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Mechanical Ventilation: State of the Art

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Abstract

Mechanical ventilation is the most used short-term life support technique worldwide and is applied daily for a diverse spectrum of indications, from scheduled surgical procedures to acute organ failure. This state-of-the-art review provides an update on the basic physiology of respiratory mechanics, the working principles, and the main ventilatory settings, as well as the potential complications of mechanical ventilation. Specific ventilatory approaches in particular situations such as acute respiratory distress syndrome and chronic obstructive pulmonary disease are detailed along with protective ventilation in patients with normal lungs. We also highlight recent data on patient-ventilator dyssynchrony, humidified high-flow oxygen through nasal cannula, extracorporeal life support, and the weaning phase. Finally, we discuss the future of mechanical ventilation, addressing avenues for improvement.

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In the 16th century, Andreas Vesalius provided what can be considered one of the first descriptions of endotracheal intubation and artificial ventilation, describing the insertion of a tube of reed into an animal's trachea and blowing air into the lungs to keep the animal alive.[1,2] Four centuries later, the iron lung[3] was the first negative-pressure ventilator successfully used in clinical practice. However, care of the patient was difficult using the iron lung because the patient's body was entirely enclosed in a metal tank. Hence, techniques that were remarkably similar to what Vesalius used were employed during the golden era of mechanical ventilation (MV), which was inaugurated during the poliomyelitis epidemics of the early 1950s. In Blegdams Hospital, Copenhagen, Denmark, Bjørn Ibsen, an anesthesiologist trained in Boston, Massachusetts, recommended tracheostomy and positive-pressure ventilation to treat patients with paralytic poliomyelitis.[4] Virtually overnight, mortality for these patients decreased from 87% to 40%.[5] Approximately 1500 medical students provided manual ventilation by squeezing rubber bags connected to endotracheal tubes for an estimated 165,000 hours.[5] For logistical reasons, these patients all received care in the same ward, essentially the first intensive care unit (ICU).

The difficulties with manual ventilation highlighted the need for mechanical devices, and both Claus Bang, a Danish physician, and Carl-Gunnar Engström, a Swedish anesthesiologist, developed the first efficient mechanical ventilators.[6] The first arterial blood gas analyzers were built shortly thereafter. The next major step in the evolution of MV was the use of positive end-expiratory pressure (PEEP), mainly encouraged by the identification of the adult (acute) respiratory distress syndrome (ARDS) by Ashbaugh et al.[7] The Servo 900A (Siemens-Eléma) released in 1972 was the first mechanical ventilator with PEEP, and the servo valves controlling flow allowed the introduction of new modes of ventilation such as pressure-controlled ventilation and pressure support ventilation (PSV).[8] Ventilators became progressively more compact, user-friendly, and electronically based than pneumatic-based ventilators and incorporated a host of modes of ventilation and advanced monitoring capabilities.[9]

A recent epidemiological study estimated that in the United States, approximately 310 persons per 100,000 adult population undergo invasive ventilation for nonsurgical indications.[10] Despite this extensive use of MV, no precise recommendations exist summarizing when to initiate MV for acute respiratory failure. The main indications are (1) airway protection for a patient with a decreased level of consciousness (eg, head trauma, stroke, drug overdose, anesthesia), (2) hypercapnic respiratory failure due to airway, chest wall, or respiratory muscle diseases, (3) hypoxemic respiratory failure, or (4) circulatory failure,

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in which sedation and MV can decrease the oxygen cost of breathing.

In this review, we provide an update on the principles underlying the management of MV for critically ill adult patients. We summarize the physiologic basis of MV, the interaction with the patient's physiology, and its major adverse effects and complications. We describe ventilation for specific patient groups such as those with ARDS[11] and chronic obstructive pulmonary disease (COPD), followed by an overview of the weaning phase. Finally, we briefly address the future of MV.

ARTICLE HIGHLIGHTS

- Mechanical ventilation is "a necessary evil": a lifesaving technique but with important potential complications.
- Decades of physiologic and clinical research have led to the concept of "protective ventilation" to minimize ventilation-induced lung injury but also minimize oxygen toxicity and optimize hemodynamics.
- Patient-ventilator dyssynchronies are frequent and associated with worse outcomes, but it is not clear whether they cause the poor outcomes or are a marker of severity of the underlying condition.
- Mechanical ventilation is part of a global strategy ("bundle") and not a stand-alone treatment: sedation management, etiologic treatment, physiotherapy, and prevention of muscle loss are all important considerations in the ventilated patient.
- Minimizing the length of mechanical ventilation is the best way to minimize complications: as soon as mechanical ventilation is initiated, clinicians should consider how and when to discontinue its use; and throughout its course, decide which weaning strategy is most appropriate.

BASIC PHYSIOLOGY

Understanding of the basic physiology of respiratory mechanics is necessary to optimally apply MV. Much of our progress in understanding and managing acute respiratory diseases comes from this understanding. The physiologic measurements obtained in the ventilated patient can be considered to be detailed pulmonary function testing and are available on a breath-to-breath basis.[12]

The forces at play during ventilation at any point in time are described by the equation of motion of the respiratory system. Pressure, volume, and flow changes during inspiration and expiration can be described by the simplified equation of motion of the respiratory system (Figure 1): $P_{aw} = P_0 + (R \times \text{flow}) + (Vt \times E_{RS})$, where P_{aw} = airway pressure (at the airway opening), P_0 = initial alveolar pressure, R = resistance to flow, Vt = tidal volume, and E_{RS} = elastance of the respiratory system. Each term of this equation impacts the pressure applied to the airways.

P_0 is the alveolar pressure at the beginning of inspiration, which can be atmospheric pressure (termed *zero*) or greater than atmospheric (called *positive*). In patients with airway obstruction (eg, COPD), the expiratory time may be too short to allow the respiratory system to return to its relaxation volume. This aspect of airway obstruction can lead to intrinsic PEEP or auto-PEEP, a situation in which the alveolar pressure at the end of expiration is higher than the set PEEP. The airway pressure, measured by an end-expiratory occlusion (in a passive patients), is referred to as total PEEP.

E_{RS} reflects the elastic characteristics of the respiratory system and is the inverse of compliance of the respiratory system (C_{RS}): $E_{RS} = 1/C_{RS}$. The airway pressure measured during an end-inspiratory occlusion is referred to as the plateau pressure (Pplat) and is a measure of the alveolar pressure, since the pressure drop due to airway resistance is zero at zero flow. Based on the equation of motion in the absence of flow (inspiratory pause), $C_{RS} = Vt/(Pplat - P_0)$.

