Mechanical Ventilation: A Tutorial for Pharmacists

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Mechanical ventilation is an integral part of the critical care environment and requires orchestration by a multidisciplinary team of clinicians to optimize therapeutic outcomes. By tradition, pharmacists have not been included on this team since this therapeutic modality is not considered relevant to their scope of practice. However, pharmacists play a critical role in the management of patients receiving mechanical ventilation by assisting in the development of institutional guidelines and protocols, by maintaining accuracy of prescribed drug dosages, by monitoring for drug-drug and drug-disease interactions, by assisting with alternative drug selections, and by maintaining continued quality assessment of drug administration. Pharmacists able to understand and integrate mechanical ventilation with the pharmacotherapeutic needs of patients are better qualified practitioners. The goal of this article is to help clinical pharmacists better understand the complexities of mechanical ventilation and to apply this information in optimizing delivery of pharmaceutical agents to critical care patients.

Key Words: mechanical ventilation, pharmacist, critical care, tutorial.

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Mechanical ventilators are devices that provide an artificial means of ventilatory support for the respiratory system. Their introduction in the modern era has revolutionized the standard of respiratory intensive care medicine by integrating microprocessor-controlled flow rate and pressure
waveform dynamics to optimize gas exchange for the critical care patient.

Educating the multidisciplinary critical care team about mechanical ventilation is primarily the responsibility of the pulmonary critical care physician and supporting members such as respiratory therapists and critical care nurses. Unfortunately, pharmacists are not routinely involved with the orchestration of the mechanical ventilatory plan, primarily because it has never been considered relevant to their scope of practice.

The pharmacy literature contains limited discussion of mechanical ventilation. However, pharmacists are vital in discussing the ventilator plan based on their expert knowledge of pharmaceutical agents routinely administered in patients receiving mechanical ventilation. Pharmacists participating in the daily discussion of the plan can help the multidisciplinary team to optimize drug selection, provide accurate dosage and titration, and monitor agents that may impede weaning from mechanical ventilatory support.

Mechanical ventilation involving positive pressure ventilation is associated with decreased cardiac output. The result is compromised organ perfusion, including renal and hepatic blood flow, theoretically altering the pharmacokinetics of drugs administered. Pharmacists must be vigilant in monitoring pharmaceutical agents that may be altered during mechanical ventilation. The goal of this article is to help pharmacists better understand the complexities of mechanical ventilation and apply this information in optimizing delivery of pharmaceutical agents to critical care patients.

History of Mechanical Ventilation

The first references of artificial respiration were recorded in both biblical and Egyptian history, but their exact meaning may initiate a debate. Despite such early recognition of this phenomenon, the most credible reference in discussing artificial respiration is Galen (175 A.D.). This Greek physician experimented with the first form of artificial respiration by using a bellows to inflate the lungs of a deceased animal. Based on Galen's work, many scientists and scholars from the 14th–19th centuries experimented with artificial respiration (e.g., Versalius, Hooke, Tossach, Priestley, Brodie, and Dalziel), laying the groundwork of practical mechanical ventilation.

The age of practical mechanical ventilation did not begin until the introduction of the tank respirator (iron lung), originally developed by Dalziel in 1838 and improved by Drinker and Shaw in 1929. The device was a large, airtight metal cylinder that enclosed the patient, exposing the head and neck. Negative pressure was generated with an electric pump, causing the patient's chest to rise. This device was particularly effective as a noninvasive form of mechanical ventilation for patients with normal airways, such as those with polio. However, it was not very useful for patients with significant respiratory disorders. It was used extensively and successfully in the mid-1950s during the poliomyelitis epidemic.

Noninvasive units advanced technologically over the decades to include the Pulmowrap (J. H. Emerson Co., Cambridge, MA) and Hayek Oscillator (Breasy Medical Equipment Ltd., London, United Kingdom) models. Both models incorporate either an airtight jacket or a flexible chest cuirass system to maintain adequate negative pressure ventilation. Both are currently in service around the world to maintain ventilator support in patients with neuromuscular disorders, chest wall deformities, and central hypoventilation syndrome.

Based on decades of research and experimentation, the 1960s and early 1970s produced both the volume-cycled 3-PV ventilator and two pressure-cycled devices, including the Bennett and Bird ventilators. These machines provide positive pressure ventilation using rudimentary ventilator parameters adequate for basic ventilatory requirements.

An advanced level of ventilator technology was required to help clinicians optimize a patient's ventilatory needs. In the early 1970s, the Ohio 560 (Ohio Medical Products, Madison, WI) and Bennett MA-I (Puritan-Bennett Corp., Kansas City, MO) ventilators were introduced. Both of these ventilators were electronically controlled, constant-volume ventilators offering many advantages, such as variable ventilator mode selection, easy-to-read display panels, accurate fraction of inspired oxygen (FiO₂) adjustment setting, physiologic “sigh breath” to limit atelectasis, positive end-expiratory pressure (PEEP), inspiratory humidification, and numerous alarm systems. Both ventilators revolutionized the standard of respiratory intensive care during the era. The MA-I ventilator is still in use today around the world.

Mechanical ventilators have evolved into microprocessor-controlled devices that allow synchronization of a patient's ventilatory
demands with augmentation of volume and pressure waveforms. Currently, mechanical ventilators are used in hospital and home settings, long-term care facilities, mobile intensive care, and life-flight helicopter transport.

**Indications for Mechanical Ventilation**

Mechanical ventilation is administered primarily in patients unable to maintain adequate alveolar ventilation. Based on the complexity of the literature, there is no consensus regarding all the indications for mechanical ventilator support. Data have identified key clinical indications for mechanical ventilator support, including apnea and impending respiratory arrest, acute exacerbation of chronic obstructive pulmonary disease (COPD), acute severe asthma, neuromuscular disease, acute hypoxic respiratory failure, heart failure, cardiogenic shock, acute brain injury, and flail chest. Technically, two basic forms of respiratory failure occur: hypoxic and hypercapnic. Examples of hypoxic respiratory failure are acute exacerbation of COPD, severe pneumonia, and pulmonary edema. Hypercapnic respiratory failure includes neuromuscular disease, such as myasthenia gravis, and other diseases causing respiratory muscle fatigue, such as asthma and COPD.

