Mechanical Ventilation and Pulmonary Procedures

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LEARNING OBJECTIVES

1. Justify the role of the clinical pharmacist in the care of mechanically ventilated patients.
2. Evaluate the key differences among the different modes of mechanical ventilation.
3. Develop a pharmacist-oriented evaluation and associated interventions for a mechanically ventilated patient.
4. Evaluate the independent effect of inspiratory positive airway pressure on the different organ systems in critically ill patients and potential for associated pharmacotherapy.
5. Justify the role of adjunctive therapy specific to the mechanically ventilated patient.
6. Account for the therapeutic use of pulmonary procedures in critically ill patients.

ABBREVIATIONS IN THIS CHAPTER

APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
BiPAP	Biphasic positive airway pressure
CO_2	Carbon dioxide
FiO_2	Fraction of inspired oxygen
I:E ratio	Inhalation/exhalation ratio
IPPV	Invasive positive pressure ventilation
MV	Mechanical ventilation
NIPPV	Noninvasive positive pressure ventilation
NMBA	Neuromuscular blocking agent
O_2	Oxygen
PaO_2	Partial pressure of oxygen
PC	Pressure control
PEEP	Positive end-expiratory pressure
PRVC	Pressure-regulated volume control
PS	Pressure support
RR	Respiratory rate
RSBI	Rapid shallow breathing index
SBT	Spontaneous breathing trial
VAP	Ventilator-acquired pneumonia
VC	Volume control
VILI	Ventilator-induced lung injury
V_T	Tidal volume

Table of other common abbreviations.

INTRODUCTION

Clinical Challenges of MV

Mechanical ventilation is a common modality in the supportive care for critically ill patients. It cannot be viewed in isolation, but is deeply intertwined with a patient's overall clinical status and pharmacotherapy regimen (Cawley 2011). Incorporation of MV assessment is vital for pharmacists to provide optimal pharmacotherapeutic care (Cawley 2007, 2011, 2019, Newsome 2018).

Epidemiology

In the United States, more than 750,000 patients annually are supported with IPPV at a cost exceeding $27 billion, or 12% of hospital costs overall. Patients supported with IPPV are critically ill and have in-hospital mortality as high as 35% (Marshall 2008, Chant 2015). The pharmacotherapy regimens associated with MV are complex, with more than 30% of these patients in the ICU setting prescribed more than 20 medications. These studies showed that 70% of these patients had more than 13 medications prescribed at any given point (Uijtendaal 2014, Newsome 2020).

Indications

Indications for IPPV are in three broad categories: hypoxemic respiratory failure, hypercapnic respiratory failure, and apnea (Tobin 2013). In addition, airway protection in patients at high risk of aspiration or loss of airway and increased work of breathing may be indications for MV. Whereas breathing accounts for about 1%–3% of total O_2 consumption in healthy adults, studies of patients with acute hypoxemic respiratory failure and shock states demonstrate that work of breathing can account for 20% of total O_2 consumption, which

is an unsustainable physiologic state (Manthous 1995). Understanding the specific underlying pathology for why a patient was intubated is vital for guiding pharmacotherapeutic care to address the underlying condition. Often, patients are intubated for one indication but must remain intubated for an entirely different reason. This cause may be iatrogenic and either preventable or reversible with pharmacotherapeutic intervention (Newsome 2018). Box 1 lists common indications for MV.

Goals of MV

Three general principles of critical care may be applied to MV goals: (1) reverse the initial indication for MV; (2) provide supportive care during this reversal process; and (3) minimize any complications of the first two processes. Specific goals include achieving appropriate oxygenation and ventilation (i.e., CO_2 removal), minimizing VILI, avoidance of patient–ventilator asynchrony and patient discomfort, and resolving the condition with the shortest duration of IPPV feasible (Tobin 2013), as shown in Figure 1.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the care of critically ill patients
- General knowledge of the pathophysiology that leads to requirement of mechanical ventilation
- General knowledge of acid-base disorders and how to interpret an arterial blood gas
- Knowledge of common ICU drugs such as those for stress ulcer prophylaxis, continuous infusion analgesics, and sedatives
- Consequences of inappropriate pharmacotherapy regimens in critically ill patients and the role of pharmacists in the ICU

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Cawley MJ. Mechanical ventilation: introduction for the pharmacy practitioner. J Pharm Pract 2011; 24:7-16.
- Cawley MJ. Advanced modes of mechanical ventilation: introduction for the critical care pharmacist. J Pharm Pract 2019;32:186-98.
- Fan E, Zakhary B, Amaral A, et al. Liberation from mechanical ventilation in critically ill adults. an official ATS/ACCP Clinical Practice Guideline. Ann Am Thorac Soc 2017;14:441-3.

Role of the Clinical Pharmacist in the Setting of MV

Pharmacotherapy and MV management are interdependent in critically ill patients. A working knowledge of IPPV may enhance pharmacists' ability to provide high-quality interventions that improve patient outcomes, such as mortality, length of stay, and duration of MV (Marshall 2008, Chant 2015, Newsome 2018).

Introduction to Associated Medication Therapy

Essential knowledge of the fundamentals of IPPV allows the pharmacist to incorporate IPPV as a medication monitoring variable; for example, increasing FiO_2 requirements because of pulmonary edema in the face of diuretic therapy may warrant escalation of deresuscitative efforts. Further, the goals of specific medications may be oriented toward IPPV. A patient who is too sedated from continuous infusions of sedative or analgesic medications to pass an SBT, for example, will remain intubated secondary to mismanagement of pain, agitation, and delirium. Further, the ICU mnemonic recommends twice daily evaluation of the 11 F_2AST HUGS BID variables: (1) feeding; (2) fluids; (3) analgesia; (4) sedation; (5) thromboembolic prophylaxis; (6) head of bed elevation; (7) ulcer (stress) prophylaxis; (8) glycemic control; (9) spontaneous breathing trial; (10) bowel regimen; (11) indwelling catheter removal; and (12) de-escalation of antibiotics (Vincent 2005, 2009; Hawkins 2019). Notably, of the 11 variables, 9 are medication related and 10 show evidence of improved adherence and outcomes with pharmacist involvement (Lat 2020).

Protocol Development and Adherence for Patients on MV

Pharmacists are champions for quality improvement processes that often include but extend beyond core pharmacotherapeutic care. In these roles, pharmacists have shown notable

Box 1. Indications for Mechanical Ventilation

Hypoxemic Respiratory Failure

- Hypoventilation—obesity-related
- Ventilation-perfusion mismatch—obstructive lung disease, pneumonia
- Right-to-left shunt—anatomic shunts
- Diffusion impairment—pulmonary fibrosis
- Reduced atmospheric pressure

Hypercapnic Respiratory Failure

- Chronic obstructive pulmonary disorder
- Severe asthma
- Neuromuscular skeletal diseases—myasthenia gravis
- Decreased respiratory-motor drive—CNS infections, malignancy, traumatic brain injury, medications

Apnea

- Traumatic brain injury
- Stroke
- Drug overdose

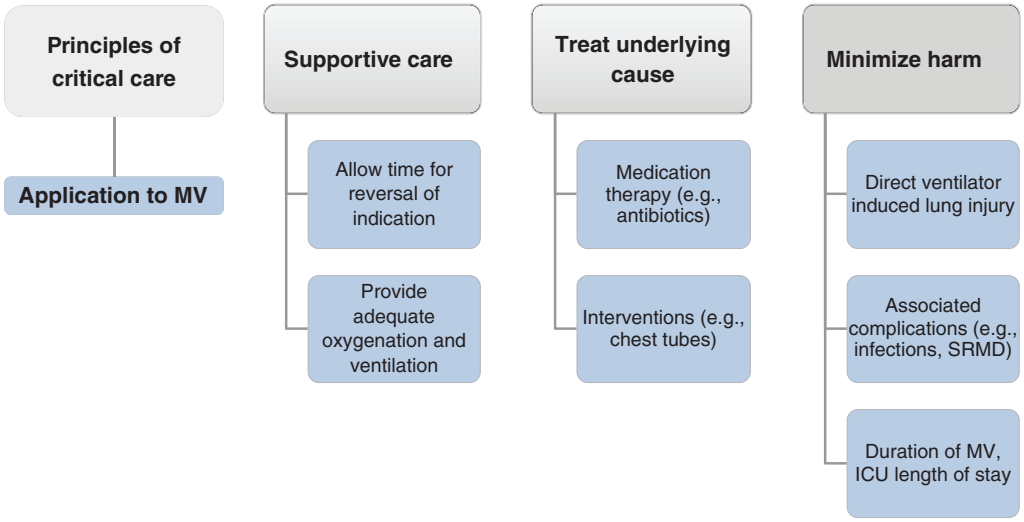

Figure 1. Goals of mechanical ventilation.

MV = mechanical ventilation; SRMD = stress-related mucosal disease.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

reductions in mortality and other patient outcomes (e.g., MV duration) and significant cost/benefit ratios (Hammond 2019, Lee 2019). This vital activity is especially present in the setting of MV, for which protocols that center around SBT coordination, diuretic management, pain, and sedation titration have proven the beneficial role of pharmacists (Newsome 2018, Bissell 2020). Thus, the importance of pharmacist involvement for the outcomes of patients receiving MV support cannot be overstated (Marshall 2008, Hahn 2013, Stollings 2015, Louzon 2017, Leguelinel-Blache 2018).

FUNDAMENTALS OF IPPV

Overall, MV can be classified as *invasive* or *noninvasive* ventilation: IPPV and NIPPV. *Invasive positive pressure ventilation* denotes the use of positive pressure through an invasive airway device, such as an endotracheal tube or tracheostomy; whereas *noninvasive positive pressure ventilation* uses a less invasive measure, such as a face mask. Box 2 summarizes key terminology for MV (Tobin 2013, Newsome 2018).

Box 2. Mechanical Ventilation Terminology

Global Terminology

- Mechanical ventilation (MV): a technique using an external device to conduct necessary gas exchange for a patient, including oxygenation and ventilation
- Invasive positive pressure ventilation (IPPV): form of MV wherein positive pressure is applied through the use of an endotracheal or tracheotomy tube
- Noninvasive positive pressure ventilation (NIPPV): form of MV wherein positive pressure is applied through a less invasive measure such as face mask
- Bilevel positive airway pressure (BiLevel): Form of NIPPV that includes two levels of positive pressure delivered through a mask, corresponding to exhalation and inhalation
- Continuous positive airway pressure (CPAP): Form of NIPPV that provides a continuous stream of positive pressure through a mask

Ventilator Variables

- Control variable: a pre-determined variable "controlled" by the machine within the equation of motion for the respiratory system
- Phase variable: any variable measured and used to start, maintain, and terminate each phase of the respiratory cycle
- Trigger variable: the measured variable to initiate inspiration
- Target variable: the variable that the ventilator device tries to achieve and/or maintain before the end of inspiration
- Cycle variable: the variable that, when reached, is used to end the inspiratory phase

Ventilator Settings

- Tidal volume (V_T): the total volume of gas inhaled and exhaled during one respiratory cycle (mL); V_T may be expressed in mL/kg of predicted body weight
- Respiratory rate (RR): the number of breaths taken (by machine, patient, or both) per minute (breaths/minute)
- Fraction of inspired oxygen (FiO_2): the percentage of O_2 in the delivered gas that is administered to the patient (%)
- Positive end-expiratory pressure (PEEP): the pressure setting that maintains positive airway pressures above atmospheric pressure during the exhalation phase (cm H_2O)

(*continued*)

Box 2. (*continued*)

- Inhalation/exhalation ratio (I:E ratio): Ratio of time spent on the inhalation versus exhalation phase in the breathing cycle
- Inspiratory time: the time over which inspiration is delivered; depending on the mode, this time may be the duration of V_T delivery or the time for which a set pressure is maintained; inspiratory time is adjusted to alter the I:E ratio.

