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Recent advances in mechanical ventilation in patients without acute respiratory distress syndrome

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Abstract

While being an essential part of general anesthesia for surgery and at times even a life-saving intervention in critically ill patients, mechanical ventilation has a strong potential to cause harm. Certain ventilation strategies could prevent, at least to some extent, the injury caused by this intervention. One essential element of so-called 'lung-protective' ventilation is the use of lower tidal volumes. It is uncertain whether higher levels of positive end-expiratory pressures have lung-protective properties as well. There are indications that too high oxygen fractions of inspired air, or too high blood oxygen targets, are harmful. Circumstantial evidence further suggests that spontaneous modes of ventilation are to be preferred over controlled ventilation to prevent harm to respiratory muscle. Finally, the use of restrictive sedation strategies in critically ill patients indirectly prevents ventilation-induced injury, as daily spontaneous awakening and breathing trials and bolus instead of continuous sedation are associated with shorter duration of ventilation and shorten the exposure to the injurious effects of ventilation.

Introduction

Mechanical ventilation should not be seen as a simple and safe intervention, either in patients under general anesthesia for surgery or in critically ill patients. Indeed, ventilation is increasingly recognized as a harmful intervention as it may cause lung injury, frequently referred to as ventilator-induced lung injury (VILI) [1], and may harm the respiratory muscles, also named ventilator-induced diaphragm dysfunction (VIDD) [2].

For a long time, VILI and VIDD were considered clinically relevant only in severely ill patients with acute respiratory distress syndrome (ARDS) [3]. There is increasing evidence, though, that patients who do not meet the consensus definition of ARDS [4] are also at risk for VILI [5] and VIDD [2] with serious short- and long-term consequences. Even patients who receive ventilation only for a very short time (for example, for general anesthesia for surgery) are at risk of VILI. Thus, those strategies proven to be effective against VILI and VIDD in patients with ARDS may also benefit patients without ARDS. The aim of this narrative review is to summarize recent advances in protective ventilation strategies, in particular in patients without ARDS.

Tidal volumes

Clinical background

The potential harmful effects of use of higher tidal volumes and higher airway pressures in patients with ARDS were uncertain until the publication of the large National Heart, Lung, and Blood Institute ARDS Network randomized controlled trial (RCT) in 2000, which convincingly showed mortality reduction with use of lower tidal volumes in 861 critically ill patients [3].

Clinicians and researchers were relatively slow to accept these findings, but currently 'lung-protective' ventilation with tidal volumes of 6 mL/kg predicted body weight (PBW) is considered the standard of care for patients with ARDS [6,7].

Meanwhile, there has been a paradigm shift from safer ventilation during ARDS to prevention of ARDS [8,9], with increased use of lower tidal volumes in patients not yet having, but at risk for, ARDS. Indeed, when we consider the lungs of intubated and ventilated patients at a constant risk of direct insults, like infection or aspiration, and indirect insults, like sepsis and shock, major trauma, transfusion-associated lung injury, and maybe even simple surgical procedures, clinicians could try to prevent ventilation strategies that could initiate additional lung injury.

Tidal volume reduction during general anesthesia for surgery

Postoperative pulmonary complications are suggested to have a strong impact on the morbidity and mortality of patients who need major surgery [10]. Postoperative ARDS is the most feared postoperative pulmonary complication [11], and recent observational studies suggest that the incidence of postoperative ARDS is high, maybe even higher than the incidence of sepsis-associated ARDS [12]. Among several intra-operative factors that can influence the development of postoperative ARDS, ventilator settings are the strongest predictors [9].

The use of higher tidal volumes was the standard of care in the operating room for many years since the use of higher tidal volumes per se constantly opens those lung parts that collapse at the end of expiration and as such prevents the need for high oxygen fractions. Furthermore, relatively short use (that is, hours) of higher tidal volumes was considered relatively safe [13], although animal as well as clinical studies show that VILI can develop shortly after initiation of ventilation [14,15]. Finally, it was hypothesized that the use of lower tidal volumes could actually increase the risk of repetitive opening and closing of partly atelectatic tissue [13].