The diagnostic test to assess degree of respiratory failure is arterial blood gas analysis. This test uses arterial pH, partial pressure of carbon dioxide in arterial blood (PaCO₂), partial pressure of oxygen in arterial blood (PaO₂), serum bicarbonate concentration, and saturation of oxygen in arterial blood (SaO₂). Ventilation is primarily monitored by PaCO₂ and oxygenation by PaO₂ and SaO₂. During hypoxic respiratory failure, the patient experiences progressive hypoxemia and cannot respond to increases in supplemental oxygen administration. Positive pressure ventilation is often required.

Hypercapnic respiratory failure involves a progressive increase in PaCO₂ and associated respiratory acidosis, requiring positive pressure ventilation. Table 1 summarizes the pulmonary parameters routinely considered clinical markers to assess the patient’s need for mechanical ventilation. These measurements are intended as a guide; clinical judgment is always warranted to assess the degree of respiratory failure indicating the need for endotracheal intubation and mechanical ventilation.

**Fundamentals of Mechanical Ventilation**

Mechanical ventilator terminology and inconsistent definitions make it difficult to understand the complexities of mechanical ventilation. Common terminology associated with mechanical ventilation, along with the respective abbreviations and definitions, are listed in Appendix 1. Ventilator terminology has been simplified by its classification into three major concepts: trigger, limit, and cycling (referred to collectively as TLC). Trigger is the signal that initiates opening of the inspiratory valve, allowing pressurized gas to enter the patient's lungs, limit regulates gas flow rate into the lungs, and cycling stops the inspiratory phase and leads to opening of the ventilator's expiratory valve.
Cycling is crucial in the ventilatory process because a pause is required between the end of the inspiratory phase and the triggering of expiration. Cycling may be triggered by preset volume (inspiration stops once the goal tidal volume is achieved), pressure (inspiration stops after a preset pressure limit is achieved), or time (inspiration stops after a preset time interval).

Volume-, pressure-, and time-cycled mechanical ventilator breaths all result in increased airway pressure. Airway pressure can be categorized as mean, peak, or plateau. Mean airway pressure is the area under a time versus pressure curve throughout the respiratory cycle. Peak inspiratory pressure is recorded at end inspiration and results from increased pressure, volume, airway resistance, or pulmonary disease. Peak inspiratory pressure should be limited to 40 cm H\textsubscript{2}O in a healthy lung to avoid epithelial-alveolar damage.\textsuperscript{13}

Plateau pressure, or the inspiratory plateau, is the pressure equilibration between the airways and alveoli. During an inspiratory cycle, the opening of the expiratory valve is delayed, resulting in a brief moment of neither gas flow nor pressure in or out of the lungs. Thus, the plateau is equivalent to the pressure in the alveoli. Clinically, a pressure below 30 cm H\textsubscript{2}O is advised to limit ventilator-induced lung injury.\textsuperscript{14} Increases in peak inspiratory pressure with normal plateau pressure may be associated with an obstruction to airflow, such as airway secretions and bronchospasm. Airway suctioning should immediately decrease the peak inspiratory pressure after removal of airway secretions. Patients experiencing acute bronchospasm receiving β-agonist therapy demonstrate a slower decrease in peak inspiratory pressure due to progressive bronchodilatory effects of the agent.

Both the peak inspiratory and plateau pressures are directly associated with pulmonary compliance; that is, the elastic properties of the lung. It is determined by dividing the change in volume by the change in pressure and is a reliable indicator for determining the volume that can enter the lungs. Compliance is categorized as static or dynamic. Static compliance is clinically evaluated and represents the recoil strength of the lung-thorax and ventilator tubing circuit. Pulmonary diseases such as COPD result in increased compliance due to greater elasticity of the lungs. Restrictive lung processes such as pulmonary fibrosis, acute lung injury, and acute respiratory distress syndrome are associated with decreased compliance due to poor lung elasticity. Normal compliance is approximately 0.1 L/cm H\textsubscript{2}O.\textsuperscript{15}

Modern mechanical ventilators are classified according to their ability to cycle from the inspiratory to the expiratory phase. Termination of the inspiratory phase can be signaled by volume-, pressure-, or time-cycled ventilation.

Classifications of Ventilation

Volume Cycled

Volume-cycled ventilation, the most common form of ventilation cycling used for adult patients, occurs as the inspiratory phase begins and gas flows through the ventilator circuit into the patient's lungs until a preset volume is delivered. Once this volume is reached, the inspiratory phase ends and the patient passively exhales. Advantages of volume-cycled ventilation are the selection of variable modes of ventilation, improved patient-ventilator synchrony, and the simplicity of tidal volume adjustment to better facilitate the ventilation process.

Pressure Cycled

Pressure-cycled ventilation occurs as the inspiratory phase begins and gas flows through the ventilator circuit into the patient's lungs until a pressure-sensing mechanism in the ventilator reaches a preset level. Once this level is reached, the inspiratory phase ends and the patient passively exhales. Delivery of adequate tidal volume during pressure-cycled ventilation is determined by the initial cycling pressure selected, the flow rate (L/min), and lung characteristics, including both pulmonary compliance and airway resistance.

In the clinical setting, reduced lung compliance and increased airway resistance shorten the inspiratory phase, thus lowering the tidal volume delivered. Due to these limitations, pressure-cycled ventilators have no role for continued use in pulmonary critical care patients due to the challenging requirements of these patients. Pressure-cycled ventilators are used as portable ventilators in health care facilities, mobile intensive care units, and life-flight helicopters.

