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Evolution of practice patterns in the management of acute respiratory distress syndrome: A secondary analysis of two successive randomized controlled trials

Kate C. Tatham^{a,b,*}, Niall D. Ferguson^{a,c}, Qi Zhou^d, Lori Hand^d, Peggy Austin^d, Ravi Taneja^e, Alejandro C. Arroliga^{f,g}, Juan F. Sanchez^{f,g}, Edgar J. Jimenez^{f,g}, Brandon P. Staub^h, Michelle E. Khoⁱ, J. Guillermo Domínguez-Cherit^{j,k}, Adam Mullaly^l, Yaseen M. Arabi^m, Maureen O. Meade^{d,n}

^a Department of Medicine, Division of Respiriology & Critical Care Medicine, University Health Network and Sinai Health System, Toronto, Canada

^b Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery & Cancer, Imperial College, London, United Kingdom

^c Interdepartmental Division of Critical Care Medicine, Departments of Medicine and Physiology, Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

^d Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University Health Sciences Centre, Hamilton, Canada

^e University of Western Ontario, Anesthesia, Medicine and Critical Care, London, Canada

^f Division of Pulmonary and Critical Care Medicine, Baylor Scott and White Health, Temple, TX, United States

^g Texas A&M Health Sciences Centre, College of Medicine, Temple, TX, United States

^h Department of Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, PA, United States

ⁱ School of Rehabilitation Science, McMaster University, Hamilton, Canada

^j Division of Critical Care, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, México City, Mexico

^k School of Medicine, Instituto Tecnológico de Monterrey, Monterrey City, Mexico

^l Main Line Health, Bryn Mawr Hospital, Philadelphia, PA, United States

^m Intensive Care Department, College of Medicine-Riyadh, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

ⁿ Interdepartmental Division of Critical Care, Hamilton Health Sciences, Critical Care, Hamilton, Canada

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ABSTRACT

Purpose: We sought to examine changes in acute respiratory distress syndrome (ARDS) management over a 12-year period of two successive randomized trials.

Methods: Analyses included baseline data, from eligible patients, prior to influence of trial protocols, and daily study data, from randomized patients, of variables not determined by trial protocols. Mixed linear regressions examined changes in practice year-on-year.

Results: A total of 2376 patients met the inclusion criteria. Over the 12-year period, baseline tidal volume index decreased (9.0 to 7.0 ml/kg, $p < 0.001$), plateau pressures decreased (30.8 to 29.0 cmH₂O, $p < 0.05$), and baseline positive end-expiratory pressures increased (10.8 to 13.2 cmH₂O, $p < 0.001$). Volume-controlled ventilation declined from 29.4 to 14.0% ($p < 0.01$). Use of corticosteroids increased (baseline: 7.7 to 30.3%; on study: 32.6 to 61.2%; both $p < 0.001$), as did neuromuscular blockade (baseline: 12.3 to 24.5%; on study: 55.5 to 70.0%; both $p < 0.01$). Inhaled nitric oxide use increased (24.9 to 65.8%, $p < 0.05$). We observed no significant change in prone positioning (16.2 to 18.9%, $p = 0.70$).

Conclusions: Clear trends were apparent in tidal volume, airway pressures, ventilator modes, adjuncts and rescue therapies. With the exception of prone positioning, and outside the context of rescue therapy, these trends appear consistent with the evolving literature on ARDS management.

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* Corresponding author at: Section of Anaesthetics, Pain Medicine and Critical Care, Dept of Surgery & Cancer, Imperial College London, Chelsea & Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom.

E-mail address: kate@imperial.ac.uk (K.C. Tatham).

1. Introduction

Advances in acute respiratory distress syndrome (ARDS)¹ research in recent decades have coincided with significant changes in mechanical ventilation practices [1]. Several clinical trials have described a mortality benefit from lung-protective ventilation strategies, specifically low tidal volume index (V_T) ventilation [2,3], increased positive end-expiratory pressure (PEEP) [4,5] and driving pressure limitation [6]. In addition to the refinement of ventilation practices, other studies have informed the use of adjuncts such as pulmonary artery catheters (PAC) [7,8], prone positioning [9], and high frequency oscillatory ventilation (HFOV) [10,11]. Experience with, and evidence for, pharmacological interventions including systemic corticosteroids [12,13], inhaled nitric oxide (iNO) [14], and neuromuscular blocking drug (NMBD) use [15] have also evolved over this period.

Several factors influence changes in practice. A wealth of evidence, from basic and clinical research, has had a major impact on the management of ARDS since the first description over 50 years ago [16]. Moreover, the mere availability of advancing technologies, offset by the changing costs of critical care, also influence prevailing practices. An awareness of changing norms for the care of critically ill patients with ARDS is fundamental to designing the next generation of clinical trials and is also useful to clinicians as a benchmark for their own clinical care.

