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Individual patient data analysis of tidal volumes used in three large randomized control trials involving patients with acute respiratory distress syndrome

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Abstract

Background. The acute respiratory distress syndrome (ARDS) is a condition with a high mortality and morbidity. Mechanical ventilation prevents immediate mortality but may further damage patients' lungs. Low tidal volume lung-protective strategies have been shown to increase survival by reducing this iatrogenic damage. Current guidelines recommend tidal volumes of 6–8 ml kg^{-1} of predicted body weight. We used data from three large randomized controlled trials of treatments for ARDS to determine compliance with these recommendations.

Methods. We used the tidal volume recorded at randomization for all patients in the OSCAR, HARP-2, and BALTI-2 studies. In addition, we used the ventilation data for control arm patients in OSCAR and all patients in HARP-2 at days 1 and 7 after randomization.

Results. The three trials enrolled 1660 patients, with tidal volume data available at least at one time point in 1412 patients. Compliance with the 6–8 ml kg^{-1} recommendation for tidal volume ranged from 20 to 39% of patients across all time points in all three trials.

Conclusion. Poor compliance with the guidelines for tidal volume in patients with ARDS has been demonstrated before in case series, but not in clinical trials where the patient population is specifically selected against standard ARDS diagnostic criteria and the investigators were encouraged to use low tidal volumes. This study may indicate a need to improve implementation and compliance with protective lung ventilation.

Key words: adult; critical care; respiratory distress syndrome; tidal volume

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Editor's key points

- In patients with acute respiratory distress syndrome (ARDS), in whom mechanical ventilation is required, a low tidal volume (6–8 ml kg^{-1} of predicted body weight) is recommended, but it is not clear whether or not this ventilation method is being used clinically.
- The authors have found from three major UK studies that the recommended ventilation method is frequently not used in routine clinical practice.

The acute respiratory distress syndrome (ARDS) describes pulmonary oedema caused by increased vascular permeability, leading to type 1 (hypoxaemic) respiratory failure. Acute respiratory distress syndrome is produced by direct pulmonary insults, such as infection or aspiration pneumonitis, or indirectly by a systemic inflammatory state caused by extrapulmonary diseases, such as pancreatitis, severe sepsis, and burns. Acute respiratory distress syndrome is associated with a high mortality, generally estimated at ~40%,[1 2] and significant long-term morbidity.[3]

A seminal study of low tidal volume artificial ventilation in 2000 by the Acute Respiratory Distress Syndrome Network in the USA (the 'ARDSnet' study)[4] reported that iatrogenic ventilator-associated lung injury may contribute up to 9% of ARDS-associated deaths. Overdistension (barotrauma) of relatively compliant lung regions and repeated opening and closing (atelectatrauma) of inflamed alveoli may cause further damage to injured lungs. Injurious ventilation may also prolong the systemic inflammatory state and induce non-pulmonary organ dysfunction, leading to an increased mortality.

After this study was published, a 'lung-protective' artificial ventilation strategy using tidal volumes of 6–8 ml kg^{-1} predicted body weight (PBW) and plateau pressure below 30 cm H_2O was widely advocated for patients with ARDS. This strategy has also shown benefit in critically ill non-ARDS patients[5] in addition to high-risk surgery patients, such as those undergoing cardiac bypass surgery.[6] Lung-protective ventilation has been shown to be cost-effective in ARDS, and an intervention to improve adherence to this strategy is also suggested to be cost-effective.[7]

In the UK, three large randomized controlled trials evaluated different treatments to improve the outcome in patients with ARDS after the ARDSnet study was published. The OSCAR[8] study evaluated a ventilation technique involving very small tidal volumes (high-frequency oscillatory ventilation or HFOV). The HARP-2[9] study investigated the use of the anti-inflammatory properties of simvastatin to treat ARDS, and BALTI-2[10] investigated increasing alveolar water clearance using i.v. salbutamol infusions. OSCAR and HARP-2 showed no treatment effect, whereas BALTI-2 demonstrated harm in the treatment group and was stopped at an interim analysis.

