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REVIEW

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Lung-protective ventilation strategy in acute respiratory distress syndrome: a critical reappraisal of current practice

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Abstract

Recognition of ventilator-induced lung injury has led to the development of lung-protective ventilation strategies, significantly influencing the management of acute respiratory distress syndrome (ARDS). By the end of the 20th century, five randomized controlled trials had compared the survival benefits of low tidal volume (VT) ventilation with those of traditional high VT ventilation. Two studies demonstrated favourable outcomes, most notably the landmark ARDS Network trial, which established the widely recommended VT of 6 mL/kg predicted body weight. However, the universal application of a fixed VT has been controversial, with poor adherence in clinical practice. The two trials used a greater contrast in VTs (6 vs. 12 mL/kg) than did the others (7–11 mL/kg) and incorporated methodological extremes, including toleration of elevated airway pressures or encouragement of unnecessary increases. In addition, disparities in underlying aetiologies and ventilatory parameters, such as unbalanced positive end-expiratory pressure and respiratory rates, may have influenced the results. There is no conclusive evidence to support the superiority of 6 mL/kg over intermediate VTs (7–10 mL/kg). Many subsequent studies have suggested that VT requirements should be individualized on the basis of lung mechanics and physiological status. The benefits of the current recommendations may be limited by factors such as the severity of hypoxemia, lung compliance, dead-space fraction, and inaccuracies in formula-based lung volume estimation. The goal of mechanical ventilation in ARDS patients is supportive rather than curative; therefore, a moderate approach is recommended in clinical practice. Further studies are needed to establish an individualized, patient-centred approach that allows more flexible and moderate settings.

Keywords Acute respiratory distress syndrome, Lung-protective strategy, Low tidal volume ventilation, Ventilator-induced lung injury, Individualized strategy

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Table 1 Comparison of the five randomized controlled trials that evaluated the survival benefit of low-tidal-volume ventilation versus traditional high-tidal-volume ventilation

Studies (first author)	Enrolment dates	Publication date	Sub-groups	No. subjects		Body weight measure applied	Tidal volume (ml/kg)			Resp. rate (/min)		
				Total	Sub-group		Target	Actual, Day 1	Actual, Day 7	Rule for setting	Day 1	Day 7
Brochard, et al. [10]	Jan 1994 – Sep 1996	Jan 14, 1998	Low VT	116	58	DBW	6–10	7.1 ± 1.3	7.37 ± 1.3	None	–	–
			High VT		58		10–15	10.3 ± 1.7	10.7 ± 1.8	Adjusted to maintain $PaCO_2$ at 38–42 mmHg	–	–
Stewart, et al. [12]	July 1995 – Sep 1996	Feb 5, 1998	Low VT	120	60	IBW	≤ 8	7.0 ± 0.7	6.8 ± 0.6	5–35/min, adjusted to maintain $PaCO_2$ at 35–45 mmHg	22.1 ± 6.2	24.9 ± 6.5
			High VT		60		10–15	10.7 ± 1.4	10.1 ± 1.4		15.6 ± 5.0	19.2 ± 4.7
Amato, et al. [9]	Dec 1990 – July 1995	Feb 5, 1998	Low VT	53	29	BW	≤ 6*			< 30/min, allowed $PaCO_2$ limit: 80 mmHg	19.3†	21.4†
			High VT		24		12*			10–24/min, adjusted to maintain $PaCO_2$ at 35–38 mmHg	15.9†	18.8†
Brower et al. [11]	May 2, 1994 – Mar 1, 1996	Aug 1999	Low VT	52	26	IBW‡	5–8	7.8§	7.3§‖	Adjusted to maintain $PaCO_2$ at 30–45 mmHg	–	–
			High VT		26		10–12	10.2§	10.2§‖		–	–
ARDSNet [13]	Mar 1996 – Mar 1999	May 2000	Low VT	861	432	PBW‡	6 (4–8)	6.2 ± 0.9	6.5 ± 1.4	Adjusted to maintain pH at 7.3–7.45	29 ± 7	30 ± 7
			High VT		429		12	11.8 ± 0.8	11.4 ± 1.4		16 ± 6	20 ± 7