Ventilator Modes

- Continuous mandatory ventilation (CMV): a mode that provides only mandatory breaths, allowing for no spontaneous breaths
- Intermittent mandatory ventilation (IMV): a mode that accommodates the patient taking spontaneous breaths between mandatory breaths
- Synchronized intermittent mandatory ventilation (SIMV): a form of IMV that synchronizes mandatory breaths by using measured patient effort to trigger the breath
- Continuous spontaneous ventilation (CSV): all breaths are spontaneously initiated and subsequently dictated by the patient
- Volume control (VC): a volume-targeted, time-cycled mode wherein the machine delivers the same V_T during each inspiration, which may be initiated by the machine or the patient
- Pressure control (PC): a pressure-targeted, time-cycled mode of ventilation with maximal airway and alveolar pressures limited by a maximal preset pressure; as such, V_T, flow, minute ventilation, and alveolar ventilation are all dependent on intrinsic resistance of the respiratory system
- Pressure-regulated volume control (PRVC): a pressure-limited, time-cycled mode of ventilation that targets average V_T
  - Similar to PC, a constant pressure is applied throughout an inspiration regardless of whether it is a machine-controlled or -assisted breath
  - The system adjusts the pressure after each breath based on measured changes in the patient's airway resistance to deliver the pre-set "goal" V_T
  - To stay within the preset goal ranges, PRVC evaluates each actual V_T with the pre-set V_T so that if the delivered volume is below goal, it can then increase the inspiratory pressure on the next breath or decrease the volume if the pressure is too high
- Pressure support (PS): a mode of pressure-targeted, partial ventilator support
  - Each breath is flow-cycled, patient-triggered, and machine supported
  - Most commonly used to facilitate ventilator weaning and as part of SBTs
- Airway pressure release ventilation (APRV): a pressure-limited, time-cycled (settings: high and low [T_{high} and T_{low}]), lung protective ventilation mode that allows for patient initiated spontaneous breathing independent of ventilator cycling—the patient can breathe at any point during the breathing cycle in addition to the machine settings
  - Ventilation occurs between the time-cycled switch between two pre-set pressure levels (settings: high and low [P_{high} and P_{low}])
  - Use of APRV is more often associated with lung-protective modes and more extreme inhalation/exhalation (I:E) ratios
- Biphasic positive airway pressure (BiPAP): from a practical perspective, this mode is almost indistinguishable from APRV when the same I:E settings are used
  - The terms *BiPAP* and *APRV* often used interchangeably in clinical practice because only minor differences exist, largely the result of proprietary distinctions
  - In this chapter, BiPAP refers to an invasive form of IPPV
- Proportional assist ventilation (PAV): an advanced mode of ventilation that is synchronized to generate PS in proportion to patient effort; no target flow, V_T, or airway pressure targets are set
- High-frequency ventilation (HFV): this lung protective mode uses extremely high RRs and very small V_T less than the dead space in the lung to maximize air flow patterns without lung damage
- High-frequency percussive ventilation (HFPV): this form of HFV combines high-frequency ventilation and conventional pressure-cycled ventilation; also known as volume diffusive respirator (VDR)
- High-frequency oscillation ventilation (HFOV): this form of HFV accomplishes gas transport with quasi-sinusoidal flow oscillations; these oscillations act as a mixing method to blend high O_2/low CO_2 content air with the air from the patient
- High-frequency jet ventilation (HFJV): this form of HFV makes use of high velocity ("jet") flow to achieve high RRs with relatively low V_T

Ventilator-related Terminology

- Mandatory breath: denotes when a breath is triggered and cycled (i.e., started and terminated) by the ventilator
- Spontaneous breath: denotes when a breath is triggered and cycled (i.e., started and terminated) by the patient
- Minute ventilation (MiV): describes the amount of air that an individual breaths per minute and is the product of respiratory rate and tidal volume ($MiV = RR \times V_T$)
- Rapid shallow breathing index (RSBI), Tobin-Yang index: a screening index for assessment of a patient's readiness for extubation
  - Calculated by division of respiratory rate by tidal volume ($RSBI = RR/V_T$)
  - RSBI values less than 105 breaths/minute/L are associated with extubation success (Tobin 2013)
- Plateau pressure (P_{PLAT}): Pressure at the end of inspiration applied to the small airways and measured using an inspiratory hold maneuver
- Driving pressure (ΔP): P_{PLAT}–PEEP; has been associated with mortality in ARDS
- Recruitment maneuver: an intervention wherein a sustained increase in airway pressure is applied with the intent to reopen (or recruit) collapsed alveoli

Information from Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

Review of Key Terminology and Concepts of IPPV

Invasive positive pressure ventilation is presented herein as a discussion of the specific variables that characterize a type of breath sequence and are organized by a chosen mode: control, phase, trigger, target, and cycle.

Ventilator Variables and Settings

Ventilator settings may be conceptualized as a series of variables—*control variables* and *phase variables*—that ultimately help to describe the associated breath sequences and ventilator modes. As an *equation of motion for the respiratory system*, ventilation is a function of three variables: (1) *force*, described as *pressure*; (2) *displacement*, described as *volume*; and (3) the *rate of changes of displacement*, described as *flow* (Otis 1950, Tobin 2013). Pressure and volume are the two primary *control variables*, with one acting as the independent variable and the other as the dependent variable. *Compliance* is a physical property denoting the change in volume of a gas or elastic stretch of a material as it is subjected to an applied force. Pulmonary (or lung) compliance measures the expansion of the lung and is calculated by dividing volume by pressure. Although compliance is a dynamic variable over time, at any instantaneous point in time it is a constant. As such, pressure can be understood as volume, and vice versa. The relationship between these variables prevents them from being controlled separately during the same breath.

The respiratory cycle consists of four phases: (1) inspiration; (2) the shift from inspiration to expiration; (3) expiration; and (4) the shift from expiration to inspiration (Marini 1998). *Phase variables* are used to start, sustain, and end each phase and may include pressure, volume, flow, and time. To mimic this finely tuned physiology, the machine has numerous settings aimed to control these phases. The most important are the trigger, target, and cycle settings (Figure 2). One breath is defined as one cycle of inspiration (e.g., positive flow) and expiration (e.g., negative flow) and is characterized by the start (the trigger) and stop (the cycle) of inspiration. As such, the trigger may be either patient- or machine-initiated based on preset criteria, including elapsed time since the last breath or patient-generated negative inspiratory pressure/volume. After this trigger is initiated, the breath may be cycled by either the patient or machine using time, volume, or pressure criteria.

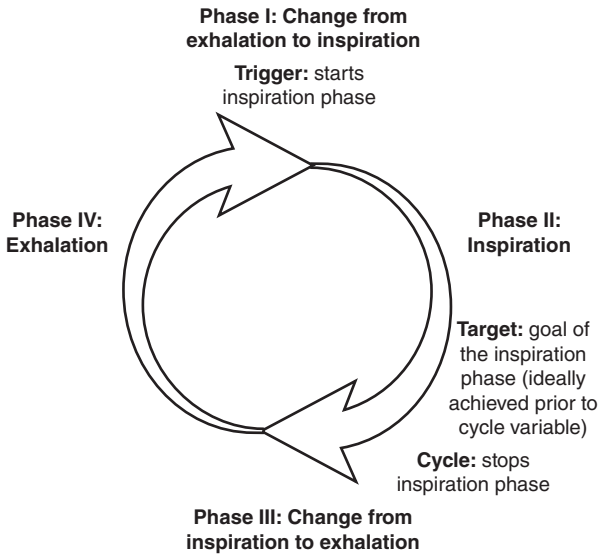

Figure 2. Conceptualization of phase variables controlling the breathing cycle.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

Breath Sequences

Three types of breaths are possible: *spontaneous breaths*, which describes patient-controlled breathing; *assisted breaths*, which describes patient-initiated but machine-assisted breathing; and *mandatory breaths*, which describes machine-controlled breathing. For a spontaneous breath, the patient determines both the timing—when inspiration is started and ended—and the V_T, whereas the machine reacts to the patient-initiated breath by recognizing the negative pressure or flow generated. For an assisted breath, the patient triggers a breath, but the ventilator provides some support by an increase in airway pressure above baseline during the inspiration and/or below baseline during expiration. For a mandatory breath, the ventilator triggers and cycles a breath. With these three types of breaths, three *breath sequences* are created: (1) *continuous mandatory ventilation* (CMV); (2) *intermittent mandatory ventilation* (IMV); and (3) *continuous spontaneous ventilation*. Many permutations within this construct are possible and form the basis of a myriad of ventilation modes, which is beyond the scope of this discussion. For example, synchronized intermittent mandatory ventilation is a common subtype of intermittent mandatory ventilation, wherein a mandatory breath is triggered by the patient through the setting of the trigger variables—and may include a series of patient- and machine-dictated breaths—with the goal to ultimately minimize dyssynchrony. Figure 3 and Figure 4 illustrate breath sequences.

Ventilator Modes

Holistically, ventilation mode may be thought of as the preset pattern of patient-ventilator interactions designed to achieve patient-specific goals and objectives. Common modes of ventilation include *pressure support* (PS), *volume control* (VC), *pressure control* (PC), and *pressure-regulated volume control* (PRVC). In VC, the V_T is held constant while pressure steadily increases throughout the inspiration as a result of the steadily increasing volume in the lungs. If a

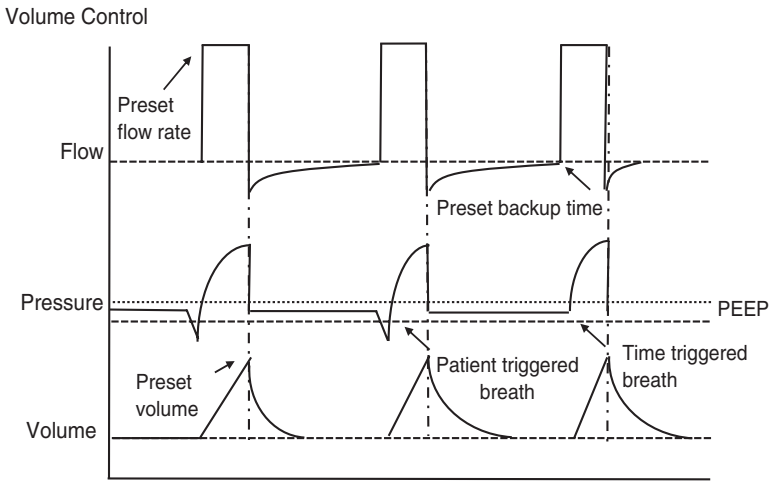

Figure 3. Patient- versus time-triggered breaths in volume control. In the patient-triggered breath, a negative inspiratory pressure prompts the machine to initiate gas flow to achieve the preset volume. In the time- (or machine-) triggered breath, the variable "time" acts as the trigger variable causing the machine to initiate a breath with the preset volume.

PEEP = positive end-expiratory pressure.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

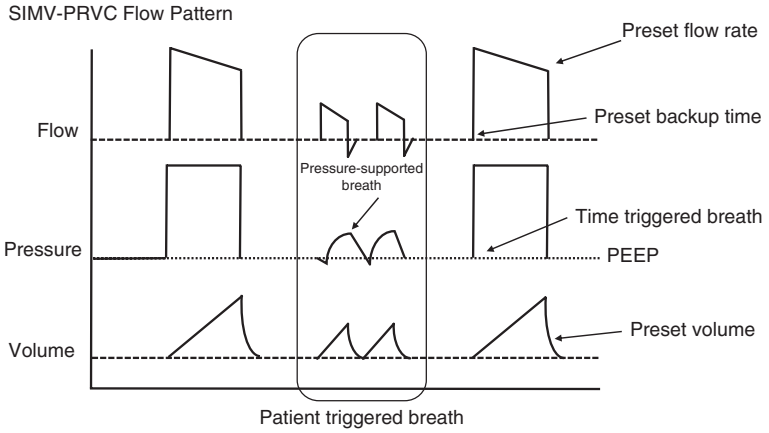

Figure 4. Synchronized intermittent mandatory ventilation (SIMV) ventilation flow pattern. In SIMV, patient-triggered breaths receive machine support through positive pressure, but the volumes are patient dictated. If the patient does not initiate a breath, a pre-set trigger (time) will initiate a breath with a pre-set volume or pressure. In patient-triggered breaths, small negative inspiratory pressures are generated and act as the trigger variable.

