Editorial introductions

Current Opinion in Critical Care was launched in 1995. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of critical care is divided into 13 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the journal's Editor and Section Editor for this issue.

EDITOR

Jean-Louis Vincent

Dr Vincent is Professor of Intensive Care at University of Brussels, Belgium and Intensivist in the Department of Intensive Care at the Erasme University Hospital in Brussels. As a specialist in internal medicine, he spent two years training at the University of Southern California, USA, with Prof. Max Harry Weil.

Dr Vincent has written more than 900 original articles, some 300 book chapters and review articles, and 850 original abstracts, and has edited 90 books. He is co-editor of the Textbook of Critical Care (Elsevier Saunders, 5th Edition) and the Encyclopedia of Intensive Care Medicine (Springer).

Dr Vincent is the editor-in-chief of Critical Care, Current Opinion in Critical Care, and ICU Management. He is member of the editorial boards of about 30 journals including Critical Care Medicine (senior editor), American Journal of Respiratory and Critical Care Medicine (AJRCCM), PLoS Medicine, Lancet Infectious Diseases, Intensive Care Medicine, Shock, and Journal of Critical Care.

He is currently President of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM). He is a Past-President of the Belgian Society of Intensive Care Medicine (SIZ), the European Society of Intensive Care Medicine (ESICM), the European Shock Society (ESS), and the International Sepsis Forum (ISF).

For 35 years he has organized an International Symposium on Intensive Care and Emergency Medicine which is held every March in Brussels.

He has received the Distinguished Investigator Award of the Society of Critical Care Medicine, the College Medalist Award of the American College of Chest Physicians, was the Recipient of the ''Society Medal'' (lifetime award) of the European Society of Intensive Care Medicine and has received the prestigious Belgian scientific award of the FRS-FNRS (Prix Scientifique Joseph Maisin-Sciences biomédicales cliniques).

SECTION EDITOR

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Dr Niall D. Ferguson is Head of Critical Care Medicine at the University Health Network and Mount Sinai Hospital, and Associate Professor in the Departments of Medicine and Physiology, and the Institute of Health Policy, Management and Evaluation at the University of Toronto, all in Toronto, Canada. He is a Senior Scientist in the Toronto General Research Institute, and the Critical Care Lead for the Toronto-Central Local Health Integration Network. He received his M.D. with honours from the University of Toronto, and went on to complete post-graduate training in Internal Medicine, Respirology, and Critical Care Medicine. Dr Ferguson completed a Master's degree in Clinical Epidemiology and Health Care Research at the University of Toronto and subsequently undertook a CIHR Post-doctoral Fellowship in Madrid, Spain. He receives research funding from local, provincial, and national agencies, including the Canadian Institutes of Health Research. Dr Ferguson's research, which is published in high-impact journals including the *New England Journal of Medicine*, *JAMA*, and the *American Journal of Respiratory & Critical Care Medicine* focuses on: (1) mechanical ventilation (epidemiology; weaning and liberation; extubation and tracheostomy); (2) acute respiratory

distress syndrome (definitions; ventilatory management; trial design); and (3) novel modes of mechanical ventilation, including extra-corporeal life support. Dr Ferguson is the Scientific Programme Chair for Critical Care Canada Forum, Canada's premier critical care conference. He is a frequent invited-speaker at national and international meetings, having given over 250 such talks.

Selecting the 'right' positive end-expiratory pressure level

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Purpose of review
To compare the positive end-expiratory pressure selection aiming either to oxygenation or to the full lung opening.

Recent findings
Increasing positive end-expiratory pressure in patients with severe hypoxemia is associated with better outcome if the oxygenation response is greater and positive end-expiratory pressure tests may be performed in a few minutes. The oxygenation response to recruitment maneuvers was associated with better outcome in patients with acute respiratory distress syndrome from influenza A (H1N1). If, after recruitment maneuver, the recruitment is not sustained by sufficient positive end-expiratory pressure, the lung will unavoidably collapse. Several papers investigated the positive end-expiratory pressure selection according to the deflation limb of the pressure–volume curve. It is still questionable whether to consider oxygenation or respiratory mechanics change as the best marker for adequate selection. A growing interest is paid to the estimate of transpulmonary pressure, although no consensus is available on which methodology is preferable. Finally, the positive end-expiratory pressure adequate for full lung opening may be computed combining the computed tomography scan variables and the chest wall elastance.

Summary
When compared, most of the methods give the same positive end-expiratory pressure values in patients with higher and lower recruitability. The positive end-expiratory pressure/inspiratory oxygen fraction tables are the only methods providing lower positive end-expiratory pressure in lower recruiters and higher positive end-expiratory pressure in higher recruiters.

Keywords
acute respiratory distress syndrome, computed tomography scan, esophageal pressure, oxygenation, positive end-expiratory pressure

INTRODUCTION

The physiology of positive end-expiratory pressure (PEEP) and its application in pulmonary edema was described by Barach *et al.* in 1938 [1]; however, its widespread clinical use began with Gregory *et al.* in pediatric patients [2] and became routine practice in the treatment of acute respiratory distress syndrome (ARDS) [3]. The target of PEEP application was to improve oxygenation; the concern was the cardiac output decrease, as described in detail by Cournand *et al.* in 1948 [4]. The decrease of cardiac output, moreover, is a mechanism that, *per se*, may improve oxygenation as described by Lemaire *et al.* [5], and confirmed by Dantzker *et al.* [6]. The best compromise to reconcile the oxygenation needs with the hemodynamic was described by Suter *et al.* [7]. These authors found that the best oxygen transport, a variable which associates oxygenation and cardiac output, is reached when the PEEP provides the best respiratory system compliance. Suter's PEEP selection according to oxygenation and respiratory system compliance has been rediscovered several times over the decades, up to the most recent papers.

In the 1990s, a new concept for PEEP use emerged, in the framework of 'lung protective strategy', starting, in our opinion, from a paper of Webb and Tierney

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KEY POINTS

- PEEP selection methods based on PEEP/FiO_2 tables are the only discriminating factors between patients with higher and lower recruitability.
- To keep the lung fully open, similar PEEP is required in patients with higher and lower potential for lung recruitment.
- PEEP selection using the inspiratory limb of the volume–pressure curve is conceptually wrong because inspiratory pressure reflects the opening pressure, whereas PEEP relates to the closing pressure of the lung.
- PEEP selection along the deflation limb of the volume–pressure curve makes more sense, but the use of oxygenation or compliance changes as a marker of adequate PEEP is questionable.
- Tailoring PEEP according to the ARDS severity, as defined by the Berlin definition, may be a reasonable approach: 5–10 cmH_2O PEEP in mild patients, 10–15 cmH_2O PEEP in moderate patients and 15–20 cmH_2O PEEP in severe patients.

[8], who described, in rats, a 'protective' effect of PEEP against damage of mechanical ventilation. The mechanism of lung protection was attributed primarily to the prevention of intratidal opening and closing based on a theoretical background provided by Mead *et al.* [9], whereas the transduction of mechanical stimuli to the inflammatory reaction was first described by Slutsky [10]. Therefore, in the context of 'open the lung and keep it open' [11], the target of PEEP was no more the oxygenation but the prevention of the intratidal collapse and decollapse.

We will describe, first, the PEEP selection according to oxygenation and, second, the PEEP selection according to the lung protective strategy, and, finally, we will attempt to describe how these different methods were compared and which are the conclusions reached so far.

SELECTING POSITIVE END-EXPIRATORY PRESSURE TO IMPROVE OXYGENATION

Setting PEEP based on PEEP/FiO_2 tables is likely the most diffused method, introduced by the ARDS Network [12] and LOVs study [13]. Higher and lower PEEP, selected by these tables, have been compared in large trials recently reviewed in a Cochrane analysis [14]. The authors concluded that the outcome was unrelated to the PEEP level and (what a surprise!) the higher the PEEP, the higher is the oxygenation. The oxygenation response to PEEP has been studied in a secondary analysis [15▪] of the LOVs [13] and ExPress [16] trials and in H1N1 patients [17]. These studies reported that the relation between oxygenation response following PEEP adjustment and decreased mortality was strongest in patients with more severe baseline hypoxemia (Pa_{O_2}/FiO_2 <150 mmHg) subjected to increased PEEP. All of these data corroborate the belief that higher PEEP could be of benefit in the most severe patients with ARDS [18,19] in whom the lung recruitability (and PEEP response) is higher [20]. It is important to note that oxygenation response to PEEP changes may be tested in a few minutes [21].

SELECTING POSITIVE END-EXPIRATORY PRESSURE TO PROTECT THE LUNG

Setting a PEEP value sufficient to keep the lung open throughout the respiratory cycle is one of the main issues of the 'lung protective strategy'. Several approaches have been proposed through the years for this purpose, from the traditional use of the volume–pressure curve to the use of transpulmonary pressure and the imaging technologies.

Respiratory mechanics-based positive end-expiratory pressure selection: the volume–pressure curve of the respiratory system

The volume–pressure curve has been largely used to individualize the PEEP selection hypothesizing that the lower inflection point indicates the end of recruitment, whereas the upper inflection point indicates the beginning of hyperinflation. Although, for decades, the PEEP was set using the inflation limb of the respiratory system curve, more recently the attention has been focused on the deflation limb. At the same pressure, the inspiratory volume is lower than the expiratory one, and, conversely, the pressure required to reach a given volume is greater along the inspiratory limb than along the expiratory one. The 'extra pressure' required during the inflation is dissipated in the system to overcome the surface tension and the tissue resistances and, eventually, to open up the collapsed lung regions.

The inspiratory limb of the volume–pressure curve: the recruitment maneuver

In contrast with previous beliefs, it has been shown consistently, in humans [22] and in different animal species [23,24], that recruitment is not limited to the pressure around the inflection point of the inspiratory volume–pressure curve but occurs along the entire curve. This indicates that the collapsed units open up at different opening pressures. As an example, at the inflation of 30 cmH_2O, a consistent part of the potentially recruitable lung, which may

be estimated from 15% to 30%, remains closed. To open up these regions, opening pressures spanning from 30 to 45–60 cmH_2O are required [22,25]. Therefore, the recruitment maneuver may open up different amounts of recruitable lung if performed at 30, 40 or 60 cmH_2O inflation pressure. Liu *et al.* [17] reported that, if the recruitment maneuver (at 30 cmH_2O for 60 s) resulted in better oxygenation, the patients with influenza A (H1N1)-associated ARDS had a better chance of survival. The same group [26] found, in a canine model, that hyperinflation after recruitment maneuver was greater in the surfactant model rather than in the oleic acid model. Engel *et al.* [27] compared two recruitment maneuvers (at 45 and 15 cmH_2O PEEP) with no recruitment. These authors concluded that recruitment maneuvers improve oxygenation with less hemodynamic impairment and inflammatory reaction at lower PEEP. Actually, the authors defined as recruitment the application of two different PEEP levels, which are expiratory phenomena related to the deflation limb of the volume–pressure curve. This fact underlines the confusion originating by concepts such as 'recruitment with PEEP.' Actually, recruitment occurs during inspiration and PEEP maintains open, if sufficient, what has been previously recruited. If the PEEP is insufficient, the recruitment is not sustained and the lung will unavoidably collapse again, as confirmed by Kheir *et al.* [28]. Keenan *et al.* [29], reviewing the recruitment issue, wisely concluded, in our opinion, that recruitment maneuvers should be guided by individual clinician experience and patients' factor.

Therefore, although the recruitment must be tailored on the inspiratory limb of the volume–pressure curve, tailoring PEEP in the same limb is misleading. Hata *et al.* [30–33] provided a systematic review of three randomized trials that used the inflation limb of the pressure–volume curve to tailor PEEP selected above the lower inflection point. The authors suggested a possible outcome benefit, although the limited number of patients prevents any real conclusion. In our opinion, in all of these studies, there is a fundamental bias. First, the authors assume that recruitment is complete or near complete above the lower inflection point, which is not true; second, when the lower inflection point cannot be identified, a PEEP approximately 15–16 cmH_2O was used. To be consistent with the hypothesis, PEEP should have been set equal to 0 cmH_2O.

The expiratory limb of the volume–pressure curve

In the last few years, several papers investigated the effects of PEEP selection on the deflation part of the volume–pressure curve, usually setting PEEP at the pressure values corresponding to the best compliance or before the oxygenation decrease. It must be noted, however, that, first, because of the sigmoid shape of the deflation limb, the compliance is always higher in the middle part of the lung, even in normal lungs. Second, the derecruitment starts, in ARDS, at very high deflation pressures (20 cmH_2O), as shown by the closing pressure curve, both in humans and in experimental animals [22,23], to continue at lower pressures along the deflation limb. Actually, in supine patients with ARDS, when PEEP is decreased, the most dependent lung regions along the sternum–vertebral direction collapse first and then the less dependent regions, as shown with the regional computed tomography (CT) scan analysis [34], and recently confirmed in 51 patients with ARDS [35▪]. This makes the use of a single unique pressure point as a marker of derecruitment highly questionable. How the commonly used physiological variables are different if measured at the same pressure during inflation or during deflation has been recently emphasized by Bikker *et al.* [36].

The lung mechanics-based positive end-expiratory pressure selection

The interest in ventilator-induced lung injury and the stress/strain applied to the lung structures renewed the attention on the esophageal pressure measurement and its clinical use in the framework of the lung protective strategy. Moreover, the use of CT scan allowed a better characterization of the lung status and the individualization of the mechanical ventilation settings.

The transpulmonary pressure-based positive end-expiratory pressure selection

The recognition that the distending pressure of the lung is the transpulmonary pressure led to a series of studies in which the PEEP level was selected to maintain the transpulmonary pressure positive through the whole respiratory cycle, to maintain the lung always open. Because the transpulmonary pressure is the difference between the airway and the pleural pressure, the estimate of this variable is mandatory and the only clinical tool available is the measurement of the esophageal pressure.

The indications and the limits of using esophageal pressure as a surrogate of pleural pressure have been reviewed by Brochard [37▪] and by Keller and Fessler [38]. Two approaches have been proposed to estimate the pleural pressure from the esophageal pressure measurement. The first one assumes that the absolute values of esophageal pressure equal the pleural pressure. To take into account the weight of

the mediastinum, a correction factor of $-5\,cmH_2O$ may be applied. The second method considers the variation of the esophageal pressure equal to the variations of the pleural pressure. Therefore, after measuring the chest wall elastance, the Δpleural pressure may be estimated as the change in airway pressure times the ratio of the chest wall to the total respiratory system elastance [35▪]. Gulati *et al.* [39▪] compared these two methods for estimating pleural pressure on the same group of patients. They concluded that the two methods cannot be considered interchangeable. Moreover, chest wall and respiratory system elastances may vary unpredictably with changes in PEEP.

The computed tomography scan-based positive end-expiratory pressure selection

The assumption behind the CT scan-based PEEP selection is that the primary reason for lung collapse in ARDS is the excessive lung weight that compresses the dependent lung regions. Therefore, the CT scan-derived PEEP is computed as the pressure sufficient to overcome the maximal hydrostatic pressure superimposed on the most dependent lung regions and the pressure necessary to lift up the chest wall [35▪]. Cressoni *et al.* found, however, that, in severe ARDS, the CT scan-derived PEEP ranged from 7 to $28\,cmH_2O$, averaging $16 \pm 5\,cmH_2O$ in mild ARDS, $16 \pm 5\,cmH_2O$ in moderate ARDS and $18 \pm 5\,cmH_2O$ in severe ARDS, and was unrelated to the lung recruitability, that is, to keep open 1 or 100 pulmonary units collapsed in the dependent lung regions, approximately the same PEEP is required.

COMPARISON BETWEEN DIFFERENT MODES OF POSITIVE END-EXPIRATORY PRESSURE SELECTION

In the last years, several papers compared different PEEP selection methods. In Table 1, we summarize the methods in comparison, their targets, and the authors' conclusions. Briefly, Chiumello *et al.* found that, within all of the bedside PEEP selection methods tested, the only one that provides appropriately lower PEEP in the less recruitable patients was the high PEEP arm of the ARDSNet table. All of the other systems, including the CT-derived PEEP, provide similar values in patients with higher or lower potential for lung recruitment. Other authors, instead of recruitability, targeted PEEP to other variables. Yang *et al.* found that better oxygenation was provided by applying a positive transpulmonary pressure than following the ARDSNet table. Huang *et al.*, during a decremental PEEP trial, measured stress index, static lung compliance, oxygenation and the inflection point in the inspiratory limb of the volume–pressure curve. These authors concluded that stress index and oxygenation methods set PEEP at higher values than indicated by the highest compliance and the inflection point. In turn, Pintado *et al.* found that the best compliance method, compared with the ARDSNet table, resulted in decreased organ dysfunction with a trend toward a better outcome. In addition to respiratory system compliance and transpulmonary pressure during decremental PEEP trial, Rodriguez *et al.* found that alveolar dead space could add further information; in fact, it increased when transpulmonary pressure became negative and oxygenation deteriorated. In a series of papers, in humans [49] and in pigs [36,45], during the PEEP changes, in addition to the usual variables such as dynamic compliance, transpulmonary pressure, oxygenation parameters and dead space, the electrical impedance tomography was applied. As expected, all of these studies showed that, when applying PEEP, we have unavoidably to compromise between regional overdistension and regional collapse. Finally, in postoperative patients, Ferrando *et al.* [47] found advantages setting PEEP during a decremental PEEP trial according to the best compliance instead of using a constant value equal to $5\,cmH_2O$ PEEP, whereas Hansen *et al.* [48], in cardiovascular patients, found that $8\,cmH_2O$ PEEP was substantially similar to $5\,cmH_2O$ PEEP.

It is evident that the different methods do provide different PEEP values as they explore different properties of the system. The target of the oxygenation method is to provide an oxygen saturation approximately 90% without negative hemodynamic effects. The PEEP level to reach this target is usually lower than the one required for mechanical targets, because the complete opening of the lung is not necessary. The stress index and the ExPress study methods aim to sustain a complete recruitment by setting PEEP approximately at the level of the upper inflection point of the inspiratory volume–pressure curve, where it loses its linearity. The healthier the lung, however, the higher is the pressure set with these two methods [40▪]. Using the deflation part of the volume–pressure curve is physiologically sound, but the variable to be considered for setting PEEP is questionable. Some authors proposed as a signal of derecruitment the decrease of oxygenation. This is not necessarily true because the changes in intrathoracic pressure are associated with changes in hemodynamics, which may influence oxygenation changes [5,6]. In contrast, some authors consider the decrease in respiratory system compliance as the beginning of derecruitment. Even in normal lung, however, the compliance during deflation first increases, then

Table 1. Positive end-expiratory pressure selection methods reported in recent literature

Author	Population	PEEP selection method	Targets	Conclusions
Chiumello *et al.* [35▪,40▪]	Patients with ARDS	Increased recruitment strategy of the ExPress study	Airway pressure up to 28–30 cmH_2O or PEEP = 20 cmH_2O at constant tidal volume 6 ml/kg IBW	$PEEP/FiO_2$ table is the only method providing appropriately lower/higher PEEP in lower/higher recruiters
		Stress index	PEEP at which the time–pressure curve loses its linearity	
		Esophageal pressure	PEEP was set equal to the absolute value of esophageal pressure measured at functional residual capacity	
		LOV study	PEEP selected according to a $PEEP/FiO_2$ table, targeting Sa_{O_2} between 88% and 93%	
		CT-derived	PEEP = maximal superimposed pressure	
Yang *et al.* [41]	Patients, with and without IAH	Transpulmonary pressure	Transpulmonary pressure = 0–10 cmH_2O at end expiration, according to a sliding scale based on Pa_{O_2} and FiO_2	Transpulmonary pressure method provided higher PEEP than $PEEP/FiO_2$ table with better oxygenation and respiratory mechanics
		ARDSNet protocol	PEEP selected according to a $PEEP/FiO_2$ table	
Gulati *et al.* [39▪]	Patients with ARDS	Pes-based method E_{CW}-based method	End-expiratory transpulmonary pressure of 0 cmH_2O End-inspiratory transpulmonary pressure of 26 cmH_2O	Absolute esophageal pressure or chest wall compliance method to set transpulmonary pressure does not yield similar results
Huang *et al.* [42]	Pulmonary patients with ARDS	Oxygenation	PEEP decremented until Pa_{O_2}/FiO_2 <400 mmHg or >5% difference in Pa_{O_2}/FiO_2 between two consecutive PEEP reduction	PEEP titration by stress index might be more beneficial for pulmonary patients with ARDS after a recruitment maneuver
		Stress index	Optimal PEEP was set to obtain a stress index value between 0.9 and 1.1	
		Cst	PEEP was reduced in steps of 2 cmH_2O starting from 20 cmH_2O, until the lowest PEEP level providing the maximal Cst	
		LIP + 2 cmH_2O	Optimal PEEP = LIP + 2 cmH_2O	
Pintado *et al.* [43]	Patients with ARDS	Compliance-guided PEEP	The highest static compliance was considered to be the best PEEP during an incremental trial. If at two different PEEPs the static compliance was identical, the one with the lowest plateau was chosen	PEEP setting by highest compliance is better than by $PEEP/FiO_2$ table to decrease organ dysfunction
		ARDSNet protocol	PEEP selected according to a $PEEP/FiO_2$ table	
Rodriguez *et al.* [44]	Patients with ARDS	Crs	The best Crs PEEP was defined as the highest value of PEEP producing the higher Crs during the decremental titration maneuver	Negative values of transpulmonary pressure during decremental PEEP are associated with increased V_D/V_T and high risk of collapse
		Transpulmonary pressure	The PEEP value corresponded to an expiratory Ptp of 0	
		Dead space		

Blankman *et al.* [45]	Postcardiac surgery patients	Dynamic compliance Pa_{O_2}/Fi_{O_2} ratio EIT	Decremental PEEP trial. An even distribution of tidal volume to the nondependent and dependent lung regions Decremental PEEP trial. Highest value Decremental PEEP trial. Highest value	In postcardiac surgery patients, the EIT-derived ITV index was comparable with dynamic compliance to indicate 'best' PEEP, that is, avoids overdistension of the nondependent regions
Bikker *et al.* [36]	Pigs (healthy and after ALI induction)	Crs EELV Transpulmonary pressure Pa_{O_2} Dead space Shunt Electrical impedance	Best PEEP at maximum compliance Best PEEP at maximum EELV Best PEEP was defined at transpulmonary pressure equal to or exceeding zero during end expiration Best PEEP at maximum Pa_{O_2} Best PEEP at lowest dead space Best PEEP at lowest shunt Minimal lung collapse and overdistension	'Best' PEEP levels are comparable with the different PEEP selection methods. EIT provides information on gas distribution
Wolf *et al.* [46]	Pigs (ARDS)	ARDSNet protocol Electrical impedance	PEEP selected according to a PEEP/Fi_{O_2} table Regional EIT-derived compliance was used to maximize the recruitment of dependent lung and minimize overdistension of nondependent lung areas	EIT-guided ventilation resulted in improved respiratory mechanics, improved gas exchange and reduced histologic evidence of ventilator-induced lung injury in an animal model
Ferrando *et al.* [47]	Patients undergoing thoracic surgery	Dynamic compliance 5 cmH_2O	PEEP decrement trial at 2 cmH_2O steps until the maximal dynamic compliance was obtained	During one-lung ventilation, best compliance method is better than 5 cmH_2O PEEP to preserve oxygenation and lung mechanics
Hansen *et al.* [48]	Mechanically ventilated patients after isolated coronary artery bypass grafting or combined CABG and valve operations	5 cmH_2O 8 cmH_2O		The use of 8 cmH_2O PEEP instead of 5 cmH_2O does not seem beneficial
Mauri *et al.* [49]	Patients recovering from ARDS after switch to pressure support ventilation	Clinical PEEP (7 ± 2 cmH_2O) Clinical PEEP + 5 cmH_2O	More homogeneous distribution by EIT	Higher PEEP and lower pressure support provides more homogeneous ventilation and, possibly, better ventilation/perfusion matching

The table summarizes the results of recent studies comparing different PEEP selection methods. It reports the methods compared, their targets and the authors' conclusions. ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass graft; Crs, respiratory system compliance; Cst, static pulmonary compliance; CT, computed tomography; E_{CW}, chest wall elastance; EELV, end-expiratory lung volume; EIT, electrical impedance tomography; Fi_{O_2}, inspiratory oxygen fraction; IBW, ideal body weight; ITV, intratidal gas distribution; LIP, lower inflection point; PEEP, positive end-expiratory pressure; Pes, esophageal pressure; Ptp, transpulmonary pressure; Sa_{O_2}, arterial oxygen saturation; V_D/V_T, dead space.

stays constant and, then, decreases again, according to the sigmoid shape of the volume–pressure curve, independent of recruitability. The use of positive transpulmonary pressure as a guide for PEEP selection assumes that esophageal pressure equals the pleural pressure. Unfortunately, in our opinion, this assumption is far from true, because the esophageal pressure is highly positive in most patients with ARDS, which, according to the theory, should have their lung completely collapsed, sometimes even at the end of inspiration. The changes of esophageal pressure, in contrast, better reflect the changes of pleural pressure. Therefore, useful information can be acquired to judge the real distending pressure of the lung once the chest wall compliance has been estimated. Finally, the CT-derived PEEP is physiologically appealing, but we do not have any proof that it should be used as a guide for therapy. It simply tells us that in ARDS, from mild to severe, if we want to keep the whole lung completely open, either a few or hundreds of units, approximately the same pressure must be used. There is no clinical sense, in our opinion, to use high pressure either in patients with higher recruitability or in patients with lower recruitability, and, unfortunately, the CT scan-derived PEEP is unrelated to recruitability.

CONCLUSION

'The best PEEP' does not exist. To pretend and claim that we may find a PEEP level that avoids intratidal recruitment–derecruitment, providing in the meantime the best compliance, best oxygenation and lowest dead space, without causing hyperinflation and affecting hemodynamics, reflects a wishful dream that has nothing to do with the reality. Therefore, in our opinion, we should use a 'better PEEP' approach as a reasonable compromise among oxygenation, hemodynamics status and intratidal opening and closing. Because the latter phenomenon depends quantitatively on the lung recruitability, which is a function of the lung severity, the best compromise should be the use of higher PEEP in severe ARDS (range 15–20 cmH_2O), lower PEEP in mild ARDS (range 5–10 cmH_2O) and intermediated in moderate ARDS, paying attention to the chest wall elastance and hemodynamic impairment [50]. This pragmatic approach [50], supported by decades of studies and experience, is likely as effective as the more laborious PEEP trials that do not provide, at the end, anything else than reported range of values.

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Conflicts of interest

The authors do not have conflicts of interest.

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- ■ of special interest
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Hypercapnia: clinical relevance and mechanisms of action

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Purpose of review
Multiple clinical and laboratory studies have been conducted to illustrate the effects of hypercapnia in a range of injuries, and to understand the mechanisms underlying these effects. The aim of this review is to highlight and interpret information obtained from these recent reports and discuss how they may inform the clinical context.

