Lung- and Diaphragm-Protective Ventilation

Ewan C. Goligher[1,2,3], Martin Dres[4,5], Bhakti K. Patel[6], Sarina K. Sahetya[7], Jeremy R. Beitler[8], Irene Telias[1,2,9], Takeshi Yoshida[10], Katerina Vaporidi[11], Domenico Luca Grieco[12,13], Tom Schepens[14], Giacomo Grasselli[15,16], Savino Spadaro[17], Jose Dianti[1,2,18], Marcelo Amato[19], Giacomo Bellani[20], Alexandre Demoule[4,5], Eddy Fan[1,2,3,21], Niall D. Ferguson[1,2,3,21,22], Dimitrios Georgopoulos[11], Claude Guérin[23], Robinder G. Khemani[24,25], Franco Laghi[26,27], Alain Mercat[28], Francesco Mojoli[29], Coen A. C. Ottenheijm[30], Samir Jaber[31], Leo Heunks[32*], Jordi Mancebo[33*], Tommaso Mauri[13,14], Antonio Pesenti[13,14], and Laurent Brochard[1,9*]; for the Pleural Pressure Working Group, Acute Respiratory Failure Section of the European Society of Intensive Care Medicine

[1]Interdepartmental Division of Critical Care Medicine, [21]Institute for Health Policy, Management, and Evaluation, and [22]Department of Physiology, University of Toronto, Toronto, Ontario, Canada; [2]Division of Respirology, Department of Medicine, University Health Network, Toronto, Ontario, Canada; [3]Toronto General Hospital Research Institute, Toronto, Ontario, Canada; [4]Service de Pneumologie, Médecine Intensive et Réanimation (Département R3S), Assistance Publique–Hopitaux de Paris, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Paris, France; [5]Unite Mixte de Recherche-Sorbonne 1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Institut National de la Sante et de la Recherche Medicale, Sorbonne Université, Paris, France; [6]Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, Chicago, Illinois; [7]Division of Pulmonary and Critical Care Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland; [8]Division of Pulmonary, Allergy, and Critical Care Medicine, Center for Acute Respiratory Failure, College of Physicians and Surgeons, Columbia University, New York, New York; [9]Keenan Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; [10]Department of Anesthesiology and Intensive Care Medicine, Graduate School of Medicine, Osaka University, Suita, Japan; [11]Department of Intensive Care Medicine, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Greece; [12]Department of Anesthesiology and Intensive Care Medicine, Catholic University of the Sacred Heart, Rome, Italy; [13]Dipartimento di Medicina d'Urgenza e di Terapia Intensiva e Anestesia, Fondazione Policlinico Universitario, A. Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy; [14]Department of Critical Care Medicine, Antwerp University Hospital, Antwerp, Belgium; [15]Department of Anesthesiology, Intensive

Abstract

Mechanical ventilation can cause acute diaphragm atrophy and injury, and this is associated with poor clinical outcomes. Although the importance and impact of lung-protective ventilation is widely appreciated and well established, the concept of diaphragm-protective ventilation has recently emerged as a potential complementary therapeutic strategy. This Perspective, developed from discussions at a meeting of international experts convened by PLUG (the Pleural Pressure Working Group) of the European Society of Intensive Care Medicine, outlines a conceptual framework for an integrated lung- and diaphragm-protective approach to mechanical ventilation on the basis of growing evidence about mechanisms of injury. We propose targets for diaphragm protection based on respiratory effort and patient–ventilator synchrony. The potential for conflict between diaphragm protection and lung protection under certain conditions is discussed; we emphasize that when conflicts arise, lung protection must be prioritized over diaphragm protection. Monitoring respiratory effort is essential to concomitantly protect both the diaphragm and the lung during mechanical ventilation. To implement lung- and diaphragm-protective ventilation, new approaches to monitoring, to setting the ventilator, and to titrating sedation will be required. Adjunctive interventions, including extracorporeal life support techniques, phrenic nerve stimulation, and clinical decision-support systems, may also play an important role in selected patients in the future. Evaluating the clinical impact of this new paradigm will be challenging, owing to the complexity of the intervention. The concept of lung- and diaphragm-protective ventilation presents a new opportunity to potentially improve clinical outcomes for critically ill patients.

Keywords: mechanical ventilation; artificial respiration; lung injury; myotrauma

(Received in original form March 16, 2020; accepted in final form June 8, 2020)

*L.H. and J.M. are Associate Editors and L.B. is Deputy Editor of *AJRCCM*. Their participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

Supported by the Smart Meeting Anesthesia Resuscitation Intensive Care (SMART) Congress (Pleural Pressure Working Group Meeting, Milan, Italy) and by Early Career Investigator Award AR7-162822 from the Canadian Institutes of Health Research (E.C.G.).

Correspondence and requests for reprints should be addressed to Ewan C. Goligher, M.D., Ph.D., Toronto General Hospital, 585 University Avenue, Peter Munk Building, Room 11-192, Toronto, ON, M5G 2N2 Canada. E-mail: ewan.goligher@utoronto.ca.

Am J Respir Crit Care Med Vol 202, Iss 7, pp 950–961, Oct 1, 2020

Originally Published in Press as DOI: 10.1164/rccm.202003-0655CP on June 9, 2020
Internet address: www.atsjournals.org

Care and Emergency, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [16]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [17]Department Morphology, Surgery and Experimental Medicine, ICU, St. Anne's Archbishop Hospital, University of Ferrara, Ferrara, Italy; [18]Intensive Care Unit, Department of Medicine, Italian Hospital of Buenos Aires, Buenos Aires, Argentina; [19]Laboratório de Pneumologia, Laboratório de Investicação Médica 9, Disciplina de Pneumologia, Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; [20]Department of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy; [23]Médecine Intensive-Réanimation, Hopital Edouard Herriot Lyon, Faculté de Médecine Lyon-Est, Université de Lyon, Institut National de la Santé et de la Recherche Médicale 955 Créteil, Lyon, France; [24]Department of Anesthesiology and Critical Care, Children's Hospital Los Angeles, Los Angeles, California; [25]Department of Pediatrics, University of Southern California, Los Angeles, California; [26]Division of Pulmonary and Critical Care Medicine, Stritch School of Medicine, Loyola University, Maywood, Illinois; [27]Division of Pulmonary and Critical Care Medicine, Hines Veterans Affairs Hospital, Hines, Illinois; [28]Département de Médecine Intensive-Réanimation et Médecine Hyperbare, Centre Hospitalier d'Angers, Angers, France; [29]Department of Anesthesia and Intensive Care, Scientific Hospitalization and Care Institute, San Matteo Polyclinic Foundation, University of Pavia, Pavia, Italy; [30]Department of Physiology and [32]Department of Intensive Care, Vrije University Location, Amsterdam University Medical Center, Amsterdam, the Netherlands; [31]Anesthesiology and Intensive Care, Anesthesia and Critical Care Department B, Saint Eloi Teaching Hospital, PhyMedExp, Montpellier University Hospital Center, University of Montpellier, Joint Research Unit 9214, National Institute of Health and Medical Research U1046, National Scientific Research Center, Montpellier, France; and [33]Servei de Medicina Intensiva Hospital de Sant Pau, Barcelona, Spain

ORCID ID: 0000-0002-0990-6701 (E.C.G.); 0000-0002-1735-1400 (G.G.); 0000-0003-2016-7003 (J.D.); 0000-0002-3089-205X (G.B.); 0000-0003-4700-6672 (C.G.).