PEEP = positive end-expiratory pressure; PRVC = pressure-regulated volume control.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

ventilator monitor is visualized, the pressure curve will be seen as increasing (as volume increases), the inspiratory flow will be held constant, and a specific consistent V_T is targeted with the volume of each breath (similar to turning on a faucet and allowing it to fill a cup to the brim). In PC, the V_T varies to obtain a consistent pressure from breath to breath and throughout inspiration, creating a "flat" pressure curve. The volume curve will vary, and the flow pattern will be decelerating to achieve this flattened curve (similar to pressing the gas pedal to accelerate to achieve a certain speed and then gradually letting off to maintain that new speed). As a breath-to-breath mode of ventilation, PRVC provides volumes within a target range while simultaneously maintaining pressures within a target range. This ability to manipulate both volume

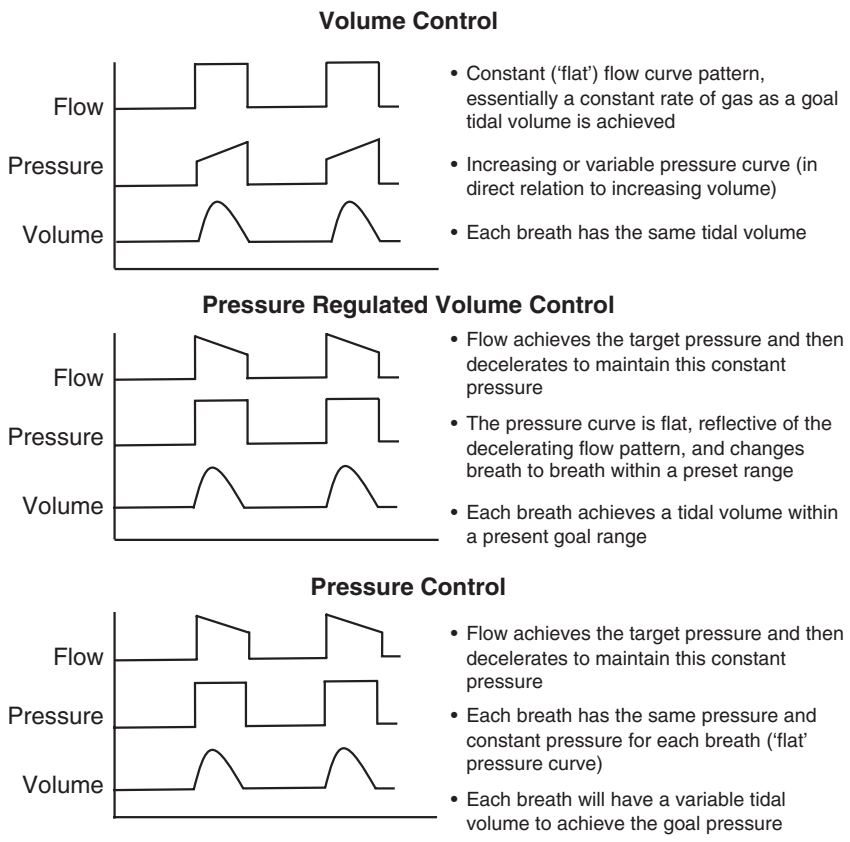

Figure 5. Flow, pressure, and volume curve patterns for volume control, pressure control, and pressure-regulated volume control.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

and pressure within a targeted range is achieved by determining the pressure needed to deliver a target V_T after every breath and using a decelerating flow pattern (Tobin 2013). As such, PRVC has a flat pressure curve (e.g., constant pressure throughout the breath) similar to PC, but ideally PRVC maintains a V_T (and minute ventilation) in a pre-specified range similar to VC. Actual V_T will vary in real-life scenarios because patient effort and asynchrony disrupt the ability of the ventilator to optimize mechanics, which can lead to significantly different minute ventilation from what was expected, and potentially VILI if not closely monitored (Figure 5).

Access

Mechanical ventilation can be applied through various access modes, including but not limited to an endotracheal device (orotracheal or nasotracheal), tracheostomy, and cricothyrotomy. Orotracheal is perhaps the most common form of invasive airway used, but nasotracheal is highly common in the setting of head/neck surgeries (Prasanna 2014). In the setting of an emergency airway or unanticipated difficult airway, the final treatment option is a cricothyrotomy, often performed in an emergency bedside setting (Frerk 2015).

IPPV: Concepts, Applications, and Pearls

Pressure Curves and Concepts

Mean airway pressure is the average pressure applied during a breathing cycle and is associated with overall alveolar ventilation, alveolar recruitment, and patient oxygenation (Figure 6). Thus, increasing mean airway pressure is directly associated with increased PaO_2. Taking advantage of this concept, APRV increases the time spent at a higher pressure level, as previously described. Because most of the time in traditional ventilator modes is spent in the exhalation phase, the easiest way to increase mean airway pressure is to increase the level of PEEP, the pressure applied during this exhalation phase. The pressure-time curve for an inspiratory hold is shown in Figure 7, and the air-trapping (auto-PEEP) that occurs is shown in Figure 8.

Pressure Support

In brief, PS is a pressure-targeted, patient-triggered mode of ventilation that provides partial respiratory support synchronized with the patient's (preserved) respiratory drive. As the least level of IPPV support, PS is most often used for a patient who was or remains intubated for nonpulmonary

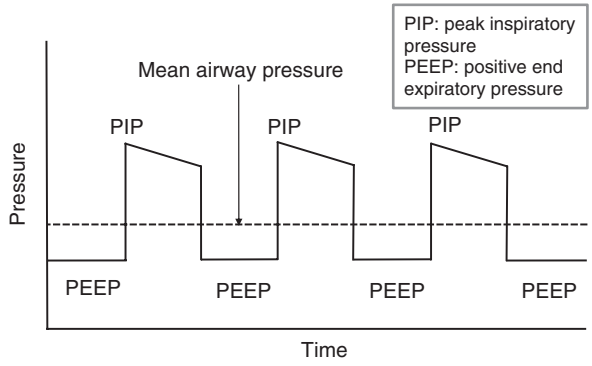

Figure 6. Pressure—time curve. The pressure during the expiratory pressure is characterized by the PEEP, whereas the highest pressure achieved during inspiration is the PIP, which is measured in the setting of positive inspiratory flow. In contrast, plateau pressure is the pressure that occurs when the flow is zero (during an inspiratory hold) and is thus a true measure of alveolar pressure. The mean airway pressure reflects the mean of time spent at all pressures during the respiratory cycle.

PEEP = positive end-expirotory pressure; PIP = peak inspiratory pressure.

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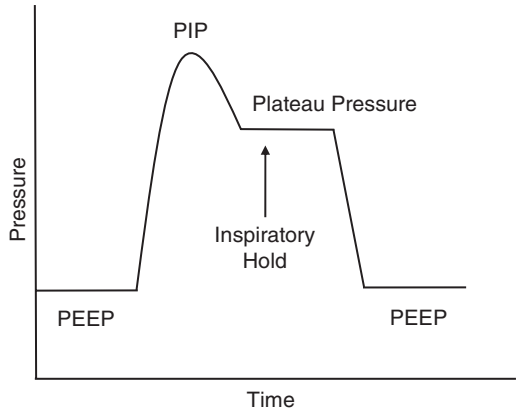

Figure 7. Pressure-time curve depicting an inspiratory hold. In this conceptualization of the pressure-time curve, PEEP can be seen as the "baseline value" during exhalation, and PIP is the highest pressure achieved during inspiration. If an inspiratory hold procedure is performed, the plateau pressure (essentially, a mean pressure during inhalation), can be obtained and monitored for associated lung injury.

PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure.

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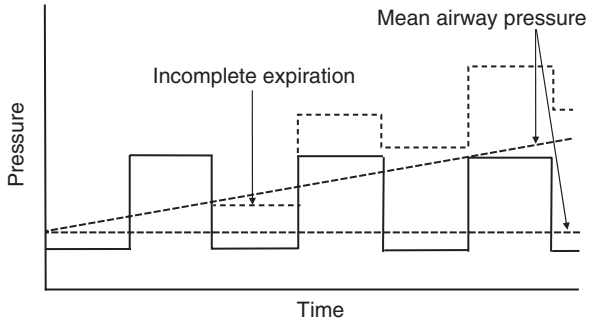

Figure 8. Air-trapping, auto-PEEP, or breath stacking. In this scenario, before the patient can completely exhale, the machine initiates another breath or "stacks" a new breath on the old breath prior to the previous breath being entirely exhaled, which creates a situation of ever-increasing pressure in the system, denoted as air-trapping or "auto-PEEP." This emergency scenario will be marked by obvious patient discomfort, alarm signals, and potential alterations in hemodynamic variables and must be rectified by allowing the trapped air to be released from the circuit and likely a change in the I:E ratio. This scenario is more likely in settings in which exhalation is hindered, such as chronic obstructive pulmonary disease and status asthmaticus, resulting in longer exhalation times.

I:E = inhalation to exhalation ratio; PEEP = positive end-expiratory pressure.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

reasons, such as airway protection, or for a patient who will soon be extubated. Trials of PS, which may also be called *spontaneous breathing trials* in clinical practice, are the cornerstone of IPPV weaning and liberation and are discussed later in text. A change from PS to PC, VC, PRVC, or an advanced mode of ventilation indicates a significant "clinical status change" for the patient. Alternatively, transition to PS may often be viewed as a sign of overall clinical improvement (Tobin 2013).

Effort-Adapted Modes of Ventilation

Beyond the "traditional" modes of MV, the next stage of IPPV technology includes adaptive support ventilation, proportional assist ventilation, mandatory minute ventilation, and neurally adjusted ventilator assistance (Singh 2014). These modes generally aim to optimize airflow patterns in the lungs, minimize VILI, and maximize patient comfort through enhanced synchrony methodology. However, inappropriate reductions of machine support in response to increase patient effort, such as in a setting of anxiety or sepsis, can potentially lead to clinical decompensation. The novel nature

of these modes means limited information is available on their place in therapy.

Inverse Ratio Ventilation

Historically, when more limited MV options were available, clinicians faced with hypoxemic respiratory failure resorted to a form of "inverse ratio ventilation." For this type of ventilation, the I:E ratio was reversed such that the inhalation time was significantly longer than the exhalation period (in both normally breathing patients and in most modes of ventilation, the exhalation period is longer than the inhalation period). These long inhalation times and short expiration times were achieved through manipulation of PC modes, and the approach was also called *bi-phasic ventilation* to denote the alternation between two distinct pressure levels. Conceptually, the advantage of this mode is that it makes the inspiratory phase the primary driver of mean airway pressure. By increasing mean airway pressure, oxygenation can be improved without increasing peak pressures known to cause VILI (Cawley 2019). This higher mean airway pressure ultimately leads to improved alveolar lung recruitment and oxygenation. This improvement in oxygenation is achieved at the risk of two issues: (1) patient discomfort with inverting traditional I:E ratios; and (2) hypercapnia, because the exhalation phase is significantly shortened and the respiratory cycle is significantly longer than is commonly used in patients with hypoxemic respiratory failure. The net effect is fewer full V_T breaths per minute, leading to lower minute ventilation. Permissive hypercapnia is a ventilation strategy that "permits" unphysiologically high partial pressures of CO_2, thus allowing for the use of lung protective ventilation with a low V_T.

Airway Pressure Release Ventilation

Building on inverse ratio ventilation, a key technological advancement allowed a patient to breathe spontaneously at any phase in the breath cycle. This mode of ventilation is generally known as *airway pressure release ventilation*, but may be referred to colloquially as other proprietary names such as BiVent or BiLevel (Tobin 2013). As an inverse-ratio, pressure-controlled mode that alternates between two pressures (high and low [P_{high} and P_{low}]) over two time-cycled periods (high and low [T_{high} and T_{low}]), APRV allows for spontaneous respirations at any point in the breathing cycle (Habashi 2005). These spontaneous respirations both improve patient comfort (deep sedation is not a pre-requisite for this mode of ventilation) and also significantly contribute to increasing minute ventilation, which mitigates the hypercapnia that may occur from the shortened expiratory times and longer respiratory cycles. Without these spontaneous respirations, an appropriate minute ventilation is unlikely to be achieved. Spontaneous breathing activity in APRV also has beneficial effects on airflow dynamics and lung recruitment that may be independently associated with its oxygenation improvements

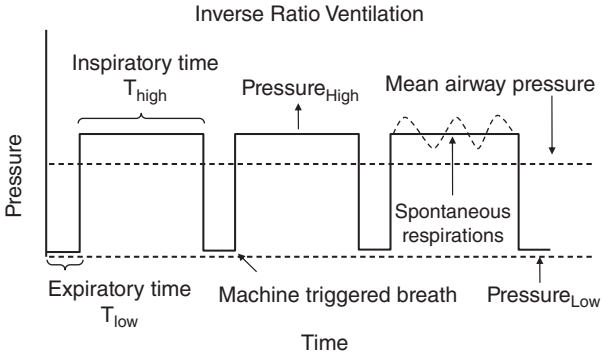

Figure 9. Airway pressure release ventilation pressure-time curve. Note the "inverse" graph with the prolonged inspiratory time at the high pressure setting and the relatively short expiratory time. This pattern is dictated by I:E. In APRV, the primary settings to evaluate daily include FiO2, I:E ratio (in particular T_{high}), P_{high} and P_{low}, and respiration pattern, such as the respiratory rate and patient- versus machine-initiated breaths.

