Critical care 1

Clinical challenges in mechanical ventilation

Ewan C Goligher, Niall D Ferguson, Laurent J Brochard

Lancet 2016; 387: 1856–66

See **Series** *Lancet Respir Med* 2016; **4:** 407–18

This is the first in a **Series** of three papers about critical care

Interdepartmental Division of Critical Care Medicine (E C Goligher MD, N D Ferguson MD, L J Brochard MD), **Department of Physiology** (E C Goligher, N D Ferguson), **and Institute for Health Policy, Management, and Evaluation** (N D Ferguson), **University of Toronto, Toronto, ON, Canada; Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, Toronto, ON, Canada** (E C Goligher, N D Ferguson); **and Li Ka Shing Knowledge Institute, Keenan Research Centre for Biomedical Science, St Michael's Hospital, Toronto, ON, Canada** (L J Brochard)

Correspondence to: Dr Laurent Brochard, Li Ka Shing Knowledge Institute, Keenan Research Centre for Biomedical Science, St Michael's Hospital, Toronto, ON M5B 1T8, Canada **brochardl@smh.ca**

Mechanical ventilation supports gas exchange and alleviates the work of breathing when the respiratory muscles are overwhelmed by an acute pulmonary or systemic insult. Although mechanical ventilation is not generally considered a treatment for acute respiratory failure per se, ventilator management warrants close attention because inappropriate ventilation can result in injury to the lungs or respiratory muscles and worsen morbidity and mortality. Key clinical challenges include averting intubation in patients with respiratory failure with non-invasive techniques for respiratory support; delivering lung-protective ventilation to prevent ventilator-induced lung injury; maintaining adequate gas exchange in severely hypoxaemic patients; avoiding the development of ventilator-induced diaphragm dysfunction; and diagnosing and treating the many pathophysiological mechanisms that impair liberation from mechanical ventilation. Personalisation of mechanical ventilation based on individual physiological characteristics and responses to therapy can further improve outcomes.

Introduction

Although efforts have been made to resuscitate patients with acute respiratory failure for centuries,[1] mechanical ventilation as used in contemporary clinical practice is a comparatively recent development. The use of positive-pressure ventilation outside the operating room was famously precipitated by an epidemic of poliomyelitis in Copenhagen in 1951.[2] Bjorn Ibsen's (then) controversial proposal to systematically apply positive-pressure ventilation for patients dying of poliomyelitis produced dramatic and immediate improvements in survival,[3] leading to the global adoption of positive-pressure ventilation to manage acute respiratory failure and revolutionising clinical medicine. The advent of mechanical ventilation introduced new clinical diseases (ie, so-called respirator lung,[4] now referred to as acute respiratory distress syndrome [ARDS]) and raised several new ethical challenges (ie, organ donation, pandemic triage, withholding or withdrawing of life-sustaining therapies).

Mechanical ventilation is used to support gas exchange and acid–base homoeostasis to preserve life when the respiratory muscles are unable to maintain normal pulmonary ventilation in the face of acute or chronic respiratory dysfunction due to pulmonary or systemic insults, generally as a bridge to recovery. Since its introduction in the 1950s, important advances have been made in adapting positive-pressure mechanical ventilation to achieve those goals. Central to these advances has been the critical insight that applying mechanical ventilation targeting normal physiological values might defeat the purpose of ventilatory support (clinical recovery) by further injuring the lungs and other organs.[5] Mechanical ventilation is not a treatment per se; it allows patients time to recover from the underlying cause of acute respiratory failure. Consequently, great care must be taken to ensure that mechanical ventilation is applied in a way that optimises conditions for recovery.

In this paper, we summarise current clinical challenges in delivering mechanical ventilatory support for patients with acute respiratory failure, emphasising the concept of protective mechanical ventilation with respect to both the lungs and the diaphragm. The panel summarises strategies to manage these clinical challenges.

Search strategy and selection criteria

We searched MEDLINE for articles published before Feb 17, 2016. We used the search terms "mechanical ventilation", "acute respiratory failure", and "artificial respiration". We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded publications. We also reviewed the reference lists of articles identified by this search strategy for relevant articles. Review articles are cited to provide readers with more details and references than this Series paper has space for.

Avoiding invasive mechanical ventilation

Patients with chronic obstructive pulmonary disease are frequently admitted to hospital with exacerbations characterised by an inability to maintain an adequate level of alveolar ventilation despite sometimes considerable inspiratory effort. Invasive mechanical ventilation was routinely used in such cases until it was shown that application of positive pressure through a facial mask covering the nose and the mouth in synchrony with the patient's effort could reduce diaphragmatic work while increasing alveolar ventilation.[8] This approach, referred to as non-invasive ventilation, has proven highly effective to prevent endotracheal intubation and reduce the risk of death in hospital in these patients.[9] Remarkably, non-invasive ventilation is associated with a low risk of nosocomial superinfection, reflecting reduced exposure to procedures associated with such infections.[10] It has been progressively used worldwide as the standard of care for this indication[11] and for similar clinical problems such as obesity–hypoventilation syndrome.

Panel: **Evidence and opinion for management of clinical challenges in mechanical ventilation**

Clinical challenge: avoiding intubation

Established evidence-based practice

- Non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease or acute decompensated heart failure

Authors' opinion (further research required)

- High-flow nasal cannula for hypoxaemic acute respiratory failure (PaO_2/F_IO_2 ≤300 mm Hg)
- Non-invasive ventilation or high-flow nasal cannula for hypoxaemic respiratory failure in immunocompromised patients

Clinical challenge: preventing ventilator-induced lung injury

Established evidence-based practice

- Maintain low tidal volumes and airway plateau pressure less than 30 cm H_2O (6 mL/kg predicted bodyweight) for patients with acute respiratory distress syndrome
- Prone positioning for at least 16 h per day in patients with acute respiratory distress syndrome and PaO_2/F_IO_2 ≤150 mm Hg

Authors' opinion (further research required)

- Maintain driving pressure* ≤15 cm H_2O
- Maintain plateau transpulmonary pressure ≤20 cm H_2O
- Ventilation with a higher PEEP strategy for patients with positive physiological response (recruitability, improvement in compliance, and oxygenation) to a trial of higher PEEP
- In PEEP-responsive patients, apply PEEP according to the PEEP-F_IO_2 table evaluated in the LOVS trial,[6] or to minimise driving pressure, or as per the ExPRESS trial[7] protocol

Clinical challenge: preventing and treating ventilator-induced diaphragm dysfunction

Authors' opinion (further research required)

- Target adequate but not excessive levels of inspiratory effort (oesophageal pressure swing of 5–10 cm H_2O, negative deflection) as soon as possible after initiating invasive mechanical ventilation
- Monitor respiratory muscle activity to facilitate recognition and management of patient–ventilator dyssynchrony
- Consider inspiratory muscle training in patients with established diaphragmatic dysfunction