Recent findings
In the last decade, several important articles have addressed key elements of how carbon dioxide interacts in critical illness states. Among them the most important insights relate to how hypercapnia affects critical illness and include the effects and mechanisms of carbon dioxide in pulmonary hypertension, infection, inflammation, diaphragm dysfunction, and cerebral ischemia. In addition, we discuss molecular insights that apply to multiple aspects of critical illness.

Summary
Experiments involving hypercapnia have covered a wide range of illness models with varying degrees of success. It is becoming evident that deliberate hypercapnia in the clinical setting should seldom be used, except wherever necessitated to avoid ventilator-associated lung injury. A more complete understanding of the molecular mechanisms must be established.

Keywords
carbon dioxide, hypercapnia, hypertension, ischemia, pneumonia

INTRODUCTION

The use of lower tidal volumes as a method of protective ventilation in patients with acute respiratory distress syndrome (ARDS) has been documented to show a significant reduction in mortality rates [1]. This protective ventilation leads to an increase in arterial carbon dioxide (hypercapnia), and the associated drop in pH resulting is termed hypercapnic acidosis (HCA). From studies spanning the last 30 years, HCA has been associated with improvement in the outcome of patients with acute lung injury/ARDS [2–6] and also with favorable effects in acute myocardial ischemia and brain injury [7] as well as gut mucosal injury due to sepsis [8]. However, in various in-vivo, ex-vivo, and in-vitro models of acute lung injury, there has also been some evidence for harmful effects of HCA, even when they seem to be outweighed by the beneficial effects [9]. Here, we highlight and interpret information obtained from more recent experimental series and, taken with what we already know, discuss their impact in leading toward the routine use of hypercapnia.

VASCULAR EFFECTS

Recent studies have focused on the pulmonary and systemic vasculature. Hypercapnia has previously been shown to reverse hypoxia-induced pulmonary hypertension in adult and neonatal rats [10,11], and a number of recent publications have recapitulated these important effects with the aim of deciphering underlying mechanisms.

In an infant rat model of right ventricular dysfunction induced by inhaled nitric oxide and hypoxia, hypercapnia was shown to normalize ventricular function by modulating interleukin-1 [12].

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KEY POINTS

- Neutrophil phagocytosis and oxidative reactions in pulmonary sepsis are impaired by hypercapnia.
- Hypercapnia protects against central nervous system ischemia by mediating levels of proapoptotic Bax and antiapoptotic B-cell CLL/lymphoma-2.
- Hypercapnia modulates cytoskeletal remodeling via cAMP induction of α-adductin activation.
- cAMP pooling has been suggested in cells that are sensitive to increased bicarbonate levels; this may have impact on buffering HCA.
- An important sheddase, ADAM-17 is impaired by hypercapnia demonstrating a new pathway by which carbon dioxide is anti-inflammatory in stretch-induced lung injury.

Here, hypercapnia inhibited interleukin-1 secretion that, in turn, reduced nitric oxide synthase 2 upregulation and therefore lessened the generation of reactive nitrogen species that contribute to hyperoxia-induced pulmonary vascular remodeling.

Another study using the same model of lung injury investigated the effects of two different levels of inhaled carbon dioxide (7 and 10%) on established pulmonary hypertension [13]. Addition of inhaled carbon dioxide to chronic hypoxia attenuated pulmonary hypertension; this was manifested as improvements in hemodynamic and structural markers of pulmonary hypertension compared to exposure to hypoxia alone. In this case, it was discovered that inhaled carbon dioxide inhibited Rho-associated protein kinase; thus, Rho-associated protein kinase-mediated vasoconstriction was diminished and pulmonary hypertension ameliorated.

Bleomycin is not only an important chemotherapeutic but also important as a contributor to lung injury in some critically ill patients. It is also used to generate lung inflammation and fibrosis for experimental models of critical illness. In experimental bleomycin-induced lung injury, inhaled carbon dioxide was shown to ameliorate deterioration of lung function, in addition to attenuating macrophage influx and the development of pulmonary hypertension [14]. In pulmonary hypertension induced by chronic hypoxia, hypercapnia attenuated pulmonary hypertension but preserved endothelial integrity [15]. Importantly, attempts to buffer HCA increased inducible nitric oxide synthase activity, and this in turn increased endothelial permeability.

A clinical study by Perry *et al.* [16] recruited 15 healthy volunteers to examine the effects of hypercapnia in steady state, nonpharmacological increases in mean arterial pressure (MAP). Hypercapnia (5% carbon dioxide in air) was shown to impair the control of blood flow velocity during steady state increases in MAP, whereas in normocapnic conditions, increases in MAP lead to a decrease in middle cerebral artery blood velocity, and hypercapnia prevented such autoregulation. Such maintenance of middle cerebral artery blood velocity suggests that hypercapnia impairs the regulatory mechanism that protects against induced hypertension.

PNEUMONIA

Previous studies have examined the effects of hypercapnia in bacterial pneumonia, with apparently conflicting results. Hypercapnia was shown to be protective in early *Escherichia coli* infection [17,18]; in contrast, another study reported that prolonged hypercapnia worsened outcome in longer-term pneumonia [19]. The overall synthesis from this work is that hypercapnia impairs neutrophil phagocytosis; while in the short term, this results in less tissue injury, in the longer term, such impairment of phagocytosis causes increased bacterial load and a greater burden of disease.

Nichol *et al.* [20] have reported an antioxidant action of hypercapnia. In a rat model of endotoxin-induced lung injury, with and without a nonspecific NOS inhibitor, hypercapnia was shown to decrease pulmonary oxidative reactions during established inflammation. In a study of the effects of therapeutic hypercapnia in endotoxin-induced lung injury, proinflammatory responses were enhanced in the lungs; however, the opposite was shown in the spleen where an anti-inflammatory cytokine milieu was observed [21]. More recently, the adverse effects of hypercapnia have been demonstrated in a mouse model of pneumonia induced by *Pseudomonas aeruginosa* [22]; here, high levels of inhaled carbon dioxide led to increased mortality. Bacterial load was increased in the lungs and neutrophil phagocytosis was decreased, and cytokine levels were reduced in early but not prolonged pneumonia.

NONINFECTIVE ACUTE LUNG INJURY

The potential for beneficial effects of hypercapnia on ventilator-induced lung injury (VILI) are promising. Peltekova *et al.* [23] – in a mouse model of VILI – demonstrated that hypercapnia attenuates the inflammatory response; this occurred in a dose (and time)-dependent manner, without adverse effects in control animals. They suggested that the positive effect of hypercapnia might be a result of the suppressed production of the COX-2 protein.

Using an isolated lung model of severe VILI, Kapetanakis *et al.* [24] have compared the effects of respiratory vs. metabolic acidosis. They reported that both respiratory acidosis and metabolic acidosis (induced by HCl) were equally effective in reducing lung edema.

An important study of the effects of hypercapnia in VILI – and possible mechanisms – was conducted by Contreras *et al.* [25]. Here, the effects of hypercapnia on moderate and severe VILI were shown to be anti-inflammatory, and were overall beneficial. In-vitro analysis demonstrated that hypercapnia inhibited the NF-κB pathway, thereby reducing levels of interleukin-8 and NF-κB-driven luciferase production.

Although not conventionally considered to be VILI, mechanical ventilation can induce significant dysfunction in the diaphragm. An experimental study in rats suggests that hypercapnia may protect against this problem [26]. Here, diaphragm myofiber myosin concentration was significantly increased compared with controls; in addition, tumor necrosis factor-α, interleukin-1β, and keratinocyte-derived chemokines were all significantly decreased in diaphragm homogenates of hypercapnia animals.

Fuchs *et al.* [27] performed an interesting study comparing progressively lower tidal volumes while permitting the resultant hypercapnia. Compared with 8–10 ml/kg, reductions in tidal volume below 4 ml/kg did not provide additional protection; reassuringly, the severe hypercapnia (i.e., 160 mmHg), which arose at extremely low tidal volume (i.e., 2 ml/kg), did not reverse the protection. The study utilized a surfactant-depletion rabbit model of ARDS.

Finally, carbon dioxide preexposure blocks degranulation of mast cells and significantly reduces histamine release implicated in allergic rhinitis in response to stimulation by compound 48/80 [28]. The mechanism of action behind this antiallergy effect was demonstrated to be in correlation with a decrease in intracellular calcium levels. This may point toward a possible mechanism by which carbon dioxide exerts some of its effects.

ISCHEMIA

Severe, sustained hypercapnia in newborn rats (10% inspired carbon dioxide) appears to impair brain growth by increasing nitrative stress, which, in turn, leads to microvascular degeneration [29]. This negative effect was not seen in animals treated with reactive nitrogen species inhibitors showing that high levels of carbon dioxide causes nitrative stress in neonatal brain development.

The effects of therapeutic hypercapnia were investigated in a rodent model, where impaired spatial memory and sensorimotor function was induced by central nervous system ischemia [30]. Hypercapnia improved both conditions via antiapoptotic mechanisms. Levels of proapoptotic Bax (and antiapoptotic B-cell CLL/lymphoma-2) proteins were decreased (and increased, respectively) in brain tissues of animals exposed to hypercapnia.

Hypercapnia improved lung injury indices such as perfusion pressure elevation, lung wet weight, bronchoalveolar lavage protein concentration, and lactate dehydrogenase, in the setting of ischemia reperfusion [6]. Filtration coefficient, an index of barrier integrity, was also reduced in the setting of hypercapnia. This study also documented the correlation between hypercapnia-associated improvements and NF-κB inhibition, via a decrease in ischemia-reperfusion-induced inhibitor of nuclear factor kappa-B kinase subunit alpha/beta (IKK-α/β) phosphorylation that, in turn, prevented degradation of IκBα and NF-κB activation and translocation.

MOLECULAR MECHANISMS

Previous studies have pointed out that hypercapnia may impair alveolar fluid clearance by decreasing the levels of Na,K-ATPase on plasma membranes [31,32]. Further investigations by this group have shown that hypercapnia induces endocytosis of the Na,K-ATPase transporter [33] and this occurs via an extracellular-signal-regulated kinase-regulated pathway [34] (see Fig. 1 [34–37,38▪▪,39]). Most recently, it has been shown that this is dependent on cyclic AMP (cAMP) production; cAMP activated PKA-Iα, which, in turn, led to phosphorylation of α-adductin, a known regulator of Na,K-ATPase endocytosis [37].

It has been suggested that pools of cAMP exist in pulmonary microvessels, and such pools are sensitive to bicarbonate [38▪▪]. Indeed, addition of bicarbonate decreased transendothelial resistance and increased filtration coefficient in isolated perfused lungs. This may ultimately be an important issue to consider when attempting to buffer the acidosis resulting from increased hypercapnia.

Hypercapnia has been shown to inhibit NF-κB-dependent cytokines and, perhaps consequentially, decrease macrophage phagocytosis [40]. However, such inhibition of cytokine production does not occur via blockade of either NF-κB activation or its translocation, and appears to occur via other transcription factors [40].

In a study by Cummins *et al.* [35], mouse embryonic fibroblast cells were exposed to 0.03% or 10% carbon dioxide, with or without pH-buffering. The group also conducted graded pH experiments to compare effects of hypercapnic and metabolic acidosis on NF-κB activity. Here, nuclear translocation of IKK-α was independent of O_2 concentration, but was

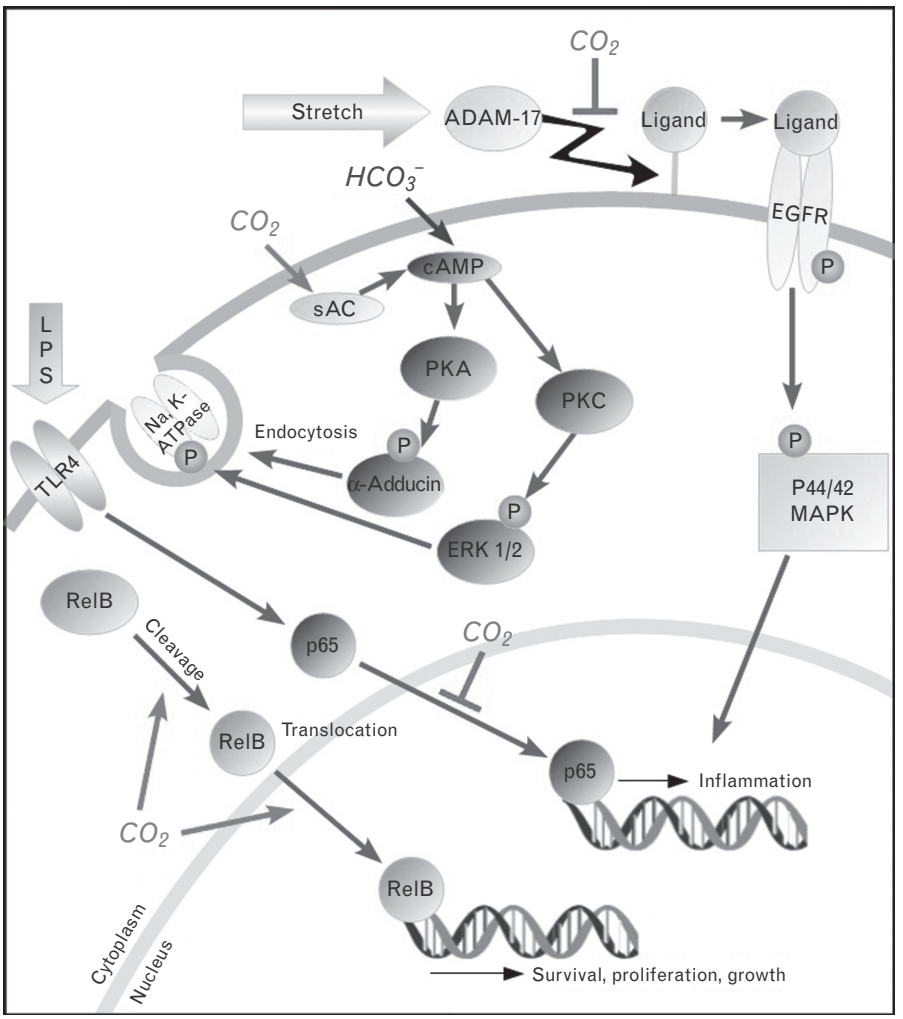

FIGURE 1. Schematic representation of the recently established intracellular molecular responses to elevated carbon dioxide. Carbon dioxide has been shown to confer positive anti-inflammatory effects by increasing the translocation of RelB and impairing the translocation of p65 [35,36]. Carbon dioxide has also been demonstrated to increase the endocytosis of the Na,K-ATPase transporter [34,37,38▪▪] leading to reduced edema clearance from injured lungs. P44/42 activation by stretch-induced injury was shown to be decreased after carbon dioxide exposure via inhibition of the sheddase ADAM-17 reducing stretch-induced inflammation [39].

dependent on carbon dioxide concentration, and the carbon dioxide effect was rapidly reversible. In the same experimental series, hypercapnia was also shown to inhibit p65 translocation in mouse embryonic fibroblast cells in response to lipopolysaccharide injury. In a further study by the same group [36], RelB – a protein of the noncanonical NF-κB pathway – was shown to undergo cleavage and subsequent translocation to the nucleus under conditions of increased carbon dioxide; these effects were independent of pH changes induced by buffering cell culture media.

A recent article by Otulakowski *et al.* [39] has pointed toward a mechanism whereby hypercapnia inhibits p44/42 mitogen activated protein kinase (MAPK) activation. Activation of p44/42 MAPK correlates with the degree of stretch-induced lung injury [41] and is mediated via epidermal growth factor receptor activity [42]. This, in turn, is dependent on the binding of endogenous ligands whose shedding is induced by a sheddase – ADAM-17 [43]. Hypercapnia was shown to prevent ligand shedding and thus prevent downstream activation of epidermal growth factor receptor and p44/42 MAPK in rodent alveolar epithelial cells [40] (see Fig. 1). Stretch-induced shedding of tumour necrosis factor receptor (another ADAM-17 substrate) was also shown to be reduced in an isolated perfused mouse lung model of injury.

The cellular mechanisms of action of carbon dioxide in cerebral microvascular endothelial cells and human fetal astrocytes have shed light on

interactions with nitrogen-derived free radical mechanisms [44]. The production of nitric oxide by these cell types is increased in hypercapnia (and decreased in hypocapnia) during stable neutral pH levels.

GASTROINTESTINAL IMPACT

Using a ventilated canine model of gastric hemorrhage, Schwartges *et al.* [45] aimed to determine the effects of hypercapnia, induced by reduced tidal volumes, in a canine model of hemorrhage. Hypooxygenation of the splanchnic region is a risk factor of hemorrhage and endangers mucosal barrier function. Here, prophylactic and therapeutic hypercapnia appeared to preserve splanchnic mucosal oxygenation. However, intraoperative hypercapnia in patients undergoing elective colon resection was shown to have little or no ability to prevent surgical site infection [46].

CONCLUSION

In conclusion, this article reviews key research developments in the study of hypercapnia in critical illness and describes many effects in experimental models of human disease, along with exploring key novel molecular mechanisms of effect. As our ability to better characterize critical illness states improves, in terms of organ and molecular-specific mechanisms, we will be better able to apply the insights learned over the last 3–5 years.

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Conflicts of interest

There are no conflicts of interest.

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Discontinuation of ventilatory support: new solutions to old dilemmas

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Purpose of review
Weaning from mechanical ventilation implies two separate but closely related aspects of care, the discontinuation of mechanical ventilation and removal of artificial airway, which implies routine clinical dilemmas. Extubation delay and extubation failure are associated with poor clinical outcomes. We sought to summarize recent evidence on weaning.

Recent findings
Tolerance to an unassisted breathing does not require routine use of weaning predictors and can be addressed using weaning protocols or by implementing automatic weaning methods. Spontaneous breathing trial can be performed on low levels of pressure support, continuous positive airway pressure, or T-piece. Echocardiographic tools may help to prevent the failure of extubation. Noninvasive ventilation can prevent respiratory failure after extubation, when used in hypercapnic patients. Recently, sedation protocols and early mobilization in ventilated critically ill patients may decrease weaning period and duration of mechanical ventilation, and prevent extubation failure and complications such as ICU-acquired weakness. New techniques have been performed to identify patients with high risk for extubation failure.

Summary
There is an interesting body of clinical research in the discontinuation of mechanical ventilation. Recent randomized controlled studies provide high-level evidence for the best approaches to weaning, especially in patients who fail the first spontaneous breathing trial or targeted populations.

Keywords
extubation, mechanical ventilation, spontaneous breathing trial, weaning

INTRODUCTION

Discontinuation of mechanical ventilation, or weaning, can be defined as the process of gradual or sudden ventilatory support withdrawal in critically ill patients and represents one of the most important challenges in intensive care units (ICUs). It has been estimated that 40% of the time a patient is mechanically ventilated is dedicated to the process of weaning [1]. Traditionally, identifying the appropriate time for extubating a patient is of great clinical importance, and based on the balance of the clinical decision to avoid both unnecessary prolongation of mechanical ventilation, and premature extubation since both aspects are related to increased risk of complications in critically ill patients [2–4]. The current clinical challenge is to improve weaning from mechanical ventilation in critically ill patients who fail the first test of spontaneous breathing. The purpose of this review is to critically update the recent literature regarding the period of weaning from mechanical ventilation, as well as the failure of extubation in adult patients.

EVALUATION OF DEPENDENCE ON VENTILATORY SUPPORT

The process of weaning from mechanical ventilation begins with the recognition of proper recovery from acute respiratory failure that led to the initiation of mechanical ventilation. It also implies two separate but closely related aspects of care, discontinuation of mechanical ventilation and removal of any artificial airway. To facilitate this process, researchers have focused on identifying objective criteria for determining the ideal time for withdrawal of mechanical ventilation (Table 1). In The International

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KEY POINTS

- Most patients who require mechanical ventilation for longer than 24 h, and who improve the condition leading to the indication of ventilatory support, can be weaned after passing a first spontaneous breathing test. Currently, the clinical dilemma is to improve the weaning of patients who fail that first test.
- The weaning predictors did not confer survival benefit or reduce the incidence of extubation failure or tracheostomy.
- The implementation of weaning protocols and computer-driven approaches may be useful as weaning strategies, and clinicians should adopt daily assessment for a trial of unassisted breathing as a well tolerated method to reduce the duration of mechanical ventilation.
- New techniques have been employed to identify patients at increased risk for extubation failure. Noninvasive ventilation, when used in high-risk patients, can decrease extubation failure.
- Recent randomized controlled trials provide high-level evidence for the best approaches to weaning and extubation. Clinical research efforts must focus on better identifying high-risk population for failure of extubation and provide approaches to improve clinical outcomes.

Consensus Conference in 2005, it was emphasized that the first test of weaning from mechanical ventilation should be performed at the earliest feasible time [5].

Weaning-predictor tests

Some parameters based on respiratory mechanics, gas exchange, and breathing pattern have been proposed as useful predictors of weaning that may guide clinicians in assessing the optimal time to discontinue mechanical ventilation. Several studies have suggested that the rapid and shallow breathing test (f/Vt, where 'f' is the respiratory rate and 'Vt' is the tidal volume measured during the initial 1–3 min of unassisted breathing) was the most frequently used in predicting the outcome of weaning. However, in the original study it was not possible to know whether f/Vt predicted their ability to tolerate spontaneous breathing, or successful extubation. No further studies have confirmed these results. Recent studies argued against the application of weaning predictors being probably unnecessary and could delay extubation decision [6]. Taking those aspects into account, a consensus conference on weaning did not recommend the routine application of predictor-weaning test for decision-making [5].

An interesting concept derived from clinical research has been recently incorporated for helping clinicians to assess the tolerance of weaning. The heart-rate variability (HRV) is a noninvasive and valuable tool to characterize autonomic function and cardiorespiratory interaction. Two recent prospective observational studies have shown that a reduced HRV during a spontaneous breathing trial (SBT) was significantly associated with extubation failure [7▪,8]. Randomized trials are needed to assess its clinical utility and validation.

STRATEGIES OF WEANING FROM MECHANICAL VENTILATION

The most important issue in critically ill patients receiving mechanical ventilation, once the underlying disease has improved, is to decide when to start the process of weaning from mechanical ventilation (Fig. 1).

Classically, pressure support with low positive end-expiratory pressure (PEEP), continuous positive airway pressure (CPAP), and T-piece is the most common method used to test the readiness for discontinuation of mechanical ventilation. Few randomized studies have evaluated the best technique for performing SBT before extubation and there is no clinical evidence of a higher reintubation risk between those methods [9,10]. However, observational results suggest that reintubation was significantly associated with the use of CPAP compared with T-tube or low pressure support tests [11,12]. Therefore, weaning tests might be performed without PEEP to better detect latent cardiac dysfunction and/or lung failure. A first attempt of weaning test before extubation can probably be performed on the ventilator using a low pressure support test without PEEP, but in many high-risk patients, a prolonged T-piece trial is probably more reliable for making extubation decisions.

The duration of SBT is strongly supported by scientific evidence; it should be at least 30 min but not longer than 120 min [13,14]. Precise criteria for terminating a weaning trial do not exist, and currently, trials are terminated on the basis of the clinical judgment of the physician (Table 1).

Regardless of the strategy of weaning from mechanical ventilation employed in the ICU, early identification of patients capable of breathing spontaneously is associated with better clinical outcomes [15]. In fact, a recent systematic trial in which patients with usual care were compared with another group with standardized weaning protocols concluded that a reduction occurred in the duration

Table 1. Clinical criteria to readiness during a spontaneous breathing trial

Clinical criteria	Readiness for starting weaning trial	Good tolerance of an SBT
Objectives	Adequate oxygenation (e.g., PaO_2/FiO_2 ratio 150–200; requiring positive end-expiratory pressure ≤5 to 8 cmH_2O; FiO_2 ≤0.4 to 0.5	RR <35 breaths/min
		Arterial oxygen saturation >90% or PaO_2 >60 mmHg on FiO_2 <0.4
	Febrile (temperature <38 °C).	HR <140 beats/minute or a sustained increase or decrease in the heart rate of >20%
	Hemodynamic stability (e.g., HR ≤140 bpm); stable BP; no (or minimal) pressors; no myocardial ischemia	Systolic BP <180 mmHg or >80 mmHg or change <20% from baseline
	Adequate hemoglobin (e.g., Hb ≥8–10 g/dl)	
	Adequate mentation (e.g., arousable, no continuous sedative infusions)	
Subjectives	Resolution of disease acute phase	No signs of increased work of breathing (accessory muscle use, paradoxical or asynchronous rib cage-abdominal breathing movements, intercostal retractions, nasal flaring).
	Adequate cough	No other signs of distress (profuse diaphoresis, agitation)

BP, blood pressure; Hb, hemoglobin; HR, heart rate; RR, respiratory rate; SBT, spontaneous breathing trial.

of mechanical ventilation, weaning, and ICU stay [16▪].

This strategy of standardized weaning protocols can be addressed by automated program weaning. These devices use closed-loop control to interpret clinical data in real time, which might facilitate weaning of mechanical ventilation by a gradual decrease in the level of pressure support and perform an SBT, telling the doctor that the patient can be disconnected from mechanical ventilation [17]. The automated program weaning has been evaluated in three different clinical trials [18–20,21▪,22▪,23] compared with protocolized weaning among patients requiring more than 24 h of mechanical ventilation and consistently showed that weaning time was reduced in the computer-driven group. Compared with a standardized protocol, automated program weaning was associated with promising weaning outcomes that warrant further clinical investigation to fill the knowledge gap that impedes the broader application of those automated systems.

