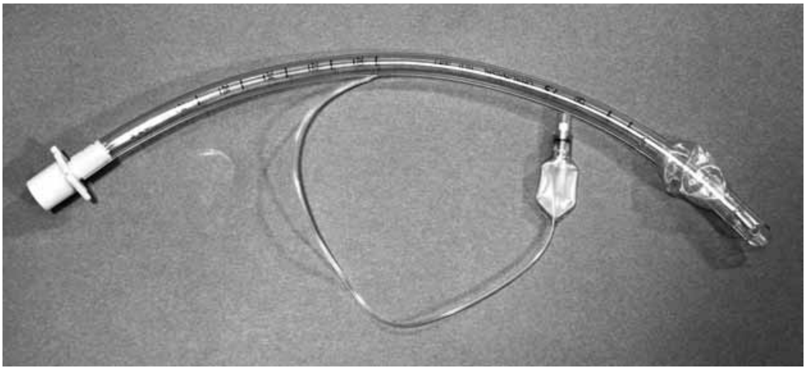

Figure 4–1 Endotracheal Tube

Physics of Mechanical Ventilation

Positive pressure invasive mechanical ventilation necessitates insertion of an endotracheal tube (ETT) illustrated in Figure 4–1. Ventilation without ETT insertion has been achieved with the advent of noninvasive ventilation techniques, and less critically ill patients may be managed without intubation. However, in this discussion, we will focus on the intubated patient on mechanical ventilation.

The ETT is smaller than the patient's natural airway, and as a result, airflow patterns change. These changes lead to increased airway resistance and increased work of breathing. The resistance in the tube can be illustrated by the equation $R = 8\eta\ell/\pi r^4$ (where η = viscosity, ℓ = length of tube, and r = internal radius of the tube), which is derived from Poiseuille's Law.[1,8,9] When the tube is lengthened or narrowed, resistance increases. Over time, new ventilator techniques have evolved to reduce the work of breathing associated with intubation and mechanical ventilation.

POSITIVE PRESSURE VENTILATION TERMINOLOGY

Airway Pressures

Positive pressure volume ventilation delivers tidal volume to the patient's lungs under pressure. Ventilated patients often have pulmonary pathology such as areas of damaged lung tissue, obstructed airways, and other structural abnormalities. It is important to remember that air behaves as a fluid, and therefore follows the path of least resistance as it enters the lungs. Therefore, it becomes necessary to understand and monitor several ventilation parameters.

Peak inspiratory pressure (PIP or P_{peak}) is the maximal airway pressure during the respiratory cycle.[5] PIP generally measures the pressures in the major airways. Significant or acute changes in PIP may indicate complications such as mucus plugging or bronchospasm, and elevated PIP necessitates clinical evaluation to identify the cause. Specific intervention or ventilator adjustment may be needed to decrease airway pressures in order to avoid the complications caused by prolonged airway pressure elevation.

Plateau pressure (P_{plat}) provides a measure of airway pressures at end inspiration, which reflects the pressure in the alveoli. P_{plat} is a major determinant of volutrauma and other ventilator complications (see Complications section). P_{plat} should be kept at or below 30 to 35 cm H_2O pressure.[10–16] In recent years, much attention has been directed toward avoiding ventilation with high pressure.

Volumes

Tidal volume (Vt) is defined as the volume of air breathed in and out during a respiratory cycle. Minute ventilation (MV—also abbreviated as Ve) is derived by multiplying respiratory rate by Vt. Minute ventilation is the primary respiratory determinant of blood CO_2 levels. Increasing MV will tend to decrease blood CO_2 by increasing CO_2 elimination. Decreasing MV will increase blood CO_2 by decreasing CO_2 elimination. The normal respiratory tract has several non-perfused areas referred to as physiologic dead space (V_{DS}),[17] which is the sum of anatomic (trachea, bronchus) and alveolar components that do not participate in CO_2 elimination. Adequate ventilation requires air ventilation and blood perfusion (sometimes denoted as V/Q) to be matched. Dead space to Tidal Volume ratio (V_{DS}/Vt) defines the ability of the lung to carry CO_2 from the pulmonary artery to the alveolus. Pathologic processes affect this ratio, as do ventilator settings. A good example of abnormal dead space is pulmonary embolism. In this situation, there is alveolar ventilation without blood perfusion, which leads to an increased V_{DS}/Vt ratio, resulting in abnormal oxygenation as well as ventilation.

Oxygen

The fraction of inspired oxygen (FiO_2) is the percentage of oxygen present in the air that is inhaled by the patient; for reference, room air has an FiO_2 of 0.21 (21%). An FiO_2 greater than 60% is associated with increased oxygen free radical production and potential cellular harm (oxygen toxicity).[1,10,18] Patients with poor respiratory function, including patients with severe acute respiratory distress syndrome (ARDS), often require FiO_2 values greater than 60% to maintain appropriate blood oxygen levels, and high FiO_2 levels should not be avoided at the expense of tissue oxygenation. The use of positive end expiratory pressure (PEEP) or other advanced ventilator recruitment techniques are directed toward reduction of FiO_2 to safe levels (i.e., <60%).[10,12,13,15]

Alveolar recruitment techniques allow alveoli that are not participating in ventilation to re-open and add to the functioning surface area for ventilation and oxygenation.[19–23] Recruitment is achieved by maximizing alveolar capillary function. Titration of PEEP is a form of alveolar recruitment that acts by adjusting the amount of pressure remaining within the lungs at the end of expiration. Using recruitment techniques encourages a higher number of alveoli to be opened or stay open. Prone positioning is also utilized in patients with ARDS to improve oxygenation via potential improvement in ventilation–perfusion match.[22,24–26]

VENTILATOR MODES AND SETTINGS

There are many ventilator settings and combinations of settings that are used in the management of critically ill patients. For simplicity, each setting will be discussed as a separate entity, but there are certainly instances where two or more settings will be used simultaneously. Table 4–2 summarizes the ventilator modes discussed in this section.

Controlled Mechanical Ventilation

In controlled mechanical ventilation (CMV), the ventilator does all of the work of breathing.[27,28] CMV restricts ventilation to only the set rate and volume prescribed. The patient cannot breath spontaneously in this mode, which typically leads to the need to deeply sedate and frequently paralyze the patient, as it is not a comfortable mode of ventilation. Strict CMV is not commonly employed, as most ventilators currently used in practice utilize settings that allow the patient to breath spontaneously and are often more comfortable for the patient.

