Review

Bench-to-bedside review: Adjuncts to mechanical ventilation in patients with acute lung injury

Jean-Jacques Rouby[1] and Qin Lu[2]

[1]Professor of Anesthesiology and Critical Care Medicine, Director of the Surgical Intensive Care Unit Pierre Viars, La Pitié-Salpêtrière Hospital, University of Paris, Paris, France
[2]Praticien Hospitalier, Surgical Intensive Care Unit Pierre Viars, Department of Anesthesiology, Research Coordinator, La Pitié-Salpêtrière Hospital, Paris, France

Corresponding author: Jean-Jacques Rouby, jjrouby.pitie@invivo.edu

Published online: 28 June 2005
This article is online at http://ccforum.com/content/9/5/465

Critical Care 2005, **9**:465-471 (DOI 10.1186/cc3763)

Abstract

Mechanical ventilation is indispensable for the survival of patients with acute lung injury and acute respiratory distress syndrome. However, excessive tidal volumes and inadequate lung recruitment may contribute to mortality by causing ventilator-induced lung injury. This bench-to-bedside review presents the scientific rationale for using adjuncts to mechanical ventilation aimed at optimizing lung recruitment and preventing the deleterious consequences of reduced tidal volume. To enhance CO_2 elimination when tidal volume is reduced, the following are possible: first, ventilator respiratory frequency can be increased without necessarily generating intrinsic positive end-expiratory pressure; second, instrumental dead space can be reduced by replacing the heat and moisture exchanger with a conventional humidifier; and third, expiratory washout can be used for replacing the CO_2-laden gas present at end expiration in the instrumental dead space by a fresh gas (this method is still experimental). For optimizing lung recruitment and preventing lung derecruitment there are the following possibilities: first, recruitment manoeuvres may be performed in the most hypoxaemic patients before implementing the preset positive end-expiratory pressure or after episodes of accidental lung derecruitment; second, the patient can be turned to the prone position; third, closed-circuit endotracheal suctioning is to be preferred to open endotracheal suctioning.

Introduction

Mechanical ventilation is indispensable for the survival of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). However, inappropriate ventilator settings may contribute to mortality by causing ventilator-induced lung injury. Tidal volumes greater than 10 ml/kg have been shown to increase mortality [1-5]. High static intrathoracic pressures may overdistend and/or overinflate parts of the lung that remain well aerated at zero end-inspiratory pressure [6-8]. Cyclic tidal recruitment and derecruitment experimentally produces bronchial damage and lung inflammation [9]. Although the clinical relevance of these experimental data has been challenged recently [10,11], the risk of mechanical ventilation-induced lung biotrauma supports the concept of optimizing lung recruitment during mechanical ventilation [12]. It has to be mentioned that the two principles aimed at reducing ventilator-induced lung injury may be associated with deleterious effects and require specific accompanying adjustments. Reducing the tidal volume below 10 ml/kg may increase the arterial partial pressure of CO_2 ($PaCO_2$) and impair tidal recruitment [13]. Optimizing lung recruitment with positive end-expiratory pressure (PEEP) may require a recruitment manoeuvre [14] and the prevention of endotracheal suctioning-induced lung derecruitment [15]. This bench-to-bedside review presents the scientific rationale supporting the clinical use of adjuncts to mechanical ventilation aimed at optimizing lung recruitment and preventing the deleterious consequences of reduced tidal volume.

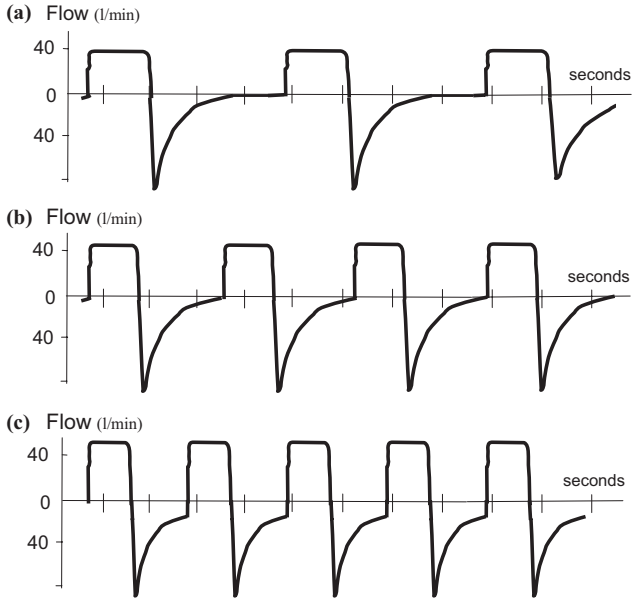
Adjuncts aimed at increasing CO_2 elimination