The possibility that mechanical ventilation could cause iatrogenic injury to the lung was first appreciated in the 18th century (1); protection of the lung from injury has become a recognized priority. Iatrogenic injury to the diaphragm from mechanical ventilation was first described in the 1980s (2), but there is as yet no established approach to protecting the diaphragm during mechanical ventilation. In this Perspective, we discuss how the current approach to mechanical ventilation might be revised to prevent ventilator-induced diaphragm atrophy, injury, and consequent weakness while maintaining lung-protective ventilation, an approach we refer to as lung- and diaphragm-protective ventilation. The mechanisms and clinical consequences of these issues are, in general, reasonably well-characterized, but it remains uncertain whether diaphragm atrophy and injury can be effectively prevented and whether this substantially improves clinical outcomes. This report proposes specific potential targets for diaphragm-protective ventilation and outlines a range of potential strategies for an integrated lung- and diaphragm-protective approach to mechanical ventilation to be tested in future clinical trials.

Methodology for Quantifying Agreement among Experts

This Perspective represents the views of a group of international experts in the field on how the complex—and sometimes competing—goals of protecting the lung and the diaphragm during mechanical ventilation might be integrated at the bedside. This was discussed at a 2-day conference sponsored by PLUG (the Pleural Pressure Working Group; https://www.plugwgroup.org), a working group of the European Society of Intensive Care Medicine, held in Milan, Italy, in May 2019. Panelists were selected from the membership of PLUG on the basis of prior publications and ongoing active research programs in relevant aspects of acute-respiratory-failure mechanical ventilation, lung injury, and diaphragm injury. After the initial meeting, the conference writing committee (E.C.G., M.D., B.K.P., S.K.S., J.R.B., I.T., T.Y., K.V., D.L.G., T.S., G.G., S.S., and L.B.) drafted and refined a series of statements intended to communicate areas of consensus and uncertainty. Input from the entire panel ($n = 31$) was obtained before finalizing the statements. All conference panelists then communicated their degree of agreement or disagreement for each statement through an online survey using the Research and Development/University of California, Los Angeles (RAND/UCLA) appropriateness rating method (rating scale from 1 to 9, 1 representing strong disagreement, 9 representing strong agreement). Support for each statement was defined according to the RAND/UCLA method as a score ≥ 7; opposition to each statement was defined as a score ≤ 3. The proportion of panelists expressing support for each statement was used to characterize the degree of expert agreement. The results are presented in Table 1. This Perspective outlines the key issues under discussion and the basis for agreement or disagreement among experts on various points.

Mechanisms of Injury

Mechanical ventilation can cause lung and diaphragm injury by a variety of putative interacting pathways (Figure 1). Several terms are employed to refer to these mechanisms and their consequences (Table 2). Lung injury is primarily mediated by mechanical stress and strain caused by the ventilator (ventilator-induced lung injury) or the respiratory muscles (patient self-inflicted lung injury). These mechanisms are discussed in detail elsewhere (3, 4).

Diaphragm atrophy and injury ("myotrauma") may occur via several mechanisms (5). The most well-established mechanism is overassistance myotrauma: excessive unloading of the diaphragm by ventilatory assistance abolishes or reduces inspiratory effort to very low amounts, resulting in disuse atrophy by a variety of cellular pathways (6). This phenomenon is well-documented in the clinical setting (7–9). Other likely mechanisms are supported primarily by experimental evidence as well as some recent clinical data (9, 10). Excessive diaphragm loading due to insufficient ventilator assistance can induce acute muscle inflammation and injury (underassistance myotrauma) (11, 12), particularly in the context of sepsis and systemic inflammation, which increase sarcolemmal fragility (13). The diaphragm is also subjected to potentially injurious eccentric (lengthening) loads when it contracts during the expiratory phase. Such eccentric contractions may occur during expiratory braking (14), nonsynchronized bilevel ventilation (airway pressure–release ventilation) (15), and specific forms of

Table 1. Proposed Principles for Lung- and Diaphragm-Protective Ventilation

Topic	Statement	Distribution of Ratings (1–9)* [*Median (IQR)*]	Range of Ratings (*Min–Max*)	Number of Panelists Expressing Support (*N = 31*) [*n (%)*]
Monitoring	Respiratory effort should be assessed routinely during mechanical ventilation as part of the risk assessment for lung and diaphragm injury.	9 (8–9)	4–9	28 (90)
	Sedation depth is not a reliable surrogate for respiratory drive. When suppressing respiratory drive is a therapeutic objective, drive should be monitored directly.	8 (7–9)	5–9	28 (90)
	Clinicians are encouraged to become skilled in the use of techniques for assessing respiratory effort, including esophageal manometry, diaphragm electrical activity, diaphragm ultrasound, and airway occlusion pressure.	9 (7–9)	3–9	25 (81)
	Automated techniques should be developed to monitor effort and synchrony.	8 (7–9)	5–9	25 (81)
	The exhaled V_T should be monitored routinely during mechanical ventilation to ensure V_T delivered is as intended. Delivered V_T may exceed preset V_T in volume-controlled modes.	8 (7–9)	3–9	25 (81)
	Esophageal manometry is the reference technique for real-time monitoring of both respiratory effort and global lung stress during mechanical ventilation.	8 (7–9)	5–9	24 (77)
Diaphragm protection	There is no single universally applicable one-size-fits-all setting for optimal mechanical ventilation. Ventilator settings should be tailored to the individual patient's characteristics on the basis of the clinician's assessment of the most pressing risks to the patient in any given situation, integrating the best available clinical and experimental evidence with a sound mechanistic evaluation of the patient's condition.	9 (9–9)	7–9	31 (100)
	Avoiding excessively low respiratory effort during mechanical ventilation is likely to prevent disuse diaphragm atrophy (overassistance myotrauma).	8 (7–9)	4–9	28 (90)
	The mere presence of patient-triggered breaths during mechanical ventilation does not guarantee sufficient diaphragm activity to prevent diaphragm atrophy.	8 (7–9)	2–9	25 (81)
	Patient–ventilator dyssynchrony may injure the lung and the diaphragm, depending on the type of dyssynchrony and the magnitude and timing of the resulting lung stress and diaphragm loading.	8 (7–9)	3–9	24 (77)
	Avoiding excessively high respiratory effort might prevent load-induced diaphragm injury (underassistance myotrauma).	7 (6–8)	1–9	21 (68)
	Proportional assistance modes have the potential to promote a lung- and diaphragm-protective ventilator strategy.	7 (5–8)	2–9	16 (52)

(Continued)

Table 1. (*Continued*)