Time Cycled

Time-cycled ventilation occurs as the inspiratory phase begins and gas flows through the ventilator circuit into the patient's lungs until a timing mechanism in the ventilator reaches a preset duration. Once the preset time is reached, the inspiratory phase ends and the patient passively
exhales. During time-cycled ventilation, tidal volume is not controlled directly. The ventilator delivers a tidal volume dependent on gas flow rate and lung compliance. A higher flow rate results in a shorter inspiratory time and vice versa. As lung compliance decreases, the peak inspiratory pressure and potential for alveolar hyperinflation increase. The gas flow rate has to be adjusted to maintain an adequate tidal volume and limit peak inspiratory pressure.

**Ventilator Parameters**

**Tidal Volume**

Tidal volume is defined as the volume of air inhaled or passively exhaled in a normal respiratory cycle. The approach to administering adequate tidal volume is maintaining adequate oxygenation and carbon dioxide levels. Selecting the optimum tidal volume for improving patient outcomes has been controversial. Tidal volumes have ranged from 4–12 ml/kg of ideal body weight. Tidal volume may be set at 10–12 ml/kg for patients with normal pulmonary physiology, 4–8 ml/kg for those with restrictive lung disease to decrease peak alveolar pressure, and 8–10 ml/kg for those with obstructive lung disease to limit trapping air. Based on the controversy regarding the ideal tidal volume setting for patients with obstructive or restrictive lung disease, most clinicians select an initial tidal volume of 5–10 ml/kg.

**Respiratory Rate**

On traditional mechanical ventilators, respiratory rate is adjusted from 0–60 breaths/minute. Respiratory rate determines the number of preset tidal volume breaths the patient will receive. Patients with either normal pulmonary physiology or obstructive lung disease usually tolerate an initial ventilator respiratory rate of 8–15 breaths/minute. Those with restrictive lung disease may require a higher initial respiratory rate of 15–20 breaths/minute to meet their ventilatory demand. Arterial blood gas analysis is obtained approximately 20–30 minutes after the initial change. The goal is to adjust the ventilator rate to optimize PaCO$_2$ and pH based on each patient’s normal physiology.

**Flow Rate**

Inspiratory flow rate is the volume of gas/minute delivered through the ventilator circuit into the patient’s lungs. Inspiratory flow is expressed in liters/minute and determines the inspiration:expiration (I:E) ratio. To determine the I:E ratio, two major parameters must be identified: respiratory rate and inspiratory time. Typically, a flow rate of 40–60 L/minute is administered in adults and titrated upward based on patient requirements and ventilatory goals. An I:E ratio of 1:2 is normal, but patients with more severe pulmonary critical illness may require an I:E or inverse ratio ventilation ranging from 2:1–4:1. The longer inspiratory time allows more efficient gas flow distribution to the alveoli, improving alveoli recruitment and alveolar ventilation. Inverse ratio ventilation can be delivered in both volume-control and pressure-control inverse ratio ventilation.

**Fraction of Inspired Oxygen**

Fraction of inspired oxygen, the percentage of oxygen that can be delivered to the patient during a mechanical-ventilator breath or a patient breath, can be adjusted from 21–100%. The goal is to provide the lowest FiO$_2$ requirements while maintaining adequate PaO$_2$ and SaO$_2$. In clinical practice, the FiO$_2$ is usually started at 100% if the patient’s oxygenation status is unknown. Arterial blood gas analysis is obtained approximately 20–30 minutes after the FiO$_2$ change. Subsequent changes in FiO$_2$ can be assessed by arterial blood gas analysis if PaCO$_2$ and arterial pH are required parameters.

The most common concern regarding administration of a high FiO$_2$ is oxygen toxicity. Oxygen toxicity is caused primarily by the formation of reactive oxygen metabolites and inflammatory mediators. Data have shown that exposure to 40% or higher FiO$_2$ for up to 30 days is associated with fibrotic pulmonary changes. Based on the consensus in the literature supporting oxygen toxicity, clinicians are vigilant in limiting the amount and duration of higher FiO$_2$ requirements for patients receiving mechanical ventilation. Concern about inducing oxygen toxicity should not interfere with treating patients with arterial hypoxemia.

**Positive End-Expiratory Pressure**

Positive end-expiratory pressure (PEEP) pertains to holding pressure in the lungs during the exhalation phase of a mechanically started breath. It primarily increases the functional residual capacity of the lungs by increasing the surface area of the alveoli. The larger surface area allows oxygen to diffuse through the alveolar
capillary membrane into the circulation. The result is increased PaO₂, SaO₂, and alveolar ventilation. Positive end-expiratory pressure can be added while the patient receives FiO₂ concentrations of 21–100%. However, PEEP is traditionally started when the FiO₂ concentration approaches 50%. This strategy can help prevent oxygen toxicity because it allows lower oxygenation requirements.

Positive end-expiratory pressure can enhance oxygenation delivery but has negative side effects. These effects include increased intrathoracic pressure, which leads to potential pulmonary volutrauma, and decreased venous return, which causes hemodynamic instability. Traditionally, PEEP is started at 5 cm H₂O and is steadily increased to achieve acceptable arterial oxygenation goals.

Traditional Modes of Invasive Mechanical Ventilation

Traditional modes of invasive mechanical ventilation use volume, pressure, and time to cycle from the inspiratory to the expiratory phase and can be administered as full or partial ventilator support. Full support provides the patient with adequate ventilatory requirements to meet metabolic demands without supplementation by the patient. Partial support provides partial ventilator assistance but requires patients to actively participate in their own spontaneous ventilation. Figure 1 provides a basic understanding of airway pressure waveforms seen in traditional modes of invasive mechanical ventilation.

Control Mode Ventilation

Control mode ventilation (CMV) is a time-cycling process. The timing mechanism generates the inspiratory tidal volume breath independent of the patient’s respiratory effort. During CMV the ventilator does not allow the patient to self-generate a tidal volume breath. Patients waking from sedation or pharmacologic paralysis may experience agitation and “air hunger” since they cannot interface with the ventilator. Control mode ventilation is used primarily with patients unable or not required to generate a voluntary respiratory effort.