Increase in respiratory rate

In patients with ARDS, increasing the ventilator respiratory rate is the simplest way to enhance CO_2 elimination when tidal volume is reduced [5,16,17]. However, an uncontrolled increase in respiratory rate may generate intrinsic PEEP [18,19], which, in turn, may promote excessive intrathoracic pressure and lung overinflation [20]. If the inspiratory time is not decreased in proportion to the increase in respiratory rate, the resulting intrinsic PEEP may even cause right ventricular function to deteriorate [21]. In addition to inappropriate ventilator settings – high respiratory rate together with high inspiratory to expiratory ratio – airflow limitation caused by bronchial injury promotes air trapping [22,23]. Acting in the opposite direction, external PEEP reduces intrinsic PEEP and provides a more homogeneous

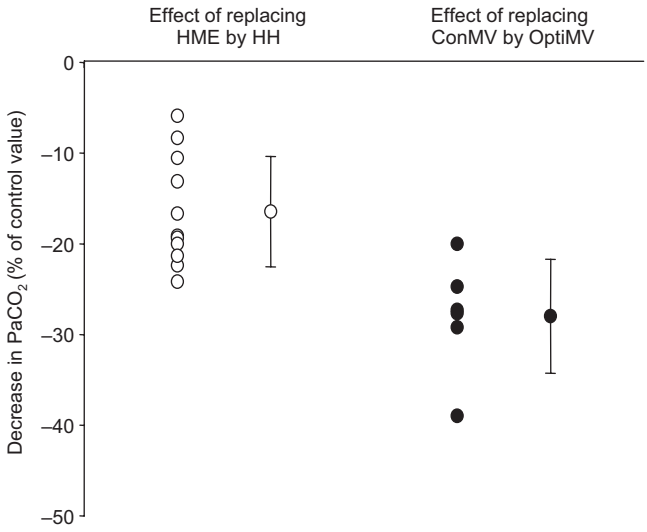
ALI = acute lung injury; ARDS = acute respiratory distress syndrome; P_aCO_2 = arterial partial pressure of CO_2; PEEP = positive end-expiratory pressure.

Figure 1



Recommendations for optimizing respiratory rate in patients with acute respiratory failure/acute respiratory distress syndrome. The clinician should increase respiratory rate while looking at inspiratory and expiratory flows displayed on the screen of the ventilator. In **(a)** too low a respiratory rate has been set: the expiratory flow ends 0.5 s before the inspiratory flow. In **(b)** the respiratory rate has been increased without generating intrinsic positive end-expiratory pressure: the end of the expiratory flow coincides with the beginning of the inspiratory flow. In **(c)** the respiratory rate has been increased excessively and causes intrinsic positive end-expiratory pressure: the inspiratory flow starts before the end of the expiratory flow. The optimum respiratory rate is represented in (b).

Figure 2



Optimization of CO_2 elimination in patients with severe acute respiratory distress syndrome (ARDS). Open circles, reduction of arterial partial pressure of CO_2 ($PaCO_2$) obtained by replacing the heat and moisture exchanger (HME) placed between the Y piece and the proximal tip of the endotracheal tube by a conventional heated humidifier (HH) on the initial part of the inspiratory limb in 11 patients with ARDS (reproduced from [27] with the permission of the publisher); filled circles, reduction of $PaCO_2$ obtained by combining the increase in respiratory rate (without generating intrinsic end-expiratory pressure) and the replacement of the HME by a conventional HH in six patients with ARDS [16]. ConMV, conventional mechanical ventilation (low respiratory rate with HME); OptiMV, optimized mechanical ventilation (optimized respiratory rate with HH). Published with kind permission of Springer Science and Business Media [27].

alveolar recruitment [24,25], whereas lung stiffness tends to accelerate lung emptying [16,26]. As a consequence, in a given patient, it is impossible to predict intrinsic PEEP induced by a high respiratory rate and no 'magic number' can be recommended. At the bedside, the clinician should increase the ventilator respiratory rate while looking at the expiratory flow displayed on the screen of the ventilator: the highest 'safe respiratory rate' is the rate at which the end of the expiratory flow coincides with the beginning of the inspiratory phase (Fig. 1).

