6 Ventilatory Support of Patients with Sepsis or Septic Shock in Resource-Limited Settings

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6.1 Introduction

Evidence for recommendations on ventilatory support in patients with sepsis or septic shock has been mainly gathered from investigations in resource-rich settings [1, 2]. Often, it is not practical to directly translate this evidence to resource-limited settings. Indeed, intensive care units (ICUs) in these settings are frequently restricted in availability of equipment, laboratory support, and skilled staff [3]. Recommendations and suggestions are summarized in Table 6.1.

6.2 The Diagnosis of the Acute Respiratory Distress Syndrome (ARDS)

ARDS is a combined clinical and radiographic diagnosis, which per the latest consensus definition [4] requires the presence of acute bilateral chest infiltrates (onset within less than 1 week), not primarily caused by hydrostatic pulmonary edema, associated with hypoxemia based on PaO_2 to FiO_2 ratio (P/F) of less than 300 mm Hg and requiring at least 5 cm H_2O of positive end-expiratory pressure (PEEP). Therefore, in order to diagnose ARDS, performance of a chest radiograph (CXR) and arterial blood gas analysis (ABG) is necessary. However, the availability (or the lack of) of CXR and ABG in resource-limited settings might preclude their timely performance and utility in diagnosing septic patient with ARDS. It is not clear whether the mere diagnosis of ARDS would impact care and/or outcomes of patients with sepsis or septic shock with acute respiratory failure. There is a growing body of evidence suggesting that the diagnostic utility of the ultrasound exam of the lung compares well with that of the CXR [5–9]. When coupled with the performance of point-of-care echocardiogram, the diagnosis of non-cardiogenic pulmonary edema can be achieved in acutely hypoxemic patients, including those with sepsis [10–12].

Low oxygen saturation to FiO_2 ratio (S/F) within 6 h of presentation to emergency room was found to predict early development of ARDS [13]. A secondary analysis of the ARDS Network trial of a lower tidal volume ventilator strategy showed that S/F correlated with P/F in patients with ARDS [14]. Another study suggests that ARDS patients diagnosed by S/F have very similar clinical characteristics and outcomes

Table 6.1 Recommendations and suggestions on ventilatory support in patients with sepsis or septic shock in resource-limited settings (with grading)

1	ARDS diagnosis	Use CXR and ABG in septic patients with acute respiratory failure to diagnose ARDS (2B); where feasible, ultrasound exam of the lungs and heart may be used to narrow down the diagnosis of non-cardiogenic pulmonary edema (2D); oxygen pulse saturation relative to delivered oxygen concentration (S/F) may be an alternative for the arterial oxygen pressure relative to delivered oxygen concentration (P/F) for decision-making and continuous monitoring in settings where blood gas analyzers are absent (2D); patients with acute respiratory failure with or without ARDS diagnosis should be managed employing the principles of lung-protective mechanical ventilation (2B)
2	Semi-recumbent position	For ventilated septic patients, use elevated head-of-bed position ranging from 30° to 45° unless their hemodynamic state precludes this (1B); lower patient's position to less than 30° head-of-bed elevation transiently for the necessary procedures and during the resuscitation of the shock state until hemodynamic status is improved (1B) or longer in cases of sacral decubitus ulcer (1C)
3	NIV	Use invasive mechanical ventilation in cases of severe hemodynamic disturbance (i.e., shock) and/or severe hypoxemia (1A). NIV could be used in selected cases of mild respiratory failure with preserved or relatively stable hemodynamic status (2A); frequent reassessments of therapeutic effect of NIV are required in order to prevent delay in intubation and mechanical ventilation (1B)
4	Spontaneous breathing trials	Use spontaneous breathing trials early and regularly, preferably daily, in all ventilated patients (1A) (notably, to increase the success of this strategy, excessive sedation should be prevented); use the low level of pressure support technique (2D); perform spontaneous breathing trials, and extubate if the trial is passed successfully only at times sufficient staff is available (2D); develop a local guideline for spontaneous breathing trials (2C)
5	Tidal volume size	Use low tidal volume ventilation in patients with ARDS diagnosis (1A) and in all ventilated patients (2B) (i.e., prevent tidal volumes higher than 10 ml/kg PBW, and consider tidal volumes of 5–7 ml/kg PBW in all patients); titrate tidal volume size using PBW and not the actual body weight (2D); timely recognize under-ventilation, where respiratory rates should be adjusted (2D); accept higher respiratory rates (i.e., do not increase sedation if the respiratory rate rises with the use of lower tidal volumes) (2C); end-tidal CO_2 monitoring could be helpful in timely recognition of under- or overventilation (2D)
6	PEEP	Use a minimum level of PEEP (5 cm H_2O) in all patients with sepsis or septic shock with acute respiratory failure (2B); consider using higher levels of PEEP only in patients with moderate or severe ARDS (2A); if lack of CXR and ABG availability hampers making an ARDS diagnosis, we suggest against liberal use of higher levels of PEEP (2D); when the team is trained and experienced in using respiratory dynamic compliance, PEEP could be titrated based on this parameter (2D); so-called PEEP/FiO_2 tables could be used for titrating PEEP, but this approach generally requires frequent ABGs (2B); patients who need higher levels of PEEP are preferably closely monitored, preferably by using an arterial line, as hypotension and circulatory depression may develop (1A)

(continued)

Table 6.1 (continued)

