Chapter 2

Ventilator strategies in severe hypoxaemic respiratory failure

A. Esan[*], *D. Hess*[#], *C. Sessler*[¶], *L. George*[*], *C. Oribabor*[+], *F. Khusid*[§] *and S. Raoof*[*]

Summary

Mechanical ventilation of patients with acute lung injury/acute respiratory distress syndrome (ARDS) should commence with low tidal volume (*V*T), low stretch and adequate positive end-expiratory pressure (PEEP), as proposed by the first ARDSnet trial. The majority of patients with ARDS will achieve their goals of oxygenation and plateau pressure, utilising the lung protective strategy. In the remaining minority of patients, these end-points may not be achieved. Such patients have a significantly high mortality and should be considered for rescue strategies relatively early on. If the patients respond positively to lung recruitment trials, using rescue strategies may open atelectactic alveoli and allow oxygenation or plateau pressure targets to be achieved. None of these rescue strategies have been shown to reduce mortality, although short-term objectives of improvement in oxygenation or reduction in plateau pressures may be achieved. Therefore, the selection of these strategies should be based on availability and level of comfort of the operators.

Keywords: Acute respiratory distress syndrome, alternative ventilator modes, hypoxaemic respiratory failure, mechanical ventilation, rescue strategies, ventilator strategies

[*]Depts of Pulmonary and Critical Care,
[+]Cardiothoracic Surgery,
[§]Respiratory Therapy, New York Methodist Hospital, Brooklyn, NY,
[#]Respiratory Care Services, Massachusetts General Hospital, Boston, MA, and
[¶]Medical College of Virginia Hospitals, Richmond, VA, USA.

Correspondence: A. Esan, Dept of Pulmonary and Critical Care, New York Methodist Hospital, 506 Sixth Street, Brooklyn, NY 11215, USA.
Email bayoesan@yahoo.com

Eur Respir Mon 2012; 55: 19–39.

European Respiratory Monograph
ISSN: 1025-448x
DOI: 10.1183/1025448x.10000412

Acute lung injury (ALI) and its more severe counterpart, acute respiratory distress syndrome (ARDS), are both syndromes of acute hypoxaemic respiratory failure that are associated with a wide variety of aetiologies. In 1994, the American-European Consensus Conference on ARDS standardised the definition of ALI and ARDS on the basis of certain clinical criteria, namely: 1) acute onset of severe respiratory distress; 2) bilateral infiltrates on a frontal chest radiograph; 3) the absence of left atrial hypertension or clinical signs of left heart failure, or a pulmonary capillary wedge pressure $\leqslant$18 mmHg; and 4) severe hypoxaemia based on the ratio of arterial oxygen tension to the inspiratory oxygen concentration ($P_{a,O_2}/F_{I,O_2} \leqslant 300$ mmHg and 200 mmHg in ALI and ARDS, respectively) [1]. This widely used definition is limited by its inability to account for the diverse pulmonary and non-

pulmonary aetiologies, or the level of positive end-expiratory pressure (PEEP) required in those patients requiring mechanical ventilation. This is further buttressed by a recent study showing that a moderate amount of PEEP was sufficient to reclassify patients from ARDS to ALI, resulting in a reduction in the expected mortality [2]. In an attempt to circumvent the problems associated with this existing definition, a new definition has been proposed [3]. The "Berlin definition" classifies ARDS into mild, moderate and severe based upon the following variables: timing, hypoxaemia, origin of oedema, radiological abnormalities and additional physiological derangements. This clinical definition aims to quantify the degree of hypoxaemia based upon the level of PEEP used. However, it has its own limitations and needs to be validated in clinical trials.

The vast majority of ALI/ARDS patients require mechanical ventilation for adequate gas exchange, as well as for alleviating the increased work of breathing. However, in addition to providing life-sustaining support, mechanical ventilation in ALI/ARDS patients can further worsen lung injury as a result of the heterogeneous manner in which the lungs are affected [4]. Ventilator-induced lung injury (VILI) is the collective term used to describe the various injuries that can occur, namely: barotrauma resulting from the use of high inspiratory pressures; volutrauma due to over-distension from employing a large tidal volume (V_T); atelectrauma following cyclic collapsing and re-opening of unstable alveolar units; and biotrauma ensuing from the release of inflammatory mediators into the systemic circulation [5–11]. Consequently, not only is the goal to provide life-sustaining support with mechanical ventilation in ALI/ARDS patients, but to do so in a manner that minimises VILI, and thereby improve outcomes.

This chapter discusses different ventilator strategies that have been utilised to achieve these goals in the management of ALI/ARDS patients, as well as the evidence from clinical trials regarding the efficacy of these different ventilator strategies. The decision to employ a specific strategy should be based on an appraisal of the benefits, strength of evidence, possible risks, familiarity of use and availability of alternative modes of mechanical ventilation. A PubMed search was performed using each strategy as a key phrase. The article search was limited to those published in English and that studied primarily human subjects. The search was also expanded to comprise further articles, as suitable, from the reference lists of those identified from our initial search. The articles specifically excluded non-ventilatory strategies to maximise oxygenation (conservative fluid strategies, extra-corporeal membrane oxygenation, prone position, *etc.*), as well as noninvasive positive pressure ventilation.

Volume-targeted ventilation

The initial ventilator strategy that should be promptly utilised is low V_T and pressure ventilation, currently regarded as the standard of care in the management of patients with ALI/ARDS. This strategy attenuates the development of VILI, thus it is considered lung protective ventilation (LPV), and is the only method of mechanical ventilation that has been demonstrated to improve survival in randomised controlled trials (RCTs) of ARDS patients [12–14]. In the largest of these trials, conducted by the ARDS Network (ARDSnet), and generally considered a pivotal study, a 9% absolute reduction in mortality, and a greater number of both ventilator-free days and non-pulmonary organ failure-free days occurred in ALI/ARDS patients mechanically ventilated in the volume assist-control mode with a target V_T of $\leqslant$6 mL·kg^{-1} predicted body weight (PBW) and a plateau pressure (P_{plat}) of $\leqslant$30 cmH_2O [14]. This was performed using an empirically but prospectively determined F_{I,O_2}–PEEP table to obtain arterial saturations of 88–95% or a P_{a,O_2} of 55–88 mmHg, often resulting in initial decreases of the $P_{a,O_2}/F_{I,O_2}$ ratio, moderate increases in arterial carbon dioxide tension (P_{a,CO_2}), and the use of high respiratory rates with or without sodium bicarbonate to maintain pH goals, while minimising the development of intrinsic auto-PEEP [14].

In contrast, three earlier RCTs of LPV (table 1) did not demonstrate an improvement in outcome [15–17]. Like the ARDSnet study, these three studies had similar PEEP in both arms associated with low *versus* high V_T, unlike other studies with LPV that included both low V_T and high PEEP [13, 18]. This inconsistency with the earlier RCTs has been attributed to differences in sample size which may not have been sufficiently powered to detect survival differences, lower differences in the tidal volumes and P_{plat} utilised between groups, utilisation of lower pH thresholds, different methods for treating

Table 1. Randomised controlled trials of lung protective ventilation

First author [ref.]	Patients n	Intervention *versus* control group		Mortality rates %	p-value
		Tidal volume mL·kg^{-1}	Pressure cmH$_2$O		
AMATO [13]	53	⩽6 *versus* 12 ABW	<20 *versus* unlimited driving pressure[#]	38 *versus* 71[¶]	0.001
BROWER [15]	52	5–8 *versus* 10–12 PBW	⩽30 *versus* ⩽45–55 P_{plat}	50 *versus* 46	0.61
STEWART [16]	120	⩽8 *versus* 10–15 IBW	⩽30 *versus* ⩽50 $P_{,peak}$	50 *versus* 47	0.72
BROCHARD [17]	116	6–10 *versus* 10–15 DBW	25–30 *versus* ⩽60 P_{plat} *versus* $P_{,peak}$	47 *versus* 38[+]	0.38
ARDSNET [14]	861	⩽6 *versus* 12 PBW	⩽30 *versus* ⩽50 P_{plat}	31 *versus* 40	0.007
VILLAR [12]	103	5–8 *versus* 9–11 PBW	Unspecified P_{plat}	34 *versus* 56	0.04

Data for mortality rate are presented as the in-hospital mortality rates of intervention *versus* control groups, unless otherwise stated. ABW: actual body weight; PBW: predicted body weight; P_{plat}: plateau pressure; IBW: ideal body weight; $P_{,peak}$: peak inspiratory pressure; DBW: dry body weight. [#]: P_{plat}–positive end-expiratory pressure; [¶]: 28-day mortality; [+]: 60-day mortality.

respiratory acidosis, as well as premature termination of the respective trials following interim analysis [19–21]. Similarly, different systemic reviews and meta-analyses of the heterogeneous LPV trials have had varying results [22–25]. In one of the early meta-analyses [23], it was reported that the two trials demonstrating a survival benefit with LPV did not represent standard of care in the control groups [13, 14], and that as long as P_{plat} was kept between 28–32 cmH$_2$O, there was no basis for the use of low V_T. This meta-analysis has been critiqued as having significant methodological errors [24, 26]. In addition, a secondary analysis of the ARDSnet study [14] implied a higher, albeit nonsignificant mortality risk, even when a P_{plat} <31 cmH$_2$O was used in the control group compared with the LPV group (fig. 1) [27]. Moreover, a subsequent physiological study has shown that regional overdistention can occur at a P_{plat} of 28–30 cmH$_2$O even with a V_T of 6 mL·kg^{-1} PBW [28]. The investigators indicate that although the existence of a "safe" P_{plat} limit remains unconfirmed, values <28 cmH$_2$O appear to be linked to more protective ventilatory parameters [28]. It is important to be mindful that although alveolar overdistension is usually estimated by P_{plat} measurement, it is the transalveolar pressure that accurately reflects the degree of alveolar distension. This is particularly important in patients with reductions in chest wall compliance such as in obesity, increased abdominal girth, abdominal compartment syndrome or pleural effusions when pleural pressures would be elevated. Such patients may consequently have elevated P_{plat} (>30 cmH$_2$O), but the transalveolar pressure would still be within acceptable levels. Therefore, measurement of the oesophageal pressure as a surrogate for the pleural pressure can provide an accurate assessment of the transalveolar pressure; this has been demonstrated in recent studies in ARDS patients and is suggested to have potential clinical benefit [29, 30]. However, the routine use of LPV is reported in several other meta-analyses to be beneficial to ALI/ARDS patients since it has been shown to improve hospital mortality [20, 22, 24, 25, 31].

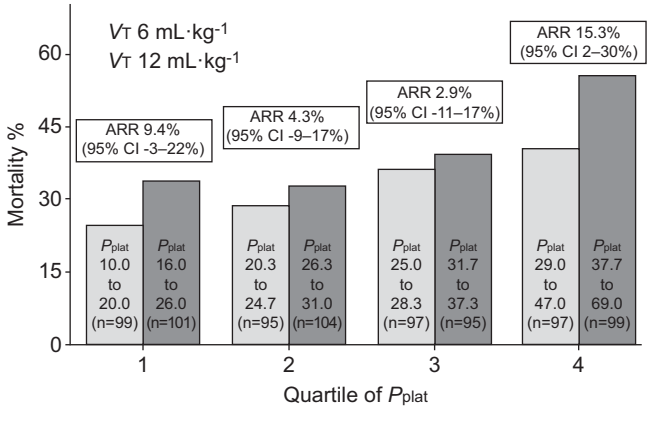


Figure 1. Mortality difference by quartile of day 1 plateau pressure (P_{plat}) in the ARDSnet trial. The range of P_{plat} in cmH$_2$O and the number of patients is detailed in each bar. ARR: absolute risk reduction; V_T: tidal volume. Reproduced from [27] with permission from the publisher.