Decrease in instrumental dead space

When CO_2 elimination is impaired by tidal volume reduction, the CO_2-laden gas present at end expiration in the physiological dead space is readministered to the patient at the beginning of the following inspiration. The physiological dead space consists of three parts: first, the instrumental dead space, defined as the volume of the ventilator tubing between the Y piece and the distal tip of the endotracheal tube; second, the anatomical dead space, defined as the volume of the patient's tracheobronchial tree from the distal tip of the endotracheal tube; and third, the alveolar dead space, defined as the volume of ventilated and nonperfused lung units. Only the former can be substantially reduced by medical intervention. Prin and colleagues have reported that replacing the heat and moisture exchanger by a conventional heated humidifier positioned on the initial part of the inspiratory limb induces a 15% decrease in $PaCO_2$ by reducing CO_2 rebreathing [27] (Fig. 2). With a conventional humidifier, the temperature of the inspired gas should be increased at 40°C at the Y piece so as to reach 37°C at the distal tip of the endotracheal tube [27]. In sedated patients, the tubing connecting the Y piece to the proximal tip of the endotracheal tube can also be removed to decrease instrumental dead space [16]. For the same reason, if a capnograph is to be used, it should be positioned on the expiratory limb, before the Y piece. Richecoeur and colleagues have shown that optimizing mechanical ventilation by selecting the appropriate respiratory rate and minimizing instrumental dead space allows a 28% decrease in $PaCO_2$ [16] (Fig. 2).

Expiratory washout

The basic principle of expiratory washout is to replace, with a fresh gas, the CO_2-laden gas present at end expiration in the

instrumental dead space [28]. It is aimed at further reducing CO_2 rebreathing and $PaCO_2$ without increasing tidal volume [29]. In contrast to tracheal gas insufflation, in which the administration of a constant gas flow is continuous over the entire respiratory cycle, gas flow is limited to the expiratory phase during expiratory washout. Fresh gas is insufflated by a gas flow generator synchronized with the expiratory phase of the ventilator at flow rates of 8 to 15 L/min through an intratracheal catheter or, more conveniently, an endotracheal tube positioned 2 cm above the carina and incorporating an internal side port opening in the internal lumen 1 cm above the distal tip [16,29]. A flow sensor connected to the inspiratory limb of the ventilator gives the signal to interrupt the expiratory washout flow when inspiration starts. At catheter flow rates of more than 10 L/min, turbulence generated at the tip of the catheter enhances distal gas mixing, and a greater portion of the proximal anatomical dead space is flushed clear of CO_2, permitting CO_2 elimination to be optimized [30,31]. Expiratory washout can be applied either to decrease $PaCO_2$ while maintaining tidal volume constant or to decrease tidal volume while keeping $PaCO_2$ constant. In the former strategy, expiratory washout is used to protect pH, whereas in the latter it is used to minimize the stretch forces acting on the lung parenchyma, to minimize ventilator-associated lung injury.

Two potential side effects should be taken into consideration if expiratory washout is used for optimizing CO_2 elimination. Intrinsic PEEP is generated if the expiratory washout flow is not interrupted a few milliseconds before the beginning of the inspiratory phase [16,29]. As a consequence, inspiratory plateau airway pressure may increase inadvertently, exposing the patient to ventilator-induced lung injury. If expiratory washout is to be used clinically in the future, the software synchronizing the expiratory washout flow should give the possibility of starting and interrupting the flow at different points of the expiratory phase. A second critical issue conditioning the clinical use of expiratory washout is the adequate heating and humidification of the delivered washout gas.

Currently, expiratory washout is still limited to experimental use. It is entering a phase in which overcoming obstacles to clinical implementation may lead to the development of commercial systems included in intensive-care-unit ventilators that may contribute to optimizing CO_2 elimination [30], in particular in patients with severe acute respiratory syndrome associated with head trauma [32].

Adjuncts aimed at optimizing lung recruitment

Sighs and recruitment manoeuvres

Periodic increases in inspiratory airway pressure may contribute to the optimization of alveolar recruitment in patients with ALI and ARDS. Sighs are characterized by intermittent increases in peak airway pressure, whereas recruitment manoeuvres are characterized by sustained increases in plateau airway pressures. The beneficial impact of sighs and recruitment manoeuvres on lung recruitment is based on the well-established principle that inspiratory pressures allowing reaeration of the injured lung are higher than the expiratory pressures at which lung aeration vanishes. At a given PEEP, the higher the pressure that is applied to the respiratory system during the preceding inspiration, the greater the lung aeration. In patients with ALI, the different pressure thresholds for lung aeration at inflation and deflation depend on the complex mechanisms regulating the removal of oedema fluid from alveoli and alveolar ducts [33,34], the reopening of bronchioles externally compressed by cardiac weight and abdominal pressure [35], and the preservation of surfactant properties.

Reaeration of the injured lung basically occurs during inspiration. The increase in airway pressure displaces the gas–liquid interface from alveolar ducts to alveolar spaces and increases the hydrostatic pressure gradient between the alveolar space and the pulmonary interstitium [36]. Under these conditions, liquid is rapidly removed from the alveolar space, thereby increasing alveolar compliance [37] and decreasing the threshold aeration pressure. Surfactant alteration, a hallmark of ALI, results from two different mechanisms: direct destruction resulting from alveolar injury, and indirect inactivation in the distal airways caused by a loss of aeration resulting from external lung compression [38]. By preventing expiratory bronchiole collapse, PEEP has been shown to prevent surfactant loss in the airways and avoid collapse of the surface film [38]. As a consequence, alveolar compliance increases and the pressure required for alveolar expansion decreases. The time scale for alveolar recruitment and derecruitment is within a few seconds [39,40], whereas the time required for fluid transfer from the alveolar space to the pulmonary interstitium is of the order of a few minutes [36]. It has been demonstrated that the beneficial effect of recruitment manoeuvres on lung recruitment can be obtained only when the high airway pressure (inspiratory or incremental PEEP) is applied over a sufficient period [41,42], probably preserving surfactant properties and increasing alveolar clearance [14].