Clinical challenge: optimising gas exchange in hypoxaemic patients

Established evidence-based practice

- Prone positioning
- Ventilation with a higher PEEP strategy
- Avoid high frequency oscillation in early acute respiratory distress aside from rescue therapy

Authors' opinion (further research required)

- Lung recruitment manoeuvres
- Consider VV-ECMO as rescue therapy in severely hypoxaemic patients if access to a high volume centre is available
- High frequency oscillation and inhaled pulmonary vasodilators are alternative options for rescue therapy in severe hypoxaemia

Clinical challenge: liberating patients from mechanical ventilation

Established evidence-based practice

- Daily trials of spontaneous breathing
- Minimise sedation
- Early mobilisation
- Early diuresis to avoid weaning-induced pulmonary oedema
- Avoid delays in reintubation if post-extubation respiratory failure develops

Authors' opinion (further research required)

- Undertake trials of spontaneous breathing on T-piece or with zero airway pressure
- Avoid the use of benzodiazepenes for sedation
- In patients who are difficult to liberate, a cardiovascular diagnostic work-up and diaphragm function assessment should be routinely obtained
- Hypoxaemic patients should be extubated to high-flow nasal cannula
- Hypercapnic patients should be extubated to non-invasive ventilation

PaO_2/F_IO_2=ratio of arterial oxygen partial pressure to fractional inspired oxygen. PEEP=positive end-expiratory pressure. VV-ECMO=veno-venous extracorporeal membrane oxygenation. *Driving pressure is the ratio of tidal volume to static respiratory compliance.

Non-invasive techniques have also been applied to other forms of acute respiratory failure. The efficacy of positive pressure in patients presenting with respiratory failure from cardiogenic pulmonary oedema was established in the 1930s.[12] Both respiratory and cardiac function can be improved by positive pressure at the mouth. Continuous positive airway pressure and non-invasive ventilation were both successfully used to support patients admitted to intensive care units with pulmonary oedema while waiting for medical therapy to take effect.[13]

The vast and heterogeneous group of patients with hypoxaemic and non-hypercapnic respiratory failure has presented the biggest challenge in trying to avoid invasive ventilation. Despite some positive results obtained with non-invasive ventilation, the overall benefit of non-invasive techniques has proven difficult to show in this population.[14] In these patients, concomitant circulatory failure might require complete respiratory muscle rest; hence, delaying intubation could worsen outcomes. Further, although non-invasive ventilation can reduce the work of breathing it is generally associated with relatively large tidal volumes. Consequently, it is challenging to achieve so-called lung-protective ventilation with non-invasive ventilation, which could contribute to treatment failure.[15]

A new form of non-invasive support based on the continuous nasal delivery of a high flow of heated and humidified gas offers a very attractive alternative. In a randomised trial in hypoxaemic patients mostly with pneumonia, oxygen delivered by high-flow nasal cannulae (HFNC) reduced mortality compared with non-invasive ventilation or conventional oxygen therapy in the whole cohort, and reduced the need for intubation in the subgroup of patients with a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/F_iO_2) less than 200 mm Hg (although differences in the primary trial endpoint, overall intubation rate, did not reach significance).[16] HFNC also effectively prevent postextubation respiratory failure.[17,18] Various mechanisms can explain the apparent benefit of this intervention:[19] heated humidification of gas improves patient comfort, the high flow delivers a modest amount of positive pressure, and the reduction in dead space ventilation due to washout of the oropharyngeal content from expired carbon dioxide reduces work of breathing.

Irrespective of the non-invasive modality or the clinical indication, the patient's physiological response to a trial of non-invasive respiratory support should be closely monitored, and intubation should be promptly considered if the patient does not improve within 1–2 h or shows signs of deteriorating gas exchange, work of breathing, or mental status. Delays in intubation can seriously worsen clinical outcome.[20]

Optimisation of gas exchange on mechanical ventilation

Most patients who need invasive mechanical ventilation are subsequently easy to oxygenate and ventilate with positive pressure and a secure airway, and require modest amounts of inspired oxygen and low to moderate levels of positive end-expiratory pressure (PEEP). An important minority of patients do, however, have persistent hypoxaemia that can pose a danger to the patient and a challenge to the clinician. In this situation our usual approach is to start with a chest radiograph: does the patient have white lungs as we expect? If not, this introduces a different set of differential diagnoses including pulmonary embolism, intracardiac right-to-left shunt, or significant intravascular volume depletion. If, as is more common, the radiograph shows diffuse airspace opacities then the patient might have ARDS,[21] although clinicians often do not recognise this syndrome.[22] Importantly, opacities that appear diffusely distributed on frontal chest radiograph are frequently heterogeneous in the ventral-dorsal plane. Findings from CT studies have shown that in ARDS the apparently diffuse opacities seen on chest radiograph are frequently a composite image of densely consolidated and atelectatic lung in the dependent regions with smaller volumes of relatively unaffected aerated lung in the anterior lung regions—the so-called baby lung.[23] This heterogeneous distribution of lung oedema and atelectasis, together with gravitational forces, gives rise to the marked shunt and ventilation–perfusion mismatching characteristic of ARDS. Consequently, oxygenation can be enhanced by increasing blood flow to well ventilated lung regions while at the same time trying to improve fresh gas delivery to dependent atelectatic lung units (figure 1).

Blood flow to well ventilated lung regions can be enhanced by increasing cardiac output or with the use of inhaled pulmonary vasodilators. Increasing cardiac output exerts complex effects on oxygenation: mixed venous oxygenation is often improved (reducing the effect of intrapulmonary shunt on arterial oxygenation) but the shunt fraction is variably increased or decreased, possibly depending on the distribution of the lung injury.[24] Indeed, high PEEP can sometimes improve oxygenation simply by depressing cardiac output.[25] Consequently, a careful cardiovascular assessment is needed to monitor and treat