Assist/Control

In current practice, CMV and the Assist/Control (A/C) mode of ventilation are essentially synonymous. In A/C, the patient receives a set rate and volume, but the patient may initiate spontaneous breaths as well.[28] All breaths delivered to the patient (spontaneous or ventilator initiated) provide the

Table 4–2 Summary of Ventilator Modes/Settings[23–27, 31–42]

Mode	Summary	Role	Sedation/Paralytics
CMV	Full support	Complete ventilation	Often required
Controlled **M**echanical **V**entilation	Set rate and volume		
A/C	Full support	Complete ventilation	Often required
Assist/**C**ontrol	Set rate and volume		Minimal paralytics if vent adjusted
	Patient may initiate breaths		
SIMV	Partial support	Weaning	Sedation OK
Synchronized **I**ntermittent **M**andatory **V**entilation	Set rate and volume	Post-operative	No paralytics
	Patient breaths not fully supported		
APRV	Full support	Improve oxygenation in specific patients	Mode often reduces need for sedation and paralysis
Airway **P**ressure **R**elease **V**entilation	P_{high} pressure maintained		
	P_{low} pressure is the release pressure		

High-Frequency	Full support Rapid, shallow breaths delivered to expanded lung	Improve oxygenation in acute respiratory distress syndrome patient	Deep sedation and paralysis commonly required
PS **P**ressure **S**upport	Minimal support Pressure delivered to assist breath at beginning of inspiration	Weaning and combination with other modes	Light sedation No paralytics
PEEP **P**ositive **E**nd **E**xpiratory **P**ressure	Pressure applied to exhalation phase to improve oxygenation	Increase oxygenation Lung recruitment	N/A
CPAP **C**ontinuous **P**ositive **A**irway **P**ressure	Minimal support PEEP without a set tidal volume	Weaning	Minimal sedation No paralytics
ATC **A**utomatic **T**ube **C**ompensation	Pressure applied to overcome increased airway resistance	Weaning Alternative to T-piece trial	Minimal sedation No paralytics

full set tidal volume. Therefore, if the ventilator set rate is 12 breaths per minute (bpm), the patient is guaranteed 12 full breaths, but if their spontaneous rate is 20 bpm, they will receive 20 full breaths. The use of low tidal volumes and titrating PEEP with A/C mode is a standard approach to ventilation in the ARDS patient.

Intermittent Mandatory Ventilation

Sometimes referred to as synchronized intermittent mechanical ventilation (SIMV), intermittent mandatory ventilation (IMV) is a mode of ventilation where the ventilator is set to deliver a specific number of full breaths each minute (rate) with a set Vt. In addition, the patient may initiate and take spontaneous breaths that they generate without ventilator assistance.[28] Pressure support (PS), which may be added to each IMV breath, is, in essence, added support at the initiation of the spontaneous breath, which is the most difficult part of inhalation in terms of energy expenditure. This decreases the work of breathing and increases the tidal volume that can be spontaneously generated by the patient.

Illustration of Synchronized Intermittent Mechanical Ventilation

Because SIMV can be a difficult mode to visualize, a patient example is provided. A patient set to the ventilator mode of SIMV, rate of 12, Vt of 600, PS 10 means that the patient will receive 12 full breaths of a Vt of 600 ml each minute, and these breaths will be synchronized with the patient's own breathing rate. If the patient breathes 20 times per minute, 12 breaths will be fully supported and 8 breaths will be supported by 10 cm H_20 pressure support only. The number of set breaths can then be weaned down over time (typically by intervals of two) so that the patient slowly takes over the additional work of breathing.

Intermittent mandatory ventilation was originally thought of as a weaning mode of ventilation.[7,29] However, newer weaning techniques have now begun to replace the use of this ventilator approach.[29,30] The work of breathing is higher in modes that do not completely support the patient's respiratory needs, and so the use of IMV in the weaning process was based on the concept that "conditioning" the respiratory muscles would facilitate extubation. However, new approaches to ventilator management suggest that the use of SIMV in this way actually leads to muscle fatigue and may delay extubation.[29] Many intensive care physicians favor resting the patient on A/C and performing daily or twice daily spontaneous breathing trials (SBT) to assess weanability.[30,31]

Pressure vs. Volume Control

In modes such as A/C, volume ventilation provides a volume (Vt) without regard to the airway pressure required to deliver that volume. Pressure control ventilation delivers a tidal volume via a set pressure, which generates a tidal breath. The advantage of pressure control ventilation is that it generates less alveolar injury by decreasing the amount of alveolar stretching during inflation in an already fragile lung (such as in ARDS). Figures 4–2a and 4–2b illustrates the contrasting air-flow patterns of pressure versus volume delivery.[27] Many of the ventilator settings discussed in this chapter, but specifically CMV and A/C, can be delivered with either a pressure control setting or a volume control setting.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is defined as continuous positive airway pressure (CPAP) with intermittent releases of pressure that produce gas exchange.[32,33] Instead of setting a specific Vt, the ventilator is set to maintain a P_{high} pressure and then release to a P_{low} pressure at regular intervals; the Vt is obtained by the change in pressure. The P_{high} pressure is

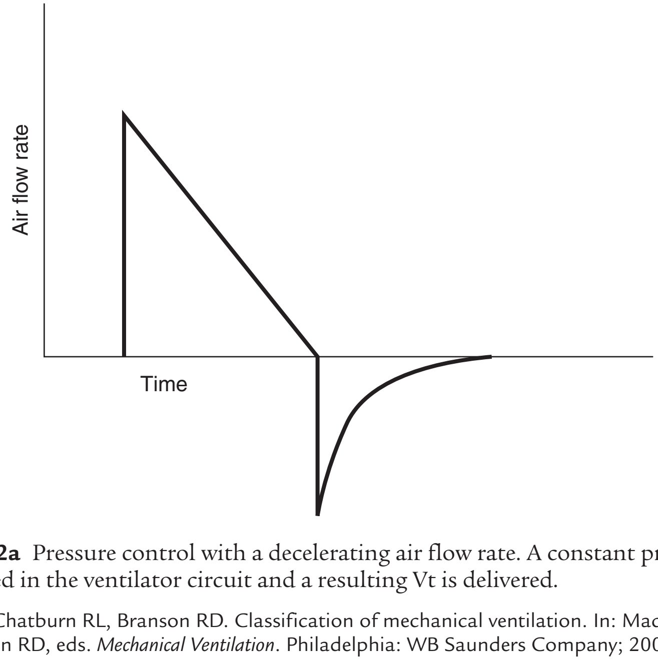

Figure 4–2a Pressure control with a decelerating air flow rate. A constant pressure is maintained in the ventilator circuit and a resulting Vt is delivered.