APRV = airway pressure release ventilation; FiO2 = fraction of inspired oxygen; I:E = inspiratory to expiratory ratio; P_{high} = pressure high; P_{low} = pressure low; T_{high} = time high.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

(Figure 9) (Varpula 2003, Putensen 2004, Habashi 2005). This mode of ventilation has been associated with improved outcomes with severe respiratory failure (Lin 2019).

These nuances of APRV have important pharmacologic implications for the practicing pharmacist. First, although a pervading perspective is that APRV requires deep sedation and possibly neuromuscular blockade, this assumption should be questioned and evaluated on an individual patient basis because many patients tolerate this mode of ventilation while using light sedation. Notably, when APRV is used in the absence of spontaneous breathing activity, the mode is essentially a time-cycled inverse I:E ratio ventilation strategy, increasing risk of hypercapnia (O'Croinin 2005, Daoud 2007). Second, hypercapnia is an expected occurrence in this mode of ventilation and does not necessarily require pharmacotherapeutic intervention (i.e., acetazolamide, theophylline) to "fix" these numbers, which has not been shown to improve patient outcomes (Faisy 2016, Newsome 2018). Nor does the associated respiratory acidosis require correction by sodium bicarbonate infusion. Third, APRV is an option in cases of refractory hypoxemic respiratory failure/ARDS (Maung 2011, Alhurani 2016). Another therapy for refractory hypoxemia, NMBAs, and the associated sedation required, reduce spontaneous respirations. Because spontaneous respirations in APRV are associated with improved oxygenation, the

possibility exists that this combination of therapies negates positive effects of the other therapies. Neuromuscular blockade has only been studied in ARDS in the setting of the VC mode (Duan 2017, National Heart Blood Institute 2019).

Prone Positioning

Prone positioning, in which the patient is placed face down to lay on the stomach, is a maneuver recommended by guidelines to improve oxygenation and mortality for refractory ARDS and is often used in conjunction with MV. Globally, the prone position is used to recruit collapsed alveoli, improve secretion management/prevent atelectasis, and optimize ventilation/perfusion matching by shifting perfusion to recruited alveoli in the anterior lung regions. In general, patients in the prone position are managed with PEEP levels based on the ARDSNet protocol and low V_T ventilation, as observed in the PROSEVA study (Guerin 2013). In the era of coronavirus disease 2019, use of the prone position for nonintubated, awake patients has shown initial success in oxygenation improvement and prevention of intubation, a key strategy when resources are limited (Ziehr 2020). These studies are generally case series and small retrospective studies, but prone positioning for awake patients does seem to improve oxygenation (potentially reducing further deterioration) and is a safe, inexpensive, and adaptable strategy (Caputo 2020, Sun 2020). The position may be paired with several supplemental O_2 forms (e.g., nasal cannula, face mask) and used for a few hours for more transient benefit versus longer periods (Scaravilli 2015, Elharrar 2020). To achieve the oxygenation benefits, patients must be in the prone position for extended periods—the protocol for PROSEVA was at least 16 hours daily (Guerin 2013). Prone positioning does require specific logistical considerations, including provision of advanced cardiovascular life support and addressing the potential for pressure ulcers and ocular edema, as well as nutrition considerations, and interprofessional protocols are helpful.

IPPV Monitoring Variables and Concepts

Two RRs are shown on a ventilator monitor and should be evaluated in patient review: the *set respiratory rate* and the patient's *actual respiratory rate*. These two values are not necessarily the same. If the patient is "over-breathing" the pre-set RR, in which the patient's RR is greater than the pre-set RR, then the patient's RR should be evaluated. Alternatively, the patient may be "riding the vent," wherein every breath the patient takes is secondary to machine initiation, which may occur for a variety of reasons, including altered mentation or sedation. Furthermore, the patient and ventilator RR may be identical, but all of the breaths are patient initiated, which may indicate an optimal level of sedation and ventilator settings.

The FiO_2 of room air is about 21%. This ventilator variable is typically titrated to O_2 saturation and/or PaO_2 and is generally set at 40%, although a setting of 30% may also be used. Higher FiO_2, generally in conjunction with higher PEEP, indicates worse oxygenation status. An FiO_2 greater than 60% is associated with O_2 toxicity because of free radical formation, and more conservative oxygenation strategies may be warranted (Tobin 2013, ICU-ROX Investigators 2020).

Positive end-expiratory pressure is the amount of pressure in the lungs at the end of expiration. Intrinsic PEEP is present in all lungs and is a physiologic adaptation to reduce the work of breathing. (For active learning, one can breathe out naturally and then force out a bit more breath–this "extra air" is one's intrinsic PEEP). A possible metaphor for understanding PEEP is to imagine the difficulty in the first few breaths when blowing up a balloon; yet after those first few breaths, it becomes much easier to stretch the rubber. With this action as those first few "balloon breaths" in the alveoli, PEEP means that, with each successive breath, one is not required to reopen collapsed or derecruited alveoli. Standard PEEP ranges are 5–10 cm H_2O, with higher values indicating the need for alveolar recruitment or difficultly oxygenating (Tobin 2013). Of note, obese patients may require slightly higher levels of baseline PEEP because of obesity-related hypoventilation and the impact of the chest wall on transpulmonary pressure (Pirrone 2016). High levels of PEEP (greater than 15 cm H_2O) may be associated with spontaneous pneumothorax. Thus, as a patient approaches relative maximums of FiO_2 and PEEP, the clinician may predict the use of advanced modes of ventilation and/or rescue therapies, such as an NMBA. However, the advent of patient-specific PEEP optimization techniques (e.g., driving pressure, esophageal balloon manometry) identifies an optimal PEEP that may be significantly higher than "usual" but one that ideally optimizes individual respiratory mechanics without excess risk from these higher static pressures.

Regarding the interrelationships among ventilation variables, generally FiO_2 and PEEP are directly associated with oxygenation and are manipulated for PaO_2. In contrast, minute ventilation (the product of RR and V_T) is inversely related to CO_2; for example, increasing the minute ventilation decreases CO_2. As such, respiratory acidosis/alkalosis may be improved through manipulations of minute ventilation on the machine (Tobin 2013).

Low V_T ventilation or protective lung ventilation remains the primary intervention to improve mortality in ARDS but has been increasingly shown to reduce VILI in other disease states as well. This type of ventilation targets lower V_T (6–8 mL/kg of predicted body weight) and thus targets lower overall airway pressures, which reduces VILI (Brower 2000). In addition, low V_T ventilation has been incorporated as a component in several pharmacist-driven quality-improvement protocols as a standard of care (Sutherasan 2014, Leguelinel-Blache 2018).

Plateau pressure is an IPPV monitoring variable in which an inspiratory hold is performed manually, wherein the machine essentially causes the patient to hold the breath for about 0.5–1 second at the end of the inspiratory phase. If an

inspiratory hold maneuver is performed, pressure will equilibrate while flow has ceased and a plateau pressure can be obtained to assess for elevated pressures in the alveoli and small airways, which is associated with barotrauma. In the setting of high peak pressures but relatively normal plateau pressure, common clinical findings are mucous plugging and bronchoconstriction, for which mucolytics and bronchodilators may be used, respectively. Evaluation for the patient biting the endotracheal tube and need for a bite block may be warranted. Elevated plateau pressures often indicate poor compliance ("stiff" lungs), but may also indicate air trapping and the need for evaluation of variables such as I:E ratio and auto-PEEP (which may be especially appropriate in settings of restrictive/obstructive airway disease).

Ventilator dyssynchrony is a common occurrence that should be managed with both ventilator manipulations and pharmacotherapy (e.g., analgosedation, NMBA). Types of ventilator dyssynchrony include but are not limited to the following: *ineffective efforts*, wherein inspiratory muscle breath is not followed by a ventilator breath; *double cycling*, wherein the inspiratory effort continues beyond the ventilator's inspiratory time creating several "breaths" before exhalation; *inspiratory airflow dyssynchrony*, wherein patient's inspiratory effort creates concavity in the pressure tracing because of inadequate gas flow; and *reverse triggering* (de Haro 2019). Reverse triggering occurs when ventilator insufflations trigger diaphragmatic muscle contractions, a form of patient-ventilator interaction called *entrainment* (Akoumianaki 2013, Bourenne 2019). This reverse triggering can promote VILI through the Pendelluft effect (literally "swinging air") (Greenblatt 2014). In this phenomenon, nonhomogeneous inflation/deflation creates regional pressure differences in the lung and airflow among them and thus increases regional V_t and transpulmonary pressures. Reverse triggering has gained increased attention because of its association with deep sedation and potential to increase mortality in ARDS and as a potential confounder in the conflicting results of the trials evaluating neuromuscular blockade in this population (ACURASYS and ROSE) (Park 2019, Slutsky 2019). Because of the highly individual nature of the ventilator-patient interaction, the possibility exists that subtle manipulations may improve patient comfort without adversely affecting oxygenation/ventilation goals and may obviate the need for further analgesia/sedation. Clinically, patients may tolerate one form of IPPV well and not another. Within established safety guidelines, efforts should be made to adapt the ventilator to the patient before adapting the patient to the ventilator.

FUNDAMENTALS OF NIPPV

Key Terminology and Concepts in NIPPV

Noninvasive positive pressure ventilation delivers positive pressure ventilation through an interface such as a nasal mask, face mask, or nasal prongs to patients with preserved respiratory drive (Nava 2009). In the critical care setting, NIPPV is used both as a final measure before intubation and as a means of facilitating successful extubation in the appropriate clinical setting. The two most common modes of NIPPV are *continuous airway pressure* (CPAP) and *biphasic positive airway pressure* (BiPAP) (Garpestad 2007).

Indications for NIPVV

Timing and use of NIPPV remains an ongoing area of research. Notably, the use of NIPPV has resulted in preventing intubation, achieving successful extubation, and other improved outcomes in chronic obstructive pulmonary disease, asthma, hypoventilation syndromes, trauma, congestive heart failure (Garpestad 2007).

Biphasic Positive Airway Pressure

In BiPAP, the machine can be set to support all breaths or only to provide support during machine-timed breaths. The two primary settings are *inspiratory positive airway pressure* and *expiratory positive airway pressure*. The difference, or "delta", between these airway pressures is directly related to the V_T received, and this difference may be used in the setting of hypercapnia to improve ventilation, such as exacerbation of chronic obstructive pulmonary disease (Garpestad 2007). Figure 10 depicts the relationship of these pressure values to continuous positive airway pressure and IPPV. Because BiPAP requires the use of a face mask, patient cooperation is an important component—some patients will not tolerate a tight-fitting mask with air being blown on them continuously. Further, BiPAP must be removed for meals and should not be used in the setting of nausea/vomiting or questionable airway protection, such as in ventilation cases as related to mental status, because the risk of aspiration is high.

Continuous Positive Airway Pressure

In continuous positive airway pressure, a continuous level of positive pressure is applied throughout the entire respiratory cycle. In contrast to BiPAP, V_T cannot be titrated as effectively; therefore, continuous positive airway pressure is often used in association with disorders of oxygenation, such as obstructive sleep apnea, pulmonary edema (Garpestad 2007).

O_2 Delivery Systems

Nasal cannula, high-flow nasal cannula, face masks, and other systems may all be used to deliver O_2 and can be classified as low- and high-flow devices, with circuits that contain a humidifier. The nasal cannula is a low-flow device for mild hypoxemia and is generally set between 1–6 L/minute. The FiO_2 increases about 4% for every 1 L increase in flow; 1–6 L/minute correlates to 24%—40% FiO_2. A simple face mask is a low-flow device that can generally be set between 5–10 L/minute (35%–55% FiO_2). A nonrebreather mask uses a reservoir bag and one-way valve to prevent inhalation of previously expired air to deliver higher concentrations of O_2 (10–15 L/minute, 80%–95% FiO_2). A venturi mask is a high-flow device

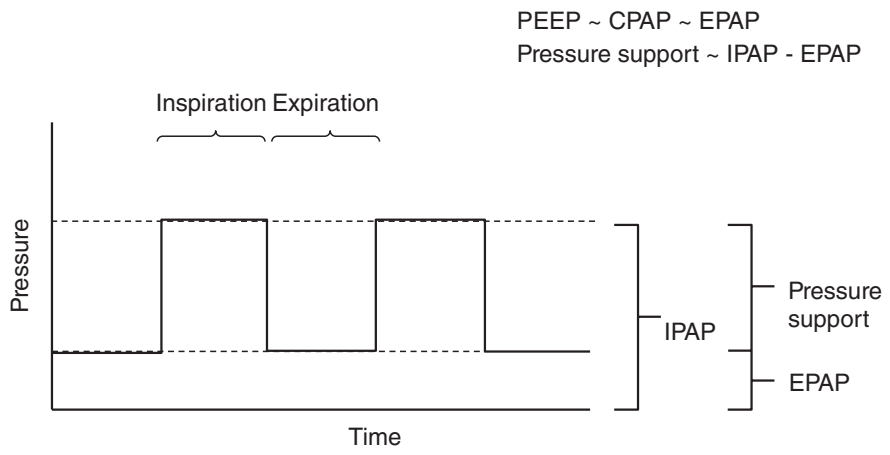

Figure 10. BiPAP pressure curve. The EPAP can be conceptualized as about equal to both the CPAP pressure and also PEEP in IPPV. Further, pressure support is the difference between EPAP and IPAP; thus the settings from a patient previously receiving IPPV can be used to inform BiPAP settings.