7	FiO_2 vs. PEEP	Low FiO_2 is preferred over high FiO_2 (2B); the target should be PaO_2 > 8 kPa [60 mm Hg] and/or SpO_2 88–95% (2A); PEEP/FiO2 tables can be used to find the best PEEP/FiO2 combination (2B); staff with experience in using PEEP could prefer to use higher levels of PEEP to treat hypoxia; in centers with little experience in using PEEP, the initial response to hypoxia should be higher FiO_2 before using higher levels of PEEP (2D)
8	Recruitment maneuvers	Use recruitment maneuvers in patients with moderate or severe ARDS (2B) and in patients with refractory hypoxemia in whom an ARDS diagnosis cannot be made due to lack of CXR and/or ABG (2D) and only when the staff is trained and experienced in performing these maneuvers (2D); use the simplest maneuver, i.e., "sustained inflation" (2D); when using recruitment maneuvers, the patient should be closely monitored, preferably by using an arterial line, to promptly detect hemodynamic compromise (2B)
9	Modes of ventilation	We recommend using "volume-controlled" modes of ventilation over "pressure-controlled" modes of ventilation (2D); we cannot recommend on whether assisted ventilation ("support" mode) is preferred over assist ventilation ("controlled mode") in all patients; use a short course of muscle paralysis (< 48 h) and thus controlled ventilation, only in patients with moderate or severe ARDS (2B)

Abbreviations: *CO_2* carbon dioxide, *CXR* chest radiograph, *ABG* arterial blood gas, *ARDS* acute respiratory distress syndrome, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *NIV* noninvasive ventilation
Grading: see online supplement for explanations

Table 6.2 Proposed S/F values as correlates to existing P/F thresholds

	P/F = 300	P/F = 200	P/F = 100
Pandharipande et al.	370	240	115
Rice et al.	315	235	–
Lobete et al.	296	236	146
Khemani et al.	264	221	–
Bilan et al.	235	181	–

Data from [14, 17–20]

compared with patients diagnosed by P/F [15]. A retrospective study from Brazil showed that a low S/F at ICU admission was associated with increased risk of death in patients with severe sepsis or septic shock [16]. However, diagnosis of ARDS or its severity categorization based on S/F alone can be difficult given a wide variability in S/F relative to P/F observed in the studies on the topic [13–20]. In addition to oxygenation impairment, bilateral infiltrates on CXR at the time of hospital presentation have also been shown to predict development of early ARDS [21].

We *suggest* using CXR and ABG in septic patients with acute respiratory failure, if available (2B). In the absence of CXR availability, frequent physical exams and the overall clinical picture will prove beneficial in monitoring patient's respiratory status and decision-making (2D). Where feasible, ultrasound exam of the lungs and heart may be used to narrow down the diagnosis of non-cardiogenic pulmonary edema (2D). In the absence of ABG availability, the S/F could be an alternative for the P/F in decision-making and continuous monitoring of an individual patient (2B) (Table 6.2).

Patients with sepsis-related acute respiratory failure with or without ARDS diagnosis should be managed employing the principles of lung-protective mechanical ventilation (2B). In the questions to follow, recommendations may vary depending on the availability of CXR and ABG (i.e., the feasibility to make diagnosis of ARDS).

6.3 The Semi-recumbent Position

Position of the septic patient with acute respiratory failure necessitating oxygen and ventilator support may have important implications in the treatment. Currently, it is recommended that ventilated patients be positioned in the bed so the head of bed is elevated at the 30° to 45° (i.e., "semi-recumbent"). This position may be important for at least two reasons: (1) decreased risk of aspiration and (2) decreased work of breathing. Some patients with a profound hemodynamic disturbance despite the resuscitation may need to transiently be placed in a flat or even in a Trendelenburg position. Others, especially obese patients or those with states that increase abdominal pressure may benefit from the higher angle, sitting position to allow better gravity support for the diaphragmatic excursions, which may reduce bibasilar atelectasis and improve ventilation–perfusion matching.

Although it may be expected that the maintenance of the head-of-bed elevation at 30° to 45° may increase the workload of nurses and other bedside providers, a single study from Brazil showed that among other interventions, maintenance of the head of bed at 30° to 45° did not additionally increase the workload of nursing professionals in the ICU [22]. A randomized controlled trial (RCT) from Vietnam, however, suggests that a semi-recumbent position does not prevent the occurrence of healthcare-associated pneumonia in severe tetanus patients [23]. Nevertheless, other RCTs from resource-rich ICUs established the role of semi-recumbent position in the prevention of aspiration and ventilator-associated pneumonia in critically ill patients [24–26]. The actual degree of elevation of head of bed needs to be individualized based on the hemodynamic and respiratory status [27], as well as the risk of pressure sores/decubitus ulcers [28].

The semi-recumbent position should be feasible even in the most resource-limited settings, where despite the lack of special hospital beds, pillows and other soft material items can be used for the upper back and head support. In practice, it could be hard to sustain 30° with pillows alone. Frequent reassessments of the angle of elevation with a target of 30° to 45° should be instituted. Whether this single intervention further increases the workload of bedside providers will depend on the local, site-specific circumstances including the degree of involvement of family members in the nursing care. Of note, the semi-recumbent position may not be suitable for some patients, such as those with acute thoracic spine fracture.

We *recommend* that the vast majority of ventilated septic patients should be placed in the semi-recumbent position with an elevated head of bed ranging from 30° to 45° unless their hemodynamic state precludes this (1B). Patient's position could be lowered to less than 30° head-of-bed elevation transiently for the necessary procedures and during the resuscitation of the shock state until hemodynamic status is improved (1B) or longer in cases of sacral decubitus ulcer (1C).

6.4 Noninvasive Ventilation (NIV)

One of the primary goals in sepsis-induced acute respiratory failure is to ensure and maintain the tissue oxygen delivery. This can be provided by simple oxygen supplementation as well as by NIV or invasive mechanical ventilation, which in addition to oxygen supplementation provides positive-pressure ventilation. Generally, patients with mild oxygen saturation impairments and noncomplicated hemodynamic status (i.e., non-shock states) can be managed with simple oxygen supplementation. NIV has potentially advantageous role in acute respiratory failure over the simple administration of oxygen [29] or invasive mechanical ventilation [30]. However, frequently patients initially started on NIV fail to improve and require intubation and invasive mechanical ventilation. Moreover, the delay in intubation and MV has been associated with adverse outcomes [31].