Resistance (R) represents the pressure difference required to generate a given flow. The resistance can be calculated in situations of constant (square) inspiratory flow as the difference between the peak inspiratory pressure and Pplat, divided by the flow (R = [peak pressure − Pplat]/flow). The major part of the inspiratory resistance is often dominated by the resistance of the endotracheal tube.

Two simple maneuvers (end-inspiratory and end-expiratory occlusions) allow determination of the major physiological abnormalities of the respiratory system, which are characterized by high resistance (R) and elevated total PEEP in COPD (or asthma), or high E_{RS} (low C_{RS}) in ARDS (Figure 2).

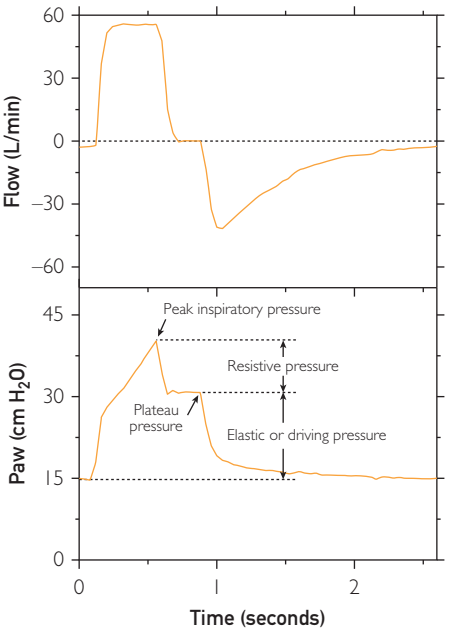

FIGURE 1. Explanation of ventilator waves. Paw = airway pressure.

WORKING PRINCIPLES OF MV MODES

Phase Variables of a Breathing Cycle

The modes of MV are commonly defined by 4 elements determining the phases of the respiratory cycle (Table 1). The trigger phase initiates a breath. When the ventilation is fully controlled, the trigger variable is time, ie, a breath is initiated at fixed intervals. When the ventilator synchronizes the breath delivery with a signal related to the patient's effort, inspiration is initiated when a given flow or pressure decrease is detected by the ventilator. The target (or controlled) phase is the pressure or flow that will be maintained until the inspiration ends. The cycling phase determines the end of the inspiratory phase. A pressure, flow, or a preset time can cycle the breath. When the variable reaches the preset value, the passive expiratory phase starts. The expiratory control variable is usually a pressure (PEEP). Any given breath can involve a combination of the patient's breathing effort and a targeted pressure/flow delivered by the ventilator.[13] Breaths can therefore be (1) fully controlled—trigger and cycling are time controlled, the target variable is reached passively, and the patient does not actively contribute to the breath; (2) partially supported or assisted—a combination of ventilator assistance and patient effort occurs in the same cycle; (3) unassisted—when the inspiratory flow is generated entirely by the patient's respiratory muscles (Table 1).

Influence on Respiratory Muscle Activity and Importance of Synchrony

Measures of a patient's effort are usually not available during MV. Complex measurements are needed to determine the patient's work of breathing or the pressure-time product, both requiring an esophageal catheter[14]; the oxygen cost of breathing requires measurements of oxygen consumption. During respiratory distress, the patient's work of breathing can be increased up to 6-fold[15]; a major goal of MV is to reduce this work. The patient's respiratory drive is modulated via chemoreceptors and modulated by sedation and by PaO_2, pH, and $PaCO_2$. The trigger sensitivity and the inspiratory peak flow also have an important influence on the respiratory drive and work of breathing.[16-19]

A fundamental but as yet unresolved question is to what extent a patient's work of breathing should be reduced by a particular ventilatory strategy. It is important to relieve dyspnea, decrease the oxygen consumption of the respiratory muscles, and avoid injury to these muscles. However, there is a growing body of evidence suggesting that excessive unloading can lead to muscle dysfunction and atrophy, with subsequent weaning difficulties.[20] During the acute phase of the patient's illness, the patient's effort needs to be decreased or suppressed. Over the recovery period, ascertaining the optimal balance between the patient's effort and ventilator assistance is challenging for the clinician, in part because of a lack of adequate monitoring and also a lack of data about the optimum ratio of effort to assistance.

Patient-ventilator dyssynchrony, defined as a mismatch between the patient's inherent inspiratory and expiratory times and those delivered by the ventilator, is a frequent problem during MV, occurring in about one-third of patients.[21-25] There are a number of different types of dyssynchronies during invasive[24-26] and noninvasive[27,28] ventilation,

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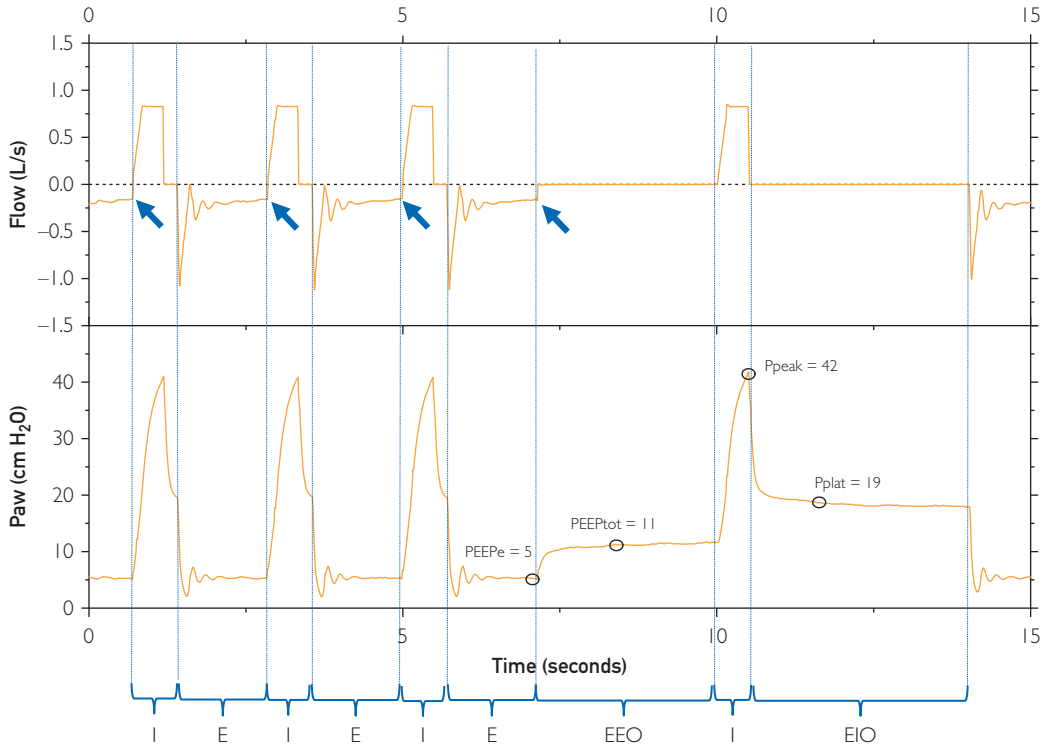