We sought to describe the evolution of practice patterns for adult patients with ARDS over a 12-year period of two randomized clinical trials. Specifically, we sought to identify changes in the adoption of lung-protective ventilation strategies (low V_T , titrated PEEP and limitation of P_{plat}) and ventilator modes (volume-controlled, pressure-controlled, pressure support). We also investigated the use of corticosteroids, NMBD and PAC, none of which were protocolized in the context of the two trials, and rescue therapies (iNO, proning, extracorporeal membrane oxygenation, and HFOV).

2. Materials and methods

2.1. Design

We conducted a secondary analysis of data from two randomized clinical trials. The Lung Open Ventilation Study (LOVS) trial [17] (August 2000 to March 2006) compared conventional to higher PEEP strategies during low V_T ventilation among 983 randomized patients from 30 hospitals primarily in Canada, and also Australia, and Saudi Arabia. The Oscillation for ARDS Treated Early (OSCILLATE) trial [10] (including both the pilot phase: July 2007 to June 2008; and full trial: July 2009 to August 2012) compared HFOV to conventional ventilation using low V_T and high PEEP. This included 548 randomized patients from 39 sites primarily in Canada, and also from the United States, Chile, Saudi Arabia and India. Both studies were coordinated through CLARITY Research at McMaster University, Canada. There was a 1-year hiatus between the LOVS and OSCILLATE studies, and between the OSCILLATE pilot and full trial.

This secondary analysis includes baseline data from patients both randomized, and eligible but not enrolled, and daily data (up to 28 days) from participants in both studies, of the variables not determined by trial protocols.

2.2. Patients

Within these ARDS trials, OSCILLATE limited enrolment to patients with a $PaO_2:FiO_2$ (P:F) ratio ≤ 200 mmHg and, therefore, for the purpose

¹ **Abbreviations:** acute respiratory distress syndrome (ARDS); high frequency oscillatory ventilation (HFOV); intensive care unit (ICU); inhaled nitric oxide (iNO); lung open ventilation trial (LOVS); neuromuscular blocking drugs (NMBD); oscillation for ARDS treated early (OSCILLATE); OSCillation in ARDS (OSCAR); partial pressure of arterial oxygen (PaO_2) to fractional inspired oxygen FiO_2 (P:F) ratio; pulmonary artery catheter (PAC); positive end-expiratory pressure (PEEP); plateau pressure (P_{plat}); tidal volume index (V_T)

of the present analyses, we included only patients from the LOVS database also meeting this criterion. In addition, most sites had Research Ethics Board authorization to provide baseline data from eligible but not enrolled patients. These patients are represented in this analysis by providing limited baseline data only.

2.3. Hypotheses

We specified study hypotheses in advance of the analyses. Analyses of baseline data allowed us to evaluate practice patterns before clinical care was influenced by LOVS or OSCILLATE study protocols. Analyses of on-study data allowed us to evaluate the evolution of practices patterns only for those variables that were not determined by study protocols. Our study hypotheses addressed several areas: lung protective ventilation, modes of ventilation, adjunct and rescue therapies as follows:

Lung protective ventilation: We hypothesized that mean baseline V_T (mL/kg predicted body weight) and mean P_{plat} decreased over time. With respect to PEEP management, we hypothesized that mean baseline PEEP levels increased over time.

Modes of ventilation: We considered the following modes of ventilation at baseline: volume-controlled, pressure-controlled and pressure support. We reasoned that OSCILLATE patient screening procedures might have influenced clinicians' choice of mode even at baseline; therefore, the analyses of baseline ventilator mode were limited to LOVS data and OSCILLATE data for patients who were eligible but not enrolled. We hypothesized that use of volume-controlled ventilation would not change, or possibly decline over time; that pressure-controlled modes would not change, or possibly increase over time; and that the use of pressure support would increase.

Adjuncts and rescue therapies: We hypothesized that the rates of corticosteroid therapy (for any indication) would initially increase in response to encouraging work by Meduri et al. [18], and then decrease in response to subsequent studies published in 2006 [12] and 2008 [19] during the period of this analysis. These data were available at baseline and on-study; however, we excluded OSCILLATE HFOV patients from on-study data analyses, reasoning that there may be an interaction between HFOV and the rates of other respiratory adjuncts. We did, however, include on-study data of the OSCILLATE control patients. The same rationale applied to analyses of NMBDs, PAC, iNO, prone positioning and HFOV as a rescue therapy. We hypothesized that NMBD, prone ventilation, and HFOV as rescue therapies increased over time among control patients; and that use of PAC and iNO decreased.

2.4. Statistics

Continuous data are presented as means and standard deviations, or medians and interquartile ranges, as appropriate. Dichotomous data are presented as proportions.

To assess the changes in practice over time for various treatments, we used study year as the unit, counting from the beginning of LOVS, OSCILLATE pilot and OSCILLATE for the analyses. There were 10 discrete study years during 2000–2012. To obtain the adjusted means or proportions over study years, we used mixed linear regressions for the continuous treatments (e.g. V_T) or the mixed logistic regression models for dichotomous treatments (e.g. inhaled NO), respectively. The model included fixed effects for study year (as categorical) adjusted for age, sepsis at baseline, P:F ratio on the first day of the treatment, or the minimum P:F ratio during the study for those who never had treatment, and use of vasopressors on the first day of treatment, or 'ever use' vasopressors during the study, for those never had treatment, and random intercepts for sites.