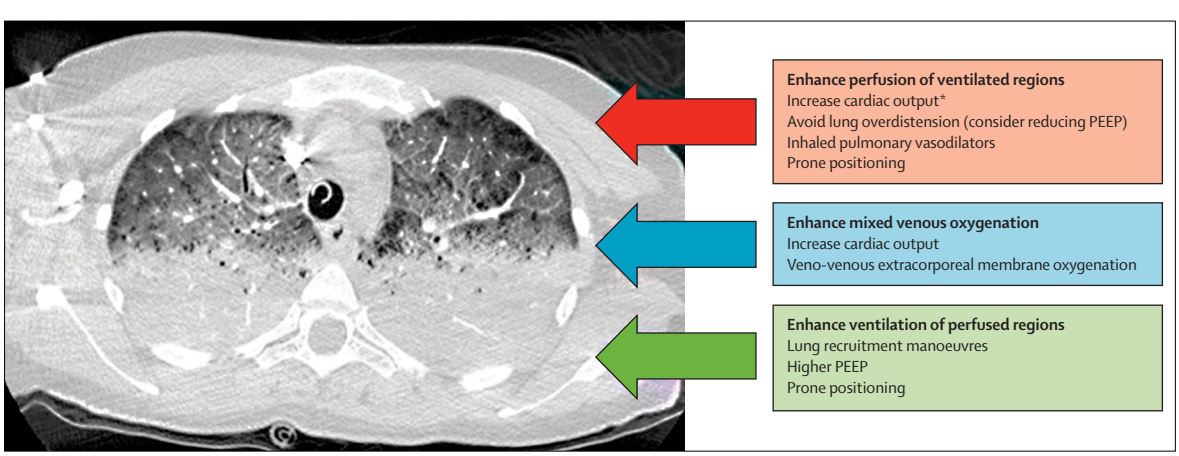

Figure 1: **Management of hypoxaemia in mechanically ventilated patients**
In acute respiratory distress syndrome, hypoxaemia results from the combination of ventilation–perfusion mismatch and marked intrapulmonary shunt. Hypoxaemia can be ameliorated by a variety of manoeuvres aimed at redirecting blood flow to ventilated regions, increasing mixed venous oxygen tension, or recruiting collapsed lung regions to participate in ventilation. PEEP=positive end-expiratory pressure. *Increasing cardiac output may also increase perfusion to non-ventilated lung regions, so that the overall effect of increased cardiac output on oxygenation can vary.

hypoxaemia, particularly in view of the deleterious effects of high positive airway pressures on the pulmonary circulation and right ventricular function.[26] Volume resuscitation ameliorates haemodynamic impairment resulting from the use of high mean airway pressures on the ventilator. Despite a beneficial effect on oxygenation, inhaled pulmonary vasodilators can be associated with an increased risk of acute kidney injury and do not reduce mortality when used in a broad population of patients with ARDS.[27] They are generally reserved for rescue therapy in the context of severe hypoxaemia.

High PEEP with or without a recruitment manoeuvre—a transient increase in airway pressure designed to keep open previously collapsed lung units—can be used to increase ventilation to atelectatic lung regions and reduce shunt fraction.[28] The extent to which collapsed lung units may be reopened (recruited) varies substantially between patients. A careful assessment of the physiological response to higher PEEP is warranted. In fact, this response may determine whether PEEP is beneficial or harmful to the patient.[29] Adjunct monitoring tools such as oesophageal manometry may help to direct PEEP titration to improve oxygenation.[30] High-frequency oscillation, an alternative method of ventilation, uses high mean airway pressures to recruit the lung and improve oxygenation, but it is probably harmful when applied as a routine intervention in early ARDS, possibly because of haemodynamic impairment. It should not be used except as rescue therapy.[31]

Prone positioning is an ideal intervention for hypoxaemia because it reverses the gradient of gravitational forces within the injured lung and facilitates recruitment of basal dorsal lung segments. Prone position also enhances secretion clearance, but precautions are required to avoid facial oedema and skin breakdown in the prone position, and accidental extubation or catheter displacement during placement into the prone position. Prone positioning has been associated with a significant reduction in mortality when applied for at least 16 h per day in ARDS patients with PaO_2/F_iO_2 persistently less than 150 mm Hg in centres experienced with prone positioning.[32] Despite the fact that findings from several previous randomised trials did not show a mortality benefit from prone positioning—possibly because of differences in patient selection, duration of prone positioning, or concomitant ventilation strategies—meta-analyses of trials of prone positioning consistently support its overall mortality benefit.[33,34] This technique should be used in many patients with moderate to severe ARDS but there is evidence that the technique is underused, possibly because of the need for experience and adequate staffing.[22]

Minimising ventilator-induced lung injury

The potential for mechanical injury to the lungs was recognised long before the era of modern mechanical ventilation. Writing in the 18th century, John Fothergill suggested that mouth-to-mouth resuscitation was preferable to attempting manual ventilation with the use of bellows because "the lungs may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined".[3] Within a decade of the widespread clinical implementation of positive-pressure ventilation, the first description of ARDS was published,[35] and a classic experiment published in the 1970s showed that mechanical ventilation per se could directly injure the lung, resulting in a histopathological lesion indistinguishable from ARDS.[36]

In parallel, the severity of pulmonary function impairment in ARDS has always been linked with the intensity of mechanical ventilation, giving rise to the suspicion that part of the severity was caused by the ventilator. Initial observations suggested that oxygen toxicity was a main provider of the pulmonary lesions.[37] Later the notion of ventilator-induced lung injury became central to understanding of ARDS management.[3,4,36] Several mechanisms of ventilator-induced lung injury have been described (figure 2). First, mechanical insufflation of the chest can cause excess stress and strain within the ventilated regions of the lungs. Excess mechanical stress, characterised by large changes in transpulmonary pressure, injures the alveolar epithelium and activates inflammatory pathways resulting in low-permeability pulmonary oedema.[38] The magnitude of strain depends on the size of the insufflated volume relative to the size of the lung participating in ventilation.[39] ARDS results in low end-expiratory lung volumes, explaining the reduced compliance of the lung.[23] Second, inhomogeneously inflated regions of lung parenchyma can amplify locally applied mechanical forces, resulting in excess mechanical stress even when insufflated volumes are relatively small.[40] Third, small airways and alveoli located at the margins of atelectatic lung regions can collapse and reopen with each mechanical breath; such tidal recruitment subjects these alveoli to high shear forces and consequent injury. Finally, because the injured lung loses its normal fluid-like inflation properties, inflation and mechanical stress can be distributed inhomogeneously, particularly when the patient is making spontaneous inspiratory efforts.[41]

The recognition of these mechanisms of injury propelled the development of lung-protective ventilation strategies and substantially improved the outcomes of mechanically ventilated patients. The first pillar of lung-protective ventilation, the use of lower tidal volumes, significantly reduced mortality in ARDS. Findings from a large randomised trial[42] comparing ventilation with tidal volumes of 6 mL/kg (along with airway plateau pressure limited to ≤30 cm H_2O) versus 12 mL/kg (predicted bodyweight) showed a 10% absolute decrease in the risk of death with lower tidal volumes. However, important gains remain to be made. Extracorporeal carbon dioxide elimination techniques—a form of extracorporeal circulation using relatively modest blood flow rates—might enable further reductions in tidal