A prospective cohort study from Brazil showed that more than half of ICU patients initially placed on NIV (54%) required subsequent intubation and mechanical ventilation, and failure of NIV was the strongest predictor of hospital mortality [31]. A 1-year observational study from India showed that almost all patients with moderate to severe acute respiratory failure required invasive mechanical ventilation (40/41) and that almost 2/3 of patients (11/17) initially managed with NIV subsequently required intubation and invasive mechanical ventilation [32]. The remaining evidence stems from resource-rich ICUs and suggests discretionary use of NIV in cases of sepsis-associated acute respiratory failure and concomitant immunosuppressed state [33], hypercapnia due to obstructive lung disease [34, 35], or hydrostatic pulmonary edema, with relatively preserved mental status and absence of shock [30, 34]. NIV could also be attempted in patients with mild hemodynamic and respiratory impairments with frequent reassessments of work of breathing, oxygenation and ventilation and prompt intubation, and invasive mechanical ventilation in cases of failure to improve after 1–2 h of intensive resuscitation and monitoring [36].

In individual ICU settings, where both NIV and invasive mechanical ventilation are available, evidence from resource-rich settings could be translated. However, it is of utmost importance that patients placed on NIV are closely monitored and assessed, so in cases of insufficient improvement, they can be intubated and placed on invasive mechanical ventilation without delays. Therefore, it is important to stress the need for appropriate staffing, which will allow close monitoring and frequent reassessments. Another potential safety concern is when NIV is applied using high tidal volumes because of underlying metabolic acidosis. Given potential for volume-induced lung injury, these patients may need invasive mechanical ventilation with adequate sedation (and maybe even short-term muscle paralysis) if there is no improvement after short-term NIV (i.e., within 1–2 h).

Based on the evidence from resource-rich ICUs, we *recommend* the use of invasive mechanical ventilation in cases of severe hemodynamic disturbance manifested as shock or severe hypoxemia (1A). We *suggest* that NIV could be used in selected cases of mild respiratory failure with preserved or relatively stable hemodynamic status (2A), especially in the above-described specific patient populations. This suggestion does not depend on the availability or lack of CXR or ABG for ARDS

diagnosis. Once NIV is started, continuous resuscitation efforts and frequent reassessments of therapeutic effect of NIV are required in order to prevent delay in intubation and MV (1B).

6.5 Spontaneous Breathing Trials

Preventing unnecessary long ventilatory support is essential in preventing harm from intubation and mechanical ventilation. Successful completion of spontaneous breathing trials, which include a low level of pressure support, continuous positive airway pressure, or the use of a T-piece, increases the likelihood of successful discontinuation of ventilation.

Three well-performed trials in resource-rich ICUs [37–39] clearly showed benefit from early spontaneous breathing trials, i.e., shorter duration of ventilation. A recent meta-analysis found no evidence of a difference between spontaneous breathing trials using low levels of pressure support and spontaneous breathing trials using a T-piece [40].

Spontaneous breathing trials are available and affordable, in particular if no additional techniques are used (e.g., when a spontaneous breathing trial uses a low level of pressure support). It could be safer to perform spontaneous breathing trials using low level of pressure support technique than spontaneous breathing trials using a T-piece, as with the first approach a minimum ventilatory support is guaranteed. Spontaneous breathing trials could be time-consuming, in particular for ICUs with restricted staffing, but if successfully implemented, this intervention could save resources including labor because it shortens duration of ventilation. For practical reasons, tracheal extubation of patients in whom a trial of spontaneous breathing is successful should take place when there is sufficient staffing around (i.e., during daytimes), as such reducing the risk of re-intubation with no adequate staffing promptly available. Notably, to increase the success of this strategy, oversedation should be prevented.

We *recommend* using spontaneous breathing trials regularly, preferably daily, in all ventilated patients in low resource-limited ICUs (1A), and we *suggest* using the low level of pressure support technique (2D). We *suggest* performing spontaneous breathing trials and to extubate if the trial is successful only when sufficient staff is available to re-intubate those patients that may still need ventilatory support (2D). Nurses and physicians should develop local protocols for spontaneous breathing trials (2C). Of note, the effectiveness of using spontaneous breathing trials depends on sedation practices.

6.6 Low Tidal Volumes

"Lung-protective" ventilation with low tidal volumes improves survival of patients with ARDS in resource-rich settings [41, 42], and this can be translated to resource-limited ICUs. Delays in diagnosing ARDS may delay timely use of low tidal volumes, a problem that could be encountered in low- and middle-income countries

(LMICs) (see also *question 1*). Restricting low tidal volume ventilation to patients with ARDS diagnosis thus could lead to underuse or delayed use of this intervention, which is not an additional burden to limited resources. Notably, evidence is growing for the benefit of low tidal volume ventilation in patients without ARDS [43–45].

One RCT in ARDS patients from Brazil showed a bundle of a low tidal volume (6 ml/kg PBW) *plus* a level of PEEP above the lower inflection point on the static pressure–volume curve, compared with a bundle of conventional tidal volumes (12 ml/kg PBW) *plus* the lowest level of PEEP to maintain acceptable oxygenation, improved 28-day survival in patients with ARDS [46]. One observational study from Korea in patients with ARDS due to H1N1 [47] compared outcomes in tidal volume size tertiles (≤7 ml/kg PBW, 7–9 ml/kg PBW, and >9 ml/kg PBW) [47]. In this study, use of low tidal volumes was associated with a higher ICU survival and a higher number of ventilation-free days, ICU-free days, and hospital-free days.