Widespread adoption of LPV in the management of ALI/ARDS was initially reported to be slow in spite of its beneficial effects [32–35]. Even though

a ventilator strategy based on the ARDSnet study [14] serves as a rational starting point, certain barriers, such as failure to recognise patients with ALI/ARDS, unwillingness to relinquish ventilator control or follow a ventilatory strategy protocol, use of actual body weight instead of PBW in calculating tidal volumes, apprehension regarding patient–ventilator asynchrony, increased need for sedation or the development of auto-PEEP, tachypnoea, hypercapnia or acidosis, had limited extensive implementation [33–35]. Nonetheless, these barriers are unfounded [14, 36–41], and recent studies indicate that clinical practices are changing in response to current clinical evidence [42, 43]. In a recent study aiming to improve adherence to LPV, an electronic medical record-based VILI alert system was used to alert bedside providers *via* text paging notifications about potentially detrimental ventilator settings, ultimately reducing patient exposure to the latter [44]. LPV remains the primary ventilatory strategy recommended in the management of ALI/ARDS patients [12–14].

Pressure-targeted ventilation

Although volume-controlled ventilation (VCV), as was utilised in the ARDSnet study, is generally recommended in the management of ALI/ARDS patients [14], the use of pressure-controlled ventilation (PCV) has been proposed as an alternative in maintaining the goals of LPV, *i.e.* V_T of 4–8 mL·kg^{-1} PBW and end-inspiratory P_{plat} of $<$30–35 cmH_2O [45, 46]. The reasons for this originate from studies that have demonstrated reduced work of breathing by the patient, improved patient-ventilator synchrony and comfort, lower peak inspiratory pressures, higher mean airway pressures and, thus, improved oxygenation due to the variable-flow, pressure-controlled breaths of PCV as opposed to the fixed-flow, flow/volume-targeted breaths of VCV [47–51]. In addition, it has been argued that PCV is inherently safer than VCV because of its ability to restrain detrimental transalveolar forces that are produced and promoted by the fixed-flow and monotonous V_T delivery of VCV [52]. In contrast, other studies have indicated that the aforementioned advantages with PCV can be achieved with VCV utilising a decelerating flow waveform as opposed to a square flow waveform [47, 53]. In acute respiratory failure patients, CHIUMELLO *et al.* [54] reported no difference in the work of breathing between PCV and VCV when V_T and peak inspiratory flow were appropriately matched. Similarly, KALLET *et al.* [55] demonstrated no difference in the work of breathing when providing LPV to ALI/ARDS patients using PCV in comparison to VCV with a high inspiratory flow rate. Furthermore, V_T was not adequately controlled as a result of an active inspiratory effort in 40% of the patients during PCV [55]. SCHMIDT *et al.* [56] reiterated that V_T and, hence, alveolar distension may be increased during active inspiratory efforts by the patient. While this may not translate to increased inspiratory pressures, it may culminate in volutrauma. Thus, one may conclude that paying particular attention to ventilator parameters such as V_T, peak inspiratory flow, P_{plat} and waveform pattern minimises the differences seen between PCV and VCV. In a recent multicentre RCT, MEADE *et al.* [57] compared a low V_T ventilation strategy using VCV with an experimental strategy (open lung approach) using PCV in which both arms targeted a V_T of 6 mL·kg^{-1} ideal body weight. There were no difference in outcome; however, a direct comparison is confounded by the fact that different PEEP strategies were utilised in both arms [58].

An adaptation to the use of PCV in ALI/ARDS patients has involved employing an inspiratory time that is longer than the expiratory time in order to increase the mean airway pressure ($\bar{P}_{aw}$), and thereby improve arterial oxygenation. This is called pressure-controlled inverted ratio ventilation (PC-IRV). Early reports of this ventilatory approach following failure of VCV indicated reductions in peak airway pressures, improvement in arterial oxygenation at lower minute ventilation and lower PEEP requirements without any worsening of haemodynamic parameters [59–63]. Although less common, volume-controlled (VC)-IRV has also being utilised in ARDS patients [64, 65]. However, later studies did not demonstrate any significant benefit of PC-IRV over VCV in terms of arterial oxygenation, haemodynamic compromise or risk of barotraumas resulting from the elevated $\bar{P}_{aw}$ and intrinsic PEEP, and that often led to the increased use of sedative and paralytic agents [66–70]. Based on current evidence, IRV is of unproven benefit in the ventilatory management of ARDS patients [71, 72]. Airway pressure release ventilation (APRV), another ventilatory mode that uses long inspiratory times will be discussed in a subsequent section.

Positive end-expiratory pressure

The use of PEEP in addition to LPV is a vital element in the ventilatory management of ALI/ARDS patients. Low V_T ventilation can lead to alveolar de-recruitment, particularly if an inadequate level of PEEP is utilised [73, 74]. The resultant cyclic collapsing and re-opening of alveoli during tidal ventilation are known to contribute to the development of VILI [5, 6, 9, 75]; thus, avoiding this situation by the addition of the necessary amount of PEEP to keep the lung open is essential in limiting its development [6, 76, 77]. Furthermore, the addition of PEEP results in enhanced oxygenation and the subsequent reduction in F_{I,O_2} requirements, believed to result from different mechanisms, namely, recruitment of alveoli, increased functional residual capacity, extravascular lung water redistribution and improvement in ventilation–perfusion matching [21, 78]. In addition, rescue therapies for severe hypoxaemia, such as inhaled nitric oxide, prone positioning, high frequency oscillation and extracorporeal membrane oxygenation, were used less frequently in some studies [57, 79]. Conversely, high levels of PEEP may result in a reduction in venous return and impairment in the right ventricle, ultimately leading to decreased cardiac output [80, 81]. However, the manner in which PEEP is selected has varied and the level required optimising its benefits while maintaining LPV has been the subject of multiple studies.

Several methods have been used to select the level of PEEP required in the ventilatory management of ALI/ARDS patients (table 2). The use of a table of F_{I,O_2}–PEEP combinations has commonly been used to select the level of PEEP required based on oxygenation targets (P_{a,O_2} 55–80 mmHg) [14, 57, 83]. Increases in these combinations are performed to maintain the oxygenation target, while also ensuring airway pressure limits are not exceeded *i.e.* $P_{plat} \leqslant 30$ cmH_2O. In contrast, regardless of its effect on oxygenation, MERCAT *et al.* [79] individually titrated PEEP to a level that did not exceed a P_{plat} of 28–30 cmH_2O. A decremental approach has been used by some authors, in which PEEP is set to $\geqslant 20$ cmH_2O, subsequently, stepwise decreases are made to identify the level that results in the best P_{a,O_2} and compliance [84, 85]. The pressure–volume (PV) curve has been used to assess the lower and upper inflection points (LIP and UIP, respectively) on the inspiratory limb of the curve to guide the level of PEEP and inflation pressure required [12, 13, 18]. The level of PEEP is usually set slightly higher than the LIP (*e.g.* 2–3 cmH_2O higher) [12, 13, 18]. GRASSO *et al.* [86] employed the stress index (SI) to determine the level of PEEP by using the pressure–time curve during constant-flow inhalation, *i.e.* tidal volume delivery. An SI >1 (upward sloping concave curve) represents overdistension, *i.e.* excessive PEEP, an SI <1 (downward sloping concave curve) represents ongoing recruitment, *i.e.* inadequate PEEP, and an SI equal to 1 (linear slope) represents no ongoing recruitment or overdistension *i.e.* adequate PEEP (fig. 2) [86, 87]. Finally, the use of an oesophageal balloon (fig. 3) to measure the

Table 2. Methods for selecting positive end-expiratory pressure (PEEP)

Method	Description
Incremental PEEP using empirical table	Combinations of F_{I,O_2} and PEEP are utilised to attain the desired oxygenation level or highest compliance
Incremental PEEP using P_{plat}	PEEP is individually titrated to a level such that P_{plat} is <30 cmH_2O
Decremental PEEP	A high level of PEEP is set (*e.g.* 20 cmH_2O); subsequently PEEP is decreased in a stepwise manner until de-recruitment takes place, typically with a decrease in P_{a,O_2} and compliance
Stress index measurement	Pressure–time curve is monitored during constant-flow inhalation for indications of tidal recruitment and over distension
Oesophageal pressure measurement	Intrapleural pressure is estimated by using an oesophageal balloon to measure oesophageal pressure; subsequently, the optimal PEEP level required is determined
Pressure–volume curve guidance	PEEP is set slightly higher than the lower inflection point

P_{plat}: plateau pressure; F_{I,O_2}: inspiratory oxygen fraction; P_{a,O_2}: arterial oxygen tension. Reproduced from [82], with permission from the publisher.

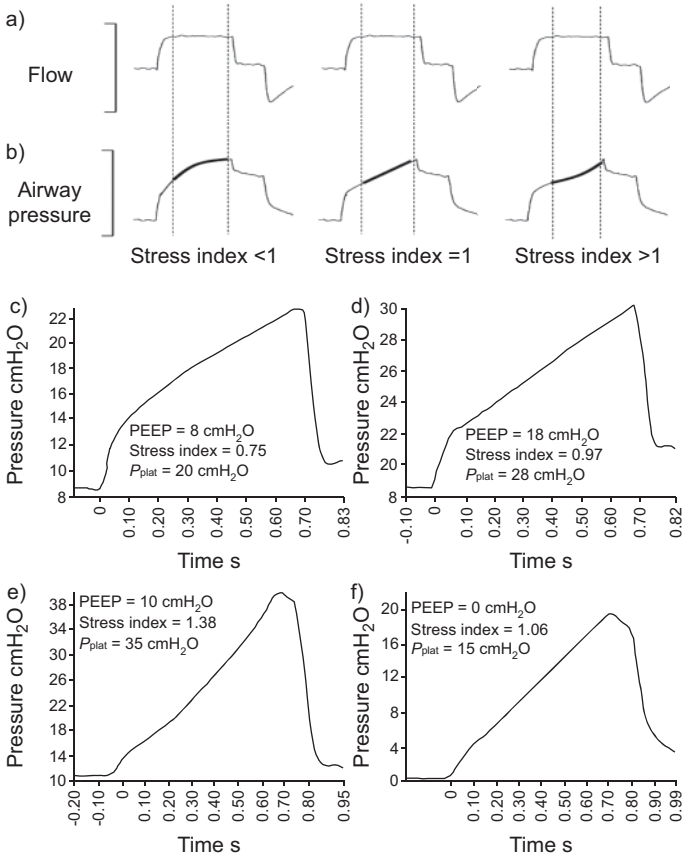


Figure 2. Stress index concept: a) flow and b) airway pressure *versus* time are demonstrated for three stress index concepts. The shape of the airway pressure waveform segment (bold lines) during constant-flow inflation of volume-cycled mechanical ventilation (·····) is used to determine the stress index. With a stress index <1, the airway pressure curve presents a downward concavity suggesting continuous decrease in elastance. With a stress index >1, the airway pressure curve presents an upward concavity suggesting continuous increase in elastance. With a stress index of 1, the airway pressure curve is straight, suggesting the absence of tidal variations in elastance. c–f) Stress index measurements in a patient with acute respiratory distress syndrome (ARDS). c, d) Early in the course of ARDS due to H1N1 infection. The stress index improves as positive end-expiratory pressure (PEEP) is increased. e, f) Late in the course of ARDS. The stress index improves as PEEP is decreased. a, c) Reproduced from [86] and c–f) reproduced from [87] with permission from the publisher.

oesophageal pressure and thereby estimate the intrapleural pressure has also been used to determine the optimal PEEP required [29, 30, 87]. Each of the aforementioned approaches has limitations, and there is currently no best method to selecting PEEP. Furthermore, most of the individualised approaches described can be technically challenging, consequently gas exchange targets using F_{I,O_2}–PEEP tables are more often clinically utilised to set PEEP.