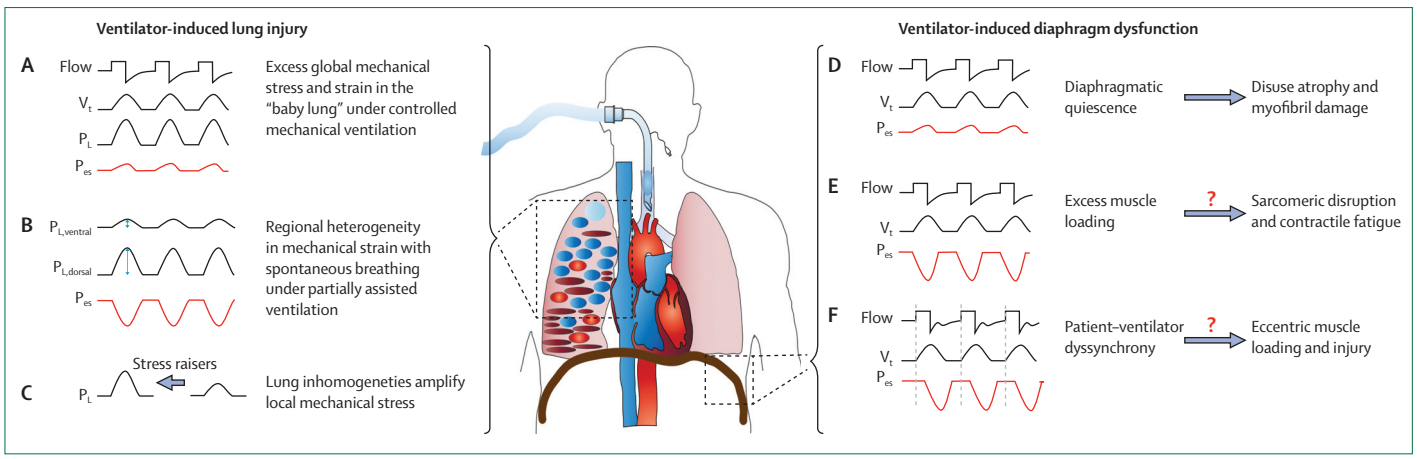

Figure 2: **Mechanisms of ventilator-mediated injury to the lungs and respiratory muscles**
Representative tracings of flow, volume (V_t), transpulmonary pressure (P_L), and oesophageal pressure (P_{es}) are given to support bedside identification of the various injury mechanisms. (A) Ventilator-induced lung injury results when passive inflation of open (uncollapsed) lung regions exceeds the stress-bearing capacity of the lung, resulting in excess mechanical stress and strain (indicated by large swings in P_L). (B) In patients with lung injury, vigorous diaphragm contraction during spontaneous breathing (indicated by negative swings in P_{es}) can result in regional heterogeneity in mechanical strain (indicated by varying ΔP_L), where ΔP_L might exceed safe limits in some regions but not others. (C) Parenchymal inhomogeneities scattered throughout the injured lung locally amplify mechanical stresses resulting in large local ΔP_L. (D) Passive mechanical ventilation in the absence of diaphragm activity (indicated by positive swings in P_{es}) mediates rapid disuse atrophy and myofibril injury. (E) However, excess inspiratory effort (indicated by relatively large swings in P_{es}) risks respiratory muscle injury from excess loading and fatigue. (F) When pressure and flow delivered by the ventilator are not synchronous with the patient's respiratory cycle (easily detected on the P_{es} tracing), the diaphragm might be forced to contract eccentrically, resulting in acute injury and weakness. The clinical significance of mechanisms E and F remains uncertain, as suggested by the question marks.

volume by averting respiratory acidosis while reducing strain (so-called ultraprotective ventilation).[43] Evidence suggests that targeting driving pressure (the quotient of tidal volume and static respiratory compliance) rather than tidal volume could further enhance lung protection by adjusting tidal volumes according to the size of the lung available for ventilation (reflected by the static compliance).[44] Despite the strong biological rationale and clinical evidence base supporting low tidal volume ventilation, clinical adoption remains inadequate, perhaps partly because of substantial under-recognition by clinicians.[22] Neuromuscular blockade can facilitate lung-protective ventilation, and a continuous infusion of cisatracurium reduced mortality in patients with early ARDS in one moderately sized multicentre trial.[45]

The second pillar of lung-protective ventilation, the application of higher PEEP to recruit collapsed lung, has achieved less impressive results. Findings from three randomised trials[6,7,46] comparing higher levels of PEEP (titrated by varying strategies) to lower levels of PEEP showed no significant difference in mortality, although a mortality benefit was detected in the subgroup of patients with moderate or severe ARDS.[47] The response to increased PEEP varies widely in patients with ARDS: some accrue large reductions in collapsed lung and (consequently) mechanical strain, whereas others exhibit minimal lung recruitment and the increased airway pressure worsens mechanical strain.[48] Indeed, a secondary analysis of these trials showed that a favourable physiological response to PEEP predicted lower mortality.[29] Clinicians need feasible and reliable tools to assess lung recruitment, and future trials should be undertaken to confirm that applying higher PEEP in patients who exhibit a favourable response to PEEP or those with a high potential for lung recruitment will improve their clinical outcomes. Some justify the use of a high PEEP-F_iO_2 table to titrate PEEP by its ease of use and by the fact that it tends to apply high PEEP in patients with greater lung recruitability and lower PEEP in patients with lower lung recruitability.[49] Others use the highest possible PEEP until a plateau pressure of 28–30 cm H_2O is reached to maximise recruitment within a safe zone.[7] Alternatively, PEEP might best be titrated to minimise driving pressure.

When mechanical ventilation fails: role for extracorporeal membrane oxygenation (ECMO)

ECMO (or more generally, extracorporeal life support [ECLS]) has undergone a resurgence in recent years. Originally introduced in the 1970s, ECMO was assessed in randomised trials that were targeting better gas exchange but were not trying to offer lung protection; extreme mortality rates led to the widespread abandonment of the technique for more than 20 years.[50] In the modern era, a combination of technical advances, new trial evidence, new goals of therapy, and high-profile successes with pandemic H1N1 influenza has led to a resurgence in adult ECMO use for acute respiratory failure.[51] For respiratory support, ECLS is usually delivered in the form of high-flow veno-venous ECMO. Blood is removed from the vena cava via a large cannula by means of a centripetal pump and passed through a hollow-fibre membrane where oxygen is added and carbon dioxide is removed, and the oxygenated blood is then returned to the right side of the heart.[52] In this way veno-venous ECMO provides respiratory but not cardiovascular support. The oxygenation effects of