The findings are in line with two meta-analyses [41, 42], including several well-performed RCTs [46, 48–51] that confirmed the benefit from low tidal volume ventilation in patients with ARDS. The precise titration of the size of tidal volumes for an individual patient could require adjustment for such factors as the presence of a profound metabolic acidosis and high obligate minute ventilation (tidal volumes may need to be as large as 8 ml/kg PBW) and the plateau pressure achieved and the level of PEEP chosen (tidal volumes may need to be as small as 4 ml/kg PBW). Notably, it is crucial to use predicted body weight for calculating the size of tidal volumes and not to use actual body weight (although actual body weight is usually equal to PBW in the normally nourished or undernourished patient).

Several recent meta-analyses [43–45], including one RCT [52] and several large observational studies in critically ill patients without ARDS in HICs [53–55], suggested a decreased risk of developing ARDS, shorter duration of ventilation, and shorter stay in hospital with low tidal volume volumes.

There are no studies on the use of end-tidal carbon dioxide (CO_2) monitoring as an alternative to ABG monitoring for patients receiving ventilation, including in LMICs, although one guideline suggests capnography to guide ventilator management [56]. Infrequent ABG in low-resource settings may preclude the early detection of harmful hypercapnia. While moderate hypercapnia is acceptable, severe hypercapnia should be prevented by closely monitoring minute ventilation. Also, in patients with brain injury, $PaCO_2$ control may be more important than in other patients. However, metabolic acidosis is frequently seen in patients with sepsis or septic shock, which may limit ventilation strategies that may cause hypercapnia. Low tidal volume ventilation comes with higher respiratory rates, which may create a feeling of discomfort, not necessarily for the patient but for the staff, which may unnecessarily trigger use of (more) sedation.

We *recommend* using low tidal volume ventilation in patients with ARDS diagnosis (1A) and *suggest* using low tidal volumes in all ventilated patients with sepsis or septic shock when lack of CXR or ABG availability hampers a timely ARDS diagnosis (i.e., prevent tidal volumes higher than 10 ml/kg PBW and consider tidal volumes of 5–7 ml/kg PBW in all patients) (2B). Notably, tidal volume size

titration must use PBW and not the actual body weight (1A). Staff should be trained in timely recognition of under-ventilation, where respiratory rates should be adjusted (2D). Staff should be trained in accepting higher respiratory rates and not using more sedation (2C). Of note, we found no literature on preferred tidal volume sizes in patients with chronic obstructive pulmonary disease, but these patients may tolerate ventilation with low tidal volumes. End-tidal CO_2 monitoring could be helpful in timely recognition of endotracheal tube dislodgement or under- or overventilation (2D).

6.7 PEEP

PEEP prevents atelectasis, as such preventing ventilation–perfusion mismatch. PEEP, however, could also induce regional overdistension, which could increase dead space and injure lung tissue. Moreover, higher levels of PEEP could cause hemodynamic compromise, especially in patients with sepsis or septic shock. Higher levels of PEEP have only been found beneficial in patients with more severe forms of ARDS [57].

One recent observational study from Brazil showed no association between the level of PEEP applied and outcome in patients without ARDS [16]. In this study the median level of PEEP was 6 cm H_2O. The findings of this study were at least in part in line with results from a RCT in patients without ARDS in the USA that showed no differences in the occurrence of ARDS and other pulmonary complications when ventilating with 8 cm H_2O of PEEP or no PEEP [58]. However, while one recent RCT in the Netherlands comparing a strategy using low tidal volumes (6 ml/kg PBW) with a strategy using conventional tidal volumes (10 ml/kg PBW) in patients without ARDS found an independent association between use of higher levels of PEEP and the development of lung injury [52], one RCT in patients without ARDS in Spain showed a lower incidence of ventilator-associated pneumonia and a lower risk of hypoxemia with 5–8 cm H_2O of PEEP compared to no PEEP [59]. Mortality was not affected in the last RCT, however, and differences in the incidence of ventilator-associated pneumonia could have reflected more a difference in the occurrence of atelectasis than a true difference in pulmonary infection rates.

One RCT in patients with ARDS from Brazil showed that a strategy that uses low tidal volumes (6 ml/kg predicted body weight, PBW) *plus* a level of PEEP above the lower inflection point of the static pressure–volume curve to be superior to a strategy that uses conventional tidal volumes (12 ml/kg PBW) *plus* the lowest level of PEEP to maintain acceptable oxygenation with respect to 28-day survival [46]. It is uncertain whether benefit came from use of lower tidal volumes, higher levels of PEEP, or both. Three large multicenter randomized controlled trials conducted in patients with ARDS in HICs individually showed no benefit from use of higher levels of PEEP, titrated on the pulmonary compliance or based on the P/F, compared to lower levels of PEEP [60–62], but a meta-analysis showed that use of higher levels of PEEP was beneficial in patients with more severe forms of ARDS [57].

A minimum level of PEEP is easily applied and safe as most if not all ventilators allow setting a certain level of PEEP, and the benefit from prevention of atelectasis could outweigh the risk of regional overdistension. Because of the increased risk of hemodynamic instability with higher levels of PEEP, continuous hemodynamic monitoring, preferably by using an arterial line, will be necessary to guarantee safety. It can be a challenge to suspect and detect regional overdistension, and it could be difficult to find the best level of PEEP in an individual patient when physicians are untrained and inexperienced in using respiratory compliance and the P/F.

We *suggest* using at least a minimum level of PEEP (5 cm H_2O) in all patients with sepsis or septic shock with acute respiratory failure in resource-limited ICUs (2B). Based on the available evidence, we *suggest* using higher levels of PEEP only in patients with moderate or severe ARDS (2A). If lack of CXR and ABG availability hampers making an ARDS diagnosis, we *suggest* against liberal use of higher levels of PEEP (2D), but when the team is trained and experienced in using respiratory compliance, PEEP could be titrated based on this parameter (2D). Alternatively, so-called PEEP/FiO_2 tables could be used for titrating PEEP, but this approach generally requires frequent ABGs (2B) or use of SpO_2 to titrate FiO_2. Patients who need higher levels of PEEP should be closely monitored, as hypotension may develop (1A).