At the time the OSCAR study was published, a very similar Canadian study (OSCILLATE)[11] reported an increased mortality in the HFOV treatment group compared with the control group. The OSCILLATE study was an efficacy design where the ventilation strategy in the control group was tightly protocolized to the 'ARDSnet' strategy. In comparison, OSCAR was an effectiveness design where the control arm received usual care (sometimes referred to as 'treatment as usual'). Treatment practice in the control arm of OSCAR is therefore an indicator of clinical practice in National Health Service (NHS) intensive care units. One possible explanation of the differing results in the OSCAR and OSCILLATE studies was a different control group mortality attributable to different ventilation strategies. This prompted us to examine the ventilation practice in the OSCAR study, to determine whether 'usual care' in a UK NHS setting was different from the 'ARDSnet' strategy. To determine whether the findings about ventilation practice in OSCAR were generalizable to other UK effectiveness studies, we examined ventilation practice in the two other large UK studies that recruited patients with ARDS in the last decade.

Methods

The chief investigators for the OSCAR (ISRTCN90110503), HARP-2 (ISRCTN88244364), and BALTI-2 (ISRCTN38366450) studies agreed to supply case report forms, protocols, instructions to investigators, and anonymized data for this analysis. The case report and database specifications for each study were examined to determine common time points when tidal volume was recorded or could be derived from minute ventilation and respiratory rate. In OSCAR and HARP-2, measures were available at baseline (before randomization), and on day 1 and day 7 after randomization. In OSCAR, baseline data were available for all patients, but after randomization the treatment group received HFOV and so only the tidal volumes in the control group were included. In BALTI-2, only baseline measures were recorded. In all studies, patients' sex and height were available to calculate PBW. In HARP-2 and BALTI-2, expired tidal volumes were recorded. In OSCAR, expired minute volume and total respiratory rate were recorded and so the tidal volume was back-calculated. Details of PEEP–fractional inspired oxygen (FI_{O_2}) combinations were available only in the OSCAR study.

All studies recorded tidal volume at baseline (before randomization). In OSCAR, variables were then collected daily as the last value charted before 08.00 h. In HARP-2, the highest tidal volume in the past 24 h was recorded.

Anonymized data covering baseline attributes, tidal volume, and PEEP– FI_{O_2} were combined on a single database for analysis. Details of the instructions to local investigators concerning ventilator management were also recorded.

Results

In OSCAR, the instructions to local investigators were as follows: 'We suggest but not mandate that control patients be managed using… limited tidal volume, pressure controlled artificial ventilation using tidal volumes of 6–8 ml kg^{-1} body weight.' A table of the recommended combinations of FI_{O_2} and PEEP based on the ARDSnet study protocol was supplied. The study teams at each site received face-to-face and video training in both HFOV and control group ventilation techniques. In both HARP-2 and BALTI-2, local investigators were 'encouraged to use a low tidal volume strategy of ventilation based on ideal body weight'. There was no on-site training in these studies. There was no feedback to sites on their ventilator management in any study.

Complete data for tidal volume and ideal (predicted) body weight were available or derivable for OSCAR patients before randomization in 96.0% (763/795 patients). At day 1 and day 7 of OSCAR, control arm data were available in 95.5% (379/397 patients) and 61.0% (242/397 patients), respectively. In HARP-2, data completeness was 90.7% (490/540 patients) at baseline. Data were available on 89.8% (485/540 patients) on day 1 and 54.1% (293/540 patients) on day 7. For both OSCAR and HARP-2,

Table 1 The characteristics of the patients included in the analysis. The ratio of arterial oxygen partial pressure to fraction of inspired oxygen (Pa_{O_2}:FI_{O_2}) was recorded at randomization. APACHE II, Acute Physiology and Chronic Health Evaluation score II, a unitless measure of overall illness severity at intensive care unit admission

Trial	Sites (*n*)	Patients (*n*)	Age [yr; mean (range)]	Males [*n* (%)]	APACHE II score [mean (SD)]	Pa_{O_2}:FI_{O_2} ratio [kPa; mean (SD)]
OSCAR (intervention)		398	54.9 (16.2–90.1)	256 (64.3)	21.8 (6.0)	15.0 (4.9)
OSCAR (control)		397	55.9 (18.8–88.3)	239 (60.2)	21.7 (6.1)	15.0 (5.1)
OSCAR (overall)	30	795	55.4 (16.2–90.1)	495 (62.3)	21.8 (6.1)	15.1 (5.1)
HARP-2 (overall)	40	539	53.9 (16.2–90.3)	307 (57.0)	18.9 (6.6)	17.1 (7.4)
BALTI-2 (overall)	46	326	55.5 (17.2–93.2)	212 (65.0)	19.2 (6.5)	13.8 (4.9)
All studies		1660	54.9 (16.2–90.3)	1014 (60.1)	19.9 (6.4)	15.3 (5.75)