Assist Control Ventilation

During assist control ventilation (A/C) the patient receives a predetermined mechanical respiratory rate and tidal volume, as with CMV, but is able to self-generate additional tidal volume breaths. The self-generated breath occurs due to negative pressure created by the patient within the ventilator circuit. The clinician

![Figure 1. Pressure waveforms of traditional modes of invasive positive pressure ventilation. CMV = control mode ventilation; A/C = assist control ventilation; IMV = intermittent mandatory ventilation; I = inspiration; E = expiration; SIMV = synchronized IMV.](image-url)
sets the negative pressure or triggering threshold to start the inspiratory breath. By tradition, a pressure of -2 cm H₂O is selected. Once the patient generates -2 cm H₂O within the ventilator circuit, the machine then triggers the self-generated tidal volume breath. Patients who have apnea or are unable to self-generate a tidal volume breath are guaranteed the predetermined mechanical respiratory rate and tidal volume.

Control mode and A/C ventilation are technically variations of each other, differentiated only by the preset triggering threshold for A/C ventilation. Clinicians traditionally choose A/C ventilation as the initial ventilator mode due to simplicity of use, comfort level, and patient ability to start a ventilator breath.

Assist control is highly successful as a primary ventilator mode but has limitations. The ventilator delivers a preset tidal volume breath and respiratory rate, resulting in an expired minute ventilation (e.g., tidal volume 500 ml x 14 breaths/min = 7 L/min). Patients can also self-generate additional tidal volume breaths (e.g., tidal volume 500 ml x 10 breaths/min = 5 L/min). The result is hyperventilation and possible respiratory alkalosis due to excessive minute ventilation (e.g., 500 ml x 24 breaths/min = 12 L/min). For patients experiencing excessive minute ventilation, the A/C mode may be changed to intermittent mandatory ventilation (IMV) or synchronized intermittent mandatory ventilation (SIMV).

Intermittent Mandatory Ventilation

Intermittent mandatory ventilation is similar to A/C ventilation but differs in that the former allows the patient to breathe spontaneously between predetermined ventilator breaths. The ventilator delivers a predetermined tidal volume at specific time intervals (e.g., tidal volume 500 ml x 12 breaths/min = 6 L/min). In addition, during spontaneous breathing, patients can determine their own tidal volume and respiratory rate (e.g., tidal volume 400–700 ml x 6 breaths/min = 2.4–4.2 L/min), resulting in a total minute ventilation of 8.4–10.2 L/minute. Intermittent mandatory ventilation allows patients to slowly increase the work of breathing and provides more independence from full ventilator support. This mode can be used for full ventilator support with a high respiratory rate or for partial ventilator support, in which the patient requires minimal mechanical ventilator breaths.

Synchronized Intermittent Mandatory Ventilation

Synchronized intermittent mandatory ventilation is almost identical to IMV; the difference is that the patient’s own spontaneous breathing pattern is synchronous with the SIMV rate. During SIMV the patient receives the predetermined number of mechanical ventilation breaths plus any additional self-generated breaths. Machine breaths plus self-generated additional breaths equal the total respiratory rate (e.g., a SIMV preset rate of 8 breaths/min and 4 self-generated spontaneous breaths would be documented as 8/12). This prevents the “stacking” of breaths that may occur between the machine tidal volume breath and the patient’s spontaneous inspiratory tidal volume.

Synchronized intermittent mandatory ventilation, like A/C ventilation, is used primarily as an initial ventilator mode. Many clinicians prefer SIMV, since the ventilator not only delivers mandated ventilatory breaths but also allows the patient to contribute voluntary respiratory effort.

Controversy exists regarding the advantage of SIMV over IMV. The former has replaced the latter in modern mechanical ventilators even though its only difference is a technical deviation.

Pressure Control Ventilation

Pressure control ventilation is a pressure-limiting, time-cycled mode in which a constant pressure is maintained throughout the preset inspiratory time. As gas flows through the ventilator circuit and into the patient’s lungs, the airway pressure rises, resulting in increased alveolar volume. The outcome is that delivered airway pressure equals intrapulmonary pressure, ending the inspiratory phase. Clinicians often change the ventilation mode from volume controlled (CMV, A/C, or SIMV) to pressure control ventilation if adequate ventilation or oxygenation goals are not achieved, or if excessive peak airway pressures are required to optimize gas exchange. Patients with acute lung injury or acute respiratory distress syndrome often require pressure control ventilation, primarily due to difficulties in optimizing ventilation and oxygenation goals with conventional volume-controlled ventilation.

Pressure Support Ventilation

Pressure support ventilation provides preset pressure assistance during each spontaneous patient breath. This mode is used primarily to overcome airway resistance of the endotracheal
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tube and dead space of the ventilator circuit to
decrease the patient’s work of breathing. Pressure
support ventilation is used as a tool for ventilator
weaning since it requires full spontaneous
respiratory effort by the patient. Data have
indicated that pressure support ventilation levels
required to achieve this goal range from 3–14 cm
H$_2$O.\textsuperscript{22, 23} Although a minimal level of pressure
support ventilation assistance has not been
clearly defined, patients can be slowly weaned
over time to a final level of 6–8 cm H$_2$O. Patients
achieving this level and breathing comfortably
should be able to tolerate extubation and removal
of mechanical ventilation.\textsuperscript{24}

Pressure support ventilation is widely used in
the critical care setting in combination with other
modes, such as SIMV. This combination provides
mandated mechanical ventilator breaths from
SIMV augmented with pressure support ventilation
during spontaneous breathing by the patient.

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP)
allows for constant pressure maintained above
atmospheric pressure throughout the respiratory
cycle. To provide this mode, the ventilator
respiratory rate is adjusted to zero so that no
controlled breaths are delivered during the cycle.
A CPAP of 5 cm H$_2$O is traditionally started to
maintain pressure above atmospheric pressure.
Continuous positive airway pressure can be
provided alone or in combination with pressure
support ventilation. During spontaneous
ventilation the patient receives a constant CPAP
above atmospheric pressure augmented with a
preset pressure support ventilation during each
spontaneous breath (e.g., CPAP 5 cm H$_2$O +
pressetsure support ventilation 10 cm H$_2$O).
Continuous positive airway pressure by itself or
in combination with pressure support ventilation
is the primary mode used to promote spontaneous
ventilation to assist with discontinuation of
mechanical ventilation.