BiPAP = biphasic positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; IPPV = invasive positive pressure ventilation; PEEP = positive end-expiratory pressure.

Information from: Tobin MJ. Principles and practice of mechanical ventilation, 3rd ed. New York: McGraw-Hill Medical, 2013.

that allows for more precise measurement of O_2 delivery. Use of a high-flow nasal cannula allows for independent control of flow and FiO_2, can deliver up to 60L/minute, and even provides a low level (about 2–5 cm H_2O) of PEEP (Brochard 1995).

MV LIBERATION

Role of the Pharmacist

Pharmacotherapy and patient liberation from IPPV are linked, and pharmacists should monitor how key pharmacotherapy, such as analgesia, sedation, or diuretics, relates to weaning guidelines and overall spontaneous awakening trial (SAT)/SBT performance. Evaluation of the level of respiratory support, including mode, FiO_2, and PEEP, all act as important monitoring variables for therapy such as diuresis, analgesia/sedation, and antibiotic therapy. For example, if a patient becomes apneic on PS, oversedation is a common etiology and evaluation of residual sedatives or current therapy is warranted. Conversely, tachypnea may result from patient anxiety that can be mitigated through the judicious use of anxiolytics (e.g., dexmedetomidine).

A patient can be evaluated for liberation from MV by considering the following questions: (1) Has the initial indication that warranted intubation been reversed? (2) Is the patient eligible for an SBT? If not, why not? (3) Did the patient pass the SBT? If not, why did the patient experience failure? Was the SBT failure related to present pharmacotherapy or can it be addressed by an intervention such as fixing a cuff leak or correcting fluid overload?

Although extubation failure is associated with worse outcomes, a causal association has been difficult to determine. An appropriate reintubation rate is likely around 15%, with lower values indicating that patients may have been intubated longer than necessary (Krinsley 2012, Thille 2013). Extubation success rates remain an area of controversy and ongoing research. Of interest, patients who self-extubate in an unplanned fashion are often able to remain extubated, with "success" rates ranging up to 70% (Penuelas 2011, Lin 2019).

Spontaneous Awakening Trial/Spontaneous Breathing Trial

Both SATs and SBTs help decrease the time to extubation and the ICU length of stay (Kress 2000, Girard 2008, Shi 2013). In particular, daily SBTs with pressure augmentation (5–8 cm H_2O) are recommended by the American Thoracic Society/ACCP clinical practice guideline for liberation from MV of critically ill adults (Fan 2017b). This use of pressure augmentation in the SBT differentiates it from a more historical "T-piece" trial in which the patient breathes spontaneously with no respiratory support. In this scenario, a patient must overcome the narrowed airway from the endotracheal tube to succeed, likened to the difficulty of "breathing through a straw." Although the T-piece trial has a respectable positive predictive value, it does not have a good negative predictive value and is thus considered overly conservative (Fan 2017a). Assessment of SBTs is highly variable, and pharmacists should investigate what specific criteria led to the "failure" of SBT. This assessment includes the conditions of the trial and evaluation of medication therapy that could have contributed to that failure. Of note, a successful SBT indicates pulmonary readiness for extubation and appropriate

respiratory drive; however, the presence of clinical scenarios such as angioedema or tracheitis (with the associated thick secretions and/or poor cough) may still preclude a patient from being extubated. Finally, a common misconception is the requirement for a patient to be able to follow commands and lack the presence of delirium or altered mental status to be extubated. Although protecting the airway is of primary concern, this ability is only partially related to a patient's ability to successfully complete a delirium assessment correctly. Pharmacy-related considerations during the SAT/SBT process include evaluation of current analgesia/sedation therapy and the use of neuromuscular blockade, as well as clinical conditions that may prohibit the safe performance of a SAT/SBT, such as an elevated intracranial pressure requiring treatment.

Weaning Parameters

To assess readiness to liberate, an SBT is performed. An SBT simulates the conditions after extubation (e.g., minimal vs. no ventilator support), evaluating whether this presently intubated patient can tolerate those conditions. In general, minimal PS and PEEP settings are applied, such as PS/PEEP of 10/5 or 5/5, for about 30–60 minutes, although ranges and settings may vary. A combination of clinical evaluation and objective indices are used to predict extubation success. Clinical evaluation may include work of breathing, high RR, obvious signs of distress or agitation, and hemodynamic stability. The RSBI or Tobin index is the most commonly used—and most validated—objective tool (Tobin 2013). Calculated by dividing the respiratory rate by tidal volume (RR/V_T), an RSBI less than 105 breaths/minute/L is the general cut-off for successful extubation, with a 78% positive predictive value and 95% negative predictive value (Yang 1991). In addition to RSBI, a reasonable minute ventilation and overall oxygenation must be maintained. Other indices studied have either been less effective, or their complexity limits clinical utility (Yang 1991). A more historical weaning parameter called the *negative inspiratory force* is assessed by having the patient breathe in maximally on a small device (low numbers denote weaker respiratory muscles and predicted less ability to successfully extubate); however, this device requires the coordinated effort of a patient who can follow directions, which may or may not be actually indicative of a patient's readiness to extubate (American Thoracic Society/European Respiratory Society 2002, Fan 2017a, Fan 2017b).

An elevated RSBI (or failed SBT) can then be evaluated for medication-related etiologies, including but not limited to fluid overload, agitation, or airway obstruction, which may be rectified by such interventions as diuretics, anxiolytics, or bronchodilators, respectively. Oversedation from opioids or benzodiazepines, which may require discontinuation, dose reduction, or more time to be cleared by the body, is another common cause of SBT failure. Because assessment of weaning parameters in conjunction with SBTs requires a highly coordinated approach, guidelines recommend a protocolized and interprofessional approach to liberation (American Thoracic Society/European Respiratory Society 2002, Devlin 2018).

IPPV-RELATED ORGAN DYSFUNCTION AND COMPLICATIONS

Infectious Complications of MV

Infectious complications of IPPV are relatively common and associated with increased mortality and morbidity. Ventilator-acquired pneumonia and ventilator-acquired sinusitis are two of the most common infectious complications and are extensively reviewed in other settings (Kalil 2016). Prevention of VAP through bundled care is a common approach and one in which pharmacists can play a key role in implementation, although supportive evidence is variable (Wip 2009, Bouadma 2010, Tokmaji 2015, Caroff 2016, Kalil 2016, Khan 2016). For example, the Institute for Healthcare Improvement recommends the use of a particular ventilator bundle to decrease VAP as follows: head of bed elevation between 30 and 45 degrees; daily sedative interruptions and assessment of readiness to extubate; stress ulcer prophylaxis; and daily use of chlorhexidine gluconate. Evidence of improvement has been demonstrated with pharmacist involvement in each of these areas (Resar 2005, Leguelinel-Blache 2018).

Hemodynamic Changes and Assessment

The net hemodynamic effect of IPPV is the result of a complex interplay of positive pressure with pre-existing cardiac function, volume status, presence of dynamic hyperinflation of the lungs, and effects specific to the disease state, such as sepsis-mediated reductions in systemic vascular resistance (Alviar 2018). For example, in a patient intubated for status asthmaticus and experiencing dynamic hyperinflation, the end-expiratory lung volume is increased, leading to elevated intrathoracic pressures. These increased intrathoracic pressures can then reduce the right ventricular venous return and also the left-ventricular afterload; however, the net effect of these alterations depends largely on the patient's pre-existing cardiac function (Figure 11). A patient with reduced cardiac output may benefit from the reduced afterload, whereas a patient with a normal cardiac output may have reduced function because of the reduced venous return or functional preload (Tobin 2013). Sepsis guidelines recommend use of dynamic indices (i.e., pulse pressure variation or stroke volume variation) for assessment of fluid responsiveness (Rhodes 2017). Because of alterations of the pulsus paradoxus, IPPV interferes with this measurement, and these measurements have been largely validated in highly controlled IPPV settings, specifically, V_T of at least 8 mL/kg and machine-controlled respirations (Michard 2000, Marik 2013). As such, the pharmacist must exercise caution when interpreting values outside of these specific conditions. Globally,

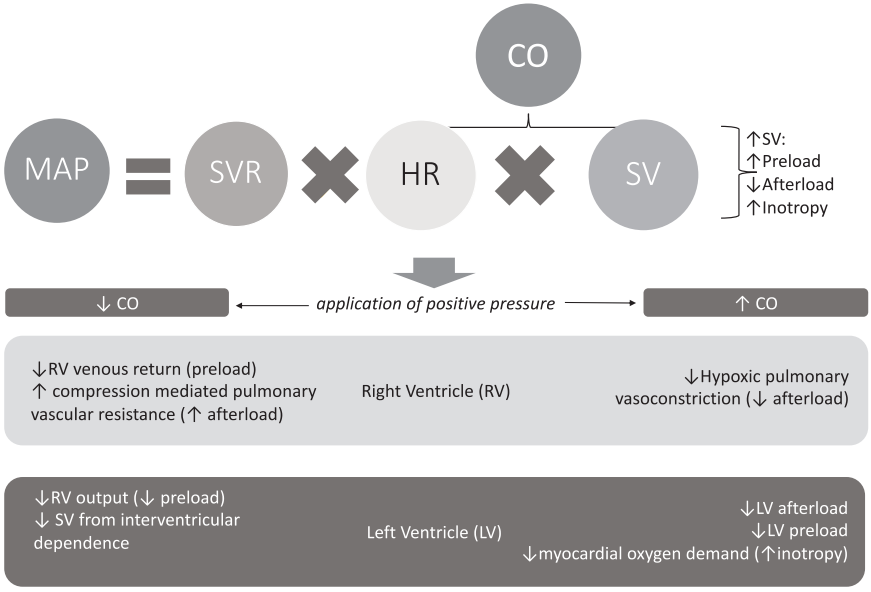

Figure 11. Hemodynamic effects of positive pressure ventilation.

= increased; = decreased; CO = cardiac output; HR = heart rate; LV = left ventricle; MAP = mean airway pressure; RV = right ventricle; SV = stroke volume; SVR = systemic vascular resistance.

Information from: Jones TW, Smith SE, Van Tuyl JS, et al. Sepsis with preexisting heart failure: management of confounding clinical features. J Intensive Care Med 2020:885066620928299.

if a patient has a sudden change in hemodynamic status, evaluation is warranted of the clinical correlation with recent changes to IPPV settings, such as a blood pressure drop after PEEP was adjusted from 5 cm H_2O to 15 cm H_2O. Hypotension after rapid sequence intubation (RSI) is a relatively common occurrence resulting from the interplay of RSI medications, new application of positive pressure, and patient-specific comorbidities (Lin 2008). Pharmacists should evaluate for this occurrence and consider the RSI agent profile and the possible requirement for peri-RSI fluids or pressors, either push-dose or continuous infusion (Weingart 2015).

The use of PEEP can have variable effects on the cardiac system based on right and left ventricular function, preload, and afterload, which is especially pronounced in the setting of heart failure. If a patient is in a preload-dependent state (e.g., right ventricular dysfunction), moderate to high PEEP may decrease cardiac output; however, in an afterload-dependent state (e.g., left ventricular dysfunction), moderate to high PEEP may increase cardiac output. Cognizance of a patient's cardiac function during changes in MV management will improve hemodynamic assessment (Alviar 2018, Jones 2020).