FIGURE 2. Ventilator waveform and values in a patient undergoing volume assist-control ventilation showing expiration flow limitation. Note typical sign of expiratory flow limitation on the flow tracing: during the expiration phase, the flow waveform reaches a peak higher than −1 L/s and abruptly returns to very low values and oscillates around this value until the next inspiration. The end of expiration is interrupted by the next insufflation before flow reaches zero (arrows), indicating dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP); total PEEP (PEEPtot) is 11 cm H_2O (obtained during end-expiratory occlusion [EEO]). In a normal patient, the flow waveform would trace a quasi-exponential curve from the peak to 0. Plateau pressure (Pplat) is assessed during the end-inspiratory occlusion (EIO: 19 cm H_2O), resulting in a driving pressure of 8 cm H_2O (Pplat − PEEPtot). The inspiratory flow is 0.8 L/s, resulting in high airway resistance of 29 cm H_2O per L/s ([peak airway pressure (Ppeak) − Pplat]/flow = [42 − 19]/0.8 = 28.75). In an intubated adult patient with normal lungs, resistances are usually less than 10 cm H_2O per L/s. E = passive expiration; I = inspiration due to ventilator insufflation; Paw = airway pressure; PEEPe = external PEEP.

which are summarized in Table 2. Figure 3 presents an example of a ventilator monitor displaying reverse triggering with double cycling. Often, these dyssynchronies indicate a mismatch between the ventilatory needs of the patient and the amount of ventilation delivered. Although association does not imply causality, patients with greater numbers of dyssynchronies have poorer outcomes including longer durations of ventilation, longer ICU stays, and higher mortality.[26,29,30] In some cases, this worse outcome may be explained by increased Vts, breath stacking, intrinsic PEEP,[31] or regional hyperinflation,[32] but dyssynchronies may also be a marker of the severity of the underlying lung pathophysiology. Although improving patient-ventilatory synchrony makes intuitive sense, we lack definitive data proving that it improves patients' outcomes.

COMPLICATIONS OF MV

Mechanical ventilation is often lifesaving but is associated with serious complications, in part because it is delivered to patients at high risk of lung or cardiac compromise. These complications may be related to the direct mechanical effects of the intrathoracic pressures generated by the ventilator, to alveolar and systemic inflammation, or to neural stimulation. There

TABLE 1. Main Ventilator Modes and Settings

Mode	Variable									
	Trigger	Cycling	Inspiratory pressure	Tidal volume	Respiratory rate	Minute ventilation	Plateau pressure	Driving pressure	PEEP	FIO_2
Ranges of values or settings	*1 to 5 L/min −0.5 to −3 cm H_2O*	*1 second 30%-70% peak flow*	*10-30 cm H_2O*	*~200-600 mL 4-8 mL/kg PBW*	*10-35 min^{-1}*	*~7-12 L/min*	*15-35 cm H_2O*	*8-20 cm H_2O*	*0-22 cm H_2O*	*0.21-1.0*
A/C in volume (or VC-CMV)	Time (controlled cycles) Flow or pressure (assisted cycles)	Time	Dep Var	V	V/P	Dep Var	Dep Var	Dep Var	V	V
A/C in pressure (or PC-CMV)	Time (controlled cycles) Flow or pressure (assisted cycles)	Time	V	Dep Var	V/P	Dep Var	V	V	V	V
PSV (CSV)	Flow or pressure	Flow	V	Dep Var	P	P	V/P	V/P	V	V
SIMV (VC or PC-IMV)	Time (controlled cycles) Flow or pressure (assisted cycles)	Time Flow	V/P	V/P	V/P	Dep Var	V/P	V/P	V	V
PRVC (PC-CMV)	Time (controlled cycles) Flow or pressure (assisted cycles)	Time	V/P	V/P	V/P	Dep Var	V	V	V	V
APRV (PC-IMV)	Time (controlled cycles)	Time	V	Dep Var	V/P	Dep Var	V	V	V	V
PAV (CSV)	Flow or pressure	Flow	P (in proportion to inspiratory effort)	P	P	P	NA	NA	V	V
NAVA (CSV)	EaDi	EaDi	P (in proportion to inspiratory effort)	P	P	P	NA	NA	V	V
CPAP (CSV)	Flow or pressure	Flow or pressure	V	P	P	P	NA	NA	V	V
Suggested settings	Minimal value with no autotriggering	High % in obstructive lung disease, low in restrictive disease	NA	6 mL/kg PBW	NA	NA	Keep <30	Less than ~14 associated with better outcome	≥5	Minimal to keep SpO_2 90%-94%

Color	Meaning
P	Controlled by the patient
V	Controlled by the ventilator
V/P	Can be controlled either by the patient or the ventilator
Dep Var	Dependent variable to be monitored (dependent on respiratory mechanics and effort)

A/C = assist-control; APRV = airway pressure release ventilation; CMV = continuous mandatory ventilation; CPAP = continuous positive airway pressure, with no inspiratory assistance above the set pressure level; CSV = continuous spontaneous ventilation; Dep Var = dependant variable; EaDi = electrical activity of the diaphragm; FIO_2 = inspired fraction of oxygen; IMV = intermittent mandatory ventilation; NA = not applicable; NAVA = neurally adjusted ventilatory assist (see text); P = patient; PAV = proportional assist ventilation (see text); PBW = predicted body weight; PC = pressure control; PEEP = positive end-expiration pressure; PRVC = pressure-regulated volume control, which delivers pressure-targeted breaths, varying from breath to breath to reach a target volume; PSV = pressure support ventilation; SIMV = synchronized intermittent mandatory ventilation, which mixes mandatory breaths and pressure support breath (PSV) each minute; SpO_2 = pulsed oximetry oxygen saturation; V = ventilator; VC = volume control.
Abbreviations adapted from *Respir Care*.[13]

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is evidence of cross-talk between the lung and the brain and between the lung and the kidneys, all influenced by MV.[33,34] Many of the complications of MV can potentially be avoided or minimized. This factor is important from a clinical perspective and is a major area of current research.

