




REVIEW

Patients with uninjured lungs may also benefit from lung-protective ventilator settings [version 1; referees: 2 approved]

Roger Alencar^{1*}, Vittorio D'Angelo^{2*}, Rachel Carmona^{2*}, Marcus J Schultz³⁻⁵, Ary Serpa Neto  ^{1,3}

¹Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil

²School of Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil

³Department of Intensive Care, Academic Medical Center, Amsterdam, Netherlands

⁴Laboratory of Experimental Intensive Care and Anesthesiology (L-E-I-C-A), Academic Medical Center, Amsterdam, Netherlands

⁵Mahidol Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand

* Equal contributors

v1 First published: 22 Nov 2017, 6(F1000 Faculty Rev):2040 (doi: [10.12688/f1000research.12225.1](https://doi.org/10.12688/f1000research.12225.1))



Latest published: 22 Nov 2017, 6(F1000 Faculty Rev):2040 (doi: [10.12688/f1000research.12225.1](https://doi.org/10.12688/f1000research.12225.1))

Abstract

Although mechanical ventilation is a life-saving strategy in critically ill patients and an indispensable tool in patients under general anesthesia for surgery, it also acts as a double-edged sword. Indeed, ventilation is increasingly recognized as a potentially dangerous intrusion that has the potential to harm lungs, in a condition known as ‘ventilator-induced lung injury’ (VILI). So-called ‘lung-protective’ ventilator settings aiming at prevention of VILI have been shown to improve outcomes in patients with acute respiratory distress syndrome (ARDS), and, over the last few years, there has been increasing interest in possible benefit of lung-protective ventilation in patients under ventilation for reasons other than ARDS. Patients without ARDS could benefit from tidal volume reduction during mechanical ventilation. However, it is uncertain whether higher levels of positive end-expiratory pressure could benefit these patients as well. Finally, recent evidence suggests that patients without ARDS should receive low driving pressures during ventilation.

Open Peer Review

Referee Status: 

	Invited Referees	
	1	2
version 1 published 22 Nov 2017		

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1 **Francisco Javier Belda**, Hospital Clínico Universitario, University of Valencia, Spain

2 **Luciano Gattinoni**, University of Göttingen, Germany

Discuss this article

Comments (0)

Corresponding author: Ary Serpa Neto (ary.neto2@einstein.br)

Author roles: **Alencar R:** Writing – Original Draft Preparation, Writing – Review & Editing; **D'Angelo V:** Writing – Original Draft Preparation, Writing – Review & Editing; **Carmona R:** Writing – Original Draft Preparation, Writing – Review & Editing; **Schultz MJ:** Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Serpa Neto A:** Conceptualization, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Alencar R, D'Angelo V, Carmona R *et al.* **Patients with uninjured lungs may also benefit from lung-protective ventilator settings [version 1; referees: 2 approved]** *F1000Research* 2017, 6(F1000 Faculty Rev):2040 (doi: [10.12688/f1000research.12225.1](https://doi.org/10.12688/f1000research.12225.1))

Copyright: © 2017 Alencar R *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: The author(s) declared that no grants were involved in supporting this work.

First published: 22 Nov 2017, 6(F1000 Faculty Rev):2040 (doi: [10.12688/f1000research.12225.1](https://doi.org/10.12688/f1000research.12225.1))

Introduction

Although mechanical ventilation is a life-saving strategy in critically ill patients and an indispensable tool in patients under general anesthesia for surgery, it also acts as a double-edged sword¹. Indeed, ventilation is increasingly recognized as a potentially dangerous intrusion that has the potential to harm lungs. Though frequently referred to as ‘ventilator-induced lung injury’ (VILI), this side effect may better be called ‘ventilation-induced lung injury’ as it is not the ventilator per se that causes harm but the way the ventilator is set¹⁻³.

So-called ‘lung-protective’ ventilator settings aiming at prevention of VILI have been shown to improve outcomes in patients with acute respiratory distress syndrome (ARDS)⁴. Nevertheless, ARDS remains a condition with high mortality and morbidity⁵, and in light of this there has been a paradigm shift from treating to preventing ARDS. Over the last few years, there has been increasing interest in a possible benefit of lung-protective ventilation in patients under ventilation for reasons other than ARDS, such as critically ill patients¹ and surgery patients^{2,3}.