Topic	Statement	Distribution of Ratings (1–9)* [*Median (IQR)*]	Range of Ratings (*Min–Max*)	Number of Panelists Expressing Support (*N = 31*) [*n (%)*]
Lung protection versus diaphragm protection	Given currently available evidence, protecting the lung should be prioritized over protecting the diaphragm when necessary, although every effort should be made to protect both organs simultaneously.	8 (7–9)	5–9	28 (90)
	Even when V_T is acceptably low, respiratory efforts may induce regional lung overdistension.	8 (7–9)	3–9	27 (87)
	When considering the application of a higher PEEP strategy, the integrated physiological response to an increase in PEEP (oxygenation, respiratory mechanics, and hemodynamics) should be carefully assessed to determine evidence of lung recruitability.	8 (7–9)	5–9	27 (87)
	Targeting a V_T of 6 ml/kg of predicted body weight is not universally protective against VILI. In some patients with severe ARDS, lower V_T may be necessary to prevent clinically significant lung injury.	8 (8–9)	5–9	26 (84)
	The dominant mechanism of ventilation-induced lung injury is excessive lung stress and strain during tidal ventilation (volutrauma), either from excessive ventilator-delivered volume and pressure or from excessive patient respiratory effort.	8 (7–9)	3–9	26 (84)
	Avoiding excessively high respiratory effort can prevent patient self-inflicted lung injury.	8 (7–9)	5–9	25 (81)
	In patients without ARDS, risk from higher V_T may be offset by benefits of preserving spontaneous breathing, less analgosedation, and early mobilization.	7 (7–8)	3–9	24 (77)
	Higher PEEP during spontaneous breathing may mitigate the risk of patient self-inflicted lung injury, provided that it recruits collapsed lung and attenuates inspiratory effort. However, these potential benefits must be balanced with the risk of VILI from hyperinflation, particularly in the setting of breath-stacking dyssynchrony.	7 (7–8)	3–9	23 (74)
Sedation and diaphragm protection	Sedation should be administered to alleviate patient–ventilator dyssynchrony only when the dyssynchrony results from excessive drive to breathe and after attempting to optimize ventilator settings, correcting metabolic derangements, and treating pain and anxiety.	8 (7.5–9)	5–9	28 (90)
	Propofol is more effective than opioid analgesics to reduce the amplitude of respiratory effort.	6 (5–8)	2–9	15 (48)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; IQR = interquartile range; Max = maximum; Min = minimum; PEEP = positive end-expiratory pressure; VILI = ventilator-induced lung injury.
*Each panelist rated each statement on a scale from 1 to 9, in which 1–3 indicates opposition, 4–6 indicates uncertainty, and 7–9 indicates support.

patient–ventilator dyssynchrony, such as reverse triggering, premature cycling, and ineffective efforts (16–18). In laboratory animals, eccentric loading is highly injurious (eccentric myotrauma) (19, 20). Finally, preliminary experimental observations suggest that maintaining the diaphragm at a relatively shorter length by the application of high positive end-expiratory pressure (PEEP) may cause acute sarcomere dropout ("longitudinal atrophy") (21). This in turn could impair the length–tension relationship of the muscle when PEEP is reduced during weaning (expiratory myotrauma).

Targets for Diaphragm Protection

On the basis of our evolving understanding of the mechanisms of diaphragm myotrauma, several diaphragm-protective ventilation targets can be proposed (Table 3).

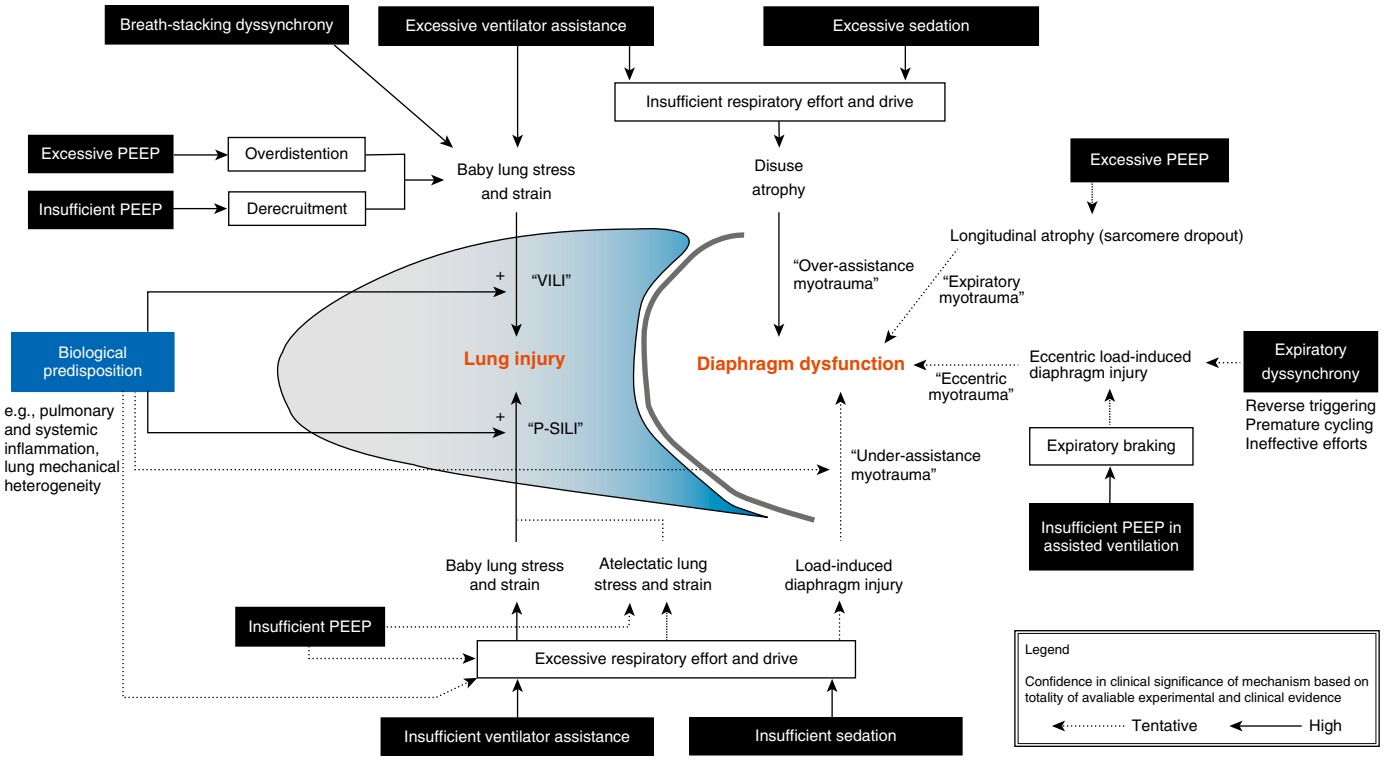

Figure 1. Mechanisms of injury to the lung and diaphragm during mechanical ventilation. Ventilator settings and sedation exert complex and interacting effects on the mechanisms of lung and diaphragm injury. Reducing ventilator-applied pressures may fail to protect the lung because of a resultant increase in respiratory effort when respiratory drive is intact. Suppressing respiratory drive to protect the lung by increasing sedation can lead to disuse diaphragm atrophy. Conversely, maintaining respiratory drive to avoid diaphragm atrophy may result in patient self-inflicted lung injury and load-induced diaphragm injury if respiratory effort is excessive. Thus, a careful balancing act between excessive and insufficient ventilation and sedation may be required to protect both the lung and the diaphragm concomitantly. Similarly, positive end-expiratory pressure (PEEP) can exert complex and competing effects on the mechanisms of injury, and all of these effects may need to be considered when setting PEEP in individual patients. The risk of injury to the lung and diaphragm is likely "dose dependent"—the injury risk depends on the magnitude of stress and strain in the baby lung and the magnitude of respiratory efforts generated during assisted breaths and asynchronies. P-SILI = patient self-inflicted lung injury; VILI = ventilator-induced lung injury.

Target 1: Maintain Modest Inspiratory Effort (Probably Important)

An inspiratory effort level consistent with resting quiet breathing is likely to avoid both diaphragm atrophy and load-induced injury. Several lines of evidence support this target. The very small efforts required to trigger the ventilator are not sufficient to prevent diaphragm atrophy (9, 22). Modest diaphragm contractions (e.g., during resting quiet breathing or intermittent diaphragm stimulation by phrenic nerve pacing) appear to be sufficient to attenuate diaphragm atrophy and restore diaphragm muscle bulk (23–25). On the other hand, avoiding excessive respiratory effort might prevent potential load-induced diaphragm injury (26).