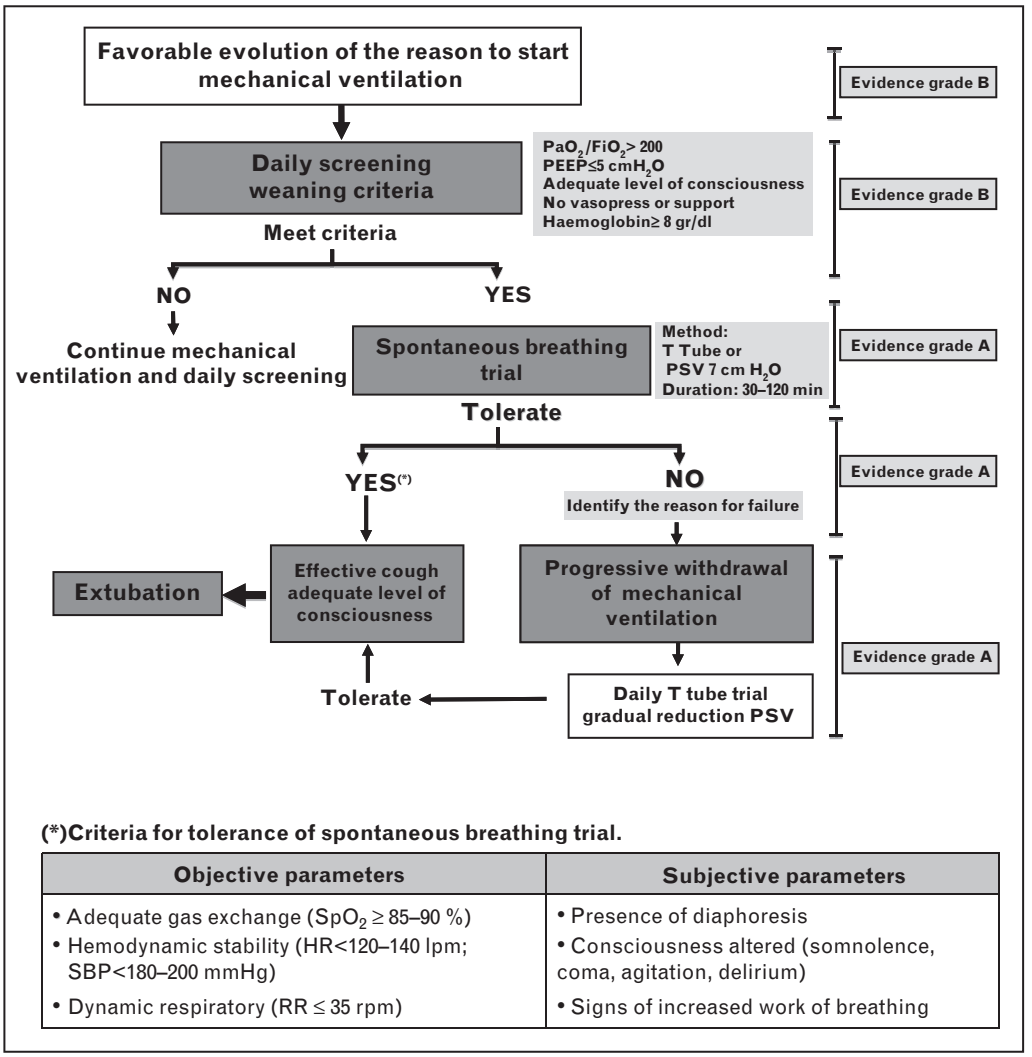
FAILURE OF WEANING FROM MECHANICAL VENTILATION

The presence of poor tolerance of an SBT represents a weaning failure. Therefore, once a patient fails an SBT, the physician must comprehensively evaluate the patient, searching for reasons to explain such failure and improve the physiological status of the patient.

To identify high-risk patients for weaning failure, an International Consensus Conference on weaning from mechanical ventilation proposed a new classification of weaning according to its difficulty of liberating [5], as shown in Table 2. This classification has been validated in several observational studies [4,24–26] with different sample size, and as conclusion, the prolonged weaning was associated with increased mortality and morbidity in the ICU. Peñuelas *et al.* [4] found that only patients with prolonged weaning, re-defined as patients with a weaning period longer than 6 days, had a higher ICU mortality (Fig. 2).

Cardiac decompensation is probably one of the most common causes of failure of the process of weaning from mechanical ventilation. In a randomized, multicenter trial involving 304 patients receiving diuretic therapy guided or guided B-type natriuretic peptide (BNP) clinical strategy, it was noted that the strategy-guided BNP shortened the duration of weaning compared with usual guided medical strategy, but did not change length of ICU stay or mortality [27].

An important component of load/capacity imbalance is reduced respiratory muscle strength. Diaphragmatic function plays a crucial role in



(*)Criteria for tolerance of spontaneous breathing trial.

Objective parameters	Subjective parameters
• Adequate gas exchange ($SpO_2 \geq 85$–90 %)	• Presence of diaphoresis
• Hemodynamic stability (HR<120–140 lpm; SBP<180–200 mmHg)	• Consciousness altered (somnolence, coma, agitation, delirium)
• Dynamic respiratory (RR ≤ 35 rpm)	• Signs of increased work of breathing

FIGURE 1. Algorithm for the withdrawal from mechanical ventilation. HR, heart rate; PSV, pressure support ventilation; RR, respiratory rate; SBP, systolic blood pressure.

determining the ability of patients to be successfully weaned from the ventilator [28]. Another approach to detect diaphragmatic dysfunction is the clinical use of direct measures of diaphragmatic function as predictors of extubation success or failure [29]. A recent observational study that included 63 patients found that ultrasound measures of diaphragm thickening (tdi) in the zone of apposition may be

Table 2. Classification of weaning from mechanical ventilation (ref [4,24–26])

Groups	Definition	Incidence	Tracheotomy	ICU mortality
Easy weaning	Extubation after successful first attempt of SBT	30%–58%	6%–7%	0%–13%
Difficult weaning	Patients who fail the first SBT and require up to three SBTs or up to 7 days to reach a successful extubation	26%–40%	6%–15%	1%–11%
Prolonged weaning	Patients who require >7 days after failure of the first SBT	6%–30%	10%–68%	13%–22%

ICU, intensive care unit; SBT, spontaneous breathing trial.

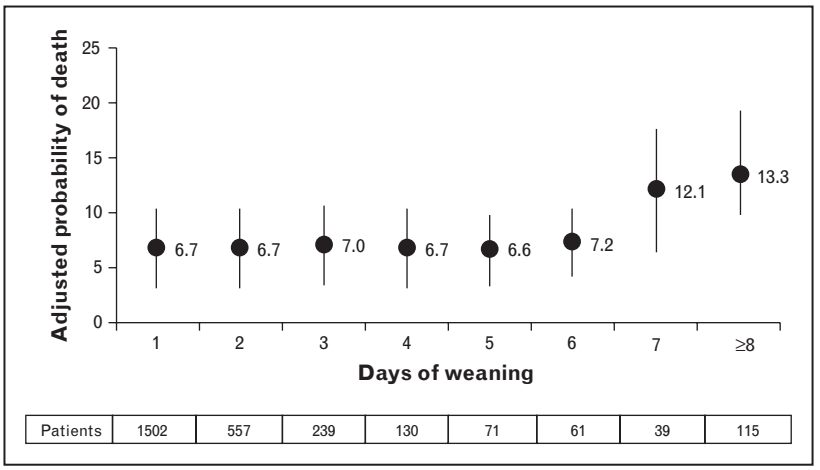


FIGURE 2. Adjusted probability of ICU mortality according to the duration of weaning time (modified from Peñuelas *et al.* [4]).

useful to predict extubation success or failure during SBT by using a threshold of Δtdi 30% or higher for extubation success [30▪].

The sonographic diaphragmatic parameters can provide valuable information in the assessment and follow-up of patients with diaphragmatic weakness, in terms of patient–ventilator interactions during controlled or assisted modalities of mechanical ventilation, and can potentially help to understand postoperative pulmonary dysfunction or weaning failure from mechanical ventilation [31▪].

In patients with repeatedly unsuccessful SBT, a gradual withdrawal from mechanical ventilation using pressure support ventilation (PSV) can be attempted. The relative efficacy of these methods has been poorly evaluated. Recently, a Cochrane systematic review including nine randomized clinical trials (RCTs) with 1208 patients showed no clear evidence of a difference between PSV and T-tube for weaning success [32]. Data from an international, prospective, and multicenter study with 927 participating ICUs and 18 302 patients undergoing mechanical ventilation for more than 12 h [33▪▪] showed that the proportion of patients who successfully completed their first SBT increased over time (49% in 1998, 55% in 2004, and 63.5% in 2010, $P < 0.001$). However, in patients who failed the first attempt of SBT, there was a significant increase in the subsequent use of PSV as the mode of weaning from mechanical ventilation, with a concomitant reduction in the use of SIMV with or without PSV (Fig. 3).

One of the most interesting fields of clinical research is to prevent the failure of discontinuation of mechanical ventilation. In this sense, the implementation of sedation protocols in mechanically ventilated patients has led to shorter duration of weaning [34]. The development of protocols for the prevention of ICU-acquired weakness (ICU-AW), which has been found to prolong the period of weaning from mechanical ventilation [35], combined with daily sedation interruption and SBT, could result in a shorter duration of mechanical ventilation [36].

Finally, noninvasive ventilation (NIV) to hasten extubation in difficult-to-wean chronic obstructive pulmonary disease (COPD) patients has been studied as a means of reducing complications among patients being weaned from invasive mechanical ventilation. A recent systematic review and meta-analysis, which included 16 trials (nine trials exclusively involved patients with COPD), found that compared with invasive weaning, noninvasive weaning significantly reduced mortality and weaning failures with moderate heterogeneity. Because of these findings, the NIV as a method of weaning from mechanical ventilation cannot be generally

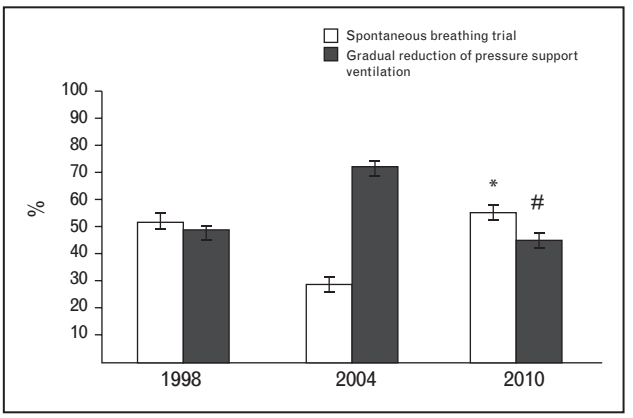


FIGURE 3. Gradual discontinuation of ventilatory support over time. Data collected from three international studies of mechanical ventilation [33▪▪]. *P value for interaction <0.001; #P value for interaction <0.001.

recommended in clinical practice, although it may have beneficial effects in selected COPD patients [37]. Therefore, new trials to support the widespread use of this strategy are needed.

FAILURE OF EXTUBATION

The extubation failure usually is defined as a need of reintubation within 48 h after a scheduled extubation [2]. Failure of a planned extubation may appear between 10% and 20%, even among patients who meet all weaning criteria and successfully perform a weaning trial. Reintubated patients experience prolonged ICU and hospital stays, greater need for tracheostomy, and more frequently require long-term acute care [3]. It is controversial whether extubation failure is a marker of poor outcome or contributes to a poor prognosis [38,39].

Strategies for preventing failure of extubation

There is growing evidence that physical rehabilitation in the ICU, when started as early as 1 or 2 days after initiating mechanical ventilation, is feasible, well tolerated, and beneficial including improved exercise capacity, functional status at hospital discharge, decreased duration of mechanical ventilation, and shorter ICU length of stay. A recent RCT [35] showed that implementation of early physical therapy and occupational therapy resulted in improved days alive and breathing without assistance.

The use of NIV as a strategy for the management of respiratory failure postextubation has gained prominence in recent years. There is evidence that the prophylactic use of NIV after extubation scheduled may be beneficial to prevent respiratory failure after extubation only in selected patients with high risk of reintubation, such as patients with hypercapnia. A meta-analysis [40] including four studies showed that NIV, compared with the standard medical therapy, did not decrease the re-intubation rate or ICU mortality in patients ($n = 302$) with postextubation respiratory failure. However, in patients ($n = 259$) who were defined to be at high risk for developing postextubation respiratory failure, NIV decreased the re-intubation rate and ICU mortality, but not the hospital mortality. Current evidence suggests that NIV should be used judiciously, if at all, in patients with postextubation respiratory failure, but it appears to be promising as a prophylaxis to prevent re-intubation in patients 'at risk' for developing postextubation respiratory failure [41].

Modern high-flow nasal cannula (HFNC) devices equipped with an active humidification chamber can provide gas flow rates up to 70 l/min, which are higher than the patient's respiratory flow, and therefore allow a controlled delivery of a defined FiO_2 up to 1. A recent RCT [42▪▪] including 105 patients with a PaO_2/FiO_2 ratio 300 or higher immediately before extubation found that the use of HFNC is associated with significantly lower reintubation rate.

MANAGEMENT OF WEANING FROM MECHANICAL VENTILATION IN PATIENTS WITH SPECIAL CONDITIONS

Recent clinical research has focused on better identifying high-risk population for failure of extubation and provides approaches to improve clinical outcomes. We have selected the following populations:

Patients with tracheostomy or prolonged mechanical ventilation

One of the most important aspects in the discontinuation from mechanical ventilation in patients with prolonged mechanical ventilation is to be initiated as soon as possible, as the best interval for successful weaning occurs in the first 3 weeks [13]. Performing a tracheostomy corresponds with good practice and the replacing tracheotomy cannula must be progressively smaller so as to keep the tube inflated to increase the diameter of the airway [43]. Swallowing dysfunction may be present and complicate the process of weaning from mechanical ventilation. Jubran *et al.* [44▪▪], in a recent RCT, found that patients with tracheotomy were faster disconnected from mechanical ventilation when testing daily disconnection made with T-tube, compared with those who were testing a gradual reduction in pressure support, although there was no influence on survival at 12 months.

Ventilatory management in the late stages of weaning with tracheostomized patients is not well established. The results from a clinical trial including 16 tracheostomized patients suggested that reconnections to the ventilator during the night time may favor sleep efficiency and showed a reasonable clinical approach based on re-connections to the ventilator at night during the first few days of transitioning from mechanical to spontaneous ventilation [45]. Most efforts were made to improve the independent breathing in tracheostomized patients by deflating the cuff of the tracheal tube. An RCT including 181 patients has recently studied the effect of deflating the cuff on weaning and showed that deflating the tracheal cuff in tracheostomized patients shortened the weaning process compared

with the inflated group (weaning time 8 days vs. 3 days, respectively; $P < 0.01$) and probably improved swallowing [46▪▪]. In patients undergoing mechanical ventilation continuously for more than 21 days a multivariate logistic regression analysis showed that the only variable associated with extubation failure was ineffective cough and that weaning parameters were not helpful in predicting extubation outcome [47].

NEUROCRITICAL PATIENTS

The decision of extubation in comatose patients is particularly delicate. According to the study by Coplin *et al.* [48], prolonged intubation should be avoided when the only concern in the clinical decision is deteriorating level of consciousness.

A prospective, multicenter, observational study showed that in patients with neurologic diseases, a systematic approach to weaning and extubation reduces the rate of reintubation secondary to extubation failure, without affecting the duration of mechanical ventilation [49]. In this sense, in before-after studies involving 299 and 200 patients, respectively, with mechanical ventilation and cerebral injury, the application of a set of measures (protective ventilation, early enteral nutrition, antibiotic therapy standardization, and systematic testing extubation) compared with a conventional strategy was associated with a reduction in the duration of mechanical ventilation and a greater likelihood of successful extubation [50▪▪].

Ultimately, although extubation failure is a risk factor for poor overall outcome in heterogeneous populations, its impact on the patient failing with neurological dysfunction has not been adequately determined.

CONCLUSION

In the last few years, there have been significant advances that have allowed an improvement in the duration and the withdrawal of mechanical ventilation in critically ill patients. However, more clinical research is needed to identify patients at high risk for extubation failure, disconnection strategies of prolonged mechanical ventilation, and application of new techniques of weaning that may contribute to decrease in the mortality in critically ill patients.

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Conflicts of interest

There are no conflicts of interest.

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How to ventilate patients without acute respiratory distress syndrome?

Ary Serpa Neto[a,b], *Fabienne D. Simonis*[b], *and Marcus J. Schultz*[b,c]

Purpose of review
There is convincing evidence for benefit from lung-protective mechanical ventilation with lower tidal volumes in patients with the acute respiratory distress syndrome (ARDS). It is uncertain whether this strategy benefits critically ill patients without ARDS also. The present article summarizes the background and clinical evidence for ventilator settings that have the potential to protect against ventilator-induced lung injury.

Recent findings
There has been a paradigm shift from treating ARDS to preventing ARDS. In surgical patients, anesthesiologists should consider ventilating patients with a tidal volume of 6–8 ml/kg predicted body weight (PBW), levels of positive end-expiratory pressure (PEEP) between 0 and 2 cmH_2O, and higher levels of FiO_2. Finally, in critically ill patients without ARDS, intensive care physicians could consider ventilating with a PEEP level of 5 cmH_2O and lower levels of FiO_2. There is insufficient evidence for the benefit of lower tidal volumes in these patients. There is, however, some evidence that tidal volumes of 6 ml/kg PBW or less are associated with better outcomes.

Summary
There is increasing and convincing evidence that the use of lower tidal volumes during mechanical ventilation of patients without ARDS prevents against ventilator-induced lung injury.

Keywords
acute respiratory distress syndrome, lower tidal volume, mechanical ventilation, protective ventilation, pulmonary complications

INTRODUCTION

Mechanical ventilation should never be seen as a simple and well tolerated intervention, neither in patients under general anesthesia for surgery nor in critically ill patients. Indeed, ventilation is increasingly recognized as a harmful intrusion that could cause lung damage and respiratory muscle injury, frequently referred to as 'ventilator-induced lung injury' (VILI) [1] and 'ventilator-induced diaphragm dysfunction' (VIDD) [2].

The aim of the present review is to summarize the background and clinical evidence for ventilator settings that have the potential to protect against VILI and VIDD, including the use of lower tidal volume size, higher levels of positive end-expiratory pressure (PEEP), lower oxygen fractions (FiO_2), and spontaneous modes of ventilation, in patients without the acute respiratory distress syndrome (ARDS). Although evidence for benefit from protective ventilation strategies mainly comes from investigations in patients with ARDS, there is a rapidly expanding understanding on how to prevent VILI and VIDD in patients who receive intraoperative ventilation in the operation room and ventilation for respiratory failure other than ARDS in the intensive care unit.

EVIDENCE FOR BENEFIT FROM PROTECTIVE VENTILATOR SETTINGS IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a severe and life-threatening complication of critical illness with a high mortality [3]. It is

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KEY POINTS

- Anesthesiologists should consider ventilating patients undergoing general anesthesia for surgery with low tidal volume, low positive end-expiratory pressure (PEEP), and higher FiO_2.
- Intensive care physicians could consider ventilating critically ill patients without acute respiratory distress syndrome (ARDS) with moderate PEEP level and lower levels of FiO_2.
- There is some evidence that low tidal volumes are associated with better outcomes in critically ill patients without ARDS.

characterized by heterogeneous lung damage causing ventilation to be a challenge. Some parts of the lung are collapsed and remain collapsed despite the use of higher airway pressures; other parts experience tidal recruitment, or repetitive opening and closing with each breath cycle, and uninjured parts are open throughout the whole cycle, but run the risk of overinflation at end-inspiration [4]. Repeated opening and closing and overinflation are considered harmful, which could be prevented by the use of higher levels of PEEP and lower tidal volumes, respectively [1].

Lower tidal volumes

The harmful effects of the use of higher tidal volumes or higher airway pressures in patients with ARDS were considered unimportant until the publication of the large ARDS Network randomized controlled trial (RCT) in 2000 convincingly showing mortality reduction with the use of lower tidal volumes [5]. Other RCTs and a large meta-analysis [6–8] confirmed benefit from tidal volume reduction in patients with ARDS. Since then, so-called 'protective ventilation' with the use of tidal volumes of 6–8 ml/kg predicted body weight (PBW) is considered standard of care in these patients [3].

Higher levels of positive end-expiratory pressure

Several RCTs [9–11] failed to show beneficial effects of higher levels of PEEP in patients with ARDS. Recently, a meta-analysis [12] showed that the use of higher levels of PEEP was associated with an improved survival, but only in patients with severe ARDS. Also, the use of higher levels of PEEP prevented the need for rescue therapies in these patients [12]. Consequently, nowadays it is advised to use higher levels of PEEP with caution, and only in patients with more severe forms of ARDS [3].

Lower levels of FiO_2

Patients with ARDS often need to be ventilated with higher levels of FiO_2 [3]. The need for higher levels of FiO_2 might even have increased with the use of lower tidal volumes, because this strategy may induce atelectasis and intrapulmonary shunting [3,5]. The use of higher levels of FiO_2, however, is associated with worse outcomes in critically ill patients [13], and it is suggested to increase the level of PEEP before increasing the level of FiO_2 in patients with ARDS [3,5], even though robust evidence for this approach is lacking.

Spontaneous versus assist modes of ventilation

Although the abbreviation VIDD suggests that the diaphragm is the only respiratory muscle that experiences misuse and disuse, probably all of the respiratory muscles are at risk of this complication. In particular, controlled forms of ventilation are associated with the development of VIDD [14]. Recently, a RCT [15] suggested that early administration of a neuromuscular blocking agent for a maximum of 48 h improved survival and increased the time off the ventilator without increasing muscle weakness in patients with ARDS, which was surprising because the use of neuromuscular blocking agents mandates the use of controlled forms of ventilation. Notably, prolonged use of neuromuscular blocking agents is associated with the development of VIDD [15]. The latter finding may suggest that spontaneous breathing should be preferred over assist-controlled forms of ventilation, at least after 48 h, but patient–ventilator asynchronies remain possible with spontaneous breathing.

Summary

On the basis of the best available evidence, patients with ARDS are considered to be ventilated with a tidal volume 6 ml/kg PBW or less [5,6], levels of PEEP greater than 5 cmH_2O according to severity [9–12], and levels of FiO_2 adjusted according to a PEEP–FiO_2 table [5,9–11].

PREVENTION OF ACUTE RESPIRATORY DISTRESS SYNDROME

There has been a paradigm shift from treating ARDS (i.e., reducing further harm by using protective ventilation in patients with ARDS) to preventing ARDS (i.e., preventing harm by using protective ventilation in patients without ARDS) [16▪▪]. Epidemiological data [17–19] suggest that ARDS is rarely present at the start of ventilation, but develops over

a period of hours to days, and maybe only in subsets of patients. One approach could be to use protective ventilator settings in all of the patients, irrespective of the indication for ventilation. Although it is uncertain whether ventilation always harms the lung of patients without ARDS, it is even more uncertain whether the strategies proven beneficial in patients with ARDS can prevent VILI in patients without ARDS. One argument against a 'general' protective ventilation approach, that is, the use of protective ventilation in all of the ventilated patients, is that possible adverse effects may offset the benefits of protective ventilation [17,18]. Robust evidence for benefit is needed, both in patients receiving intraoperative ventilation and in critically ill patients with respiratory failure not meeting the definition of ARDS, before we start using protective ventilation in all of the ventilated patients.

PROTECTIVE VENTILATION IN PATIENTS UNDER GENERAL ANESTHESIA FOR SURGERY

Postoperative complications after surgery are an important cause of morbidity and even mortality [20▪]. In particular, the development of postoperative pulmonary complications is strongly associated with a worse postoperative outcome (Fig. 1) [20▪,21]. Postoperative ARDS is the most feared postoperative pulmonary complication with a reported incidence of as high as 25% [22▪,23,24], and recent observational studies [19,24] suggest that the incidence of postoperative ARDS is maybe even higher than the incidence of sepsis-associated ARDS. Among several intraoperative factors that can influence the development of postoperative ARDS, tidal volume size and level of PEEP are the strongest predictors.

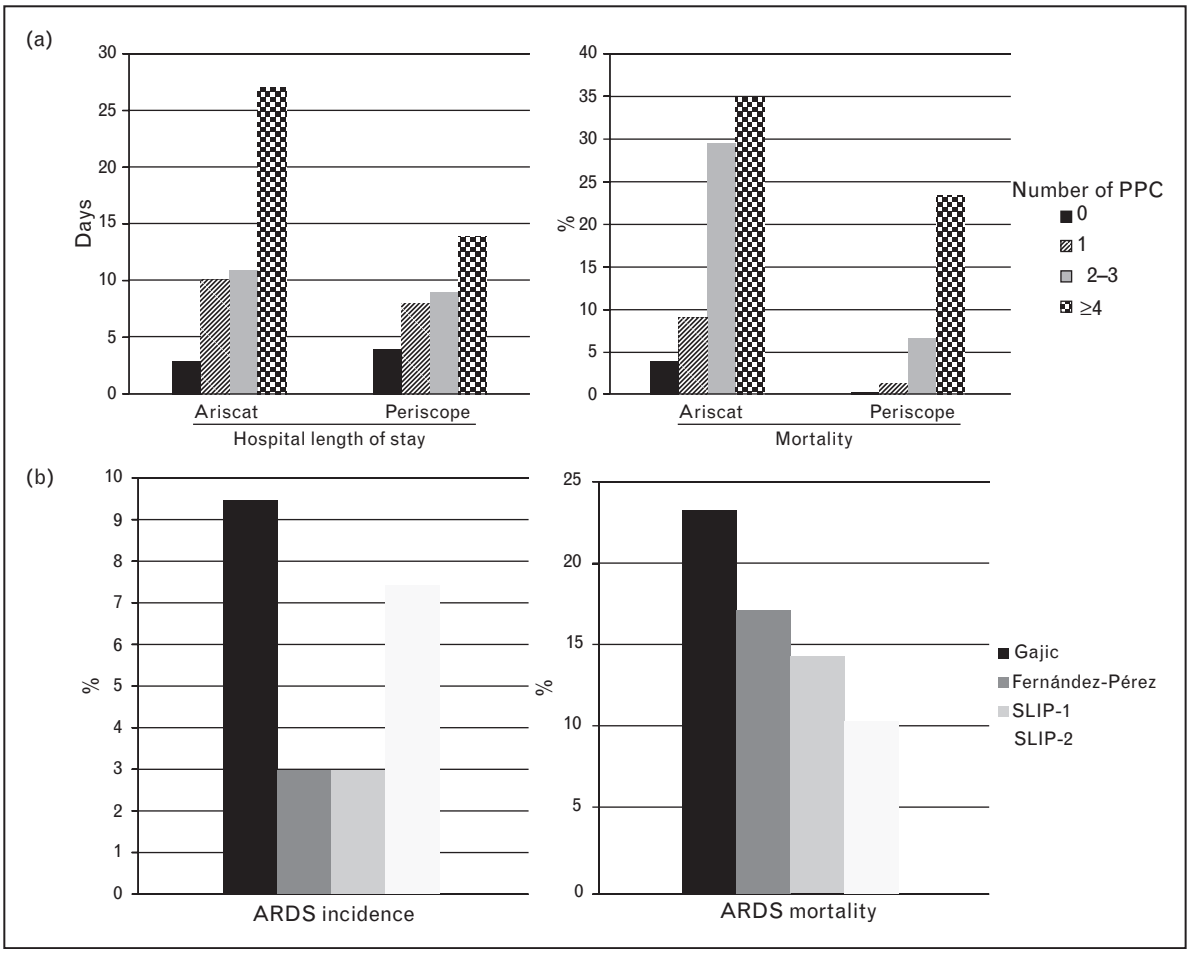

FIGURE 1. (a) Hospital length of stay and short-term mortality according to the number of postoperative pulmonary complications (PPC) in the PERISCOPE [20▪] and ARISCAT [21]; (b) incidence and mortality of postoperative ARDS according to published studies [19,22▪,23,24]. ARDS, acute respiratory distress syndrome.

Lower tidal volumes

The use of higher tidal volumes was standard of care in the operating room for many years. The rationale behind this strategy was that higher tidal volumes would constantly open those lung parts that collapsed at the end of expiration, preventing shunt, and thus preventing the need for higher levels of FiO_2. Recently, however, several studies [25–27] suggested that this approach actually causes harm: numerous smaller studies [16▪▪] showed that tidal volume reduction is associated with less alveolar overdistention, reducing the lesion caused by overstretching of the open lung parts.