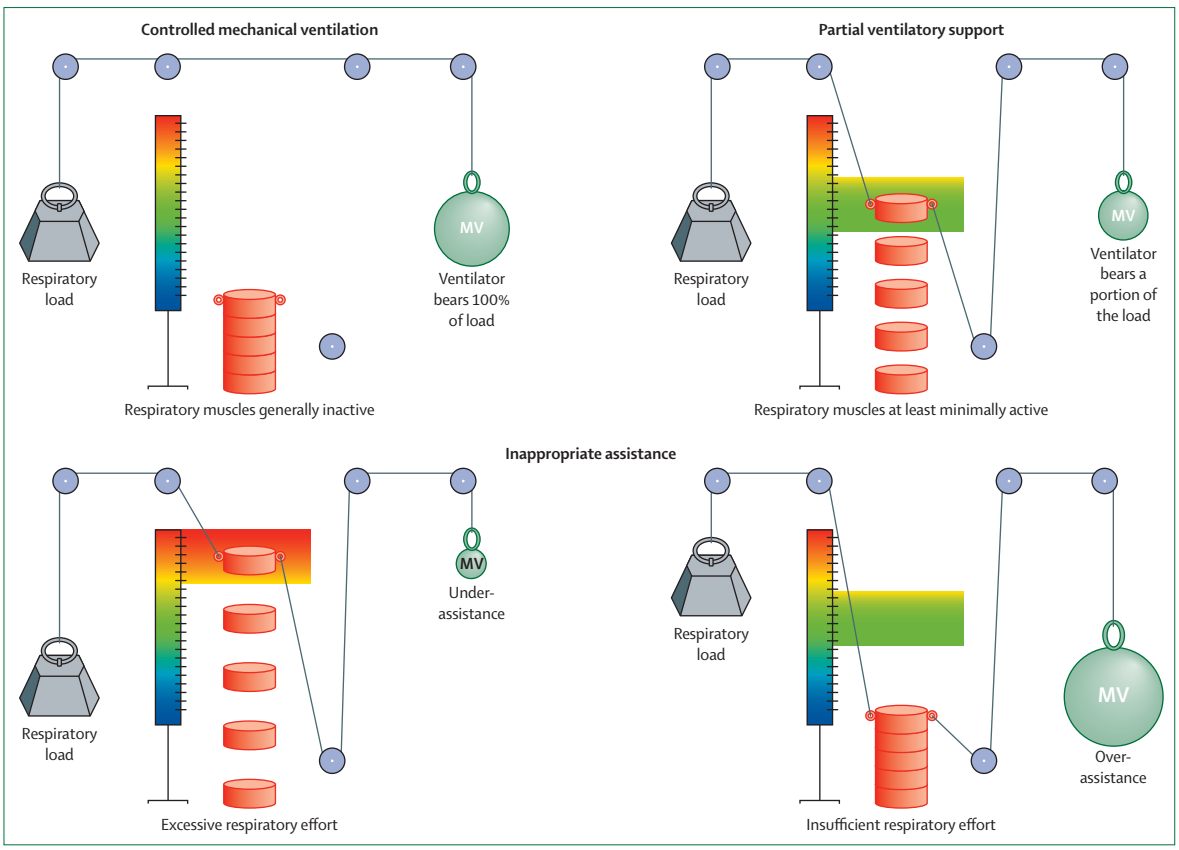

Figure 3: **Patient–ventilator interaction**
By contrast with controlled mechanical ventilation (MV), under partial ventilatory support the inspiratory load is shared by both the ventilator and the patient's respiratory muscles. When ventilatory support is insufficient, the patient faces an intolerable respiratory load resulting in patient distress or muscle injury, or both. Conversely, when ventilatory support is excessive, the patient's muscles are excessively unloaded, which if prolonged can also result in diaphragm atrophy and contractile dysfunction. Ventilatory strategies should aim to achieve the appropriate level of inspiratory effort depending on the clinical context (generally a normal level of inspiratory effort in the range of 50–150 cm H_2O-seconds per min is considered reasonable). Modified with permission from Carteaux G (Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, DHU A-TVB, Service de Réanimation Médicale, Créteil, France).

ECMO rely on high flow through the circuit (often 4–6 L/min) and the relative matching of ECMO circuit flow to intrinsic cardiac output. By contrast, carbon dioxide is highly soluble in plasma and its clearance is more dependent on the flow of sweep gas through the membrane oxygenator. Veno-arterial ECMO provides circulatory support in addition to gas exchange and is often used for refractory cardiogenic shock states.[53]

The role for ECMO for the management of severe ARDS and refractory hypoxaemia in clinical practice remains uncertain. Case series showing impressively low mortality with H1N1 managed with ECMO[54] are countered by similarly low death rates in cohorts managed without ECMO.[55] Matched analyses suggest variable benefit of ECMO in H1N1 cases, but success of matching cases varied between studies.[56,57] Finally, the only modern trial published thus far—the CESAR trial[58]—again suggests benefit of ECMO, but is confounded by potentially injurious ventilation in the control group, regionalisation effects, and because a significant proportion of the ECMO group did not actually receive this therapy. While we await more evidence from ongoing trials, many clinicians are applying variations of the entry criteria used in the CESAR trial. We should, however, exercise collective caution in the expansion of this technique.[51] There seems to be a volume–outcome relationship with veno-venous ECMO that might be even stronger than that seen for mechanical ventilation in ARDS.[59,60]

Mechanical ventilation and the respiratory muscles

The mechanical ventilator functions to support or even replace the respiratory muscles in the context of acute respiratory failure, when respiratory muscle capacity is impaired or overwhelmed by an acute pulmonary insult, or both. Safe and effective ventilation depends on a smooth interaction between the patient's respiratory muscles and the mechanical ventilator (figure 3). Modern ventilators and methods of ventilation are designed to deliver flow and pressure in synchrony with the timing of the patient's respiratory cycle by sensing the activity of the

respiratory muscles (based on airway pressure and flow or electrical activity generated by the muscles). Effective patient–ventilator interaction requires careful attention to ventilator settings, and patient–ventilator dyssynchrony is associated with poor patient outcomes.[61]

Respiratory muscle function is a key determinant of successful liberation from mechanical ventilation[62] and is an important determinant of recovery from critical illness.[63] Respiratory muscle weakness is prevalent in mechanically ventilated patients, and a myriad of factors associated with critical illness contribute to this weakness.[64] Mechanical ventilation is now widely recognised to injure the respiratory muscles, particularly the diaphragm (ventilator-induced diaphragm dysfunction). Mounting evidence suggests that diaphragm inactivity during mechanical ventilation mediates rapid diaphragm atrophy and contractile dysfunction.[65–67] One cohort study[68] showed that more than 40% of patients developed thinning of the diaphragm as visualised by ultrasound. Moreover, injurious loading conditions—due to insufficient unloading from the ventilator[69,70] or eccentric (lengthening) contractions[71] during patient–ventilator dyssynchrony[72,73]—could also lead to ventilator-induced diaphragm dysfunction.

Although the effect of ventilator-induced diaphragm dysfunction on clinical outcomes has not yet been quantified, it presents an important new challenge to the field of mechanical ventilation. Muscle-protective ventilation strategies will aim to titrate ventilation to maintain appropriate levels of inspiratory muscle effort and optimise synchrony between patient and ventilator. Methods of ventilation ideal for these purposes are already available in clinical practice (proportional assist ventilation[74] and neurally adjusted ventilatory assist[75]); these methods have not been studied in large randomised trials, but strategies to apply them early and optimally are being assessed. In these methods, the patient, not the clinician, determines the level of inspiratory pressure support breath-by-breath, an important shift in the way in which ventilation is delivered. Adjunctive strategies, such as pharmacological agents or electrical stimulation of the diaphragm, are also under active investigation. In patients with established diaphragm dysfunction, respiratory muscle rehabilitation might accelerate liberation from ventilation and prevent reintubation.[76] The optimum timing and strategies for respiratory muscle training need to be established.