The exact upper limit for acceptable respiratory effort is uncertain, although effort should probably be kept low enough to keep tension-time index values below 0.12–0.15 (tension-time index is a dimensionless index quantifying the magnitude and duration of load on the respiratory muscles relative to force-generating capacity and duty cycle) (27). This would imply esophageal pressure swings below 10–15 cm H_2O (assuming the patient's maximal inspiratory pressure is 30–50 cm H_2O and inspiratory time is approximately 50% of expiratory time). Patients successfully liberated from ventilation generally exhibit a relatively low inspiratory effort (esophageal pressure swings of 4–10 cm H_2O) during a T-piece trial (28) and after extubation (29), suggesting that this level of effort is sustainable and noninjurious. By contrast, patients who fail spontaneous breathing trials usually exhibit much larger inspiratory efforts, suggesting that these levels are not sustainable (30). It is important to appreciate that the upper limit of effort associated with injury likely varies with diaphragm force-generating capacity, the presence of muscular inflammation, and muscle perfusion.

A diaphragm thickening fraction in the intermediate range of 15–30% (similar to that of healthy subjects breathing at rest) was associated with the shortest duration of mechanical ventilation in comparison with lower or higher thickening fraction values (10). Moreover, this association was mediated by changes in diaphragm thickness over time, corroborating (but not confirming) a causal pathway linking mechanical ventilation to insufficient or excessive respiratory effort, diaphragm atrophy and injury, and poor clinical outcomes (5). Although these clinical observations do not confirm a causal relationship, these data in combination with the large body of experimental evidence showing the deleterious effects

Table 2. Definitions of Terminology

Term	Definition
Atelectrauma	Shear stress injury in the small airways and alveoli as a consequence of repetitive opening and closing of atelectatic lung regions during tidal ventilation
Barotrauma	Gross morphologic injury to the lung (manifesting as pneumothorax, pneumomediastinum, subcutaneous emphysema, etc.) as a consequence of excessive inspiratory pressures
Biotrauma	Systemic inflammation generated by pulmonary inflammation from volutrauma and atelectrauma; initiates inflammation and injury in other organs (brain, kidneys, etc.), leading to multiorgan failure
Critical illness-associated diaphragm weakness	A loss of diaphragmatic force–generating capacity developing during critical illness, regardless of the cause and timing
Diaphragm-protective ventilation	Theoretical ventilation strategy designed to avert or mitigate the various forms of myotrauma to preserve diaphragm function and accelerate liberation from mechanical ventilation
Dyssynchrony (also termed, asynchrony)	Dissociation between the patient's neural respiratory rhythm and the mechanical ventilator's respiratory timing, occurring at the onset of neural inspiration or the onset of neural expiration (or both); often also referred to as "asynchrony." Dyssynchrony is also sometimes used to refer to a mismatch between patient ventilatory demands and delivered flow and pressure (i.e., "flow starvation" dyssynchrony)
Eccentric myotrauma	Deleterious changes in the diaphragm resulting from diaphragm contractile loads applied under eccentric (lengthening) conditions; possible contributor to VIDD
Lung strain	The deformation experienced by the lungs during inflation relative to the lung's resting volume (under zero stress); strain is approximated by the ratio of V_T to FRC
Lung stress	The mechanical force applied to the lung to inflate the lung and generate V_T (under zero-flow conditions, the stress on the whole lung is quantified by transpulmonary pressure)
Lung-protective ventilation	Ventilation strategy aiming to reduce the mechanical stress placed on the injured lung to prevent further lung injury and accelerate recovery
Overassistance myotrauma	Deleterious changes in the diaphragm (including disuse atrophy, myofibrillar proteolysis, and autophagy) resulting from suppression of respiratory effort due to excess pressure and flow delivered by the ventilator; common cause of VIDD
Patient self-inflicted lung injury (P-SILI)	Adverse structural and functional changes in the lung arising from excessive global or regional lung stress and strain as a consequence of respiratory muscle action
Underassistance myotrauma	Deleterious changes in the diaphragm (sarcolemmal disruption, inflammatory infiltrates, sarcomeric disarray) resulting from inadequate unloading of respiratory muscles due to insufficient pressure and flow delivered by the ventilator; probable contributor to VIDD
Ventilator-induced diaphragm dysfunction (VIDD)	A loss of diaphragmatic force–generating capacity specifically attributable to exposure to mechanical ventilation
Ventilator-induced lung injury (VILI)	Adverse structural and functional changes in the lung due to pulmonary injury and inflammation from excessive global or regional lung stress and strain during mechanical ventilation
Volutrauma	Increased alveolar-capillary membrane permeability and alveolar inflammation as a consequence of excessive cyclic alveolar stress and strain

of absent or excessive respiratory effort, suggest that modest inspiratory effort is probably the optimal target for diaphragm protection during mechanical ventilation. The panel reached strong consensus that maintaining a modest amount of respiratory effort would prevent diaphragm atrophy; there was moderate consensus that avoiding excess respiratory effort would prevent load-induced injury.

Target 2: Maintain Synchronous Expiratory Cycling (Possibly Important)

Eccentric contractions may occur with several forms of dyssynchrony (e.g., premature cycling, reverse triggering, ineffective efforts during expiration). When detected, these dyssynchronies can often be avoided by ensuring that the ventilator cycles into expiration at the same time as the patient's inspiratory effort ends. Close inspection of the airway pressure and flow waveforms can suggest whether patient inspiratory effort ceases before or after the ventilator cycles into the expiratory phase (18). Detecting expiratory cycling dyssynchrony can be facilitated by directly monitoring respiratory effort with esophageal pressure or diaphragm electrical activity (EAdi) signals. It is

Table 3. Potential Therapeutic Targets for Diaphragm Protection

Goal	Potential Therapeutic Target*
Prevent overassistance myotrauma	Any 1 of: Pmus $\geq$ 3 to 5 cm H_2O ΔPdi $\geq$ 3 to 5 cm H_2O ΔPes ≤ -3 to -2 cm H_2O $P_{0.1} > 1$ to 1.5 cm H_2O TFdi $\geq$ 15% EAdi $\geq$ target value selected on the basis of Pocc-EAdi index and above targets
Prevent underassistance myotrauma	Any 1 of: Pmus $\leq$ 10 to 15 cm H_2O ΔPdi $\leq$ 10 to 15 cm H_2O ΔPes ≥ -12 to -8 cm H_2O Pocc ≥ -20 to -15 cm H_2O $P_{0.1} < 3.5$ to 5 cm H_2O TFdi $\leq$ 30% to 40% EAdi $\leq$ limit value selected on the basis of Pocc-EAdi index and above targets
Prevent eccentric myotrauma	Avoid ineffective triggering and reverse triggering Avoid premature cycling Minimize expiratory braking

Definition of abbreviations: ΔPdi = inspiratory swing in transdiaphragmatic pressure; ΔPes = inspiratory swing in esophageal pressure; EAdi = diaphragm electrical activity; $P_{0.1}$ = airway occlusion pressure; Pmus = the pressure generated by the respiratory muscles to inflate both the lung and the chest wall; Pocc = expiratory occlusion pressure; TFdi = diaphragm thickening fraction.
*The specification of ranges for the target values reflects uncertainty on the part of the authors about the safe upper limit for inspiratory effort; values specified represent suggested targets based on available physiological and clinical evidence.

possible that the amplitude of the effort is an important determinant for this risk of injury, but the threshold determining this risk is currently unknown. There was moderate consensus for this target among panelists.