6.8 Low Oxygen Fractions with High PEEP or High Oxygen Fractions with Low PEEP

When high levels of PEEP are considered dangerous, or when it is difficult or impossible to find the best level of PEEP in an individual patient (see *question 6*) and when the team is inexperienced in performing recruitment maneuvers (see *question 8*), hypoxemia may trigger use of higher FiO_2. High FiO_2, however, induces the production of large amounts of reactive oxygen species that overwhelm natural antioxidant defenses, which could then injure cellular structures and consequently may induce pulmonary injury. In particular inflamed lungs are more susceptible to oxygen toxicity. Furthermore, ventilation with high FiO_2 could induce reabsorption atelectasis.

While studies suggest that "normoxia" should be targeted in patients with ARDS, there is increasing evidence for harm from strategies that use high FiO_2 aiming for higher blood oxygen levels in general ICU patients [63, 64]. Associations between ventilation strategies that use high FiO_2 and increased mortality have also been found in patients following resuscitation from cardiac arrest [65] and patients with ischemic stroke [66] or traumatic brain injury [67]. Two recent meta-analyses confirm arterial hyperoxia to be associated with worse hospital outcome in various subsets of critically ill patients [68, 69]. As discussed above (*question 6*), higher levels of PEEP have only been found beneficial in patients with more severe forms of ARDS [57].

Table 6.3 Allowable combinations of PEEP and FiO_2

Strategy in which first FiO_2 is raised in response to hypoxemia (originally called the low PEEP group)														
FiO_2	0.21	0.3	0.4	0.4	0.5	0.5	0.6	> 0.6						
PEEP	5	5	5	8	8	10	10	10						
Strategy in which first PEEP is raised in response to hypoxemia (originally called the high PEEP group)														
FiO_2	0.21	0.3	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	0.9	1.0
PEEP	5–12	14	14	16	16	18	20	20	20	20	22	22	22	> 22

Adapted from [58]

A certain extent of hypoxemia with a target PaO_2 > 8 kPa [60 mmHg] has been suggested to be safe [51]. A SpO_2 of 88–95% could be targeted when ABGs are not or only scarcely available [51].

Using "PEEP/FiO_2 tables" with the aim to ventilate patients with ARDS with the lowest level of PEEP and the lowest level of FiO_2 is feasible and safe in LMICs, but this approach mandates frequent ABGs or use of SpO_2 to titrate FiO_2 [47–49]. Implementation of this strategy could be more complex in LMICs where ABGs typically are less often available. Alternatively, SpO_2 could be used to titrate PEEP and FiO_2. Also, when continuous hemodynamic monitoring is lacking, use of high levels of PEEP could be dangerous. In such settings it could be safer to prefer higher FiO_2 than higher levels of PEEP.

Based on the available evidence, we *suggest* being cautious with liberal use of high FiO_2 (2B). The target should be PaO_2 > 8 kPa [60 mmHg] and/or SpO_2 88–95% (2A). PEEP/FiO_2 tables can be used to find the best PEEP/FiO_2 combination in individual patients in LMICs (2B). We *suggest* preferring low FiO_2 with high levels of PEEP, if the team is trained and experienced in (safe) the use of higher levels of PEEP; if not, it is probably safer to use high FiO_2 with lower levels of PEEP (2D). An example of a "PEEP/FiO_2 table" is provided (Table 6.3) [60].

6.9 Recruitment Maneuvers

It is generally considered necessary to combine higher levels of PEEP with recruitment maneuvers, as early use of recruitment maneuvers could open additional lung units that remain closed when only applying higher levels of PEEP. Recruitment maneuvers, however, are complex interventions that could also cause pulmonary and extra-pulmonary harm, especially in inexperienced hands.

In an RCT from Brazil [46], the two arms of the study also differed in respect to using recruitment maneuvers. The same applies for other RCTs comparing higher levels of PEEP with lower levels of PEEP in patients with ARDS in HICs [60–62]. One systematic review of four randomized controlled trials investigating the benefit

of recruitment maneuvers remained inconclusive [70]; a more recent meta-analysis suggested that strategies that use recruitment maneuvers are associated with a lower mortality in patients with ARDS [71].

Recruitment maneuvers can cause episodes of severe hemodynamic compromise [61], especially in patients with sepsis or septic shock. Recruitment maneuvers could also induce regional overdistension. In HIC the performance of recruitment maneuvers is seen as a complex intervention, with associated risks if not applied properly [61]. Therefore, it is only applied in patients with refractory and severe hypoxemia and only in patients with a stabilized circulation and preferably with an arterial line in situ.

The recruitment maneuvers are variable, which is a general limitation of the technique because it is not standardized. The earliest recruitment maneuver ever used during mechanical ventilation is probably the "sigh," which consists of increasing tidal volume or level of PEEP [72]. However, there is a potential safety concern given that this maneuver transiently elevates plateau pressure above the recommended threshold of 30 cm H_2O, in patients with ARDS. The most frequently investigated recruitment maneuver, due to its apparent simplicity, is the sustained inflation, which consists of pressurizing the airways at a specific level and maintaining it for a given duration. A common combination is the application of 40 cm H_2O airway pressure for 40 s ("40/40") [73]. Sustained inflation is transient and simple recruitment maneuver, which is likely an overall safe procedure as it can potentially obviate the need for ongoing use of higher intrathoracic pressures. High PEEP and pressure-controlled ventilation with a fixed driving pressure (i.e., the level of inspiratory pressure minus the level of PEEP) are other ways to perform recruitment maneuvers [74].