The management of patient inspiratory effort presents an important and related clinical challenge. Because many patients with sepsis and acute lung injury exhibit high levels of respiratory drive, permitting spontaneous breathing to prevent diaphragm injury can result in large mechanical stresses within the lung[41] and impair haemodynamics and tissue oxygen delivery.[77] However, spontaneous breathing can improve ventilation homogeneity and reduce regional mechanical stress, perhaps depending on the severity of lung injury.[78] The decision to lighten sedation and permit spontaneous breathing is therefore frequently challenging. The development of strategies to fine-tune respiratory drive might allow a safe compromise between the benefits and risks of spontaneous breathing during mechanical ventilation.

Liberating patients from mechanical ventilation

Although most patients needing mechanical ventilation are easily separated from the ventilator after resolution of their initial syndrome, 20–40% of all patients submitted to mechanical ventilation will encounter difficulties breathing without ventilatory support. Understanding of the mechanisms of these difficulties is important and complex (figure 4). Prolongation of mechanical ventilation, with concomitant bed rest, increases mortality and contributes to morbidity both in the intensive care unit and after hospital discharge, sometimes enduring for years.[80] The weaning phase accounts for the majority of time on the ventilator in some patients, and centres specialised in prolonged weaning have been developed to manage challenging cases. Patients requiring prolonged ventilation are usually tracheostomised and require specific management including the treatment of mood or sleep disorders.[81,82] Several specific clinical problems, acquired in the intensive care unit, impair liberation from the ventilator.[79] An important finding has been the demonstration of weaning-induced pulmonary oedema.[83] Because intrathoracic pressure changes abruptly at the time that the patient is separated from the ventilator as the respiratory muscles assume the entire work of breathing, venous return significantly increases and an acute increase in both preload and afterload is imposed on the left ventricle. Fluid overload often persists from the initial resuscitation in these patients, as shown by increased concentrations of brain natriuretic peptides.[84] Pulmonary oedema can then rapidly develop in these patients, impairing separation from the ventilator. Once recognised, appropriate interventions based on a cardiovascular diagnostic work-up (electrocardiogram, echocardiography, biomarkers of cardiac dysfunction, and, in appropriately selected cases, cardiac catheterisation and angiography) can considerably facilitate weaning.[85,86]

Weakness of the respiratory muscles is particularly common in mechanically ventilated patients and can result in weaning difficulties. Monitoring techniques introduced in the intensive care unit, such as diaphragm ultrasound examination, have helped to better delineate this problem.[68,87,88] Weakness acquired in the intensive care unit affects all skeletal muscles, making mobilisation of the patient difficult and contributing to problems with the weaning process and coping with secretions.[89]

Weaning is also complex because it involves clinician behaviour. Systematic screening to determine when a patient is ready to be separated from the ventilator has been shown to be better than clinical judgment while the patient is under mechanical ventilation, and has become an essential part of the weaning process.[90] The more

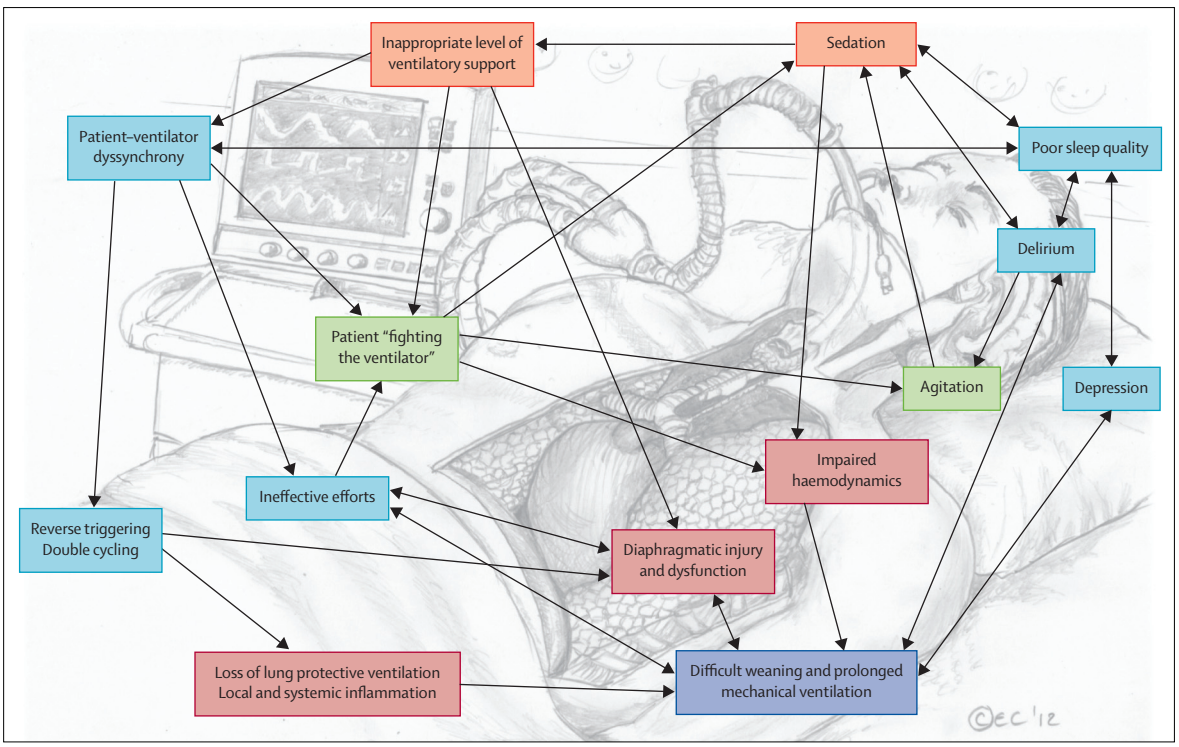

Figure 4: **Mechanisms of difficult weaning from mechanical ventilation**
Breathing without ventilatory assistance depends on coordinated function of the heart, lungs, respiratory and axial skeletal muscles, and brain. Impairments in any of these systems contribute (often synergistically) to impede weaning from mechanical ventilation. Unidirectional arrows signify putative causal pathways; bidirectional arrows signify putative associations (with unproven causality). Orange blocks represent clinical interventions; light blue blocks represent injury mechanisms; green blocks represent clinical manifestations of injury mechanisms; pink blocks represent organ dysfunction consequent to injury mechanisms; and the dark blue block highlights the effect of these mechanisms on clinical outcome. Modified with permission from Perren and Brochard.[79]

efficient approach is to test the patient's ability during spontaneous breathing. Exposing the patient too early might present some risks but the observation of a rapid shallow breathing pattern after only 1–2 min of disconnection is already an excellent predictor of subsequent clinical failure.[91] Why patients adopt this particular pattern so rapidly is unknown but the pattern represents very useful clinical information.