In 2000, however, Chaney *et al.* showed in an RCT that tidal volume reduction from 12 to 6 mL/kg PBW improved pulmonary mechanics in 25 patients submitted to surgery using cardiopulmonary bypass [16]. Five years later, an RCT conducted by Zupancich *et al.* demonstrated that tidal volume reduction from 12 to 8 mL/kg PBW in 40 patients undergoing cardiac surgery was associated with reduction of inflammatory markers in the bronchoalveolar lavage [17]. Furthermore, an RCT by Michelet *et al.* demonstrated that tidal volume reduction from 9 to 5 mL/kg PBW was associated with improved oxygenation and shorter duration of postoperative ventilation in 52 patients undergoing esophagectomy [18]. Numerous, albeit small, trials followed these initial investigations, all showing that tidal volume reduction prevents harm from short-term ventilation during general anesthesia for surgery [9,19].

More definitive results came recently from three larger RCTs [20–22]. Severgnini *et al.* showed that tidal volume reduction from 9 to 7 mL/kg PBW in 56 patients undergoing abdominal surgery was associated with better postoperative pulmonary function and lower 'Clinical Pulmonary Infection Scores' [20]. In 2013, Futier *et al.* published the Intraoperative Protective Ventilation (IMPROVE) trial, a large French study showing that a protective strategy using lower tidal volumes of 6 mL/kg PBW as compared with 12 mL/kg PBW was associated with a reduction in postoperative pulmonary complications by almost two thirds in 400 patients undergoing abdominal surgery [21]. These results were confirmed in a Chinese trial in 60 patients undergoing spinal fusion operation, in which an even more impressive benefit was found from tidal volume reduction from 10 to 12 mL/kg PBW to 6 mL/kg PBW [22].

According to this recent evidence, anesthesiologists must strongly consider using lower tidal volumes (for example, approximately 6 mL/kg PBW) during general anesthesia for major surgery (Table 1). The use of low tidal volumes in minor short procedures is encouraging but needs more evidence.

Tidal volume reduction in critically ill patients without acute respiratory distress syndrome

In the intensive care unit (ICU), the size of tidal volumes has progressively decreased from higher than 12 to 9 mL/kg in recent years [23]. Observational studies, though, show that tidal volumes remain far above 6 mL/kg PBW, especially in patients without ARDS [1,5,8,9,14,15].

Already in 1990, Lee *et al.* showed in an RCT that tidal volume reduction was associated with a lower incidence of pulmonary infection and duration of ventilation in 103 surgical ICU patients [24]. An observational study by Yilmaz *et al.* confirmed this by showing that protocol-guided ventilation aiming at prevention of use of too high tidal volumes decreased the incidence of lung injury by almost two thirds [25]. Determann *et al.* showed that tidal volume reduction from 10 to 6 mL/kg PBW was associated with a lower incidence of ARDS in a mixed clinical population of 150 ICU patients. The main limitation of this RCT is its early stopping due to harm in the conventional arm [15].

Table 1. Characteristics of some randomized controlled trials on protective ventilation in surgical patients

Study	Tidal volume, mL/kg predicted body weight		Positive end-expiratory pressure, cm H_2O		Outcome
	Protective	Conventional	Protective	Conventional	
Chaney *et al.* [16] (2000)	6	12	5	5	Decrease in pulmonary damage (evaluated by pressures)
Zupancich *et al.* [17] (2005)	8	10–12	10	2–3	Decrease in inflammatory markers in bronchoalveolar lavage and plasma
Michelet *et al.* [18] (2006)	5	9	5	0	Decrease in inflammatory markers in plasma and earlier extubation
Severgnini *et al.* [20] (2013)	7	9	10	0	Improved respiratory function and reduced modified Clinical Pulmonary Infection Score
Futier *et al.* [21] (2013)	6–8	10–12	6–8	0	Decrease in pulmonary and extrapulmonary complications
Ge *et al.* [22] (2013)	6	10–12	10	0	Decrease in pulmonary complications and improvement in arterial oxygenation
Hemmes *et al.* [42] (2014)	8	8	10–12	0–3	Similar pulmonary complications and more hypotension with higher positive end-expiratory pressure