Studies (first author)	Subgroups	PEEP (cmH_2O)			Set pressure limit (cmH_2O)	Pplat (cmH_2O)		Primary outcome of interest	Survival analysis	Administration of Na bicarbonate
		Rule for setting	Day 1	Day 7		Day 1	Day 7			
Brochard, et al. [10]	Low VT	Increments of 5 mH_2O (0–15) for the greatest improvement in oxygenation or the first level allowing PaO_2/FIO_2 >200 mmHg	10.7 ± 2.9	9.6 ± 3.0	Pplat ≤ 25-30	25.7 ± 5.0	24.5 ± 5.7	60-d mortality	NS	If pH < 7.05
	High VT		10.7 ± 2.3	8.5 ± 2.8	Ppeak ≤ 60	31.7 ± 6.6	30.5 ± 9.4			
Stewart, et al. [12]	Low VT	5–20 cmH_2O, increments of 2.5 cmH_2O to maintain the FiO2 ≤ 0.5, SaO2 = 89–93%	8.6 ± 3.0	9.6 ± 3.9	Ppeak ≤ 30	22.3 ± 5.4	20.0 ± 4.7	In-hospital mortality	NS	If pH ≤ 7.0, 2 mmol/kg every four h (up to three doses)
	High VT		7.2 ± 3.3	8.0 ± 3.6	Ppeak ≤ 50	26.8 ± 6.7	28.6 ± 7.2			
Amato, et al. [9]	Low VT	2 cmH_2O higher than Pflex	16.3 ± 0.7	13.2 ± 0.4¶	Pdriv < 20, Ppeak < 40	31.8 ± 1.4	23.9 ± 0.7¶	28-d mortality	Significant	If pH < 7.2, 50 mmol/h
	High VT		6.9 ± 0.8	9.3 ± 0.5¶	None	34.4 ± 1.9	37.8 ± 1.2¶			
Brower, et al. [11]	Low VT	Specific protocol combinations of PEEP and FIO_2	9.5§	6.8§‖	Pplat ≤ 30	26.5§	23§‖	In-hospital mortality	NS	If pH was < 7.30, permissible; if pH was < 7.20, ≥ 10 mEq/h
	High VT		8.2§	6.0§‖	Pplat ≤ 45–55	30.5§	29§‖			
ARDSNet [13]	Low VT	Specific protocol combinations of PEEP and FIO_2	9.4 ± 3.6	8.1 ± 3.4	25 ≤ Pplat ≤ 30	25 ± 7	26 ± 7	In-hospital mortality	Significant	Applied, but not described
	High VT		8.6 ± 3.6	9.1 ± 4.2	45 ≤ Pplat ≤ 50	33 ± 9	37 ± 9			

Data are presented as numbers (n) and means ± SEMs (Amato and Brower studies) or means ± SDs (the other three studies). ARDS, acute respiratory distress syndrome; ARDSNet, ARDS Network; VT, Tidal volume; Low VT, low-tidal-volume ventilation group; High VT, high-tidal-volume ventilation group; DBW, dry body weight; IBW, ideal body weight; BW, body weight; PBW, predicted body weight; Resp. rate, respiratory rate; PEEP, positive end-expiratory pressure; Pplat, plateau airway pressure; Ppeak, peak airway pressure; Pdriv, driving pressure (Pplat – PEEP); NS, not significant; Pflex, the lower inflection point on the inspiratory pressure–volume curve; Na bicarbonate, sodium bicarbonate

* These levels were strictly maintained with minimal variations according to the study design, although actual tidal volumes cannot be presented without body weight data; †estimated from tidal volume and minute volume data; ‡Devine's formula; §visually estimated values from the figures; ‖values on Day 5; ¶ mean values on Days 2–7

Background

Acute respiratory distress syndrome (ARDS) is associated with high mortality, although outcomes have improved with advancements in ventilatory strategies and overall supportive care [1]. Since its initial clinical description by Ashbaugh and Petty in 1967, mechanical ventilation (MV) has remained the cornerstone of ARDS management [2, 3]. Initially, high tidal volumes (VTs) of 12–15 mL/kg were commonly used to compensate for the loss of functional lung units due to atelectasis and alveolar oedema [4]. However, the concept of ventilator-induced lung injury (VILI) soon emerged and was supported by animal studies and clinical evidence in humans [5–7]. These insights prompted a paradigm shift towards lung-protective ventilation, emphasizing the limitation of VT and airway pressure to mitigate iatrogenic injury [8].