The accumulation of sedative drugs administered during the initial phase of resuscitation can also prolong ventilator dependence. These drugs can have very prolonged effects, resulting in poor sleep quality, delirium, and even long-term neurocognitive deficits. Every effort is now made to minimise or avoid sedation in ventilated patients,[92] especially benzodiazepine administration.[93] The best clinical approach to optimise analgesia and sedation is a very challenging aspect of the patient's management.[94]

Finally, when patients are deemed ready to be separated, the endotracheal tube is removed. About 15% of patients will require re-intubation within the next 3 days, and these patients have a considerably higher mortality than do those who are successfully extubated, making the medical decision of extubation an important and challenging one.[95] Non-invasive ventilation and HFNC can prevent postextubation respiratory failure in patients at risk for failure.[17,18,96] Once postextubation failure develops, however, intubation should promptly be considered, because delays in intubation resulting from prolonged application of non-invasive ventilation can worsen mortality.[20]

Overcoming the clinical challenges: personalised mechanical ventilation

In the 65 years since Bjorn Ibsen's intervention with positive-pressure ventilation in the Copenhagen poliomyelitis outbreak, the most important lesson has been that the outcomes of mechanically ventilated patients can best be improved by finding ways to prevent iatrogenic injury from the ventilator itself. Further advances in prevention of injury from mechanical ventilation might be achieved by tailoring mechanical ventilation to the physiological characteristics of the individual patient. Sizing tidal volume in proportion to the size of the so-called baby lung by targeting driving pressure (the ratio of tidal volume to static respiratory compliance) rather than tidal volume might better protect the lung in patients with more severe lung injury and low end-expiratory lung volumes.[44] At the same time, this approach would allow the use of larger tidal volumes in patients with larger end-expiratory lung volumes, potentially avoiding the need for sedation to suppress

respiratory drive with its attendant harms. Application of higher end-expiratory pressures only in patients who exhibit significant lung recruitment in response to higher mean airway pressures could help to further reduce mechanical stress and strain in these patients while avoiding harmful lung overdistension in patients who exhibit minimal lung recruitment.[97] Tailoring of ventilatory support to achieve acceptable levels of inspiratory effort and to avoid injurious dyssynchrony between patient and ventilator might prevent diaphragm injury and accelerate liberation from ventilation.

Individualisation of mechanical ventilation in this way will require the development and widespread adoption of clinical respiratory monitoring techniques. Monitoring pleural pressure with oesophageal manometry enables clinicians to account for derangements in chest wall mechanics when titrating ventilator pressures and allows bedside quantification of the mechanical stresses specifically applied to the lung.[98] Estimation of pleural pressure might also provide a useful guide to set end-expiratory pressure to prevent lung derecruitment.[30] A range of bedside measurement techniques have been proposed to assess potential lung recruitability to guide PEEP titration but none has achieved widespread acceptance.[99] Because patient inspiratory effort cannot be predicted directly from applied ventilator pressures or by physical examination, direct measures of inspiratory effort are required to properly titrate partially assisted ventilatory support. Inspiratory effort can be monitored with oesophageal manometry, electromyography, and even ultrasound.[100] Ultimately, the benefit of individually tailored mechanical ventilation strategies must be assessed in randomised clinical trials using protocolised ventilation strategies guided by bedside monitoring data. In view of the steady progress in both mechanistic insight and clinical outcome over the first six decades of mechanical ventilation and the continued advances in understanding of the many facets of patient–ventilator interaction, the potential for continued improvements in the clinical outcomes of patients with acute respiratory failure is strong.

Contributors

All authors contributed equally to the conception, planning, literature review, and writing of the manuscript.

Declaration of interests

LJB reports receiving support in the form of grants and equipment from Covidien, Philips, Fisher-Paykel, Maquet, and General Electric. ECG and NDF declare no competing interests.

Acknowledgments

We thank Alberto Goffi, Andreas Perren, and Guillaume Carteaux for their assistance with the preparation of graphic materials for this paper.

References

1 Baker AB. Artificial respiration, the history of an idea. *Med Hist* 1971; **15:** 336–51.

2 Ibsen B. Intensive therapy: background and development. *Int Anesthesiol Clin* 1966; **4:** 277–94.

3 Slutsky AS. History of mechanical ventilation. From Vesalius to ventilator-induced lung injury. *Am J Respir Crit Care Med* 2015; **191:** 1106–15.

4 Dreyfuss D, Saumon G. Ventilator-induced lung injury. Lessons from experimental studies. *Am J Respir Crit Care Med* 1998; **157:** 294–323.

5 Kavanagh BP, Meyer LJ. Normalizing physiological variables in acute illness: five reasons for caution. *Intensive Care Med* 2005; **31:** 1161–67.

6 Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; **299:** 637–45.

7 Mercat A, Richard J, Vielle B, Jaber S. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; **299:** 646–55.

8 Brochard L, Isabey D, Piquet J, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med* 1990; **323:** 1523–30.

9 Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; **333:** 817–22.

10 Girou E, Schortgen F, Delclaux C, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; **284:** 2361–67.

11 Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008. *Am J Respir Crit Care Med* 2012; **185:** 152–59.

12 Poulton EP. Left-sided heart failure with pulmonary edema: its treatment with the "pulmonary plus pressure machine". *Lancet* 1936; **228:** 981–83.

13 Masip J, Roque M, Sánchez B, Fernandez R, Subirana M, Expósito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA* 2005; **294:** 3124–30.

14 Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; **339:** 429–35.

15 Carteaux G, Millán-Guilarte T, de Prost N, et al. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med* 2016; **44:** 282–90.

16 Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; **372:** 2185–96.

17 Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med* 2014; **190:** 282–88.

18 Hernández G, Vaquero C, González P, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA* 2016; **315:** 1354–61.

19 Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest* 2015; **148:** 253–61.

20 Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; **350:** 2452–60.

21 ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307:** 2526–33.

22 Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; **315:** 788–800.

23 Gattinoni L, Marini JJ, Pesenti A, Quintel M, Mancebo J, Brochard L. The 'baby lung' became an adult. *Intensive Care Med* 2016; **42:** 663–73.

24 Cheney FW, Colley PS. The effect of cardiac output on arterial blood oxygenation. *Anesthesiology* 1980; **52:** 496–503.

25 Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. *Chest* 1980; **77:** 636–42.

26 Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med* 2016; **42:** 862–70.

27 Adhikari NKJ, Burns KEA, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007; **334:** 779.

28 Fan E, Wilcox ME, Brower RG, et al. Recruitment maneuvers for acute lung injury. *Am J Respir Crit Care Med* 2008; **178:** 1156–63.

29 Goligher EC, Kavanagh BP, Rubenfeld GD, et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress Trials. *Am J Respir Crit Care Med* 2014; **190:** 70–76.

30 Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; **359:** 2095–104.

31 Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; **368:** 795–805.

32 Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; **368:** 2159–68.

33 Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014; **40:** 332–41.

34 Sud S, Friedrich JO, Adhikari NKJ, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2014; **186:** E381–90.

35 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **290:** 319–23.

36 Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974; **110:** 556–65.

37 Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artifical ventilation. *N Engl J Med* 1967; **276:** 368–74.

38 Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997; **99:** 944–52.

39 Chiumello D, Carlesso E, Cadringher P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008; **178:** 346–55.

40 Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol* 1970; **28:** 596–608.