Multiple randomised controlled studies (table 3) have been conducted to determine the optimal level of PEEP required in managing ALI/ARDS patients by comparing a lower/modest (conservative) *versus* a higher (aggressive) PEEP strategy, resulting in conflicting results [12, 13, 18, 30, 57, 79, 83]. Similarly, several meta-analyses of these studies (table 4) have been carried out to distinguish the outcomes in these patients when utilising a lower *versus* higher PEEP strategy, also resulting in varying results [20, 88–91]. Comparisons are challenging as the earlier studies [12, 13, 18] utilised ventilator strategies of high PEEP with low V_T against low PEEP with high V_T in ARDS patients, while the later studies [30, 57, 79, 83] compared high *versus* low PEEP with low V_T strategies in ALI/ARDS patients. In addition, different criteria were used for PEEP selection in the various aforementioned studies. Overall, there was a trend towards a mortality benefit in the high PEEP groups compared with the low PEEP groups in the different meta-analyses [20, 88–91]. In the only patient-level meta-analysis conducted using individual data from the three larger studies [91], as opposed to aggregated data used in other study-level meta-analyses [20, 88, 89], BRIEL *et al.* [91] concluded that although there was no overall difference in hospital mortality between the high and low PEEP groups, there was a significant reduction in mortality in the intensive care unit patients assigned to the high PEEP group. Furthermore, the subgroup of patients with ARDS at baseline had a reduced hospital mortality and were more likely to achieve liberation from ventilatory support earlier. Conversely, patients without ARDS at baseline who were assigned to the high PEEP group had a higher mortality risk. The authors conclude that higher levels of PEEP may be associated with reduction in hospital mortality in ARDS patients but may be detrimental to patients with less severe lung injury, *i.e.* ALI.

Although both the best strategy to determine PEEP and the most favourable level of PEEP required in the management of ALI/ARDS patients are unclear, it is vital to maintain the goals of LPV. High PEEP levels have been reported to result in lung overinflation in the caudal and non-dependent regions in ALI patients with a focal morphological pattern [92]. Similarly, as stated earlier, lung overinflation has been described in one-third of ARDS patients undergoing LPV with small, nondependent, normally aerated lung regions and large, dependent, nonaerated lung regions, resulting in the suggestion by the investigators of a more protective ventilator setting, *i.e.* P_{plat} <28 cmH_2O [28]. However, when determining the level of PEEP required, in order to avoid the development of VILI, it is important to consider both the potential for recruitment as well as the risk of alveolar overinflation, in addition to maintaining the goals of LPV [28, 92, 93].

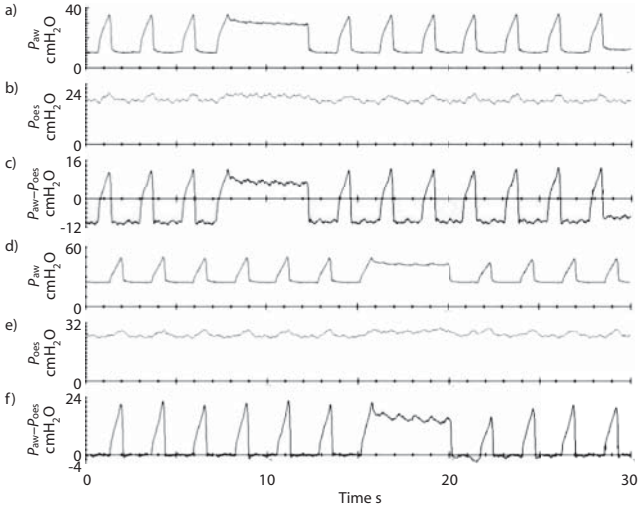


Figure 3. Positive end-expiratory pressure (PEEP) titration using oesophageal monitoring in a patient with morbid obesity. a) Oesophageal pressure (P_{oes}), used as a surrogate for pleural pressure, is greater than the PEEP setting. b) The PEEP setting is increased so that the collapsing effect of the intrapleural pressure is offset. Although the plateau pressure is 40 cmH_2O, the alveolar distending pressure is only 14 cmH_2O. P_{aw}: airway pressure. Reproduced from [87] with permission from the publisher.

Recruitment manoeuvres

A recruitment manoeuvre (RM) is a process whereby the reopening of collapsed alveoli occurs by means of a deliberate transient increase in the transpulmonary pressure, with the aim of improving gas exchange and respiratory mechanics [94–97]. As stated previously, in patients with ALI/ARDS, the use of LPV can result in alveolar collapse due to low V_T [73, 74], and just like with PEEP, RMs have been utilised to open up collapsed lung [94]. However, there is currently no clear evidence demonstrating a beneficial clinical outcome with the use of RM in ALI/ARDS patients.

Various methods have been used to describe RMs [94, 96]. In a recent systematic review of 1,185 ALI/ARDS patients [94], the most frequently used methods were sustained inflation (45%), high PCV (23%), incremental PEEP (20%) and high V_T/sigh (10%). The efficacy of sustained inflation, although the most commonly used RM, has been reported to be ineffective [98, 99], fleeting [100], coupled with haemodynamic impairment [101], associated with an increased risk of baro- and volutrauma [102], reduced net alveolar fluid clearance [103] and deterioration in oxygenation [104]. In a recent study [105], in contrast to the usual practice of applying a continuous pressure of 40 cmH_2O to the airways for up to 60 seconds, ARNAL *et al.* [105] demonstrated that most of the recruitment with sustained inflation occurs in the first 10 seconds in early-onset ARDS patients, subsequently followed by haemodynamic compromise after 10 seconds. In the corresponding article, it is suggested that sustained inflation should be abandoned for more effective RMs or, if utilised, should be closely monitored and applied for only a limited duration [106]. Some of these more effective techniques have recently been described and include [98]: 1) incremental increase in PEEP with limitation of the maximal inspiratory pressure [107]; 2) protracted lower pressure RM with elevation in PEEP of up to 15 cmH_2O and end-inspiratory pauses for 7 seconds twice a minute during a 15-minute period [108]; 3) PCV applied with increasing PEEP and constant driving pressure [99]; 4) intermittent sighs to reach a specific P_{plat} with either VCV or PCV [109]; and 5) a long slow increase in inspiratory pressure up to 40 cmH_2O [110]. The superiority of one method over the other remains undecided, and similarly the most favourable pressure, duration and regularity of RMs required is yet to be determined.

Table 3. Randomised controlled trials of high *versus* low positive end-expiratory pressure (PEEP) strategy

	First author [ref.]	Patients n	Intervention		Mortality %
			High PEEP group	Low PEEP group	
High PEEP + low *Vt versus* low PEEP + high *Vt*	AMATO [13]	53	PEEP: 16.3±0.7 cmH_2O *Vt*: 6 $mL \cdot kg^{-1}$ *P*plat: 31.8±1.4 cmH_2O	PEEP: 6.9±0.8 cmH_2O *Vt*: 12 $mL \cdot kg^{-1}$ *P*plat:34.4±1.9 cmH_2O	38 *versus* 71# (p<0.001) 45 *versus* 71¶ (p=0.37)
	RANERI [18]	37	PEEP: 14.8±2.7 cmH_2O *Vt*: 7.6±1.1 $mL \cdot kg^{-1}$ *P*plat: 24.6±2.4 cmH_2O	PEEP: 6.5±1.7 cmH_2O *Vt*: 11.1±1.9 $mL \cdot kg^{-1}$ *P*plat:31.0±4.5 cmH_2O	38 *versus* 58# (p=0.19)
	VILLAR [12]	95	PEEP: 14.1±2.8 cmH_2O *Vt*: 7.3±0.9 $mL \cdot kg^{-1}$ *P*plat: 30.6±6.0 cmH_2O	PEEP: 9.0±2.7 cmH_2O *Vt*:10.2±1.2 $mL \cdot kg^{-1}$ *P*plat:32.6±6.2 cmH_2O	32 *versus* 53.3+ (p=0.040) 34 *versus* 55.5¶ (p=0.041)
High PEEP + low *Vt versus* low PEEP + low *Vt*	BROWER [82]	549	PEEP: 14.7±3.5 cmH_2O *Vt*: 6.0±0.9 $mL \cdot kg^{-1}$ *P*plat: 27±6 cmH_2O	PEEP: 8.9±3.5 cmH_2O *Vt*: 6.1±0.8 $mL \cdot kg^{-1}$ *P*plat: 24±7 cmH_2O	25.1 *versus* 27.5¶ (p=0.48)
	MERCAT [79]	767	PEEP: 14.6±3.2 cmH_2O *Vt*: 6.1±0.3 $mL \cdot kg^{-1}$ *P*plat: 27.5±2.4 cmH_2O	PEEP: 7.1±1.8 cm H_2O *Vt*: 6.1±0.4 $mL \cdot kg^{-1}$ *P*plat: 21.1±4.7 cmH_2O	27.8 *versus* 31.2# (p=0.31) 35.9 *versus* 39.5¶ (p=0.31)
	MEADE [57]	983	PEEP: 15.6±3.9 cmH_2O *Vt*: 6.8±1.4 $mL \cdot kg^{-1}$ *P*plat: 30.2±6.3 cmH_2O	PEEP: 10.1±3.0 cmH_2O *Vt*: 6.8±1.3 $mL \cdot kg^{-1}$ *P*plat: 24.9±5.1 cmH_2O	36.4 *versus* 40.4¶ (p=0.19) 28.4 *versus* 32.3# (p=0.20)
	TALMOR [30]	61	PEEP: 17±6 cmH_2O *Vt*: 7.1±1.3 $mL \cdot kg^{-1}$ *P*plat:28±7 cmH_2O	PEEP: 10±4 cmH_2O *Vt*: 6.8±1 $mL \cdot kg^{-1}$ *P*plat: 25±6 cmH_2O	17 *versus* 39# (p=0.055)

Data for intervention were obtained on day 1, except for the study by TALMOR [30] when the data were obtained on day 3. *V*T: tidal volume; *P*plat: plateau pressure. #: 28-day mortality; ¶: hospital mortality; +: ICU mortality.

In the aforementioned review [94], an improvement in oxygenation was also reported following the RMs (P_{a,O_2} 106 *versus* 193 mmHg (p=0.001) and $P_{a,O_2}/F_{I,O_2}$ ratio 139 *versus* 251 mmHg (p<0.001)), although a rapid decline in the oxygenation benefits was reported to occur, sometimes within 15 to 20 minutes of the RM. Conversely, studies that have utilised a decremental PEEP strategy following an RM have sustained oxygenation benefits for up to 4–6 hours [83, 111], thus suggesting that the utilisation of higher PEEP levels after an RM may influence the sustainability of the effect. The timing of an RM also appears to play a role such that the longer the duration of ALI/ARDS, the less likely a beneficial effect will be derived [73, 112, 113]. GRASSO *et al.* [112] studied ARDS patients being ventilated with the ARDSnet strategy and demonstrated a response to a RM in those patients who received RM early, *i.e.* mean±SD 1±0.3 days, as opposed to no response in those who received it late, *i.e.* 7±1 days. In the study by GATTINONI *et al.* [113], limited benefit was derived from an RM; however, the average duration of mechanical ventilation prior to recruitment was 5±6 days. Again, no significant improvement in oxygenation occurred in the study by VILLAGRA *et al.* [99] in both the early (ventilation <3 days) ARDS group as opposed to the late (ventilation >7 days) ARDS group, although oxygenation improvement in the latter group was less responsive to RMs than in the former group. However, baseline PEEP levels in the early and late ARDS groups were 14±1.3 and 15±1.9 cmH_2O, respectively [99]. Consequently, it was suggested that no benefit may be obtained from RMs if the lung has been optimally recruited from the level of PEEP applied [99]. Further modalities that are being employed to determine the potential for response to an RM include, pressure–volume curves by evaluating hysteresis [114], lung ultrasound [115, 116], electrical impedance tomography [117, 118] and computed tomography scan of the chest (not available at bedside) to determine lung morphology, *i.e.* focal, patchy or diffuse lung densities [113, 119].