The use of recruitment maneuvers during ventilation is feasible and safe, but only in experienced hands. The lack of experience and absence of hemodynamic monitoring may hamper the safe and widespread use in LMICs. Moreover, it can be challenging to detect overdistension. Of all recruitment maneuvers, sustained inflation is probably the simplest and the safest maneuver.

We *suggest* using recruitment maneuvers in resource-limited ICUs in patients with moderate or severe ARDS (2B) and suggest using recruitment maneuvers in patients in resource-limited ICUs with refractory hypoxemia in whom a diagnosis of ARDS cannot be made due to lack of CXR and/or ABG (2D), but only when the staff is trained and experienced in performing these maneuvers (2D). We *suggest* using the simplest maneuver, i.e., "sustained inflation" (2D). When using recruitment maneuvers, the patient should be closely monitored to detect hemodynamic compromise (2B).

6.10 Ventilation Modes

Traditionally reserved for use in weaning patients from ventilation, assisted ventilation modes are now used in all phases of ventilation. Controlled ventilation is associated with incapability of reversing alveolar collapse in dependent lung parts and an increased risk of ventilator-induced diaphragmatic dysfunction. Assisted ventilation could be preferred over controlled ventilation, because assisted ventilation can be tolerated with

reduced sedation requirements, and may be associated with less hemodynamic deterioration, and lung protection compared to controlled ventilation [75, 76].

"Volume-controlled" ventilation and "pressure-controlled" ventilation are not different ventilatory modes but are different control variables within a mode [77]. "Volume-controlled" ventilation offers the safety of a preset tidal volume and minute ventilation, while "pressure-controlled" ventilation offers a flow that better mimics the flow during inspiration of a spontaneously breathing individual. Investigations comparing the effects of "volume-controlled" ventilation and "pressure-controlled" ventilation are not well controlled and offer no evidence for benefit of the one mode over the other [77].

One small RCT, including patients with and patients without ARDS, demonstrated shorter length of stay in the ICU with use of assisted ventilation compared to controlled ventilation [78]. Another RCT in patients with ARDS showed a higher number of ventilator-free days with assisted ventilation, although the difference was not statistically significant, but in both groups, some sort of support was applied [79]. Beneficial effects of assisted ventilation could include improvement of gas exchange, hemodynamics, and non-pulmonary organ perfusion and function, as well as improved quality of sleep, and are associated with a decreased need for sedation and paralysis [80].

Assisted ventilation is available, feasible, and affordable in all patients in LMICs, where its use is probably also safe. One exception could be patients with severe and early ARDS in whom a short course of muscle paralysis, and thus use of controlled ventilation, has been found to be beneficial [81], though evidence for benefit of a short course of muscle paralysis in these patients in LMICs is lacking. Notably, with assisted ventilation tidal volumes are usually larger than with controlled ventilation. This is probably due to an active diaphragm, which largely prevents dorsal atelectasis. A rise in tidal volumes >6 ml/kg PBW, while using the lowest level of pressure support, may not be a reason to switch back to controlled ventilation. Since minute volume and tidal volume size are guaranteed with "volume-controlled" modes of ventilation and not with "pressure-controlled" modes of ventilation, "volume-controlled" modes could be safer than "pressure-controlled" modes, in particular in settings with restricted physician and nursing staff.

Therefore we *suggest* using "volume-controlled" modes of ventilation rather than "pressure-controlled" modes of ventilation in resource-limited settings. However, teams with experience and expertise in "pressure-controlled" modes of ventilation could continue to use this mode (2D). We *make no recommendations* regarding assisted ventilation over controlled ventilation in all patients in LMICs. We *suggest* a short course of muscle paralysis (<48 h) and thus the use of controlled ventilation, in patients with severe ARDS (2B).

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima

S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486–552.

2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304–77.
3. Schultz MJ, Dunser MW, Dondorp AM, Adhikari NK, Iyer S, Kwizera A, Lubell Y, Papali A, Pisani L, Riviello BD, Angus DC, Azevedo LC, Baker T, Diaz JV, Festic E, Haniffa R, Jawa R, Jacob ST, Kissoon N, Lodha R, Martin-Loeches I, Lundeg G, Misango D, Mer M, Mohanty S, Murthy S, Musa N, Nakibuuka J, Serpa Neto A, Nguyen Thi Hoang M, Nguyen Thien B, Pattnaik R, Phua J, Preller J, Povoa P, Ranjit S, Talmor D, Thevanayagam J, Thwaites CL, Global Intensive Care Working Group of the European Society of Intensive Care Medicine. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med. 2017;43:612–24.
4. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33.
5. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. Anesthesiology. 2004;100:9–15.
6. Bouhemad B, Zhang M, Lu Q, Rouby JJ. Clinical review: bedside lung ultrasound in critical care practice. Crit Care. 2007;11:205.
7. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, Dean A, Tsung JW, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby JJ, Arbelot C, Liteplo A, Sargsyan A, Silva F, Hoppmann R, Breitkreutz R, Seibel A, Neri L, Storti E, Petrovic T, International Liaison Committee on Lung Ultrasound for International Consensus Conference on Lung Ultrasound. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38:577–91.
8. Lichtenstein DA, Meziere GA, Lagoueyte JF, Biderman P, Goldstein I, Gepner A. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. Chest. 2009;136:1014–20.
9. Bass CM, Sajed DR, Adedipe AA, West TE. Pulmonary ultrasound and pulse oximetry versus chest radiography and arterial blood gas analysis for the diagnosis of acute respiratory distress syndrome: a pilot study. Crit Care. 2015;19:282.
10. Melamed R, Sprenkle MD, Ulstad VK, Herzog CA, Leatherman JW. Assessment of left ventricular function by intensivists using hand-held echocardiography. Chest. 2009;135:1416–20.
11. Chimot L, Legrand M, Canet E, Lemiale V, Azoulay E. Echocardiography in hemodynamic monitoring. Chest. 2010;137:501–2.
12. Kaplan A, Mayo PH. Echocardiography performed by the pulmonary/critical care medicine physician. Chest. 2009;135:529–35.
13. Festic E, Bansal V, Kor DJ, Gajic O, US Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG–LIPS). SpO2/FiO2 ratio on hospital admission is