Three recently published well powered RCTs of intraoperative ventilation [28,29▪▪,30] tested the hypothesis that the use of lower tidal volumes prevents postoperative pulmonary complications. An Italian single-center RCT in patients planned for open abdominal surgery [28] showed that tidal volume reduction from 9 to 7 ml/kg PBW during abdominal surgery prevented postoperative pulmonary dysfunction and resulted in a lower modified 'Clinical Pulmonary Infection Score.' A French multicenter RCT in patients planned for major abdominal surgery (IMPROVE) [29▪▪] confirmed these findings by showing tidal volume reduction from 12 to 6 ml/kg PBW to result in a reduction in postoperative pulmonary complications by almost two thirds. Similar results came from a Chinese single-center RCT in patients planned for spinal fusion surgery [30], showing an even larger reduction of postoperative pulmonary complications with tidal volume reduction from 12 to 6 ml/kg PBW.

Higher levels of positive end-expiratory pressure

The abovementioned RCTs of intraoperative ventilation actually studied the effects of a bundle of protective settings: lower tidal volumes and higher levels of PEEP with recruitment maneuvers. The rationale behind using a bundle of lower tidal volumes and higher levels of PEEP with recruitment maneuvers was that tidal volume reduction would induce atelectasis and consequently could increase harm by tidal recruitment of those lung parts that collapse at the end of expiration. Higher levels of PEEP with recruitment maneuvers could stabilize these parts during the respiratory cycle [31]. In line with these suggestions, a large retrospective study [32] showed that the use of lower tidal volumes during general anesthesia for surgery was associated with increased 30-day mortality. The investigators of that study [31] suggested that the negative association between tidal volume reduction and outcome was because of the lack of use of higher levels of PEEP.

A more recent international multicenter RCT of patients planned for major abdominal surgery and at risk for postoperative pulmonary complications (PROVHILO) [33▪▪] compared a lower level of PEEP ($<2\,cmH_2O$) with higher levels of PEEP ($12\,cmH_2O$) with recruitment maneuvers during lower tidal volume ventilation with tidal volumes of 8 ml/kg PBW. The incidence of postoperative pulmonary complications was not different in the two arms of the trial. Moreover, the higher PEEP strategy was associated with a higher incidence of hypotension during surgery [33▪▪]. The results of this RCT thus suggest that anesthesiologists should not use higher levels of PEEP with lower tidal volume ventilation, at least in nonobese patients planned for major abdominal surgery and at risk for postoperative pulmonary complications.

Lower or higher levels of FiO_2

There are several reasons for using higher levels of FiO_2 with ventilation during general anesthesia for surgery. First, supplemental oxygen has been suggested to reduce postoperative nausea and vomiting and the incidence of wound infection [34,35]. Second, as pointed out above, use of lower tidal volumes, especially with lower levels of PEEP, could promote atelectasis and thus increase intrapulmonary shunt. Hyperoxia, however, may induce pulmonary injury and increase oxidative stress, and is associated with the development of reabsorption atelectasis with increased shunting [36].

At present, there are no sufficiently powered studies that investigated the effects of higher levels of FiO_2 in patients receiving ventilation for general anesthesia for surgery. Seeing the convincing positive effects of tidal volume reduction [28,29▪▪,30], and the potential harmful effects of higher levels of PEEP [33▪▪], however, anesthesiologists may want to consider increasing the level of FiO_2 before raising the level of PEEP.

Summary

On the basis of the best available evidence, anesthesiologists should consider ventilating patients undergoing general anesthesia for surgery with tidal volume of 6–8 ml/kg PBW [25–28,29▪▪,30,31], levels of PEEP between 0 and $2\,cmH_2O$ [31,33▪▪], and higher levels of FiO_2 [34,35].

PROTECTIVE VENTILATION IN CRITICALLY ILL PATIENTS

The number of investigations that focused on the effects of protective ventilation in critically ill

patients with respiratory failure other than ARDS is severely limited. The size of tidal volumes has progressively decreased from higher than 12 to 9 ml/kg in recent years in patients without ARDS [37]. Observational studies [38▪,39,40], however, show impressive variation in tidal volume size, and tidal volume sizes remain far above the level that is at present considered protective in patients with ARDS. These findings are in line with the results from a recent survey on preferred initial ventilator settings [41] that was conducted among respiratory therapists and intensivists in Canada. Most respondents reported to use protective ventilation, but in half of the patients the selected tidal volume was still at least 8 ml/kg PBW.

Lower tidal volumes

Recently, a large observational study [42] showed that protocol-guided ventilation aiming at prevention of use of high tidal volumes (>12 ml/kg PBW) decreased the incidence of lung injury by almost two thirds.

So far, only two RCTs [43,44] have tested the hypothesis whether tidal volume reduction would improve outcome of ventilated critically ill patients. A North-American single-center RCT in surgical ICU patients who received ventilation because of respiratory failure other than ARDS [43] showed that tidal volume reduction from 12 to 6 ml/kg PBW was associated with a lower incidence of pulmonary complications, including pulmonary infections. Duration of ventilation was reduced by almost half, although this difference did not reach statistical difference because of the low number of included patients. A Dutch multicenter RCT in medical and surgical ICU patients who were expected to need ventilation for longer than 48 h because of respiratory failure other than ARDS [44] showed that tidal volume reduction from 10 to 6 ml/kg PBW was associated with a lower incidence of development of ARDS. Duration of ventilation was not different between the two study arms, but it should be kept in mind that as soon as a patient met ARDS definitions tidal volumes had to be reduced to 6 ml/kg PBW, probably preventing further harm from the use of higher tidal volumes.

Two recent meta-analyses [16▪▪,44] confirmed the benefit of lower tidal volume ventilation in ICU patients without ARDS. Another meta-analysis [45▪▪] suggested the use of lower tidal volumes (≤6 ml/kg PBW) to shorten the duration of ventilation (Fig. 2). Notably, the use of lower tidal volumes did not increase sedation needs, which is cited as one of the main arguments against the use of lower tidal volumes. Notably, all of the meta-analyzed studies had methodological shortcomings, making it difficult to draw firm conclusions regarding the best tidal volume size in ICU patients without ARDS.

Positive end-expiratory pressure

Use of lower tidal volumes could promote atelectasis, even more with a longer duration of ventilation, which could be a reason to use higher levels of PEEP. Higher levels of PEEP, however, have been found beneficial only in patients with more severe forms of ARDS, and higher levels of PEEP may induce hemodynamic compromise and hyperinflation, as such maybe causing more harm than benefit. Although it could be that higher levels of PEEP may benefit certain ICU patients, like obese patients, or patients with increased chest wall elastance, robust evidence for any suggestion on the best level of PEEP in ICU patients without ARDS is lacking.

Inspired fraction of oxygen

Observational studies show that excess oxygen delivery or 'liberal' oxygen therapy is common in ventilated ICU patients [46] and that unnecessary hyperoxia is often accepted by physicians [13]. Long-standing hyperoxia, however, may be injurious [47], and high FiO_2 may potentially be toxic, although the mechanism remains largely unclear. In addition, interventions other than raiding the level of FiO_2 aiming at high arterial oxygen levels may also come with serious consequences.

A recent observational study [13] showed that both higher levels of FiO_2 and higher levels of PaO_2 are independently associated with increased mortality in ICU patients. An association between higher levels of PaO_2 and worse outcome has been found in several patient populations. One multicenter cohort study [48] showed hyperoxia to be associated with increased in-hospital mortality in patients admitted to intensive care unit following resuscitation from cardiac arrest. A retrospective cohort study [49] showed an independent relation between hyperoxia and mortality. Finally, higher levels of PaO_2 have been shown to reduce coronary blood flow in patients with cardiac disease, causing a decline in oxygen delivery to the heart [50].

Maintaining diaphragmatic function

Longer duration of ventilation is associated with diaphragmatic weakness, injury and loss of muscle fibers, and marked atrophy of diaphragm myofibers can already be found within 3 days of controlled ventilation with complete diaphragmatic inactivity [2,51]. Maintaining diaphragmatic contractile

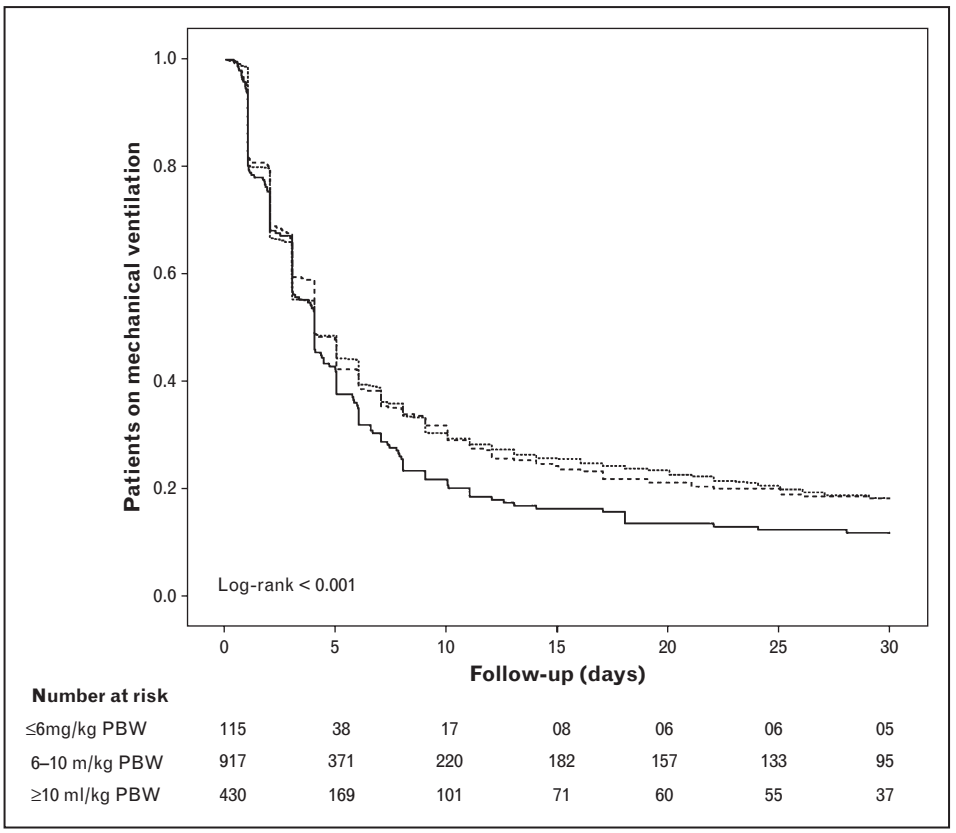

FIGURE 2. Data for the Kaplan–Meier estimates of the probability of the primary outcome of patients breathing without assistance by day 28 in 6 ml/kg PBW or less (black solid line), 6–10 ml/kg PBW (black knurled line), and at least 10 ml/kg PBW (black dotted line) were censored at 30 days after inclusion. $P < 0.001$ by the log-rank test for the between-group difference in the probability of the primary outcome. Adapted and modified from Serpa Neto *et al.* [45▪▪]. PBW, predicted body weight.

activity by using spontaneous breathing activity, therefore, may protect the diaphragm against the deleterious effect of prolonged ventilation [52,53].

Summary

On the basis of the best available evidence, intensive care physicians could consider ventilating critically ill patients without ARDS with a PEEP level of 5 cmH_2O and lower levels of FiO_2. There is insufficient evidence for the benefit of lower tidal volumes in these patients. There, however, is some evidence that tidal volumes 6 ml/kg PBW or less are associated with better outcomes.

FUTURE TRIALS OF PROTECTIVE VENTILATION IN PATIENTS WITHOUT ACUTE RESPIRATORY DISTRESS SYNDROME

There are several trials running trying to explain the benefits of protective ventilation in patients without ARDS.

Intraoperative ventilation

The abovementioned PROVHILO trial [33▪▪] compared higher with lower levels of PEEP with ventilation during general anesthesia for abdominal surgery in a general population. Obese patients were excluded from participation, though. PROVHILO, therefore, cannot exclude that higher levels of PEEP are beneficial in obese or severe obese patients. Recently, the PROVE Network Investigators initiated an international multicenter RCT in obese patients planned for abdominal surgery and at high risk for postoperative pulmonary complications. The 'Protective Ventilation With Higher Versus Lower PEEP During General Anesthesia for Surgery in Obese Patients' (PROBESE) trial [54] will compare higher with lower levels of PEEP with lower tidal volume ventilation in obese patients planned for major abdominal surgery.

Similarly, it is uncertain whether intraoperative ventilation with higher levels of PEEP is protective in other surgical procedures, for example, during thoracic surgery. The results of a large RCT [55] comparing protective with conventional ventilation (tidal

	ICU patients with ARDS	ICU patients without ARDS	OR patients without ARDS
tidal volume size	tidal volume ≤6 ml/kg PBW	uncertain	tidal volume 6–8 ml/kg PBW
evidence	*RCT [5–7], and meta-analysis [8]*	*RCTs [43, 44] and meta-analysis [16,45••,64]*	*RCTs [25–28, 29••, 30] and meta-analysis [31,64]*
level of PEEP	PEEP > 5 cmH_2O depending on severity	PEEP 5 cmH_2O	PEEP 0–2 cmH_2O
evidence	*RCTs [6,7,9–11] and meta-analysis [12]*	*no evidence*	*RCT [33••] and meta-analysis [31]*
level of FIO_2	FIO_2 according to table	lower FIO_2	higher FIO_2
evidence	*RCTs [5,9–11]*	*no evidence*	*RCT [34] and meta-analysis [35]*

FIGURE 3. Suggested strategies of ventilation in critically ill patients with and without ARDS and in surgical patients. ARDS, acute respiratory distress syndrome; OR, operation room; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial.

volume of 5 ml/kg PBW and PEEP versus tidal volume of 10 ml/kg PBW without PEEP) in surgery for lung cancer are waited. The PROVE Network Investigators are planning a large RCT in patients planned for thoracic surgery. The 'Protective Ventilation With Higher Versus Lower PEEP During General Anesthesia for Thorax Surgery' trial [56] is planned to compare higher with lower levels of PEEP with lower tidal volume ventilation in patients planned for thorax surgery.

Ventilation of patients without acute respiratory distress syndrome in the intensive care unit

There are numerous arguments against the use of lower tidal volumes in all of the ventilated ICU patients, irrespective of the presence of ARDS. First, as mentioned above, ventilation with lower tidal volumes could promote atelectasis [57]. But it has also been argued that lower tidal volume ventilation could increase the risk of patient–ventilator asynchrony [58,59]. In addition, the increased efforts of patients with spontaneous ventilation using lower tidal volumes could cause fatigue and induce so-called *pendelluft*, thereby increasing the risk of lung injury [60]. All of these could offset the potential beneficial effects of lower tidal volume ventilation as found in other patient groups. At present, two large RCTs are about to start: the 'Protective Ventilation in Patients without ARDS at Start of Ventilation' (PReVENT) trial and the 'Preventive Strategies in Acute Respiratory Distress Syndrome' (EPALI) trial. PReVENT [61] is a Dutch multicenter RCT comparing ventilation with lower tidal volumes (4–6 ml/kg PBW) with ventilation using conventional tidal volumes (8–10 ml/kg PBW) in critically ill patients not fulfilling the consensus definition for moderate or severe ARDS. EPALI [62] is a Spanish RCT comparing ventilation with lower tidal volumes (≤6 ml/kg PBW) with ventilation using conventional ventilation (8 ml/kg PBW) in critically ill patients at risk for ARDS. The primary endpoint of the PReVENT trial is the number of ventilator-free days and alive at day 28; the endpoint of EPALI is the development of ARDS.

Studies into levels of FiO_2

The 'Oxygen Target' study [63], an implementation project in three Dutch intensive care units, aims at using lower oxygen targets. The target PaO_2 and SpO_2 are 8 kPa and 92%, respectively. The 'Oxygen Target' study will look at the association between the use of lower arterial oxygen levels and the duration of ventilation and stay in the intensive care unit.

CONCLUSION

There is increasing and convincing evidence that the use of lower tidal volumes during intraoperative

ventilation prevents against postoperative pulmonary complications. Whether lower tidal volumes should be part of protective ventilation in ICU patients without ARDS is less certain, but some evidence so far suggests that these patients also could benefit from tidal volume reductions. Although higher levels of PEEP, as part of a lung-protective ventilation strategy during general anesthesia for surgery, seem to prevent postoperative pulmonary complications, recent findings suggest that the use of lower levels of PEEP does not protect against postoperative ventilation, and maybe even causes harm, at least in nonobese patients planned for abdominal surgery. Finally, it is uncertain what levels of FiO_2 should be used in ventilation of patients without ARDS, because higher levels of FiO_2 seem to benefit surgery patients, whereas they are associated with worse outcome in critically ill patients [64] (Fig. 3).

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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Prevention of acute respiratory distress syndrome

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Purpose of review
The paucity of effective therapeutic interventions in patients with the acute respiratory distress syndrome (ARDS) combined with overwhelming evidence on the importance of timely implementation of effective therapies to critically ill patients has resulted in a recent shift in ARDS research. Increasingly, efforts are being directed toward early identification of patients at risk with a goal of prevention and early treatment, prior to development of the fully established syndrome. The focus of the present review is on the prevention of ARDS in patients without this condition at the time of their healthcare encounter.

Recent findings
The primary thematic categories presented in the present review article include early identification of patients at risk of developing ARDS, optimization of care delivery and its impact on the incidence of ARDS, pharmacological prevention of ARDS, prevention of postoperative ARDS, and challenges and opportunities with ARDS prevention studies.

Summary
Recent improvements in clinical care delivery have been associated with a decrease in the incidence of hospital-acquired ARDS. Despite the initial challenges, research in ARDS prevention has become increasingly feasible with several randomized controlled trials on ARDS prevention completed or on the way.

Keywords
acute respiratory distress syndrome, prevention, quality improvement

INTRODUCTION

Almost 40 years after the initial description of acute respiratory distress syndrome (ARDS) [1], only a few interventions demonstrated outcome benefit in this devastating complication of critical illness or injury. The current therapy is largely supportive, including lung-protective mechanical ventilation [2–4] and restrictive fluid and blood product administration [5]. These 'supportive' therapies, however, do not reverse the pathophysiological processes underlying ARDS; instead, they limit further iatrogenic injury to lungs in patients with prevalent ARDS. Therefore, current supportive therapies for ARDS are perhaps better regarded as prevention of further complications or worsening of the underlying disease (tertiary prevention) instead of effective therapies for inflammatory lung edema.

The relative lack of effective therapeutic interventions in ARDS combined with overwhelming evidence on the importance of timely implementation of effective therapies in the setting of critical illness has resulted in a recent shift in ARDS research. More specifically, research efforts are increasingly being directed toward the early identification of patients at risk with a goal of prevention before ARDS is fully established. In 2010, a National Heart, Lung, and Blood Institute workshop on future clinical research in acute lung injury recommended development of strategies to perform acute lung injury prevention trials [6]. In 2013, the ARDS Network was retired and replaced with the Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL/-14-014.html, accessed 21 August 2014). This paradigm shift in ARDS research emphasizes the increasingly recognized importance of ARDS prevention. The focus of the present review is on the prevention of ARDS in patients without lung injury at the time of the healthcare encounter.

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KEY POINTS

- Novel risk prediction tools can assist in timely identification of patients at risk of developing acute respiratory distress syndrome (ARDS).
- Improvements in clinical care delivery have been associated with decreased incidence of hospital-acquired ARDS.
- Prevention and early treatment of ARDS is a current priority in investigative efforts to curtail this devastating syndrome.

EARLY IDENTIFICATION OF PATIENTS AT RISK OF DEVELOPING ACUTE RESPIRATORY DISTRESS SYNDROME

In order to study plausible interventions and treatments for the prevention of ARDS, a key barrier is its relatively low (~1%) prevalence among hospitalized patients [7]. A recent multicenter observational cohort study of 5584 patients from 22 hospitals [8] identified key predisposing conditions and risk modifiers for ARDS and refined and validated a prediction model to identify patients at high risk for ARDS at the time of hospital admission. On the basis of routinely available clinical data, a novel Lung Injury Prediction Score (LIPS) at a cutoff of at least 4 demonstrated a positive predictive value for ARDS of 18% with a negative predictive value of 97% (Fig. 1). Although the suboptimal predictive accuracy does not support its use in everyday clinical practice, LIPS has enabled enrollment in novel clinical trials of ARDS prevention [actively recruiting Lung Injury Prevention Study with Aspirin (LIPS-A), NCT01504867, and Lung Injury Prevention Study With Budesonide and Beta Agonist Formoterol (LIPS-B), NCT017 83821]. Using similar methodologies, two surgical lung injury prediction models [Surgical Lung Prediction Score (SLIP) and SLIP-2)] have also been developed for the identification of patients at high risk of postoperative lung injury [9,10▪].

Notably, there have been other recent attempts to predict early ARDS. Levitt *et al.* [11▪] derived an early acute lung injury score, dependent on the oxygen requirement, respiratory rate and presence of immunosuppression in patients with bilateral infiltrates on chest imaging. The score performed similarly to the LIPS, was not limited to the first 6 h of hospitalization and is relatively simple to calculate. In a secondary analysis of the LIPS cohort, we have shown that the ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen (Spo_2/Fio_2) is an independent predictor of early ARDS development, even after adjustment for age, comorbidities, the Acute Physiology, and Chronic Health Evaluation (APACHE) 2 score and all of the other LIPS variables [12▪]. The main limitation to the clinical use of Spo_2/Fio_2 in prediction of ARDS is the lack of standardized measurement of Fio_2 in spontaneously breathing patients. Nevertheless, the broad availability and the simplicity of Spo_2/Fio_2 calculations are obvious advantages.

IMPROVEMENTS IN CLINICAL CARE DELIVERY AND THE IMPACT ON ACUTE RESPIRATORY DISTRESS SYNDROME DEVELOPMENT

Importantly, ARDS is rarely present at the time of the initial healthcare encounter. Instead, it typically develops during the hospital course, usually between days 2 and 5 in patients with predisposing conditions or risk factors [8]. Therefore, ARDS may be thought of as an iatrogenic complication with the potential for avoidance with optimal care delivery. Hospitalized patients are frequently exposed to various potentially harmful factors that may modify the inherent risk of ARDS development. This concept is often referred to as the multihit theory of ARDS pathogenesis. The number of such 'hits' or harmful in-hospital exposures is directly proportional to the likelihood of ARDS development [13▪▪]. If one accepts these plausible concepts, two essential conclusions arise: there is a window of opportunity for ARDS prevention that begins at the time of the initial healthcare encounter, and by limiting high-risk exposures, ARDS may be preventable.

Olmsted County data experience

A retrospective, population-based study of Olmsted County residents reported a decrease in the incidence of hospital-acquired ARDS by more than half during the 8-year evaluation interval. Although causal relations could not be determined, multiple changes in critical care structure and care delivery were implemented concurrent with the falling rate of ARDS [14]. Notably, the decrease in ARDS incidence was observed despite a stable incidence of community-acquired ARDS, an increase in the population's severity of illness and comorbid burden, and a higher prevalence of predisposing conditions for ARDS during the same 8-year period. The ARDS case fatality rate during this same interval did not change, highlighting a potentially more meaningful opportunity for ARDS prevention when compared with the treatment of established ARDS. Several of the factors associated with ARDS development in this study have been confirmed in other pertinent publications [15–17]. In a single-center

Predisposing conditions	LIPS points
Shock	2
Aspiration	2
Sepsis	1
Pneumonia	1.5
High-risk surgery[a]	
Orthopedic spine	1
Acute abdomen	2
Cardiac	2.5
Aortic vascular	3.5
High-risk trauma	
Traumatic brain injury	2
Smoke inhalation	2
Near drowning	2
Lung contusion	1.5
Multiple fractures	1.5
Risk modifiers	
Alcohol abuse	1
Obesity (BMI >30)	1
Hypoalbuminemia	1
Chemotherapy	1
FiO_2 >0.35 (>4 l/min)	2
Tachypnea (RR >30)	1.5
Spo_2 <95%	1
Acidosis (pH <7.35)	1.5
Diabetes mellitus[b]	–1

Examples

(1) Patient with a history of alcohol abuse with septic shock from pneumonia requiring Fio_2 >0.35 in the emergency room:

Sepsis + shock + pneumonia + alcohol abuse + FIO_2 >0.35

1 + 2 + 1.5 + 1 + 2 = 7.5

(2) Motor vehicle accident with traumatic brain injury, lung contusion and shock requiring FiO_2 >0.35

Traumatic brain injury + lung contusion + shock + FiO_2 >0.35

2 + 1.5 + 2 + 2 = 7.5

(3) Patient with a history of diabetes mellitus and urosepsis with shock

Sepsis + shock + diabetes

1 + 2 – 1 = 2

FIGURE 1. Lung Injury Prediction Score (LIPS) calculation worksheet. [a]Add 1.5 points if emergency surgery. [b]Only if sepsis present. Fio_2, fractional inspired oxygen concentration; RR, respiratory rate; Spo_2, oxygen saturation by pulse oximetry. Reproduced from [8].

study of ventilated patients without ARDS at the onset of mechanical ventilation, we have shown the importance of high tidal volume ventilation [15], which has been confirmed in a recent meta-analysis [18▪]. The importance of restrictive transfusion, use of male donor–predominant plasma transfusion [16] and timely treatment of sepsis [17] have all been subsequently confirmed.

Other factors that can serve as potential prevention targets

The role of atelectasis and recumbency in ARDS pathogenesis, particularly in obese patients, has recently been highlighted [19]. This intriguing perspective focuses on the adverse effects of body position, spontaneous and mechanical hyperventilation on surfactant, surface tension and development of atelectasis (Fig. 2). Therefore, the modification of current care relative to patient positioning and sedation may impact surfactant dysfunction and resulting atelectasis, ultimately mitigating risk for ARDS.

Gastric to pulmonary aspiration was identified as a principal cause of hospital-acquired ARDS back in 1980s [20]. In the LIPS cohort, aspiration represented one of the most common major risk factors for ARDS [21▪]. Additional potentially modifiable risk factors include the use of strict lung-protective ventilation at the outset (NCT02070666), neuromuscular blockade [3], limitation of oxygen support with lower oxygen saturation targets [22▪], targeted fluid resuscitation and restrictive transfusion of blood products [23], avoidance of hyperventilation in spontaneously breathing patients and striving for early extubation and early mobilization [19], among others. All of these interventions have the potential to limit unnecessary and potentially harmful 'hits' that may eventually result in fully established ARDS.

Checklist for Lung Injury Prevention

To be truly effective in mitigating the occurrence of ARDS, the simple identification of potentially modifiable factors is not sufficient. It is important to ensure that best evidence is not only disseminated but also implemented in a timely manner and continually assessed for its use and impact [24–26]. To this extent, LIPS investigators have formulated and implemented the Checklist for Lung Injury Prevention [27], which contains the key elements for standardizing the care of patients at risk enrolled in clinical trials of ARDS (Fig. 3).