In surfactant-depleted collapse-prone lungs, recruitment manoeuvres increase arterial oxygenation by boosting the ventilatory cycle onto the deflation limb of the pressure–volume curve [42]. However, in different experimental models of lung injury, recruitment manoeuvres do not provide similar beneficial effects [43]. In patients with ARDS, recruitment manoeuvres and sighs are effective in improving arterial oxygenation only at low PEEP and small tidal volumes [44,45]. When PEEP is optimized, recruitment manoeuvres are either poorly effective [46] or deleterious, inducing overinflation of the most compliant lung regions [47] and haemodynamic instability and worsening pulmonary shunt by redistributing pulmonary blood flow towards non-aerated lung regions [48]. However, after a recruitment manoeuvre, a

sufficient PEEP level is required for preventing end-expiratory alveolar derecruitment [49]. Furthermore, recruitment manoeuvres are less effective when ALI/ARDS is due to pneumonia or haemorrhagic oedema [43].

Different types of recruitment manoeuvre have been proposed for enhancing alveolar recruitment and improving arterial oxygenation in the presence of ALI [50]. A plateau inspiratory pressure can be maintained at 40 cmH_2O for 40 s. Stepwise increases and decreases in PEEP can be performed while maintaining a constant plateau inspiratory pressure of 40 cmH_2O [42]. Pressure-controlled ventilation using high PEEP and a peak airway pressure of 45 cmH_2O can be applied for 2 min [51]. The efficacy and haemodynamic side effects have been compared between three different recruitment manoeuvres in patients and animals with ARDS [49,51]. Pressure-controlled ventilation with high PEEP seems more effective in terms of oxygenation improvement, whereas a sustained inflation lasting 40 seconds seems more deleterious to cardiac output [49,51].

Studies reporting the potential deleterious effects of recruitment manoeuvres on lung injury of regions remaining fully aerated are still lacking. As a consequence, the administration of recruitment manoeuvres should be restricted to individualized clinical decisions aimed at improving arterial oxygenation in patients remaining severely hypoxaemic. As an example, recruitment manoeuvres are quite efficient for rapidly reversing aeration loss resulting from endotracheal suctioning [52] or accidental disconnection from the ventilator. In patients with severe head injury, recruitment manoeuvres may cause cerebral haemodynamics to deteriorate [53]. As a consequence, careful monitoring of intracranial pressure should be provided in case of severe hypoxaemia requiring recruitment manoeuvres.

Prone position

Turning the patient into the prone position restricts the expansion of the cephalic and parasternal lung regions and relieves the cardiac and abdominal compression exerted on the lower lobes. Prone positioning induces a more uniform distribution of gas and tissue along the sternovertebral and cephalocaudal axis by reducing the gas/tissue ratio of the parasternal and cephalic lung regions [54,55]. It reduces regional ventilation-to-perfusion mismatch, prevents the free expansion of anterior parts of the chest wall, promotes PEEP-induced alveolar recruitment [56], facilitates the drainage of bronchial secretions and potentiates the beneficial effect of recruitment manoeuvres [57], all factors that contribute to improving arterial oxygenation in most patients with early acute respiratory failure [55] and may reduce ventilator-induced lung overinflation.