an indicator of early acute respiratory distress syndrome development among patients at risk. J Intensive Care Med. 2015;30:209–16.
14. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest. 2007;132:410–7.
15. Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB. Clinical characteristics and outcomes are similar in ARDS diagnosed by SpO2/FiO2 ratio compared with PaO2/FiO2 ratio. Chest. 2015;148(6):1477–83.
16. Serpa Neto A, Cardoso SO, Ong DS, Esposito DC, Pereira VG, Manetta JA, Slooter AJ, Cremer OL. The use of the pulse oximetric saturation/fraction of inspired oxygen ratio for risk stratification of patients with severe sepsis and septic shock. J Crit Care. 2013;28:681–6.
17. Bilan N, Dastranji A, Ghalehgolab Behbahani A. Comparison of the spo2/fio2 ratio and the pao2/fio2 ratio in patients with acute lung injury or acute respiratory distress syndrome. J Cardiovasc Thorac Res. 2015;7:28–31.
18. Khemani RG, Thomas NJ, Venkatachalam V, Scimeme JP, Berutti T, Schneider JB, Ross PA, Willson DF, Hall MW, Newth CJ, Pediatric Acute Lung Injury and Sepsis Network Investigators (PALISI). Comparison of SpO2 to PaO2 based markers of lung disease severity for children with acute lung injury. Crit Care Med. 2012;40:1309–16.
19. Lobete C, Medina A, Rey C, Mayordomo-Colunga J, Concha A, Menendez S. Correlation of oxygen saturation as measured by pulse oximetry/fraction of inspired oxygen ratio with Pao2/fraction of inspired oxygen ratio in a heterogeneous sample of critically ill children. J Crit Care. 2013;28(538):e531–7.
20. Pandharipande PP, Shintani AK, Hagerman HE, St Jacques PJ, Rice TW, Sanders NW, Ware LB, Bernard GR, Ely EW. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. Crit Care Med. 2009;37:1317–21.
21. Rackley CR, Levitt JE, Zhuo H, Matthay MA, Calfee CS. Clinical evidence of early acute lung injury often precedes the diagnosis of ALI. J Intensive Care Med. 2013;28:241–6.
22. Colaco AD, Nascimento ER. Nursing intervention bundle for enteral nutrition in intensive care: a collective construction. Rev Esc Enferm USP. 2014;48:844–50.
23. Loan HT, Parry J, Nga NT, Yen LM, Binh NT, Thuy TT, Duong NM, Campbell JI, Thwaites L, Farrar JJ, Parry CM. Semi-recumbent body position fails to prevent healthcare-associated pneumonia in Vietnamese patients with severe tetanus. Trans R Soc Trop Med Hyg. 2012;106:90–7.
24. Torres A, Serra-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, Lomena F, Rodriguez-Roisin R. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med. 1992;116:540–3.
25. Orozco-Levi M, Torres A, Ferrer M, Piera C, el-Ebiary M, de la Bellacasa JP, Rodriguez-Roisin R. Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med. 1995;152:1387–90.
26. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999;354:1851–8.
27. Gocze I, Strenge F, Zeman F, Creutzenberg M, Graf BM, Schlitt HJ, Bein T. The effects of the semirecumbent position on hemodynamic status in patients on invasive mechanical ventilation: prospective randomized multivariable analysis. Crit Care. 2013;17:R80.
28. Metheny NA, Frantz RA. Head-of-bed elevation in critically ill patients: a review. Crit Care Nurse. 2013;33:53–66. quiz 67
29. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med. 2003;168:1438–44.

30. Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, Gasparetto A, Meduri GU. 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.
31. Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, Varaschin P, Oliveira MC, Tierno PF, dal-Pizzol F, Silva UV, Knibel M, Nassar AP Jr, Alves RA, Ferreira JC, Teixeira C, Rezende V, Martinez A, Luciano PM, Schettino G, Soares M, ERICC (Epidemiology of Respiratory Insufficiency in Critical Care) investigators. Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. Crit Care. 2013;17:R63.
32. Bhadade RR, de Souza RA, Harde MJ, Khot A. Clinical characteristics and outcomes of patients with acute lung injury and ARDS. J Postgrad Med. 2011;57:286–90.
33. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001;344:481–7.
34. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest. 1996;109:179–93.
35. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000;355:1931–5.
36. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, Guerin C, Schortgen F, Lefort Y, Antonelli M, Lepage E, Lemaire F, Brochard L. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA. 2000;284:2352–60.
37. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med. 1996;335:1864–9.
38. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371:126–34.
39. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342:1471–7.
40. Ladeira MT, Vital FM, Andriolo RB, Andriolo BN, Atallah AN, Peccin MS. Pressure support versus T-tube for weaning from mechanical ventilation in adults. Cochrane Database Syst Rev. 2014;5:CD006056.
41. Burns KE, Adhikari NK, Slutsky AS, Guyatt GH, Villar J, Zhang H, Zhou Q, Cook DJ, Stewart TE, Meade MO. Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: a systematic review and meta-analysis. PLoS One. 2011;6:e14623.
42. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med. 2009;151:566–76.
43. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Esposito DC, Pasqualucci Mde O, Damasceno MC, Schultz MJ. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308:1651–9.
44. Serpa Neto A, Simonis FD, Barbas CS, Biehl M, Determann RM, Elmer J, Friedman G, Gajic O, Goldstein JN, Horn J, Juffermans NP, Linko R, de Oliveira RP, Sundar S, Talmor D, Wolthuis EK, de Abreu MG, Pelosi P, Schultz MJ. Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med. 2014;40:950–7.