We estimated the least square means or proportions of the treatment for every study year and performed the linear regression analysis for the time trend. We plotted the adjusted regression line for the means or proportions over the time along with their 95% confidence

interval if the time trend was significant. In addition, we reported the effects of the adjusted variables in odds ratios or beta-coefficients, and where appropriate, the 95% confidence intervals and the *p*-values for each model (see supplemental tables).

3. Results

3.1. Study/patient demographics and characteristics

A total of 2376 patients were included in these analyses from the constituent trials (see Supplemental Table S1). Characteristics of these trials, and patients, are summarized in Table 1. There were 21 sites common to both studies; these sites randomized 879 (89%) of the LOVS patients and 428 (78%) of the OSCILLATE patients.

3.2. Lung protective strategies

Progressive adoption of lung-protective strategies was observed over the study period. Baseline V_T decreased consistently from 9.0 ± 2.6 (mean \pm SD) to 7.0 ± 3.4 ml/kg ($p < 0.001$, Fig. 1A), a trend that remained significant in multivariable analysis and was independently associated with site, age, sepsis at baseline and vasopressor use (see Supplemental Table S2). A progressive reduction in baseline P_{plat} was also apparent from 30.8 ± 7.4 to 29.0 ± 10.4 cmH₂O ($p < 0.05$; Fig. 1B). Meanwhile, baseline PEEP increased from 10.8 ± 5.0 to 13.2 ± 6.1 cmH₂O over the same period ($p < 0.001$; Fig. 1C). Again, these trends remained significant after adjusting for age and site, and a significant association with P:F ratio and vasopressor use at baseline was observed (Supplemental Tables S3–S4).

Table 1
Baseline characteristics per 2-year time interval.

Years of study	2000–2002	2003–2004	2005–2006	2007–2008	2009–2010	2011–2012
Number of patients*	422	318	344	174	485	318
Female sex <i>n</i> (%)	152 (36.1)	128 (40.3)	142 (41.4)	79 (43.6)	216 (43.5)	118 (36.6)
Age (years) <i>mean</i> (<i>SD</i>)	55.87 (16.7)	56.74 (15.6)	55.55 (17.1)	54.86 (17.3)	52.64 (16.2)	54.24 (15.4)
APACHE II score <i>mean</i> (<i>SD</i>)	22.22 (7.2)	23.26 (7.7)	23.67 (7.9)	28.27 (7.8)	27.32 (8.1)	27.16 (7.6)
ARDS risk factors:						
Sepsis <i>n</i> (%)	181 (42.9)	150 (47.2)	160 (46.5)	90 (49.7)	202 (40.1)	145 (45.0)
Aspiration <i>n</i> (%)	78 (18.5)	62 (19.5)	54 (15.7)	29 (16.0)	61 (12.3)	52 (16.1)
Pneumonia <i>n</i> (%)	22 (5.2)	6 (1.9)	7 (2.0)	9 (5.0)	24 (4.8)	12 (3.7)
Trauma <i>n</i> (%)**	–	–	–	10 (5.5)	15 (3.0)	11 (3.4)
Other <i>n</i> (%)	163 (38.8)	120 (37.9)	139 (40.5)	53 (29.3)	211 (42.5)	123 (38.2)
PaO ₂ :FiO ₂ ratio (mmHg) <i>mean</i> (<i>SD</i>)	–	127.86 (39.6)	128.21 (39.5)	121.25 (41.8)	115.67 (39.8)	113.13 (41.7)
Arterial pH <i>mean</i> (<i>SD</i>)**	–	–	–	7.31 (0.11)	7.32 (0.13)	7.31 (0.11)
PaCO ₂ (mmHg) <i>mean</i> (<i>SD</i>)	42.51 (11.11)	42.93 (10.34)	43.57 (10.38)	44.09 (12.40)	45.27 (14.69)	44.13 (13.87)
Respiratory rate (breaths/min) <i>mean</i> (<i>SD</i>)	21.58 (6.54)	22.44 (6.83)	22.64 (6.35)	22.19 (6.12)	25.27 (6.81)	25.13 (8.03)
Vasoactive use <i>n</i> (%)***	223 (52.8)	190 (51.2)	179 (44.4)	70 (74.5)	169 (62.5)	116 (63.0)
Renal replacement <i>n</i> (%)***	16 (3.2)	7 (1.9)	5 (1.2)	15 (16.0)	25 (9.3)	17 (9.2)
Ventilator days <i>median</i> (<i>q1-q3</i>)*	2 (1–3)	2(1–4)	1 (1–3)	1 (1–2)	1 (1–3)	1 (1–3)
Hospital stay (days) <i>median</i> (<i>q1-q3</i>)*	3 (1–6)	3 (2–5)	3 (1–6)	4 (1–7)	3 (1–5)	3 (1–5)

NB. Owing to the large number of overall observations ($n > 1000$), the missing values were regarded as missing at random. Therefore non-missing data was used for the analysis. No missing data imputation was conducted.