Recent meta-analyses of studies in patients without ARDS suggested that protective ventilation with lower tidal volumes was associated with better clinical outcomes, as reduction of development of lung injury and pulmonary infections [9], and that use of lower tidal volumes reduced the duration of ventilation [26]. It should be noted, though, that the majority of the meta-analyzed studies were observational and the only randomized trial available was small and was interrupted early.

Several arguments against indiscriminate use of lower tidal volume strategies have been raised [27]. One argument is that use of lower tidal volumes needs compensatory higher respiratory rates, which could increase sedation needs, the incidence of ICU delirium, and ICU-acquired weakness [27]. This is somewhat surprising since one recent meta-analysis using individual patient data showed that use of lower tidal volumes did not affect sedation, analgesia, or neuromuscular blockade use in patients without ARDS [26]. This is in line with the findings in patients with ARDS, where the use of low tidal volumes was not associated with increased sedation needs [28,29]. Other arguments are that use of lower tidal volumes could promote collapse of lung tissue [30] and could increase the risk of patient-ventilator asynchrony [31]. Another alleged side effect of use of lower tidal volumes with higher respiratory rates is the risk of patient fatigue, although there are no studies that support this.

According to available evidence, intensivists should consider using lower tidal volumes (for example, 6 to 8 mL/kg PBW) in patients without ARDS. Robust well-powered RCTs using clinically relevant endpoints are needed to further support use of lower tidal volumes in these patients.

'Ultraprotective' ventilation

Tidal hyperinflation may still occur in patients under ventilation, even with the use of lower tidal volumes of 6 mL/kg PBW [32–34]. The idea behind so-called 'ultraprotective ventilation' is that tidal volumes lower than 6 mL/kg PBW could better protect the lungs from harm caused by ventilation than tidal volumes of 6 mL/kg PBW. However, use of 'ultralow' tidal volumes is restricted because of retention of carbon dioxide (CO_2) and associated severe respiratory acidosis [34]. Using extracorporeal CO_2 removal systems such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO_2 removal ($ECCO_2R$) [34] may overcome this problem. Especially, pump-less $ECCO_2R$ could be an appealing method to use when CO_2 retention is the major concern and patients are hemodynamically stable [33,34]. This method is very effective in removing CO_2, allowing the use of very low tidal volume, and may also improve oxygenation, albeit slightly [33,34]. A *post hoc* analysis in an RCT showed that use of very low tidal volumes (3 mL/kg PBW) combined with $ECCO_2R$ had the potential to improve outcome in 79 patients with severe ARDS [35]. Based on available evidence, it remains uncertain whether 'ultraprotective' ventilation could benefit ICU patients under mechanical ventilation.

Positive end-expiratory pressures

Clinical background

The overall degree of lung distension is one of the most harmful factors that contribute to the development of VILI. Use of positive end-expiratory pressure (PEEP) could increase functional residual capacity, and when end-inspiratory volume is kept constant, use of PEEP could decrease tissue stress and capillary filtration,

reducing the edema formation and the severity of cell damage [36]. In 1998, an RCT by Amato *et al.* showed that, combined with the use of lower tidal volumes, use of higher levels of PEEP was associated with improved outcome in 53 patients with ARDS [37]. Nevertheless, follow-up trials comparing different levels of PEEP, with or without recruitment strategies, did not show improved outcomes with use of higher levels of PEEP in patients with ARDS [38–40]. These trials could have been underpowered to detect small but potentially important effects on mortality. Briel *et al.* conducted an individual patient data meta-analysis and found that use of higher levels of PEEP improves survival only in patients with more severe forms of ARDS [41].