Table 4. Meta-analyses of high *versus* low positive end-expiratory pressure (PEEP) strategy

Meta-analysis	RCT	Patients n	Summary of results
Oba [90]	A, C, D–F	2447	Small but significantly decreased hospital mortality with high PEEP[#] RR 0.89; 95% CI 0.80–0.99; p=0.03[¶] Trend toward decreased 28-day mortality with high PEEP[#] RR 0.88, 95% CI 0.76–1.01; p=0.06[+] No significant difference in incidence of barotraumas OR 1.19, 95% CI 0.89–1.58; p=0.25 No difference in ICU-free, ventilator-free and organ failure-free days Benefits of high PEEP are higher in patients with higher ICU severity scores
Pheonix [89]	A–F	2484	Significantly decreased early and hospital mortality with high PEEP[#] RR 0.87, 95% CI 0.78–0.96; p=0.007 (A – F)[§] RR 0.87, 95% CI 0.77–0.97; p=0.0199 (A, C – F)[¶] In the three larger studies: trend towards decreased mortality in high PEEP[#] RR 0.90, 95% CI 0.81–1.01; p=0.077 (D – F)[¶] No significant difference in incidence of barotraumas in all five trials, but trend towards increased risk in three large trials with high PEEP[#] RR 0.95, 95% CI 0.62–1.45; p=0.81 (A, C, D – F) RR 1.17, 95% CI 0.90 1.52; p=0.25 (D – F)
Putensen [20]	A, C, D–F	2447	No significant difference in hospital mortality or barotrauma in studies D–F (lower *Vt*) with high PEEP[#] OR 0.86, 95% CI 0.72–1.02; p=0.08[¶] OR 1.19, 95% CI 0.89–1.58; p=0.25 High PEEP reduced need of rescue therapy for life-threatening hypoxaemia and reduced mortality in those patients receiving rescue therapy in studies E and F OR 0.51, 95% CI 0.36–0.71; p<0.001 OR 0.51, 95% CI 0.36–0.71; p<0.001 Decreased mortality and barotraumas with high PEEP in studies A and C[#] OR 0.38, 95% CI 0.20–0.75; p=0.005[¶] OR 0.20, 95% CI 0.06–0.63; p=0.006
Briel [91]	D–F	2299	No difference in hospital mortality between high *versus* low PEEP (32.9% *versus* 35.2%) RR 0.94, 95% CI 0.86–1.04; p=0.25[¶] Decreased ICU mortality with high PEEP (28.5% *versus* 32.8%) RR 0.87, 95% CI 0.78–0.97; p=0.01[ƒ] High PEEP resulted in decreased hospital mortality in patients with ARDS at baseline 34.1% *versus* 39.1%) but non-significant increase in patients without ARDS at baseline (27.2% *versus* 19.4%) RR 0.90, 95% CI 0.81–1.00; p=0.049[¶] RR 1.37, 95% CI 0.98–1.92; p=0.07[¶] Increased ventilator-free days in ARDS patients with high PEEP (64.3% *versus* 57.8% at 28 days), but decreased in non-ARDS patients (70.1% *versus* 80.9%) HR 1.16, 95% CI 1.03–1.30; p=0.01 HR 0.79, 95% CI 0.62–0.99; p=0.04 Reduced use of rescue therapy or death following rescue therapy with high PEEP RR 0.64, 95% CI 0.54–0.75; p<0.001 RR 0.65, 95% CI 0.52–0.80; p<0.001 No difference in incidence of barotraumas or vasopressor use RR 1.19, 95% CI 0.89 .60; p=0.24 RR 0.93, 95% CI 0.75 .14; p=0.49
Dasenbrook [88]	D–G	2360	Non-significant 28-day mortality trend favouring high PEEP (27% *versus* 30%), but no difference in hospital mortality[#] RR 0.90, 95% CI 0.79–1.02 (D –G)[+] RR 0.94, 95% CI 0.84–1.05; p=0.25 (D – F)[¶] Non-significant increase in barotraumas in high PEEP (9% *versus* 8%)[#] RR 1.17, 95% CI 0.90–1.52

RCT: randomised controlled trials; ICU: intensive care unit; *Vt*: tidal volume; ARDS: acute respiratory distress syndrome. A: Amato *et al.* [13]; B: Ranieri *et al.* [18]; C: Villar *et al.* [12]; D: Brower *et al.* [83]; E: Mercat *et al.* [79]; F: Meade *et al.* [57]; G: Talmor *et al.* [30]. [#]: pooled analysis; [¶]: hospital mortality; [+]: 28-day mortality; [§]: early mortality *i.e.* hospital plus 28-day mortality; [ƒ]: ICU mortality.

Patients occasionally require sedation and/or neuromuscular blockade during the utilisation of RMs. The most concerning complications that have been described are haemodynamic compromise and barotrauma. In their systemic review of RM, Fan *et al.* [94] reported the most common complications as being hypotension (10%) and desaturation (8%), with the more severe complications of barotraumas (1%) and arrhythmias (1%) being relatively rare. Consequently, the presence of clinical

situations, such as haemodynamic compromise and barotrauma in ALI/ARDS patients, should preclude the use of RMs [120].

Current evidence suggests that the indiscriminate use of RMs in unselected ALI/ARDS patients may be non-beneficial. No prospective study has demonstrated a favourable clinical outcome. Considering its minimal risk for harm as well as the possibility for improvement in oxygenation, RMs may be considered on an individual basis in ALI/ARDS patients with life-threatening hypoxaemia with non-aerated lung zones, to aid in determining the appropriate level of PEEP required and also to recruit lungs that have undergone interventions associated with de-recruitment such as endotracheal suctioning or ventilator disconnections [94, 96, 121, 122].

Airway pressure release ventilation

APRV is a pressure-limited, time-cycled ventilatory approach that utilises a high continuous airway pressure level (P_{high}) with a periodic pressure release to a lower airway pressure level (P_{low}), while simultaneously permitting patients to take spontaneous breaths at any point of the ventilator cycle (fig. 4) [123, 124]. Different time ratios for P_{high} to P_{low} have been utilised with APRV, ranging from 1:1 to 9:1 in different studies [125, 126]. Optimising the time spent at P_{high}, *i.e.* T_{high}, potentially ensures adequate alveolar recruitment occurs, which in addition to the $F_{I,O2}$, can determine and improve the level of oxygenation. The periodicity and usually short duration of the pressure release to P_{low}, together with the patient's ability to breathe spontaneously, determine the level of alveolar ventilation that takes place. Consequently, the V_T generated is a function of the lung compliance, airway resistance, periodicity and duration of the pressure release phase [127]. The patient's spontaneous breathing can occur throughout the ventilator cycle as a result of an active exhalation valve; however, it tends to occur more frequently during P_{high} which usually represents 80–95% of the ventilator cycle, as opposed to P_{low} which tends to last for 0.2–0.8 seconds in adults [128]. This short duration during P_{low}, *i.e.* T_{low}, can result in an incomplete expiration resulting in the development of auto-PEEP from trapped gas volume [125].This is occasionally permitted to occur, particularly if the approach to APRV being used sets P_{low} at 0 cmH_2O, so as to prevent de-recruitment [128]. Notably, in the absence of spontaneous breathing, APRV is functionally identical to PC-IRV. In contrast, because spontaneous breathing is preserved, the need for heavy sedation and paralysis is unlikely [129, 130]. A further benefit of the maintenance of spontaneous breathing in APRV, particularly in ALI/ARDS patients, is the resultant diaphragmatic contractions that take place. In conventional mechanical ventilation, such as in VCV and PCV, diaphragmatic contraction is absent in fully ventilated patients. In addition, the dependent (dorsal) regions of the lung are inadequately ventilated in the supine patient. However, spontaneous breathing during APRV leads to recruitment of these dependent, juxtadiaphragmatic lung regions, thereby improving ventilation–perfusion matching, reducing intrapulmonary shunt, enhancing oxygenation and potentially reducing the likelihood of VILI [130–133]. However, care must be taken as spontaneous breaths during P_{high} can potentially produce negative pleural pressures that add to the V_T being generated by the ventilator, resulting in over-distension and subsequent volutrauma (fig. 4). Similarly, de-recruitment and subsequent atelectrauma can develop if T_{low} is not sufficiently short in duration [128].

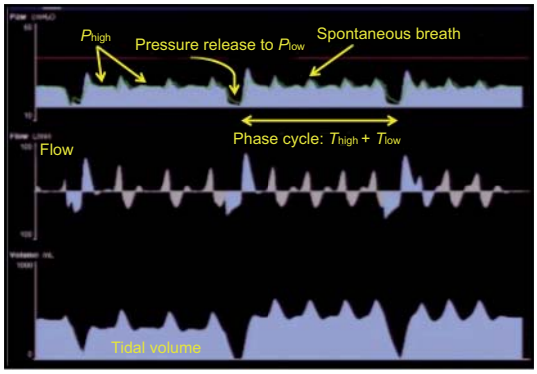


Figure 4. Airway pressure release ventilation in a spontaneously breathing patient. Airway pressure, flow and tidal volume are displayed during airway pressure release ventilation. Spontaneous breaths are seen occurring at P_{high}, followed by a pressure release to P_{low}. The corresponding effect of spontaneous breaths during P_{high} are seen on the tidal volumes generated (T_{high} and T_{low}), underscoring the possible risk of overinflation.

There are a small number of clinical studies evaluating the use the APRV in ALI/ARDS

patients. In comparison to other forms of mechanical ventilation (*e.g.* synchronised intermittent mechanical ventilation (SIMV), PCV, VC-IRV, PC-IRV), some crossover studies have reported lower peak airway pressure requirements, less need for sedation or paralysis and improved oxygenation [129, 134–137]. A few moderately sized RCTs have also been performed with APRV [130, 138–140]. PUTENSEN *et al.* [130] randomised 30 multiple trauma patients who had or were at risk for developing ALI/ARDS to APRV *versus* PCV. The use of APRV resulted in increased lung compliance and oxygenation, as well as a reduction in the duration of ventilator support (15 *versus* 21 days), intensive care unit stay (23 *versus* 30 days) and less sedation and vasopressor requirements. However, these results are questionable because patients in the PCV group were initially paralysed for 72 hours. VARPULA *et al.* [139] initially randomised 45 ALI patients within 72 hours of mechanical ventilation to APRV *versus* pressure-controlled SIMV with pressure support (SIMV-PC/PS) in order to evaluate the effect of prone positioning on these ventilator strategies. The procedure for prone positioning was identical in both groups, and 33 out of the 45 patients who underwent prone positioning were analysed. Oxygenation was significantly improved in the APRV group following randomisation ($P_{a,O_2}/F_{I,O_2}$ 162 *versus* 123 mmHg; p=0.02) and this was further enhanced following two 6-hour sessions of prone positioning ($P_{a,O_2}/F_{I,O_2}$ 216 *versus* 180 mmHg; p=0.02). Sedation and analgesia requirements, incidence of adverse events and 28-day mortality were similar in both groups. In a subsequent RCT performed by the same investigators [140], 58 ALI patients were randomised to APRV *versus* SIMV-PC/PS. As in the previous study [139], it preceded the publication of the ARDSnet study [14], so liberal V_T (8–10 mL·kg^{-1}) was utilised in the ventilation protocol. However, this study was terminated early for futility after enrolling just 58 of the targeted 80 patients. There were no significant differences in ventilator-free days, sedation and analgesia requirements, as well as 28-day and 1-year mortality. In a recent randomised trial of 63 trauma patients (40% of them had ALI/ARDS) [138], APRV was compared to low V_T ventilation using volume-control SIMV with pressure support (SIMV-VC/PS). The results demonstrated a similar safety profile in both groups; however, there was a nonsignificant trend towards an increase in ventilator days (10.49±7.23 *versus* 8.00±4.01 days), intensive care unit length of stay (16.47±12.83 *versus* 14.18±13.26 days) and ventilator-associated pneumonia in the APRV group. Notably, low V_T ventilation was performed using SIMV-VC/PS instead of VCV which was in the ARDSnet study [14].

APRV is an alternative mode of mechanical ventilation that has potential benefits of lung recruitment, oxygenation and sedation requirements, and is being increasingly used as a primary ventilator strategy, as well as a rescue modality in ALI/ARDS patients. However, properly designed and powered RCTs are required to determine any potential outcome benefits with the use of APRV and thereby elucidate its precise role in the ventilatory management of ALI/ARDS patients. A concern with APRV is that at P_{high}, in an actively breathing patient, alveolar overdistension may occur. The mechanism is one of reduced pleural pressures during patient's inspiratory effort. This is especially true if the spontaneous breaths are supported by pressure support ventilation or automatic tube compensation.