Initiation of MV

Endotracheal intubation is a critical procedure in which patients are at risk of respiratory and/or circulatory compromise.[35,36] Before intubation, the patient should be assessed for factors indicating a possible difficult intubation; there are specific scoring systems for the ICU.[37] Preoxygenation is essential, and different techniques such as noninvasive ventilation (NIV)[38] or high flow delivered via nasal cannula have been proposed for patients with the most severe disease. To avoid gastric aspiration, rapid-sequence intubation using a sedative drug and a neuromuscular blocking agent is often recommended.[39] Recommendations and algorithms have been developed for patients with a "difficult airway".[40,41]

Hemodynamic Effects

Positive-pressure ventilation has long been known to have hemodynamic effects through heart-lung interactions. These effects have been better understood, managed, and often prevented over the past few decades by an increased understanding of the following mechanisms. First, high intrathoracic pressure, especially high plateau pressures can negatively impact right ventricular afterload and function.[42] Our understanding of auto-PEEP and the use of protective lung ventilation have markedly reduced the incidence of hemodynamic complications through the use of lower volumes and pressures.[43,44] Echographic studies in patients with ARDS have reported a prevalence of acute cor pulmonale of about 22%,[45,46] which is still quite high, but markedly lower than previously reported.[44,47] Second, hypotensive effects of sedative agents acting via negative inotropy, vasodilation, or central mechanisms are managed by appropriate use of vasoactive drugs or fluids. Third, the use of partial ventilatory assist reduces intrathoracic pressures and minimizes sedation needs, facilitating the hemodynamic tolerance of MV. Finally, pulmonary hypertension and PEEP, especially in patients with ARDS, can result in a right-to-left shunting across a patent foramen ovale and worsen hypoxemia in up to 20% of patients with ARDS.[48]

Complications of Sedation

In the early phase of MV, sedation with or without paralysis is often required, especially for patients with shock or ARDS or for those "fighting the ventilator."[49] The slow metabolism of sedative agents may unduly prolong the duration of MV and lead to detrimental short- and long-term outcomes.[50,51] Each sedative agent has specific effects, and the appropriate choice of the type and dose of sedative drugs may impact outcome. Data suggest that benzodiazepines are particularly associated with poorer long-term outcomes.[52] Propofol is frequently used because of a relatively short half-life, but there are concerns associated with prolonged infusion.[53] Dexmedetomidine has been proposed as a promising alternative to usual sedation because it reduces the rate of delirium,[54,55] but results from clinical trials have not been consistent. If sedation cannot be avoided, it is important to carefully monitor the depth of a patient's sedation and to use a sedation protocol, including daily interruption of sedation to avoid a state of deep sedation.[56,57]

Oxygen Toxicity

Mechanical ventilation allows patients to receive a fraction of inspired oxygen (FIO_2) of up to 1.0, which may be necessary for patients with severe hypoxemia. However, high levels of oxygen have toxic effects, which have been a concern since the early days of MV.[58] In low ventilation-perfusion ratio lung units, high FIO_2 can lead to reabsorption atelectasis,[59] which can be minimized using higher levels of PEEP.[60] Oxygen also has extrapulmonary effects—it can decrease cardiac output by decreasing parasympathetic tone[61] and increasing vascular resistance, and it has vasoconstrictive effects on cerebral and coronary perfusion.[62,63] Several studies have suggested an independent association between hyperoxemia and hospital mortality in some groups of patients (eg, those with cardiac arrest or stroke).[64] Clinicians, however, tend to be much more sensitive to hypoxemia than to hyperoxemia. Recent preliminary

TABLE 2. Main Patient-Ventilator Dyssynchronies and Interactions

Dyssynchrony or patient-ventilator interaction	Description	Pathophysiology	Risks	Main modes of MV	Suggestions
During inspiration					
Flow starvation	Delivered flow does not match patient's demand	• Insufficient peak flow • High respiratory drive	• Dyspnea • High levels of work of breathing	• A/C ventilation (volume)	• Increase peak flow >50 L/min (direct setting or shorten inspiratory time to obtain the same volume faster)
Short cycles	Continuation of inspiratory effort after the end of insufflation	• Insufficient inspiratory time • High respiratory drive	• Eccentric contractions of respiratory muscles • Double triggering	• A/C ventilation (pressure or volume)	Increase inspiratory time
Prolonged insufflation	Continuation of insufflation after the end of inspiratory effort	• Inadequate cycling mechanism • Gas trapping	• Shorten neural expiration and promote gas trapping • Dyspnea	• A/C ventilation (pressure) • PSV • NIV	Modify cycling to make the inspiration shorter
Reverse triggering	Diaphragmatic contraction triggered by mechanical insufflation	Reflex mechanism in highly sedated patient	• Loss of protective ventilation • Monitoring of plateau pressure inoperative • Eccentric contractions of respiratory muscles	• A/C ventilation (pressure or volume)	• Paralyze if VT too high or double cycle • Decrease sedation
Double cycles (during inspiration or expiration)					
Double cycles after reverse triggering	Reverse triggering of a second cycle	Reflex mechanism in highly sedated patient	Double the mechanical stress on the lung	• A/C ventilation (pressure or volume)	• Paralyze if VT too high or double cycle • Decrease sedation
Double (or triple) triggering after short cycles (breath stacking)	Continuation of inspiratory effort after the end of insufflation	• Insufficient inspiratory time • High respiratory drive	Double or triple the mechanical stress on the lung	• A/C ventilation (pressure or volume) • PSV	• Increase inspiratory time • Increase VT • Modify cycling to make the inspiration longer
During expiration					
Autotriggering	Cycles not triggered by the patient	• Leaks • Water in the circuit • Excessively sensitive trigger • Cardiac oscillations	• Dyspnea • Misleading information on breathing pattern • Severe hyperventilation (eg, arrhythmias, reduced cerebral blood flow) • Increase rate of lung stress	• A/C ventilation (pressure or volume) • PSV • NIV	• Inspect tubing • Decrease trigger sensitivity