Higher positive end-expiratory pressure in patients under general anesthesia for surgery

The majority of the trials studying the effects of protective ventilation during general anesthesia for surgery compared the combination of lower tidal volumes with higher levels of PEEP with the combination of higher tidal volume with lower levels of PEEP. For example, Zupancich *et al.* used 3 cm H_2O of PEEP combined with higher tidal volumes against 10 cm H_2O in the lower tidal volume group [17]. Similarly, in the largest trial in the field, Futier *et al.* compared 0 cm H_2O of PEEP in the conventional arm against 8 cm H_2O in the protective arm [21]. In these trials, it was difficult, if not impossible, to discriminate benefit from these two ventilator settings.

Recently, an RCT by Hemmes *et al.* compared 0-2 with 12 cm H_2O of PEEP in 900 non-obese patients undergoing planned abdominal surgery and ventilation with lower tidal volume (8 mL/kg PBW) [42]. Although it was hypothesized that high levels of PEEP would protect against postoperative pulmonary complications, the trial showed no effect of this strategy. Notably, the higher PEEP strategy was associated with higher incidence of hypotension during surgery [42].

Based on the latest evidence, use of higher levels of PEEP is not recommended, at least not in non-obese patients receiving ventilation during general anesthesia for abdominal surgery (Table 1). The possible benefits of higher PEEP levels in obese patients and in other types of surgeries need to be determined in robust well-powered RCTs using clinically relevant endpoints.

Higher positive end-expiratory pressure in critically ill patients without acute respiratory distress syndrome

Although use of higher levels of PEEP could prevent diffuse alveolar damage, no RCT has compared different levels of PEEP in critically ill patients without ARDS. Recently, an RCT by Mascia *et al.* showed that the use of high PEEP levels combined with low tidal volumes in 118 potential organ donors with brain death increased the number of eligible and harvested lungs compared with a conventional strategy combining low PEEP levels and high tidal volumes [43]. Based on available evidence, it remains uncertain whether higher levels of PEEP could benefit ICU patients without ARDS.

Inspired oxygen fractions

Clinical background

Supplemental oxygen has been suggested to reduce postoperative nausea and vomiting by ameliorating subtle intestinal ischemia [44]. Two RCTs showed that use of 80% oxygen as compared with 30% oxygen in the perioperative period lowered the incidence of postoperative nausea and vomiting [45,46]. A recent meta-analysis of published studies showed that intraoperative high fraction of inspired oxygen (FiO_2) indeed has some beneficial effect on postoperative nausea and vomiting [47]. Supplemental administration of oxygen has also been suggested to reduce the incidence of wound infection [48]. Greif *et al.* showed that perioperative administration of supplemental oxygen indeed reduced the incidence of surgical wound infections in 500 patients included in the RCT [48]. This was recently confirmed, at least in part, in an RCT of 222 patients by Stall *et al.* [49]. A meta-analysis of published studies in perioperative patients shows a clear association between high intraoperative oxygen fractions and a reduction in surgical site infection [47].

Higher oxygen fractions in patients under general anesthesia for surgery

Hyperoxia may induce pulmonary injury and may increase oxidative stress. In experimental studies, the use of high FiO_2 is associated with increased levels of reactive oxygen-derived free radicals, an influx of inflammatory cells, increased permeability and endothelial cell injury [50]. Also, another detrimental effect of hyperoxia is the development of reabsorption atelectasis with increased shunting [51]. Owing to this mechanism of injury, a certain extent of hypoxemia with a target arterial oxygen tension (PaO_2) of more than 60 mm Hg is suggested [11]. So far, no sufficiently powered studies have investigated the effects of higher oxygen fractions in patients receiving ventilation for general anesthesia for surgery. Based on available evidence, anesthesiologists are suggested to use higher oxygen fractions in patients who need ventilation for general anesthesia for surgery, but investigations that study safety of higher oxygen levels are urgently needed.