Data from: Chatburn RL, Branson RD. Classification of mechanical ventilation. In: MacIntyre NR and Branson RD, eds. *Mechanical Ventilation*. Philadelphia: WB Saunders Company; 2001:2–50.

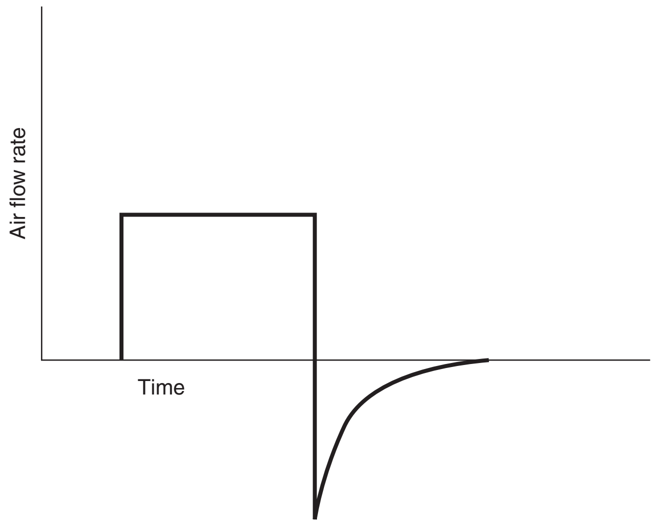

Figure 4–2b Volume control mode with a constant air flow rate, represented by the square waveform seen here. Constant air flow continues until the set Vt is delivered.

Data from: Chatburn RL, Branson RD. Classification of mechanical ventilation. In: MacIntyre NR and Branson RD, eds. *Mechanical Ventilation*. Philadelphia: WB Saunders Company; 2001:2–50.

maintained for the majority of time, and therefore maintains lung expansion and encourages alveolar recruitment. Generally, patients should be allowed to breathe spontaneously on top of the P_{high} pressure.[33] Paralytic use and deep sedation are needed significantly less often with APRV (as compared to some other ventilator settings) to allow the patient to accept this type of ventilation. Figure 4–3 provides a visual representation of airway pressure during APRV.

High-Frequency Ventilation

High-frequency ventilation is most commonly used in the neonatal and pediatric patient population.[34] The underlying concept is somewhat similar to that of APRV in that the lungs are expanded and then small, rapid breaths (~300 bpm) are delivered to the patient.[35] This high rate of breath delivery maintains open alveoli, yet still allows for oxygen delivery and the elimination of carbon dioxide. Unlike APRV, deep sedation and paralytics are usually required for the patient to tolerate this setting. Current indications in adults are rather limited, and further data and trials demonstrating improved outcomes with high-frequency ventilation are needed to support widespread use in adults.[34–37]

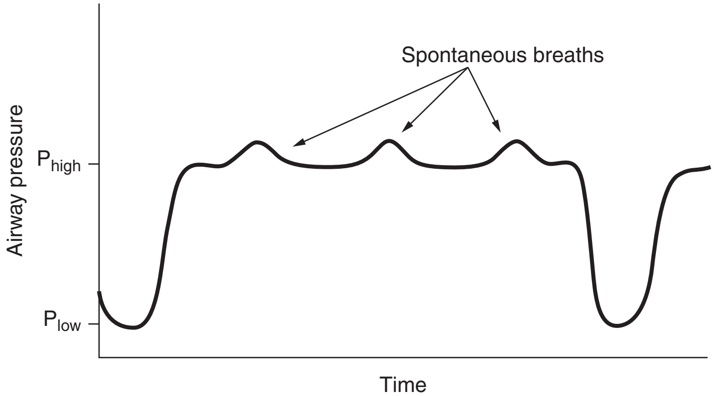

Figure 4–3 Airway Pressure Release Ventilation (APRV). This representative waveform shows the set P_{high} and P_{low} pressure levels as well as the spontaneous breaths generated by the patient.

Data from: Habashi NM. Other approaches to open-lung ventilation: Airway pressure release ventilation. *Crit Care Med* 2005;33(Suppl.):S228–S240. DOI: 10.1097/01.CCM.0000155920.11893.37.

Pressure Support

Pressure support (PS) may be used alone or in combination with other ventilation settings.[28] In this setting, the ventilator is set to deliver a specific pressure (e.g., 10 cm H_20) at the initiation of a spontaneous breath to assist with overcoming initial airway resistance. Pressure support is generally considered a weaning mode of ventilation,[29,30] and as a lone setting has no set ventilatory rate. As the level of PS is decreased, the patient must assume more of the work of breathing.

Positive End Expiratory Pressure

Positive end expiratory pressure (PEEP) is positive pressure maintained in the airways during the exhalation phase of the respiratory cycle. It is used in conjunction with other modes of ventilation to improve oxygenation and prevent lung collapse. As described earlier, increasing levels of PEEP is a lung recruitment strategy and allows alveoli to remain open longer;[19–23] by remaining open, more lung surface area is available for oxygen exchange. The ARDSnet protocol for ventilation in patients with ARDS utilized a low tidal volume combined with progressively higher levels of PEEP and oxygen to maintain oxygenation.[12] This low tidal volume strategy reduces the sheering injury caused by high pressures that is felt to lead to worsened lung injury.[38]

Continuous Positive Airway Pressure

Both inspiratory pressure (PS) and end expiratory pressure (PEEP) can be delivered alone or in conjunction with other ventilator modes. When PEEP is delivered without a set Vt, it is referred to as continuous positive airway pressure (CPAP). CPAP is also considered a weaning mode of ventilation, as patients often are placed on this setting to determine if they have a reasonable chance of progressing to extubation.

Automatic Tube Compensation

Automatic tube compensation (ATC) is available on newer ventilators. Similar to the PS setting, ATC delivers set pressure to the distal end of the artificial airway. In ATC, the pressure is calculated specifically to compensate for the increased resistance caused by the ETT, therefore simulating breathing without the tube in place.