* Data not available for all 'eligible, not enrolled' patients.

** Data not available for first three time points.

*** Data not available for OSCILLATE 'eligible, not enrolled' patients.

3.3. Ventilator modes

The use of volume-controlled ventilation exhibited a consistent decline from 29.4 ± 7.9 (mean \pm SE) to $14.0 \pm 5.2\%$ over the 12-year period ($p < 0.01$, Fig. 2A), which was unaffected after adjusting for site (Supplemental Table S5). However, no overall pattern of change was seen in the use of pressure-controlled or pressure support ventilation, in contrast to the original hypothesis (Fig. 2B–C). Pressure control use was associated with age and P:F ratio at baseline (Supplemental Table S6). Similarly, pressure support ventilation use was associated with age, P:F ratio at baseline and site (Supplemental Table S7).

3.4. Adjunctive therapies

Adjuncts to ventilatory management were assessed both at baseline and on study. Corticosteroid administration increased substantially at baseline, from 7.7 ± 1.9 (% mean \pm SE) to 30.3 ± 4.2 ($p < 0.001$), and on-study, from 32.6 ± 4.8 to 61.2 ± 6.2 ($p < 0.001$) (Fig. 3A–B). As predicted, baseline steroid use was associated with age, sepsis, vasopressor use and site (Supplemental Table S8). On study use was predicted by age, sepsis, P:F ratio and site (Supplemental Table S9).

These data were mirrored by a concomitant increase in NMBDs at baseline (12.0 ± 2.9 to $24.5 \pm 4.4\%$, $p < 0.01$) and on study (55.5 ± 5.2 to $70.0 \pm 5.6\%$, $p < 0.01$) (Fig. 3C–D). Baseline use was associated with age, P:F ratio, vasopressor use and site, and on study use was only associated with site (Supplemental Tables S10–11).

PAC use declined progressively, from 31.8 ± 5.9 to $0.6 \pm 0.4\%$ at baseline ($p < 0.01$; Fig. 3E) and from 54.7 ± 7.0 to $2.4 \pm 1.5\%$ ($p < 0.01$; Fig. 3F) on study. At baseline, this was also the case, when adjusting for age, sepsis, vasopressor use and site (Supplemental Table S12). Association with age, sepsis and site was also observed during the study period (Supplemental Table S13).

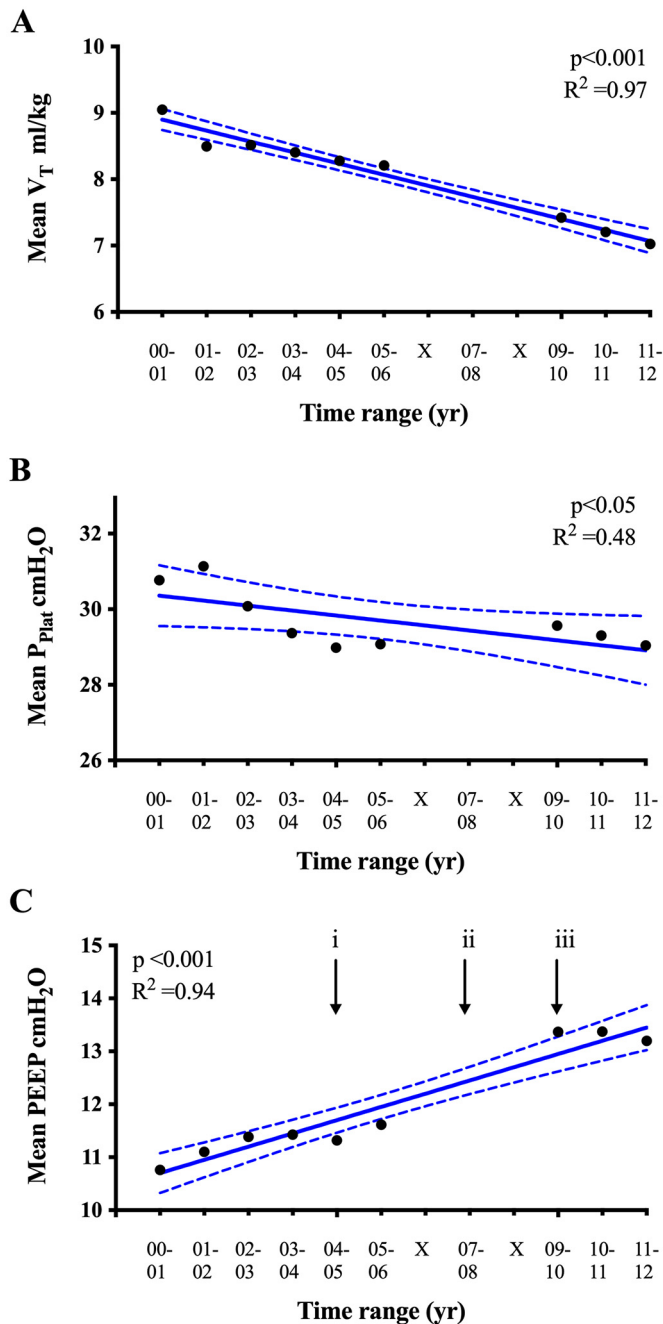


Fig. 1. Trends in ventilation parameters (V_T , P_{plat} and PEEP): Protective lung ventilation strategies have increased over time.