High-frequency ventilation

High-frequency ventilation (HFV) can be broadly defined as a mechanical ventilatory strategy that utilises respiratory rates >100 breaths per minute in conjunction with the generation of small V_T, usually smaller than traditional estimations of both anatomical and physiological dead space, and ranging from ~1–5 mL·kg^{-1} [141, 142]. Different forms of HFV exist and include high-frequency oscillatory ventilation (HFOV), high-frequency percussive ventilation (HFPV), high-frequency positive pressure ventilation and high-frequency jet ventilation. The two forms of HFV that will be discussed in more detail are HFOV and HFPV. HFOV is more commonly described in ARDS compared to HFPV. Both modes, in theory, meet the goals of LPV from the generation of small V_T and constant lung recruitment [143]. Unlike in conventional ventilation where gas transport takes place by bulk delivery of gas, additional theoretical mechanisms believed to enhance gas exchange in these forms of HFV have been described in the literature and include: asymmetric velocity profiles, longitudinal (Taylor) dispersion, pendelluft, cardiogenic mixing and molecular diffusion [141, 144–146]. However, none of the forms of HFV have demonstrated clinical outcome benefit. Nonetheless,

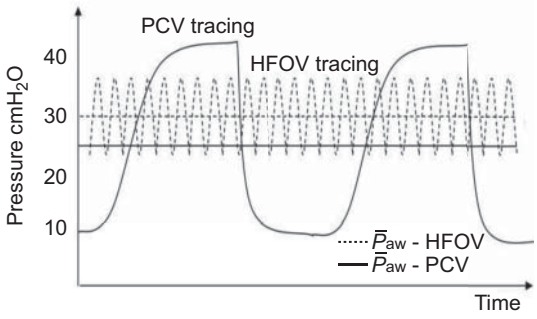


Figure 5. Schematic representation of perceived waveforms of high-frequency oscillatory ventilation (HFOV) and conventional pressure-controlled ventilation (PCV) in the distal airways. Large oscillatory pressure swings above and below a constant mean airway pressure ($\bar{P}_{aw}$) are present at the proximal airways during HFOV, but are significantly reduced by the time the distal airways/alveoli are reached. The $\bar{P}_{aw}$ in HFOV tend to be higher than that in conventional ventilation contributing thereby to recruitment and increased oxygenation. Reproduced from [149] with permission from the publisher.

they both have been used as rescue modalities in ALI/ARDS patients with refractory/severe hypoxaemia.

High-frequency oscillatory ventilation

HFOV is characterised by the generation of small tidal volumes as a result of the oscillation of a bias gas flow resulting in pressure swings within the airway at frequencies ranging from 3 to 15 Hz (usually 3–6 Hz in adults) [147]. The oscillations are produced by an oscillatory diaphragm/piston pump, and result in an active inspiratory and expiratory phase. The rapid oscillations of gas are delivered at pressures above and below a constant $\bar{P}_{aw}$ which, in addition to F_{I,O_2}, determine the level of oxygenation. The $\bar{P}_{aw}$ at the outset is usually set approximately 5 cmH_2O above that obtained with conventional ventilation; however, the oscillatory pressure swings, which may be significant in the proximal airways, are substantially attenuated by the time the distal airways/alveoli are reached (fig. 5), resulting in the small V_T [147, 148]. Ventilation, however, is directly related to the pressure amplitude of oscillation, *i.e.* degree of displacement by the oscillatory diaphragm/piston pump, but inversely related to the set frequency [149]. The combined effects of a high $\bar{P}_{aw}$ and small V_T potentially result in improved recruitment of alveoli associated with a reduced risk of overdistension, thereby improving gas exchange and maintaining the goal of lung protection.

The majority of evidence associated with the use of HFOV in adults has been small observational (retrospective and prospective) studies in patients with refractory hypoxaemia or severe ARDS usually failing conventional ventilation [150–160]. These studies demonstrated that HFOV improved oxygenation without haemodynamic compromise, was safe and effective in patients failing conventional ventilation, was more likely to be beneficial if used early in the course of ARDS, and that failure to improve oxygenation was associated with high mortality. However, in several of these observational studies a high percentage of patients received sedation and paralysis [151, 153, 155–161]. To further improve gas exchange, HFOV has also been used in conjunction with RMs [152], prone positioning [162] and inhaled nitric oxide [161]. Other studies have been performed that have compared HFOV (occasionally in combination with other therapy) to conventional ventilation as the primary ventilatory strategy in ALI/ARDS, rather than as rescue therapy in refractory hypoxaemia. In the largest of the RCTs, DERDAK *et al.* [163] randomised 148 adult ARDS patients to HFOV *versus* conventional ventilation (PCV at 6–10 $mL \cdot kg^{-1}$ actual body weight), to compare safety and effectiveness. The applied $\bar{P}_{aw}$ was significantly higher in the HFOV group, and an early augmentation in the $P_{a,O_2}/F_{I,O_2}$ ratio was also seen. However, this did not continue beyond 24 hours. Furthermore, when comparing both the HFOV and conventional ventilation groups, there was no significant difference in terms of 30-day mortality (37 *versus* 52%; p=0.102), haemodynamic parameters, oxygenation and ventilation failure, barotraumas or mucus plugging. This study, in addition to being designed prior to the publication of the ARDSnet study [14], did not utilise 6 $mL \cdot kg^{-1}$ or lower V_T in the control group and was not powered to evaluate mortality. BOLLEN *et al.* [164] similarly compared safety and effectiveness between HFOV and conventional ventilation (PCV) in 61 adult ARDS patients. There was no significant difference between both groups in terms of cumulative survival without oxygenation dependency or being on ventilatory support at 30 days (primary end-point), in addition there was no difference in mortality, therapy failure or cross-over rates of treatment arms. This study was, however, stopped early due to low patient recruitment which also contributed to an uneven randomisation of patients. Nonetheless, *post hoc* analysis suggested that HFOV may be more beneficial in patients with a higher

baseline oxygenation index ($\bar{P}aw \times FI,O_2/Pa,O_2$). In a Cochrane database systemic review of RCTs comparing treatment with HFOV *versus* conventional ventilation in children and adults with ALI/ARDS, only two RCTs met the inclusion criteria [165]. The authors surmised that there was insufficient data to conclude whether HFOV reduced mortality or long-term morbidity in ALI/ARDS patients. In a subsequent systemic review of 419 patients [143], HFOV was compared to conventional ventilation as a primary ventilatory strategy for ALI/ARDS patients in contrast to rescue treatment for refractory hypoxaemia. A majority of the patients from the reviewed trials were adults (80%). In contrast to the earlier systemic review [165], HFOV was reported to significantly reduce mortality at hospital discharge or 30 days (risk ratio 0.77, 95% CI 0.61–0.98; p=0.03), but this was stated to be based on relatively few patients and outcome events, with analysis demonstrating wide confidence intervals. There was also a decreased risk of treatment failure with HFOV, but no difference in duration of mechanical ventilation or ventilator-free days. HFOV was also reported to increase the $Pa,O_2/FI,O_2$ ratio by 16–24% within the first 72 hours and increased $\bar{P}aw$ by 23–33% in comparison to conventional ventilation. No differences in adverse events such as barotrauma, hypotension and endotracheal obstruction were reported. The authors conclude that HFOV may decrease mortality in ARDS patients compared with conventional ventilation and is unlikely to cause harm. However, completion of ongoing multicentre randomised trials (OSCILLATE trial: ISRCTN 87124254; and OSCAR trial: ISRCT N10416500) comparing HFOV to current conventional LPV should provide more definitive data with regards to mortality and safety [143].

High-frequency percussive ventilation

HFPV is a pressure-limited, flow-regulated and time-cycled ventilator mode that delivers a sequence of high-frequency (200–900 cycles per minute), small volumes in a consecutive stepwise stacking pattern, leading to the formation of low-frequency (up to 40–60 cycles per minute), convective, pressure-limited breathing cycles (fig. 6) [87, 166–168]. Gas exchange is a function of the percussion frequency, such that at high percussion frequencies (300–600 cycles per minute) oxygenation is augmented, while at low percussion frequencies, carbon dioxide clearance is augmented [87, 167, 169, 170]. The volumetric diffusive respirator is the only ventilator that provides HFPV and an interplay of its control variables, either individually or in combination, play a role in determining the $\bar{P}aw$ and degree of gas exchange [87, 167, 169, 171–173].

There are a limited number of small studies on the use of HFPV in ALI/ARDS patients. GALLAGHER *et al.* [174]

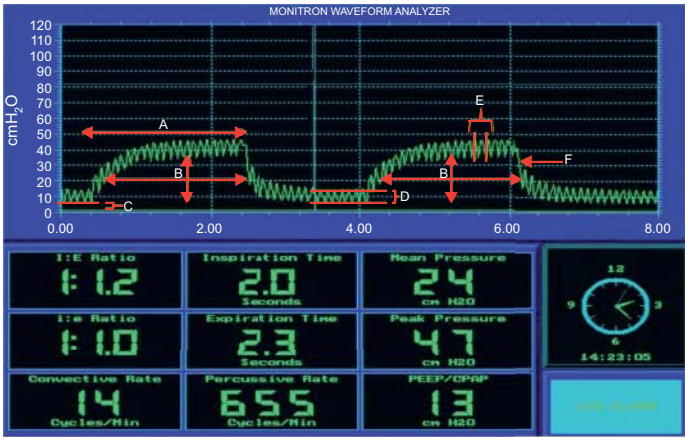
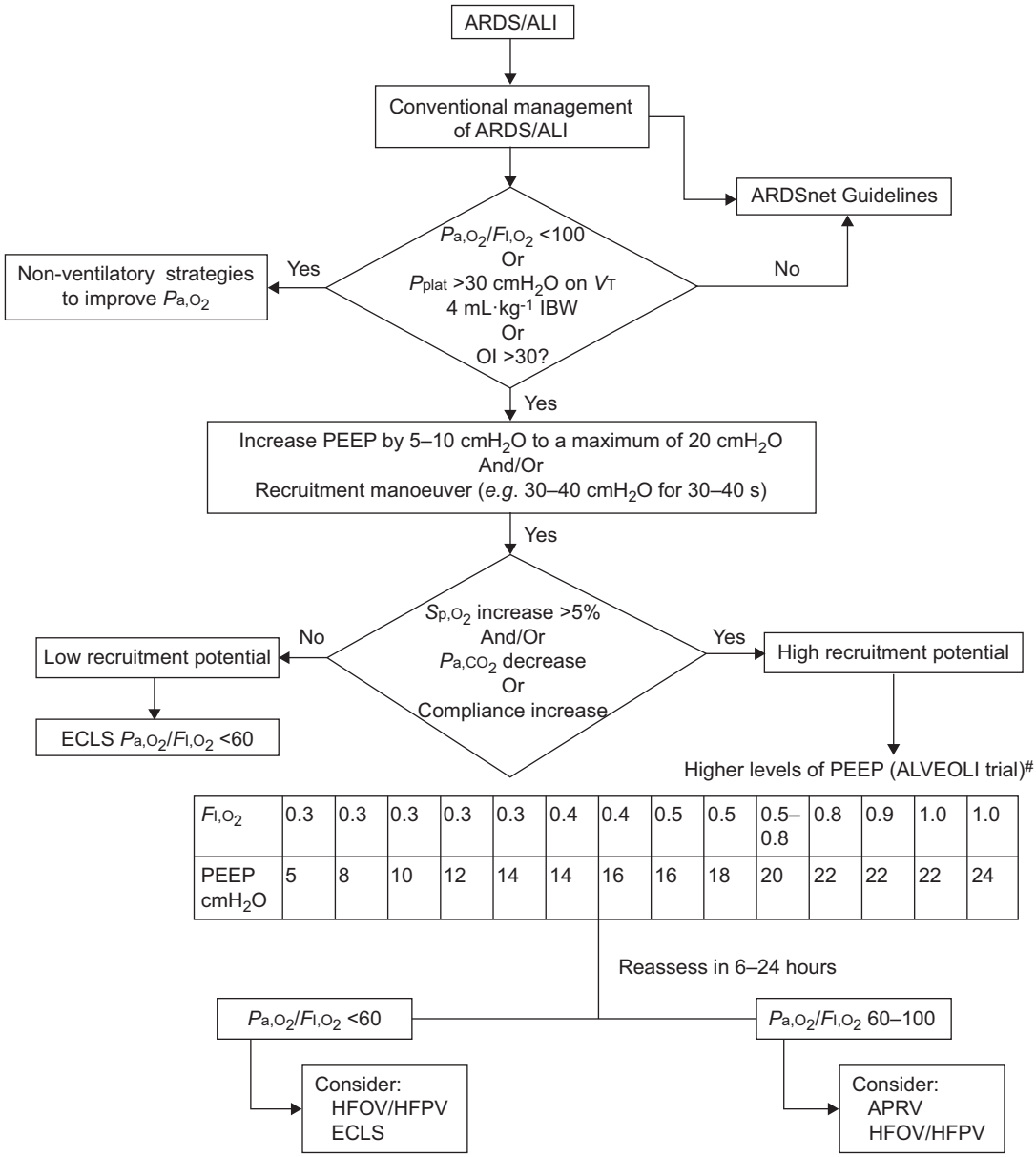