Continued on next page

TABLE 2. Continued

Dyssynchrony or patient-ventilator interaction	Description	Pathophysiology	Risks	Main modes of MV	Suggestions
During expiration, continued					
Gas trapping	Next inspiration starts before end of exhalation	High time constant	• Poor diaphragm function • Hemodynamic effects • Ineffective efforts	• Any assisted mode • NIV	Decrease hyperdynamic inflation: • Increase expiration time • Decrease minute ventilation (decreased VT and/or RR) • Decrease frequency
Ineffective effort	Effort unable to trigger the ventilator	• Inadequate cycling • Excessive support • Large time constant • Low respiratory drive	• Repeated pleiometric work • Erroneous display of respiratory rate • Prolonged duration of ventilation	• Any assisted mode • NIV	• Increase trigger sensitivity • Decrease sedation • Increase expiration time • Increase PEEP (to equal intrinsic PEEP)

A/C = assist-control; MV = mechanical ventilation; NIV = noninvasive ventilation; PEEP = postive end-expiratory pressure; PSV= pressure support ventilation; RR = respiratory rate; VT = tidal volume.

data suggest that conservative oxygen therapy targeting a PaO_2 of 70 to 100 mm Hg or a pulse oximetry oxygen saturation (SpO_2) of 94% to 98% results in lower ICU mortality than a conventional, more "liberal" approach with higher PaO_2 and SpO_2 targets.[65]

Effects on Respiratory Muscles and Respiratory Infections

Mechanical ventilation has been associated with respiratory muscle dysfunction and weaning difficulties.[20,66-68] Disuse atrophy of the diaphragm appears to be a key mechanism for these detrimental effects, suggesting the need to better monitor respiratory muscle activity. Partial modes of ventilation do not always prevent this atrophy. Several studies examining diaphragm biopsies have found that changes in structure occur early after intubation.[66] More than 50% of patients experience dysfunction related to an excessive level of assistance (controlled or partial ventilation) or to insufficient assistance.[67] Limb muscle weakness, referred to as ICU-acquired weakness, and diaphragm dysfunction have only minimal overlap. Respiratory muscle dysfunction is at least twice as prevalent as limb muscle weakness at the time of separation from MV and has a strong impact on weaning.[20]

Intubated and ventilated patients are at risk for ventilation-acquired pneumonia due to microaspiration from the oropharyngeal cavity and diminished host defense due to decreased cough efficiency and impaired mucociliary clearance. Recent guidelines recommend limitation of sedation and shortening the duration of MV in order to minimize the risk of ventilation-acquired pneumonia.[69]

Ventilator-Induced Lung Injury

Mechanical ventilation can induce or worsen lung injury, referred to as ventilator-induced lung injury (VILI).[70-75] This disorder has become a major concern in the modern era of MV, profoundly modifying the clinical targets of MV. Ventilator-induced lung injury may impact a large number of patients, most specifically those with or at risk for ARDS. Prevention is described in greater detail in the "Acute Respiratory Distress Syndrome" section.

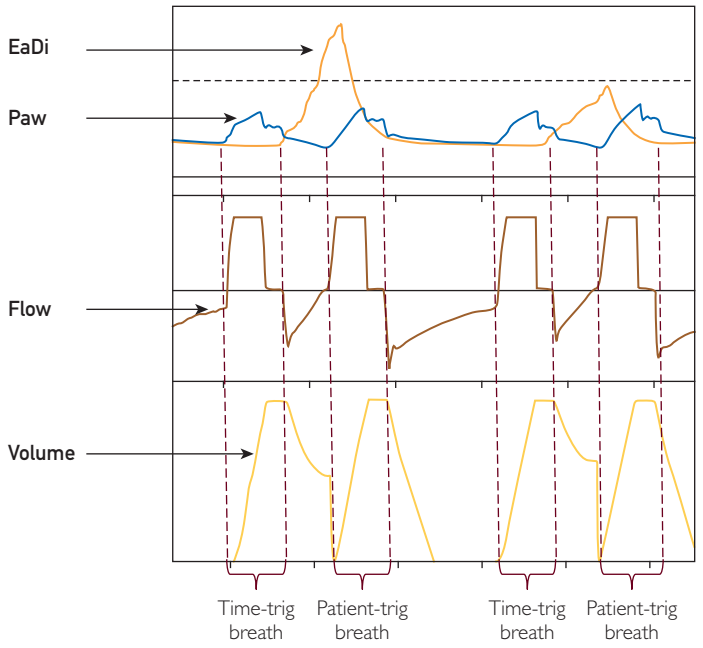

FIGURE 3. Tracings of airway pressure (Paw), flow, and volume in a sedated patient undergoing assist-control mechanical ventilation, depicting classic and frequent dyssynchrony of double cycling. Despite a set rate of 20/min, the actual rate is 40/min. Diaphragmatic electrical activity signal (EaDi), superimposed on the Paw curve, provides the mechanism, called reverse triggering. Diaphragmatic contractions are triggered by the mechanical insufflations on a 1:1 basis and explain the second cycle. Patient-trig = patient-triggered occurring after each mandatory breath; Time-trig = time-triggered.

Long-term Consequences

Mechanical ventilation of at least one week's duration is associated with important consequences on the long-term physical, cognitive, and mental health of ICU survivors.[76] Whether this condition, sometimes referred to as the post–intensive care syndrome,[77] is specific to MV or a manifestation of critical illness is unclear. For instance, cognitive impairment is a devastating complication in ICU survivors, with 26% of patients having a cognitive score 1 year after ICU admission, similar to patients with mild Alzheimer disease.[78] It is likely that the impairment is multifactorial, including factors such as the patient's pre-ICU trajectory, severity of illness, sedation, delirium, and sleep disruption[79,80] linked to MV.[81]

Survivors of ICU care who have undergone prolonged MV (more than 2 weeks) have an in-hospital mortality of 30% and a 1-year mortality rate as high as 60%.[82] Interestingly, most ARDS survivors regain virtually normal pulmonary function in a few months, but their major functional disabilities are often a consequence of ICU-acquired weakness and complications of bed rest.[83] A recent study also found that caregivers of patients with prolonged ventilation had increased depressive symptoms 1 year after ICU discharge.[84]

MAIN VENTILATOR SETTINGS

Assist-control ventilation using volume or pressure as the target and PSV are currently the 3 main modes of ventilation used worldwide.[85,86] These modes allow the clinician to set FIO_2, PEEP, and a target variable (pressure or volume). There is, however, a wide variety of pressure-controlled modes, including airway pressure release ventilation or dual modes, which has been addressed elsewhere.[13,87]

Oxygenation

Although FIO_2 can be set from 0.21 to 1.0, it should be set at the lowest value required to reach the oxygenation target. This target varies from patient to patient, but an SpO_2 of 92% to 96% is a reasonable goal. Of note, in patients with a large shunt, increasing FIO_2 has only minimal impact on arterial oxygenation.