Ventilator Parameters

While subjective criteria such as level of alertness and strength of cough are certainly used to determine if a patient may be ready for extubation, objective measures are also available. The rapid shallow breathing index (RSBI) is one example. The RSBI is calculated by dividing the respiratory rate by the Vt (in liters); an RSBI less than 100 is a reasonable indication that the patient is ready for extubation. Another example is the negative inspiratory force (NIF), which is a measure of the patient's ability to generate a breath. Pharmacists will often hear these terms, as well as others, and should at least have a working knowledge of the application of these measures.

Ventilator Settings Summary

An example of how ventilator settings may be ordered or otherwise reported would include the following elements: setting, rate, volume, FiO_2 (e.g., CMV, rate - 12, Vt - 700 mls, O_2 - 60%). Beyond the specific ventilator settings, it is important for the new practitioner with minimal experience working with and around ventilators to remember some simple concepts. First of all, ventilators are means to support the movement of air in and out of a patient's lungs. This is accomplished by delivering and allowing for exhalation of a Vt, which must be done at a set rate. Secondly, ventilators are capable of being set to do all of the work of breathing, or essentially none of the work of breathing, so it is important to understand how much a patient is participating in their own air exchange. Finally, remembering and understanding terms like recruitment, PEEP, low-volume ventilation, weaning, and breathing trials will be helpful during the care decision discussions that occur in ventilated, critically ill patients.

VENTILATOR COMPLICATIONS

Three of the most common complications associated with ventilatory support include volutrauma, hypotension, and ventilator-associated pneumonia (VAP).[39] Volutrauma is the result of overdistension of the alveoli unit in the lung, leading to overstretching of the alveoli and compression of the capillary bed, which then results in a ventilation/perfusion (V/Q) mismatch and increased shear force on adjacent collapsed alveoli.[4] Appropriate ventilator techniques can prevent this by maintaining low plateau pressures.

Initiation of positive pressure ventilation or titration of PEEP can affect the pleural (intrathoracic) pressure and result in systemic hypotension due to reduced venous return.[7] Hypotension secondary to mechanical ventilation can typically be addressed by fluid administration and ventilator adjustment, although occasionally vasopressors may be needed. However, hypotension in the critically ill patient is often multi-factorial, and mechanical ventilation may be only one element of a patient's hypotension.

Ventilator-associated pneumonia is a major complication of ventilation. The development of VAP is associated with increased morbidity and mortality as well as leading to longer ventilatory support time. Ventilator-associated pneumonia is nosocomial bacterial pneumonia that occurs in patients receiving mechanical ventilation for more than 48 hours after intubation.[40,41] Definitive diagnosis can be difficult as there are multiple comorbidities often present in ventilated patients.[42] Invasive treatment strategies including bronchoscopy procedures and appropriate initial antibiotics have been shown to decrease mortality and shorten treatment courses.[43] Appropriate initial antibiotic selection based upon suspected pathogens and local resistance patterns is extremely important to minimize mortality and complications associated with VAP.[44,45] Prediction of these pathogens may be based on time of pneumonia onset, as well as many other factors.[46,47] The clinician must carefully consider all of these factors in ventilated patients to ensure appropriate treatment of VAP.

The financial implications of VAP in the United States are significant, and so multiple strategies have been developed to prevent VAP. Shortening ventilation times is an obvious method for preventing VAP.[40,41] Body position also has been described in the prevention of VAP; a semirecumbent position, as compared to supine body position, decreased both clinically-suspected and microbiologically-confirmed VAP in one study.[48] Subsequent studies have not reproduced these results, but the trial designs were different.[49,50] Semirecumbency is an easy, noninvasive intervention, so elevation of the head of the bed to 30 to 45 degrees is generally recommended for the prevention of VAP and aspiration.[40,41,51]

Continuous subglottic suctioning utilizes a special endotracheal tube with a suction port in the dorsal area just above the ETT cuff. Continuous aspiration of subglottic secretions has been shown to decrease the rate of VAP.[52] While these special ET tubes are more expensive than standard tubes, there is some evidence that the reduction of VAP results in overall cost savings.[53] New types of ventilator strategies, oral cares, silver-coated tubes, and other interventions are being developed continuously, and many institutions utilize checklists of procedures and patient care techniques commonly referred to as "ventilator bundles" to help minimize or eliminate VAP as a complication.

NON-INVASIVE VENTILATION STRATEGIES

Bi-Level Positive Airway Pressure and Continuous Positive Airway Pressure

Non-invasive positive pressure ventilation (NPPV) strategies are becoming more common for several reasons. One reason is that more patients are using non-invasive ventilation at home to treat sleep disordered breathing (i.e., sleep apnea and related conditions). Further, because of the adverse events and discomfort associated with invasive mechanical ventilation, the use of non-invasive ventilation or ventilatory support continues to be investigated and trialed.

The two most common modes of non-invasive ventilation are continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP). Both of these forms of non-invasive mechanical ventilation do not require an ET tube, but instead use a tight-fitting mask that covers either the nose or both the nose and mouth. This allows for higher pressures to be applied to the upper and lower airways, resulting in relief of upper airway obstruction and an increase in Vt and PEEP, which ultimately results in improvements in ventilation and oxygenation. The patient needs to be reasonably alert and not have any significant risk of aspiration in order to be a candidate for this type of ventilatory support.

Depending on the mode used, different pressures can be applied. The pressures are adjusted by a physician or respiratory therapist in order to decrease patient work of breathing, improve patient comfort, and improve variables such as ventilation and oxygenation. Non-invasive positive pressure ventilation can be used as a treatment for sleep disordered breathing, as an attempt to prevent intubation (especially in patients with chronic lung disease or congestive heart failure), and as a supportive therapy to prevent re-intubation in patients previously intubated and mechanically ventilated.