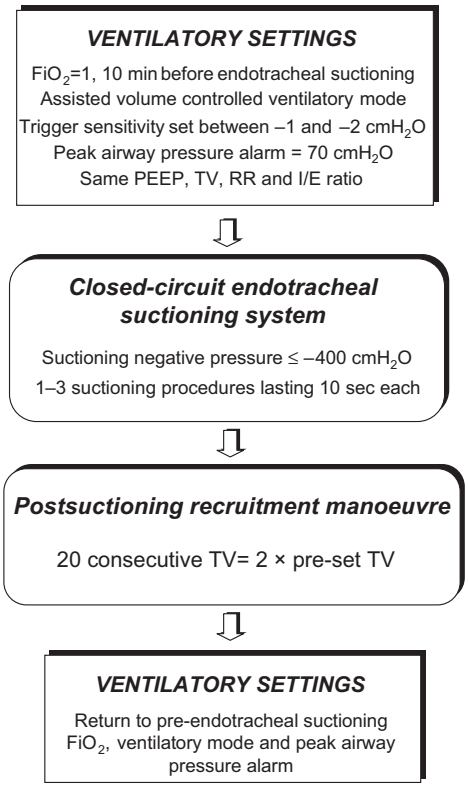
It is recommended that the ventilatory settings be optimized before the patient is turned into the prone position [35]. If arterial saturation remains below 90% at an inspiratory fraction of oxygen of at least 60% and after absolute contraindications such as burns, open wounds of the face or ventral body surface, recent thoracoabdominal surgical incisions, spinal instability, pelvic fractures, life-threatening circulatory shock and increased intracranial pressure have been ruled out [56], the patient should be turned to prone in accordance with a predefined written turning procedure [56]. The optimum duration of prone positioning remains uncertain. In clinical practice, the duration of pronation can be maintained for 6 to 12 hours daily and may be safely increased to 24 hours [58]. The number of pronations can be adapted to the observed changes in arterial oxygenation after supine repositioning [55]. Whether the abdomen should be suspended during the period of prone position is still debated [56]. Complications are facial oedema, pressure sores and accidental loss of the endotracheal tube, drains and central venous catheters. Despite its beneficial effects on arterial oxygenation, clinical trials have failed to show an increase in survival rate by prone positioning in patients with acute respiratory failure [59,60]. Whether it might reduce mortality and limit ventilator-associated pneumonia in the most severely hypoxaemic patients [59,60] requires additional study.

Closed-circuit endotracheal suctioning

Endotracheal suctioning is routinely performed in patients with ALI/ARDS. A negative pressure is generated into the tracheobronchial tree for the removal of bronchial secretions from the distal airways. Two factors contribute to lung derecruitment during endotracheal suctioning: the disconnection of the endotracheal tube from the ventilator and the suctioning procedure itself. Many studies have shown that the sudden discontinuation of PEEP is the predominant factor causing lung derecruitment in patients with ALI [52,61]. During a suctioning procedure lasting 10 to 30 seconds, the high negative pressure generated into the airways further decreases lung volume [15]. A rapid and long-lasting decrease in arterial oxygenation invariably results from open endotracheal suctioning [62]. It is caused by a lung derecruitment-induced increase in pulmonary shunt and a reflex bronchoconstriction-induced increase in venous admixture; both factors increase the ventilation/perfusion ratio mismatch [52]. The decrease in arterial oxygenation is immediate and continues for more than 15 min despite the re-establishment of the initial positive end-expiratory level. A recruitment manoeuvre performed immediately after the reconnection of the patient to the ventilator allows a rapid recovery of end-expiratory lung volume and arterial oxygenation [62]. However, in the most severely hypoxaemic patients the open suctioning procedure itself may be associated with dangerous hypoxaemia [62].

Closed-circuit endotracheal suctioning is generally advocated for preventing arterial oxygenation impairment caused by ventilator disconnection [63,64]. However, a loss of lung volume may still be observed, resulting from the suctioning procedure itself and appearing dependent on the applied

Figure 3



Recommendations concerning endotracheal suctioning in patients with severe acute respiratory distress syndrome. FIO_2, inspiratory fraction of oxygen; I/E ratio, inspiratory to expiratory ratio; PEEP, positive end-expiratory pressure; RR, respiratory rate; TV, tidal volume.

negative pressure [15,63]. Both experimental studies and clinical experience suggest that closed-circuit endotracheal suctioning is less efficient than open endotracheal suctioning for removing tracheobronchial secretions [64,65]. As a consequence, the clinician is faced with two opposite goals: preventing lung derecruitment and ensuring the efficient removal of secretions [66]. Further clinical studies are needed to evaluate an optimum method that takes both goals into account.

In patients with ALI/ARDS, closed-circuit endotracheal suctioning should be considered the clinical standard. In severe ARDS, endotracheal suctioning should be optimized by pre-suction hyperoxygenation and followed by post-suction recruitment manoeuvres. In addition to the methods described above, two other types of recruitment manoeuvre have been proposed to prevent a loss of lung volume and reverse atelectasis resulting from endotracheal suctioning: the administration of triggered pressure-supported breaths at a peak inspiratory pressure of 40 cmH_2O during suctioning [15] and the administration of 20 consecutive hyperinflations set at twice the baseline tidal volume immediately after suctioning [52].

There is as yet no guideline for endotracheal suctioning in patients with severe ARDS. An algorithm is proposed in Fig. 3 aimed at preventing lung derecruitment and deterioration of gas exchange during endotracheal suctioning in hypoxaemic patients receiving mechanical ventilation with PEEP.