Higher oxygen fractions in critically ill patients

The relationship between oxygen fractions in inspired air, oxygen levels in blood, and outcome has been the subject

of several studies in different clinical scenarios other than during surgery. Recently, an observational study by de Jonge *et al.* demonstrated that high oxygen fractions in inspired air as well as high oxygen levels in blood in the first 24 hours after ICU admission were independently associated with in-hospital mortality in 3322 critically ill patients [52]. Hyperoxia was also shown to have an association with increased in-hospital mortality in 6326 patients admitted to the ICU following resuscitation from cardiac arrest [53]. Interestingly, Farquhar *et al.* showed that hyperoxia from high-concentration oxygen therapy causes a marked reduction in coronary blood flow and consequently myocardial oxygen consumption, suggesting harm from use of high-concentration oxygen therapy in the treatment of cardiac and other disorders [54]. Finally, an observational study by Cornet *et al.* reported that hyperoxia was associated with poor outcomes in patients with ischemic stroke [55]. Despite these reports, a recent observation study suggested that hyperoxia is frequently encountered and that it does not lead to adjustment of ventilator settings [51].

In the neonatal population, although the use of supplemental oxygen has a long history resulting in both significant health-care benefits and harms, uncertainty remains as to the most appropriate range to target blood oxygen levels in preterm and low-birth-weight infants. A large systematic review and meta-analysis confirm that a policy of unrestricted, unmonitored oxygen therapy has potential harms without clear benefits [56]. Also, a recent RCT showed that, in extremely preterm infants, targeting oxygen saturations of 85% to 89% compared with 91% to 95% had no significant effect on the rate of death or disability at 18 months [57]. Finally, it is suggested that, among infants presenting with mild to moderate bronchiolitis to an emergency department, oxygen saturation should not be the only factor in the decision to admit, and its use may need to be re-evaluated [58]. Despite the problems in comparing pediatric with adult studies, these studies provide more evidence against the use of high levels of oxygen. Based on available evidence, though, intensivists are suggested to avoid the use of high oxygen fractions in inspired air and to avoid hyperoxia in critically ill patients.

Measures to prevent respiratory muscle harm

Clinical background

VIDD has several implications for the management of patients on mechanical ventilation [59,60]. It was believed that diaphragmatic rest during ventilation, achieved through the use of controlled ventilation, could prevent diaphragmatic fatigue. Currently, there is strong evidence that controlled ventilation is associated with adverse effects on multiple aspects of diaphragmatic structure and function [61]. Nevertheless, an RCT by Papazian *et al.* demonstrated that a limited period of cisatracurium administration, mandating controlled ventilation, was associated with an improved outcome in 340 patients with severe ARDS [62]. This approach is, at least in part, conflicting with the recent trend toward the use of more spontaneous breathing in patients under mechanical ventilation trying to use less sedation and avoid the incidence of VIDD [63].

It is worth noting that most of the evidence in favor of the use of spontaneous breathing activity originates from unsupported breathing [64]. In patients with ARDS, unsupported spontaneous breathing has been shown to increase lung aeration, redistribute ventilation and perfusion, improve gas exchange, reduce the need for sedation and cardiocirculatory drug therapy, and speed weaning, with no effect on mortality [64].

Prevention of muscle harm in patients under general anesthesia for surgery

There are no clinical trials assessing the effects of spontaneous modes of ventilation during surgery on postoperative muscle harm, preventing any recommendation.

Prevention of muscle harm in critically ill patients

An observational study by Levine *et al.* showed that a relative short period of controlled ventilation of up to three days was associated with marked atrophy of the diaphragm [2]. Also,Jaber *et al.* showed that diaphragmatic weakness, injury, and atrophy occur rapidly in critically ill patients during mechanical ventilation and are significantly correlated with the duration of ventilator support [65].