MECHANICAL VENTILATION IMPACT ON PHARMACOTHERAPY

Sedation and Analgesia

In the past, the initiation of mechanical ventilation most often meant that deep sedation and muscle paralysis were required for the patient to accept ventilation, which often resulted in prolonged ventilator times. Appropriate and comfortable ventilator adjustment is an important component of controlling anxiety and agitation in the ventilated patient. There are multiple studies indicating that daily wake-up and use of short-term sedatives lead to decreased ventilator times.[54–58] Less sedated patients are able to undergo more aggressive physical therapy and mobilization.[59] Despite attention to ventilation and patient comfort with the mode of ventilation, patient anxiety and agitation may still exist and require treatment.[60]

Ventilator strategies vary in the way they affect patient/ventilator synchrony, and therefore comfort. The overall goals of sedation and medication choice are dependent on many factors. When the patient is receiving ventilation through a full support mode such as CMV or A/C, the ventilator is completely supporting ventilation, thus allowing for deeper sedation without fear of respiratory depression. Patients on these modes may require and will tolerate paralysis, continuous sedative infusions, and continuous analgesics without adverse effects on the ventilation. It is important to note that mechanical ventilation by itself is not an indication for sedation; the indications for sedation are anxiety or agitation not relieved by non-pharmacologic methods.[59,60] As described in detail in Chapter 5, inappropriate use of sedatives and analgesics increases the risk of delirium, prolongs ventilation times, and further places the patient at risk for ventilator-associated complications.[61–63]

Modes of ventilation such as IMV, PS, or CPAP require different treatment strategies for anxiety, agitation, and delirium as deep sedation will suppress patient respiratory drive, and these modes require the patient to initiate their own breaths. Continuous benzodiazepines, propofol, and narcotic analgesics may be needed for patients on these weaning modes, but caution must be used to minimize the potential for respiratory depression. Dexmedetomidine (DEX), a central alpha-2 agonist, is a potential alternative as there is no respiratory depression associated with this agent.[64] DEX has been successfully used in small studies and case reports to facilitate weaning from mechanical ventilation after long-term sedation with other agents,[65–69] and may be particularly useful in patients suffering from physical withdrawal symptoms of recreational drugs such as alcohol or narcotics[70] or medications used for prolonged sedation and analgesia.[67–68] Additional studies have suggested a lower rate of delirium in certain populations treated with DEX.[71–75] Drug cost, especially at higher doses, is a disadvantage of DEX, and so additional larger scale studies are needed to more clearly define the role of this agent in mechanically ventilated patients to identify cost-effective strategies for use. It should be noted that any patient on non-invasive ventilation should only receive sedation medications under the specific guidance of a physician, as alterations in wakefulness can lead to disastrous results in patients with a confined mask over their mouth and nose.

Neuromuscular Blockade

Neuromuscular blockade is appropriate only in patients who are difficult to ventilate due to poor lung compliance, high airway pressures, or the inability to maintain a comfortable respiratory cycle with sedation and analgesia alone. Only after initiation of adequate sedative medications should neuromuscular blockers (NMBs) be used, as they have no sedative or analgesic properties. Common NMBs used for acceptance of ventilation include pancuronium, vecuronium, atracurium, and cisatracurium, and are discussed in detail in Chapter 5.[76] A peripheral nerve stimulator should be used to ensure patients achieve therapeutic goals with the minimum amount of medication, as excessive paralytic doses can lead to prolonged muscle weakness, prolonged ventilator times, and possible hemodynamic compromise. NMBs must be stopped prior to changing ventilator settings to a mode that does not provide full support as patients will not be able to breathe spontaneously.

Nutrition

Nutrition provision to the mechanically ventilated patient will be impacted by multiple factors. Ventilator settings or medications used to facilitate mechanical ventilation may alter nutrition measurements via indirect calorimetry or affect total caloric requirements. Mechanical ventilation and lung function may also affect the delivery or type of nutrition provided.

Indirect calorimetry (IC) directly measures oxygen consumed and carbon dioxide produced during the respiratory cycle to derive the patient's resting energy expenditure (REE) via the modified Weir equation.[77–79] The results are very helpful in designing patient-specific nutrition regimens, especially in patients with multiple co-morbidities or extremes of body habitus, although unfortunately many institutions do not have this technology readily available. General requirements to perform an accurate IC are FiO_2 <60%, consistent ventilator settings, a ventilator circuit that ensures direct gas measurement, a patient at rest or baseline level of arousal, and appropriate equipment and personnel. While mechanical ventilation is not required to perform this procedure, the intubated patient typically ensures a closed ventilatory circuit to minimize gas leaks that adversely affect test results. To maximize accuracy of IC, the test should not be performed within two hours of ventilator setting changes.[80]

There is minimal data directly correlating energy expenditure to specific ventilator modes, though increasing levels of sedation and chemical paralysis have both been shown to reduce energy expenditure in ventilated patients.[81,82] While this may indicate a relationship between energy expenditure and the work of breathing, further studies are needed to determine a direct correlation between ventilator modes and nutrition requirements of the patient. Increased minute ventilation has been linked to increased energy expenditure and has been included in some energy estimation equations,[83,84] though it is unclear if the increase in minute ventilation is the cause or the result of an increased metabolic rate.

Other factors that may affect nutrition delivery in the mechanically ventilated patient include concerns about aspiration, prone positioning, and weaning from mechanical ventilation. Gastric residual volume (GRV) is often used to assess tolerance of gastric tube feedings; however, the risk of aspiration does not correlate to measured GRV.[85] Clinicians are now generally using more liberalized limits for GRV in critically ill patients.[86] Prone positioning of mechanically ventilated patients presents challenges for providing enteral feeding, and published data is somewhat conflicting on the safety and effectiveness of enteral feeding in proned patients.[87,88] Interventions such as prokinetics, transpyloric feeding tube placement, and placing the patient in a semi-recumbent position may aid in tolerance of enteral feeds. Enteral feedings are also often held for weaning and discontinuation of ventilation. One study in a pediatric population has shown the safety of continuing transpyloric feedings during the weaning and extubation process, with equivalent adverse events in the group that continued nutrition versus the group that held nutrition.[89] Additional studies in adults will need to be completed to compel clinicians to alter the common practice of holding enteral feeds during the weaning and extubation process.