Table 2 The median (interquartile range) tidal volumes and percentage of patients ventilated in the recommended range of 6–8 ml kg^{-1} PBW across the three studies. IQR, interquartile range; NA, not available; PBW, predicted body weight; Vt, expired tidal volume expressed as millilitres per kilogram PBW. Day 1 and day 7 are days after randomization

Trial	Baseline Vt [ml kg^{-1} PBW; median (IQR)]	Baseline percentage of patients with 6–8 ml kg^{-1} (%)	Day 1 Vt [ml kg^{-1} PBW; median (IQR)]	Day 1 percentage of patients with 6–8 ml kg^{-1} (%)	Day 7 Vt [ml kg^{-1} PBW; median (IQR)]	Day 7 percentage of patients with 6–8 ml kg^{-1} (%)
OSCAR	7.6 (6.6–9.4)	38.5	7.9 (6.6–9.4)	26.7	8.4 (6.9–10.3)	28.5
HARP-2	7.7 (6.2–9.7)	35.9	9.8 (7.9–12.3)	25.6	10.3 (8.3–12.6)	19.7
BALTI-2	8.3 (7.1–9.8)	37.1	NA	NA	NA	NA

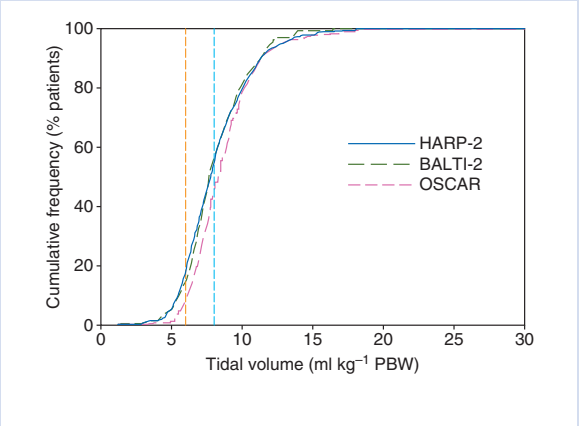

Fig 1 Cumulative frequency plot of tidal volume before randomization for all three trials. The dashed vertical lines represent the recommended range of 6–8 ml kg^{-1} predicted body weight.

the reduced number of patients with data available at day 1 and 7 was accounted for by patients who had died or recovered. In BALTI-2 at baseline, completeness was 48.8% (159/326 patients). Only OSCAR recorded PEEP, and data completeness was 98.3% (782/795 patients) at baseline, decreasing to 70.8% (281/397 patients) on day 1 and 60.7% (241/397 patients) on day 7.

Patient details are shown in Table 1.

The patients were broadly similar. Patients in OSCAR had the highest admission Acute Physiology and Chronic Health Evaluation score II (APACHE II) score, and the worst oxygenation was found in patients in BALTI-2.

The proportion of patients across all three studies receiving tidal volumes of 6–8 ml kg^{-1} PBW was determined. This percentage ranged from 20 to 39% (Table 2) across baseline, day 1, and day 7.

Figure 1 shows the cumulative frequency of the number of patients over the different tidal volume values for each of the studies at baseline. The results were similar for all studies. About 50% of patients were ventilated with a tidal volume in excess of 8 ml kg^{-1} PBW and ~20% in excess of 10 ml kg^{-1} PBW.

OSCAR

Patients included for OSCAR had tidal volumes recorded at baseline (n=763), day 1 (n=379), and day 7 (n=243). The median expired tidal volume increased with the time from randomization.

In OSCAR, PEEP and FI_{O_2} were also recorded. Inspired oxygen fraction–PEEP relationships across all 3 days in OSCAR were compared with the guidelines regarding PEEP escalation from the ARDSnet study that were supplied to the local investigators. This is displayed in Fig. 2. There was considerable variability, but there was a general trend towards using higher PEEP than ARDSnet recommendations at the extremes of range of FI_{O_2}.