Target 3: Avoid Excessive Expiratory Braking (Possibly Important)

Continued contractile activation of the diaphragm into the expiratory phase is referred to as "expiratory braking" or "postinspiratory effort." Although expiratory braking may be present at low amounts in healthy subjects, increased expiratory braking to maintain end-expiratory lung volume in the presence of significant atelectasis and increased lung elastance may result in a potentially substantial eccentric load to the diaphragm that can be attenuated by the application of sufficient PEEP (14). As yet, methods for detecting and monitoring expiratory braking at the bedside and determining whether postinspiratory loading is excessive are not well defined. This target remains largely theoretical; the magnitude of expiratory braking in patients with acute hypoxemic respiratory failure is unknown.

Protecting the Lung while Protecting the Diaphragm

In some patients, maintaining patient respiratory effort to protect the diaphragm can make it challenging to maintain lung protection. The challenge of managing spontaneous breathing in patients with moderate or severe acute respiratory distress syndrome (ARDS) is widely appreciated (31). Indeed, patient respiratory drive and effort may be very high in ARDS because of markedly increased dead space, metabolic acidosis, stimulation of pulmonary parenchymal receptors, brainstem inflammation, and cortical stimuli (32).

In this context, monitoring respiratory effort is important for maintaining lung protection. During spontaneous breathing, airway pressures displayed by the ventilator may significantly underestimate the true magnitude of cyclic lung stress (33); the pressure applied to the lung by the respiratory muscles must be considered (Figure 2). The risk of injurious regional cyclic stress and strain depends on the magnitude of respiratory effort (34). Therefore, lung protection during spontaneous breathing requires close attention primarily to respiratory effort as well as to V_T and global lung-distending (transpulmonary) pressure.

Respiratory drive may be excessive and may give rise to high lung stress with or without high V_T. Even when V_T is adequately controlled (e.g., using volume-controlled ventilation), regional lung stress may be excessive in the presence of high respiratory effort (35). In addition, breath-stacking dyssynchrony from high respiratory drive also markedly increases lung stress (36). Adequate lung protection therefore sometimes requires suppression of respiratory muscle effort. In many patients, respiratory drive and effort can be controlled to some extent with sedation; the adequacy of the effect of sedation on drive and effort should be closely monitored. In some patients, sedation alone cannot adequately reduce effort, and neuromuscular blockade should be considered. In this case, priority should be given to lung protection. Routine neuromuscular blockade in all patients with moderate/severe ARDS cannot be recommended, given the results of a recent clinical trial (37). Other strategies for controlling respiratory drive, such as adjusting ventilatory settings, may prove effective in this context (see below).

The risk of lung injury as a consequence of maintaining patient respiratory effort likely varies considerably between patients. Biological and pulmonary mechanical heterogeneity entail that the stress and strain required to generate lung injury varies (38); patients with ARDS with pulmonary inflammation and significantly reduced FRC and lung compliance (and hence elevated driving pressures) are probably at highest risk (39). Conversely, maintaining spontaneous respiratory effort can sometimes lower cyclic lung stress and improve homogeneity of ventilation by recruiting atelectasis (40).

There was strong consensus among panelists that when conflicts arise, lung protection must take priority over diaphragm protection because of the established mortality benefit associated with lung-protective ventilation.

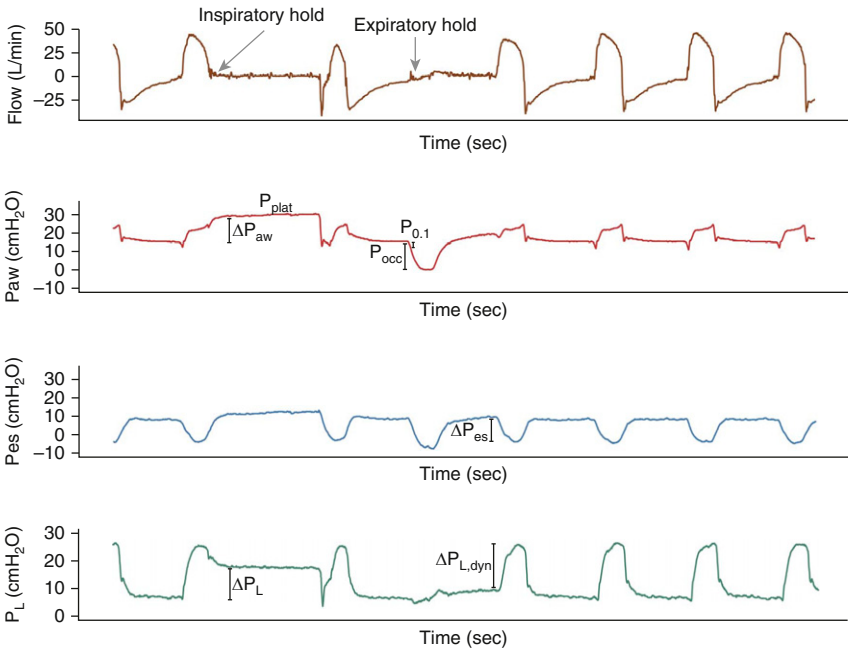

Figure 2. Monitoring strategies for lung- and diaphragm-protective ventilation. These tracings illustrate the utility of semiinvasive monitoring by esophageal manometry and noninvasive monitoring strategies using respiratory maneuvers on the ventilator. Esophageal pressure (Pes) swings (ΔPes) reflect patient respiratory effort. Transpulmonary pressure (P_L) swings ($\Delta P_{L,dyn}$; the difference between airway pressure [Paw] and Pes) directly assess dynamic lung stress. Driving Paw (ΔPaw) and transpulmonary driving pressure (ΔP_L) can be quantified even when patients make spontaneous respiratory efforts by applying an end-inspiratory occlusion to measuring plateau pressure (Pplat). Pplat may be higher than peak Paw when patients make spontaneous respiratory efforts (as shown) because the lung is inflated by respiratory muscle effort as well as positive pressure from the ventilator. The Paw swing during Pocc can be used to predict both $\Delta P_{L,dyn}$ and respiratory effort (53). Airway occlusion pressure ($P_{0.1}$) can be used to detect insufficient or excessive respiratory drive. Pocc = expiratory occlusion pressure.

How Can Lung- and Diaphragm-Protective Ventilation Be Implemented?

A conceptual approach to lung- and diaphragm-protective ventilation is presented in Figure 3.

Monitoring

On the basis of the mechanisms and targets presented above, the foundation of a diaphragm-protective ventilation strategy is close monitoring of patient respiratory effort. There was strong agreement among panelists that respiratory effort should be assessed routinely during mechanical ventilation (Table 1).

Respiratory rate is insensitive to changes in respiratory load and effort and should not be relied on to monitor respiratory effort (41). Esophageal manometry provides direct measurements of patient respiratory effort and driving transpulmonary pressure (cyclic lung stress) and can directly guide ventilatory settings (Figure 2).

Three simple measurements can also be made on any ventilator without additional monitoring equipment to evaluate effort and drive and the resulting lung stress. First, respiratory drive can be quantified noninvasively using the airway occlusion pressure (42). Second, the magnitude of the airway pressure swing during a single-breath expiratory occlusion can detect excess respiratory muscle effort and excess dynamic lung stress (33). Third, an end-inspiratory occlusion can be used to assess plateau pressure and driving pressure in pressure support, while carefully assessing for expiratory muscle contraction (43), or in proportional modes (44, 45). These various measurements are represented in Figure 2.

EAdi provides continuous monitoring of diaphragmatic activation. Because of marked interindividual variability in the signal, no specific target value for EAdi can be established (although values below 10 μV are nearly always abnormally low) (46). However, respiratory muscle pressure can be estimated from EAdi by measuring the ratio between airway pressure deflection during a single-breath expiratory occlusion (Pocc) and EAdi (47). Ultrasound has also proven to be an informative technique for the assessment of respiratory muscle activity and function (48). One particular mode of ventilation, proportional assist ventilation, allows respiratory muscle effort to be estimated noninvasively (49).