Maintaining diaphragmatic contractile activity by using spontaneous breathing activity may protect the diaphragm against the deleterious effect of prolonged controlled ventilation, as demonstrated recently both *in vitro* and *in vivo*, in healthy piglets [66]. Recently, Futier *et al.* showed that the use of pressure support ventilation is efficient at reducing mechanical ventilation-induced proteolysis and inhibition of protein synthesis in the diaphragm compared with continuous mechanical ventilation [67]. Given the available evidence, intensivists should consider supporting their patients with spontaneous modes of ventilation as soon as possible. The administration of neuromuscular blocking in patients without ARDS must be discouraged [68].

Long-term outcomes of patients mechanically ventilated

Clinical background

Prospective systematic evaluations of long-term outcomes among survivors of respiratory failure requiring ventilation are rare and limited to a few years of follow-up.

Herridge *et al*. conducted a 5-year observational follow-up study describing the extent of physical and quality-of-life impairments after ARDS [69]. Among 109 survivors of ARDS, it was demonstrated that faster resolution of ARDS during ICU stay was associated with better functional outcome. Patients had normal or near-normal volumetric and spirometric test results, and 77% of the patients had returned to work. However, the ability to do vigorous exercise and the quality of life were reduced, showing that ICU-acquired weakness might be related to long-term function in survivors of ARDS.

Long-term outcomes in patients under general anesthesia for surgery

Development of postoperative pulmonary complications (PPCs) increases long-term morbidity and mortality of surgical patients [70]. Several factors are associated with development of PPC, including age, preoperative oxygen saturation as measured by pulse oximetry (SpO_2), presence of respiratory infection, anemia, type of incision, and duration of surgery [70,71]. Pappalardo *et al*. showed that hospital mortality of patients requiring prolonged ventilation after cardiac surgery is high [72].

Based on available evidence, anesthesiologists should identify those patients at risk for postoperative pulmonary complications so that they can adjust perioperative care, including ventilation strategies and postoperative observation, in such a way that postoperative pulmonary complications are maximally prevented and, when they develop, the patients receive the most optimal care.

Long-term outcomes in critically ill patients

Recent studies showed that mortality rate after prolonged ventilation is high. Many survivors needed assistance after discharge from the hospital, and more than half still required caregiver assistance at 1 year [73]. Rose *et al*. showed that delusional memories and anxiety disorders are prevalent in survivors of prolonged mechanical ventilation [74]. Combes *et al*. showed that prolonged ventilation is associated with impaired health-related quality of life compared with that of a matched general population [75].

Because survivors from prolonged ventilation are at high risk of having a poor quality of life, they should be assessed periodically. Future studies should focus on physical or psychosocial rehabilitation that could lead to improved management of patients after their stay in the ICU.

Cognitive function of mechanically ventilated patients

Clinical background

Analgesia and sedation are routinely administered in critically ill patients to permit invasive procedures, prevent pain and anxiety, reduce stress and oxygen consumption, and allow mechanical ventilation [76]. Acute forms of brain dysfunction, such as delirium, have been associated with use of these medications and might contribute to long-term cognitive impairment [77]. Use of restrictive sedation strategies in critically ill patients, as daily spontaneous awakening and breathing trials and bolus instead of continuous sedation, is associated with shorter duration of ventilation and shortens the exposure to the injurious effects of ventilation [78].

Cognitive function in patients under general anesthesia for surgery

The majority of the studies of cognitive function in surgical patients were performed in patients receiving surgery including cardiopulmonary bypass. Li *et al*. showed that delirium is common after coronary artery bypass graft surgery and could be predicted by the presence of risk factors for delirium [79]. Delirium and postoperative cognitive dysfunction are extremely common in geriatric surgical patients [80], and it is suggested that the incidence of these complications far exceeds the rate of other complications [81]. Delirium and postoperative cognitive dysfunction are associated with prolonged length of stay, discharge to a place other than home, and higher 1-year mortality [82]. In addition, delirium is associated with an accelerated trajectory of cognitive decline to dementia, and patients with postoperative cognitive dysfunction are more likely to leave the workforce [80]. Based on available evidence, delirium and postoperative cognitive dysfunction are important, expensive complications, the outcome of which could be improved by standardizing management in a perioperative surgical home.