PRACTICAL CONSIDERATIONS

Nebulizers vs. Inhalers

Several medications may be delivered by aerosol administration, most commonly beta-2 agonists and anticholinergic medications, and guidelines for selection of appropriate delivery devices have been published.[90] Either metered dose inhalers (MDI) or nebulizers may be used in mechanically ventilated patients.[91,92] A spacer device should be used with MDIs and the inhaler should be actuated precisely with initiation of inspiration, with the dose for bronchodilators and anticholinergics roughly doubled from doses used in non-ventilated patients. Institution-specific equipment will influence the decision regarding routine use of nebulizers or MDIs for beta-2 agonist administration.[91] Techniques for the delivery of medication via a dry powder inhaler (DPI) have been described, but further studies are needed to determine optimal technique to achieve adequate drug deposition in the lungs with DPIs.[93]

Inhaled Antibiotics

There has been increasing interest over the last few years in the use of aerosolized antibiotics in mechanically ventilated patients.[94,95] With increases in multi-drug resistant organisms, the use of higher doses and more toxic medications is becoming more commonplace. To try to minimize systemic exposure and also to try to get high concentrations of antibiotic directly to the site of infection, inhaled antimicrobials have been employed. The most common medications used are the aminoglycosides, and positive effects have primarily been seen in clearing upper airway cultures and decreasing secretions in tracheobronchitis.

Some level of technical expertise is required to ensure adequate drug delivery to the target tissues, be it for antibiotics or other medications. The specifics of these techniques can be found in other reviews on the topic.[91–93,96]

NOVEL PHARMACOLOGIC INTERVENTIONS

Heliox

If we recall the physics of air flow in mechanical ventilation ($R = 8\eta\ell/\pi r^4$), resistance is determined by pressure and laminar flow, and laminar flow is affected by both the density and viscosity of the gas.[9] Since a helium/oxygen mixture has a lower density and higher viscosity than a standard nitrogen/oxygen mixture, flow is improved and resistance is reduced. Heliox in mechanically ventilated patients has been shown to decrease peak inspiratory airway pressures.[97,98] Large, randomized, controlled trials have not yet been completed, so the indications for heliox remain relatively limited to some severe asthma patients.[98,99]

Surfactant

Surfactant replacement has been used for many years in neonates to correct surfactant deficiencies in premature lungs. Adult patients with ARDS-associated respiratory failure exhibit alterations in both production and function of the different subtypes of surfactant.[100,101] Trials involving the recombinant form of surfactant protein C over the last several years have shown promise in animal models[102–104] and in subgroups of human trials,[105,106] but confirmatory trials are still needed to address the patient selection and usefulness of surfactant in adult patients with respiratory failure requiring intubation.[107]

SUMMARY

The pharmacist that works with mechanically ventilated patients should have a fundamental knowledge of mechanical ventilation to provide optimal pharmaceutical care. Many medication regimens impact or are impacted by the modes or types of mechanical ventilation. Ventilation and pharmacologic therapies continue to evolve quickly for critically ill patients, and new treatment strategies may be on the horizon.

Key Points

- Mechanical ventilation is a key component of critical care practice.
- The various mechanical ventilation settings can affect the approach to sedation and analgesia, as well as how certain medications are delivered to the patient.
- Weaning or liberation from the mechanical ventilator is important to shorten length of ICU stay and minimize complications.
- Non-invasive ventilation is becoming a larger part of critical care management.

Selected Suggested Readings

- Cawley MJ. Mechanical ventilation: a tutorial for pharmacists. *Pharmacotherapy.* 2007;27:250–266.
- Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2006;354:1775–1786.

- AARC Clinical Practice Guideline: Metabolic measurement using indirect calorimetry during mechanical ventilation – 2004 revision & update. *Respir Care.* 2004;49(9):1073–1079.
- Dhand R. Aerosol delivery during mechanical ventilation: from basic techniques to new devices. *J Aerosol Med Pulm Drug Deliv.* 2008;21:45–60.

References

1. Marino PL, Sutin KM. *The ICU book. 3rd ed.* Philadelphia: Lippincott Williams & Wilkins; 2007.
2. Cawley MJ. Mechanical ventilation: a tutorial for pharmacists. *Pharmacotherapy.* 2007;27:250–266.
3. Barbarash RA, Smith LA, Godwin JE, Sahn SA. Mechanical ventilation. *Ann Pharmacother.* 1990;24:959–970.
4. Gluck E, Sarrigianidis A, Dellinger RP. Mechanical Ventilation. In: Parrillo JE and Dellinger RP, eds. *Critical care medicine: Principles of diagnosis and management in the adult. 2nd ed.* St. Louis: Mosby, Inc.; 2002:137–161.
5. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med.* 2001;344(26): 1986–1996.
6. Pierson DJ. Indications for mechanical ventilation in adults with acute respiratory failure. *Resp Care.* 2002;47(3):249–265.
7. Slutsky AS. ACCP Consensus Conference: mechanical ventilation. *Chest.* 1993;104:1833–1859.
8. Nave CR. Poiseuille's Law. (Accessed July 18, 2011 at http://hyperphysics.phy-astr.gsu.edu/hbase/ppois.html).
9. Hess DR, Fink JB, Venkataraman ST, Kim IK, Myers TR, Tano BD. The history and physics of Heliox. *Respir Care.* 2006;51(6):608–612.
10. Brower RG, Rubenfeld GD. Lung-protective ventilation strategies in acute lung injury. *Crit Care Med.* 2003;31(Suppl.):S312–S316.
11. Cordingley JJ, Keogh BF. The pulmonary physician in critical care – 8: ventilatory management of ALI/ARDS. *Thorax.* 2002;57:729–734.
12. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301–1308.
13. McIntyre RC, Pulido EJ, Bensard DD, Shames BD, Abraham E. Thirty years of clinical trials in acute respiratory distress syndrome. *Crit Care Med.* 2000;28:3314–3331.
14. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1334–1349.
15. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med.* 2006;34:1311–1318.
16. Slutsky AS, Ranieri VM. Mechanical Ventilation: Lessons from the ARDSNet trial. *Respir Res.* 2000;1:73–77.