The choice of technique may vary according to local expertise and preference. Importantly, all of these techniques are now available in the clinical setting and are accessible to clinicians.

Mechanical Ventilator Settings

With respect to diaphragm protection, how a mode of ventilation is applied and monitored probably matters more than the selection of mode *per se*. In theory, proportional assistance modes should facilitate diaphragm-protective targets: asynchronies are reduced through improved patient–ventilator interaction, and overassistance is prevented because there is no guaranteed minimum V_T (50). Neurally adjusted ventilatory assist was associated with improved diaphragm function in one study (51), but, in a clinical trial, no significant improvement in clinical outcome was observed, possibly because the mode was applied after diaphragm myotrauma had already developed (52).

In a lung- and diaphragm-protective approach, inspiratory pressure, flow, and cycling would be set while bearing in mind *1*) the resulting patient inspiratory effort amount, *2*) the dynamic lung stress and, *3*) the adequacy of gas exchange. For clinicians, understanding the determinants of the patient's effort when setting the ventilator is essential. Inspiratory effort responds to changes in peak flow rate and pattern in volume-controlled ventilation (53) and to changes in inspiratory pressure and cycling in pressure-targeted modes. Increases in FI_{O_2} over relatively moderate ranges of Pa_{O_2} can reduce respiratory drive in some patients without reaching hyperoxemia (54). Patient–ventilator dyssynchrony can often be resolved by adjustments to inspiratory trigger setting, present inspiratory time, or cycling criteria.

Applying higher PEEP may reduce the risk of both lung and diaphragm injury in some patients: by recruiting atelectatic dependent lung regions to reduce

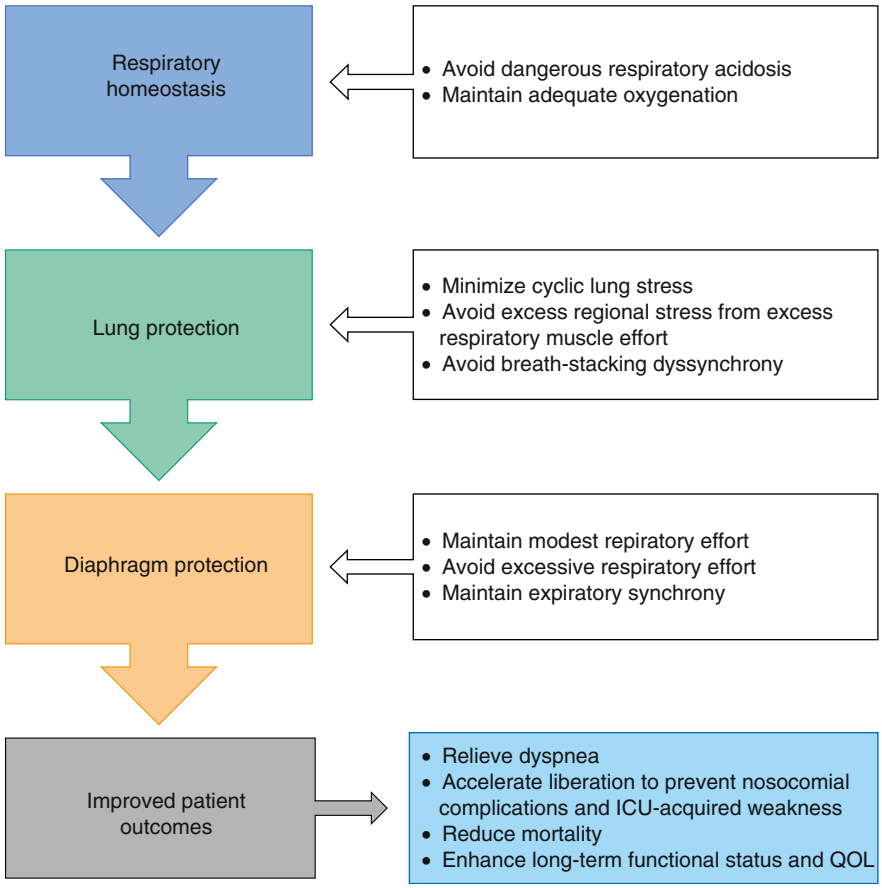

Figure 3. Conceptual framework for lung- and diaphragm-protective ventilation. Major goals (homeostasis, lung protection, and diaphragm protection) are achieved by delivering mechanical ventilation according to proposed therapeutic targets. The goal of the strategy is not primarily to restore normal physiology but to minimize injury and optimize patient outcomes. QOL = quality of life.

global and regional cyclic lung stress, attenuating inspiratory effort (55), and alleviating expiratory braking (14), PEEP may have important protective effects. However, patients vary markedly in their response to PEEP, and this setting requires careful individualized management.

Sedation

The effect of sedation on respiratory drive requires specific monitoring: sedation depth is poorly correlated with diaphragm activity (33) and cannot not be used as a surrogate for respiratory drive. If excessive respiratory effort persists despite adequate analgesia or ventilator titration, sedatives can be useful to attenuate potentially injurious drive and effort.

The effects of different analgesics and sedatives on breathing pattern and drive should be familiar to clinicians: opioids primarily depress respiratory rate, increasing the risk of apnea under mechanical ventilation, and propofol primarily decreases respiratory effort rather than respiratory rate (56). Benzodiazepines have an effect on respiratory pattern that is similar to propofol, but they confer a higher delirium risk and prolong mechanical ventilation (57, 58). Dexmedetomidine is a selective α_2-agonist that provides sedation, anxiolysis, and analgesia without reducing respiratory drive (59).

Although sedation is commonly used to treat dyssynchrony, the panel agreed that sedation administration to alleviate dyssynchrony is only appropriate when poor patient–ventilator interaction results from excessive respiratory drive and only after other sources of respiratory drive have been addressed (e.g., peak flow and pressure settings, PEEP, metabolic acidosis, pain, etc.). Reverse triggering may be alleviated by lightening sedation to obtain a spontaneous respiratory rhythm (16).

Adjunctive Therapies

Additional interventions may be required to control respiratory drive in more severely ill patients. Extracorporeal CO_2 removal can reduce respiratory drive and effort, potentially facilitating lung-protective ventilation during spontaneous breathing (60). Partial neuromuscular blockade can attenuate excess respiratory effort unresponsive to ventilator titration or sedation without entirely abolishing diaphragm activity (61), but the feasibility of maintaining partial neuromuscular blockade for prolonged periods is unknown. If sedation cannot be lifted to obtain spontaneous diaphragm activity, phrenic nerve stimulation permits controlled activation of the diaphragm when respiratory drive is minimal or absent (23).

Testing the Hypothesis

The effect of diaphragm-protective ventilation on patient-important outcomes requires evaluation, and this presents several substantial challenges. First, the effect of interventions to mitigate diaphragm atrophy and injury on outcomes may vary considerably between patients depending on the patient's risk of poor outcome, the individual risk of diaphragm atrophy or injury, the competing risk of lung injury, and the presence or absence of other competing mechanisms driving outcomes. For example, recent data suggest that diaphragm atrophy primarily occurs in patients with higher baseline diaphragm muscle mass (62). This problem of patient heterogeneity is a well-documented and widely discussed challenge for clinical trials in the ICU (63). Trials can account for this heterogeneity—provided it is adequately recognized—through patient selection and prespecified subgroup analyses. Bayesian adaptive clinical trial designs may be well suited to efficiently identifying patient subpopulations most likely to benefit from or be harmed by a diaphragm-protective ventilation strategy.