A significant drop in mean V_T index ($p < 0.001$, $n = 1272$) and P_{plat} ($p < 0.05$, total $n = 1090$) at the point of trial eligibility was observed over the 12-year study period (Fig. 1A, B). Conversely mean PEEP values (1C) exhibited a significant increase over time ($p < 0.001$, $n = 1509$), which may be attributable to the large studies published concomitantly in the years indicated (i. 2004: 'ALVEOLI' [20], ii. 2008: 'LOVS' [17] and 'ExPress' [21], iii. 2010: Briel et al. [5]). (Adjusted data shown; raw data: V_T $p < 0.001$; P_{plat} $p < 0.01$; PEEP $p < 0.001$.)

3.5. Rescue therapies

There was a significant increase in use of iNO over the study period from 24.9 ± 8.2 to $65.8 \pm 15.7\%$ ($p < 0.05$, Fig. 4A). This change was associated with site, P:F ratio and sepsis (Supplemental Table S14). Similarly, HFOV use also increased between 2000 and 2012, peaking in 2009–2010 at 68.2% (overall 4.4 ± 3.1 to $34.6 \pm 17.9\%$; $p < 0.05$, Fig. 4B), predicted by P:F ratio and site (Supplemental Table S15).

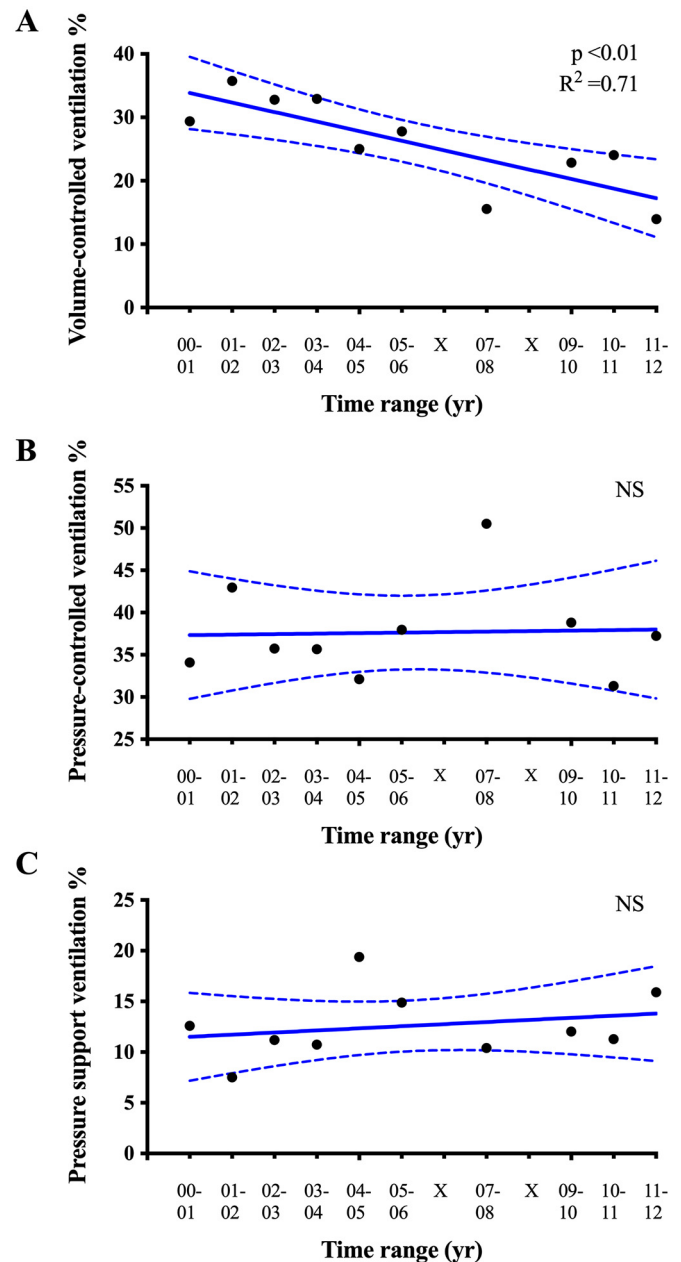


Fig. 2. Trends in ventilation modes: Volume-controlled ventilation use has declined over time.

A significant drop in the use of volume-controlled ventilation (2A) was observed over the study period ($p < 0.01$, $n = 1495$). No such pattern was seen in the use of pressure-controlled and pressure support ventilation (2B–C). (Adjusted data shown; raw data: all modes - not significant (NS).)