After a brief summary of the existing evidence of benefit of lung-protective ventilation in patients with ARDS, this review discusses the potential role of these ventilation strategies in patients with uninjured lungs. We cite the literature according to the available ‘best’ evidence, where results of meta-analysis using individual patient data are seen as better evidence than conventional meta-analysis, followed by randomized controlled trials (RCTs) and finally observational studies. Where possible, we also cite the literature on ongoing RCTs.

Lung-protective ventilation in patients with acute respiratory distress syndrome

In patients with ARDS, outcomes could be improved by adjusting three more or less simple ventilator settings: tidal volume, positive end-expiratory pressure (PEEP), and driving pressure⁶. One way to protect the lungs of patients with ARDS is to prevent ‘volutrauma’ by using low tidal volumes⁷. Pivotal RCTs performed almost 20 year ago showed that ventilation with low tidal volumes improved the survival of patients with ARDS^{4,8}, a finding that was convincingly confirmed in one meta-analysis⁷. The results of more recent investigations even suggest that a further reduction in tidal volume size, supported by the use of extracorporeal removal of carbon dioxide, could improve the survival of patients with severe forms of ARDS even further^{9,10}.

Another way to protect the lungs of patients with ARDS is to prevent ‘atelectrauma’ by using higher PEEP¹¹. Three pivotal RCTs showed no benefit of higher PEEP¹²⁻¹⁴, but the results of one meta-analysis using individual patient data from these three RCTs compellingly suggested that patients with moderate or severe ARDS die less frequently when higher PEEP is used¹⁵. Of note, the same meta-analysis also showed an association between use of high PEEP and a worse outcome in patients with mild ARDS. Nevertheless, a recent RCT showed that, in patients with moderate to severe ARDS, the use of lung recruitment maneuvers and titrated higher levels of PEEP were associated with higher mortality, increased risk of barotrauma, and longer duration

of ventilation compared with lower levels of PEEP¹⁶. Indeed, these findings do not support the routine use of lung recruitment maneuver and higher PEEP in these patients.

Finally, the lungs of patients with ARDS could be protected against so-called ‘energytrauma’ by using low driving pressures¹⁷. Indeed, one large meta-analysis using individual patient data from nine RCTs strongly suggests that patients with ARDS have a better outcome when driving pressures remain low¹⁸ and these findings were confirmed in a recent study in a large population of patients with ARDS¹⁹. Of note, none of the original RCTs used in this meta-analysis tested directly whether a low driving pressure reduced mortality; we thus need to be careful in interpreting the findings. Nevertheless, the results of yet another meta-analysis using individual patient data also suggest that outcomes improve when driving pressures are low, this time in ARDS patients receiving extracorporeal membrane oxygenation because of refractory hypoxemia²⁰.

Evidence of benefit of lung-protective ventilation strategies in patients with uninjured lungs

For a long time, prevention of VILI was considered relevant only in patients with ARDS and only when mechanical ventilation was applied for a substantial period of time (that is, for days)^{21,22}. Recent investigations, however, show that lung injury can develop in all types of patients, thus also in patients with uninjured lungs, and also when ventilation is applied for short periods of time (that is, for hours)^{23,24}. Several types of patients thus could benefit from lung-protective ventilation strategies²⁵.

Tidal volume

Until recently, ventilation strategies with high tidal volumes were preferred over strategies with low tidal volumes in patients with uninjured lungs, as ventilation with high tidal volumes could prevent or at least reduce the amount of atelectasis²⁶, thereby preventing the need for high oxygen fractions. However, two individual patient data meta-analyses strongly suggest that intensive care unit (ICU) patients with uninjured lungs could also benefit from ventilation with low tidal volumes^{27,28}. Paradoxically, in contrast with the results of these two meta-analyses, the recent ‘Practice of Ventilation in critically ill patients without ARDS’ (PRoVENT) study, an international prospective study of ventilation practices in ICU patients without ARDS, found no association between tidal volume size and diverse outcomes²⁹. However, in the PRoVENT study, tidal volumes were noticeably lower in comparison with almost all preceding investigations, and also the range of tidal volumes was much smaller²⁹. Secondly, results from a meta-analysis using individual patient data need to be looked at with caution, as such analyses sometimes are little more than so-called ‘per protocol’ analyses in which patients who actually received the intervention of interest are compared with patients who did not receive that intervention³⁰. Intentional as well as unintentional reasons could be responsible for not receiving the intervention of interest, in this case low tidal volumes, and some of these reasons, recognized or unrecognized, could have an association with the outcome³⁰. For example, in ICU patients with severe acidosis, who often need ventilation with high tidal volumes to have an acceptable arterial pH, (reasons for) severe acidosis could