Advanced Modes of Invasive Mechanical
Ventilation

Advances in microprocessor technology have
resulted in a greater number of sophisticated and
complex modes of mechanical ventilation.
Examples of advanced modes of ventilation
available for adults include the following:
pressure regulated volume control, bilevel
ventilation (biphasic intermittent positive airway
pressure) and airway pressure release ventilation,
slowly increased to optimize the exhaled tidal volume. A back-up mandatory ventilator rate is typically set at 4–12 breaths/minute in case the patient experiences apnea. Expiratory positive airway pressure is started at 4–6 cm H\textsubscript{2}O, which can be increased in increments of 2–3 cm H\textsubscript{2}O for patients experiencing hypoxia. Oxygen may be titrated into the circuit at 0.5–6 L/minute to alleviate hypoxemia. Total duration of ventilation depends on the underlying disease. Further studies are needed regarding noninvasive positive-pressure ventilation to determine its full potential in the clinical setting.

Continuous Positive Airway Pressure

Continuous positive airway pressure is traditionally used as a weaning tool for mechanical ventilation; however, it is also used as a form of noninvasive mechanical ventilator support. Continuous positive airway pressure is used for patients with obstructive sleep apnea and heart failure with respiratory muscle weakness.\textsuperscript{26} It is usually started at 2.5–15 cm H\textsubscript{2}O, based on ventilatory goals. Oxygen may be titrated into the circuit at 0.5–6 L/minute to alleviate hypoxemia.

Both CPAP and BiPAP devices have limitations, including poor patient compliance due to discomfort of the device. Data from a population-based study indicated that compliance rates greater than 85% could be achieved over a 6-month period.\textsuperscript{27} The study involved a CPAP program consisting of patient follow-up, device troubleshooting, and feedback from both patients and physicians.

Humidification

Natural humidification of the inspired air occurs as the air enters the nostrils and passes over a warm, ciliated mucous layer before passing to the nasopharynx. During mechanical ventilation the patient's natural humidification process is bypassed due to placement of an endotracheal or tracheostomy tube. Based on the placement of this artificial airway, oxygen and compressed-air source gases for mechanical ventilation require humidification before delivery to the patient. Humidified gas can involve a system with a heated or nonheated unit. Heating the unit increases the capacity of the gas to carry water vapor, thus increasing humidifier output.

As gas flows from the ventilator through the humidifier to the patient, it cools rapidly; condensation develops in the ventilator circuit, which requires periodic emptying. The condensate may become contaminated with bacteria that may inadvertently be lavaged into the patient's trachea, possibly precipitating ventilator-associated pneumonia. Advantages of a heated-unit system are that it maintains adequate humidification required for mucociliary transport and can be used as an adjunctive measure in rewarming patients experiencing hypothermia. A disadvantage is the risk of bacterial colonization, which requires periodic sterilization.

A popular type of humidifier is the condensing humidifier or heat-moisture exchange system, which consists of a passive humidification system placed at the end of the ventilator circuit connected to the endotracheal or tracheostomy tube. As the patient exhales and heats the hygroscopic filter, water is condensed. During the next inhalation phase the gas is warmed and humidified as it passes through the heat-moisture exchange system. Advantages of this system are that no moving parts are required, no electricity is needed for operation, and the device is replaced every 24–48 hours, making it economical.\textsuperscript{28} Disadvantages are occlusion with blood, secretions, or condensate, thus increasing airway resistance and resulting in increased peak airway pressure, auto-PEEP, and work of breathing.\textsuperscript{29}

Alarms

Mechanical ventilators are equipped with several alarm systems to ensure patient safety. Alarms are available for low or high pressure, low or high minute volume, low or high respiratory rate, low or high PEEP or CPAP, low or high FiO\textsubscript{2}, I:E ratio limitations, apnea, electrical power, and compressed gas failure. All alarm systems are routinely checked by the respiratory therapist and are documented as part of a comprehensive, specific department protocol. Many units have a back-up battery in case of an electrical power failure. To avoid endangering patients, alarm systems should never be turned off; unfortunately, fatalities have occurred due to violation of department protocols.

Complications of Mechanical Ventilation

Complications of mechanical ventilation can occur due to many factors, including the artificial airway, organ-related effects, mechanical ventilator malfunction, and operator error. Pharmacists must be familiar with complications of mechanical ventilation, such as health care-associated
pneumonia, sinusitis, gastrointestinal complications, and cardiovascular effects, that may require a pharmacotherapeutic solution.

Health Care–Associated Pneumonia

Health care–associated pneumonia encompasses both hospital-acquired pneumonia and ventilator-associated pneumonia. These pneumonias are defined as follows:

- Health care–associated pneumonia: pneumonia occurring in a patient who is hospitalized in an acute-care facility for 2 or more days within 90 days of the infection; who resides in a nursing home or long-term care facility; or who received antibiotic treatment, chemotherapy, or wound care within 30 days of the current infection.
- Hospital-acquired pneumonia: pneumonia occurring at least 48 hours after admission.
- Ventilator-associated pneumonia: pneumonia occurring at least 48 hours after intubation.

Hospital-acquired and ventilator-associated pneumonia result in costs for the health care system of $10,000–40,000/patient. Common bacteria associated with these three types of pneumonia include *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter* species. Many risk factors are associated with these pneumonias, including use of endotracheal and tracheostomy tubes, improper body positioning to prevent aspiration, oropharyngeal colonization of bacteria, lack of stress bleeding prophylaxis, use of transfusions, uncontrolled glucose level, improper aseptic technique during airway suctioning, and use of drug nebulizers.