Second, diaphragm-protective ventilation is a paradigmatic example of a "complex intervention": it involves multiple interacting components (monitoring, ventilation, sedation, adjuncts), requires behavioral change on the part of multiple stakeholders (physicians, respiratory therapists, nurses, manufacturers), and entails extensive tailoring to the individual

patient. Any trial of such an intervention is at high risk of failing to detect an important clinical benefit because of difficulties in implementation rather than a true lack of benefit. The complex behavioral changes associated with the intervention may "contaminate" usual care, decreasing the apparent treatment effect. Standardization may be difficult, and the intervention design may need to adapt to local ICU practices. These challenges are not new in the ICU; careful process evaluation and use of alternative trial designs such as cluster randomization or stepped wedge designs may help to surmount these challenges (64).

Third, it may well be time-consuming and challenging for busy clinicians to optimize ventilation and sedation along three dimensions (gas exchange, lung stress, and respiratory effort). Clinical decision-support systems might facilitate lung- and diaphragm-protective ventilation by providing real-time guidance for ventilator settings and sedation on the basis of rule- or model-based algorithms that integrate various clinical data points (65). These models can be tuned in individual patients using machine-learning and artificial intelligence techniques (66). Such systems have already been designed to optimize mechanical ventilation; preliminary testing in the clinical setting offers promising results (67, 68), and randomized trials are ongoing (69).

Conclusions

This paper outlines a lung- and diaphragm-protective approach to mechanical ventilation focused on optimizing respiratory effort and synchrony to prevent diaphragm atrophy and injury while maintaining lung protection. Mounting evidence supports the contention that protecting the diaphragm (together with the lung) during mechanical ventilation might improve patient outcomes. In several instances, monitoring respiratory effort or drive can be beneficial for both lung protection and diaphragm protection. This approach presents new challenges for the bedside clinician, and a broad program of research is required to explore the feasibility, safety, and benefit of this complex intervention, particularly in patients with a substantial competing risk of ventilation-induced lung injury. It remains to be shown whether lung- and diaphragm-protective ventilation can be effectively implemented in the clinical setting and whether this approach improves outcomes for critically ill patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Prof. Arthur Slutsky, University of Toronto, for providing valuable comments and critique of a draft of this manuscript. Prof. Brian Kavanagh, University of Toronto (deceased), was involved in the conception of this project.

References

1. Slutsky AS. History of mechanical ventilation: from Vesalius to ventilator-induced lung injury. *Am J Respir Crit Care Med* 2015; 191:1106–1115.
2. Knisely AS, Leal SM, Singer DB. Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. *J Pediatr* 1988;113:1074–1077.
3. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369:2126–2136.
4. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017;195:438–442.
5. Goligher EC, Brochard LJ, Reid WD, Fan E, Saarela O, Slutsky AS, *et al*. Diaphragmatic myotrauma: a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure. *Lancet Respir Med* 2019;7:90–98.
6. Petrof BJ. Diaphragm weakness in the critically ill: basic mechanisms reveal therapeutic opportunities. *Chest* 2018;154:1395–1403.
7. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, *et al*. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327–1335.
8. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, *et al*. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med* 2011; 183:364–371.
9. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, *et al*. Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. *Am J Respir Crit Care Med* 2015;192:1080–1088.
10. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, *et al*. Mechanical ventilation–induced diaphragm atrophy strongly impacts clinical outcomes. *Am J Respir Crit Care Med* 2018;197:204–213.
11. Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164:1734–1739.
12. Jiang TX, Reid WD, Belcastro A, Road JD. Load dependence of secondary diaphragm inflammation and injury after acute inspiratory loading. *Am J Respir Crit Care Med* 1998;157:230–236.
13. Ebihara S, Hussain SN, Danialou G, Cho WK, Gottfried SB, Petrof BJ. Mechanical ventilation protects against diaphragm injury in sepsis: interaction of oxidative and mechanical stresses. *Am J Respir Crit Care Med* 2002;165:221–228.
14. Pellegrini M, Hedenstierna G, Roneus A, Segelsjö M, Larsson A, Perchiazzi G. The diaphragm acts as a brake during expiration to prevent lung collapse. *Am J Respir Crit Care Med* 2017;195:1608–1616.
15. Rittayamai N, Beloncle F, Goligher EC, Chen L, Mancebo J, Richard JM, *et al*. Effect of inspiratory synchronization during pressure-controlled ventilation on lung distension and inspiratory effort. *Ann Intensive Care* 2017;7:100.
16. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, *et al*. Mechanical ventilation–induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest* 2013;143:927–938.
17. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, *et al*. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015;41:633–641.
18. Mojoli F, Iotti GA, Arnal JM, Braschi A. Is the ventilator switching from inspiration to expiration at the right time? Look at waveforms! *Intensive Care Med* 2016;42:914–915.
19. Gea J, Zhu E, Gáldiz JB, Comtois N, Salazkin I, Fiz JA, *et al*. Functional consequences of eccentric contractions of the diaphragm [in Spanish]. *Arch Bronconeumol* 2009;45:68–74.
20. Barton ER, Wang BJ, Brisson BK, Sweeney HL. Diaphragm displays early and progressive functional deficits in dysferlin-deficient mice. *Muscle Nerve* 2010;42:22–29.
21. Lindqvist J, van den Berg M, van der Pijl R, Hooijman PE, Beishuizen A, Elshof J, *et al*. Positive end-expiratory pressure ventilation induces longitudinal atrophy in diaphragm fibers. *Am J Respir Crit Care Med* 2018;198:472–485.
22. Hudson MB, Smuder AJ, Nelson WB, Bruells CS, Levine S, Powers SK. Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. *Crit Care Med* 2012;40:1254–1260.
23. Reynolds SC, Meyyappan R, Thakkar V, Tran BD, Nolette MA, Sadarangani G, *et al*. Mitigation of ventilator-induced diaphragm atrophy by transvenous phrenic nerve stimulation. *Am J Respir Crit Care Med* 2017;195:339–348.