Towards the end of the 20th century, five randomized controlled trials (RCTs) were conducted to compare traditional high-VT ventilation directly with lung-protective low-VT strategies and evaluate the prognostic implications (Table 1) [9–13]. Of these, two studies demonstrated a survival benefit, and the pivotal ARDS Network (ARDSNet) trial led to the recommendation of a VT of 6 mL/kg predicted body weight (PBW) as the standard for ARDS management [13–15]. Furthermore, low-VT ventilation has been increasingly applied in patients without ARDS [16–18]. Efforts have been made to explore even lower VTs (< 6 mL/kg PBW) in the management of ARDS [19–21].

Adherence to the recommended VT of 6 mL/kg PBW has been consistently low, at 20–39%, with actual clinical practice often involving higher VTs [22–24]. This suboptimal compliance has been attributed to multiple factors, including challenges in calculating and applying PBW accurately, limited clinician awareness or acceptance of permissive hypercapnia, concerns regarding increased sedation requirements, and the risk of hypoventilation and refractory hypoxemia [25–27]. Notably, deviations from guideline-recommended volumes should not always be interpreted as disregard for protocols. In many cases, clinicians may determine that the standardized VT is inappropriate or inadequate for a given patient's physiological condition and may elect to increase it for safety and individualized care considerations.

Methods

The primary candidates for this review were clinical studies that assessed outcome parameters on the basis of the VT settings used in the MV of patients with ARDS.

The five aforementioned RCTs are key articles in this review. Although those studies are somewhat outdated, having been published between 1998 and 2000, they continue to exert the most significant influence on current ventilatory care in ARDS management because no comparable studies have been conducted since 2000 [9–13] (Table 1).

Two uncontrolled, retrospective real-world analyses were also selected for this review because they provided comprehensive evaluations involving relatively large numbers of patients [26, 28].

Additionally, two articles that addressed the five RCTs were selected. In one study, a meta-analysis of the data was conducted [29]; in the other study, a secondary analysis was performed in which the original data was used as the basis for assessing the implications of the physiological and mechanical ventilatory parameters [30].

In addition to these primary articles, various relevant clinical research and review papers were selected and analysed.

Integrated results and discussion

Reassessment of landmark studies on mechanical ventilation in ARDS

To evaluate the efficacy of lung-protective low-VT ventilation compared to conventional high-VT ventilation, five RCTs have been conducted using comparable methodologies. Of these, three studies reported no significant difference in survival outcomes, and two studies demonstrated a survival benefit with the low-VT strategy. Notably, the ARDSNet trial received the greatest recognition and established the foundation for current MV standards; its influence stems from its rigorous design as a well-controlled, multicentre study with superior statistical power and a relatively large patient population [13].

Concerns have been raised regarding the fixed application of low-VT ventilation, as the benefit thereof may vary according to mechanical parameters such as the driving pressure. It can also lead to air hunger and double triggering, requiring excessive sedation, and may be detrimental in patients with severe hypoventilation and acidosis or obstructive lung disease [31–35]. Several studies have suggested that the benefits of low-VT ventilation may be limited in severe ARDS patients and that its effectiveness can vary depending on the elastance or compliance of the respiratory system [30, 36]. Accordingly, it has been proposed that VT should be individualized on the basis of driving pressure and the severity of hypoxemia [37–39]. As there is no single, definitive method to quantify the ventilation requirements of any given individual, integrated observations of vital physiology remain the best guide for moment-by-moment lung protection at the bedside. VILI risk varies not only inversely with the size of the aerated lung but also with the nature, severity, and stage of acute injury. Single numerical values for ventilation parameters, such as VT, pressure and positive end-expiratory pressure (PEEP), are not relevant for all individuals [8, 40, 41].