17. Peruzzi WT, Shapiro BA. Arterial blood gases. In: Parrillo JE and Dellinger RP, eds. *Critical care medicine: Principles of diagnosis and management in the adult. 2nd ed*. St. Louis: Mosby, Inc.; 2002:202–223.
18. Gammon RB, Strickland JH, Kennedy JI, Young KR. Mechanical ventilation: a review for the internist. *Am J Med.* 1995;99:553–562.
19. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2006;354:1775–1786.
20. Richard JC, Maggiore SM, Jonson B, Mancebo J, LeMaire F, Brochard L. Influence of tidal volume on alveolar recruitment: respective role of PEEP and a recruitment maneuver. *Am J Respir Crit Care Med.* 2001;163: 1609–1613.
21. Richard JC, Brochard L, Vandelet P, et al. Respective effects of end-expiratory and end-inspiratory pressures on alveolar recruitment in acute lung injury. *Crit Care Med.* 2003;31:89–92.
22. Lim CM, Jung H, Koh Y, et al. Effect of alveolar recruitment maneuver in early acute respiratory distress syndrome according to antiderecruitment strategy, etiological category of diffuse lung injury, and body position of the patient. *Crit Care Med.* 2003;31:411–418.
23. Mols G, Priebe HJ, Guttmann J. Alveolar recruitment in acute lung injury. *Br J Anaesth.* 2006;96(2):156–166.
24. Galiatsou E, Kostanti E, Svarna E, et al. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med.* 2006;174:187–197.
25. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med.* 2008;36: 603–609.
26. Fan E, Mehta S. High-frequency oscillatory ventilation and adjunctive therapies: inhaled nitric oxide and prone positioning. *Crit Care Med.* 2005;33(Suppl.):S182–S187.
27. Chatburn RL, Branson RD. Classification of mechanical ventilation. In: MacIntyre NR and Branson RD, eds. *Mechanical Ventilation*. Philadelphia: WB Saunders Company; 2001:2–50.
28. Branson RD, Campbell RS. Modes of ventilator operation. In: MacIntyre NR and Branson RD, eds. *Mechanical Ventilation*. Philadelphia: WB Saunders Company; 2001:51–84.
29. Hess D. Ventilator modes used in weaning. *Chest.* 2001;120:474S–476S.
30. MacIntyre NR, Cook DJ, Ely EW, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest.* 2001;120:375S–395S.
31. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371:126–134.

32. McCunn M, Habashi NM. Airway pressure release ventilation in the acute respiratory distress syndrome following traumatic injury. *Int Anesthesiol Clin.* 2002 Summer;40(3):89–102.
33. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. *Crit Care Med.* 2005;33(Suppl.):S228–S240.
34. Derdak S. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adult patients. *Crit Care Med.* 2003;31(Suppl.):S317–S323.
35. Salim A, Martin M. High-frequency percussive ventilation. *Crit Care Med.* 2005;33(Suppl.):S241–S245.
36. Chan KPW, Stewart TE. Clinical use of high-frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome. *Crit Care Med.* 2005;33(Suppl.):S170–S174.
37. Imai Y, Slutsky AS. High-frequency oscillatory ventilation and ventilator-induced lung injury. *Crit Care Med.* 2005;33(Suppl.):S219–S314.
38. Piantoadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med.* 2004;141:460–470.
39. Chatila WM, Criner GJ. Complications of long-term mechanical ventilation. *Resp Care Clin.* 2002;8:631–647.
40. Kollef MH. The prevention of ventilator-associated pneumonia. *N Engl J Med.* 1999;340:627–633.
41. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med.* 2004;32:1396–1405.
42. Wunderink RG. Clinical criteria in the diagnosis of ventilator-associated pneumonia. *Chest.* 2000;117:191S–194S.
43. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. *Ann Intern Med.* 2000;132:621–630.
44. Fowler RA, Flavin KE, Barr J, Weinacker AB, Parsonnet J, Gould MK. Variability in antibiotic prescribing patterns and outcomes in patients with clinically suspected ventilator-associated pneumonia. *Chest* 2003;123:835–844.
45. Kuti EL, Patel AA, Coleman CI. Impact of inappropriate antibiotic therapy on mortality in patients with ventilator-associated pneumonia and blood stream infection: a meta-analysis. *J Crit Care.* 2008;23:91–100.
46. Singh N, Falestiny MN, Rogers P, et al. Pulmonary infiltrates in the surgical ICU: prospective assessment of predictors of etiology and mortality. *Chest.* 1998;114:1129–1136.
47. Ibrahim EH, Ward S, Sherman G, Kollef MH. A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. *Chest.* 2000;117:1434–1442.
48. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomized trial. *Lancet.* 1999;354:1851–1858.
49. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med.* 2006;34:396–402.

50. Girou E, Buu-Hoi A, Stephan F, et al. Airway colonization in long-term mechanically ventilated patients. *Intensive Care Med.* 2004;30:225–233. Epub 29 Nov 2003.
51. Scolapio JS. Methods for decreasing risk of aspiration pneumonia in critically ill patients. *JPEN.* 2002;26:S58–S61.
52. Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. *Am J Respir Crit Care Med.* 2010;182:910–917.
53. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia. *Chest.* 2001;119:228–235.
54. Schweickert WD, Gehlbach BK, Pohlman AS, Hall JB, Kress JP. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med.* 2004;32:1272–1276.
55. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med.* 2006;34:1326–1332.
56. Wittbrodt ET. Daily interruption of continuous sedation. *Pharmacotherapy.* 2005;25(5):3S–7S.
57. Muellejans B, Matthey T, Schlopp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised open-label, pharmacoeconomic trial. *Crit Care.* 2006;10:R91.
58. Richman PS, Baram D, Varela M, Glass PS. Sedation during mechanical ventilation: a trial of benzodiazepine and opiate in combination. *Crit Care Med.* 2006;34:1395–1401.
59. Kress JP, Hall JB. Sedation in the mechanically ventilated patient. *Crit Care Med.* 2006;34:2541–2546.
60. Society of Critical Care Medicine and American Society of Health-System Pharmacists: Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult. *Am J Health-Syst Pharm.* 2002;59:150–178.
61. Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguia C, Soto L, Anzueto A. Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. *Chest.* 2005;128:496–506.
62. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104:21–26.
63. Riker RR, Fraser GL. Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. *Pharmacotherapy.* 2005;25(5):8S–18S.
64. Venn RM, Newman PJ, Grounds RM. A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. *Intensive Care Med.* 2003;29:201–207.
65. Multz AS. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. *Anesth Analg.* 2003;96:1064–1065.
66. Tobias JD. Dexmedetomidine to treat withdrawal following prolonged opioid administration to infants and children. *Anesthesiology.* 2005;103:A1369 [abstract].