Altered Pharmacokinetics

Renal and hepatic function, and thus drug pharmacokinetics, may be altered by the hemodynamic and neurohormonal effects of MV. Increased intrathoracic pressure from the use of positive pressure ventilation results in decreased venous return (and thus cardiac output) and leads to compensatory homeostatic responses, including neurohormonal alterations that increase intravascular volume. These responses include increased antidiuretic hormone secretion, reduced atrial natriuretic peptide secretion, up-regulation of the renin-angiotensin-aldosterone system, and increased sympathetic outflow (Frazier 1999). Alterations in intra-abdominal pressure may decrease hepatosplanchnic perfusion, with higher inspiratory pressure, V_T, and PEEP exaggerating this effect (Jakob 2010). Invasive positive pressure ventilation is associated with decreased urine output, sodium and water retention, and reduced renal perfusion, all contributing to reduced renal clearance. This reduced renal function is thought to be mediated by renal vasoconstriction and ischemia from increased CO_2 and decreased oxygen; the use of PEEP, resulting in reduced cardiac output and thus renal perfusion; inflammatory cytokines released from volutrauma or barotrauma; and, finally, neurohormonal alterations (Moore 1974, Priebe 1981, Kuiper 2005). In the complex interplay of critical illness that includes the potential for a hypermetabolic state, hepatic or renal dysfunction, use of renal replacement therapy, and altered volume of distribution, IPPV is just one factor. As such, pharmacists should use therapeutic drug monitoring and drug dosing specific to critical illness whenever possible (Vitrat 2014).

Stress-Related Mucosal Disease

The 1994 Cook et al. study identified IPPV as one of the two strongest risk factors for stress-related mucosal disease; therefore, stress ulcer prophylaxis has remained a key component of most ventilator bundles (Cook 1994, Barletta 2016). Risk of stress-related mucosal disease in the modern era of critical care management and agent selection remain ongoing areas of clinical debate and research. Presently, both histamine-2 receptor antagonists and proton pump inhibitors have demonstrated superiority over other acid-suppression agents and may be considered based on patient-specific factors (ASHP Commission 1999, Barletta 2014, 2016, Alhazzani 2018, Krag 2018, Barbateskovic 2019, Marker 2019).

Post-Extubation Stridor

Inflammation and edema around the endotracheal tube can create a narrowed airway, resulting in a high-pitched sound, or post-extubation stridor (PES), which can lead to increased rates of extubation failure (Epstein 1998). Pharmacologic interventions for PES are efficacious when coordinated appropriately (Pluijms 2015). Guidelines recommend evaluation for the risk of PES using a cuff leak test (CLT) for patients on MV who meet extubation criteria and are at high risk of PES, and the administration of systemic steroids at least 4 hours before extubation in patients for whom the CLT has failed (Girard 2017). High-risk features include at least one of the following criteria: (1) traumatic intubation, (2) female sex, (3) endotracheal intubation 6 days or more, (4) trauma to upper airway anatomy, (5) reintubation after unexpected extubation, or (6) a large endotracheal tube (greater than 8 mm) (Jaber 2003, Wittekamp 2009, Girard 2017). The CLT compares the expiratory V_T with cuff inflation and deflation; however, variation in measurement methods and cut-off values exist. An absolute volume less than 110 mL for failure is used most consistently (Miller 1996, Sandhu 2000, Pluijms 2015, Smith 2018). Steroids are the primary pharmacologic prevention and treatment, but many regimens have been proposed. Intravenous methylprednisolone has demonstrated the most promising results, administered as 20 mg every 4 hours starting 12 hours before extubation, with significant reduction in laryngeal edema and reintubation rates (Francois 2007, Wittekamp 2009). Dexamethasone has also been studied, but results are inconsistent (Darmon 1992, Lee 2007). Protocolized management of mechanically ventilated patients at risk of PES may be a reasonable method to coordinate patient identification, testing, treatment, and extubation (Wittekamp 2009, Girard 2017, Smith 2018). Beyond prevention, management strategies vary widely and are largely extrapolated from studies of patients with asthma. Treatment consistently includes steroids (e.g., intravenous methylprednisolone 40 mg as a one-time dose) and nebulized epinephrine (e.g., 2.25% racemic epinephrine 0.5-mL solution as needed) (Pluijms 2015).

Pain, Agitation, and Delirium

Pain, agitation, and delirium management is a fluctuating target in patients receiving MV, with goals assessed daily for the individual patient. Core components of analgesia and sedation management include such tenets as first-line use of analgosedation, use of nonbenzodiazepine agents (propofol or dexmedetomidine), targeting light levels of sedation (Richmond Agitation-Sedation Scale 0 to −2), and use of delirium prevention, sedation interruption, and SBTs (Barr 2013, Devlin 2018). Delirium prevention requires a multifaceted approach. Pharmacist-led optimization of analgosedation, especially combined with their familiarity of pharmacokinetic profiles, improves outcomes for these patients (Rudis 2000, Louzon 2017).

Ventilator-Induced Lung Injury

Ventilator-induced lung injury is a preventable cause of lung injury secondary to the use of MV and is a significant contributor to morbidity and mortality for critically ill patients (Slutsky 2013). One of the most definitive "positive" trials in all of critical care medicine focuses on the mitigation of VILI through the use of low V_T ventilation and targeting lower plateau pressures (Brower 2000). Mediation of VILI is through alveolar overdistension and subsequent damage from volutrauma, barotrauma, atelectrauma, shear strain, and inflammatory damage. Also, VILI appears to be increased with comorbid physiologic insults such as sepsis or trauma (Beitler 2016). Efforts to mitigate VILI can lead to difficult trade-offs among adequate oxygenation and ventilation while doing so with the minimum V_T and positive pressure support necessary (Beitler 2016). The use of PEEP, the prone position, and the more advanced modes of ventilation (e.g., APRV) all aim to minimize the factors that cause VILI while still achieving appropriate ventilation targets.

ICU-Acquired Muscle Weakness

Prolonged MV is a significant risk factor for ICU-acquired muscle weakness, which can lead to worse patient outcomes. Early mobility efforts, even in patients who are undergoing MV, are an important consideration and recommended by the MV liberation guidelines. Medication-oriented considerations include the shortest duration possible of paralytics, use of light sedation, and early nutrition and appropriate protein intake (Hermans 2015, Fan 2017b).

Obesity-Related Considerations

Obesity is a commonly encountered comorbidity in patients undergoing MV and poses specific challenges (De Jong 2017). Obesity causes atelectasis and decreased lung volumes, increases airway resistance and work of breathing, and limits the ability to ventilate (termed *obesity hypoventilation*). Overall, oxygenation decreases as weight increases because of both increased O_2 consumption (about 1.5 times that for the normal-weight individual) and increased work of

breathing. Although patients with an extremely high BMI are excluded from the studies of low V_T ventilation, lung protective ventilation with 6–8 mL/kg using predicted body weight is often recommended, and, generally, obese patients seem to benefit from slightly higher levels of PEEP (De Jong 2017). Furthermore, appropriate positioning and head of bed considerations are of high importance because of the risk of obesity supine death syndrome or the alteration of thoracic compliance secondary to the weight of the panniculus (Lemyze 2018).

Refractory Hypoxemia Management

Invasive positive pressure ventilation remains a core component of refractory hypoxemia management with techniques including recruitment maneuvers and advanced modes of ventilation (e.g., high-frequency oscillation ventilation, APRV) in conjunction with rescue therapies such as NMBAs, inhaled pulmonary vasodilators, extracorporeal membrane oxygenation, and higher hemoglobin goals. High-quality data are lacking, and management is characterized by widespread variation (Duan 2017).

MV ADJUNCTIVE THERAPIES

General Overview of IPPV-Acquired Medication Interventions

In addition to many of the higher-level interventions discussed for a patient receiving MV, routine interventions regarding medication administration logistics are a necessary role of pharmacists. These types of interventions may include but are not limited to evaluation and modification of medications that cannot be crushed (e.g., extended release formulations, enteric coated, teratogenic medications, capsules); addition of IPPV-related prophylaxis (e.g., chlorhexidine gluconate, stress ulcer prophylaxis); opportunities to incorporate fluid stewardship by means of concentrating or minimizing excessive fluid intake; promoting deresuscitation; and changing other variables or continuous infusion targets as needed.

Chlorhexidine Gluconate

Chlorhexidine gluconate (CHG), as either a 0.12% or 0.2% solution, applied to the mouth for oral hygiene up to four times daily throughout the period of intubation reduces VAP. A meta-analysis evaluating 18 randomized controlled trials determined that the use of CHG reduced VAP with an impressive number needed to treat of 17 (Hua 2016). Combined with this efficacy, a small acquisition cost and a minimal adverse effect profile (most commonly including dysgeusia and mouth discoloration) have led to CHG being recommended in many VAP bundles (Andresen 1996). More recently, the role of CHG has come into question because it has been associated with increased bacterial resistance (although the incidence is thought to be low), and several meta-analyses have shown that CHG may increase the mortality risk (Bouadma 2018). The mechanism of increased mortality is unknown, but it is hypothesized to be secondary to aspiration of CHG and development of ARDS (Kampf 2016). Many regimens have been evaluated, but a commonly observed version is 0.12% chlorhexidine gluconate administered as 15 mL, available in unit dose cups, applied to the mouth twice daily throughout the period of MV (Munro 2009, Zuckerman 2016).

Bronchodilators

Bronchodilators are often used in patients receiving MV for the proposed benefits of enhanced mucociliary clearance, optimization of lung mechanics, decreased work of breathing, and reduced pulmonary edema. Anticholinergic agents are used to decrease mucous hypersecretion (Manocha 2006, Chang 2007, Ari 2012, Bassford 2012). Whereas patients with indications such as chronic obstructive pulmonary disease or asthma have primary indications for the use of inhaled agents while receiving MV, IPPV as a primary indication for these agents remains uncertain. Although these agents have been associated with metrics of improved mechanics, these theoretical benefits have not translated to patient-oriented outcomes such as ventilator-free days or reductions in length of stay (Morina 1997, Perkins 2006, Acute Respiratory Distress Syndrome Clinical Trials Network 2011). Although β-2 agonists do carry the theoretical risk of causing tachycardia and arrhythmias, no difference in tachycardia risk has been seen between albuterol and levalbuterol (Asmus 2000, Lam 2003, Scott 2003, Khorfan 2011, Acute Respiratory Distress Syndrome Clinical Trials Network 2011).

Neuromuscular Blocking Agents

In combination with MV, an NMBA is used to improve oxygenation (PaO_2/FiO_2 ratios) and reduce VILI in patients with refractory hypoxemia. An NMBA can reduce ventilator asynchrony. By improving synchrony, elevated airway pressures, which can lead to VILI and associated up-regulation of inflammatory biomarkers, are avoided (Gainnier 2004, Forel 2006, Murray 2016). All patients receiving an NMBA should be treated based on the most recent guidelines, including the use of scheduled eye care with lubricating drops to avoid corneal abrasions and exposure keratitis, and deep sedation (achieved before paralysis) with continuous infusions of opioid analgesics and amnestic sedatives (i.e., propofol, midazolam) (Murray 2016). In addition, pharmacists should evaluate patients on an NMBA for signs of efficacy, defined as improved oxygenation or ventilator synchrony; signs of overblockade, defined as train of four (less than 1–2 twitches of 4 twitches); and lack of appropriate analgesia and sedation, such as lacrimation and diaphoresis (Murray 2016). Of note regarding the train of four, although it is still often used in the ICU, it was not used in either the ACURASYS or ROSE trials and has conflicting literature regarding its overall utility in monitoring the safety and efficacy of neuromuscular blockade (Baumann 2004, Papazian 2010, National Heart, Blood Institute 2019).

Phosphate Replacement

Phosphorus replacement improves diaphragmatic activity and potentially reduces IPPV weaning failure (Agusti 1984, Brunelli 2007, Miller 2020). Large, randomized studies that show the benefits of phosphate repletion for a specific goal are lacking; however, the relationship of phosphorus concentrations with both respiratory failure and worse outcomes in critically ill patients makes phosphorus replacement a reasonable intervention to support IPPV liberation. In general, concentrations greater than 3 mg/dL, using either intravenous or oral replacement strategies, seem to show the most beneficial effects (Gravelyn 1988, Kraft 2005, Zhao 2016, Lemon 2017).

Acetazolamide

Acetazolamide has been proposed as an intervention to correct metabolic alkalosis, which has been associated with hypoventilation and failure to wean. Through increasing the urinary excretion of bicarbonate, acetazolamide can help reverse metabolic alkalosis, but its benefit on clinically meaningful outcomes, such as duration of MV, has yet to be definitively shown (Gallagher 1979, Mazur 1999, Faisy 2010, 2016, Mishra 2016). Acetazolamide is a nonspecific carbonic anhydrase inhibitor having activity in both renal and pulmonary sites, and thus its use may result in a variety of physiologic alterations, especially in critically ill patients (Heming 2012). One recent review recommends that acetazolamide only be considered in patients with significant alkalosis (defined as pH greater than 7.5) with clinically important correlates such as reduced respiration rate. This value may help reduce the inclination for arbitrary optimization of laboratory values without clinically meaningful effects (i.e., "number fixing") (Adamson 2017).