For prevention of health care–associated pneumonia, guidelines recommend educating and involving staff in infection prevention, infection and microbiologic surveillance, prevention and transmission of microorganisms, and modifying host risk factors for infection. Health care providers should adhere to hospital infection control policies to limit health care–associated pneumonia in critical care areas.

Sinusitis

Nosocomial sinusitis is common in patients receiving mechanical ventilation and may be considered based on unexplained fever associated with nasal discharge. Diagnosis is based on radiologic or computed tomographic findings and on microbiologic culture of sinus aspirate. Oral and nasal endotracheal tubes provide a conduit for translocation of infectious matter to the sphenoid, ethmoid, and frontal sinuses. Infectious sinusitis occurs in approximately 20–30% of patients with intubation placed for at least 7 days. Main causative agents include *P. aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae; *S. aureus* and yeast species are less common. Treatment of nosocomial sinusitis is based on removing nasal tubes, applying topical decongestants, and draining the sinuses. Antibiotic therapy for patients with nonventilated sinusitis is controversial but often required for those needing nasotracheal ventilation.

Gastrointestinal Complications

Gastrointestinal complications in critically ill patients receiving mechanical ventilation include gastrointestinal hemorrhage, distention, and ileus. Gastrointestinal hemorrhage accounts for considerable increases in hospital mortality and costs of $4000–11,000 and more. Stress-related hemorrhage is a major determinant of bleeding in the intensive care unit, but improvements in care, such as developing and implementing guidelines and protocols, have reduced stress-related hemorrhage since the 1980s. Two major risk factors—mechanical ventilation and coagulopathy—are associated with the development of stress-related injuries.

For prevention of stress ulcer formation, guidelines recommend histamine2-receptor antagonists, proton pump inhibitors, antacids, and sucralfate. The choice of agent depends on individual hospital rates of stress ulcer formation and gastrointestinal complications, pharmacokinetic advantages, accessible delivery route to the patient, and cost. All agents have demonstrated variable success rates in preventing stress ulcer formation and recurrent gastrointestinal hemorrhage. Therapeutic guidelines regarding stress ulcer prophylaxis provide a more thorough overview than is provided here.

Cardiovascular Effects

Positive pressure ventilation, including alternative modes of ventilation, increased tidal volume, mean airway pressure, and PEEP, decreases cardiac output. A decrease in cardiac output may require an increase in intravascular volume expansion or administration of vasopressor...
or inotropic agents to maintain hemodynamic goals. Patients receiving mechanical ventilation may also experience cardiac arrhythmias that may be attributed to hypoxemia, acid-base or electrolyte abnormalities, or pharmacologic agents. Pharmacists must monitor the potential adverse effects associated with all therapeutic categories of pharmacologic agents during mechanical ventilation to limit these effects and modify therapeutic regimens to achieve hemodynamic goals.

Pharmacokinetic Differences in Patients Receiving Mechanical Ventilation

Pharmacokinetic evaluation of pharmaceutical agents is studied primarily with healthy volunteers or clinically stable patients. Critically ill patients receiving mechanical ventilation pose a greater dilemma in understanding the degree of pharmacokinetic changes in agents traditionally administered to critical care patients. Positive pressure mechanical ventilation is associated with producing physiologic changes in organ perfusion, including decreases in cardiac output, renal and hepatic blood flow, glomerular filtration rate, and urine output. Theoretically, these changes alter pharmacokinetic parameters such as drug clearance and rate of elimination of agents dependent on renal and hepatic perfusion. The potential result is a subtherapeutic or toxic drug concentration.

Data have shown that mechanical ventilation directly affects the pharmacokinetic profile of many pharmaceutical agents, including gentamicin, midazolam, lidocaine, ofloxacin, levofloxacin, dexmedetomidine, cisatracurium, atracurium, propofol, and midazolam. Administration technique may include direct endotracheal instillation, nebulizer, or metered-dose inhaler (MDI). The endotracheal route may be used for mucolytic agents during pulmonary bronchoscopy procedures to decrease mucous viscosity. Endotracheal administration is also used for cardiovascular agents during advanced cardiac life support when intravenous access is delayed or inaccessible. Agents administered by endotracheal route are atropine, epinephrine, lidocaine, and vasopressin. Atropine, epinephrine, and lidocaine can be administered at 2–2.5 times the intravenous dose diluted in 10 ml of normal saline or distilled water. Vasopressin, given at the same dose as the intravenous dose (40 U), can be administered as a single dose.

After endotracheal instillation, the patient receives manual ventilation to maximize aerosol dispersion of the drug into the pulmonary circulation. Tracheal instillation of mucolytic and cardiovascular agents is a novel delivery system to optimize therapeutic outcomes. However, β-agonists, anticholinergics, and corticosteroids are traditionally administered in aerosol form (e.g., nebulizer or MDI) during mechanical ventilation.

A number of factors have been identified that affect aerosol deposition to the lower respiratory tract during mechanical ventilation. These factors include the ventilator mode and settings, heat and humidification of inspired gas, density of the inhaled gas, endotracheal tube size, and method of connection of the MDI to the ventilator circuit. Based on these variables, the amount of drug deposited in both in vitro and in vivo models differs significantly. In vivo data have determined that the deposition of radiolabeled aerosols varies from 2.2–15.3% with a nebulizer, versus 3.2–10.8% with an MDI. In vitro bench models have demonstrated 0–42% with a nebulizer and 0.3–97.5% with an MDI. It was concluded that the factors listed above contributed to the wide variability in the observed results.

Aerosol Therapy

Patients who start receiving mechanical ventilation often require pharmacologic agents administered through the endotracheal or tracheostomy tube. Administration technique may include direct endotracheal instillation, nebulizer, or metered-dose inhaler (MDI). The endotracheal route may be used for mucolytic agents during pulmonary bronchoscopy procedures to decrease mucous viscosity. Endotracheal administration is also used for cardiovascular agents during advanced cardiac life support when intravenous access is delayed or inaccessible. Agents administered by endotracheal route are atropine, epinephrine, lidocaine, and vasopressin. Atropine, epinephrine, and lidocaine can be administered at 2–2.5 times the intravenous dose diluted in 10 ml of normal saline or distilled water. Vasopressin, given at the same dose as the intravenous dose (40 U), can be administered as a single dose.