PEEP can be adjusted to improve oxygenation in patients with collapsed lung units (eg, patients with ARDS), mainly by increasing functional residual capacity. In recruitable lungs, PEEP can maintain open recruited lung areas and hence reduce repeated alveolar opening and closure.[88] PEEP can also lead to overdistention of the more compliant areas of the lungs and can decrease cardiac output and oxygen delivery even in the presence of an increased PaO_2.[89]

Ventilation

The target variable for assist-control ventilation can be volume or pressure; neither has proven to be superior in terms of outcome.[90] Pressures must be monitored when the Vt is set, and volumes must be monitored when the pressure is set. Table 1 provides a summary of possible settings based on the mode of MV.

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In the past, a major goal of MV was to ensure that patients had normal arterial blood gas levels, with little regard to the harms caused by MV. Currently, a priority is to ensure that VILI is minimized while maintaining adequate, but not necessarily normal, gas exchange. The best oxygenation is not always the most protective, and moderate levels of hypercapnia are considered acceptable. In the past, high Vts were recommended on the basis of studies in anesthetized patients that found that small Vts led to atelectasis and hypoxemia.[91] Atelectasis was related to the combined effects of high FIO_2, anesthesia, and lack of PEEP. It took years of research to realize that high Vts, despite having favorable effects on oxygenation, were harmful for the lungs and increased mortality.[92]

Current recommendations for setting Vt are based on predicted body weight (PBW) and not actual body weight because (normal) lung size scales with PBW. One formula is: PBW (kg) = 50.0 + 0.91 (height in cm − 152.4) for males and PBW (kg) = 45.5 + 0.91 (height in cm − 152.4) for females. The recommended range is 6 to 8 mL/kg PBW.

Partial modes of assist are very popular, based on the delivery of a pressure support level. They are frequently used and generally well tolerated.[93] There are 2 concerns with these modes. One is that patients can be easily overassisted[29,94]; experimental[68] and clinical[67] data suggest that despite the use of partial support, insufficient muscle use can lead to atrophy and dysfunction. Second, because the Vt cannot be controlled, patients with high respiratory drive may generate excessive Vts, which can lead to a form of patient self-inflicted lung injury.[95,96]

Proportional Modes of Ventilation

Two modes of ventilation are based on a different principle and address some of the concerns discussed previously. These 2 modes, which require a relatively preserved neuroventilatory drive, deliver pressure in proportion to the patient's demand and let the patient regulate Vt. One mode called proportional assist ventilation requires real time calculation of the equation of motion of the respiratory system based on automated measurements of respiratory system compliance and resistance. The second mode uses the electrical activity of the diaphragm and is called neurally adjusted ventilatory assist (NAVA). The only setting required from the clinician is the amount of assistance: during proportional assist ventilation, it is set as a percentage of assistance, and for neurally adjusted ventilatory assist, it is set by the proportionality factor between electrical activity of the diaphragm and pressure. For both modes, Vt, frequency, and pressure are not set by the clinician. Both modes are very effective in reducing dyssynchronies and in adapting to changes in ventilatory demand, explaining improvement in sleep quality observed with their use.[97-99] However, few outcome data are available.[100,101] Some experimental or human data suggest that they may allow a safer control of ventilation than routine lung protective ventilation.[102,103]

ACUTE RESPIRATORY DISTRESS SYNDROME

No other ICU syndrome has been studied as much as ARDS. Understanding the impact of MV on patients with ARDS has resulted in major changes in ventilator management over the past 25 years.

A consensus definition of ARDS was released in 1994, more than 25 years after its initial description.[104] The most recent Berlin definition tried to overcome some of the limitations of previous definitions.[11,105] ARDS is currently defined by a new onset or worsening of respiratory symptoms with bilateral opacities on chest radiography and a PaO_2:FIO_2 ratio 300 mm Hg or less while receiving PEEP of 5 cm H_2O or higher. Concomitant heart failure can be present, but if no known risk factor for ARDS has been identified, congestive heart failure must be objectively ruled out.

There are many predisposing factors that can lead to the development of ARDS, but the lungs of patients with ARDS share several common biological, cellular, and mechanical characteristics. The lungs are edematous and heavy, adding considerable superimposed pressure to the dependent lung regions. Normally aerated tissue is greatly reduced and has been described as a "baby lung."[106,107] The baby lung concept explains the low respiratory system compliance, high pressures, and high risk for VILI. Minimizing

the risk of VILI has improved survival.[70,74,108] In contrast, pharmacological approaches for treating ARDS have been disappointing.

Different techniques have been used to try to prevent intubation in patients with acute hypoxemic respiratory failure, including NIV. A high-flow nasal cannula is used increasingly in patients with acute hypoxemic respiratory failure and has improved comfort, decreased dyspnea, and decreased mouth and airway dryness sensation compared with conventional oxygen therapy.[109,110] A recent study found a similar rate of intubation but a reduced mortality rate in the group of patients treated with high-flow nasal cannula compared with NIV or standard oxygen.[111] Intubation was reduced in those with a PaO_2:FIO_2 ratio lower than 200 mm Hg. It may work in part by reducing the oropharyngeal dead space by a washout effect and by increasing end-expiratory pressure.[112]

The Acute Respiratory Distress Syndrome Network Lower Tidal Volume (ARMA) trial was the first large multicenter clinical trial to document the benefit of a lung protective strategy using lower than traditional Vts (~6 mL/kg PBW) and limiting Pplat to 30 cm H_2O.[113] Since then, accumulating evidence has demonstrated that low Vts, with or without a certain degree of acidosis (permissive hypercapnia), are efficient in limiting VILI.[114] Reducing instrumental dead space (eg, filters) is necessary, and increasing the respiratory rate to 35 breaths/min is recommended to minimize hypercapnia. There is some evidence that decreasing Vt even further may improve outcomes.[115] Clinical trials are exploring the impact of lower Vts using extracorporeal circulation to remove carbon dioxide.[116]

How to best set the PEEP level for any patient has been a matter of debate for 5 decades. The initial focus was to improve oxygenation with higher PEEP, but the current thinking is that any improvement in outcomes with higher PEEP levels is due to decreased VILI. Individual trials have failed to document decreased mortality with a higher PEEP strategy,[71,117,118] but an individual patient data meta-analysis found that higher PEEP was associated with a 5% lower mortality rate in patients with moderate or severe ARDS (PaO_2:FIO_2 ratio <200 mm Hg) but not in patients with a PaO_2:FIO_2 ratio higher than 200 mm Hg.[73] The high PEEP strategy improved several secondary end points such as hypoxemia, use of rescue therapies, and duration of organ failure and MV.