41 Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013; **188:** 1420–27.

42 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342:** 1301–08.

43 Zanella A, Castagna L, Salerno D, et al. Respiratory electrodialysis. A novel, highly efficient extracorporeal CO_2 removal technique. *Am J Respir Crit Care Med* 2015; **192:** 719–26.

44 Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; **372:** 747–55.

45 Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363:** 1107–16.

46 Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; **351:** 327–36.

47 Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; **303:** 865–73.

48 Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; **354:** 1775–86.

49 Chiumello D, Cressoni M, Carlesso E, et al. Bedside selection of positive end-expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome. *Crit Care Med* 2014; **42:** 252–64.

50 Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979; **242:** 2193–96.

51 Combes A, Brodie D, Bartlett R, et al. Position Paper for the Organization of Extracorporeal Membrane Oxygenation Programs for Acute Respiratory Failure in Adult Patients. *Am J Respir Crit Care Med* 2014; **190:** 488–96.

52 Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. *Lancet Respir Med* 2014; **2:** 154–64.

53 Lorusso R, Centofanti P, Gelsomino S, et al. Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: a 5-year multi-institutional experience. *Ann Thorac Surg* 2016; **101:** 919–26.

54 Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; **302:** 1888–95.

55 Miller DR, Christie GL, Molyneaux P, Currie GP. An outbreak of H1N1 influenza in a respiratory unit. *Thorax* 2010; **65:** 938–39.

56 Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; **306:** 1659–68.

57 Pham T, Combes A, Rozé H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; **187:** 276–85.

58 Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374:** 1351–63.

59 Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015; **191:** 894–901.

60 Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med* 2006; **355:** 41–50.

61 Blanch L, Villagrà A, Sales B, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015; **41:** 633–41.

62 Vassilakopoulos T, Zakynthinos S, Roussos C. The tension–time index and the frequency/ tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. *Am J Respir Crit Care Med* 1998; **158:** 378–85.

63 Adler D, Dupuis-Lozeron E, Richard J-C, Janssens J-P, Brochard L. Does inspiratory muscle dysfunction predict readmission after intensive care unit discharge? *Am J Respir Crit Care Med* 2014; **190:** 347–50.

64 Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. *Crit Care* 2013; **17:** R120.

65 Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med* 2004; **169:** 336–41.

66 Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008; **358:** 1327–35.

67 Hooijman PE, Beishuizen A, Witt CC, et al. Diaphragm muscle fiber weakness and ubiquitin–proteasome activation in critically ill patients. *Am J Respir Crit Care Med* 2015; **191:** 1126–38.

68 Goligher EC, Fan E, Herridge MS, et al. Evolution of diaphragm thickness during mechanical ventilation. impact of inspiratory effort. *Am J Respir Crit Care Med* 2015; **192:** 1080–88.

69 Jiang T-X, Reid WD, Road JD. Delayed diaphragm injury and diaphragm force production. *Am J Respir Crit Care Med* 1998; **157:** 736–42.

70 Ebihara S, Hussain SNA, Danialou G, Cho W-K, Gottfried SB, Petrof BJ. Mechanical ventilation protects against diaphragm injury in sepsis: interaction of oxidative and mechanical stresses. *Am J Respir Crit Care Med* 2002; **165:** 221–28.

71 Gea J, Zhu E, Gáldiz JB, et al. Functional consequences of eccentric contractions of the diaphragm. *Arch Bronconeumol* 2009; **45:** 68–74.

72 Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006; **32:** 1515–22.

73 Akoumianaki E, Lyazidi A, Rey N, et al. Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest* 2013; **143:** 927–38.

74 Carteaux G, Mancebo J, Mercat A, et al. Bedside adjustment of proportional assist ventilation to target a predefined range of respiratory effort. *Crit Care Med* 2013; **41:** 2125–32.

75 Piastra M, De Luca D, Costa R, et al. Neurally adjusted ventilatory assist vs pressure support ventilation in infants recovering from severe acute respiratory distress syndrome: nested study. *J Crit Care* 2014; **29:** 312.e1–5.

76 Martin AD, Smith BK, Davenport PD, et al. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care* 2011; **15:** R84.

77 Rutledge FS, Hussain SN, Roussos C, Magder S. Diaphragmatic energetics and blood flow during pulmonary edema and hypotension. *J Appl Physiol* 1988; **64:** 1908–15.

78 Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. *Crit Care Med* 2013; **41**: 536–45.

79 Perren A, Brochard L. Managing the apparent and hidden difficulties of weaning from mechanical ventilation. *Intensive Care Med* 2013; **39:** 1885–95.

80 Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364:** 1293–304.

81 Jubran A, Lawm G, Kelly J, et al. Depressive disorders during weaning from prolonged mechanical ventilation. *Intensive Care Med* 2010; **36:** 828–35.

82 Jubran A, Grant BJB, Duffner LA, et al. Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. *JAMA* 2013; **309:** 671–77.

83 Lemaire F, Teboul JL, Cinotti L, et al. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988; **69:** 171–79.

84 Mekontso Dessap A, de Prost N, Girou E, et al. B-type natriuretic peptide and weaning from mechanical ventilation. *Intensive Care Med* 2006; **32:** 1529–36.

85 Dessap AM, Roche-Campo F, Kouatchet A, et al. Natriuretic peptide-driven fluid management during ventilator weaning. *Am J Respir Crit Care Med* 2012; **186:** 1256–63.

86 Demoule A, Lefort Y, Lopes M-E, Lemaire F. Successful weaning from mechanical ventilation after coronary angioplasty. *Br J Anaesth* 2004; **93:** 295–97.

87 Matamis D, Soilemezi E, Tsagourias M, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. *Intensive Care Med* 2013; **39:** 801–10.

88 Goligher EC, Laghi F, Detsky ME, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. *Intensive Care Med* 2015; **41:** 642–49.

89 Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA* 2013; **310:** 1591–600.

90 Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; **335:** 1864–69.

91 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.

92 Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010; **375:** 475–80.

93 Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41:** 263–306.

94 Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA* 2012; **308:** 1985–92.

95 Thille AW, Richard J-CM, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med* 2013; **187:** 1294–302.

96 Jaber S, Lescot T, Futier E, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. *JAMA* 2016; **15:** 1345–53.

97 Goligher EC, Kavanagh BP, Rubenfeld GD, Ferguson ND. Physiologic responsiveness should guide entry into randomized controlled trials. *Am J Respir Crit Care Med* 2015; **192:** 1416–19.

98 Akoumianaki E, Maggiore SM, Valenza F, et al. The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014; **189:** 520–31.

99 Chiumello D, Marino A, Brioni M, et al. Lung recruitment assessed by respiratory mechanics and by CT scan: what is the relationship? *Am J Respir Crit Care Med* 2015; published online Dec 23. DOI:10.1164/rccm.201507-1413OC.

100 Bellani G, Pesenti A. Assessing effort and work of breathing. *Curr Opin Crit Care* 2014; **20:** 352–58.