Conclusion

Mechanical ventilation in patients with ALI/ARDS requires specific adjustments of tidal volume and PEEP. Clinical use of adjuncts to mechanical ventilation allows optimization of alveolar recruitment resulting from PEEP and prevention of deleterious consequences of reduced tidal volume. Appropriate increases in respiratory rate, replacement of heat and moisture exchanger by a conventional humidifier. administration of recruitment manoeuvre in case of accidental episode of derecruitment, prone positioning and closed-circuit endotracheal suctioning all contribute to optimization of arterial oxygenation and O_2 elimination

Competing interests

The author(s) declare that they have no competing interests.

References

1. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, *et al.*: **Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome.** *N Engl J Med* 1998, **338:**347-354.
2. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D, *et al.*: **Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume reduction in ARDS.** *Am J Respir Crit Care Med* 1998, **158:**1831-1838.
3. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, *et al.*: **Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group.** *N Engl J Med* 1998, **338:**355-361.
4. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S: **Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients.** *Crit Care Med* 1999, **27:**1492-1498.
5. The Acute Respiratory Distress Syndrome Network: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.** *N Engl J Med* 2000, **342:**1301-1308.
6. Vieira SR, Puybasset L, Lu Q, Richecoeur J, Cluzel P, Coriat P, Rouby JJ: **A scanographic assessment of pulmonary morphology in acute lung injury. Significance of the lower inflection point detected on the lung pressure-volume curve.** *Am J Respir Crit Care Med* 1999, **159:**1612-1623.
7. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ: **Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome.** *Intensive Care Med* 2000, **26:**1215-1227.
8. Nieszkowska A, Lu Q, Vieira S, Elman M, Fetita C, Rouby JJ: **Incidence and regional distribution of lung overinflation during mechanical ventilation with positive end-expiratory pressure.** *Crit Care Med* 2004, **32:**1496-1503.
9. Dos Santos CC, Slutsky AS: **Invited review: mechanisms of ventilator-induced lung injury: a perspective.** *J Appl Physiol* 2000, **89:**1645-1655.