PHARMACOLOGICAL PREVENTION

In addition to the improvements in clinical care delivery, we must continue efforts to identify

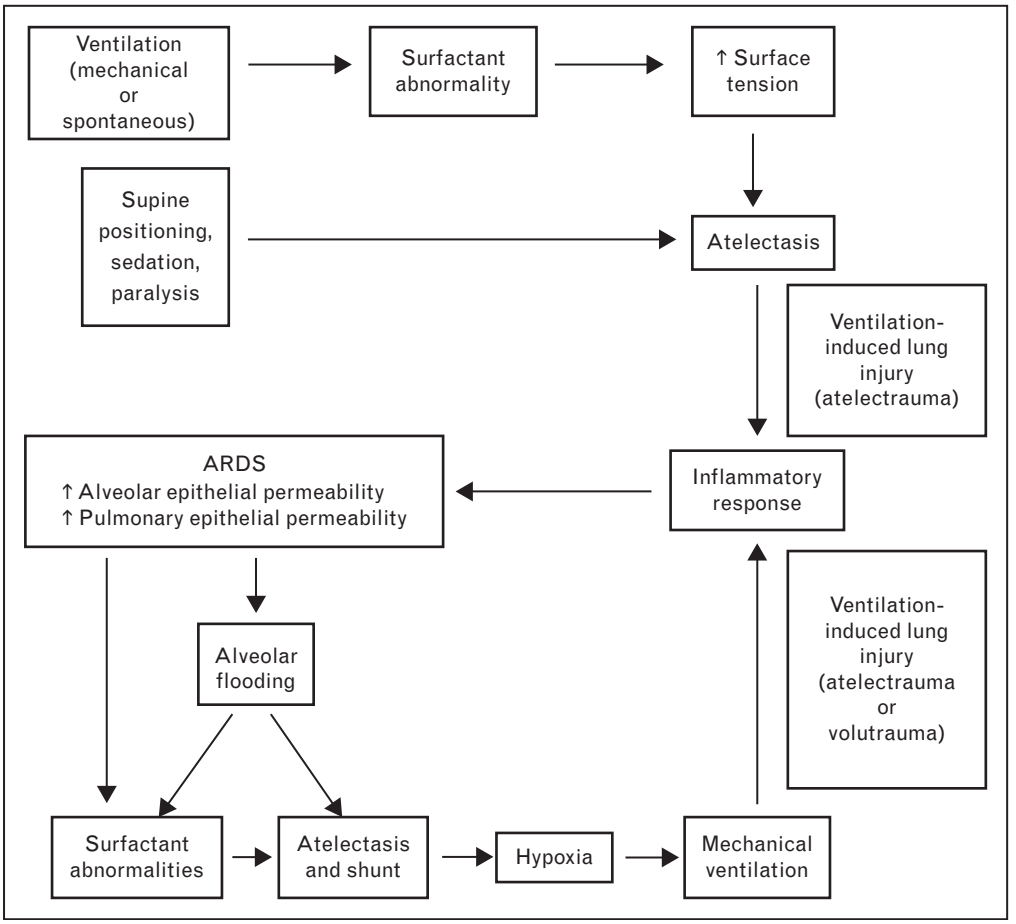

FIGURE 2. Proposed alternative pathophysiology of acute respiratory distress syndrome (ARDS). Reproduced from [19].

CLIP elements	Definition
Lung-protective mechanical ventilation	Tidal volume between 6 and 8 ml/kg predicted body weight and plateau pressure <30 cmH_2O; PEEP ≥ 5 cmH_2O, minimize Fio_2 (target O_2 saturation 88–92% after early shock)
Aspiration precautions	Intubation supervised by experienced providers, elevated head of the bed, oral care with chlorhexidine, gastric acid neutralization in those not receiving tube feeds
Adequate empirical antimicrobial treatment and source control	According to suspected site of infection, healthcare exposure and immune suppression
Limiting fluid overload	Modified ARDS Network FACCT protocol (National Heart, 2006 #124) after early shock
Restrictive transfusion	Hemoglobin target >7 g/dl
Assess readiness for extubation	Limit continuous sedation and perform spontaneous breathing trial as soon as feasible

FIGURE 3. Checklist for Lung Injury Prevention (CLIP). ARDS, acute respiratory distress syndrome; Fio_2, fractional inspired oxygen concentration; PEEP, positive end-expiratory pressure.

effective new therapies that target the pathophysiological pathways underlying ARDS. Figure 4 provides a list of emerging pharmacological interventions for ARDS prevention [28▪].

Inhaled medications

The notion of delivering medications with preventive potential directly to the lungs, thereby avoiding systemic adverse effects, is very attractive. Perkins *et al.* [29▪▪] recently investigated inhaled salmeterol for ARDS prevention. During a 3-year period, they recruited 362 patients undergoing esophagectomy in 12 centers in the United Kingdom. Although the incidence of ARDS did not differ between salmeterol and placebo groups, postoperative adverse events (primarily pneumonia) were less frequent in the former. Additionally, in a translational substudy of 53 patients, salmeterol reduced several biomarkers of alveolar inflammation and epithelial injury.

The ongoing LIPS-B is the first phase 2 clinical trial to study inhaled corticosteroids in combination with a long-acting beta agonist for prevention of ARDS (NCT01783821). In addition to direct anti-inflammatory properties [30,31], these drugs may act synergistically to improve peripheral delivery of the drugs [32]. In the LIPS-B trial, the patients at risk for ARDS, as judged by a high LIPS score (≥4), are recruited less than 12 h from their presentation to the hospital, and receive inhaled medications or identically appearing placebo twice daily for up to 10 doses. The primary aim of the study is to inform whether the treatment with inhaled budesonide and formoterol can alleviate pulmonary dysfunction in patients at risk for ARDS.

In a small clinical trial enrolling 50 patients requiring mechanical ventilation for longer than 48 h, inhaled heparin was associated with fewer days of mechanical ventilation when compared with placebo [33]. Experimental and observational clinical data suggested that inhaled anticoagulants may be associated with improved survival in patients with smoke inhalation-induced lung injury [34]. Several animal studies have demonstrated potential of nebulized hypertonic saline to improve inflammatory and oxidative stress pathways of lung injury [35,36], and the phase I/II clinical trial is on the way.

Systemic medications

Dysregulated inflammation, coagulation and oxidative stress play central roles in ARDS pathophysiology [37], and future mechanistic ARDS prevention trials are likely to target these pathways. In addition, platelet activation has been increasingly linked to both ARDS development and resolution [38,39]. Both animal data and observational studies suggest that aspirin can modulate these platelet-mediated processes and prevent or attenuate lung injury [40–43]. Given its wide availability, good safety profile, potential to decrease both inflammation and vascular permeability, and potential impact on immune function, aspirin is a prime candidate for prevention of ARDS by systemic delivery. The ongoing National Institutes of Health (NIH)-sponsored, multicenter, randomized, placebo-controlled

Medication	Mechanism of action	Animal studies	Human studies
Aspirin	Inhibition of platelet-mediated cyclooxygenase metabolism involved in bronchoconstriction and vasoconstriction and inhibits platelet–neutrophil–endothelial interactions	Mice treated with aspirin have less pulmonary platelet and neutrophil sequestration. Also, treated animals have improved survival and decreased lung weights	Observational studies conflicting in terms of their findings. The largest cohort found a non significant trend toward a protective effect
Systemic corticosteroids	Multipotent; inhibit inflammatory cytokines; induced apoptosis of macrophages; maintain endothelial cellular barrier	Majority show improvement of hypoxemia, pulmonary vascular pressure and extravascular lung water	Older studies performed in the 1980s show no benefit in administering short-course high-dose steroids
Inhaled heparin	In addition to potentiating antithrombin III, inhibits adhesion of neutrophils to endothelium and degrades intravascular and bronchial fibrin	Conflicting results with improvement of hypoxemia histology scores and shunt fraction	No published human studies
Inhaled corticosteroids	Same as systemic corticosteroids. In theory, may spare patients from hyperglycemia, myopathy, superinfection, etc.	Most studies conducted in mice indicate that physiological surrogates are improved by treatment prior to or after direct/indirect lung injury	No published human studies
Inhaled beta-agonists	Enhanced alveolar fluid clearance and inhibit neutrophil adhesion to the endothelium	Improved pulmonary mechanics; decrease neutrophil sequestration, inflammatory cytokine concentrations and enhanced surfactant secretion	One published human study [29**] no difference in ARDS incidence but less pulmonary complications, mainly pneumonia. Another study found that treatment prevented high-altitude pulmonary edema
Statins	Decrease inflammatory cytokine levels, adhesion molecule expression and neutrophil proliferation	Improvement in oxygenation, hemodynamic surrogates, neutrophil sequestration and decreased cytokine concentration	Human observational studies have not been consistent. One study showed a protective effect, whereas two, including the largest cohort, did not
Renin–angiotensin axis blockers	Angiotensin-2 positively modulates nuclear factor-κB gene expression. ACE type 2 receptor with angiotensin as its ligand, prevents endothelial damage	Effective in preventing endothelial damage and inflammatory cytokine expression	Two observational studies showed a protective effect
Peroxisome proliferator receptor agonists	Nuclear receptor superfamily related to the retinoid, steroid and thyroid receptors with three subtypes. They decrease inflammatory cytokine expression, neutrophil and macrophage chemotaxis plus inhibit oxidative burst in neutrophils	Decreased wet to dry ratios and inflammatory cytokine expression, and improved static compliance	No human studies to date
Curcumin	Upregulation of PPAR-γ in various inflammatory cells (neutrophils, monocytes, T lymphocytes, endothelial and epithelial cells). Downregulation of inflammatory transcription factors, enzymes and cytokines	Decreased wet to dry ratios, and inflammatory cytokine secretion	No human studies to date

FIGURE 4. Emerging pharmacological therapies for prevention of acute respiratory distress syndrome (ARDS). ACE, angiotensin converting enzyme; PPAR, peroxisome proliferator-activated receptor. Reproduced from [28▪].

trial, LIPS-A trial (NCT01504867), will address whether the daily administration of aspirin up to 7 days can prevent or attenuate ARDS in patients at risk [27].

Other systemic medications have shown to be effective in improving lung injury and are being currently investigated. A selective inhibitor of p38 alpha mitogen-activated protein kinase plays a major role in the regulation of the inflammatory cytokines. It is currently being investigated in a multicenter clinical trial accruing patients at risk for ARDS because of trauma (NCT00996840). Efficacy in ARDS prevention of bevacizumab, a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor A, has also been studied in an ongoing clinical trial (NCT01314066).

PREVENTION OF POSTOPERATIVE ACUTE RESPIRATORY DISTRESS SYNDROME: EXPERIMENTAL CLINICAL LABORATORY FOR PREVENTION STUDIES

ARDS is a common and frequently lethal cause of postoperative respiratory failure, accounting for approximately 35% of patients [44]. The overall incidence of postoperative ARDS is estimated at approximately 3% [44], but rates vary greatly for

different surgical procedures [8,9]. Specifically, complex cardiac, thoracic and aortic vascular surgeries have been consistently associated with the highest rates of postoperative ARDS. Likewise, emergency surgery also appears to portend increased risk for this life-threatening postoperative respiratory complication [10▪,45▪▪]. Notably, postoperative ARDS has been associated with up to 45% mortality [44].

As in the nonsurgical setting, a key barrier to preventing postoperative ARDS has been our inability to identify those at greatest risk. In an effort to address this limitation, recent investigations have reported prediction models that can be used to identify a more targeted study population with greater risk for developing postoperative ARDS [9,46]. More recently, a prediction model has been developed for more heterogeneous surgical populations including those undergoing both elective and emergency surgery and those with concomitant major risk factors for ARDS [10▪].

The perioperative environment provides a unique opportunity to better understand ARDS mechanisms. Specifically, the abovementioned ARDS prediction models can be used to facilitate the identification of patients at particular risk for postoperative ARDS prior to their surgical procedure. In doing so, patients may be enrolled before the major risks for ARDS have been experienced. As a result, ARDS pathogenesis can be studied from a relatively healthy (preoperative) state to the full ARDS phenotype, in contrast to patients who are admitted through the emergency department.

CHALLENGES AND OPPORTUNITIES OF ACUTE RESPIRATORY DISTRESS SYNDROME PREVENTION STUDIES

The design and conduct of ARDS prevention trials pose numerous challenges. Patients need to be identified, consented and enrolled very early in their hospital course. For example, the inhaled medications in the LIPS-B trial are to be delivered not later than 4 h after the randomization, regardless of the time of the day (or night). The time-sensitive nature of these interventional trials raises challenges that require innovative patient enrollment strategies (e.g. novel informatics approaches to patient identification [47]), different approaches to informed consent (surrogate, phone, deferred or community consent) and multispecialty collaboration (emergency medicine physicians, hospitalists, intensivists, anesthesiologists, surgeons, pharmacists, respiratory therapists, etc.).

In addition to the challenges of early identification and enrollment, there are other barriers that must also be addressed. Although the development of ARDS is a logical primary outcome, the relatively low positive predictive value of the prediction scores poses limitations. Specifically, only a small proportion of patients at risk will progress to fully established ARDS, which increases the sample size requirement, duration and associated cost of the clinical trials. Therefore, the use of alternative, surrogate outcomes may be considered. Particularly attractive seems to be derangement in oxygenation, given its increasingly recognized importance in likelihood for the development and prognosis of ARDS [11▪,12▪,48]. Alternatively, an extravascular lung water measurement could potentially be a useful surrogate outcome [49,50]. An intervention that positively affects surrogate outcome, however, may not necessarily improve but instead could pose harmful effect on patient-important outcomes [2].

CONCLUSION

The importance of ARDS prevention has been increasingly recognized by the scientific community. Identifying patients at risk for ARDS early in their healthcare encounter and improvements in care delivery for those deemed to be at risk of this life-threatening syndrome have been associated with reduced incidence of ARDS among hospitalized patients. Moreover, systematic testing and implementation of pharmacological prevention strategies has a potential to further decrease the burden of ARDS.

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Conflicts of interest

E.F. has no conflicts of interest relevant to the present publication. D.J.K. receives royalties from Up-to-Date for authoring a chapter on the topic of transfusion-related acute lung injury. Mayo Clinic and O.G. hold the patent application on critical care-related software applications licensed to Ambient Clinical Analytics Inc.

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Neurally adjusted ventilatory assist

Paolo Navalesi[a,b,c] *and Federico Longhini*[a]

Purpose of review
Compared with the conventional forms of partial support, neurally adjusted ventilatory assist was repeatedly shown to improve patient–ventilator synchrony and reduce the risk of overassistance, while guaranteeing adequate inspiratory effort and gas exchange. A few animal studies also suggested the potential of neurally adjusted ventilatory assist in averting the risk of ventilator-induced lung injury. Recent work adds new information on the physiological effects of neurally adjusted ventilatory assist.

Recent findings
Compared with pressure support, neurally adjusted ventilatory assist has been shown to improve patient–ventilator interaction and synchrony in patients with the most challenging respiratory system mechanics, such as very low compliance consequent to severe acute respiratory distress syndrome and high resistance and air trapping due to chronic airflow obstruction; enhance redistribution of the ventilation in the dependent lung regions; avert the risk of patient–ventilator asynchrony due to sedation; avoid central apneas; limit the risk of high (injurious) tidal volumes in patients with acute respiratory distress syndrome of varied severity; and improve patient–ventilator interaction and synchrony during noninvasive ventilation, irrespective of the interface utilized.

Summary
Several studies nowadays prove the physiological benefits of neurally adjusted ventilatory assist, as opposed to the conventional modes of partial support. Whether these advantages translate into improvement of clinical outcomes remains to be determined.

Keywords
acute respiratory failure, mechanical ventilation, neurally adjusted ventilatory assist, noninvasive ventilation, patient–ventilator interaction

INTRODUCTION

First described in its general principles 15 years ago [1], neurally adjusted ventilatory assist (NAVA) is a mode of partial ventilatory assistance that has become commercially available in the last few years. With proportional assist ventilation (PAV), NAVA is the only mode of ventilation delivering assistance in proportion to a patient's demand [2]. Although with both PAV and NAVA the assistance remains under the patient's control, PAV utilizes 'conventional' pneumatic signals, such as flow and volume, whereas NAVA has the unique feature to control ventilator functioning through the electrical activity of the diaphragm (EAdi). In NAVA, in fact, the mechanical support is on-triggered and off-triggered by the EAdi, as assessed by transesophageal electromyography, and is proportional to EAdi throughout each inspiration [1]. The EAdi signal is obtained through a dedicated feeding tube, mounting a distal array of multiple electrodes, and processed to provide the highest possible quality of signal [1]. EAdi, expressed in microvolts, is multiplied by a user-controlled gain factor, the NAVA level ($NAVA_L$), whose unit is $cmH_2O/\mu V$. The airway pressure applied by the ventilator depends on the magnitude of both EAdi and $NAVA_L$. For a given $NAVA_L$, the airway pressure varies breath-by-breath in proportion to EAdi, whose profile resembles as mirror image.

Since its introduction in clinical use, a growing number of studies investigating the effects of NAVA have been performed in animal models, healthy individuals, and adult and pediatric patients during both invasive and noninvasive ventilation (NIV) (Fig. 1). Because the studies dealing with pediatric

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KEY POINTS

- Neurally adjusted ventilatory assist (NAVA) is a proportional mode of ventilation in which the ventilator is driven and controlled by the electrical activity of the diaphragm rather than by the conventional pneumatic signals.
- Irrespective of the interface adopted and the cause of acute respiratory failure, NAVA guarantees adequate gas exchange and, compared with pressure support, improves patient–ventilator interaction, averts the risk of overassistance, and minimizes the occurrence of asynchronies.
- At increasing levels of assistance, as opposed to pressure support, NAVA results in minimal changes in breathing pattern and determines tidal volumes that frequently do not exceed 6 ml/kg and in general do not reach 8 ml/kg; also, compared with NAVA, tidal volume is more variable and ventilation more distributed in the dependent lung regions.
- NAVA has been repeatedly shown to offer several physiological advantages compared with the conventional forms of partial assistance. Whether these advantages translate in improvement of clinical outcomes remains to be assessed.

patients represent nowadays a consistent fraction of the overall published articles on NAVA, we prefer not to include them in the present review article, leaving the pediatric population to further dedicated work. Accordingly, the present review addresses the current knowledge on NAVA in adult intensive care unit (ICU) patients, either intubated or receiving NIV, focusing, in particular, on the most recent studies.

NEURALLY ADJUSTED VENTILATORY ASSIST IN INTUBATED PATIENTS

The effects of NAVA have been assessed with respect to several physiological outcomes.

Respiratory drive and effort

EAdi is the best (i.e., closest to respiratory centers) signal available for clinical assessment of the respiratory drive, and provides an estimate of the pressure generated by the principal inspiratory muscle [3]. As depicted in Fig. 2, during partial ventilatory assistance, EAdi is influenced by multiple factors, including the amount of assistance and sedation [4,5▪▪]. With NAVA and PAV, the mechanical support delivered by the ventilator is directly (NAVA) or indirectly (PAV) driven and regulated by the effort exerted by the respiratory muscles [2]; this does not occur with the other assisted modes, in which the mechanical support is not affected by the patient's drive and effort.

When the assistance delivered is insufficiently low, regardless of the mode, the respiratory muscles are not efficiently unloaded and the drive remains high. When the assistance is high, the overall effect on drive and effort varies with the different forms of partial assistance. As indicated in Fig. 2, with NAVA and PAV increasing, ventilator assistance decreases drive, effort, and ventilatory output, which reduce in turn the ventilator support, thereby resetting the equilibrium between effort and assistance at a different point. With the other forms of partial assistance, conversely, an excessive support decreases the drive and makes respiratory muscle effort small, often just sufficient to trigger the ventilator and sometime even insufficient at that purpose [6,7]. In patients with acute respiratory failure (ARF) of different causes, NAVA has been demonstrated to efficiently unload the diaphragm [4,8,9,10▪,11]; differently from pressure support, however, the reduction of EAdi obtained with NAVA is contained and never excessive, and the risk of overassistance is therefore averted [4,8,11]. Stepwise increase of $NAVA_L$ produces a progressive decrease in EAdi that was shown to be approximately 50% at the highest $NAVA_L$ in a mixed population of patients with ARF [12].

EAdi, however, is not affected only by the amount of ventilator support. The output of the respiratory centers is also influenced, with respect to both drive and timing, by sedative administration, through either direct (respiratory centers) or indirect (cortical and limbic) effects (Fig. 2). As a consequence of the direct and tight relation between neural drive and delivered support, NAVA could, in principle, be more detrimentally affected by sedatives than pressure support, assist/control, and the other conventional forms of partial assistance. In a recent study [5▪▪], three levels of sedation (none, light, and deep), obtained by varying rates of propofol infusion, were evaluated and compared in ICU patients with ARF undergoing NAVA and pressure support administered at comparable levels of assistance. With both modes increasing, propofol infusion progressively decreased EAdi (drive) with no effect on the neural duty cycle (timing). Although gas exchange was not significantly different between the two modes, at deep sedation EAdi was lower in pressure support than in NAVA, which led to ineffective triggering in some patients with the former mode, but not with the latter [5▪▪]. Unpublished data presented in abstract form suggest different effects on drive and timing by varying doses of other sedatives.

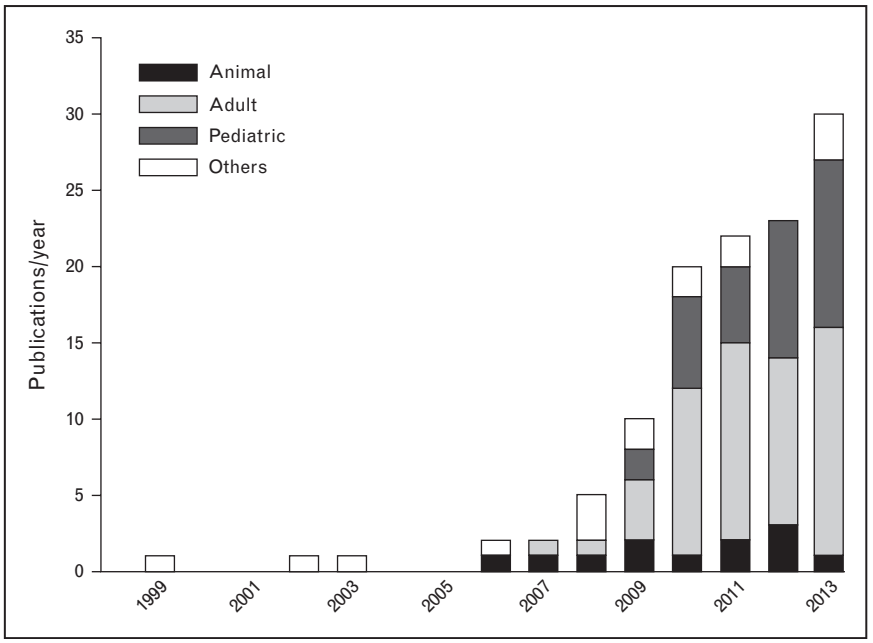

FIGURE 1. Publications on neurally adjusted ventilatory assist (NAVA) from 1999 to 2013. The studies related to NAVA yearly published from 1999 (first description of the technique) to 2013 are shown as a whole and divided according to the type of study: animal (black), adult (light gray) and pediatric patients (dark gray), and others (white), including reviews, editorials, and investigations on healthy individuals. After the introduction of NAVA in clinical use in 2008, the studies related to this mode progressively increased every year, either overall or considering the studies performed on adult and pediatric patients.

Breathing pattern and lung volumes

NAVA being driven by the patient's drive, concerns exist on the possibility of excessively high tidal volumes (V_T), not suited for protective ventilation strategies [13]. In an animal model of acute respiratory distress syndrome (ARDS), incrementing $NAVA_L$ reduced EAdi with minimal changes in respiratory rate and V_T, which remained on average less than 4 ml/kg [14]. These results were subsequently confirmed in the same animal model: EAdi was also reduced when increasing pressure support, but V_T significantly rose at increasing pressure support levels [15]. After injuring the lungs of 27 rabbits, Brander *et al.* [16] compared, at the same positive end-expiratory pressure (PEEP), NAVA and the low-V_T strategy (6 ml/kg) with injurious ventilation (15 ml/kg and no PEEP). Lung injury and nonpulmonary organ dysfunction were significantly lower in both groups, as opposed to injurious ventilation. In the NAVA group, V_T was 3.1 ± 0.9 ml/kg; compared with the conventional low V_T strategy, respiratory rate, arterial oxygen (Pa_{O_2}), and carbon dioxide (Pa_{CO_2}) partial pressures were higher, whereas lung wet-to-dry ratio and bronchoalveolar fluid and systemic biomarkers were similar between the two groups.

Differences in breathing pattern between NAVA and pressure support have been repeatedly shown in mechanically ventilated ICU patients [4,8,11,17▪▪,18,19▪,20]. Colombo *et al.* [4] first demonstrated, in intubated patients with ARF of different causes, the breathing pattern to be differently affected when varying the amount of assistance with the two modes. Increasing the amount of assistance by 50% determined different rises in V_T, from 6.2 to 9.1 ml/kg in pressure support, whereas from 6.4 to 7.1 ml/kg in NAVA. Moreover, both spontaneous and mechanical respiratory rate and duty cycles decreased during pressure support, but not in NAVA. The ability of NAVA to maintain a reduced (protective) V_T was subsequently confirmed in patients with ARDS in the acute phase [21,22▪▪], in the most severe patients undergoing extracorporeal membrane oxygenation [17▪▪,23], and during recovery [8]. The same was found in other patient populations such as postoperative [20] and chronic obstructive pulmonary disease [11]. Recently, in a mixed population of patients with ARF, Patroniti *et al.* [10▪] increased $NAVA_L$ (from 0.5 up to 5 $cmH_2O/\mu V$) and found that, on average, V_T did not exceed 6 ml/kg. In 30% of patients, nonetheless, at the highest $NAVA_L$, periodical delivery of elevated (>8 ml/kg) V_T was observed; in three patients, V_T exceeded 10 ml/kg.