Figure 6. High-frequency percussive ventilation. An interplay of the percussive frequency, peak inspiratory pressure, inspiratory and expiratory times (of both percussive and convective breaths) and the oscillatory and demand continuous positive airway pressure (CPAP) levels either alone or in combination, are involved in determining mean arterial wedge pressure as well as the degree of gas exchange. The percussions are of lower amplitude at oscillatory CPAP (baseline oscillations) during exhalation, and are of higher amplitude during inspiration as a result of the selected pulsatile flow rate (see pressure-time display). During inspiration, the lung volumes progressively increase in a cumulative, stepwise manner by continually diminishing sub-tidal deliveries that result in stacking of breaths. Once an oscillatory pressure peak is reached and sustained, periodic programmed interruptions occur at specific times for predetermined intervals, allowing the return of airway pressures to baseline oscillatory pressure levels *i.e.* oscillatory CPAP, thereby passively emptying the lungs. A: pulsatile flow during inspiration at a percussive rate of 655 cycles·min^{-1}; B: convective pressure-limited breath with low-frequency cycle (14 cycles·min^{-1}); C: demand CPAP (provides static baseline pressure); D: oscillatory CPAP (provides high-frequency baseline pressure as a mean of the peak and nadir of the oscillations during exhalation); E: single percussive breath; F: periodic programmed interruptions signifying the end of inspiration and subsequent onset of exhalation. Reproduced from [87] with permission from the publisher.



F_{I,O_2}	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	1.0
PEEP cmH_2O	5	8	10	12	14	14	16	16	18	20	22	22	22	24

Figure 7. Ventilatory strategy algorithm for the management of acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) patients. The algorithm shows ventilator strategies that can be utilised in ARDS/ALI patients. The ARDSnet serves as the standard and the starting point. The other strategies can be employed following optimisation with the ARDSnet strategy. In patients with recruitable lungs, different methods can be used to determine the level of positive end-expiratory pressure (PEEP) required, such as higher levels of PEEP per the inspiratory oxygen fraction (F_{I,O_2})/PEEP table (PEEP may be set so as to reach a plateau pressure (P_{plat}) of 28–30 cmH_2O) use of oesophageal pressure monitoring or the stress index. V_T: tidal volume; IBW: ideal body weight; OI: oxygenation index; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; P_{a,CO_2}: arterial carbon dioxide tension; ALVEOLI: Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; ECLS: extracorporeal life support; HFOV: high-frequency oscillatory ventilation; APRV: airway pressure release ventilation; HFPV: high-frequency percussive ventilation. #: failure of the aforementioned can result in the use of the alternative ventilatory strategies in centres familiar with their use. Reproduced from [87] with permission from the publisher.

reported on seven ARDS patients who were switched from conventional ventilation to HFPV at the same level of airway pressure and F_{I,O_2}. There was a significant increase in P_{a,O_2}, a slight decrease in P_{a,CO_2} and no change in cardiac output. In an RCT comparing HFPV with conventional ventilation in 100 adult patients with acute respiratory failure, there was no difference between the two patient groups in the time it took to reach the therapeutic end-points of $P_{a,O_2}/F_{I,O_2} > 225$ mmHg or shunt $<20\%$. However, in the subgroup of patients with ARDS, HFPV provided equivalent oxygenation and ventilation at significantly lower airway pressures. Nonetheless, there was no difference in mortality, intensive care unit days, hospital days or incidence of barotrauma. In two retrospective studies of ARDS patients failing conventional ventilation, HFPV was found to significantly improve oxygenation [172, 175]. In the former study [172], oxygenation is reported to have improved in association with a decreased peak inspiratory pressure but decreased $\bar{P}_{aw}$. However, in the latter study [175], improved oxygenation was not associated with an increase in $\bar{P}_{aw}$. The investigators suggest that other mechanisms of HFV may have contributed to the improvement in oxygenation. In a recent RCT, CHUNG *et al.* [168] compared HFPV with a low V_T ventilation-based strategy in 62 burns patients with respiratory failure. At baseline, 12 (39%) out of 31 of the patients in the HFPV group and 14 (45%) out of 31 of the patients in the low V_T group had ALI/ARDS. The investigators reported no significant difference between both groups in the primary outcome, *i.e.* mean ventilator-free days (12 ± 9 *versus* 11 ± 9 days). There was also no significant difference in secondary outcomes such as 28-day mortality, days free from non-pulmonary organ failure, ventilator-associated pneumonia and barotraumas. However, there was a significant difference in the need for a rescue modality as 29% (nine patients) of the low V_T group did not meet oxygenation and ventilation goals and were subsequently transitioned to a rescue mode as opposed to 6% (two patients) in the HFPV group. This was found to occur more commonly in the patients with inhalational injury. The investigators also reported the $P_{a,O_2}/F_{I,O2}$ ratio was significantly higher in the HFPV group over the first week after randomisation in spite of equivalent $\bar{P}_{aw}$ and PEEP settings and lower peak inspiratory pressures in the HFPV group. There was also no significant difference in cytokine release between both groups over the first 7 days. The authors concluded by saying HFPV resulted in similar clinical outcomes when compared to a low V_T-based strategy.

No definitive conclusions can be made about the role of HFPV in the ventilatory management of ALI/ARDS patients. Oxygenation and ventilation improve at lower airway pressures in comparison to conventional ventilation; however, no mortality benefit has been demonstrated to date. Like the other alternative/rescue strategies that have been described, large RCTs are needed to accurately elucidate their role in the ventilatory management of ALI/ARDS patients.

Conclusions

A proposed algorithm to manage patients with severe hypoxaemic respiratory failure is depicted in figure 7. It is important to emphasise that patients with ARDS who are intubated and mechanically ventilated, should first be placed on low V_T lung protective strategy. In general, the patients are given V_T of 4–6 $mL \cdot kg^{-1}$ ideal body weight with adequate levels of PEEP. A vigilant eye is kept on the P_{plat}, with an endeavour to keep them <30 cmH_2O or as low as possible, ensuring adequate oxygenation. If within a reasonable period of time, usually a few hours, the end points of oxygenation or P_{plat} are not achieved, or if the patient demonstrates declining oxygenation or requires a PEEP of approximately >15 cmH_2O, the patient has a higher mortality and should be considered for rescue strategies. The first step may be to assess if the patient demonstrates alveolar recruitment in response to higher levels of PEEP. If so, a higher level of PEEP may be selected utilising different techniques outlined. However, if raising the level of PEEP does not improve oxygenation, or results in high P_{plat}, other rescue strategies may be utilised, including airway pressure release ventilation, HFOV and HFPV. In specialised centres where extra-corporeal membrane oxygenation may be available, such a mode may also be considered. It is important to point out that these modes have not been shown to reduce mortality. Selection of these modes should be based on availability and comfort of use of the operator. If these rescue modes are used, periodic assessment of end-points for their use should be checked.

Statement of interest

A. Esan has received consultancy fees from United Therapeutics Corporation. D. Hess is a consultant for Philips Respironics, ResMed, Breathe Technologies and Pari. He has also received honoraria from Covidien. S. Raoof received $1,000 from the ACCP for a postgraduate course that he had presented at the 2011 Chest meeting. He is in the process of donating the money to the Chest Foundation.

References

1. Bernard GR, Artigas A, Brigham KL, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–824.
2. Villar J, Perez-Mendez L, Lopez J, *et al.* An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 176: 795–804.
3. Ranieri M. Acute Respiratory Distress Syndrome (ARDS): The "Berlin Definition". European Society of Intensive Care Medicine, 24th Annual Congress. October 1–5, 2011. Available from: www.esicm.org/07-congresses/0A-annual-congress/webTv_ranieri.asp.
4. Gattinoni L, Caironi P, Pelosi P, *et al.* What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2001; 164: 1701–1711.
5. Slutsky AS. Lung injury caused by mechanical ventilation. *Chest* 1999; 116: Suppl. 1, 9S–15S.
6. Muscedere JG, Mullen JB, Gan K, *et al.* Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; 149: 1327–1334.
7. 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: 1159–1164.
8. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. *Intensive Care Med* 2006; 32: 24–33.
9. International consensus conferences in intensive care medicine: Ventilator-associated Lung Injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise, and was approved by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 1999; 160: 2118–2124.
10. Plotz FB, Slutsky AS, van Vught AJ, *et al.* Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. *Intensive Care Med* 2004; 30: 1865–1872.
11. Ricard JD, Dreyfuss D, Saumon G. Production of inflammatory cytokines in ventilator-induced lung injury: a reappraisal. *Am J Respir Crit Care Med* 2001; 163: 1176–1180.
12. Villar J, Kacmarek RM, Perez-Mendez L, *et al.* A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med* 2006; 34: 1311–1318.
13. 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: 347–354.
14. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301–1308.
15. Brower RG, Shanholtz CB, Fessler HE, *et al.* 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.
16. Stewart TE, Meade MO, Cook DJ, *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.
17. Brochard L, Roudot-Thoraval F, Roupie E, *et al.* Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158: 1831–1838.
18. Ranieri VM, Suter PM, Tortorella C, *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999; 282: 54–61.
19. Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. *Lancet* 2007; 369: 1553–1564.
20. 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: 566–576.
21. Yilmaz M, Gajic O. Optimal ventilator settings in acute lung injury and acute respiratory distress syndrome. *Eur J Anaesthesiol* 2008; 25: 89–96.
22. Moran JL, Bersten AD, Solomon PJ. Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective. *Intensive Care Med* 2005; 31: 227–235.