There is no basis to regard the recommended VT of 6 mL/kg PBW as optimal; this volume was directly compared only to 12 mL/kg, without evaluation against intermediate volumes of 7–11 mL/kg [33, 34]. The ARDSNet trial addressed this concern by comparing its results with those of three trials that did not demonstrate a survival benefit. In the ARDSNet study, the low-VT group received approximately 6 mL/kg PBW, whereas in the studies that did not show a benefit, the low VTs were closer to 7 mL/kg. Notably, the high-VT arms in both the ARDSNet and other trials were comparable, averaging approximately 12 mL/kg PBW when adjusted using the PBW. On the basis of these comparisons, a possible inference was drawn: since 6 mL/kg yielded better outcomes than 12 mL/kg in the ARDSNet trial did, and 12 mL/kg resulted in outcomes similar to those of 7 mL/kg in the studies that did not show a benefit, 6 mL/kg was hypothesized to also be superior to the range of higher VTs of 7–12 mL/kg. However, this conclusion remains inferential because direct comparisons with intermediate volumes have not been systematically tested.

Several concerns have been raised regarding the interpretation of the findings of the studies that reported a survival benefit. First, discrepancies in the adjustment of body weight across studies complicate direct comparisons. Of the three trials that did not show a benefit, two used ideal body weight (IBW), and one used dry body weight [10–12]. Although these methods are conceptually similar and are intended to reflect lean body mass and lung size, they were selected on the basis of prevailing trends or individual preferences. Furthermore, all weight estimates were calculated indirectly using height and sex rather than being obtained through direct measurement. In the ARDSNet trial, the PBW was calculated using the Devine formula, which is also widely used to determine IBW [11, 42]. Notably, IBW and PBW yield very similar values, regardless of the specific formula applied [43]. Dry body weight is typically estimated using formulas such as the Devine equation because accurate measurement is challenging even when advanced technologies are used [44]. Thus, converting estimated body weights across studies offers limited value and may introduce unnecessary inconsistencies, and analysing the data using the originally reported values without adjustment may be more appropriate. The initial VTs in the ARDSNet trial were approximately 6.2 and 11.8 ml/kg, whereas in the three studies that did not show a benefit, they ranged from approximately 7–10.7 ml/kg (rather than 7–12 ml/kg, as previously stated) (Table 1). Thus, the VT ranges in the ARDSNet study did not overlap with those in the trials that did not show a benefit, thereby precluding direct and indirect comparisons between 6 mL/kg and higher VTs of 7–11 mL/kg. As a result, although the ARDSNet trial primarily demonstrated the harm of excessively high VTs, it did not definitively establish 6 mL/kg PBW as the optimal target. To date, no RCT has directly compared the ARDSNet-recommended low VT (6 mL/kg PBW) with intermediate volumes (7–10 ml/kg PBW). However, one multicentre retrospective study revealed no significant difference in outcomes between groups receiving mean VTs of 6.7 ml/kg and 11.2 ml/kg PBW [28]. Similarly, a retrospective review of 111 real-world ARDS patients revealed that a mean VT of 9.5 ml/kg PBW was not inferior to that of 6.1 ml/kg PBW in terms of 28-day or 1-year mortality [26].

Second, the two studies that demonstrated a survival benefit employed fixed VTs of 6 and 12 mL/kg PBW for the intervention and control groups, respectively. In contrast, the three studies that did not show a benefit adopted a more flexible approach, setting VTs within the 7–11 ml/kg range and adjusting them based on airway pressure parameters such as peak airway pressure (Ppeak) and plateau airway pressure (Pplat) (Table 1). Notably, in the ARDSNet trial, a lower limit Pplat threshold of 45 cmH_2O was established in the high-VT group, below which the VT was titrated up to 12 mL/kg [13]. Another study applied a similarly rigid protocol, enforcing fixed VTs without incorporating a pressure safety margin in the high-VT arm. This approach resulted in substantial differences in Pplat between groups, despite the small sample size [9]. Such protocols may not have reflected the prevailing standards of care at the time, particularly because the risks of VILI had been recognized for more than a decade [5–7, 45–48]. These rigid and arguably excessive methodologies may have contributed to the poorer outcomes observed in the high-VT groups of the two studies showing a benefit. A meta-analysis of the above five RCTs revealed that Pplat values in the high-VT groups were significantly higher in studies that showed a benefit than those that did not but did not specifically address the methodological issues [29]. The unregulated application of high VTs, irrespective of these pressure thresholds, may have led to exaggerated elevations in Pplat, contributing to the observed outcome disparities.