In 10 patients with mild to moderate ARDS, Blankman *et al.* [22▪▪] evaluated the aeration of the dependent and nondependent lung regions by

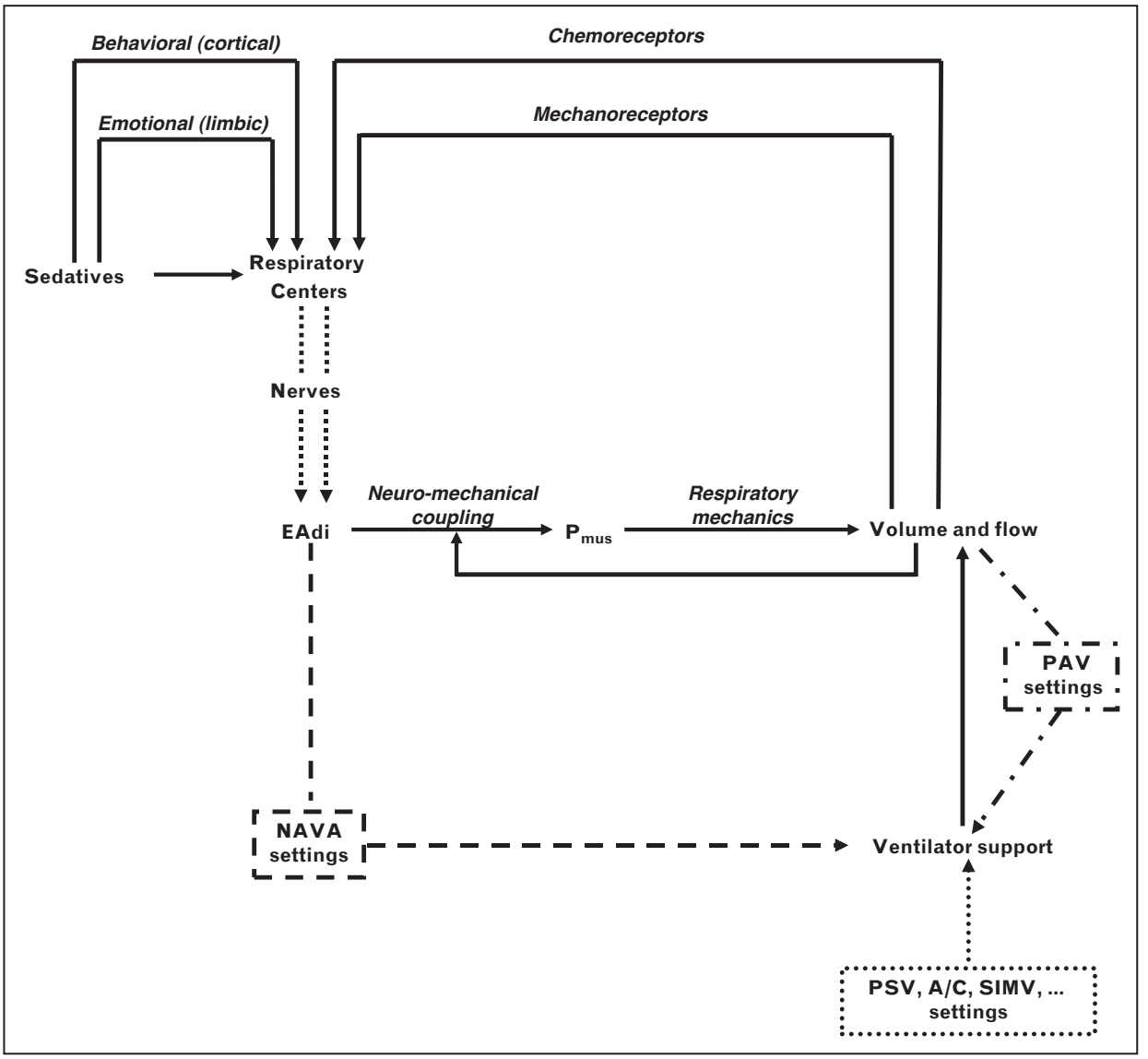

FIGURE 2. Relation between patient's demand and ventilator support with different modes of partial assistance. The figure depicts the composite interplay among respiratory drive, pressure generated by the respiratory muscles (P_{mus}), and ventilatory output (i.e., volume and flow) during partial ventilator assist with different modes of ventilation. The output of the respiratory centers is modulated by stimuli from mechanoreceptors and chemoreceptors, and the cortical or limbic system. Sedatives also affect, directly or indirectly, the output of the respiratory centers. The amount of assistance delivered by the ventilator with the conventional modes (single dotted line), such as pressure support (PSV), assist control (A/C), and synchronized intermittent mandatory ventilation (SIMV), is not influenced by either drive or effort or ventilator output, which exposes this mode to the risk of overassistance. In contrast, with the proportional modes, the delivered support is affected by patient's demand indirectly, by the ventilatory output in proportional assist ventilation (PAV) (dashed-dotted line), or directly, by the neural output of the respiratory centers, as obtained by the electrical activity of the diaphragm (EAdi), in neurally adjusted ventilatory assist (NAVA) (dashed line). With NAVA, moreover, a changed neuromechanical coupling, changes in respiratory mechanics, or air leaks may not disturb the relation between neural output and mechanical support. See text for further explanations. Modified with permission from [2].

means of electrical impedance tomography at varying levels of NAVA and pressure support. Although confirming with an analogous study design the reduced risk of overassistance with NAVA described by Colombo *et al.* [4], this study showed a beneficial effect on the ventilation of the dependent lung region with NAVA, as opposed to pressure support.

Compared with pressure support, V_T variability was repeatedly found to be higher in NAVA [4,9,10▪], resembling the variability observed in

healthy individuals [24]. Conversely, EAdi variability was similar [9] or even higher [4,20] with pressure support than NAVA. Variability might improve oxygenation while reducing the proinflammatory response [25]. The preserved breathing pattern variability associated with the reduced risk of overassistance in NAVA has been proposed to explain the absence of central apneas during weaning in nonsedated patients, as opposed to pressure support [26▪].

Arterial blood gases

One of the primary reasons to institute mechanical ventilation is to improve arterial blood gases. Considering that NAVA is characterized by high V_T variability [4,9,20], shown in other settings to improve arterial oxygenation [25], and redistribution of the ventilation in the dependent lung regions [22▪▪], an improvement in oxygenation would be somewhat expected. Most of the studies, nonetheless, report no differences in oxygenation between NAVA and pressure support [4,5▪▪,8,9,11,17▪▪,27]. These studies, however, were short term (the time of the experimental trial varying between 10 and 30 min), which may explain why no improvement in oxygenation was observed. The effects of both V_T variability and redistribution of ventilation are related to parenchymal recruitment, which takes time. Indeed, in the only study reporting an improvement in arterial oxygenation with NAVA [20], as compared with pressure support, the two modes were delivered for 24-h periods.

NAVA has been repeatedly shown to be as effective as pressure support in guaranteeing adequate values of $Paco_2$ and pH [4,8,11,17▪▪,20,27]. Vaschetto *et al.* [5▪▪] found the $Paco_2$ equally increased with NAVA and pressure support in patients receiving deep sedation by propofol.

Dyspnea

Surprisingly, no study has so far specifically evaluated in intubated patients the effects of NAVA on dyspnea, although Vagheggini *et al.* [28] used the Borg scale to determine comparable levels of pressure support and NAVA in patients with prolonged weaning.

Patient–ventilator synchrony

During partial ventilatory assistance, the ventilator is driven by the patient's spontaneous breathing activity. An optimal interaction between the patient and the ventilator, however, is not guaranteed. In particular, when patient effort and ventilator support lack concurrence in time, asynchronies occur. Patient–ventilator asynchrony is increasingly recognized as a clinical problem. In fact, patients with a rate of asynchronous breaths exceeding 10% of the overall breath count are characterized by worsened outcome (i.e., longer durations of mechanical ventilation [29–31] and ICU stay [30,31], reduced number of ventilator-free days [31], higher rate of tracheotomy [30], and lower probabilities of survival [29] and home discharge [31]). It remains unclear whether asynchronies are just markers of changed respiratory function in the most severe patients, or rather cause themselves the increased morbidity by prolonging the duration of mechanical ventilation [32]. In the latter case, reducing the rate of asynchrony would determine an improvement of patients' outcomes. Visual inspection of the ventilator waveforms was shown inaccurate in detecting asynchronies, suggesting the use of an additional signal for recognizing their occurrence, such as EAdi or esophageal pressure [7].

Compared with conventional modes of ventilation, NAVA has been repeatedly demonstrated to improve the patient–ventilator synchrony in different clinical conditions [4,5▪▪,8,17▪▪,18,19▪]. Incremental ventilator assistance affects the patient's effort during conventional modes, whereas NAVA limits EAdi reduction and the risk of excessively low efforts [4,8,11].

Mechanical properties of the respiratory system may also affect patient–ventilator synchrony. In patients with low respiratory system compliance, pressure support is characterized by a high incidence of premature cycling (i.e., the mechanical breath is shorter than the patient's inspiration) [33]. This was recently confirmed, irrespective of the cycling-off settings, in patients with severe ARDS breathing in pressure support while undergoing extracorporeal membrane oxygenation; in the same patients, NAVA was able to improve patient–ventilator synchrony to suboptimal level [17▪▪]. Some premature cycling, autotriggering, and double triggering prevented an optimal patient–ventilator synchrony [17▪▪]. Ineffective triggering and delayed cycling are common during pressure support in patients with airway obstruction, determining dynamic hyperinflation and auto-PEEP [34]. In pressure support, applying PEEP helps reduce ineffective efforts and varying the cycling-off setting to a higher flow threshold limits delayed cycling. Compared with pressure support, NAVA was shown to eliminate ineffective efforts and drastically decrease on-trigger and off-trigger delays, regardless of the level of assistance [11]. Consistently, in a mixed population including approximately 30% of patients with chronic obstructive pulmonary disease, Piquilloud

et al. [18] observed neither ineffective efforts nor delayed cycling during NAVA, although a few premature cycling and double triggering were detected. Recently, in a population with clinical suspicion of air trapping, Bellani *et al.* [19▪] confirmed that NAVA is able to improve triggering performance at different levels of applied PEEP, in comparison with pressure support.

NONINVASIVE NEURALLY ADJUSTED VENTILATORY ASSIST

The use of NIV to avoid ARF deterioration and avert the need for endotracheal intubation and invasive ventilation has markedly increased [35,36]. NIV is delivered most commonly in pressure support mode using automated software for air-leak compensation. Recent work indicates rates of asynchrony as high as 40% during NIV [37].

Beck *et al.* [38] first described noninvasive NAVA in 2008 in an experimental animal model of ARDS; NAVA, delivered through a single nasal prong, efficiently unloaded the respiratory muscles [38]. At increasing level of assistance, in contrast to NIV delivered by conventional modes, NAVA has been shown to avoid glottis closure during inspiration in lambs [39].

Cammarota *et al.* [40▪] compared NAVA with pressure support in patients with postextubation hypoxemic ARF receiving NIV through a helmet, a well tolerated interface often characterized by high rate of asynchronies [41]. Respiratory rate, EAdi, and blood gases were no different with the two modes. Compared with pressure support, however, NAVA reduced the inspiratory trigger delay, prolonged the time of inspiration during which the diaphragm was active and the ventilator was concurrently delivering assistance, and eliminated the asynchronies [40▪].

These findings were subsequently confirmed to varying extent during NIV delivered by mask [42▪–44▪]. Piquilloud *et al.* [42▪] compared pressure support and NAVA in delivering NIV via face mask in a series of patients with ARF or at risk of postextubation respiratory failure. They [42▪] also found EAdi and arterial blood gases no different between the two modes, and the trigger delays and asynchronies significantly improved with NAVA, compared with pressure support.

In patients receiving postextubation prophylactic NIV, Schmidt *et al.* [43▪] delivered both pressure support and NAVA either with or without automatic air-leak compensation. No differences in breathing pattern and EAdi were found among the four tested combinations; regardless of the algorithm for air-leak compensation, NAVA reduced the delays and improved synchrony, as opposed to pressure support [43▪]. Noteworthy, the NIV algorithm significantly reduced the incidence of asynchronous events during pressure support, but not with NAVA [43▪]. Comfort and dyspnea, as assessed by a Visual Analogue Scale, were no different among conditions [43▪]. A further study in a population of patients with ARF of varying cause [44▪] confirmed similar breathing pattern and improved patient–ventilator interaction and synchrony in NAVA, compared with pressure support.

CONCLUSION

NAVA is a novel form of proportional assistance offering several physiological advantages, compared with the conventional modes of partial support, during either invasive ventilation or NIV. In particular, NAVA improves patient–ventilator interaction, averting the risk of overassistance and limiting the occurrence of asynchronies. Whether these physiological improvements translate into clinical benefits remains to be determined by randomized trials assessing clinical outcomes.

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Conflicts of interest

Paolo Navalesi contributed to the development of a new interface for noninvasive ventilation (not mentioned in the present work), whose license for patent belongs to Intersurgical S.p.A., and receives royalties for that invention. His research laboratory has received equipment and grants from Maquet Critical Care and Intersurgical S.p.A. He also received honoraria/speaking fees from Maquet Critical Care, Covidien AG, Breas, Hill-Rom, and Linde AG. Federico Longhini has no conflict of interest to declare.

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This study confirms in patients receiving NIV through a facial mask that NAVA improves the patient–ventilator interaction and synchrony and results in similar values of arterial blood gases and diaphragm electrical activity, as compared with pressure support.

Novel approaches to minimize ventilator-induced lung injury

Pierpaolo Terragni, Vito Marco Ranieri, and Luca Brazzi

Purpose of review
To discuss the mechanisms of ventilator-induced lung injury and the pro and cons of the different approaches proposed by literature to minimize its impact in patients with acute respiratory distress syndrome.

Recent findings
Mechanical ventilation is indispensable to manage respiratory failure. The evolution of knowledge of the physiological principles and of the clinical implementation of mechanical ventilation is characterized by the shift of interest from its capability to restore 'normal gas exchange' to its capability of causing further lung damage and multisystem organ failure.

Summary
If one of the essential teachings to young intensivists in the 1980s was to ensure mechanical ventilation restored being able to immediately drain a pneumothorax (barotrauma), nowadays priority we teach to young intensivists is to implement 'protective' ventilation to protect the lungs from the pulmonary and systemic effects of ventilator-induced lung injury (biotrauma). At the same time, priority of clinical research shifted from the search of optimal ventilator settings (best positive end-expiratory pressure) and to the evaluation of 'super-protective' ventilation that integrating partial or total extracorporeal support tries to minimize the use of mechanical ventilation.

Keywords
acute respiratory distress syndrome, low tidal volume, respiratory mechanics, ultraprotective mechanical ventilation, ventilator-induced lung injury

INTRODUCTION

Even if mechanical ventilation remains the cornerstone of treatment for respiratory failure, it is now clear that it can itself aggravate or cause lung damage inducing the so called ventilator-induced lung injury (VILI) through a variety of mechanisms.

The main mechanical determinant of VILI is regional lung overdistension due to high trans-pulmonary pressure (stress) that causes the lung to deform above its resting volume (strain) [1].

In experimental models, VILI has been found to develop when a lung strain (estimated as the ratio between lung volume change and resting volume) greater than 2 is achieved, corresponding to a tidal volume approximately greater than 20 ml/kg in healthy animals [1,2]. Thus, the smaller the resting lung volume, the greater the strain for a given lung volume change (inflation).

But low lung volume ventilation may also be deleterious due to regional amplification of forces and repetitive opening and closing of distal, collapsed lung units (atelectrauma) [3,4]. This condition has been advocated to provide augmented pulmonary injury when tidal ventilation starts below and ends above the lower inflection point on the pressure/volume curve, as compared with ventilation starting above the lower inflection point.

The biotrauma concept relies on the hypothesis that lung tissue stretching might result in lung epithelium damage through the release of inflammatory mediators and leukocyte recruitment. Two mechanisms are believed to be responsible for this mechanical ventilator-induced inflammatory response. The first is direct trauma to the cell with

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KEY POINTS

- Mechanical ventilation, although necessary to preserve life, can itself aggravate or cause the so called VILI through a variety of mechanisms resulting in injury to the blood–gas barrier (endothelial, epithelial, and basement membrane) with consequent increase in microvascular permeability and lung rupture.
- A large number of trials tried to identify strategies to improve the outcome of mechanically ventilated patients but only studies based on the physiological approaches for minimizing VILI really improved the outcome.
- In the last years, the most important innovation is represented by the progressive change of approach, from basic mechanical respiratory support, to protective or ultraprotective noninjurious ventilation.
- It is advisable for clinicians to integrate physiological principles with clinical data through a 'running assessment' of respiratory mechanics at the bedside so as to set up the most protective (tailor made) ventilatory strategy.

disruption of cell walls, resulting in the release of cytokines into both the alveolar space and the systemic circulation [5]. Regarding the second, in-vitro studies have shown that most pulmonary cells can produce cytokines in response to cyclic stretch [6].

Ranieri *et al.* [7] were the first to suggest that the mechanical ventilator-induced inflammatory response may contribute to development of multiple system organ dysfunction seen in mechanically ventilated patients with acute respiratory distress syndrome (ARDS) by initiating or propagating a malignant, systemic inflammatory response. Although it remains unclear how inflammatory mediators exert their detrimental effects on distal organs, experimental studies and clinical trials in ARDS have shown that the application of protective ventilator strategies is associated with decreased serum cytokine levels [8,9], decreased extrapulmonary organ dysfunction [7], and decreased mortality [10].

Many factors contribute to the development of VILI: the type, duration and intensity of physical forces generated by the ventilation (volume and pressure) as well as the cause, timing of lung injury and the general progression of the disease, and a large number of trials reported the clinical efficacy of a 'protective' ventilatory strategy based on the reduction of tidal volume to 6 ml/kg of ideal body weight and the limitation of end-inspiratory pressure to 30 cmH_2O.

However, these recommendations are challenged by results of recent studies showing that patients with ARDS may be exposed to forces that can induce injurious ventilation despite values of plateau pressure (Pplat) of 30 cmH_2O or less [11–13]; and impairment of chest wall mechanics compromises the ability of Pplat to reflect overdistension [1,14,15].

In the present study, we will discuss the pros and cons of the different approaches proposed to minimize VILI in patients with ARDS.

'PROTECTIVE' VENTILATORY STRATEGIES

Different approaches have been proposed to minimize VILI in patients with ARDS.

Low tidal volume

Experimental and clinical data showed that a reduction of tidal volume reduced mortality in ARDS ventilated patients [10,16,17] but controversy exists regarding the extent to which tidal volume should be reduced to protect the lungs from VILI.

The ARDS*net* study demonstrated that a 22% reduction in mortality could be obtained by using a tidal volume of 6 ml/kg predicted body weight (PBW) instead of 12 ml/kg PBW [10]. But it is still debated whether the tidal volume should be strictly set to 6 ml/kg PBW in all patients with ARDS, as the resulting strain will depend on the amount of ventilated tissue rather than on PBW [11].

The development of tools for measurement of the amount of lung open to ventilation at bedside might allow for individual adjustment of tidal volume. These include promising noninvasive imaging methods, such as electrical impedance tomography and lung ultrasound, but also functional dynamic indexes, such as the stress index, which describes the shape of the airway pressure-time curve profile and may indicate tidal recruitment or tidal overdistension [18▪▪]. Of note, patients with ARDS often 'fight the ventilator,' and this may aggravate VILI [19]. In a recent multicenter, placebo controlled, randomized trial involving 340 patients with ARDS and a $Pao_2:Fio_2$ ratio of less than 150 mmHg, Papazian *et al.* [20] found that the adjusted 90-day mortality was lower among those who received a neuromuscular blocking agent for 48 h than among those who received placebo, without any increase in residual muscle weakness. The precise mechanism for the decreased mortality is unclear [19] but a previous study showed reduced serum cytokine levels among patients receiving a neuromuscular blocking agent [21].

'High' positive end-expiratory pressure

Early trials comparing lower with higher levels of positive end-expiratory pressure (PEEP) in patients with ARDS found no difference in mortality between the two groups. However, lower rates of hypoxemia were observed when higher PEEP and recruitment maneuvers were combined with protective ventilation in an 'open lung' strategy. Furthermore, the results of a large randomized controlled trial demonstrated that an 'increased recruitment strategy', wherein PEEP was used to reach a plateau pressure of 28–30 cm H_2O, resulted in a greater number of ventilator-free days and days free of organ failure [22–24]. There is some evidence to suggest that higher levels of PEEP may benefit patients with a greater degree of lung injury. One recent meta-analysis demonstrated a statistically significant reduction in hospital mortality with the use of higher PEEP when compared with lower PEEP in the subset of patients with Pa_{O_2}:Fi_{O_2} less than 200 mmHg. No such benefit was seen in those with less severe hypoxemias [25]. This adds weight to a previous subgroup analysis of earlier trials, which concluded that higher levels of PEEP benefit the most-hypoxemic patients with ARDS [26].

Recruitment maneuvers

Although such maneuvers were used in some trials that were included in the meta-analysis described above [25] and were implemented in a protective strategy that increased the number of lungs retrieved from heart-beating donors [27], the role of recruitment maneuvers in clinical practice remains uncertain because of questions about its effect on outcomes and concerns regarding complications (e.g., hemodynamic compromise or pneumothorax) [28].

Prone position

Prone positioning may mitigate VILI in three key ways: first, by providing a more homogeneous distribution of transpulmonary pressure throughout the lung, second, by 'resting' anterior lung units, which are subjected to the most overdistension, and third, by improving ventilation-perfusion matching, thereby allowing for a decrease in the inspired oxygen concentration [29,30].

Despite this, four randomized clinical trials [31–34] have so far failed to demonstrate a reduction in mortality with its routine use in ARDS even if four meta-analyses concluded that although routine prone position ventilation offers no survival benefit in patients with ARDS, it does improve oxygenation [35–38]. One more demonstrated the efficacy only in a selected category of very hypoxemic patients lowering absolute mortality. Starting from these assumptions, Guérin *et al.* [39▪] designed a prospective, multicenter, randomized controlled trial to explore whether early application of prone positioning would improve survival among patients with ARDS who, at the time of enrollment, were receiving mechanical ventilation with PEEP of at least 5 cmH_2O and in whom the Pa_{O_2}/Fi_{O_2} ratio was less than 150 mmHg. The trial confirmed the improvement in patient survival with prone positioning reducing the rate of 28-day mortality from 32.8% (supine group) to 16.0% (prone group) [39▪].

High-frequency oscillatory ventilation

Theoretically, this technique should be ideal for minimizing VILI [40]. In a meta-analysis of eight randomized, controlled trials involving a total of 419 adults with ARDS [41], high-frequency oscillatory ventilation-treated patients had significantly lower mortality than did patients treated with conventional ventilation (risk ratio, 0.77; $P = 0.03$), which suggested that high-frequency oscillatory ventilation might improve survival and is unlikely to cause harm. Unfortunately, these benefits usually come at the expense of markedly increased mean airway pressures [42] and the potential deterioration in right heart function and organ perfusion.

Transpulmonary pressure

ARDS patients are particularly prone to VILI due to inhomogeneous parenchyma damage that presents areas not aerated (with atelectasis, infiltrates, or effusions), areas with low ventilation in which the opening-closing phenomenon is prevalent, areas normally aerated without signs of stress, and lastly areas overinflated. In this context, the best ventilatory strategy should be ideally adapted to the size of the aerated lung. It is hence necessary to move from the selection of mode and setting of the ventilator based on a fixed set of numbers, to take into account the transpulmonary pressure [43▪▪], that is, the difference between alveolar pressure and pleural pressure, which is considered by some as the main determinant of VILI [44].

The importance of transpulmonary pressure in adjusting mechanical ventilation setting in ARDS patients has even been studied by Talmor *et al.* [45] in 2008. In a randomized, single-center trial, they found an improvement in oxygenation and a reduction in 28-day mortality by setting the PEEP at such a level that transpulmonary pressure during end-expiratory occlusion ranged between 0 and 10 cmH_2O and during end-inspiratory occlusion remained lower than 25 cmH_2O.

Different methods have been proposed in literature to estimate transpulmonary pressure:

(1) $Pplat_L = Pplat_{RS} - Pplat_{CW}$ (where $Pplat_{CW} = Pplat_{RS} \times E_{CW}/E_{RS}$) [1]
(2) $Pplat_L = Pplat_{RS} - Pplat_{CW}$ [45]

Recently, Chiumello *et al.* [46] reported that the two methods are similar and concluded that the transpulmonary pressure can be satisfactorily estimated by the first one, which does not require any disconnection from the ventilator, thereby avoiding possible risks of lung derecruitment and hypoxemia due to the loss of PEEP.

'SUPER PROTECTIVE' VENTILATORY STRATEGY

Extracorporeal life support (ECLS) techniques, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO_2 removal ($ECCO_2R$), are known to provide adequate gas exchange in patients with ARDS [47]. Vast improvements in ECLS technology over the last decade have made these devices less invasive, more biocompatible, and easier and safer to use. Moreover, ECLS can facilitate the use of 'ultra' protective mechanical ventilation (e.g., employing tidal volume <6 ml/kg PBW and lower airway pressures) in patients supported with ECLS, minimizing the risk of VILI. More radically, patients supported with ECLS may not require intubation or invasive mechanical ventilation at all: no ventilation, no VILI.

EXTRACOPOREAL MEMBRANE OXYGENATION

The safety, clinical efficacy and cost-effectiveness of extracoporeal membrane oxygenation (ECMO) compared with conventional ventilation support has been recently been studied in the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) study [48]. A significant improvement in survival without severe disability at 6 months was found in patients transferred to a specialist center for consideration for ECMO compared with continued conventional ventilation. This result has been attributed to the fact that ECMO was able to sustain life in acute lung failure long enough for diagnosis, treatment and recovery. Moreover, ECMO was able to rest the lungs from high pressure and Fio_2 ventilation, thereby keeping to minimum the iatrogenic contribution to lung injury.

EXTRACORPOREAL CO_2 REMOVAL

In a recent study, Terragni *et al.* [12] evaluated whether tidal volume less than 6 ml/kg PBW may enhance lung protection. In 32 patients with ARDS ventilated with a tidal volume of 6 ml/kg PBW, those with plateau pressures between 28 and 30 cm H_2O had their tidal volume reduced to achieve plateau pressures between 25 and 28 cm H_2O. Respiratory acidosis (pH $\leq$7.25) was managed with $ECCO_2R$ for at least 72 h. Patients who already had plateau pressures between 25 and 28 cm H_2O continued to receive mechanical ventilation with tidal volume of 6 ml/kg PBW. In the $ECCO_2R$ group (10 patients), $PaCO_2$ (mean 50 mmHg) and pH (mean 7.32) were normalized, and tidal volume was reduced from 6 to 4 ml/kg PBW and plateau pressure decreased from 29 to 25 cmH_2O ($P < 0.001$). Moreover, there was a significant reduction in the morphological markers of lung injury and pulmonary cytokines ($P < 0.01$) in the $ECCO_2R$ group after 72 h of mechanical ventilation with tidal volume lower than 6 ml/kg PBW. Of note, no patient-related complications occurred in patients receiving $ECCO_2R$.

Although promising, the putative benefits of 'ultra' protective mechanical ventilation with $ECCO_2R$, or more complete gas exchange support with ECMO, in patients with ARDS requires confirmation in large, randomized controlled trials [49].

CONCLUSION

From a theoretical prospective, all patients receiving ventilator support should benefit from noninjurious strategies. It is advisable for clinicians to integrate physiological principles with clinical data through a 'running assessment' of respiratory mechanics at the bedside so useful to contain VILI by the early identification of specific lung alterations and the resulting most-protective (tailor made) ventilatory strategy.