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The optimal dose administered with an MDI for patients receiving mechanical ventilation is unknown. Clinicians have advocated higher doses to compensate for factors affecting the deposition of aerosol to the lower respiratory tract. Although in theory this approach seems practical, data have shown otherwise. A group of authors examined the respiratory mechanics of 4, 8, and 16 puffs of albuterol administered at 15-
minute intervals to patients with COPD receiving mechanical ventilation. The decrease in airway resistance with 4 puffs was comparable to that with cumulative doses of 12 puffs (p=0.12) and 28 puffs (p=0.25). Heart rate increased significantly (p<0.01) after the cumulative dose of 28 puffs. The authors concluded that 4 puffs of albuterol provided the best bronchodilatory response and safety profile compared with higher doses.

An MDI has several advantages over a nebulizer, such as lower cost, dose reliability, ease of administration, and lower risk of contamination. An MDI is actuated to synchronize with the onset of inspiratory flow of the volume- or pressure-controlled cycle breath to maximize aerosol dispersion and deposition into the pulmonary system. A strategy has been recommended regarding MDI use and basic techniques for aerosol delivery in patients receiving invasive mechanical ventilation.

A nebulizer is powered by either a continuous oxygen source or pulse gas source depending on the mechanical ventilator used. With older ventilators a nebulizer must be connected to an oxygen or compressed-air gas source independent of the ventilator to deliver the drug. The oxygen or compressed-air flow meter is traditionally started at 6–8 L/minute to provide adequate aerosol output. Newer ventilators offer an independent control for nebulizer use. The advantages of the ventilator-powered nebulizer are that it wastes less drug and does not distort mechanical ventilator readings, such as the sensitivity or triggering of the assisted or spontaneous breath, or the delivered tidal volume, respiratory rate, or minute volume. A disadvantage is that a nebulizer is associated with bacterial contamination and requires cleaning after each treatment.

Weaning from Invasive Mechanical Ventilation

Improved pulmonary status in a patient receiving invasive mechanical ventilation requires consideration of ventilator weaning. By tradition, ventilator weaning is discussed in relation to the ventilator; modes and parameters are modified to achieve successful discontinuation of ventilator support. Also, ventilator weaning must incorporate a pharmacologic weaning component that includes discussion of narcotic analgesics, sedatives, and neuromuscular blocking agents (NMBAs). These drug classes depress or cease respiratory drive and spontaneous ventilation, resulting in direct effects on ventilator weaning outcomes. When determining if a patient is ready to be weaned, a clinician must comprehensively assess the patient’s status of pulmonary infection; neurologic and nutritional condition; respiratory muscle strength; narcotic analgesic, sedative, and NMBA administration; presence of anemia and cardiac arrhythmia; and acid-base level.

One of four major techniques for weaning a patient from invasive mechanical ventilation: IMV or SIMV, pressure support ventilation, intermittent spontaneous breathing trials several times/day, and a trial of spontaneous breathing once/day, can be used. Each method has advantages and disadvantages, but data have demonstrated that a once-daily trial or spontaneous breathing trials several times/day lead to extubation 3 times sooner than intermittent mandatory ventilation and 2 times sooner than pressure support ventilation.

Spontaneous breathing trials are usually conducted using a T-piece with CPAP or low levels of pressure support ventilation (5–7 cm H2O). Successful completion of a spontaneous breathing trial is highly predictive of successful weaning. Evidence-based guidelines have identified four primary criteria that a patient must meet to be considered a candidate for ventilator weaning: evidence of reversal or stability of the cause of acute respiratory failure; adequate oxygenation as determined by a PaO2/FiO2 ratio greater than 150–200, requiring PEEP less than or equal to 5–8 cm H2O, FiO2 less than or equal to 40–50%, and pH greater than or equal to 7.25; hemodynamic stability (blood pressure adequate without vasopressor support or evidence of myocardial ischemia); and the ability to generate an adequate inspiratory effort. Extubation from mechanical ventilation is attempted if the patient meets all four primary criteria, has reached optimum physiologic conditioning, and successfully completes a spontaneous breathing trial. After extubation, the patient is maintained with supplemental humidified oxygen and is observed for signs of distress such as changes in respiratory rate, blood pressure, oxygen saturation, agitation, diaphoresis, or anxiety.

Pharmacologic intervention is often the first therapeutic option for patients who demonstrate acute agitation, including “fighting” or “bucking” the ventilator, or who have difficulty synchronizing their breathing pattern with the machine. Pharmacologic agents administered are narcotic...
The -agonist administration may be needed if acute mechanical complications may require treatment for patients requiring noninvasive positive pressure ventilation. If dyssynchrony with the ventilator continues despite multiple as-needed doses of both narcotic analgesics and sedatives, the pharmacist, in conjunction with the patient’s nurse, must routinely assess patient response to the as-needed dose of each agent for improving analgesia control, anxiolysis, and acceptance of mechanical ventilation. Overuse of analgesics and/or sedatives can produce detrimental effects, inhibiting spontaneous ventilation. The result may be the failure of weaning from mechanical ventilation, requiring the restart of full ventilatory support or intubation for patients requiring noninvasive positive pressure ventilation. If dyssynchrony with the ventilator continues despite multiple as-needed doses of both narcotic analgesics and sedatives more often than every 2 hours, continuous infusion of either or both of these agents may be required. Continuous infusion with frequent assessment of degree of agitation or sedation may assist with titration of the sedative or analgesic dosage to a predetermined end point. The goal of starting a continuous infusion would be to improve ventilator acceptance and optimize oxygenation and ventilation. Patients must be assessed for delirium if they continue to demonstrate dyssynchrony with the ventilator despite having no physical or mechanical complications and receiving continuous infusions of narcotic analgesics and sedatives. Patients with delirium who are inadvertently treated with sedatives may become more agitated and confused. Many diagnostic scales and instruments are available to diagnose delirium. The primary
During haloperidol administration, the appropriate level of sedation is seen when a calm patient awakens easily in response to touch or verbal stimuli. However, some patients may require a deeper level of sedation to facilitate and maintain mechanical ventilator support. Neuromuscular blocking agents are often started with a bolus dose to facilitate endotracheal intubation or with continuous infusion to maintain mechanical ventilatory support. The primary indication for continued administration of these agents in patients receiving mechanical ventilation is to decrease oxygen consumption. The choice of agent may depend on formulary selection, degree of organ dysfunction, or duration of induced paralysis required. The use of these agents to maintain mechanical ventilator support has declined due to strong supportive evidence that severe skeletal muscle anomalies are associated with these agents. Examples of such anomalies are critical illness polynuropathy, acute myopathy of critical illness, and acute quadriplegic myopathy syndrome.