45. Serpa Neto A, Simonis FD, Barbas CS, Biehl M, Determann RM, Elmer J, Friedman G, Gajic O, Goldstein JN, Linko R, Pinheiro de Oliveira R, Sundar S, Talmor D, Wolthuis EK, Gama de Abreu M, Pelosi P, Schultz MJ. Lung protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without ARDS: a systematic review and individual patient data metaanalysis. Crit Care Med. 2015;43(10):2155–63.
46. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338:347–54.
47. Oh DK, Lee MG, Choi EY, Lim J, Lee HK, Kim SC, Lim CM, Koh Y, Hong SB, Korean Society of Critical Care Medicine HNc. Low-tidal volume mechanical ventilation in patients with acute respiratory distress syndrome caused by pandemic influenza A/H1N1 infection. J Crit Care. 2013;28:358–64.
48. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med. 1998;158:1831–8.
49. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med. 1998;338:355–61.
50. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999;27:1492–8.
51. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
52. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, Hofstra JJ, de Graaff MJ, Korevaar JC, Schultz MJ. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care. 2010;14:R1.
53. Elmer J, Hou P, Wilcox SR, Chang Y, Schreiber H, Okechukwu I, Pontes-Neto O, Bajwa E, Hess DR, Avery L, Duran-Mendicuti MA, Camargo CA Jr, Greenberg SM, Rosand J, Pallin DJ, Goldstein JN. Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage*. Crit Care Med. 2013;41:1992–2001.
54. Linko R, Okkonen M, Pettila V, Perttila J, Parviainen I, Ruokonen E, Tenhunen J, Ala-Kokko T, Varpula T, FINNALI-study group. Acute respiratory failure in intensive care units. FINNALI: a prospective cohort study. Intensive Care Med. 2009;35:1352–61.
55. Yilmaz M, Keegan MT, Iscimen R, Afessa B, Buck CF, Hubmayr RD, Gajic O. Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. Crit Care Med. 2007;35:1660–6. quiz 1667
56. Walsh BK, Crotwell DN, Restrepo RD. Capnography/Capnometry during mechanical ventilation: 2011. Respir Care. 2011;56:503–9.
57. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G. 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.
58. Pepe PE, Hudson LD, Carrico CJ. Early application of positive end-expiratory pressure in patients at risk for the adult respiratory-distress syndrome. N Engl J Med. 1984;311:281–6.

59. Manzano F, Fernandez-Mondejar E, Colmenero M, Poyatos ME, Rivera R, Machado J, Catalan I, Artigas A. Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit Care Med. 2008;36:2225–31.
60. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT, National Heart L, Blood Institute ACTN. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351:327–36.
61. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE, Lung Open Ventilation Study Investigators. 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.
62. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L, Expiratory Pressure (Express) Study Group. 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.
63. Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. Curr Opin Crit Care. 2007;13:73–8.
64. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, Bosman RJ, de Waal RA, Wesselink R, de Keizer NF. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12:R156.
65. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, Parrillo JE, Trzeciak S, Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303:2165–71.
66. Cornet AD, Kooter AJ, Peters MJ, Smulders YM. Supplemental oxygen therapy in medical emergencies: more harm than benefit? Arch Intern Med. 2012;172:289–90.
67. Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, Steele J, Coimbra R. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma. 2009;26:2217–23.
68. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, Donati A. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014;18:711.
69. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, metaanalysis, and meta-regression of cohort studies. Crit Care Med. 2015;43(7):1508–19.
70. Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, Meade MO, Ferguson ND. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med. 2008;178:1156–63.
71. Suzumura EA, Figueiro M, Normilio-Silva K, Laranjeira L, Oliveira C, Buehler AM, Bugano D, Passos Amato MB, Ribeiro Carvalho CR, Berwanger O, Cavalcanti AB. Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med. 2014;40:1227–40.
72. Levine M, Gilbert R, Auchincloss JH Jr. A comparison of the effects of sighs, large tidal volumes, and positive end expiratory pressure in assisted ventilation. Scand J Respir Dis. 1972;53:101–8.
73. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. Anesthesiology. 2002;96:795–802.
74. Borges CR, Lake DF. Oxidative protein folding: nature's knotty challenge. Antioxid Redox Signal. 2014;21:392–5.
75. Saddy F, Sutherasan Y, Rocco PR, Pelosi P. Ventilator-associated lung injury during assisted mechanical ventilation. Semin Respir Crit Care Med. 2014;35:409–17.

76. Guldner A, Pelosi P, Gama de Abreu M. Spontaneous breathing in mild and moderate versus severe acute respiratory distress syndrome. Curr Opin Crit Care. 2014;20:69–76.
77. Campbell RS, Davis BR. Pressure-controlled versus volume-controlled ventilation: does it matter? Respir Care. 2002;47:416–24. discussion 424-416
78. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med. 2001;164:43–9.
79. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesthesiol Scand. 2004;48:722–31.
80. McMullen SM, Meade M, Rose L, Burns K, Mehta S, Doyle R, Henzler D, Canadian Critical Care Trials Group (CCCTG). Partial ventilatory support modalities in acute lung injury and acute respiratory distress syndrome-a systematic review. PLoS One. 2012;7:e40190.
81. Neto AS, Pereira VG, Esposito DC, Damasceno MC, Schultz MJ. Neuromuscular blocking agents in patients with acute respiratory distress syndrome: a summary of the current evidence from three randomized controlled trials. Ann Intensive Care. 2012;2:33.