Third, respiratory rates were set unusually high in the low-VT groups to compensate for reduced minute ventilation, whereas PEEP levels were lower in the high-VT groups [9, 13]. These discrepancies in ventilator parameters introduce significant confounding factors that undermine the fairness of the comparison and deviate from reasonable ventilation practices.

Another potential contributor to the outcome differences in the ARDSNet trial lies in the distribution of the underlying aetiologies of ARDS. Notably, trauma-related ARDS is associated with more favourable outcomes than ARDS due to pulmonary causes such as pneumonia [49, 50]. A simple chi-square estimation based on published

data revealed that the number of pneumonia cases was slightly greater and that the number of trauma cases was significantly lower in the high-VT group than in the low-VT group [13].

The ARDSNet trial suggested that the use of parenteral bicarbonate to mitigate acidosis may have influenced outcomes. However, this rationale is unconvincing because all three studies that did not show a benefit explicitly reported the administration of sodium bicarbonate for acid–base management [10–13] (Table 1).

Further considerations when low-tidal-volume ventilation is applied

The normal VT in mammals, including humans, is approximately 6.3 mL/kg IBW at rest [51]. Considering variation and changing demands, the physiological VT in healthy individuals is typically 6–8 mL/kg [13, 52]. In ARDS, however, the number of functioning lung units is significantly reduced because of alveolar collapse, oedema, or consolidation. To minimize regional overdistension and VILI, the VT must be proportionally decreased to match the diminished aerated lung volume [53, 54]. However, volume- and pressure-induced injuries are not the only factors that must be considered when ventilatory parameters are set in ARDS. The primary objective of MV is to maintain adequate gas exchange and avoid further damage to the lungs. In ARDS, the physiological dead-space fraction can rise dramatically—often exceeding 0.5–0.6 compared with normal values < 0.3—and this increase is independently associated with greater mortality [55–58]. In patients with a significantly elevated dead space fraction, the application of a low-VT strategy may result in significant hypoventilation and severe hypoxemia. To compensate for this impaired gas exchange, clinicians are often compelled to use excessively high respiratory rates and elevated PEEP levels. These compensatory measures carry potential drawbacks, such as intrinsic PEEP, and may contribute to the lack of consistent survival benefits associated with low-VT ventilation, particularly in patients with high respiratory system elastance or profound hypoxia [30, 39].

Beyond these physiological concerns, the use of formula-based estimations to determine VT introduces additional limitations. VT may be inappropriately set for individual patients because of inaccuracies in height measurement, estimation errors, and interindividual variability in lung capacity [59, 60]. In critically ill patients, even a small degree of underestimation can have serious or catastrophic consequences. When life-support parameters, such as VT, are determined on the basis of crude estimations rather than direct physiological assessment, overly rigid adherence to calculated values—without allowance for individual variation—may be detrimental.

The result of the five RCTs discussed above show that the actual VTs administered to patients in the low-VT groups consistently exceeded the protocol-defined targets, including in the ARDSNet trial. This observation implies that the prescribed VTs may have been perceived as insufficient by the treating physicians, who likely adjusted them upwards in response to clinical needs, such as ensuring adequate ventilation or addressing safety concerns.