During NMBA administration proper monitoring is paramount, including use of a peripheral nerve stimulator. The peripheral nerve stimulator determines the optimum train-of-four to assess the degree of neuromuscular block. The optimum train-of-four is 1–2 twitches of a 4-point scale. However, the number of twitches required is based on the degree of critical illness and level of sedation required. The pharmacist should be familiar with the operation of the peripheral nerve stimulator and be vigilant in monitoring and maintaining optimum train-of-four goals. Changing the train-of-four may require dosage adjustment or possibly switching to another NMBA due to change in physiologic function.

Weaning from NMBA is based on improvements in the patient's pulmonary status, such as improved chest radiographs, arterial blood gases, and changing modes of mechanical ventilation to less ventilatory requirements. Weaning from NMBA can be accomplished by decreasing the infusion dose to achieve a train-of-four goal or discontinuing the infusion. Discontinuing the NMBA daily or providing a drug holiday is recommended and may decrease the frequency of neuromuscular complications.

A major mechanical complication associated with administration of NMBA in patients receiving mechanical ventilation is the risk of ventilator disconnect, or airway mishaps such as accidental patient extubation. Ventilator alarms must be documented, verified, and checked for audio performance and level. Patients with severe pulmonary illness who are receiving NMBA treatment and become disconnected from the ventilator can rapidly decompensate and require manual ventilation until reintubation is possible.
Pharmacists may recommend administering an acetylcholinesterase inhibitor and anticholinergic agent (edrophonium besylate and atropine sulfate) at bedside during NMBA infusion for patients who inadvertently become disconnected from the ventilator. This approach may help reverse the NMBA, alleviate increased cholinergic response, and facilitate manual ventilation pending endotracheal reintubation.

Pharmacists who understand the daily mechanical ventilation weaning schedule can assist the medical team in weaning patients from certain narcotic analgesics, sedatives, or NMBA.s. Optimum drug selection and dosage titration may limit neurologic and respiratory depression and lead to successful discontinuation of mechanical ventilation.

Conclusion

Mechanical ventilation will continue to evolve as advanced microprocessor-controlled machines are integrated with degree of pulmonary illness. Pharmacists must not be excluded from the multidisciplinary team orchestrating the care of patients receiving mechanical ventilation. Pharmacists who understand the basic concepts of mechanical ventilation can assist the team in the development, implementation, monitoring, and adherence to guidelines or protocols regarding patients receiving mechanical ventilation. Pharmacists can also assist in the selection and proper administration of pharmaceutical agents to achieve optimum therapeutic outcomes. As future pharmaceutical agents are developed and used in these patients, the expertise of the pharmacist will be required to optimize the quality of patient care.

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References


Appendix 1. Glossary of Mechanical Ventilation Terminology

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<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Tidal volume: volume of gas inhaled or exhaled during a normal respiratory cycle.</td>
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<td>Minute ventilation: volume of gas exhaled in one minute and is the product of tidal volume and respiratory rate.</td>
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<td>Fraction of inspired oxygen: percentage of oxygen that can be administered, ranging from 21–100%.</td>
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<td>Control mode ventilation: a time-cycling, volume-control mode generating an inspiratory tidal volume breath independent of the patient's respiratory effort.</td>
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<td>A/C: Assist control ventilation: a time-cycle mode of ventilator support administering a predetermined tidal volume and respiratory rate such as CMV, but the patient may also trigger additional tidal volume breaths above the preset ventilator settings.</td>
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<tr>
<td>Intermittent mandatory ventilation: a mode of mechanical ventilator support in which a patient receives a preset tidal volume and respiratory rate, but it allows the patient to breathe spontaneously between predetermined ventilatory breaths.</td>
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<tr>
<td>Synchronized intermittent mandatory ventilation: a mode of ventilator support similar to IMV but prevents “stacking” of inspiratory tidal volume breaths.</td>
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<td>Positive end-expiratory pressure: maintains pressure held above atmospheric pressure during the exhalation phase of a mechanical initiated breath.</td>
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<td>Continuous positive airway pressure: maintains constant pressure held above atmospheric pressure throughout the respiratory cycle.</td>
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<td>Pressure support ventilation: provides preset inspiratory pressure assistance during each spontaneous patient breath.</td>
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<tr>
<td>Pressure control ventilation: a pressure-limiting, time-cycled mode where a constant pressure is maintained throughout the preset inspiratory time.</td>
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<tr>
<td>Bilevel positive airway pressure: a form of noninvasive positive pressure ventilation that provides continuous high-flow positive airway pressures that cycle between a preset high (inspiratory positive airway pressure [IPAP]) and low (expiratory positive airway pressure [EPAP]) levels.</td>
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<tr>
<td>Inspiratory positive airway pressure: amount of inspiratory pressure preset and administered during noninvasive mechanical ventilation; IPAP is equivalent to PSV.</td>
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<td>Expiratory positive airway pressure: amount of expiratory pressure preset and administered during noninvasive mechanical ventilation; EPAP is equivalent to CPAP.</td>
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