67. Siobal MS, Kallet RH, Kivett VA, Tang JF. Use of dexmedetomidine to facilitate extubation in surgical intensive-care-unit patients who failed previous weaning attempts following prolonged mechanical ventilation: a pilot study. *Respir Care.* 2006;51(5):492–496.
68. Kent CD, Kaufman BS, Lowy J. Dexmedetomidine facilitates the withdrawal of ventilatory support in palliative care. *Anesthesiology.* 2005;103:439–441.
69. Marcel R, Weido J, Hebeler RF, Ramsay MA. Early extubation in cardiovascular surgery facilitated by dexmedetomidine. *Anesthesiology.* 2004;101:A392 [abstract].
70. Rovasalo A, Tohmo H, Aantaa R, Kettunen E, Palojoki R. Dexmedetomidine as an adjuvant in the treatment of alcohol withdrawal delirium: a case report. *Gen Hospl Psych.* 2006;28:362–363.
71. Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intensive Care Med.* 2004;30:2188–2196.
72. Guinter JR, Kristeller JL. Prolonged infusions of dexmedetomidine in critically ill patients. *Am J Health Syst Pharm.* 2010;67:1246–1253.
73. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301:489–499.
74. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA.* 2007;298:2644–2653.
75. Darrouj J, Puri N, Prince E, Lomonaco A, Spevetz A, Gerber DR. Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. *Ann Pharmacother.* 2008;42:1703–1705.
76. Society of Critical Care Medicine and American Society of Health-System Pharmacists. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Am J Health Syst Pharm*. 2002;59:179–195.
77. McClave SA, McClain CJ, Snider HL. Should indirect calorimetry be used as part of nutritional assessment? *J Clin Gantroenterol.* 2001;33(1):14–19.
78. AARC Clinical Practice Guideline: Metabolic measurement using indirect calorimetry during mechanical ventilation – 2004 revision & update. *Respir Care.* 2004;49(9):1073–1079.
79. Smyrnios NA, Curley FJ, Shaker KG. Accuracy of 30-minute indirect calorimetry studies in predicting 24-hour energy expenditure in mechanically ventilated, critically ill patients. *JPEN.* 1997;21:168–174.
80. Brandi LS, Bertolini R, Santini L, Cavani S. Effects of ventilator resetting on indirect calorimetry measurement in the critically ill surgical patient. *Crit Care Med.* 1999;27:531–539.
81. Barton RG, Craft WB, Mone MC, Saffle JR. Chemical paralysis reduces energy expenditure in patients with burns and severe respiratory failure treated with mechanical ventilation. *J Burn Care Rehabil.* 1997;18:461–468.
82. Terao Y, Miura K, Saito M, Sekino M, Fukusaki M, Sumikawa K. Quantitative analysis of the relationship between sedation and resting energy expenditure in postoperative patients. *Crit Care Med.* 2003;31:830–833.

83. Frankenfield DC, Coleman A, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. *JPEN.* 2009;33:27–36.
84. Frankenfield D, Smith S, Cooney RN. Validation of 2 approaches to predicting resting metabolic rate in critically ill patients. *JPEN.* 2004;28:259–264.
85. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med.* 2005;33:324–330.
86. Montejo JC, Minambres E, Bordeje L, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med.* 2010;36:1386–1393.
87. Reignier J, Thenoz-Jost N, Fiancette M, et al. Early enteral nutrition in mechanically ventilated patients in the prone position. *Crit Care Med.* 2004;32:94–99.
88. van der Voort PH, Zandstra DF. Enteral feeding in the critically ill: comparison between the supine and prone positions: a prospective crossover study in mechanically ventilated patients. *Crit Care.* 2001;5:216–220.
89. Lyons KA, Brilli RJ, Wieman RA, Jacobs BR. Continuation of transpyloric feeding during weaning of mechanical ventilation and tracheal extubation in children: a randomized controlled trial. *JPEN.* 2002;26:209–213.
90. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest.* 2005;127:335–371.
91. Duarte AG. Inhaled bronchodilator administration during mechanical ventilation. *Respir Care.* 2004;49(6):623–634.
92. Dhand R. Basic techniques for aerosol delivery during mechanical ventilation. *Respir Care.* 2004;49(6):611–622.
93. Dhand R. Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. *Respir Care.* 2005;50(10):1331–1344.
94. Palmer LB. Aerosolized antibiotics in critically acutely ill ventilated patients. *Curr Opin Crit Care.* 2009;15:413–418.
95. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit Care Med.* 2008;36:2008–2013.
96. Dhand R. Aerosol delivery during mechanical ventilation: from basic techniques to new devices. *J Aerosol Med Pulm Drug Deliv.* 2008;21:45–60.
97. Pizov R, Oppenheim A, Eidelman LA, Weiss YG, Sprung CL, Cotev S. Helium versus oxygen for tracheal gas insufflation during mechanical ventilation. *Crit Care Med.* 1998;26:290–295.
98. Venkataraman ST. Heliox during mechanical ventilation. *Respir Care.* 2006;51(6):632–639.
99. Brenner B, Corbridge T, Kazzi A. Intubation and mechanical ventilation of the asthmatic patient in respiratory failure. *Proc Am Thorac Soc.* 2009;6:371–379.
100. Poynter SE, LeVine AM. Surfactant biology and clinical application. *Crit Care Clin.* 2003;19(3):459–472.

101. Eisner MD, Parsons P, Matthay MA, Ware L, Greene K. Plasma surfactant protein levels and clinical outcomes in patients with acute lung injury. *Thorax.* 2003;58:983–988.
102. Elsasser S, Schächinger H, Strobel W. Adjunctive drug treatment in severe hypoxic respiratory failure. *Drugs.* 1999;58(3):429–446.
103. Häfner D, Germann PG, Hauschke D. Comparison of rSP-C surfactant with natural and synthetic surfactants after late treatment in a rat model of the acute respiratory distress syndrome. *British J Pharm.* 1998;124:1083–1090.
104. Mikawa K, Nishina K, Takao Y, Obara H. Intratracheal application of recombinant surfactant protein-C surfactant to rabbits attenuates acute lung injury induced by intratracheal acidified infant formula. *Anesth Analg.* 2004;98:1273–1279.
105. Spragg RG, Lewis JF, Wurst W, Häfner D, Baughman RP, Wewers MD, Marsh JJ. Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. *Am J Respir Crit Care Med.* 2003;167:1562–1566.
106. Spragg RG, Lewis JF, Walmrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Eng J Med.* 2004;351:884–892.
107. Spragg RG, Taut FJH, Lewis JF, et al. Recombinant surfactant protein C based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med.* 2011;183(8):1055–1061.