Measurement of esophageal pressure to estimate transpulmonary pressure at end-expiration is a promising approach.[119,120] A strategy titrating PEEP on the basis of transpulmonary pressures revealed improved oxygenation and compliance compared with standard settings,[121] and a larger clinical trial of this approach is currently ongoing (NCT01681225).

Recently, a reanalysis of 9 of the main randomized controlled trials (RCTs) in ARDS compared the impact of Vt, PEEP, Pplat, and driving pressure (ΔP = Pplat − PEEP) on outcomes. Driving pressure change was the variable that best predicted mortality,[122,123] perhaps because it is equal to (Vt/C_{RS})—ie, Vt normalized to respiratory system compliance, the latter being related to lung size. Conversely, PBW is a good predictor of lung size in healthy individuals but not in patients with ARDS, who can have markedly decreased lung volumes. The recent international multicenter observational LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study also found an association between both higher Pplat and ΔP with mortality.[86] These studies suggest that a safe ventilatory strategy should first use a Vt of 6mL/kg PBW, while limiting plateau and driving pressure. Keeping ΔP below a risky level (eg, <15 cm H_2O) may help, although no prospective data are available. High PEEP levels (>10-15 cm H_2O) seem beneficial in moderate and especially severe ARDS (PaO_2:FIO_2 ratio <200 mm Hg).

In moderately severe to severe ARDS with a PaO_2:FIO_2 ratio of less than 150 mm Hg, adjunctive therapies such as neuromuscular blockade for the first 48 hours[49] or prone positioning also result in improved survival.[124,125] Implementation of the prone position requires training by the clinical team, but the evidence strongly suggests that it should be applied when the PaO_2:FIO_2 ratio remains lower than 120 mm Hg despite protective ventilation.

Extracorporeal membrane oxygenation may be beneficial in patients with the most severe ARDS and is currently under

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investigation. The results of the EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) trial (clinicaltrials.gov Identifier: NCT01470703) will provide valuable information.[126,127] At present, it seems reasonable to apply extracorporeal membrane oxygenation if prone positioning is ineffective.

Alveolar recruitment techniques vary and may have adverse effects. Recent data indicate that most of the effect of a sustained inflation (35-40 cm H_2O) is obtained after 10 seconds, suggesting that such maneuvers can be terminated relatively early before adverse events occur.[128] Even if recruitment maneuvers substantially improve oxygenation, this effect is transient, and the benefit on patient outcomes is still controversial.[129,130]

Two RCTs using high-frequency oscillation found no benefit for moderate and severe ARDS, and one of them even found a higher mortality rate for patients treated with this technique.[131,132] Therefore, high-frequency oscillation is not recommended as first-line therapy for patients with ARDS. However, a recent meta-analysis suggests that it may be beneficial in very severely hypoxemic patients.[133] Inhaled nitric oxide can lead to vasodilation of the well-ventilated alveoli with subsequent improvement in oxygenation but has been found in multiple studies to not impact mortality and may have adverse effects such as increased risk of renal dysfunction.[134,135]

PROTECTIVE VENTILATION FOR PATIENTS WITH RELATIVELY NORMAL LUNGS

There is accumulating evidence for the beneficial effects of lung protective ventilation in patients without ARDS,[136] including those undergoing major surgical procedures, patients without ARDS at presentation, and in brain-dead patients who are potential lung donors.

For surgical patients with previously healthy lungs, the conventional strategy has previously been to combine high Vts (~10-15 mL/kg) with high FIO_2 using low or no PEEP. The goal with this strategy was to prevent atelectasis.[137,138] In recent years, several studies have examined lung protective ventilation strategies (low Vt, PEEP with or without recruitment maneuvers) in the operating room. One study reported a 3-fold reduction in postoperative complications and in the requirement of postoperative MV with this strategy compared with conventional ventilation in patients undergoing major abdominal operations.[139] Other studies in patients undergoing thoracic and abdominal surgical procedures have documented reduced postoperative pulmonary and extrapulmonary complications with lower health care utilization when a protective ventilation strategy was used.[139,140] Protective ventilation is not associated with additional risk of intraoperative complications.

In intubated ICU patients not presenting with ARDS on admission, a strategy using lower Vts was associated with shorter duration of MV.[141] A meta-analysis examining surgical and ICU patients found that lower Vts were beneficial for all important outcomes including evolution to ARDS, pneumonia, hospital length of stay, and mortality.[136]

Finally, in brain-dead potential organ donors, a lung protective ventilation strategy maintaining sufficient PEEP and avoiding derecruitment allowed optimization of lung transplant leading to a 2-fold increase in harvested lungs compared with a conventional strategy with the same rate of success and 6-month survival rate.[142]

VENTILATION IN PATIENTS WITH COPD

Exacerbations of COPD are characterized by a marked worsening of respiratory mechanics secondary to increased airway resistance, expiratory collapse of small airways limiting expiratory flow, development of auto-PEEP and hyperinflation, and increased work of breathing. The development of auto-PEEP has important consequences including increased work of breathing (inspiratory threshold loading), decreased respiratory muscle efficiency (flattened diaphragms), and hemodynamic compromise. Patients are unable to achieve sufficient Vts despite strong respiratory efforts and have markedly elevated oxygen cost of breathing. In these patients, the physiologic rationale for NIV is very strong—NIV improves ventilatory efficiency, decreases respiratory rate, decreases the work of breathing, and increases alveolar ventilation by increasing Vt.[143] This approach often improves the patient's level of consciousness.[144] Many studies have found that the use of NIV

can prevent the need for intubation and reduce mortality,[145,146] often in very severe cases.[147-149]

If the patient requires intubation because of a decreased level of consciousness, severe respiratory acidosis despite NIV, or because the initial presentation is too severe for an NIV attempt, the goals of MV can be considered within the context of 2 distinct periods. In the first, often short, period, the aim is to minimize dynamic hyperinflation while obtaining reasonably acceptable values of pH and oxygenation but not normal $PaCO_2$. To achieve these goals, the patient usually undergoes ventilation in a controlled pressure or volume mode. The strategy largely consists of minimizing minute ventilation and increasing inspiratory flow to prolong the duration of expiration and permit lung deflation in the presence of a high respiratory system time constant[150] (Figure 2).