Secretion Management

Patients who are receiving MV are at risk of impaired secretion removal and subsequent infection risk because of impaired mucociliary removal from the endotracheal tube, atelectasis, impaired cough, and medications, such as ketamine-induced hypersalivation (Branson 2007). Secretion management is thus a routine part of care of patients undergoing IPPV. The primary treatments are adequate humidification and suctioning. Mucolytic agents (e.g., saline, acetylcysteine) and anticholinergic agents (e.g., scopolamine, glycopyrrolate) have been used (Branson 2007, Kallet 2013). Anticholinergic agents are associated with delirium, and although they do reduce volume of secretions, they can also lead to hyperviscosity, resulting in secretions that are harder to clear. As such, anticholinergic agents to reduce oropharyngeal secretions (e.g., drooling) may be quite useful, but lower airway secretions may become harder to manage when thickened through the use of these agents. Although various forms of saline have been used to "loosen" thick secretions, mucus generally does not easily absorb topically applied water. The

Patient Care Scenario

A 58-year-old man (weight 80 kg) with a history of asthma, stage 1 chronic kidney disease, and hypertension was intubated 4 days ago for acute respiratory failure secondary to pneumonia. On evaluation today, his weight today is 89 kg. He undergoes discontinuation of fentanyl (150–250 mcg/hour) and midazolam (2–4 mg/hour) for an SBT with the following settings: RSBI 25 breaths/minute/L and minute ventilation of 1 L/minute (average RR 5 breaths/minute, 200 mL V_T). Chest radiography shows diffuse pulmonary edema. His results for the confusion assessment method for the ICU are negative. A cuff leak is detected. His blood gas values after a 30-minute SBT are pH 7.22, partial pressure of CO_2 50 mm Hg, PaO_2 61 mm Hg, and bicarbonate 20 mEq/L. Interpret his performance on his SBT and the possible pharmacotherapeutic interventions as next steps in his care.

ANSWER

His RSBI of 25 breaths/minute/L is below the cutoff of 105 breaths/minute/L, which is associated with extubation success. However, his RR and V_T are low and not likely associated with the ability to be extubated. The low RR and V_T potentially explain his poor blood gas values, indicated by his acidosis, elevated CO_2, and low oxygen. The presence of a cuff leak indicates that he likely will not have issues with post-extubation stridor. His negative results on assessment for confusion in the ICU indicate that delirium was not contributory to his SBT performance. He does demonstrate greater than 10% weight gain since admission and he has pulmonary edema, which may indicate the presence of fluid overload and the need for diuresis or other fluid removal strategies. Perhaps most contributory was his high opioid and benzodiazepine doses over the previous 4 days, which may be a causative factor for his low respiratory drive. He may need a sedation holiday to allow these medications to wash out before his extubation.

1. Fan E, Zakhary B, Amaral A, et al. Liberation from mechanical ventilation in critically ill adults. an official ATS/ACCP Clinical Practice Guideline. Ann Am Thorac Soc 2017;14:441-3.
2. Stollings JL, Foss JJ, Ely EW, et al. Pharmacist leadership in ICU quality improvement: coordinating spontaneous awakening and breathing trials Ann Pharmacother 2015;49:883-91.
3. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation N Engl J Med 1991;324:1445-50.

mechanism of benefit is likely more because of the irritant nature, causing bronchoconstriction rather than true mucolysis (Jelic 2008). Acetylcysteine breaks disulfide bonds in mucus, thereby reducing its viscosity; however, data are extremely limited for its role in mucus clearance with several key adverse effects (Jelic 2008). Acetylcysteine antagonizes both aminoglycosides and ß-lactam antibiotics in vitro and can cause false negative cultures for *Pseudomonas aeruginosa* (Jelie 2008). Acetylcysteine is an irritant that can cause bronchoconstriction and must generally be administered with a $ß_2$-agonist. Given little outcomes data and notable limitations, acetylcysteine should likely be avoided for routine use. Although more often used for secretion management in end-of-life care, scopolamine, atropine eye drops, and glycopyrrolate may also reduce excess secretions through their anticholinergic properties (Clary 2009). In sum, these agents are symptomatic treatment only with limited outcomes data and should be used sparingly in a patient-specific manner.

OTHER ICU PULMONARY PROCEDURES

Thoracentesis

Thoracentesis is a procedure that involves the insertion of a needle into the pleural space to remove fluid either to diagnose the cause of a pleural effusion or to therapeutically drain larger effusions with potential to cause respiratory compromise (Figure 11) (Thomsen 2006). The Light criteria can be used to delineate whether the fluid is transudative or exudative, which may help guide therapy, such as using antibiotics for pneumonia (Light 2002). Criteria and etiology are summarized in Table 1. As a minimally invasive procedure, thoracentesis is generally considered safe, even in settings of coagulopathy, and the decision to administer platelets or anticoagulant reversal agents is highly patient specific. Tension pneumothorax, from the needle puncturing the lung, is one of the biggest safety concerns (Thomsen 2006, Pathak 2017).

Table 1. Light Criteria

Criteria	Transudate	Exudate
Pleural fluid protein/serum protein ratio	<0.5	>0.6
Pleural fluid LDH/serum LDH ratio	<0.6	>0.5
Pleural fluid LDH	<2/3 ULN for serum	>2/3 ULN for serum
Etiology	• Congestive heart failure • Cirrhosis • Pulmonary embolism • Nephrotic syndrome	• Pneumonia • Cancer • Trauma • Systemic lupus erythematosus • Fluid overload

LDH = lactate dehydrogenase; ULN = upper limit of normal.

Light RW. Clinical practice. Pleural effusion. N Engl J Med 2002;346:1971-7.

Bronchoscopy

Bronchoscopy is a procedure that involves the insertion of a thin tube with a light and camera for visualization of the tracheobronchial tree (Figure 12). This procedure may be used both diagnostically and therapeutically (Table 2) (Esquinas 2013, La Combe 2016). Bronchoscopy can be associated with decreased respiratory and cardiac function intraprocedurally (especially related to medications used for procedural

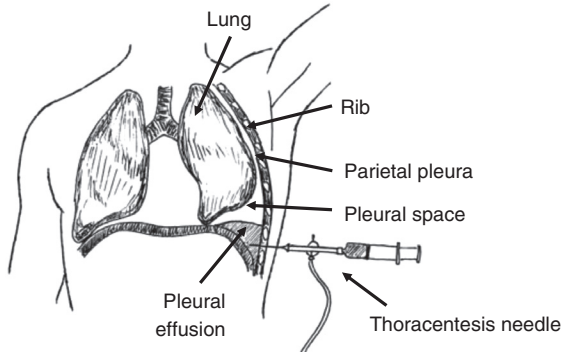

Figure 11. Schematic of a thoracentesis.

Information from: Thomsen TW, DeLaPena J, Setnik GS. Videos in clinical medicine Thoracentesis. N Engl J Med 2006;355:e16.

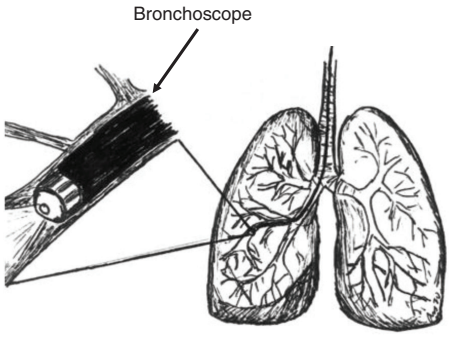

Figure 12. Schematic of a bronchoscopy.

Information from: Esquinas A, Zuil M, Scala R, et al. Bronchoscopy during noninvasive mechanical ventilation: a review of techniques and procedures. Arch Bronconeumol 2013;49:105-12.

Table 2. Indications for Bronchoscopy

Indication	Visualization	Biopsy	Therapy
Aspiration	✓	✓	✓
Infection	✓		✓
Atelectasis	✓		✓
Airway management	✓		✓
Airway assessment, such as for burns	✓		✓
Foreign body	✓		✓
Hemorrhage	✓		✓

sedation), and risks and benefits in hemodynamically unstable patients must be carefully weighed (Ergan 2018). For elective bronchoscopy, holding warfarin/full anticoagulation and normalized laboratory coagulation values are recommended; in the case of emergency bronchoscopy, rapid reversal may be warranted based on patient-specific risk factors (Douketis 2012, Pathak 2017, Youness 2017). Topical lidocaine or benzocaine have been used to alleviate patient discomfort; however, the risk of methemoglobinemia is present, and some studies have shown no difference as an addition to appropriate procedural sedation (Stolz 2005, Kwok 2008).

Chest Tubes

Insertion of chest tubes or thoracostomy tubes are a common procedure with applications ranging from emergency use to evacuate hemothorax to routine use for postoperative chest drainage after elective surgery (Figure 13). Indications include pneumothorax, penetrating chest trauma, blunt chest trauma, chylothorax, pleural effusion, post-operatively, and empyema. In general, a tube is placed into the intrapleural space to facilitate breathing by draining fluid (Miller 1987, Kwiatt 2014). Both digital and three-chamber (using wet or dry suction) systems may be used to facilitate the drainage process. The large bore nature of surgically placed chest tubes makes them quite painful, thus they are listed in the guidelines for PADIS procedures–those that may cause pain, agitation, delirium, immobility, or sleep disruption. Pre- and periprocedural pain assessment and pre-emptive analgesia with the use of opioids is recommended. Strategies often include both topical (e.g., lidocaine patches) and systemic analgesia (Miller 1987, Kwiatt 2014, Porcel 2018). Furthermore, evaluation of fluid output is recommended to assess the appropriateness of anticoagulation therapy.

Pleurodesis

Pleurodesis is a procedure conducted to create the symphysis of the parietal and visceral pleura and is used to prevent

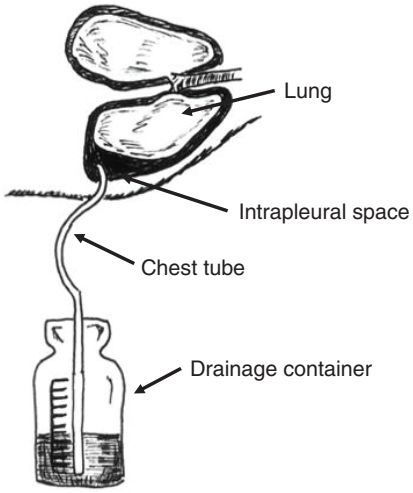

Figure 13. Schematic of a chest tube.

Information from: Miller KS, Sahn SA. Chest tubes. Indications, technique, management and complications. Chest 1987; 91:258-64.

recurrent spontaneous pneumothorax and pleural effusions, often in the setting of malignancy (Mierzejewski 2019) (Figure 14). Pleurodesis may be achieved by direct injury to the pleura using mechanical or chemical methods through administration of sclerosing agents, such as talc, bleomycin, and tetracycline antibiotics (Mierzejewski 2019). Application of a sclerosing agent sets off an inflammatory process leading to activation of pleural cells, the coagulation cascade, fibrin chain formation, and fibrinogenesis, all leading to the

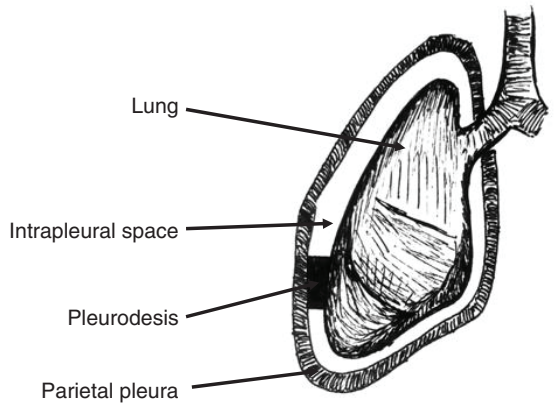

Figure 14. Pleurodesis schematic.

Information from: Mierzejewski M, Korczynski P, Krenke R, et al. Chemical pleurodesis—a review of mechanisms involved in pleural space obliteration. Respir Res 2019; 20:247.

bonding of the pleura (Mierzejewski 2019). Talc has been repeatedly shown to be the most efficacious agent in terms of successful pleurodesis; however, universal acceptance has been slower because of its temporal association with ARDS. Therefore, despite lower efficacy rates, tetracyclines are commonly used (Webb 1992, Hartman 1993, Walker-Renard 1994, Viallat 1996). Pleurodesis is often painful, and procedural opioid/anxiolytic agents are warranted. In addition, intrapleural administration of lidocaine is recommended (Antunes 2003).