have a much stronger association with outcome than tidal volume size. One recent study in France showed that implementation of the use of low tidal volumes is not so simple, and many factors such as the use of spontaneous modes of ventilation, higher metabolic demands, and lower sedation levels could be responsible for it^{30,31}. Nevertheless, a recent study in the US suggested that tidal volume reduction after out-of-hospital cardiac arrest could be associated with favorable neurocognitive outcome, more ventilator-free days, and even more shock-free days³². Altogether, these data suggest that, in fact, low tidal volume is physiological tidal volume, as suggested by animal studies³³.

Whether ICU patients with uninjured lungs truly benefit from a reduction in tidal volume size thus remains uncertain. Two ongoing RCTs could answer the question of whether tidal volumes should be kept low in ICU patients with uninjured lungs. The ‘Protective Ventilation in patients without ARDS at start of ventilation’ (PREVENT) trial³⁴ is a Dutch national multicenter RCT that compares ventilation with a tidal volume between 4 and 6 mL/kg predicted body weight (PBW) with ventilation with a tidal volume between 8 and 10 mL/kg PBW in 952 invasively ventilated ICU patients without ARDS. The ‘Preventive Strategies in Acute Respiratory Distress Syndrome’ (EPALI) trial³⁵ is a Spanish national multicenter RCT comparing ventilation with a tidal volume between 4 and 6 mL/kg PBW with ventilation with a tidal volume between 8 and 10 mL/kg PBW in 400 invasively ventilated ICU patients at risk for ARDS. The results of these two RCTs are expected soon.

Patients receiving ‘emergency’ ventilation could also benefit from use of low tidal volumes. A ventilation protocol including use of low tidal volumes in an emergency department (ED) was feasible and associated with improved outcomes not only in emergency patients with ARDS³⁶ but also in emergency patients with uninjured lungs³⁷. Yet implementation of lung-protective ventilation with low tidal volumes remains poor in these patients³⁸.

One individual patient data meta-analysis suggests that ventilation with low tidal volumes results in less postoperative pulmonary complications in surgery patients under general anesthesia³⁹. This, however, was not found in the recent ‘Local Assessment of Ventilatory Management During General Anesthesia for Surgery and effects on Postoperative Pulmonary Complications’ (LAS VEGAS) study; this international prospective study on ventilation practices in the operating room found no association between tidal volume size and diverse outcomes⁴⁰. However, in the LAS VEGAS study, as in the above-cited PROVENT study, tidal volumes were also lower than almost all preceding studies, and the range of tidal volumes was remarkably small⁴⁰.

Positive end-expiratory pressure

Ventilation with low tidal volumes could induce alveolar instability, resulting in cyclic opening and closing of alveoli^{1,11}, frequently referred to as ‘tidal recruitment’. PEEP may keep these lung regions open at the end of expiration and thus prevent tidal recruitment. However, use of PEEP comes ‘at a price’, as PEEP could also cause regional overdistension, in particular of the non-dependent lung parts, and has negative effects on cardiac

performance⁴¹. The balance between benefit and harm of PEEP may very well differ between patients receiving mechanical ventilation for various reasons other than ARDS^{39,42,43}.

One conventional meta-analysis of studies in critically ill patients with uninjured lungs clearly showed that evidence of benefit of PEEP is lacking, when focusing on important patient-centered endpoints such as mortality and duration of ventilation⁴³. The PROVENT study showed higher PEEP in ICU patients at risk for ARDS compared with patients not at risk for this complication²⁹, although the differences were small. A recent RCT in ICU patients after cardiac surgery showed that high PEEP resulted in less severe pulmonary complications⁴⁴. It should be noted, though, that the patients in this RCT probably had lung injury⁴⁵.

Whether ICU patients with uninjured lungs could benefit from higher levels of PEEP is currently uncertain. The ‘Restricted versus Liberal positive end-expiratory pressure in patients without Acute respiratory distress syndrome’ (RELAX) trial, a Dutch national multicenter RCT that compares ventilation with PEEP of 8 cm H₂O against restricted PEEP (lowest possible) in 980 invasively ventilated ICU patients with uninjured lungs, may help to answer the question of what the best level of PEEP in these patients is⁴⁶.