10. Dreyfuss D, Ricard JD, Saumon G: **On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury.** *Am J Respir Crit Care Med* 2003, **167:** 1467-1471.
11. Dreyfuss D, Rouby JJ: **Mechanical ventilation-induced lung release of cytokines: a key for the future or Pandora's box?** *Anesthesiology* 2004, **101:**1-3.
12. Crimi E, Slutsky AS: **Inflammation and the acute respiratory distress syndrome.** *Best Pract Res Clin Anaesthesiol* 2004, **18:** 477-492.
13. Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire F, Brochard L: **Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver.** *Am J Respir Crit Care Med* 2001, **163:**1609-1613.
14. Rouby JJ: **Optimizing lung aeration in positive end-expiratory pressure.** *Am J Respir Crit Care Med* 2004, **170:**1039-1040.
15. Maggiore SM, Lellouche F, Pigeot J, Taille S, Deye N, Durrmeyer X, Richard JC, Mancebo J, Lemaire F, Brochard L: **Prevention of endotracheal suctioning-induced alveolar derecruitment in acute lung injury.** *Am J Respir Crit Care Med* 2003, **167:**1215-1224.
16. Richecoeur J, Lu Q, Vieira SR, Puybasset L, Kalfon P, Coriat P, Rouby JJ: **Expiratory washout versus optimization of mechanical ventilation during permissive hypercapnia in patients with severe acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 1999, **160:**77-85.
17. Tobin MJ: **Culmination of an era in research on the acute respiratory distress syndrome.** *N Engl J Med* 2000, **342:**1360-1361.
18. Richard JC, Brochard L, Breton L, Aboab J, Vandelet P, Tamion F, Maggiore SM, Mercat A, Bonmarchand G: **Influence of respiratory rate on gas trapping during low volume ventilation of patients with acute lung injury.** *Intensive Care Med* 2002, **28:** 1078-1083.
19. de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, Slutsky AS, Ranieri VM: **ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 2002, **165:**1271-1274.
20. Vieillard-Baron A, Jardin F: **The issue of dynamic hyperinflation in acute respiratory distress syndrome patients.** *Eur Respir J Suppl* 2003, **42:**43s-47s.
21. Vieillard-Baron A, Prin S, Augarde R, Desfonds P, Page B, Beauchet A, Jardin F: **Increasing respiratory rate to improve CO2 clearance during mechanical ventilation is not a panacea in acute respiratory failure.** *Crit Care Med* 2002, **30:**1407-1412.
22. Armaganidis A, Stavrakaki-Kallergi K, Koutsoukou A, Lymberis A, Milic-Emili J, Roussos C: **Intrinsic positive end-expiratory pressure in mechanically ventilated patients with and without tidal expiratory flow limitation.** *Crit Care Med* 2000, **28:**3837-3842.
23. Koutsoukou A, Armaganidis A, Stavrakaki-Kallergi C, Vassilakopoulos T, Lymberis A, Roussos C, Milic-Emili J: **Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome.** *Am J Respir Crit Care Med* 2000, **161:**1590-1596.
24. Munoz J, Guerrero JE, De La Calle B, Escalante JL: **Interaction between intrinsic positive end-expiratory pressure and externally applied positive end-expiratory pressure during controlled mechanical ventilation.** *Crit Care Med* 1993, **21:** 348-356.
25. Kacmarek RM, Kirmse M, Nishimura M, Mang H, Kimball WR: **The effects of applied vs auto-PEEP on local lung unit pressure and volume in a four-unit lung model.** *Chest* 1995, **108:**1073-1079.
26. Rouby JJ, Simonneau G, Benhamou D, Sartene R, Sardnal F, Deriaz H, Duroux P, Viars P: **Factors influencing pulmonary volumes and CO_2 elimination during high-frequency jet ventilation.** *Anesthesiology* 1985, **63:**473-482.
27. Prin S, Chergui K, Augarde R, Page B, Jardin F, Vieillard-Baron A: **Ability and safety of a heated humidifier to control hypercapnic acidosis in severe ARDS.** *Intensive Care Med* 2002, **28:** 1756-1760.
28. Jonson B, Similowski T, Levy P, Viires N, Pariente R: **Expiratory flushing of airways: a method to reduce deadspace ventilation.** *Eur Respir J* 1990, **3:**1202-1205.
29. Kalfon P, Rao GS, Gallart L, Puybasset L, Coriat P, Rouby JJ: **Permissive hypercapnia with and without expiratory washout in patients with severe acute respiratory distress syndrome.** *Anesthesiology* 1997, **87:**6-17.
30. Nahum A: **Tracheal gas insufflation as an adjunct to mechanical ventilation.** *Respir Care Clin N Am* 2002, **8:**171-185.
31. Nahum A: **Animal and lung model studies of tracheal gas insufflation.** *Respir Care* 2001, **46:**149-157.
32. Martinez-Perez M, Bernabe F, Pena R, Fernandez R, Nahum A, Blanch L: **Effects of expiratory tracheal gas insufflation in patients with severe head trauma and acute lung injury.** *Intensive Care Med* 2004, **30:**2021-2027.
33. Hubmayr RD: **Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story.** *Am J Respir Crit Care Med* 2002, **165:**1647-1653.
34. Rouby JJ, Puybasset L, Nieszkowska A, Lu Q: **Acute Respiratory Distress Syndrome: lessons from computed tomography of the whole lung.** *Crit Care Med* 2003, **31(Suppl):**S285-S295.
35. Rouby JJ, Constantin JM, Roberto De AGC, Zhang M, Lu Q: **Mechanical ventilation in patients with acute respiratory distress syndrome.** *Anesthesiology* 2004, **101:**228-234.
36. Martynowicz MA, Walters BJ, Hubmayr RD: **Mechanisms of recruitment in oleic acid-injured lungs.** *J Appl Physiol* 2001, **90:**1744-1753.
37. Wilson TA, Anafi RC, Hubmayr RD: **Mechanics of edematous lungs.** *J Appl Physiol* 2001, **90:**2088-2093.
38. Dreyfuss D, Saumon G: **Ventilator-induced lung injury: lessons from experimental studies.** *Am J Respir Crit Care Med* 1998, **157:**294-323.
39. Neumann P, Berglund JE, Mondejar EF, Magnusson A, Hedenstierna G: **Effect of different pressure levels on the dynamics of lung collapse and recruitment in oleic-acid-induced lung injury.** *Am J Respir Crit Care Med* 1998, **158:**1636-1643.
40. Neumann P, Berglund JE, Mondejar EF, Magnusson A, Hedenstierna G: **Dynamics of lung collapse and recruitment during prolonged breathing in porcine lung injury.** *J Appl Physiol* 1998, **85:**1533-1543.
41. Walsh MC, Carlo WA: **Sustained inflation during HFOV improves pulmonary mechanics and oxygenation.** *J Appl Physiol* 1988, **65:**368-372.
42. Lim CM, Soon Lee S, Seoung Lee J, Koh Y, Sun Shim T, Do Lee S, Sung Kim W, Kim DS, Dong Kim W: **Morphometric effects of the recruitment maneuver on saline-lavaged canine lungs. A computed tomographic analysis.** *Anesthesiology* 2003, **99:**71-80.
43. Kloot TE, Blanch L, Melynne Youngblood A, Weinert C, Adams AB, Marini JJ, Shapiro RS, Nahum A: **Recruitment maneuvers in three experimental models of acute lung injury. Effect on lung volume and gas exchange.** *Am J Respir Crit Care Med* 2000, **161:**1485-1494.
44. Pelosi P, Cadringher P, Bottino N, Panigada M, Carrieri F, Riva E, Lissoni A, Gattinoni L: **Sigh in acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 1999, **159:**872-880.
45. Patroniti N, Foti G, Cortinovis B, Maggioni E, Bigatello LM, Cereda M, Pesenti A: **Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation.** *Anesthesiology* 2002, **96:**788-794.
46. Cakar N, der Kloot TV, Youngblood M, Adams A, Nahum A: **Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model.** *Am J Respir Crit Care Med* 2000, **161:**1949-1956.
47. Rouby JJ: **Lung overinflation. The hidden face of alveolar recruitment.** *Anesthesiology* 2003, **99:**2-4.
48. Villagra A, Ochagavia A, Vatua S, Murias G, Del Mar Fernandez M, Lopez Aguilar J, Fernandez R, Blanch L: **Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 2002, **165:**165-170.
49. Lim CM, Jung H, Koh Y, Lee JS, Shim TS, Lee SD, Kim WS, Kim DS, Kim WD: **Effect of alveolar recruitment maneuver in early acute respiratory distress syndrome according to antiderecruitment strategy, etiological category of diffuse lung injury, and body position of the patient.** *Crit Care Med* 2003, **31:**411-418.
50. Richard JC, Maggiore S, Mercat A: **Where are we with recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome?** *Curr Opin Crit Care* 2003, **9:** 22-27.