Tracheostomy

A tracheostomy tube is placed surgically into the trachea and can be either open to air or attached to a ventilator (Figure 15). A tracheostomy tube can be temporary or permanent and facilitates airway protection and weaning from the ventilator. Tracheostomy can provide increased quality of life because it provides the patient with the ability to eat and speak. A Passy Muir valve may ultimately be placed, which allows for the patient to speak (Engels 2009). Tracheostomy may be performed at the bedside and is considered to pose a low bleeding risk. Depending on patient-specific factors, antiplatelet therapy and anticoagulation therapy may be continued. The decision to hold therapy is based on specific assessment of bleeding and clotting risk and the ability to plan patient care around the procedure (Pathak 2017). Although endotracheal intubation avoids the surgical complications associated with tracheostomy, such as bleeding, nerve/tracheal wall injury, and wound infection, tracheostomy does offer specific benefits, including improved patient comfort, easier oral care, reduced sedation/analgesia requirements, reduced unplanned extubation, and faster rehabilitation and ventilator weaning. Timing and patient selection remain areas of ongoing discussion; however, for cases in which a patient is predicted to have prolonged ventilator requirements, tracheostomy becomes preferable. Although minor postoperative pain is expected and may be managed symptomatically, the pharmacist may expect reduced analgesia and sedation requirements in a clinical setting (Terragni 2014, Bice 2015).

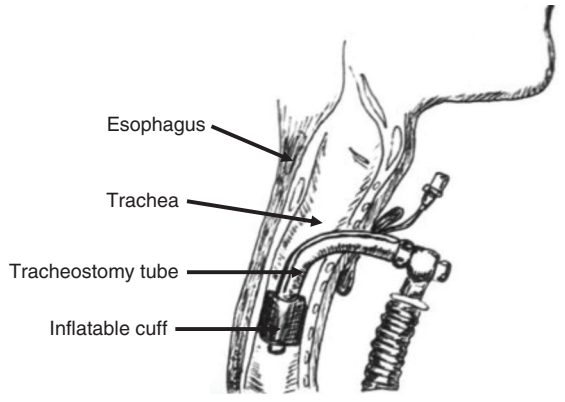

Figure 15. Tracheostomy schematic.

Information from: Pathak V, Allender JE, Grant MW. Management of anticoagulant and antiplatelet therapy in patients undergoing interventional pulmonary procedures Eur Respir Rev 2017;26:170020.

Practice Points

Clinical pharmacist face many challenges in their efforts to optimize pharmacotherapy for patients receiving MV. As a result, guidelines/recommendations, best practices, new indications for existing medications, and new roles for pharmacists continue to evolve.

- **A working understanding of the principles of MV supports the development of timely and effective pharmacotherapeutic interventions. Furthermore, pharmacists play a key role in quality improvement and protocol implementation for critically ill patients on MV.**
- **When evaluating a patient's respiratory support, the type of MV (invasive vs. noninvasive), mode (e.g., PS, VC), and key settings (e.g., FiO_2, PEEP, RR) provide a clinical picture of the patient's status.**
- **The use of MV is associated with a host of consequences that contribute both to prolonged duration of intubation and prolonged ICU length of stay as well as other deleterious outcomes. Thus, reducing the duration of MV reduces the associated complications and may improve patient outcomes.**
- **Patients often experience failure on an SBT because of medication-related issues, including but not limited to oversedation, agitation, fluid overload, or restrictive and obstructed airways.**
- **Both MV and hemodynamic status are often intertwined, and careful hemodynamic assessment in patients undergoing changes in respiratory support is warranted.**

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Self-Assessment Questions

1. A 72-year-old man with community acquired pneumonia (CAP) is intubated for hypoxemic respiratory failure and increased work of breathing. In keeping with the three primary goals of mechanical ventilation, which one of the following is best to recommend for this patient?
   A. Appropriate antibiotic therapy for CAP; mechanical ventilation to alleviate hypoxemia; minimizing duration of mechanical ventilation
   B. Inhaled bronchodilators for hypoxemia; achieving appropriate peak pressures; reducing ventilator induced lung injury (VILI)
   C. Reversal of hypoxemia; resolution of tachypnea; avoiding patient discomfort
   D. Reducing work of breathing; bronchodilators for hypoxemia; minimizing patient-ventilator asynchrony

Questions 2 and 3 pertain to the following case.

B.M. is a 64-year-old man with a medical history of hypertension, tobacco abuse, chronic obstructive pulmonary disease, and hypercholesterolemia. He is intubated for the following arterial blood gas: pH 7.23 $paCO_2$ 58 paO_2 68 HCO_3 23.

2. On the basis of his medical history, which one of the following is most likely to require B.M. to have mechanical ventilation for supportive care?
   A. Hyperventilation
   B. Ventilation-perfusion mismatch
   C. Increased fraction of inspired oxygen
   D. Diffusion impairment
3. On day 2 of intubation, B.M. begins to show signs of ventilator dyssynchrony (i.e., increased sedation requirements, high peak pressure alarms from the machine). On the basis of his medical history, which one of the following assessments is the most likely to reveal the etiology of B.M.'s discomfort?
   A. Inspiratory hold
   B. Pressure support trial
   C. Rapid shallow breathing index
   D. T-piece trial
4. A 54-year-old woman with no contributory medical history is intubated for airway protection. Today, she underwent discontinuation of fentanyl and propofol for an SBT with the following RSBI 125 breaths/min/L. Chest radiography is notable for diffuse pulmonary edema; her admission weight was 70 kg while today she weighs 82 kg. She was CAM-ICU negative. She has a cuff leak. Which one of the following is best to recommend for this patient?
   A. The addition of dexmedetomidine to manage anxiety and rapid respiratory rate
   B. Fluid removal prior to extubation to manage the presence of fluid overload
   C. Sedation holiday to allow fentanyl/propofol to 'wash-out' from her system
   D. Albuterol for potential presence of restrictive airway disease
5. A 67-year-old man is intubated for acute respiratory distress syndrome. Despite high settings on PRVC (PEEP 15 cmH2O, FiO_2 100%), his oxygenation is critically low (PaO_2/FiO_2 ratio <100). Currently, the patient is sedated to RASS -4 to -5 to facilitate oxygenation and is not initiating his own breaths. His care team is considering switching the patient from PRVC to APRV and asks about the best course of action regarding sedation level when switching between PRVC and APRV. Given how spontaneous breaths contribute to minute ventilation in APRV and PRVC, which one of the following is best to recommend for this patient?
   A. Continue the current sedation level.
   B. Change to RASS 0 to -2.
   C. Add cisatracurium.
   D. Decrease the respiratory rate.
6. A 65-year-old man is intubated for drug overdose and aspiration pneumonia. On day 2, the team reports the patient's ABG reads as: pH 7.35 $paCO_2$ 45 paO_2 106 HCO_3 23. His current ventilator settings are PRVC with a set RR 14 breaths/minute, tidal volume 450 mL/breath (6 mL/kg), FiO_2 40%, and PEEP 15 cm H2O. In an effort to manage worsening oxygenation and ARDS, the patient is switched from PRVC to APRV as a ventilator mode. After 24 hours on APRV, his arterial blood gas values are: pH 7.29 $paCO_2$ 54 paO_2 102 HCO_3 22 with a PaO_2/FiO_2 128. The team discusses intervening on the $paCO_2$. Which one of the following is best to recommend for this patient?
   A. Initiate acetazolamide to correct acidosis.
   B. Sedate to RASS -3 to decrease spontaneous respirations.
   C. Switch to PRVC for better $paCO_2$ management.
   D. No intervention is necessary because permissive hypercapnia is acceptable.
7. A 58-year-old man was intubated 48 hours ago for mixed hypoxic-hypercapnic respiratory failure. Today, his ABG reads as: pH 7.29 $paCO_2$ 47 paO_2 48 HCO_3 23. His current ventilator settings are pressure-regulated volume control with a RR 12 breaths/minute, tidal volume 400 mL/breath (6mL/kg predicted body weight), FiO_2 40%, and PEEP 8 cm H_2O. Which one of the following is best to recommend for this patient?
   A. Increase both the FiO_2 and PEEP.
   B. Increase his minute ventilation.
   C. Increase his respiratory rate and tidal volume.
   D. Increase FiO_2 but decrease the PEEP.

8. A 48-year-old woman was intubated 48 hours ago for mixed hypoxic-hypercapnic respiratory failure. Today, her ABG reads as: pH 7.24 $paCO_2$ 68 paO_2 98 HCO_3 28. Her current ventilator settings are pressure-regulated volume control with a RR 14 breaths/minute, tidal volume 350 mL/breath (6mL/kg), FiO_2 40%, and PEEP 5 cm H_2O. Which one of the following is best to recommend for this patient?

   A. Increase both the FiO_2 and PEEP.
   B. Increase her respiratory rate but reduce the tidal volume.
   C. Increase her minute ventilation.
   D. Increase the FiO_2 but decrease the PEEP.

Questions 9 and 10 pertain to the following case.

P.O., a 20-year-old man (weight 73 kg), has a medical history of asthma for which he uses an albuterol inhaler as needed. He is intubated after a motor vehicle collision and is managed on continuous infusions of fentanyl and propofol. P.O.'s chest radiography is clear except for some signs of bronchial wall thickening.

9. On day 4 of admission, P.O. experiences failure of an SBT (RSBI 185 breaths/min/L with obvious signs of increased work of breathing). Which one of the following is the most likely cause of P.O.'s respiratory failure?

   A. Delirium
   B. Fluid overload
   C. Restrictive airway disease
   D. Anxiety

10. P.O. has a spontaneous breathing trial performed, and the following parameters are recorded: RSBI 200 breaths/min/L on a T-piece trial. Upon physical assessment, the patient is euvolemic, able to follow commands during SBT, and initiates his own breaths on PRVC. The care team requests the pharmacist's input regarding the use of dexmedetomidine for extubation. Which one of the following is best to recommend for P.O.?

    A. PS SBT has been shown to have a better negative predictive value of extubation success compared to T-piece trials, so an SBT using PS should be conducted first prior to initiation of any drug therapy.
    B. Because of the performance on the T-piece trial, the patient is unlikely to benefit from dexmedetomidine and likely will benefit from another day on the ventilator.
    C. The patient does not need dexmedetomidine because he is able to follow commands and have appropriate respiratory drive.
    D. A T-piece trial should be repeated with dexmedetomidine to mitigate anxiety as a potential reason for why the patient failed the T-piece trial.

11. A woman with CHF (LVEF 25%) is intubated, and her PEEP is increased from 5 to 10 cm H_2O to improve alveolar recruitment. The team notes decreased milrinone and norepinephrine requirements. Which one of the following best evaluates this patient's reaction to the increased positive pressure?

    A. Reduced left ventricular afterload
    B. Reduced right ventricular output
    C. Decreased stroke volume
    D. Increased pulmonary vascular resistance

12. A 66-year-old woman who has been intubated for 8 days is being assessed for extubation. Which one of the following is best to recommend for this patient?

    A. A cuff leak test is not necessary.
    B. Administer methylprednisolone 20 mg every 4 hours x 3 doses.
    C. Perform a cuff leak test and delay extubation for a value < 110 mL.
    D. Perform a cuff leak test and delay extubation to give steroids for a value < 110 mL.

13. A 56-year-old man (BMI 45 kg/m^2) is brought to the ED with respiratory distress of unknown etiology. He has been placed on nasal cannula at 6 L/min and shows obvious work of breathing, and the team is concerned about having to intubate. Which one of the following oxygen delivery systems is best to recommend for this patient?

    A. Simple face mask at 6 L/min
    B. Non-rebreather mask at 4 L/min
    C. Non-rebreather mask at 8 L/min
    D. HFNC at 30 L/min providing 2 cm H_2O PEEP

14. A 57-year-old woman experiences failure of her SBT. Her laboratory parameters are: magnesium 1.8 mg/dL, potassium 3.7 mEq/L, Ca 8.3 mg/dL, Na 134 mEq/L, and phosphorus 2.2 mg/dL. Which one of the following is the best intervention to support extubation success and why it is justified in this patient?

    A. Phosphate replacement; diaphragmatic weakness
    B. Magnesium replacement; delirium
    C. Potassium replacement; cardiac instability
    D. Sodium replacement; altered mental status

15. A patient is about to undergo large-bore chest tube placement. Which one of the following is the best analgesia regimen to recommend for this patient?

    A. Pre-emptive IV acetaminophen and PRN opiate therapy post-procedure
    B. Pre-emptive IV acetaminophen and PRN topical lidocaine post-procedure
    C. Pre-emptive IV opioid therapy with no PRN therapy post-procedure
    D. Pre-emptive IV opioid therapy and PRN opiate therapy post-procedure