Future study, already planned, is expected to improve further the clinical outcomes compared with standard-of-care lung-protective ventilation in patients with ARDS. The EOLIA trial (ECMO to rescue lung injury in severe ARDS; ClinicalTrials.gov NCT01470703) is going to evaluate the impact of ECMO, instituted early after the diagnosis of ARDS not evolving favorably after 3–6 h under optimal ventilatory management and maximum medical treatment, on the morbidity and mortality associated with this disease, whereas the SUPERNOVA trial (A Strategy of UltraProtective lung ventilation with Extracorporeal CO_2 Removal for New-Onset moderate to seVere ARDS; ESICM trial group-registration ongoing) will evaluate whether a strategy of enhanced lung-protective (lower tidal volume and lower pressure) ventilation, along with control of the ensuing hypercapnia using the latest

generation $ECCO_2R$ devices, will improve clinical outcomes.

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Conflicts of interest

V.M.R. received payment for serving on advisory boards at Hemodec and received consulting fees from Hemodec, and Faron Pharmaceuticals.

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Balancing neuromuscular blockade versus preserved muscle activity

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Purpose of review
Acute respiratory distress syndrome (ARDS) is still associated with a high mortality. The best way to ensure mechanical ventilation in ARDS patients is still debated, recent data arguing for a muscle paralysis and a controlled ventilation whereas other elements being in favor of a preserved spontaneous breathing. The purpose of this review is to discuss the benefits and the disadvantages of both strategies.

Recent findings
Randomized controlled trials have brought the evidence that at the acute phase of ARDS, a 48-h administration of cisatracurium is associated with a decrease in mortality for the most severe hypoxemic patients. Other studies suggest that spontaneous breathing could be deleterious at this period. In the less severe patients (mild ARDS), however, a few studies have demonstrated the benefits of preserving spontaneous breathing with an improvement in oxygenation and a decrease in the length of mechanical ventilation.

Summary
In ARDS patients, the ventilator strategy should be a balance between muscle paralysis in the most hypoxemic patients and preserved spontaneous breathing after improvement or from the acute phase in less severe forms. However, monitoring plateau pressure, tidal volume and perhaps also transpulmonary pressure seems crucial to limit the occurrence of ventilator-induced lung injury.

Keywords
acute respiratory distress syndrome, mechanical ventilation, neuromuscular blockers, spontaneous breathing

INTRODUCTION

Mechanical ventilation is the cornerstone of the treatment of patients presenting with acute respiratory distress syndrome (ARDS). However, despite certain therapeutics having been shown to reduce the mortality [1,2▪▪,3], the debate concerning the best way to ventilate ARDS patients is still going on. In particular, the respective place of mechanical ventilation with preserved spontaneous breathing or totally controlled mechanical ventilation using neuromuscular blocking agents (NMBAs) is not clearly defined. Previous studies have demonstrated that maintaining spontaneous breathing during mechanical ventilation improved alveolar recruitment, oxygenation and hemodynamics [4,5], saved sedation and permitted to decrease the incidence of diaphragmatic dysfunction [6]. However, data concerning ARDS are scarce, in particular for the most hypoxemic patients. In the acute phase of ARDS, especially in the most severe cases [defined as PaO_2/FIO_2 ratio $\leq$100 mmHg in $\geq$5 cm H_2O positive end-expiratory pressure (PEEP) [7]] spontaneous breathing during mechanical ventilation could be deleterious by increasing ventilator-induced lung injury (VILI). On the contrary, in those patients, deep sedation with continuous muscle relaxation is often necessary to ensure protective ventilation, limit derecruitment and allow prone positioning explaining widespread use of NMBAs in ARDS [8,9]. Finally, clear recommendations regarding the place of NMBAs and spontaneous breathing in mechanically ventilated ARDS patients are not

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KEY POINTS

- Preserving spontaneous breathing during mild ARDS probably favors oxygenation and decreases length of mechanical ventilation, but could increase the occurrence of VILI in severe ARDS.
- For the most hypoxemic ARDS, a strategy using neuromuscular blockers for a short course can reduce the mortality.
- Ventilatory strategies allowing spontaneous breathing and mechanical ventilation with muscle paralysis during ARDS should not be opposed but rather integrated in a strategy taking into account both the severity of ARDS and the possibility of ensuring a protective ventilation.

available. Thereby, the purpose of this review is to present an updated discussion on the respective roles of spontaneous breathing and muscle paralysis during mechanical ventilation in ARDS patients, based both on pathophysiological concepts and data obtained from clinical studies.

PATHOPHYSIOLOGICAL ASPECTS

Pathophysiology of mechanical ventilation during ARDS can help us to understand the benefits and risks of the use of neuromuscular blockers or the preservation of spontaneous breathing that have been noted in clinical studies.

Theoretical benefits of neuromuscular blocking agents in acute respiratory distress syndrome

Several pathophysiological hypotheses can be proposed to explain the interest of using NMBAs on oxygenation and mortality at the acute phase of severe ARDS. Slutsky [10] proposed a summary of the effects of NMBAs that are mainly because of:

(1) The reduction of patient-to-ventilator dysynchrony, with a better control of tidal volume leading to a decrease of baro and volu trauma as well as a decrease of atelectrauma owing to the inhibition of active expiration and the better control of PEEP. This is associated with a decrease of lung blood flow and alveolar–capillary permeability.
(2) A decrease of respiratory drive classically associated with hypoxemia and permissive hypercapnia.
(3) A decrease in muscle oxygen-consumption and in cardiac output.
(4) A decrease of biotrauma with an inhibition of translocation of inflammatory mediators from alveolar space to circulation with less organ failure. This is suggested by the decreased production of proinflammatory cytokines in both the lung and blood observed by Forel *et al.* [11]. Moreover, the direct anti-inflammatory role of muscle relaxants cannot be excluded and deserves to be confirmed.
(5) An increase in the functional residual capacity and a decrease in the intrapulmonary shunt. An improvement in the ventilation-perfusion ratios may also be related to a more uniform distribution of pulmonary perfusion owing to the application of lower pulmonary pressures, favoring the perfusion of ventilated areas and decreasing intrapulmonary shunt.

Lung ventilation in healthy versus injured lungs

During mechanical ventilation, the portion of the applied pressure inflating the lung (i.e. transpulmonary pressure, P_L) varies widely, depending on chest wall characteristics [12,13]:

(1) Transpulmonary pressure (P_L) = airway pressure (P_{aw}) – pleural pressure (P_{pl})
(2) Where, P_L: the pressure to inflate the lung, surrogate of lung tissue stress; P_{aw}: the pressure applied by positive-pressure ventilation via trachea; and P_{PL}: the lung surface pressure imposed by chest wall.

Spontaneous efforts can elevate P_L with the same P_{aw} applied in muscle paralysis [14▪]. When spontaneous breathing is preserved during mechanical ventilation, negative changes in P_{pl} may be coupled with positive pressure changes from the ventilator, magnifying P_L. Spontaneous breathing is traditionally encouraged in patients receiving mechanical ventilation [15,16]. It has been generally believed to provide lung expansion at lower levels of P_{aw}, a strategy that would result in better local (especially dependent) lung aeration, thereby enhancing gas exchange and potentially improving hemodynamics [4,17–20].

Contrasting with hard belief on the beneficial effects of spontaneous breathing in ARDS, recent experimental studies shed light on the 'dark side' of spontaneous breathing in ARDS, from the perspective of P_L and regional lung ventilation, using esophageal pressure manometry and dynamic imaging such as dynamic computed tomography (CT) and electrical impedance tomography [14▪,21,22].

Classical physiological studies showed that under normal conditions, the lung parenchyma is

homogeneous and is considered to be a continuous elastic system –exhibiting fluid-like behavior – such that distending pressure applied to a local region of the pleura becomes generalized over the whole lung (pleural) surface (Fig. 1) [23–26]. It means that local changes in P_{pl} generated by diaphragmatic contraction tend to be transmitted all over the lung surface, creating a fairly uniform increase in P_L [25,26].

In contrast, once lung has been injured (i.e. ARDS), the negative change in P_{pl} generated by diaphragmatic contraction is not uniformly transmitted across the lung surface, but rather concentrated in dependent lung regions (i.e. solid-like behavior) (Fig. 1) [16]. Lung injury involves tissue inflammation and fluid-filled alveoli in a heterogeneous distribution; thus, some areas will be well aerated and others collapsed or filled with fluid and inflammatory cells [27]. Such dense tissue may behave less like a fluid and more as a frame of 'solid' areas resisting shape deformation. Locally elevated change in P_L causes unsuspected local overstretch in dependent lung regions where such pressure generated first, accompanying alveolar air shift from nondependent to dependent parts of the lung (i.e. Pendelluft) (Fig. 2) [22]. Using dynamic CT (based on absolute air content) and electrical impedance tomography (based on relative air content), the evidence of Pendelluft was confirmed in an experimental model of ARDS and also in a postoperative ARDS patient.

BENEFITS ASSOCIATED WITH SPONTANEOUS BREATHING IN ACUTE RESPIRATORY DISTRESS SYNDROME

The activity of inspiratory muscles can lower the pleural components surrounding the lung, leading to increase and sustain P_L during the entire respiratory cycle [28]. First, tonic activity of inspiratory muscles has been proven to maintain the end-expiratory lung volume, by augmenting the elastic recoil of the chest wall [29]. Indeed, paralysis decreases the end-expiratory lung volume by 0.4–0.5 l, leading to decrease in compliance of the respiratory system and increase in atelectasis near the diaphragm in normal subjects [29]. The tidal increase in P_L during inspiration (owing to diaphragmatic contraction) distributes preferentially tidal volume to dependent lung regions [14▪,17,19,20,30]. Thus, the maintenance of spontaneous breathing during mechanical ventilation is considered as the least invasive method of lung recruitment by alteration of the pleural components [31].

Spontaneous breathing during mechanical ventilation improved gas exchange, associated with better lung aeration in CT analysis, in experimental and clinical studies with less severe form of ARDS [14▪,16,17,20,30]. However, it is important to emphasize that the evidence for beneficial effects of spontaneous breathing has been gathered in less severe form of ARDS with modest ventilatory demands [14▪,16,17,20,30,32].

Spontaneous effort is generally modest in less severe form of ARDS, evident from less duration and less amplitude of the negative change in P_{pl} that diaphragmatic contraction generates [14▪]. Importantly, Pendelluft size (i.e. the amount of alveolar air translocating from nondependent to dependent lung regions) becomes larger as spontaneous effort becomes stronger during mechanical ventilation [22]. Thus, mild spontaneous effort can be beneficial to recruit the collapsed lung, whereas excessive spontaneous efforts could cause local overstretch because of large size of Pendelluft.

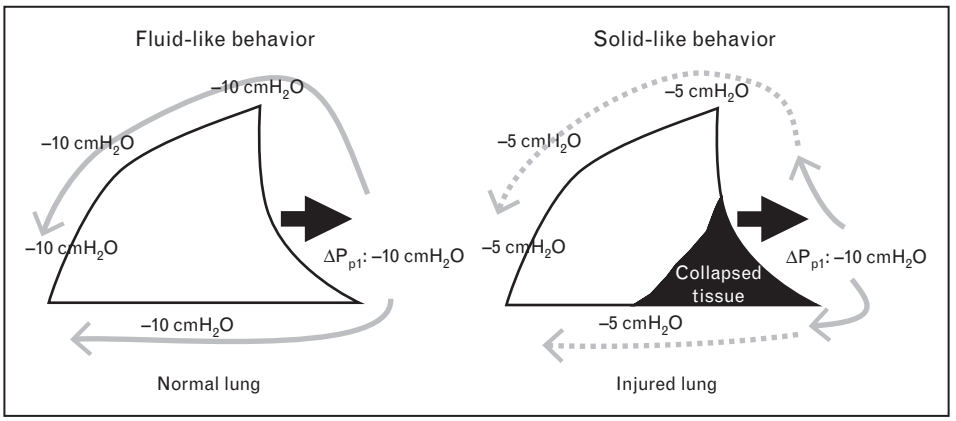

FIGURE 1. Different pressure transmission – normal lung versus injured lung. Contrasting with homogeneous distributions of pressures observed in normal lung, in injured lung, negative pleural pressures generated by diaphragmatic contraction are rather concentrated in dorsal parts of the lung.

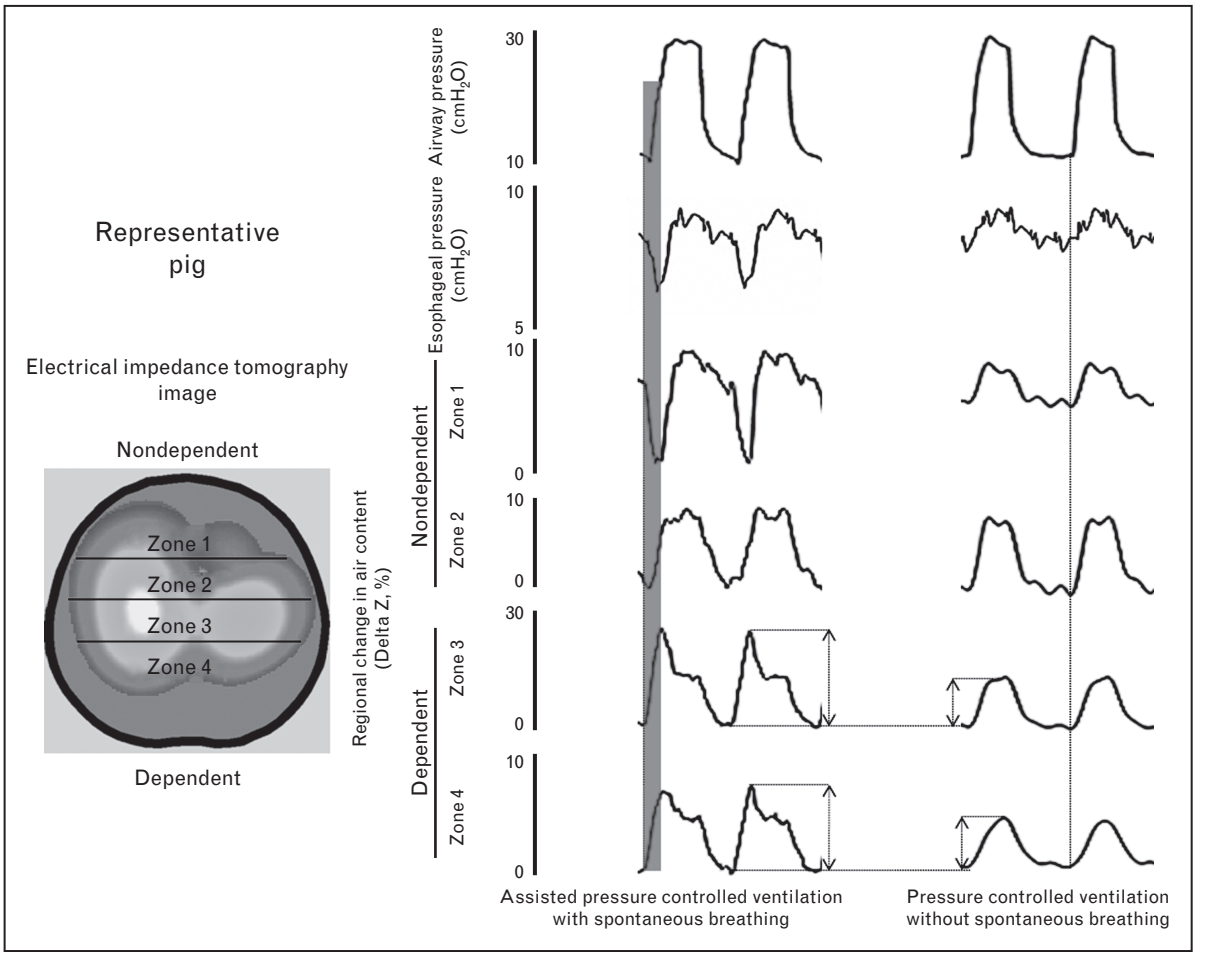

FIGURE 2. Electrical impedance tomography waveforms in experimental lung injury – spontaneous versus mechanical breaths. Note that the early inflation in the dependent region (Zone 3, 4) was accompanied by concomitant deflation of nondependent region (Zone 1, 2), indicating movement of air from nondependent to dependent lung (i.e. Pendelluft). With permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society [22].

POTENTIAL DELETERIOUS EFFECTS OF SPONTANEOUS BREATHING IN ACUTE RESPIRATORY DISTRESS SYNDROME

First, spontaneous breathing during mechanical ventilation could cause uncontrolled increases in P_L even when limiting plateau pressure [14▪,21,22]. Indeed, increased histological lung injury resulting from added spontaneous effort has been demonstrated in an experimental ARDS model [14▪,21]. In severe ARDS, combined with the already high plateau pressure and higher demands of spontaneous breathing, the injuriously high P_L increased histological lung injury and tidal recruitment [14▪]. In the ACURASYS study [1], the placebo group (i.e. no neuromuscular blockade use) had a higher incidence of barotrauma even at the comparable plateau pressure and tidal volume to the muscle paralysis group, suggesting that spontaneous effort may have generated injuriously high P_L and unsuspected local overstretch of dependent lung regions, associated with Pendelluft. Second, in an experimental ARDS model, despite limitation of tidal volume to less than 6 ml/kg, strong spontaneous effort resulted in unsuspected local overstretch of the dependent lung because of the large Pendelluft; indeed, matching this degree of regional overstretch during neuromuscular paralysis required an overall tidal volume of 15 ml/kg (i.e. a highly injurious lung stretch) [22]. Third, the high respiratory drive also activates expiratory muscles. Such expiratory muscles' activity shifts the diaphragm to cephalad direction, leading to elevated P_{pl} during expiration and lower P_L during expiration: P_L during expiration = PEEP – P_{pl} during expiration. As a result, it can cause hypoxemia by decreasing end-expiratory lung volume [32,33].

Besides strictly limiting tidal volume and plateau pressure during mechanical ventilation, it

is also important to avoid excessive spontaneous effort especially in severe form of ARDS, to decrease the risk of VILI.

BENEFITS ASSOCIATED WITH MUSCLE PARALYSIS IN CLINICAL PRACTICE

Two prospective randomized controlled trials (PRCTs) have demonstrated a beneficial effect of the use of NMBAs on the oxygenation of ARDS patients. In a first multicenter PRCT [34], a significant improvement in the PaO_2/FiO_2 ratio in patients with ARDS receiving neuromuscular blockade continuously for 48 h as compared with a placebo was shown. The beneficial effects were observed as early as the 48th hour and persisted throughout the study period (120 h after randomization). Interestingly, a strong tendency toward a lower mortality rate was observed in the group of patients receiving NMBAs. In a second study [11], designed to evaluate the role of cisatracurium in lung and systemic inflammation in ARDS patients, the same group of authors confirmed the beneficial effects of NMBAs on oxygenation. Decreases in the plateau pressure, FiO_2 and PEEP were also observed during the study period of 120 h in the NMBAs group. In this study, the same trend toward decreased mortality in patients receiving the neuromuscular blockers was observed. This decrease was the rationale for designing of the ACURASYS study [1]. In this multicenter double-blind trial, patients with a severe ARDS lasting for less than 48 h (i.e. with a PaO_2/FiO_2 ratio <150 mmHg and PEEP ≥ 5 cm H_2O) were randomized into 2 groups: a group receiving a continuous infusion of cisatracurium besylate and a placebo group both administered over a 48-h period. The group of patients treated with cisatracurium showed an improvement in the adjusted 90-day survival rate compared with the placebo group. After adjusting for the baseline PaO_2/FiO_2 ratio, the plateau pressure and the Simplified Acute Physiology Score II, the hazard ratio for death at 90 days in the cisatracurium group compared with the placebo group was 0.68. Interestingly, the beneficial effects of cisatracurium on the mortality of the most severe patients included a PaO_2/FiO_2 ratio of less than 120 mmHg. The cisatracurium group had significantly more ventilator-free days than the placebo group and more days free of organ failure (other than the lung) during the first 28 days. Finally, these studies provide strong argument in favor of using a 48-h infusion of cisatracurium in patients with most hypoxemic ARDS (especially with a PaO_2/FiO_2 ratio <120 mmHg) with a direct benefit on survival. The main criticism that can be objected is that all three PRCTs were conducted by the same group of authors. Thereby, confirmatory studies are needed. Interestingly, in a recent large retrospective study, Steingrub *et al.* [35] investigated the outcomes of mechanically ventilated patients with severe sepsis who had received NMBAs within the 2 days following their admission into the ICU. The unadjusted in-hospital mortality rate of those patients initially treated with NMBAs was 31.9% versus 38.3% among those who did not receive NMBAs ($P < 0.001$). The authors showed that the risk ratio of in-hospital mortality was 0.88 in favor of the treated group. Even if all the patients included were not ARDS patients and were most likely less severe than in the ACURASYS study, these results are in line with those recovered in this latter study.

POTENTIAL DELETERIOUS EFFECTS OF NEUROMUSCULAR BLOCKING AGENTS

Among the potential disadvantages of using NMBAs during ARDS, ICU-acquired weakness and occurrence of atelectasis and derecruitment are the most often cited. However, the data issued from the literature are not univocal concerning this field.

ICU-acquired weakness

Owing to the severe and durable morbidity that it is responsible for, ICU-acquired weakness (ICUAW) is a major concern [36]. In a recent review [37], the incidence of ICUAW was 34%–60% in patients with ARDS. The supposed association between ICUAW and NMBAs was often responsible for a distrust of paralytics. However, independent risk factors of ICUAW clearly identified regroup female sex, multiple organ dysfunctions (≥ 2), duration of mechanical ventilation and administration of corticosteroids [38]. Duration of vasopressor support, duration of ICU stay, hyperglycemia, low serum albumin and neurological failure have also been described as risk factors [39–41]. As far as NMBAs are concerned, several studies [42,43] found that they were not associated with muscular weakness. Three circumstances, however, appeared to favor the development of ICUAW: the concomitant use of NMBAs and corticosteroids, the use of steroid NMBAs and the length of infusion exceeding 48 h [44–46]. Confirming these data, in the ACURASYS study [1], in which patients received a short course of nonsteroid NMBAs, the incidence of ICU-acquired paresis was not higher in paralyzed patients than in the control group. Furthermore, in a recent meta-analysis of the PRCT evaluating the use of NMBAs in ARDS [47], cisatracurium was not associated with an increased risk of ICUAW.

To summarize, there is actually no evidence that nonsteroid NMBAs, when used for a short duration and without the simultaneous administration of corticosteroids, increase the risk of ICUAW.

Atelectasis and derecruitment

By paralyzing the diaphragm, NMBAs associated with sedation could be responsible for the occurrence of lung atelectasis. This has been investigated particularly in patients with healthy lungs in whom atelectasis occurs rapidly after anesthesia with muscular paralysis [48,49]. However, these ascertainments were not observed in ARDS patients in whom NMBAs improved oxygenation and probably favored recruitment. One can suppose that in ARDS patients, the application of a sufficient PEEP level was able to counterbalance the effects of the loss of diaphragmatic tone [50].

CONCLUSION

Ventilatory strategies allowing spontaneous breathing and mechanical ventilation with muscle paralysis during ARDS should not be opposed but rather both integrated in a strategy taking into account both the severity of ARDS and the possibility of ensuring a protective ventilation. This supposes a careful monitoring of mechanical ventilation including not only tidal volume and plateau pressure assessment but also possibly, at least in the most severe cases, the evaluation of transpulmonary pressure. At the acute phase of severe ARDS, one major goal is to limit VILI and to favor recruitment by using a short course of NMBAs. After improvement or even at the early phase of mild or moderate ARDS, preserving spontaneous breathing should probably be encouraged (Fig. 3). However, several points remain to be studied: first, when to decide to paralyze patients with moderate-to-severe ARDS? Should the decision be based on PaO_2/FiO_2 ratio? Second, is it preferable to use a nonsynchronized mode when spontaneous breathing is preserved? This strategy has been recently suggested [51] to limit tidal volume and transpulmonary pressure and be less harmful. Third, the percentage of spontaneous breathing that may be beneficial for the

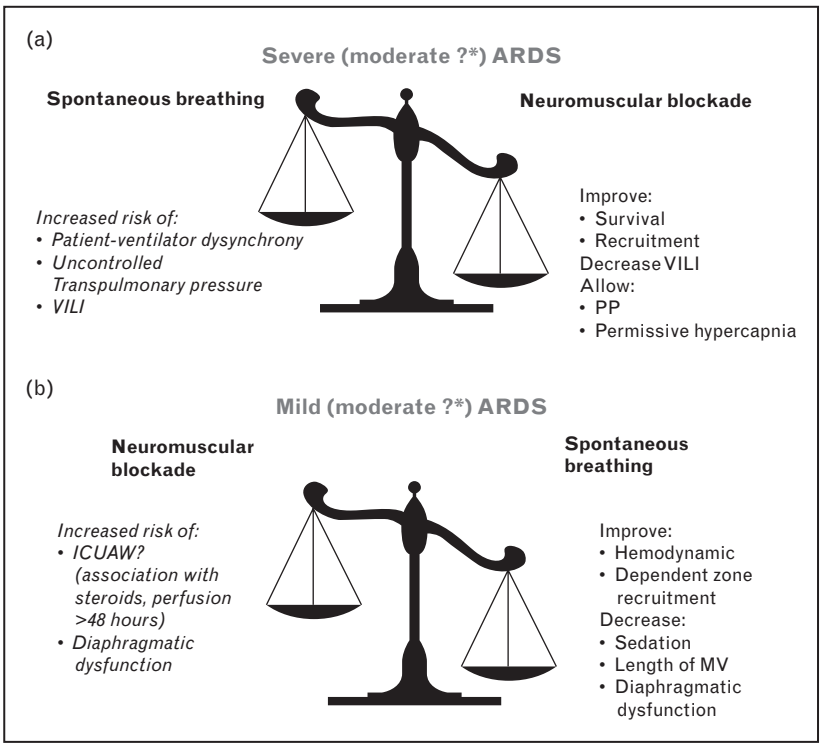

FIGURE 3. Risks and benefits associated with preserved spontaneous breathing or muscle paralysis during ARDS. (a) During severe ARDS, the balance is in favor of the use of neuromuscular blockers for a short period because of the benefits on mortality and the risks of increasing VILI associated to spontaneous breathing. (b) During mild ARDS, preserving a spontaneous breathing can be beneficial to increase the recruitment of dependent zones and limit diaphragmatic dysfunction. *For moderate ARDS, both strategies can be proposed depending on the severity. In the ACURASYS study, the benefit on the mortality was observed for patients with a PaO_2/FiO_2 ratio <120. ARDS, acute respiratory distress syndrome; VILI, ventilator-induced lung injury.

improvement of gas exchange is also under question [52].

To conclude, balancing neuromuscular blockade and preserved spontaneous ventilation during ARDS are crucial and must be a daily concern. New data are necessary especially concerning the role of spontaneous breathing in moderate and severe ARDS.

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Conflicts of interest

There are no conflicts of interest.

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Monitoring and preventing diaphragm injury

Leo M.A. Heunks, Jonne Doorduin, and Johannes G. van der Hoeven

Purpose of review
The present review summarizes developments in the field of respiratory muscle monitoring, in particular in critically ill patients.