An implementation study focusing on the liberal use of PEEP in ED patients resulted in higher PEEP in patients with ARDS³⁶ but also in patients with uninjured lungs³⁷. The latter was associated with improved outcomes. Of note, however, the investigators focused not only on implementation of liberal use of PEEP but also on use of low tidal volume, head-of-bed elevation, and timely oxygen weaning^{36,37}, which all could explain the better outcomes.

The ‘Protective Ventilation using High versus Low positive end-expiratory pressure’ (PROVHILO) trial, an international RCT that compared high PEEP versus low PEEP during intraoperative ventilation in surgery patients, showed that high PEEP did not prevent postoperative pulmonary complications⁴². Nevertheless, it is important to note that the PROVHILO trial did not assess moderate levels of PEEP, such as 5–8 cm H₂O; thus, the effects of these levels of PEEP in surgical patients are still open for debate.

Driving pressure

There has been only one single study that showed an association between driving pressure and development of ARDS in patients with uninjured lungs⁴⁷. This study showed a better outcome of brain injury patients who received ventilation with low driving pressures. Studies on driving pressure during ventilation in emergency patients are lacking at present.

Most evidence of benefit of ventilation with low driving pressures in patients with uninjured lungs comes from one individual patient data meta-analysis of studies in surgery patients receiving intraoperative ventilation⁴⁸. This analysis shows an independent association not only between absolute driving pressures and the occurrence of postoperative pulmonary complications

but also between changes in driving pressure due to changes in PEEP and occurrence of postoperative pulmonary complications. Recruitment of lung tissue through use of higher PEEP could explain, in part, the decrease in driving pressure^{41,45}. The LAS VEGAS study also showed an association between higher driving pressure and development of postoperative pulmonary complications⁴⁰.

The ‘Individualized Perioperative Open Lung Ventilatory Strategy’ (iPROVE) study will assess whether an individualized strategy of ventilation combining recruitment maneuvers and PEEP titration according to the compliance of the respiratory system is beneficial in surgical patients at risk for postoperative pulmonary complications⁴⁹. Also, the ‘Driving Pressure during General Anesthesia for Abdominal surgery’ (DESIGNATION) study will test whether a PEEP titration aiming at the lowest driving pressure possible during surgery, compared with a standard PEEP of 5 cm H₂O, decreases the incidence of postoperative

pulmonary complications in patients at risk for postoperative pulmonary complications and undergoing abdominal surgery.

Conclusions

The lungs of patients with uninjured lungs may very well be as vulnerable to the harmful effects of mechanical ventilation as the lungs of patients with ARDS, and probably the same three ventilator settings—tidal volume, PEEP, and driving pressure—play a role. The results of ongoing RCTs are eagerly awaited.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References



- Slutsky AS, Ranieri VM: **Ventilator-induced lung injury.** *N Engl J Med.* 2013; **369**(22): 2126–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Serpa Neto A, Schultz MJ, Slutsky AS: **Current concepts of protective ventilation during general anaesthesia.** *Swiss Med Wkly.* 2015; **145**: w14211.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Güldner A, Kiss T, Serpa Neto A, *et al.*: **Intraoperative protective mechanical ventilation for prevention of postoperative pulmonary complications: a comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers.** *Anesthesiology.* 2015; **123**(3): 692–713.
[PubMed Abstract](#) | [Publisher Full Text](#)
- F** Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, *et al.*: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.** *N Engl J Med.* 2000; **342**(18): 1301–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Bellani G, Laffey JG, Pham T, *et al.*: **Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries.** *JAMA.* 2016; **315**(8): 788–800.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Fan E, Del Sorbo L, Goligher EC, *et al.*: **An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome.** *Am J Respir Crit Care Med.* 2017; **195**(9): 1253–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Putensen C, Theuerkauf N, Zinserling J, *et al.*: **Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury.** *Ann Intern Med.* 2009; **151**(8): 566–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Amato MB, Barbas CS, Medeiros DM, *et al.*: **Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome.** *N Engl J Med.* 1998; **338**(6): 347–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
- F** Terragni PP, Del Sorbo L, Mascia L, *et al.*: **Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal.** *Anesthesiology.* 2009; **111**(4): 826–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Bein T, Weber-Carstens S, Goldmann A, *et al.*: **Lower tidal volume strategy (=3 ml/kg) combined with extracorporeal CO₂ removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study.** *Intensive Care Med.* 2013; **39**(5): 847–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Dreyfuss D, Soler P, Basset G, *et al.*: **High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure.** *Am Rev Respir Dis.* 1988; **137**(5): 1159–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Brower RG, Lanken PN, MacIntyre N, *et al.*: **Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome.** *N Engl J Med.* 2004; **351**(4): 327–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
- F** Mercat A, Richard JM, Vielle B, *et al.*: **Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.** *JAMA.* 2008; **299**(6): 646–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Meade MO, Cook DJ, Guyatt GH, *et al.*: **Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.** *JAMA.* 2008; **299**(6): 637–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Briel M, Meade M, Mercat A, *et al.*: **Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis.** *JAMA.* 2010; **303**(9): 865–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, *et al.*: **Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial.** *JAMA.* 2017; **318**(14): 1335–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Serpa Neto A, Amato MB, Schultz MJ: **Dissipated Energy is a Key Mediator of VILI: Rationale for Using Low Driving Pressures.** In: Vincent J, editor. *Annual Update in Intensive Care and Emergency Medicine 2016.* Cham: Springer International Publishing; 2016; 311–321.
[Publisher Full Text](#)
- F** Amato MB, Meade MO, Slutsky AS, *et al.*: **Driving pressure and survival in the acute respiratory distress syndrome.** *N Engl J Med.* 2015; **372**(8): 747–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- F** Villar J, Martín-Rodríguez C, Domínguez-Berrot AM, *et al.*: **A Quantile Analysis of Plateau and Driving Pressures: Effects on Mortality in Patients With Acute Respiratory Distress Syndrome Receiving Lung-Protective Ventilation.** *Crit Care Med.* 2017; **45**(5): 843–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Serpa Neto A, Schmidt M, Azevedo LC, *et al.*: **Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis: Mechanical ventilation during**