Cognitive function in critically ill patients

In a prospective study, Pandharipande *et al*. showed that patients in medical and surgical ICUs are at high risk for long-term cognitive impairment and that a longer duration of delirium in the hospital was associated with worse global cognition and executive function scores at up to 1 year [77]. The effects of sedatives on outcomes are influenced by the depth of sedation, making it imperative to reduce the total exposure to these medications [83]. However, insufficient pain relief also contributes to sleep disturbances and disorientation and may increase the development of long-term impairments such as post-traumatic stress disorder [84]. In addition to balancing the widespread necessity and use of sedation with the cost of cognitive dysfunction, physicians must balance the demand needed for comfort with avoiding harm to patients.

The class of sedative agent is also important since an association between benzoadiazepines, delirium, and

worse outcomes has been found in mechanically ventilated patients [85]. Importantly, the data on opioids and brain dysfunction are not consistent, whereas those for benzodiazepines are, especially if used only in low doses to control pain [83].

In a landmark RCT, Kress *et al*. showed that, in 128 patients receiving mechanical ventilation, daily interruption of sedative-drug infusions decreases the duration of ventilation and the length of stay in the ICU [86]. Since then, several sedation scores were developed, and the sedation goal changed from deeply sedated patients to patients awake and collaborative [87]. Strøm *et al*. demonstrated that the use of no sedation in 140 critically ill patients receiving ventilation is feasible and associated with an increase in days without ventilation [88]. Also, Girard *et al*. showed that a wake-up-and-breathe protocol that pairs daily spontaneous awakening trials with daily spontaneous breathing trials results in better outcomes for 336 ventilated critically ill patients, including shorter ICU and hospital length of stay and reduced 1-year mortality [89]. Balas *et al*. went on to test a similar program (adding delirium and early mobility to complete the Awakening and Breathing Coordination, Delirium Monitoring and Management, and Early Mobility [ABCDE] bundle) and found in a quality improvement project that similar outcomes were improved, including more days alive and free of mechanical ventilation plus strong reductions in delirium and indications of improved survival [90]. In support of the notion that one of the main mediators of improved outcomes is the reduction in exposure to excess sedatives and analgesics, an RCT by Mehta *et al*. showed that, for mechanically ventilated adults managed with protocolized sedation, the addition of daily sedation interruption in itself did not reduce the duration of mechanical ventilation or ICU stay in 430 critically ill patients [91]. Because the intervention patients actually received increased exposure to benzodiazepines (rather than the intended reduction in dose) and because of the reported low adherence to extubation once a patient passed a spontaneous breathing trial, this study is best seen as a call for compliance and adherence checks when implementing a protocol that involves culture change (in this case, from deep to light sedation, which was not effectively accomplished in this population).

Based on available evidence, use of restrictive sedation in all ventilated patients in order to keep the duration of ventilation as short as possible is suggested. Restrictive sedation includes reduced use of benzodiazepines (preferably via boluses instead of continuous infusion) and includes institution of daily spontaneous awakening and breathing trials and target-based sedation.

Conclusions

According to the most recent evidence, surgical patients should receive low tidal volumes, low to moderate levels of PEEP, and high FiO_2. Critically ill patients without ARDS should receive ventilation with low tidal volume, low FiO_2, spontaneous breathing activity, and a restrictive strategy of sedation.

Abbreviations

ARDS, acute respiratory distress syndrome; CO_2, carbon dioxide; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PPC, postoperative pulmonary complication; RCT, randomized controlled trial; VIDD, ventilator-induced diaphragm dysfunction; VILI, ventilator-induced lung injury.

Disclosures

The authors declare that they have no disclosures.

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