51. Lim SC, Adams AB, Simonson DA, Dries DJ, Broccard AF, Hotchkiss JR, Marini JJ: **Intercomparison of recruitment maneuver efficacy in three models of acute lung injury.** *Crit Care Med* 2004, **32:**2371-2377.
52. Lu Q, Capderou A, Cluzel P, Mourgeon E, Abdennour L, Law-Koune JD, Straus C, Grenier P, Zelter M, Rouby JJ: **A computed tomographic scan assessment of endotracheal suctioning-induced bronchoconstriction in ventilated sheep.** *Am J Respir Crit Care Med* 2000, **162:**1898-1904.
53. Bein T, Kuhr LP, Bele S, Ploner F, Keyl C, Taeger K: **Lung recruitment maneuver in patients with cerebral injury: effects on intracranial pressure and cerebral metabolism.** *Intensive Care Med* 2002, **28:**554-558.
54. Lee HJ, Im JG, Goo JM, Kim YI, Lee MW, Ryu HG, Bahk JH, Yoo CG: **Acute lung injury: effects of prone positioning on cephalocaudal distribution of lung inflation – CT assessment in dogs.** *Radiology* 2005, **234:**151-161.
55. Pelosi P, Brazzi L, Gattinoni L: **Prone position in acute respiratory distress syndrome.** *Eur Respir J* 2002, **20:**1017-1028.
56. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK: **The pragmatics of prone positioning.** *Am J Respir Crit Care Med* 2002, **165:**1359-1363.
57. Pelosi P, Bottino N, Chiumello D, Caironi P, Panigada M, Gamberoni C, Colombo G, Bigatello LM, Gattinoni L: **Sigh in supine and prone position during acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 2003, **167:**521-527.
58. McAuley DF, Giles S, Fichter H, Perkins GD, Gao F: **What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome?** *Intensive Care Med* 2002, **28:**414-418.
59. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, *et al.*: **Effect of prone positioning on the survival of patients with acute respiratory failure.** *N Engl J Med* 2001, **345:**568-573.
60. Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, Palmier B, Le QV, Sirodot M, Rosselli S, *et al.*: **Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial.** *Jama* 2004, **292:**2379-2387.
61. Brochard L, Mion G, Isabey D, Bertrand C, Messadi AA, Mancebo J, Boussignac G, Vasile N, Lemaire F, Harf A: **Constant-flow insufflation prevents arterial oxygen desaturation during endotracheal suctioning.** *Am Rev Respir Dis* 1991, **144:**395-400.
62. Dyhr T, Bonde J, Larsson A: **Lung recruitment manoeuvres are effective in regaining lung volume and oxygenation after open endotracheal suctioning in acute respiratory distress syndrome.** *Crit Care* 2003, **7:**55-62.
63. Cereda M, Villa F, Colombo E, Greco G, Nacoti M, Pesenti A: **Closed system endotracheal suctioning maintains lung volume during volume-controlled mechanical ventilation.** *Intensive Care Med* 2001, **27:**648-654.
64. Lindgren S, Almgren B, Hogman M, Lethvall S, Houltz E, Lundin S, Stenqvist O: **Effectiveness and side effects of closed and open suctioning: an experimental evaluation.** *Intensive Care Med* 2004, **30:**1630-1637.
65. Blackwood B: **The practice and perception of intensive care staff using the closed suctioning system.** *J Adv Nurs* 1998, **28:** 1020-1029.
66. Morrow BM, Futter MJ, Argent AC: **Endotracheal suctioning: from principles to practice.** *Intensive Care Med* 2004, **30:**1167-1174.