There was no change in the adoption of prone positioning (16.2 ± 6.2 to $18.9 \pm 11.2\%$, $p = 0.70$; Fig. 4C), and only P:F ratio predicted its use (Supplemental Table S16). Extracorporeal membrane oxygenation was used infrequently across the period of these analyses, with no discernible change.

4. Discussion

This study demonstrates that following publication of the landmark ARDSNET trial in 2000 [2], a significant drop in V_T from approximately 9 to 7 ml/kg occurred (Fig. 1A) over a 12-year period. This suggests that lower V_T is increasingly the standard of care. Adoption of other lung protective ventilation strategies was evidenced over this time period with a

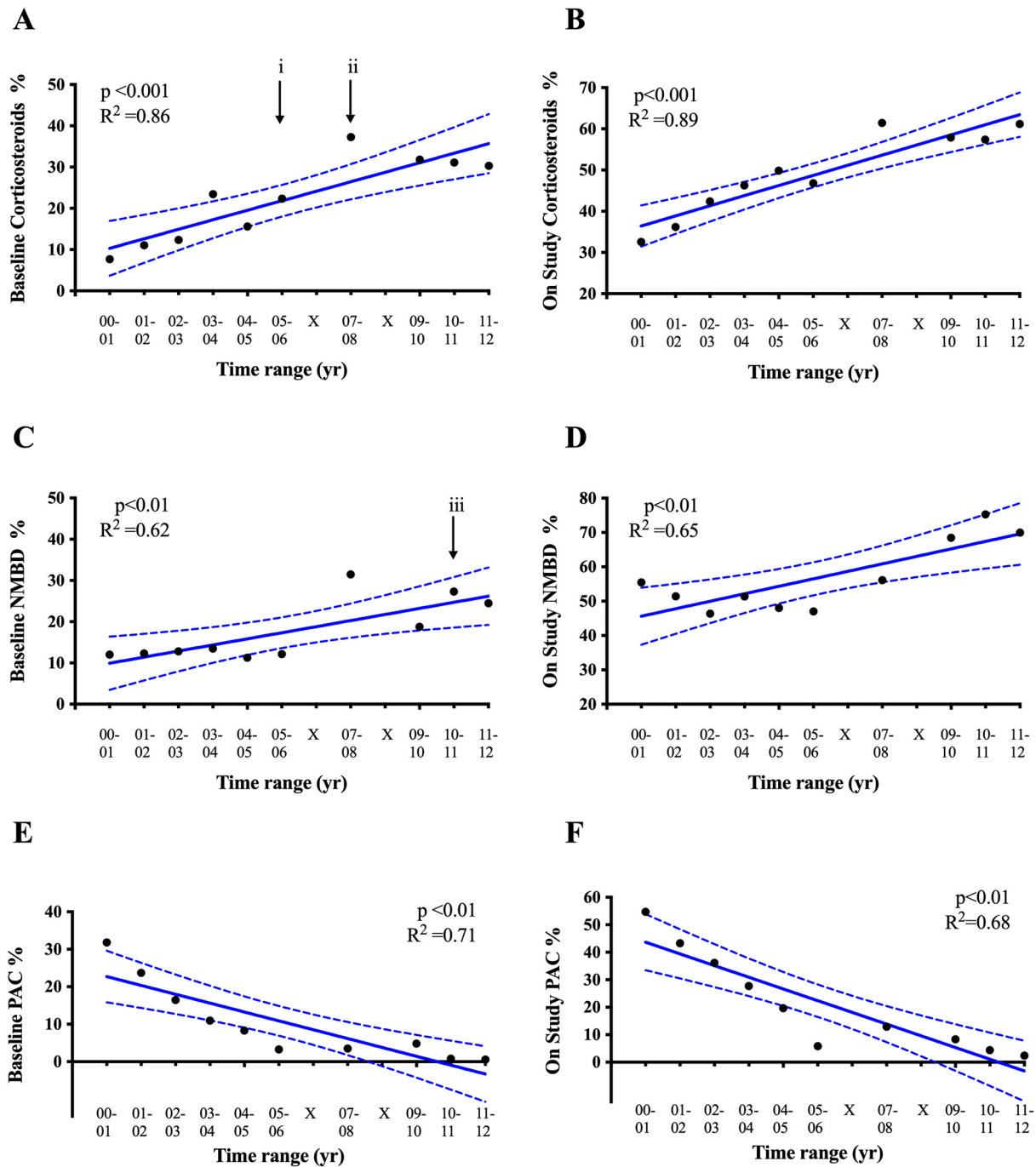


Fig. 3. Trends in adjuncts: Pharmacological interventions (corticosteroids and NMBDs) increased in use over time, whereas PAC use declined.