In the second period, the major goal is to wean the patient from the ventilator while decreasing the work of breathing. In this period, the patient is allowed to generate spontaneous breathing efforts, often using PSV. Appropriately set external PEEP (just sufficient to overcome auto-PEEP) may help reduce the added elastic load at the start the inspiration. Care must be taken to avoid excessive levels of pressure support (and Vts), which are associated with lengthening of the inspiratory time and ineffective efforts that are strongly associated with poor outcomes.[151] When the patient undergoes PSV, the level of pressure should be set to decrease the work of breathing but also to limit Vt; high Vts lead to dynamic hyperinflation and ineffective effort, and dyssynchronies are observed very frequently in these patients. Tidal volumes of approximately 6 mL/kg PBW may be necessary to minimize ineffective efforts.[29]

WEANING

The weaning process can compose as much as 40% of the total duration of MV.[152] However, many uncertainties exist when one tries to describe this phase of the MV journey because various aspects are ill-defined. For example, when does the weaning start? As soon as the patient is intubated, or when the sedation decreased, or when the ventilator is switched to a mode allowing spontaneous breathing? A common framework is important to enable comparison of weaning duration among groups of patients. Shortening this period is essential because weaning duration is associated with survival.[152] Minimizing sedative drugs[56] and neuromuscular blocking agents to prevent muscle weakness,[20] switching early to a mode of ventilation that allows spontaneous breathing, use of weaning protocols,[153] or even automated weaning[154] are all reasonable strategies to shorten the weaning period.

Determining when a patient can be separated from the ventilator is challenging while the patient is still undergoing MV. Therefore, general criteria have been defined to systematically screen patients for their ability to breathe alone, whatever the ventilator settings. These criteria have challenged the notion that weaning should always be gradual and progressive. How to perform the test to decide for extubation—usually referred to as a spontaneous breathing trial (SBT)—is a matter of debate,[155] as explained below. A recent study classified weaning on the basis of the timing of weaning success after the first separation attempt (defined as an SBT or any extubation attempt)[155] and reported increased mortality for patients having prolonged weaning. Recent guidelines for liberation from MV recommend using protocols for sedation and weaning, mobilization of patients as early as possible, performance of an SBT with PSV rather than a T-piece, cuff leak tests and corticosteroid administration if there is no leak, and prophylactic NIV for patients at high risk for reintubation.[156]

The choice of the appropriate SBT technique is not as simple as it appears. A recent physiologic meta-analysis found that compared with all other SBT modalities, both T-piece and ventilation with no PSV and no PEEP best and equally simulate the patient's postextubation scenario.[157]

After extubation, prophylactic use of NIV may benefit patients at risk for respiratory failure and reintubation, such as elderly patients with COPD or congestive heart failure.[158,159] Noninvasive ventilation in the weaning strategy might reduce the rate of ventilation-acquired pneumonia and mortality.[160] In 2 recent RCTs, the high-flow nasal cannula technique was noninferior to NIV in postextubation settings for patients at high risk for

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respiratory failure[161] and even decreased the rate of reintubation for patients at low risk.[162]

AVENUES FOR IMPROVEMENT

Our understanding of the pathophysiology of acute respiratory diseases, the impact of ventilator settings on dyssynchronies, and the complications of MV have all markedly improved during the past few decades. Nevertheless, many unanswered questions remain. Given the potential iatrogenic consequences of inadequate delivery of MV, one might assume that avoiding invasive MV at any cost would benefit the patient. However, recent data suggest that spontaneous ventilation can also lead to lung injury in patients with high respiratory drive.[163] Patients breathing spontaneously, whether intubated or not, can experience self-inflicted lung injury due to high minute ventilation and increased Vts.[96,164] Thus, spontaneous ventilation can also be harmful, and very high respiratory drive with the development of very large Vts may be an indication for intubation with heavy sedation or neuromuscular blocking agents. Identifying which spontaneously breathing patients are at increased risk for this type of injury is an important area of future research.

A promising approach to limiting complications from MV in patients with ARDS or COPD is the use of extracorporeal life support. These techniques range from extracorporeal carbon dioxide removal, which is the least invasive and can be delivered through a relatively small-bore cannula (dual-lumen 13-17Fr diameter) at a blood flow of less than 500 mL/min, to full extracorporeal membrane oxygenation requiring a large venous cannula (with a minimum diameter of 23Fr) to allow flow rates of more than 4 L/min. The relative efficacy of each of these techniques is currently being examined in clinical trials.

CONCLUSION

Decades of research, progress, and clinical monitoring has led to an increased understanding of the physiology of MV. A conceptual revolution occurred when the goal of MV moved from normalizing blood gas levels to minimizing VILI while maintaining adequate (albeit not necessarily normal) gas exchange. We now know that management during the acute phase has a strong impact on long-term outcome and disabilities, and this focus on long-term outcomes will be a focus for future research. The MV journey is making progress but is still far from its ultimate destination.

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Abbreviations and Acronyms: **ARDS** = acute respiratory distress syndrome; **COPD** = chronic obstructive pulmonary disease; $\mathbf{C_{RS}}$ = compliance of the respiratory system; $\mathbf{E_{RS}}$ = elastance of the respiratory system; $\mathbf{FIO_2}$ = fraction of inspired oxygen; **ICU** = intensive care unit; **MV** = mechanical ventilation; **NIV** = noninvasive ventilation; **ΔP** = pressure change; **PBW** = predicted body weight; **PEEP** = positive end-expiratory pressure; $\mathbf{P_0}$ = initial alveolar pressure; **Pplat** = plateau pressure; **PSV** = pressure support ventilation; **RCT** = randomized controlled trial; **SBT** = spontaneous breathing trial; $\mathbf{SpO_2}$ = pulse oximetry oxygen saturation; **VILI** = ventilator-induced lung injury; **Vt** = tidal volume

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