24. Masmoudi H, Coirault C, Demoule A, Mayaux J, Beuvin M, Romero N, *et al*. Can phrenic stimulation protect the diaphragm from mechanical ventilation-induced damage? *Eur Respir J* 2013;42: 280–283.
25. Ayas NT, McCool FD, Gore R, Lieberman SL, Brown R. Prevention of human diaphragm atrophy with short periods of electrical stimulation. *Am J Respir Crit Care Med* 1999;159:2018–2020.
26. Laghi F, D'Alfonso N, Tobin MJ. Pattern of recovery from diaphragmatic fatigue over 24 hours. *J Appl Physiol (1985)* 1995;79: 539–546.
27. Zocchi L, Fitting JW, Majani U, Fracchia C, Rampulla C, Grassino A. Effect of pressure and timing of contraction on human rib cage muscle fatigue. *Am Rev Respir Dis* 1993;147:857–864.
28. Jubran A, Grant BJ, Laghi F, Parthasarathy S, Tobin MJ. Weaning prediction: esophageal pressure monitoring complements readiness testing. *Am J Respir Crit Care Med* 2005;171:1252–1259.
29. Khemani RG, Sekayan T, Hotz J, Flink RC, Rafferty GF, Iyer N, *et al*. Risk factors for pediatric extubation failure: the importance of respiratory muscle strength. *Crit Care Med* 2017;45: e798–e805.
30. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997;155:906–915.
31. Yoshida T, Fujino Y, Amato MB, Kavanagh BP. Fifty years of research in ARDS: spontaneous breathing during mechanical ventilation. Risks, mechanisms, and management. *Am J Respir Crit Care Med* 2017;195:985–992.
32. Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D. Respiratory drive in critically ill patients: pathophysiology and clinical implications. *Am J Respir Crit Care Med* 2020;201:20–32.
33. Bertoni M, Telias I, Urner M, Long M, Del Sorbo L, Fan E, *et al*. A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. *Crit Care* 2019;23:346.
34. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, *et al*. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:1420–1427.
35. Yoshida T, Nakahashi S, Nakamura MAM, Koyama Y, Roldan R, Torsani V, *et al*. Volume-controlled ventilation does not prevent injurious inflation during spontaneous effort. *Am J Respir Crit Care Med* 2017;196:590–601.
36. Beitler JR, Sands SA, Loring SH, Owens RL, Malhotra A, Spragg RG, *et al*. Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: the BREATHE criteria. *Intensive Care Med* 2016;42:1427–1436.
37. Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, *et al*.; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019;380:1997–2008.
38. Frank JA, Gutierrez JA, Jones KD, Allen L, Dobbs L, Matthay MA. Low tidal volume reduces epithelial and endothelial injury in acid-injured rat lungs. *Am J Respir Crit Care Med* 2002;165: 242–249.
39. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–755.
40. Mauri T, Bellani G, Confalonieri A, Tagliabue P, Turella M, Coppadoro A, *et al*. Topographic distribution of tidal ventilation in acute respiratory distress syndrome: effects of positive end-expiratory pressure and pressure support. *Crit Care Med* 2013;41: 1664–1673.
41. Akoumianaki E, Vaporidi K, Georgopoulos D. The injurious effects of elevated or nonelevated respiratory rate during mechanical ventilation. *Am J Respir Crit Care Med* 2019;199:149–157.
42. Telias I, Junhasavasdikul D, Rittayamai N, Piquilloud L, Chen L, Ferguson ND, *et al*. Airway occlusion pressure as an estimate of respiratory drive and inspiratory effort during assisted ventilation. *Am J Respir Crit Care Med* 2020;201:1086–1098.
43. Bellani G, Grassi A, Sosio S, Gatti S, Kavanagh BP, Pesenti A, *et al*. Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome. *Anesthesiology* 2019;131:594–604.
44. Vaporidi K, Psarologakis C, Proklou A, Pediaditis E, Akoumianaki E, Koutsiana E, *et al*. Driving pressure during proportional assist ventilation: an observational study. *Ann Intensive Care* 2019;9:1.
45. Grasselli G, Castagna L, Abbruzzese C, Corcione N, Colombo SM, Guzzardella A, *et al*. Assessment of airway driving pressure and respiratory system mechanics during neurally adjusted ventilatory assist. *Am J Respir Crit Care Med* 2019;200: 785–788.
46. Piquilloud L, Beloncle F, Richard JM, Mancebo J, Mercat A, Brochard L. Information conveyed by electrical diaphragmatic activity during unstressed, stressed and assisted spontaneous breathing: a physiological study. *Ann Intensive Care* 2019;9:89.
47. Bellani G, Mauri T, Coppadoro A, Grasselli G, Patroniti N, Spadaro S, *et al*. Estimation of patient's inspiratory effort from the electrical activity of the diaphragm. *Crit Care Med* 2013;41: 1483–1491.
48. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, *et al*. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. *Intensive Care Med* 2020;46:594–605.
49. Carteaux G, Mancebo J, Mercat A, Dellamonica J, Richard JC, Aguirre-Bermeo H, *et al*. Bedside adjustment of proportional assist ventilation to target a predefined range of respiratory effort. *Crit Care Med* 2013;41:2125–2132.
50. Vaporidi K. NAVA and PAV+ for lung and diaphragm protection. *Curr Opin Crit Care* 2020;26:41–46.
51. Di Mussi R, Spadaro S, Mirabella L, Volta CA, Serio G, Staffieri F, *et al*. Impact of prolonged assisted ventilation on diaphragmatic efficiency: NAVA versus PSV. *Crit Care* 2016;20:1.
52. Demoule A, Clavel M, Rolland-Debord C, Perbet S, Terzi N, Kouatchet A, *et al*. Neurally adjusted ventilatory assist as an alternative to pressure support ventilation in adults: a French multicentre randomized trial. *Intensive Care Med* 2016;42:1723–1732.
53. Ward ME, Corbeil C, Gibbons W, Newman S, Macklem PT. Optimization of respiratory muscle relaxation during mechanical ventilation. *Anesthesiology* 1988;69:29–35.
54. Pesenti A, Rossi N, Calori A, Foti G, Rossi GP. Effects of short-term oxygenation changes on acute lung injury patients undergoing pressure support ventilation. *Chest* 1993;103:1185–1189.
55. Morais CCA, Koyama Y, Yoshida T, Plens GM, Gomes S, Lima CAS, *et al*. High positive end-expiratory pressure renders spontaneous effort noninjurious. *Am J Respir Crit Care Med* 2018;197: 1285–1296.
56. Vaschetto R, Cammarota G, Colombo D, Longhini F, Grossi F, Giovanniello A, *et al*. Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Crit Care Med* 2014;42: 74–82.
57. Forster A, Gardaz JP, Suter PM, Gemperle M. Respiratory depression by midazolam and diazepam. *Anesthesiology* 1980;53:494–497.
58. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, *et al*. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006;34:1326–1332.
59. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992;77:1125–1133.
60. Crotti S, Bottino N, Ruggeri GM, Spinelli E, Tubiolo D, Lissoni A, *et al*. Spontaneous breathing during extracorporeal membrane oxygenation in acute respiratory failure. *Anesthesiology* 2017;126: 678–687.
61. Doorduin J, Nollet JL, Roesthuis LH, van Hees HW, Brochard LJ, Sinderby CA, *et al*. Partial neuromuscular blockade during partial ventilatory support in sedated patients with high tidal volumes. *Am J Respir Crit Care Med* 2017;195:1033–1042.

62. Sklar MC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, *et al*. Association of low baseline diaphragm muscle mass with prolonged mechanical ventilation and mortality among critically ill adults. *JAMA Netw Open* 2020;3:e1921520.
63. Iwashyna TJ, Burke JF, Sussman JB, Prescott HC, Hayward RA, Angus DC. Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med* 2015;192:1045–1051.
64. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, *et al*. Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000;321:694–696.
65. Zhang B, Ratano D, Brochard LJ, Georgopoulos D, Duffin J, Long M, *et al*. A physiology-based mathematical model for the selection of appropriate ventilator controls for lung and diaphragm protection. *J Clin Monit Comput* [online ahead of print] 1 Feb 2020; DOI: 10.1007/s10877-020-00479-x.
66. Shortliffe EH, Sepúlveda MJ. Clinical decision support in the era of artificial intelligence. *JAMA* 2018;320:2199–2200.
67. Sward KA, Newth CJL, Khemani RG, Page K, Meert KL, Carcillo JA, *et al*.; Eunice Kennedy Shriver National Institute for Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN). Potential acceptability of a pediatric ventilator management computer protocol. *Pediatr Crit Care Med* 2017;18: 1027–1034.
68. Spadaro S, Karbing DS, Dalla Corte F, Mauri T, Moro F, Gioia A, *et al*. An open-loop, physiological model based decision support system can reduce pressure support while acting to preserve respiratory muscle function. *J Crit Care* 2018;48:407–413.
69. Khemani RG, Hotz JC, Klein MJ, Kwok J, Park C, Lane C, *et al*. A phase II randomized controlled trial for lung and diaphragm protective ventilation (Real-time Effort Driven VENTilator management). *Contemp Clin Trials* 2020;88:105893.