- ECMO.** *Intensive Care Med.* 2016; **42**(11): 1672–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Weil MH, Tang W: **From intensive care to critical care medicine: a historical perspective.** *Am J Respir Crit Care Med.* 2011; **183**(11): 1451–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Marini JJ: **Mechanical ventilation: past lessons and the near future.** *Crit Care.* 2013; **17** Suppl 1: S1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. Wolthuis EK, Vlaar AP, Choi G, *et al.*: **Mechanical ventilation using non-injurious ventilation settings causes lung injury in the absence of pre-existing lung injury in healthy mice.** *Crit Care.* 2009; **13**(1): R1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. Gajic O, Dabbagh O, Park PK, *et al.*: **Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study.** *Am J Respir Crit Care Med.* 2011; **183**(4): 462–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 25. Neto AS, Jaber S: **What's new in mechanical ventilation in patients without ARDS: lessons from the ARDS literature.** *Intensive Care Med.* 2016; **42**(5): 787–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Bendixen HH, Hedley-Whyte J, Laver MB: **Impaired Oxygenation In Surgical Patients During General Anesthesia With Controlled Ventilation. A Concept Of Atelectasis.** *N Engl J Med.* 1963; **269**: 991–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Neto AS, Simonis FD, Barbas CS, *et al.*: **Lung-Protective Ventilation With Low Tidal Volumes and the Occurrence of Pulmonary Complications in Patients Without Acute Respiratory Distress Syndrome: A Systematic Review and Individual Patient Data Analysis.** *Crit Care Med.* 2015; **43**(10): 2155–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Serpa Neto A, Simonis FD, Barbas CS, *et al.*: **Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis.** *Intensive Care Med.* 2014; **40**(7): 950–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Neto AS, Barbas CS, Simonis FD, *et al.*: **Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PROVENT): an international, multicentre, prospective study.** *Lancet Respir Med.* 2016; **4**(11): 882–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Serpa Neto A, Schultz MJ, Asehnoune K, *et al.*: **Known and unknown potentially modifiable factors contributing to outcome in brain-injured patients who need mechanical ventilatory support. Discussion on 'The BI-VILI project: a nationwide quality improvement project'.** *Intensive Care Med.* 2017; **43**(7): 1071–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Asehnoune K, Mrozek S, Perrigault PF, *et al.*: **A multi-faceted strategy to reduce ventilation-associated mortality in brain-injured patients. The BI-VILI project: a nationwide quality improvement project.** *Intensive Care Med.* 2017; **43**(7): 957–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 32. Beitler JR, Ghafouri TB, Jinadasa SP, *et al.*: **Favorable Neurocognitive Outcome with Low Tidal Volume Ventilation after Cardiac Arrest.** *Am J Respir Crit Care Med.* 2017; **195**(9): 1198–206.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 33. Tenney SM, Remmers JE: **Comparative quantitative morphology of the mammalian lung: diffusing area.** *Nature.* 1963; **197**: 54–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Simonis FD, Binnekade JM, Braber A, *et al.*: **PREVENT—protective ventilation in patients without ARDS at start of ventilation: study protocol for a randomized controlled trial.** *Trials.* 2015; **16**: 226.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 35. Corporacion Parc Taulli: **Preventive Strategies in Acute Respiratory Distress Syndrome (ARDS) (EPALI).** In: *ClinicalTrials.gov* [Internet]. Bethesda, MD: National Library of Medicine; 2000; [cited 03 July 2017].
[Reference Source](#)