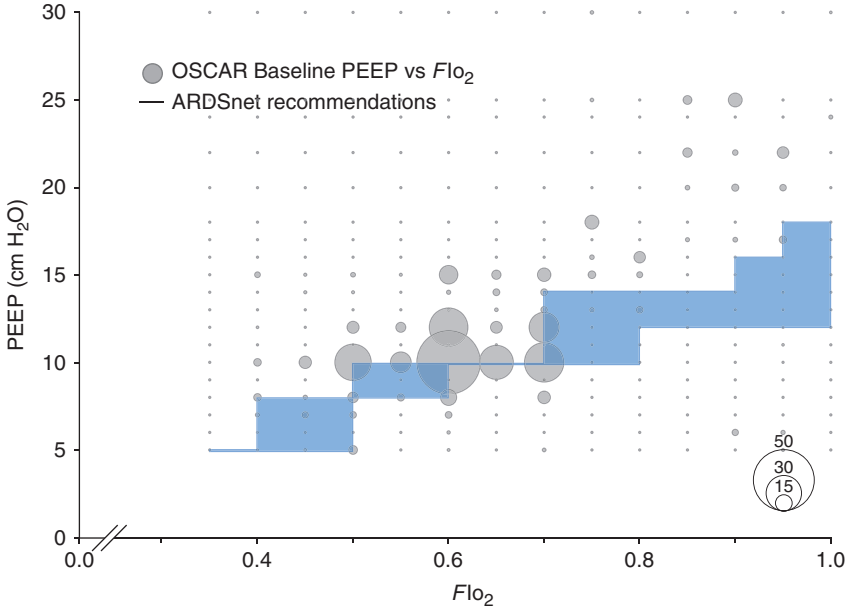

Fig 2 OSCAR study: bubble plot displaying inspired oxygen fraction (FI_{O_2}) *vs* PEEP at baseline. The diameter of the circles represents the number of patients. The blue shaded area represents the recommended PEEP– FI_{O_2} relationships.

Average (SD) PEEP was 11.4 (3.4), 11.4 (3.6), and 9.1 cm H_2O (3.4) at randomization, day 1, and day 7, respectively.

HARP-2

HARP-2 patients included were from baseline (n=490), day 1 (n=485), and day 7 (n=293). Percentages ARDSnet compliant were 35.9, 25.6, and 19.7%, respectively, and as with the OSCAR study the median expired tidal volume increased with the time from randomization.

BALTI-2

Tidal volumes were available only at baseline in BALTI-2 (n=159), and 37.1% patients received tidal volumes between 6 and 8 ml kg^{-1} PBW with a median of 8.3 (interquartile range 7.1–9.8) ml kg^{-1}.

Discussion

Overall, the results show that considerably less than half of the patients in these trials received lung-protective ventilation. The exact percentage (35–38.5%) was consistent across the three studies. This represents similar compliance to that found in the London Hospital Critical Care audit at 50%[12] and a similar adherence as international audits of 41% (USA),[13] 10–79% (USA),[14] 44% (Taiwan),[15] and 13% (Australia),[16] although less than the 65% found in an international cross-sectional study.[17] However, these figures were obtained from audit data or case series. The studies reported here had strict entry criteria, so all the patients were recognized to have ARDS at randomization. In addition, the local investigators had been encouraged to use low tidal volume ventilation and were reporting tidal volumes in the case report forms. It is therefore surprising that compliance was so poor.

Several audits, surveys, and studies have addressed staff knowledge with respect to identification of ARDS, calculation of PBW, and the clinical importance of adhering to a lung-protective ventilation strategy.[18–20] Unsurprisingly, experienced staff with a greater number of years of intensive care unit employment were both more aware and more likely to use lung-protective ventilation. However, in a clinical trial staff are usually trained as part of the study, and local investigators oversee the study. As a result, outcomes are often better than those seen in case series (the Hawthorne effect). There was no evidence of this when compliance was compared with historical figures.