A significant increase in corticosteroid use was observed at baseline (Fig. 3A, $p < 0.001$, $n = 1805$) and over the study period (Fig. 3B, $p < 0.001$, $n = 1094$). Timing of relevant concomitant trials is indicated; i. 2006 Steinberg et al. [12] and ii. 2008: 'CORTICUS' [19]. A similar pattern was observed with the use of NMBDs at baseline (Fig. 3C, $p < 0.01$, $n = 1805$) and on study (Fig. 3D, $p < 0.01$, $n = 1093$). The timing of the 'ACURASYS' trial (2010) is shown (iii) [15]. The use of the PACs was observed to trend downwards at baseline and over the same period at baseline (Fig. 3E, $p < 0.01$, $n = 1805$) and on study (Fig. 3F, $p < 0.01$, $n = 1093$). (Adjusted data shown; raw data: p values all < 0.01).

reduction in P_{plat} from 31 to 29 cm H₂O (Fig. 1B). The significance of this overall decline in P_{plat} is reinforced by the fact that this occurred despite an observed increase in PEEP, over the same time period. While individual subsequent large studies were unable to demonstrate a clear mortality benefit of higher versus lower PEEP [17,20,21], an individual patient data meta-analysis did show improved survival among patients with moderate-severe ARDS treated with higher PEEP [5]. In addition, a secondary analysis of clinical trials in ARDS found that mortality is reduced specifically for those patients that exhibit improved oxygenation in response to increased PEEP [4].

A modest decline in volume-controlled ventilation was observed to rates below 15%, despite no clear increase in the utilization of pressure-controlled ventilation being observed (Fig. 2). However, a non-significant increase in the use of pressure support ventilation modes was noted. Substantial improvements in ventilator technology, using novel modes to limit delivered pressures and volumes, may explain these findings, which will be relevant to the design and interpretation of future clinical trials in ARDS management.

The use of pharmacological adjuncts in ARDS management demonstrated an increase in use for both corticosteroids and NMBDs. For

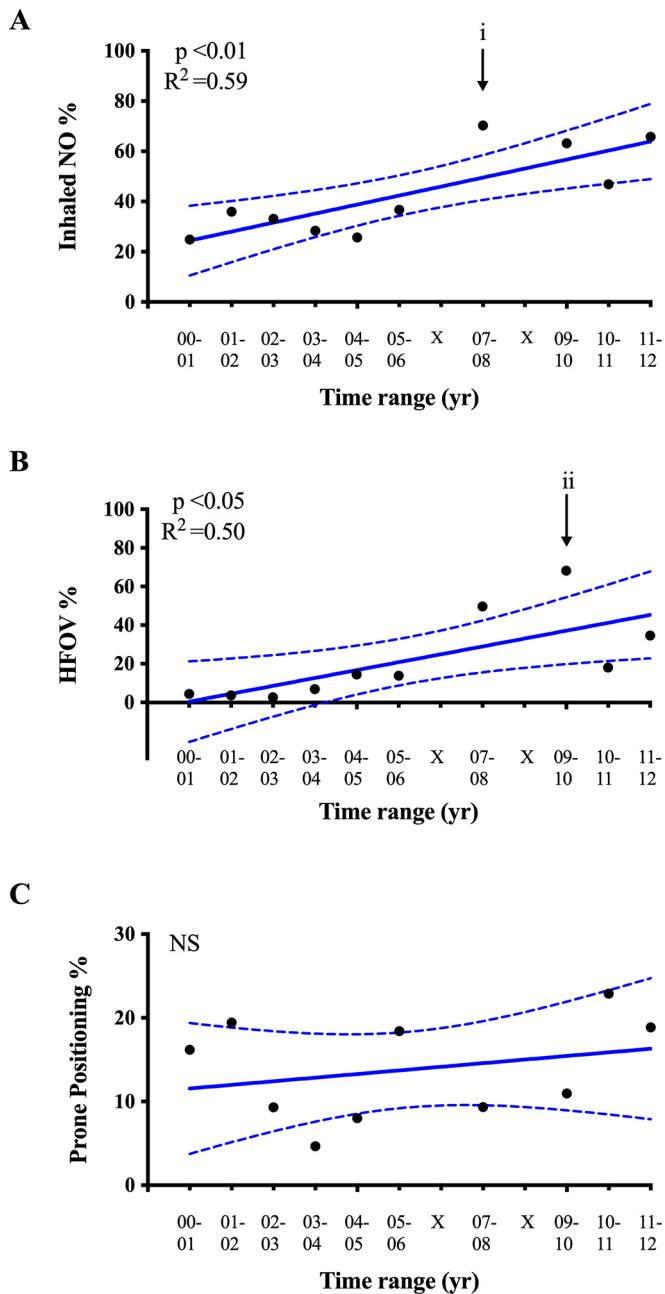


Fig. 4. Trends in rescue therapy use: Adoption of iNO and HFOV increased over time. The use of iNO demonstrated a significant increase over the twelve years (Fig. 4A, $p < 0.05$, $n = 261$), despite the negative findings reported on its use, in a systematic review during the study period by Adhikari et al. in 2007 (i). [26] HFOV use also increased significantly over the study period (Fig. 4B, $p < 0.05$, $n = 263$), as a rescue therapy for ARDS, coinciding with publication of a large meta-analysis and systematic review in 2010 (ii) [27]. (Adjusted data shown; raw data: $p < 0.01$ for both). No significant trend was exhibited with the use of prone positioning before or after adjustment (Fig. 4C, $p =$ non-significant (NS), $n = 261$).

corticosteroids, as hypothesized, we observed an overall increase in use which may correspond to high-profile work such as that by Meduri et al. [18] in the late 1990's (Fig. 3A–B). Over the course of this study we predicted that steroid use would decrease over time given the several high-profile trials demonstrating no clear benefit and a potential harm in steroid use for ARDS [12] and septic shock [19]. Steroid use did not however fall, as predicted, with only a plateau in use, and no clear decrease in use in more recent years. A decrease in use may be more evident however, in the subsequent years. Of note, severity of hypoxemia was not predictive of steroid use.