23. Eichacker PQ, Gerstenberger EP, Banks SM, *et al.* Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. *Am J Respir Crit Care Med* 2002; 166: 1510–1514.
24. Petrucci N, Iacovelli W. Ventilation with smaller tidal volumes: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2004; 99: 193–200.
25. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2007; 3: CD003844.
26. Brower RG, Matthay M, Schoenfeld D. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials. *Am J Respir Crit Care Med* 2002; 166: 1515–1517.
27. Hager DN, Krishnan JA, Hayden DL, *et al.* Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172: 1241–1245.
28. Terragni PP, Rosboch G, Tealdi A, *et al.* Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 175: 160–166.
29. Talmor D, Sarge T, O'Donnell CR, *et al.* Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med* 2006; 34: 1389–1394.
30. Talmor D, Sarge T, Malhotra A, *et al.* Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359: 2095–2104.
31. Burns KE, Adhikari NK, Slutsky AS, *et al.* Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: a systematic review and meta-analysis. *PLoS One*, 6: e14623.
32. Weinert CR, Gross CR, Marinelli WA. Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. *Am J Respir Crit Care Med* 2003; 167: 1304–1309.
33. Young MP, Manning HL, Wilson DL, *et al.* Ventilation of patients with acute lung injury and acute respiratory distress syndrome: has new evidence changed clinical practice? *Crit Care Med* 2004; 32: 1260–1265.
34. Rubenfeld GD, Cooper C, Carter G, *et al.* Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med* 2004; 32: 1289–1293.
35. Kalhan R, Mikkelsen M, Dedhiya P, *et al.* Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med* 2006; 34: 300–306.
36. Laffey JG, O'Croinin D, McLoughlin P, *et al.* Permissive hypercapnia-role in protective lung ventilatory strategies. *Intensive Care Med* 2004; 30: 347–356.
37. Hickling KG, Walsh J, Henderson S, *et al.* Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994; 22: 1568–1578.
38. Kahn JM, Andersson L, Karir V, *et al.* Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. *Crit Care Med* 2005; 33: 766–771.
39. Bidani A, Tzouanakis AE, Cardenas VJ Jr, *et al.* Permissive hypercapnia in acute respiratory failure. *JAMA* 1994; 272: 957–962.
40. Cheng IW, Eisner MD, Thompson BT, *et al.* Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. *Crit Care Med* 2005; 33: 63–70.
41. Hough CL, Kallet RH, Ranieri VM, *et al.* Intrinsic positive end-expiratory pressure in Acute Respiratory Distress Syndrome (ARDS) Network subjects. *Crit Care Med* 2005; 33: 527–532.
42. Esteban A, Ferguson ND, Meade MO, *et al.* Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008; 177: 170–177.
43. Checkley W, Brower R, Korpak A, *et al.* Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008; 177: 1215–1222.
44. Herasevich V, Tsapenko M, Kojicic M, *et al.* Limiting ventilator-induced lung injury through individual electronic medical record surveillance. *Crit Care Med* 2011; 39: 34–39.
45. MacIntyre NR, Sessler CN. Are there benefits or harm from pressure targeting during lung-protective ventilation? *Respir Care*, 55: 175–180.
46. Haas CF. Mechanical ventilation with lung protective strategies: what works? *Crit Care Clin* 2011; 27: 469–486.
47. Davis K Jr, Branson RD, Campbell RS, *et al.* Comparison of volume control and pressure control ventilation: is flow waveform the difference? *J Trauma* 1996; 41: 808–814.
48. MacIntyre NR, McConnell R, Cheng KC, *et al.* Patient-ventilator flow dyssynchrony: flow-limited *versus* pressure-limited breaths. *Crit Care Med* 1997; 25: 1671–1677.
49. Cinnella G, Conti G, Lofaso F, *et al.* Effects of assisted ventilation on the work of breathing: volume-controlled *versus* pressure-controlled ventilation. *Am J Respir Crit Care Med* 1996; 153: 1025–1033.
50. Rappaport SH, Shpiner R, Yoshihara G, *et al.* Randomized, prospective trial of pressure-limited *versus* volume-controlled ventilation in severe respiratory failure. *Crit Care Med* 1994; 22: 22–32.
51. Yang LY, Huang YC, Macintyre NR. Patient-ventilator synchrony during pressure-targeted *versus* flow-targeted small tidal volume assisted ventilation. *J Crit Care* 2007; 22: 252–257.
52. Marini JJ. Point: is pressure assist-control preferred over volume assist-control mode for lung protective ventilation in patients with ARDS? Yes. *Chest* 2011; 140: 286–290.
53. Munoz J, Guerrero JE, Escalante JL, *et al.* Pressure-controlled ventilation *versus* controlled mechanical ventilation with decelerating inspiratory flow. *Crit Care Med* 1993; 21: 1143–1148.
54. Chiumello D, Pelosi P, Calvi E, *et al.* Different modes of assisted ventilation in patients with acute respiratory failure. *Eur Respir J* 2002; 20: 925–933.

55. Kallet RH, Campbell AR, Dicker RA, *et al.* Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. *Respir Care* 2005; 50: 1623–1631.
56. Schmidt UH, Hess DR. Does spontaneous breathing produce harm in patients with the acute respiratory distress syndrome? *Respir Care* 2010; 55: 784–786.
57. 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: 637–645.
58. MacIntyre N. Counterpoint: is pressure assist-control preferred over volume assist-control mode for lung protective ventilation in patients with ARDS? No. *Chest* 2011; 140: 290–292.
59. Papadakos PJ, Halloran W, Hessney JI, *et al.* The use of pressure-controlled inverse ratio ventilation in the surgical intensive care unit. *J Trauma* 1991; 31: 1211–1214.
60. Abraham E, Yoshihara G. Cardiorespiratory effects of pressure controlled inverse ratio ventilation in severe respiratory failure. *Chest* 1989; 96: 1356–1359.
61. Gurevitch MJ, Van Dyke J, Young ES, *et al.* Improved oxygenation and lower peak airway pressure in severe adult respiratory distress syndrome. Treatment with inverse ratio ventilation. *Chest* 1986; 89: 211–213.
62. Tharratt RS, Allen RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe adult respiratory failure. *Chest* 1988; 94: 755–762.
63. Lain DC, Di Benedetto R, Morris SL, *et al.* Pressure control inverse ratio ventilation as a method to reduce peak inspiratory pressure and provide adequate ventilation and oxygenation. *Chest* 1989; 95: 1081–1088.
64. Valta P, Takala J. Volume-controlled inverse ratio ventilation: effect on dynamic hyperinflation and auto-PEEP. *Acta Anaesthesiol Scand* 1993; 37: 323–328.
65. Cole AG, Weller SF, Sykes MK. Inverse ratio ventilation compared with PEEP in adult respiratory failure. *Intensive Care Med* 1984; 10: 227–232.
66. Zavala E, Ferrer M, Polese G, *et al.* Effect of inverse I:E ratio ventilation on pulmonary gas exchange in acute respiratory distress syndrome. *Anesthesiology* 1998; 88: 35–42.
67. Mancebo J, Vallverdu I, Bak E, *et al.* Volume-controlled ventilation and pressure-controlled inverse ratio ventilation: a comparison of their effects in ARDS patients. *Monaldi Arch Chest Dis* 1994; 49: 201–207.
68. Mercat A, Graini L, Teboul JL, *et al.* Cardiorespiratory effects of pressure-controlled ventilation with and without inverse ratio in the adult respiratory distress syndrome. *Chest* 1993; 104: 871–875.
69. Lessard MR, Guerot E, Lorino H, *et al.* Effects of pressure-controlled with different I:E ratios *versus* volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. *Anesthesiology* 1994; 80: 983–991.
70. Mercat A, Titiriga M, Anguel N, *et al.* Inverse ratio ventilation (I/E=2/1) in acute respiratory distress syndrome: a six-hour controlled study. *Am J Respir Crit Care Med* 1997; 155: 1637–1642.
71. Duncan SR, Rizk NW, Raffin TA. Inverse ratio ventilation. PEEP in disguise? *Chest* 1987; 92: 390–392.
72. Shanholtz C, Brower R. Should inverse ratio ventilation be used in adult respiratory distress syndrome? *Am J Respir Crit Care Med* 1994; 149: 1354–1358.
73. Crotti S, Mascheroni D, Caironi P, *et al.* Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med* 2001; 164: 131–140.
74. Richard JC, Maggiore SM, Jonson B, *et al.* 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.
75. Caironi P, Cressoni M, Chiumello D, *et al.* Lung opening and closing during ventilation of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2010; 181: 578–586.
76. Hemmila MR, Napolitano LM. Severe respiratory failure: advanced treatment options. *Crit Care Med* 2006; 34: Suppl. 9, S278–S290.
77. Ferguson ND, Frutos-Vivar F, Esteban A, *et al.* Airway pressures, tidal volumes, and mortality in patients with acute respiratory distress syndrome. *Crit Care Med* 2005; 33: 21–30.
78. Guerin C. The preventive role of higher PEEP in treating severely hypoxemic ARDS. *Minerva Anestesiol* 2011; 77: 835–845.
79. Mercat A, Richard JC, 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: 646–655.
80. Schmitt JM, Vieillard-Baron A, Augarde R, *et al.* Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. *Crit Care Med* 2001; 29: 1154–1158.
81. Jardin F, Vieillard-Baron A. Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings. *Intensive Care Med* 2003; 29: 1426–1434.
82. Esan A, Hess DR, Raoof S, *et al.* Severe hypoxemic respiratory failure: part 1– ventilatory strategies. *Chest* 2010; 137: 1203–1216.
83. 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: 327–336.
84. Girgis K, Hamed H, Khater Y, *et al.* A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment. *Respir Care* 2006; 51: 1132–1139.

85. Badet M, Bayle F, Richard JC, *et al.* Comparison of optimal positive end-expiratory pressure and recruitment maneuvers during lung-protective mechanical ventilation in patients with acute lung injury/acute respiratory distress syndrome. *Respir Care* 2009; 54: 847–854.
86. Grasso S, Stripoli T, De Michele M, *et al.* ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med* 2007; 176: 761–767.
87. Hess DR. Approaches to conventional mechanical ventilation of the patient with acute respiratory distress syndrome. *Respir Care* 2011; 56: 1555–1572.
88. Dasenbrook EC, Needham DM, Brower RG, *et al.* Higher PEEP in patients with acute lung injury: a systematic review and meta-analysis. *Respir Care* 2011; 56: 568–575.
89. Phoenix SI, Paravastu S, Columb M, *et al.* Does a higher positive end expiratory pressure decrease mortality in acute respiratory distress syndrome? A systematic review and meta-analysis. *Anesthesiology* 2009; 110: 1098–1105.
90. Oba Y, Thameem DM, Zaza T. High levels of PEEP may improve survival in acute respiratory distress syndrome: a meta-analysis. *Respir Med* 2009; 103: 1174–1181.
91. 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: 865–873.
92. Nieszkowska A, Lu Q, Vieira S, *et al.* Incidence and regional distribution of lung overinflation during mechanical ventilation with positive end-expiratory pressure. *Crit Care Med* 2004; 32: 1496–1503.
93. Grasso S, Fanelli V, Cafarelli A, *et al.* Effects of high *versus* low positive end-expiratory pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005; 171: 1002–1008.
94. Fan E, Wilcox ME, Brower RG, *et al.* Recruitment maneuvers for acute lung injury: a systematic review. *Am J Respir Crit Care Med* 2008; 178: 1156–1163.
95. Hess DR, Bigatello LM. Lung recruitment: the role of recruitment maneuvers. *Respir Care* 2002; 47: 308–317.
96. Lapinsky SE, Mehta S. Bench-to-bedside review: recruitment and recruiting maneuvers. *Crit Care* 2005; 9: 60–65.
97. Rocco PR, Pelosi P, de Abreu MG. Pros and cons of recruitment maneuvers in acute lung injury and acute respiratory distress syndrome. *Expert Rev Respir Med* 2010; 4: 479–489.
98. Pelosi P, Gama de Abreu M, Rocco PR. New and conventional strategies for lung recruitment in acute respiratory distress syndrome. *Crit Care* 2010; 14: 210.
99. Villagra A, Ochagavia A, Vatua S, *et al.* Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; 165: 165–170.
100. Brower RG, Morris A, MacIntyre N, *et al.* Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med* 2003; 31: 2592–2597.
101. Odenstedt H, Aneman A, Karason S, *et al.* Acute hemodynamic changes during lung recruitment in lavage and endotoxin-induced ALI. *Intensive Care Med* 2005; 31: 112–120.
102. Meade MO, Cook DJ, Griffith LE, *et al.* A study of the physiologic responses to a lung recruitment maneuver in acute lung injury and acute respiratory distress syndrome. *Respir Care* 2008; 53: 1441–1449.
103. Constantin JM, Cayot-Constantin S, Roszyk L, *et al.* Response to recruitment maneuver influences net alveolar fluid clearance in acute respiratory distress syndrome. *Anesthesiology* 2007; 106: 944–951.
104. Musch G, Harris RS, Vidal Melo MF, *et al.* Mechanism by which a sustained inflation can worsen oxygenation in acute lung injury. *Anesthesiology* 2004; 100: 323–330.
105. Arnal JM, Paquet J, Wysocki M, *et al.* Optimal duration of a sustained inflation recruitment maneuver in ARDS patients. *Intensive Care Med* 2011; 37: 1588–1594.
106. Marini JJ. Recruitment by sustained inflation: time for a change. *Intensive Care Med* 2011; 37: 1572–1574.
107. Rzezinski AF, Oliveira GP, Santiago VR, *et al.* Prolonged recruitment manoeuvre improves lung function with less ultrastructural damage in experimental mild acute lung injury. *Respir Physiol Neurobiol* 2009; 169: 271–281.
108. Odenstedt H, Lindgren S, Olegard C, *et al.* Slow moderate pressure recruitment maneuver minimizes negative circulatory and lung mechanic side effects: evaluation of recruitment maneuvers using electric impedance tomography. *Intensive Care Med* 2005; 31: 1706–1714.
109. Steimback PW, Oliveira GP, Rzezinski AF, *et al.* Effects of frequency and inspiratory plateau pressure during recruitment manoeuvres on lung and distal organs in acute lung injury. *Intensive Care Med* 2009; 35: 1120–1128.
110. Riva DR, Oliveira MB, Rzezinski AF, *et al.* Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury. *Crit Care Med* 2008; 36: 1900–1908.
111. Tugrul S, Akinci O, Ozcan PE, *et al.* Effects of sustained inflation and postinflation positive end-expiratory pressure in acute respiratory distress syndrome: focusing on pulmonary and extrapulmonary forms. *Crit Care Med* 2003; 31: 738–744.
112. Grasso S, Mascia L, Del Turco M, *et al.* Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology* 2002; 96: 795–802.
113. Gattinoni L, Caironi P, Cressoni M, *et al.* Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354: 1775–1786.
114. Demory D, Arnal JM, Wysocki M, *et al.* Recruitability of the lung estimated by the pressure volume curve hysteresis in ARDS patients. *Intensive Care Med* 2008; 34: 2019–2025.
115. Arbelot C, Ferrari F, Bouhemad B, *et al.* Lung ultrasound in acute respiratory distress syndrome and acute lung injury. *Curr Opin Crit Care* 2008; 14: 70–74.