VILI arises from mechanical stress and biologically mediated processes, collectively referred to as "biotrauma" [61]. MV triggers the release of inflammatory mediators, such as cytokines [62, 63]. This cytokine surge has been associated with the development of multiorgan failure, a key determinant of poor outcomes in ARDS, although definitive evidence that inflammatory mediators are direct causative agents of multiorgan dysfunction remains lacking [64, 65]. These mediators may represent epiphenomena, which are byproducts of the disease process rather than primary drivers of pathology. Moreover, inflammatory cytokines play essential roles in host defence, tissue repair, and immune regulation [66, 67].

Back to basics and lessons from the past

The primary function of MV is to provide supportive care rather than to serve as a definitive therapeutic intervention. A prudent and restrained approach is warranted when advanced respiratory support modalities are applied. Although numerous adjunctive strategies for MV have been investigated, their clinical outcomes have generally fallen short of initial expectations, and many are not routinely used in contemporary critical care practice. In particular, inhaled nitric oxide, which was once widely used, is no longer recommended, nor is high-frequency ventilation [68, 69].

Although the concepts of VILI and biotrauma from excessive ventilation are well known and have significantly advanced the field of critical care medicine, paradoxically, overly aggressive ventilatory strategies may lead to further harm.

Dr. David O. Ashbaugh, who first described ARDS, passed away in 2016. A surgeon by training, Dr. Ashbaugh was not extensively involved in critical care research. However, he remains one of the most influential pioneers in the field of critical-care medicine, having saved more lives than many of the most celebrated figures have. His discovery of the profound and immediate benefits of PEEP occurred somewhat serendipitously during a desperate attempt to save a young patient's life. The clinical improvement was so dramatic and unequivocal that conducting further trials to assess the necessity of PEEP was deemed unnecessary and ethically unjustifiable. Dr. Ashbaugh, together with the late Dr. Thomas L. Petty and colleagues, first reported cases of ARDS in *The*

Lancet after their manuscript had been rejected by leading American journals. Notably, one of the main reasons for rejection was the inclusion of PEEP, which at the time was considered potentially harmful during MV. This historical episode highlights how seemingly rational judgements, grounded in the prevailing knowledge of the time, may later be recognized as clear misjudgements. Similarly, the current emphasis on low-VT ventilation may, in retrospect, be viewed as a misplaced endeavour. As previously discussed, life-sustaining interventions should not be based on overly rigid application of low-VT settings derived from crude conversion formulas without careful consideration of the physiological status of the patient and the mechanical parameters of the respiratory system. Low-VT ventilation, although beneficial in many cases, may function as a double-edged sword: further reduction in VT in pursuit of uncertain and marginal gains may pose significant risks, particularly in the absence of precise and individualized methods for determining optimal ventilatory requirements.

Conclusion

Lung protection strategies, including low-VT ventilation in ARDS patients, represent among the most significant advancements in critical care medicine. However, there is no definitive evidence to support the superiority of a fixed VT of 6 mL/kg PBW or lower over intermediate VTs. Both excessively high and overly low VTs may be harmful in patients with ARDS, particularly in the context of severe hypoxia, markedly reduced pulmonary compliance, or a high dead-space fraction. To ensure safe and effective MV, existing protocols should be critically re-evaluated in light of emerging evidence. A therapeutic approach grounded in moderation, individualized assessment, and clinical prudence is essential for the optimal management of ARDS.

Abbreviations

ARDS	Acute respiratory distress syndrome
MV	Mechanical ventilation
VT	Tidal volume
VILI	Ventilator-induced lung injury
RCT	Randomized controlled trial
ARDSNet	ARDS Network
PBW	Predicted body weight
PEEP	Positive end-expiratory pressure
IBW	Ideal body weight
Ppeak	Peak airway pressure
Pplat	Plateau airway pressure
Pdriv	Driving pressure

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This review did not require ethical approval, as it is a synthesis of the literature. The original studies included in this review may have required ethical approval, and the author has referenced the relevant ethical statements and approvals of those studies. Specifically, the author has noted whether the original studies obtained ethical approval from an institutional or national research ethics committee and whether informed consent was obtained from participants where relevant. The author has also adhered to ethical guidelines for scholarly publication throughout this review.

Consent for publication
This study does not contain any identifiable individual data; thus, consent for publication is not needed.

Competing interests
The authors declare no competing interests.

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