Recent findings
Patients admitted to the ICU may develop severe respiratory muscle dysfunction in a very short time span. Among other factors, disuse and sepsis have been associated with respiratory muscle dysfunction in these patients. Because weakness is associated with adverse outcome, including prolonged mechanical ventilation and mortality, it is surprising that respiratory muscle dysfunction largely develops without being noticed by the clinician. Respiratory muscle monitoring is not standard of care in most ICUs. Improvements in technology have opened windows for monitoring the respiratory muscles in critically ill patients. Diaphragm electromyography and esophageal pressure measurement are feasible techniques for respiratory muscle monitoring, although the effect on outcome remains to be investigated.

Summary
Respiratory muscle dysfunction develops rapidly in selected critically ill patients and is associated with adverse outcome. Recent technological advances allow real-time monitoring of respiratory muscle activity in these patients. Although this field is in its infancy, from a physiological perspective, it is reasonable to assume that monitoring respiratory muscle activity improves outcome in these patients.

Keywords
electromyography, esophageal pressure, mechanical ventilation, monitoring, respiratory muscles

INTRODUCTION

Monitoring can be arbitrarily defined as a (nearly) continuous evaluation of the physiological functions of a patient in real time to guide management decisions, including therapeutic interventions, and assessment of those interventions [1]. In practice, it is not easy to distinguish between monitoring and diagnostic testing, and, in fact, they may overlap. Monitoring vital functions is the hallmark of modern intensive care. In the majority of ICU patients, vital functions are monitored using invasive and noninvasive equipment. In very few ICUs, however, respiratory muscle activity is routinely monitored. Reasons for not monitoring may include unawareness of the effects of critical illness on the respiratory muscles, underestimating the importance of respiratory muscle dysfunction on patient outcome, lack of evidence that monitoring improves outcome and technical difficulties [2]. It is our opinion that monitoring respiratory muscle activity should be considered in a selected group of ventilated ICU patients.

EFFECTS OF CRITICAL ILLNESS ON THE RESPIRATORY MUSCLES

Acute ventilatory failure is among the most common reasons for ICU admission. In these patients, the respiratory muscle pump cannot meet the demands because of excessive loading, weakness or, less common, reduced central drive. Unloading of the respiratory muscles by mechanical ventilation is lifesaving in these patients. Recent studies, however, have demonstrated that both critical illness and mechanical ventilation may have adverse effects on the respiratory muscles. In-depth discussion of the pathophysiological mechanisms is beyond the scope of the present article [3▪]. Briefly, in a landmark paper, Levine *et al.* [4] reported the

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KEY POINTS

- Respiratory muscle weakness frequently develops in critically ill patients and is associated with adverse outcome.
- Development of respiratory muscle weakness in these patients goes largely unnoticed because monitoring tools are infrequently used to assess respiratory muscle activity.
- Diaphragm electromyography and esophageal pressure measurement are feasible tools to monitor respiratory muscle activity in ventilated patients.
- Despite the strong rationale for monitoring, no studies have been conducted to evaluate the effect of respiratory muscle monitoring on outcome in critically ill patients.

development of muscle fiber atrophy and activation of proteolytic enzymes in the human diaphragm after only 18–69 h of controlled mechanical ventilation. Subsequent studies [5] showed that 5–6 days of controlled mechanical ventilation reduce pressure-generating capacity of the diaphragm by ±30%. Moreover, Demoule *et al.* [6▪▪] found that force-generating capacity of the diaphragm is already impaired at ICU admission, in particular in patients with sepsis, suggesting the development of septic respiratory muscle myopathy. This is important because several studies have shown that respiratory muscle weakness is associated with adverse outcome, including longer duration of mechanical ventilation and mortality [5,7,8].

It is therefore remarkable that ICU-acquired respiratory muscle weakness largely develops out of the clinician's sight. No monitoring tool is used to assess respiratory muscle activity. In contrast, a patient with acute circulatory failure would likely be monitored with an intra-arterial catheter, continuous electrocardiogram and possibly a pulmonary artery catheter to evaluate the response to therapeutic interventions, despite the absence of evidence that these devices improve outcome in large groups of patients. It is, however, likely that additional physiological data are helpful to the clinician if interpreted appropriately.

TECHNIQUES FOR RESPIRATORY MUSCLE MONITORING

Today, various tools are available to evaluate respiratory muscle activity and function. These techniques have been used extensively for research purposes but have not really found their way into clinical routine. In general, the ideal monitoring device allows tracking of respiratory muscle activity or function during the period a patient is admitted to the ICU. Additional features should include minimal invasiveness, easy and real-time interpretation of the data and no interference with routine clinical care or mobilization. Table 1 summarizes techniques to assess respiratory muscle function and activity. Below, we will discuss only those techniques that are feasible in clinical care.

Pressure and flow

Monitoring pressure and flow in the thoracic cage or ventilator circuit is widely used to assess respiratory muscle activity.

Ventilator waveforms

Modern ventilators continuously display pressure and flow as measured within the ventilator circuit. The pressure reported by the ventilator is the final result of a complex interaction between the patient and the ventilator. Observing ventilator pressure tracing would be an attractive monitoring technique because it is available in every patient, real time, noninvasive and at low cost. Ventilator waveform analysis, however, is not a very sensitive method for the assessment of respiratory muscle activity. In an elegant study, Colombo *et al.* [9] demonstrated that even experienced intensivists have difficulty recognizing activity of the respiratory muscles during mechanical ventilation from the airway pressure and flow signals of the ventilator. For experienced intensivists, the sensitivity for detecting asynchrony between respiratory muscle activity and ventilator support was approximately 28%, obviously much too low for a reliable monitoring tool.

Esophageal and transdiaphragmatic pressure

Esophageal pressure (Pes) provides an estimate of pleural pressure [10▪▪] and has been used for decades in physiological studies and more recently in clinical studies in ICU patients [11]. When both Pes and gastric pressure (Pga) are measured simultaneously, transdiaphragmatic pressure (Pdi) can be calculated (Pes – Pga), which is a specific measure of diaphragm activity. Pes and Pga can be measured by using air-filled or liquid-filled balloons attached to a nasogastric tube connected to a pressure transducer. Nasogastric feeding tubes with esophageal and gastric balloons are commercially available, and some ventilators (i.e. Hamilton G5) have auxiliary ports for the continuous measurement of Pes. Otherwise,

Table 1. Techniques to assess respiratory muscle function and activity

Technique	Comment	Monitoring	Diagnostic testing
Airway pressure and flow waveforms	Real time available in most ventilators, but of limited value in monitoring respiratory muscle function (see main text)	+	+
Occlusion pressure ($P_{0.1}$)	Used as an index for neural respiratory drive. Real time available in most mechanical ventilators, but not specific for respiratory muscle function	−	+
Esophageal (and gastric) pressure waveforms	Available in real time. Useful for detecting and quantifying respiratory muscle function (discussed in detail in main text). A (double) balloon catheter is required	+++	+++
Maximal (sniff) inspiratory/expiratory maneuvers	These maneuvers are useful for quantifying global respiratory muscle function. High values exclude respiratory muscle weakness, whereas low values may reflect poor technique or effort instead of respiratory muscle weakness. Cumbersome to perform in critically ill patients	−	+
Magnetic twitch airway pressure/transdiaphragmatic pressure	Nonvoluntary specific evaluation of diaphragm function using magnetic phrenic nerve stimulation, fairly invasive and technically difficult. Magnetic twitch airway pressure is without balloon catheter	−	++
Diaphragm EMG (EAdi)	Specific measure of neural respiratory drive (discussed in detail in main text). Real time available on only one ventilator, requires esophageal catheter with electrodes	+++	++
Ultrasonography (B/M-mode)	Well characterized, noninvasive and easy to perform at the bedside, but real time not available (see main text)	+	+++
Chest X-ray and fluoroscopy	Used for detection of diaphragm paralysis. Atelectasis and diaphragmatic eventration may complicate findings. Misleading in patients with bilateral paralysis. High radiation exposure with fluoroscopy	−	+/−

EAdi, electrical activity of the diaphragm; EMG, electromyography.

stand-alone pressure transducers are needed. Clinical trials [12] have demonstrated that prolonged Pes measurement is feasible in ICU patients. Practical issues related to the choice of catheter type, positioning and validation have recently been described [10▪▪].

Solid-state transducers for Pes measurement are used in gastroenterology, but because of fragility and high costs, these transducers are less suitable for monitoring purposes in the ICU. Because most ventilated patients need a nasogastric tube for feeding anyway, a dedicated feeding tube with balloons does not pose an additional patient risk.

Monitoring Pes can be used to track and even quantify activity of the inspiratory and expiratory muscles and detect patient–ventilator asynchrony (Fig. 1).

More in-depth analysis of Pes over time may provide valuable information including the work of breathing and energy expenditure [13]. Today, no software is available to calculate these sophisticated parameters in real time. In addition, interpretation of the data is rather complex and therefore not yet suitable for routine monitoring. When Pes is used to monitor respiratory muscle activity, a simple algorithm should be adopted, as discussed below. In addition, but beyond the scope of the present article, Pes can be used to calculate transpulmonary pressure, intrinsic positive end-expiratory pressure and respiratory mechanics [14].

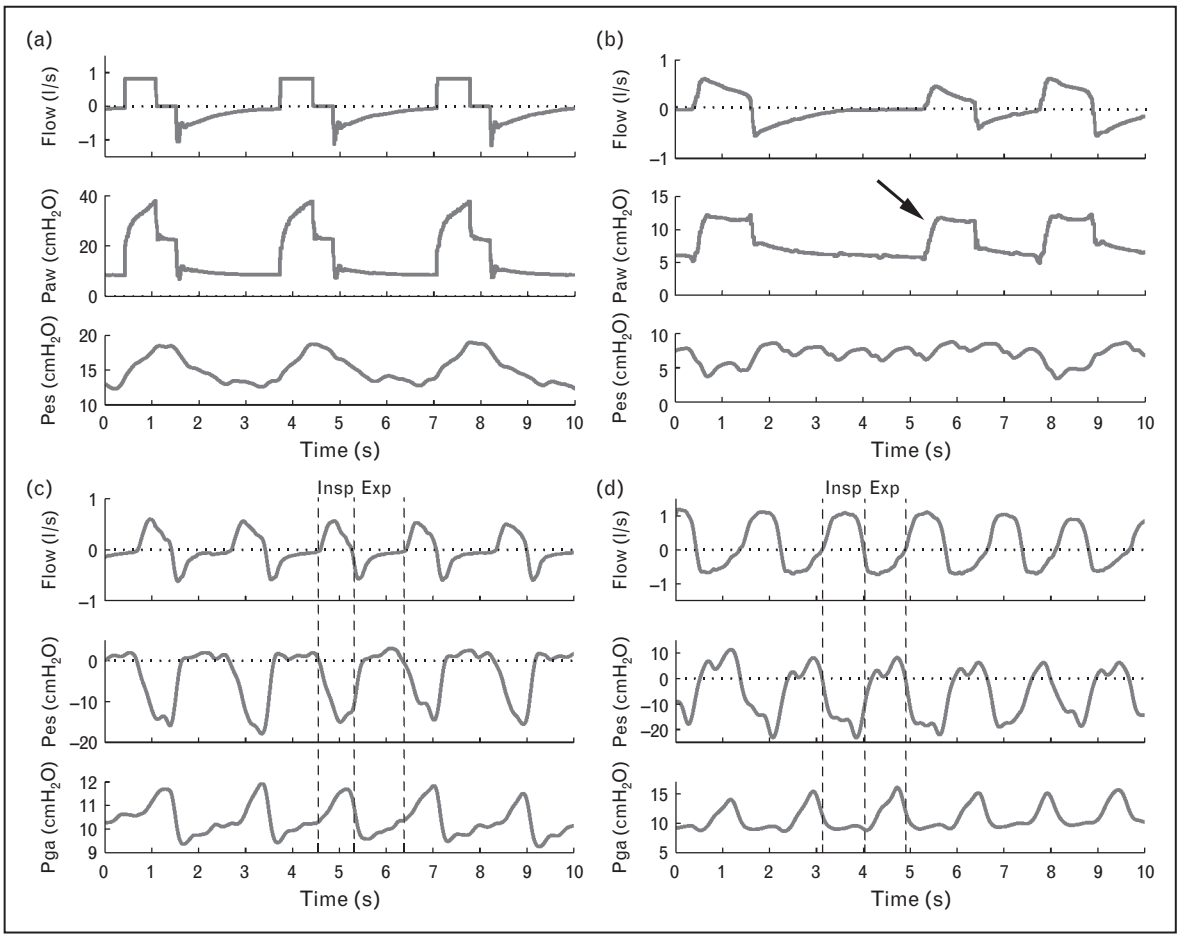

FIGURE 1. Monitoring of respiratory muscle function using esophageal pressure (Pes). Tracings of flow, airway pressure (Paw), Pes and gastric pressure (Pga) under different conditions. (a) Patient on controlled mechanical ventilation. Pes increases during mechanical inspiration. There is no decrease in Pes before mechanical inspiration, indicating absence of respiratory muscle activity. Note the perturbations in Pes resulting from cardiac activity. (b) Patient–ventilator asynchrony during pressure support ventilation; arrow indicates an autotriggered breath. Note the absence of a deflection in Pes in this breath, which is present in the other two breaths. (c) Weaning patient during a successful spontaneous breathing trial with T-piece, showing negative Pes and positive Pga swings during inspiration. (d) Weaning patient during a failed spontaneous breathing trial with T-piece. Note the increase in Pga during the expiratory phase to compensate for diaphragm weakness or high intrinsic positive end-expiratory pressure. Note that in this case, the decrease in Pes at the beginning of inspiration (e.g. the breath just after $T = 3$ s) results from both relaxation of the abdominal muscles (note decrease in Pga) and contraction of the diaphragm.

Diaphragm and accessory muscle electromyography

Electromyography (EMG) reflects the temporal and spatial summation of muscle action potentials. Characteristics of the EMG signal depend on the neural drive and muscle membrane characteristics. Diaphragm EMG can be acquired with surface or esophageal electrodes. The latter has been shown to be more reliable mostly because of reduced cross talk from other muscles. Diaphragm EMG has been used for research purposes for decades. More recently, diaphragm EMG acquired with esophageal electrodes (Edi catheter) is used clinically to control the ventilator during neurally adjusted ventilatory assist [15]. In this mode, the processed diaphragm EMG signal (EAdi) is available in real time as long as the EAdi catheter is connected to the ventilator. EAdi is suitable for monitoring of diaphragm activity under different clinical conditions (Fig. 2). A limitation is that this mode is available only on ventilators from one company (Maquet Solna, Sweden). The amplitude of the EAdi signal reflects breathing effort during mechanical ventilation in patients with acute respiratory failure [16]. In general, reducing ventilator support will increase the amplitude of the EAdi signal (Fig. 2).

The commercially available EAdi catheter serves as a feeding tube also, and therefore EAdi monitoring does not impose an additional patient risk, despite its invasive nature. Alternatively, surface EMG can be used to detect electrical activity of the diaphragm and other respiratory muscles. Practical aspects including cross talk from other muscles, low signal-to-noise ratio in certain patients (obesity, edema) and impaired patient mobilization, however, limit routine use of surface EMG in clinical practice.

Although relatively simple EAdi parameters, such as peak activity, are available today for monitoring diaphragm muscle function, more advanced EAdi monitoring holds promise for the

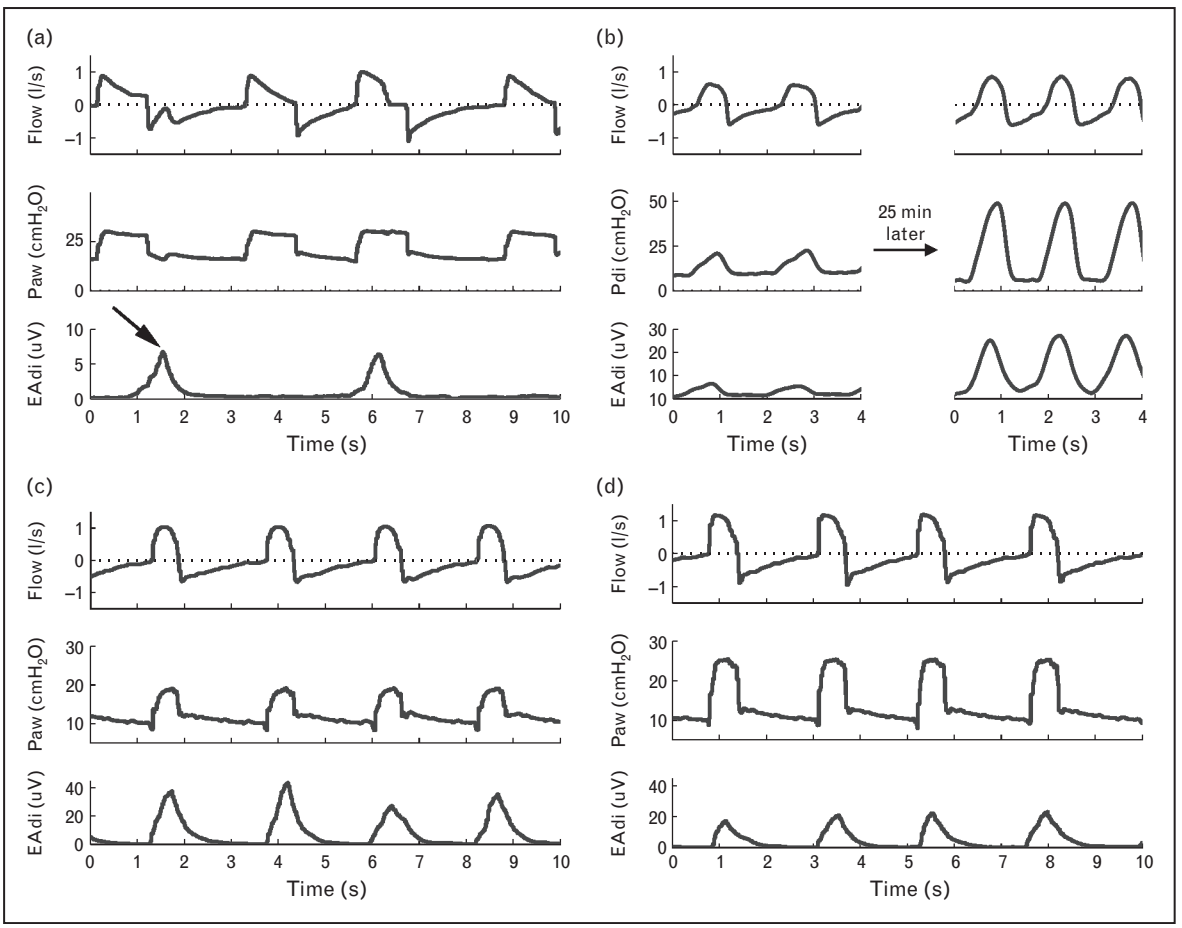

FIGURE 2. Monitoring diaphragm function using processed EMG. Tracings of flow, airway pressure (Paw), electrical activity of the diaphragm (EAdi) and transdiaphragmatic pressure (Pdi) under different conditions. (a) Patient–ventilator asynchrony during assist control ventilation. Arrow indicates a wasted effort following a machine-cycled breath. (b) Weaning patient during a failed spontaneous breathing trial with T-piece. Left panel shows tracings in first minute of the trial and right panel 25 min later. Note the increase in EAdi and Pdi. Subparts (c) and (d) represent same patient, ventilated with low (c) and high (d) pressure support. Note the decrease in EAdi resulting from a reduction in pressure support level. EMG, electromyography.

future. First, a computer algorithm has been developed that automatically quantifies asynchrony and dyssynchrony between patient and the ventilator using EAdi [17]. This tool is of potential interest, because it allows a breath-by-breath insight in patient–ventilator interaction. Second, power spectrum analysis can detect changes in the characteristics of the EMG signal that are compatible with certain type of muscle fatigue [18–20]. Third, during assisted mechanical ventilation, part of the work of breathing is delivered by the patient and part by the ventilator. Animal studies have shown that during neurally adjusted ventilatory assist, the EAdi can be used to calculate the percentage of the total work of breathing that is performed by the patient, the so-called patient–ventilator breath contribution [21]. Although these three examples are of interest, the benefits and feasibility should be tested before widespread use in patients.

Ultrasonography

Ultrasound is widely available, portable, noninvasive and easy to use, and therefore a popular tool in the ICU. It, however, is not suitable for continuous data acquisition and therefore in the gray zone between a monitoring tool and a diagnostic tool. Roughly, ultrasound is used to assess diaphragm thickness and movement. Thickness at the end of expiration can detect atrophy [22]. Measuring change in thickness between inspiration and expiration (thickening fraction) has been used to assess work of breathing [23]. Ultrasound is an excellent tool to assess diaphragm movement. Reference values are available for diaphragm displacement in healthy individuals [24]. Caution should be taken in evaluating movement of the diaphragm. The diaphragm moves caudally with active inspiration, but also passively during positive pressure ventilation. Simultaneous recording of airway pressure and diaphragm M-mode is helpful for the detection of wasted efforts. Also, trigger delay can be calculated if signals are displayed simultaneously [25]. Autotriggering may be harder to detect because, with inspiration, the diaphragm moves downward, even in the absence of muscle contraction.

CLINICAL APPLICATION OF RESPIRATORY MUSCLE MONITORING

Today, Pes (±Pga) and EAdi are probably the best tools to monitor respiratory muscle activity in ICU patients. Both techniques allow continuous and real-time tracking of respiratory muscle activity. They pose no additional risk to the patients, despite their invasive nature, assuming that the patient needs a nasogastric tube for feeding anyway. Ideally, target values should be defined for respiratory muscle activity. The values are not available, neither for EAdi nor for Pes or Pdi. Moreover, the desired level of activity may change during ICU stay, depending on the clinical condition of the patient. This will be discussed below, and we have for clarity divided ICU stay in three phases, which of course may not be applicable to all of our patients.

Early phase

In patients with severe acute respiratory distress syndrome (ARDS) or severe hypercapnic exacerbation of chronic obstructive pulmonary disease (COPD), respiratory muscle activity may enhance lung injury [26]. In these patients, neuromuscular blockers may be used to inactivate the respiratory muscles [27]. Both EAdi and Pes monitoring are suitable to confirm the absence of respiratory muscle activity (Figs. 1 and 2). Absence of EAdi during inspiration virtually excludes diaphragm activation. Also, absence of deflection of Pes at the beginning of inspiration excludes activity of the respiratory muscles. Both techniques may be considered to titrate the dose of neuromuscular blockers accomplishing complete muscle relaxation and the lowest drug dose.

Recovery phase

Once the patient recovers from acute respiratory failure, assisted modes for ventilation are usually instituted. At this time, the focus of monitoring changes to the prevention of overassist and optimal synchrony between the respiratory muscles and the ventilator.

A rationale for using assisted ventilation is to limit the development of respiratory muscle atrophy because of disuse [4], and therefore overassist should be prevented. However, inadequate unloading will result in discomfort and may have adverse effects on the respiratory muscles [28]. Unfortunately, the optimal level of diaphragm muscle activity in ventilated patients is unknown. Therefore, a more pragmatic approach is reasonable. When EAdi is used to monitor diaphragm activity, electrical activity should be clearly visible with each ventilator assist (no overassist), but the patient should be adequately unloaded based on clinical characteristics. When using Pes as a monitoring tool, at least a decrease in pressure at the initiation of inspiration should be visible with all of the assisted breaths, while the patient is adequately unloaded from the clinical perspective. Note that the interpretation of these pressure signals may be complex, in particular when the patient uses expiratory muscles. In these patients, a drop in pressure at the initiation of

inspiration may result from contraction of the inspiratory muscles, relaxation of the expiratory muscles or both. This can be differentiated by simultaneous measurement of Pga, but makes monitoring more complex (Fig. 1d).

Patient–ventilator asynchrony is very common during assisted ventilation [29]. Both EAdi and Pes monitoring are suitable to monitor patient–ventilator asynchrony [9,30]. A limitation today is that no software is commercially available that tracks and quantifies asynchronies in real time. Sinderby *et al.* [17] recently developed and tested such an algorithm. The value of this monitor in clinical care needs to be established.

Weaning phase

In this phase, patients are subjected to weaning trials when the level of assist is acutely reduced. Besides continued monitoring for asynchronies, the effect of reduced assist on respiratory muscle performance can be monitored. Estimating patient effort during a weaning trial may help to predict success of extubation. Jubran *et al.* [13] demonstrated that repeated measurement of Pes swings is helpful in predicting weaning outcome. Moreover, detailed analysis of the Pes swings versus tidal volume allows calculation of the work of breathing and insight in the case of elevated work of breathing (Fig. 1b). As mentioned, interpretation of Pes in ventilated patients, or during a weaning trial, may be complex. Patients with imminent respiratory failure will recruit expiratory muscles, which will affect Pes independent from inspiratory muscle activity. The value of Pes monitoring in the weaning phase needs to be evaluated in future studies.

More recently, EAdi has been used to monitor diaphragm activity during weaning trials. Liu and colleagues demonstrated that EAdi during a weaning trial (CPAP 5 cmH_2O) was significantly higher in weaning failure patients compared with that in weaning success patients. More sophisticated indices, such as neuroventilatory efficiency (EAdi/tidal volume) and neuromechanical efficiency (EAdi/Pdi), were lower in weaning failure patients compared with those in weaning success patients. It should be noted that these are only preliminary studies, but show promise for more intensive monitoring in the near future.

CLINICAL RELEVANCE OF RESPIRATORY MUSCLE MONITORING

The ultimate goal of monitoring is to improve outcome. Monitoring of the respiratory muscles is in its infancy, and no clinical trials have been conducted to test the effects of respiratory muscle monitoring on clinically relevant outcome parameters. Although solid evidence that respiratory muscle monitoring improves outcome (and is cost-effective) would be welcome, it is extremely challenging to demonstrate the clinical benefit of any monitoring technique [31]. Until then, a physiological and clinical judgment is important for the decision to apply any monitoring of any vital function, including the respiratory muscles. In our opinion, it is reasonable to consider monitoring in patients with the highest likelihood of developing muscle weakness in the ICU and in patients with a high likelihood of asynchrony. Supinski and Ann Callahan [8] reported that infection is a major risk factor for the development of ICU-acquired weakness. Patients with preexistent muscle dysfunction may be prone to the adverse effects of critical illness on the respiratory muscles and are more likely to exhibit asynchrony. Accordingly, in our opinion, respiratory muscle monitoring should be considered in the following patient categories: septic shock, severe ARDS and severe exacerbation of COPD.

CONCLUSION

Every clinician will use monitoring tools to track changes in physiological function and guide management decisions in patients with acute circulatory failure. It is therefore surprising that in the case of severe respiratory failure, no tools are used to monitor respiratory muscle function. It has been shown that critical illness and ICU treatment may adversely affect the respiratory muscles. Therefore, clinicians should more often consider the use of monitoring tools to evaluate respiratory muscle activity. Both diaphragm EMG and Pes can be used for monitoring. Scientists and industry should work together to improve techniques for monitoring the respiratory muscles in our patients.

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