116. Bouhemad B, Brisson H, Le-Guen M, *et al.* Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. *Am J Respir Crit Care Med* 2011; 183: 341–347.
117. Costa EL, Borges JB, Melo A, *et al.* Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. *Intensive Care Med* 2009; 35: 1132–1137.
118. Victorino JA, Borges JB, Okamoto VN, *et al.* Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *Am J Respir Crit Care Med* 2004; 169: 791–800.
119. Constantin JM, Grasso S, Chanques G, *et al.* Lung morphology predicts response to recruitment maneuver in patients with acute respiratory distress syndrome. *Crit Care Med* 2010; 38: 1108–1117.
120. Kacmarek RM, Kallet RH. Respiratory controversies in the critical care setting. Should recruitment maneuvers be used in the management of ALI and ARDS? *Respir Care* 2007; 52: 622–631.
121. Maggiore SM, Lellouche F, Pigeot J, *et al.* Prevention of endotracheal suctioning-induced alveolar derecruitment in acute lung injury. *Am J Respir Crit Care Med* 2003; 167: 1215–1224.
122. Marini JJ, Gattinoni L. Ventilatory management of acute respiratory distress syndrome: a consensus of two. *Crit Care Med* 2004; 32: 250–255.
123. Downs JB, Stock MC. Airway pressure release ventilation: a new concept in ventilatory support. *Crit Care Med* 1987; 15: 459–461.
124. Stock MC, Downs JB, Frolicher DA. Airway pressure release ventilation. *Crit Care Med* 1987; 15: 462–466.
125. Neumann P, Golisch W, Strohmeyer A, *et al.* Influence of different release times on spontaneous breathing pattern during airway pressure release ventilation. *Intensive Care Med* 2002; 28: 1742–1749.
126. Rose L, Hawkins M. Airway pressure release ventilation and biphasic positive airway pressure: a systematic review of definitional criteria. *Intensive Care Med* 2008; 34: 1766–1773.
127. Siau C, Stewart TE. Current role of high frequency oscillatory ventilation and airway pressure release ventilation in acute lung injury and acute respiratory distress syndrome. *Clin Chest Med* 2008; 29: 265–275.
128. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. *Crit Care Med* 2005; 33: Suppl. 3, S228–S240.
129. Kaplan LJ, Bailey H, Formosa V. Airway pressure release ventilation increases cardiac performance in patients with acute lung injury/adult respiratory distress syndrome. *Crit Care* 2001; 5: 221–226.
130. Putensen C, Zech S, Wrigge H, *et al.* Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001; 164: 43–49.
131. Putensen C, Muders T, Varelmann D, *et al.* The impact of spontaneous breathing during mechanical ventilation. *Curr Opin Crit Care* 2006; 12: 13–18.
132. Putensen C, Mutz NJ, Putensen-Himmer G, *et al.* Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; 159: 1241–1248.
133. Yoshida T, Rinka H, Kaji A, *et al.* The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: airway pressure release ventilation *versus* pressure support ventilation. *Anesth Analg* 2009; 109: 1892–1900.
134. Dart BW 4th, Maxwell RA, Richart CM, et al. Preliminary experience with airway pressure release ventilation in a trauma/surgical intensive care unit. *J Trauma* 2005; 59: 71–76.
135. Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe acute respiratory failure. *Chest* 1991; 100: 460–463.
136. Rasanen J, Cane RD, Downs JB, *et al.* Airway pressure release ventilation during acute lung injury: a prospective multicenter trial. *Crit Care Med* 1991; 19: 1234–1241.
137. Sydow M, Burchardi H, Ephraim E, *et al.* Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. *Am J Respir Crit Care Med* 1994; 149: 1550–1556.
138. Maxwell RA, Green JM, Waldrop J, *et al.* A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma* 2010; 69: 501–510.
139. Varpula T, Jousela I, Niemi R, *et al.* Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury. *Acta Anaesthesiol Scand* 2003; 47: 516–524.
140. Varpula T, Valta P, Niemi R, *et al.* Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. *Acta Anaesthesiol Scand* 2004; 48: 722–731.
141. Krishnan JA, Brower RG. High-frequency ventilation for acute lung injury and ARDS. *Chest* 2000; 118: 795–807.
142. Fessler HE, Hess DR. Respiratory controversies in the critical care setting. Does high-frequency ventilation offer benefits over conventional ventilation in adult patients with acute respiratory distress syndrome? *Respir Care* 2007; 52: 595–605.
143. Sud S, Sud M, Friedrich JO, *et al.* High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ* 2010; 340: c2327.
144. Slutsky AS, Drazen JM. Ventilation with small tidal volumes. *N Engl J Med* 2002; 347: 630–631.
145. dos Santos CC, Slutsky AS. Overview of high-frequency ventilation modes, clinical rationale, and gas transport mechanisms. *Respir Care Clin N Am* 2001; 7: 549–575.
146. Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. *J Appl Physiol* 1984; 56: 553–563.

147. Fessler HE, Hager DN, Brower RG. Feasibility of very high-frequency ventilation in adults with acute respiratory distress syndrome. *Crit Care Med* 2008; 36: 1043–1048.
148. Ritacca FV, Stewart TE. Clinical review: high-frequency oscillatory ventilation in adults – a review of the literature and practical applications. *Crit Care* 2003; 7: 385–390.
149. Chan KP, Stewart TE, Mehta S. High-frequency oscillatory ventilation for adult patients with ARDS. *Chest* 2007; 131: 1907–1916.
150. Kao KC, Tsai YH, Wu YK, *et al.* High frequency oscillatory ventilation for surgical patients with acute respiratory distress syndrome. *J Trauma* 2006; 61: 837–843.
151. Andersen FA, Guttormsen AB, Flaatten HK. High frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome–a retrospective study. *Acta Anaesthesiol Scand* 2002; 46: 1082–1088.
152. Ferguson ND, Chiche JD, Kacmarek RM, *et al.* Combining high-frequency oscillatory ventilation and recruitment maneuvers in adults with early acute respiratory distress syndrome: the Treatment with Oscillation and an Open Lung Strategy (TOOLS) Trial pilot study. *Crit Care Med* 2005; 33: 479–486.
153. Mehta S, Granton J, MacDonald RJ, *et al.* High-frequency oscillatory ventilation in adults: the Toronto experience. *Chest* 2004; 126: 518–527.
154. David M, Weiler N, Heinrichs W, *et al.* High-frequency oscillatory ventilation in adult acute respiratory distress syndrome. *Intensive Care Med* 2003; 29: 1656–1665.
155. Fort P, Farmer C, Westerman J, *et al.* High-frequency oscillatory ventilation for adult respiratory distress syndrome – a pilot study. *Crit Care Med* 1997; 25: 937–947.
156. Mehta S, Lapinsky SE, Hallett DC, *et al.* Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome. *Crit Care Med* 2001; 29: 1360–1369.
157. Cartotto R, Cooper AB, Esmond JR, *et al.* Early clinical experience with high-frequency oscillatory ventilation for ARDS in adult burn patients. *J Burn Care Rehabil* 2001; 22: 325–333.
158. Cartotto R, Ellis S, Gomez M, *et al.* High frequency oscillatory ventilation in burn patients with the acute respiratory distress syndrome. *Burns* 2004; 30: 453–463.
159. Claridge JA, Hostetter RG, Lowson SM, *et al.* High-frequency oscillatory ventilation can be effective as rescue therapy for refractory acute lung dysfunction. *Am Surg* 1999; 65: 1092–1096.
160. Finkielman JD, Gajic O, Farmer JC, *et al.* The initial Mayo Clinic experience using high-frequency oscillatory ventilation for adult patients: a retrospective study. *BMC Emerg Med* 2006; 6: 2.
161. Mehta S, MacDonald R, Hallett DC, *et al.* Acute oxygenation response to inhaled nitric oxide when combined with high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med* 2003; 31: 383–389.
162. Demory D, Michelet P, Arnal JM, *et al.* High-frequency oscillatory ventilation following prone positioning prevents a further impairment in oxygenation. *Crit Care Med* 2007; 35: 106–111.
163. Derdak S, Mehta S, Stewart TE, *et al.* High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med* 2002; 166: 801–808.
164. Bollen CW, van Well GT, Sherry T, *et al.* High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. *Crit Care* 2005; 9: R430–R439.
165. Wunsch H, Mapstone J. High-frequency ventilation *versus* conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2004; 1: CD004085.
166. Allan PF, Osborn EC, Chung KK, *et al.* High-frequency percussive ventilation revisited. *J Burn Care Res* 2010; 31: 510–520.
167. Lucangelo U, Fontanesi L, Antonaglia V, *et al.* High frequency percussive ventilation (HFPV). Principles and technique. *Minerva Anestesiol* 2003; 69: 841–848.
168. Chung KK, Wolf SE, Renz EM, *et al.* High-frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial. *Crit Care Med* 2010; 38: 1970–1977.
169. Salim A, Martin M. High-frequency percussive ventilation. *Crit Care Med* 2005; 33: Suppl. 3, S241–S245.
170. Lucangelo U, Zin WA, Antonaglia V, *et al.* High-frequency percussive ventilation during surgical bronchial repair in a patient with one lung. *Br J Anaesth* 2006; 96: 533–536.
171. Hurst JM, Branson RD, Davis K Jr, *et al.* Comparison of conventional mechanical ventilation and high-frequency ventilation. A prospective, randomized trial in patients with respiratory failure. *Ann Surg* 1990; 211: 486–491.
172. Velmahos GC, Chan LS, Tatevossian R, *et al.* High-frequency percussive ventilation improves oxygenation in patients with ARDS. *Chest* 1999; 116: 440–446.
173. Paulsen SM, Killyon GW, Barillo DJ. High-frequency percussive ventilation as a salvage modality in adult respiratory distress syndrome: a preliminary study. *Am Surg* 2002; 68: 852–856.
174. Gallagher TJ, Boysen PG, Davidson DD, *et al.* High-frequency percussive ventilation compared with conventional mechanical ventilation. *Crit Care Med* 1989; 17: 364–366.
175. Eastman A, Holland D, Higgins J, *et al.* High-frequency percussive ventilation improves oxygenation in trauma patients with acute respiratory distress syndrome: a retrospective review. *Am J Surg* 2006; 192: 191–195.