These guidelines presuppose that clinicians are able to control tidal volume. In the ARDSnet study, this was achieved using patient-triggered volume-controlled ventilation (assist-control mode). However, practice in the UK and Europe has now moved towards patient-triggered pressure-controlled modes (usually pressure support mode). If patients are making significant respiratory effort it may not be possible to control tidal volumes simply by reducing the level of pressure support, especially in patients with good respiratory compliance. This may in part explain the increasing tidal volume with time from randomization, as recovering patients may have been switched from controlled to supported ventilation modes. Unfortunately, ventilation mode was not recorded in any of the studies.

One reason we undertook this analysis was to address the difference in control arm mortality between OSCAR[8] and OSCILLATE,[11] two large randomized control trials assessing the use of HFOV in ARDS. OSCILLATE found increased mortality amongst the HFOV cohort at 47%, *vs* 35% of controls ($P < 0.005$),

whereas OSCAR found no significant difference, with 42% mortality in the HFOV group and 41% in the control group (P=0.85).

It had been postulated that OSCAR had higher than expected mortality in its control group secondary to poor adherence to low tidal volume in the control group. In OSCILLATE, the tidal volume was set at 6 ml kg^{-1} PBW as an entry criterion for the study, and averaged 6.1 (SD 1.35) ml kg^{-1} PBW on day 1. Although further data on ventilation practice in OSCILLATE are not available, lung-protective ventilation was mandated in the control arm until weaning commenced. It is therefore possible that the suboptimal ventilatory practice we determined in the control arm of the OSCAR study remains a plausible explanation for the difference in primary outcomes between the two studies. An individual patient data meta-analysis across all published randomized controlled trials of HFOV is underway to investigate this in more detail.

Improved adherence to low tidal volume lung-protective ventilation strategies can be achieved in clinical practice. A UK audit demonstrated significant reduction in tidal volumes after targeted nurse and clinician education relating to ARDS, predicted bodyweight calculations, and lung-protective strategies.[18] A specific daily teleconference 'ventilator round' using offsite data collection, monitoring, and observation by an intensive care unit nurse improved adherence from an average 30% to 45%.[14] Computer-assisted checks have also been shown to improve compliance significantly. One study found that a pop-up on a computerized clinical information system advising the correct tidal volume limit after evaluating the patient's PBW reduced average tidal volume by 0.84 ml kg^{-1} PBW,[21] and a similar intervention advising initial ventilation settings of 6–8 ml kg^{-1} that also calculated the PBW reduced by 18% the number of patients receiving larger tidal volumes than desired.[22] It is now possible to configure some ventilators so the default settings are low tidal volumes.

However, it may also be time to review the ARDSnet guidelines in light of current practice. It is not clear when low tidal volume ceases to be beneficial, and the advantages of lighter sedation and the associated spontaneous breathing modes of ventilation become more important. One study found a particular detriment associated with high tidal volumes at early onset of ARDS, suggesting a time window when lung-protective ventilation is beneficial.[13] Also, the ARDSnet study took place a decade and a half ago, when assist-control mode was in common use in the USA and the 'usual care' control group received 12 ml kg^{-1} PBW with peak inspiratory pressures up to 50 cm H_2O. Only 6.2–30.7% of patients in these studies received tidal volumes at or above this level.

Analysis of these three studies reveals an adherence of <50% with low tidal volume ventilation, in keeping with other UK audits, even in the controlled environment of a clinical trial. Given the importance of low tidal volume ventilation in improving outcomes in ARDS, the causes for this stubborn non-compliance both in the UK and internationally need to be examined to determine the barriers to improving implementation and compliance with protective lung ventilation.

Authors' contributions

Substantial contribution to conception and design: J.P., C.M., R.L., G.P., D.M., F.G., D.Y.
Acquisition of data: C.M., R.L., G.P., D.M., F.G., D.Y.
Analysis and interpretation of data: J.P., C.M., R.L., G.P., D.M., F.G., D.Y.
Drafting the article: J.P., D.Y.
Revising the article critically for important intellectual content: J.P., C.M., R.L., G.P., D.M., F.G., D.Y.
Final approval of the version to be published: J.P., C.M., R.L., G.P., D.M., F.G., D.Y.
Agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: J.P., C.M., R.L., G.P., D.M., F.G., D.Y.

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Declaration of interest

None declared.

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