 36. Fuller BM, Ferguson IT, Mohr NM, *et al.*: **A Quasi-Experimental, Before-After Trial Examining the Impact of an Emergency Department Mechanical Ventilator Protocol on Clinical Outcomes and Lung-Protective Ventilation in Acute Respiratory Distress Syndrome.** *Crit Care Med.* 2017; **45**(4): 645–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 37. Fuller BM, Ferguson IT, Mohr NM, *et al.*: **Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED): A Quasi-Experimental, Before-After Trial.** *Ann Emerg Med.* 2017; **70**(3): 406–418.e4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 38. Fuller BM, Mohr NM, Miller CN, *et al.*: **Mechanical Ventilation and ARDS in the ED: A Multicenter, Observational, Prospective, Cross-sectional Study.** *Chest.* 2015; **148**(2): 365–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 39. Serpa Neto A, Hemmes SN, Barbas CS, *et al.*: **Protective versus Conventional Ventilation for Surgery: A Systematic Review and Individual Patient Data Meta-analysis.** *Anesthesiology.* 2015; **123**(1): 66–78.
[PubMed Abstract](#) | [Publisher Full Text](#)
 40. LAS VEGAS investigators: **Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - an observational study in 29 countries.** *Eur J Anaesthesiol.* 2017; **34**(8): 492–507.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 41. Retamal J, Borges JB, Bruhn A, *et al.*: **High respiratory rate is associated with early reduction of lung edema clearance in an experimental model of ARDS.** *Acta Anaesthesiol Scand.* 2016; **60**(1): 79–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 42. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, *et al.*: **High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial.** *Lancet.* 2014; **384**(9942): 495–503.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 43. Serpa Neto A, Filho RR, Cherpanath T, *et al.*: **Associations between positive end-expiratory pressure and outcome of patients without ARDS at onset of ventilation: a systematic review and meta-analysis of randomized controlled trials.** *Ann Intensive Care.* 2016; **6**(1): 109.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. Costa Leme A, Hajjar LA, Volpe MS, *et al.*: **Effect of Intensive vs Moderate Alveolar Recruitment Strategies Added to Lung-Protective Ventilation on Postoperative Pulmonary Complications: A Randomized Clinical Trial.** *JAMA.* 2017; **317**(14): 1422–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 45. Serpa Neto A, Schultz MJ: **Optimizing the Settings on the Ventilator: High PEEP for All?** *JAMA.* 2017; **317**(14): 1413–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-Uva): **REstricted Versus Liberal Positive End-Expiratory Pressure in Patients Without ARDS (RELAX).** In: *ClinicalTrials.gov* [Internet]. Bethesda, MD: National Library of Medicine; 2000; [cited 03 July 2017].
[Reference Source](#)
 47. Tejerina E, Pelosi P, Muriel A, *et al.*: **Association between ventilatory settings and development of acute respiratory distress syndrome in mechanically ventilated patients due to brain injury.** *J Crit Care.* 2017; **38**: 341–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 48. Neto AS, Hemmes SN, Barbas CS, *et al.*: **Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data.** *Lancet Respir Med.* 2016; **4**(4): 272–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Ferrando C, Soro M, Canet J, *et al.*: **Rationale and study design for an individualized perioperative open lung ventilatory strategy (iPROVE): study protocol for a randomized controlled trial.** *Trials.* 2015; **16**: 193.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Referee Status:  

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

- 1 **Luciano Gattinoni** Department of Anesthesiology, Emergency and Intensive Care Medicine, University of Göttingen, Göttingen, Germany
Competing Interests: No competing interests were disclosed.
- 1 **Francisco Javier Belda** Anesthesiology and Critical Care Department, Hospital Clínico Universitario, University of Valencia, Valencia, Spain
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research