NMBD use initially fell, and then rose over time, appearing to plateau more recently (Fig. 3D). This overall increase may be partially attributable to the contemporaneous publication of the multicenter 'ACURASYS' trial in 2010 [15], demonstrating a 90-day mortality benefit in patients with severe ARDS, receiving a 48 h infusion of cisatracurium. The 'ROSE' trial, published in 2019, was unable to replicate this benefit however, and therefore may have subsequently impacted on the trend we demonstrate here [22].

Similarly, following several publications indicating a lack of utility, and increased risk of complications, PAC utilization [8,23–25] dropped dramatically to levels of less than 1% (Fig. 3E–F).

Regarding rescue therapies, contrary to prediction, the use of iNO increased over the study period (Fig. 4A). This is despite several large systematic reviews and meta analyses [14,26] recommending against its use, with no mortality benefit and potential for harm being demonstrated. Its ongoing popularity may be of concern, and could be attributable to its ability to induce a short term improvement in oxygenation, despite no evidence for any established benefit thereafter [26].

HFOV increased dramatically over time (Fig. 4B), possibly related to the meta-analysis and systematic review demonstrating an improvement in oxygenation and outcome in 2010 [27]. However, this trend seemed to decline in the final two years of this study, which may be related to limited oscillator availability. Subsequently in 2013, the OSCILLATE and the OSCillation in ARDS (OSCAR) multi-center trials, which both randomized ARDS patients with $P:F \leq 200$ mmHg to HFOV, or conventional ventilation, within 72 h or one week of commencing ventilation respectively. They both concluded that HFOV was unlikely to be of benefit in ARDS, and may even indicate a propensity to harm [10,11]. Thus, a subsequent decline in HFOV use is anticipated.

Of note, study site appeared to significantly influence all interventions, except for iNO, supporting a prominent role for local culture in the approach to ARDS management.

This study, and others involving similar datasets [1,28], provide not only a benchmark for clinicians, against which to compare and improve their local practice, but can also inform future research, practice and data dissemination. An example of this is tidal volume. Since the 2000 ARDSNET trial compared V_T of 12 to 6 ml/kg [2], we report a gradual decline in V_T from about 9 to around 7 ml/kg. Work studying more recent worldwide trends indicate that this level has since plateaued, with a mean of 7.6 ml/kg being reported by Bellani et al. in the LUNG SAFE study published in 2016 [28]. Crucially, however, they found that fewer than two-thirds of patients were ventilated at V_T less than 8 ml/kg. Our findings are also similar those reported by Esteban et al. [1] who studied three separate sequential cohorts of ARDS patients ($n = 660$) between 1998 and 2010, predominantly from Europe, but also including North and South America, Africa and Asia. They reported a drop in V_T from 8.5 (1998) to 7.4 (2004) to 6.9 (2010) ml/kg actual body weight, corresponding to 9.3 (2004) and 8.2 (2010) ml/kg predicted body weight. This group also described an overall reduction in mortality associated with these data, although the reasons behind this trend are difficult to attribute to changes in ARDS management and mechanical ventilation practice alone. The data described herein differs from these two observational studies however, in that it benefits from the novelty of being derived from randomized controlled trials, with hypotheses defined a priori. This design therefore inherently affords superior fidelity of data collection and ARDS identification.

These findings also emphasize the relatively gradual and progressive assimilation of research findings into clinical practice. For example, this current study shows that it has taken over a decade for average V_T to reach just 7 ml/kg; notwithstanding that since 2000, evidence that 6 ml/kg [2], or more recently even less [29], might be preferable and associated with a survival benefit [30].

We also observed that, despite evidence recommending against their use, rescue therapies for hypoxemia such as iNO and HFOV, continued to increase. This may be indicative of the fluctuating evidence for these interventions over recent years [31,32], and through these studies, an increased awareness and familiarity with their use. As might be

expected, the use of HFOV has reportedly fallen significantly since the OSCILLATE and OSCAR trials were both published in 2013 [28].

A more abrupt change was observed, however, for PAC, with use plummeting to almost zero. This may be due to the sequential publication of several high-quality studies indicating that PAC do not improve outcome [8,24,25], and removal of pulmonary capillary wedge pressure measurement in the most recent ARDS definition [33]. It therefore seems prudent that the trends observed here, guide future trial design, and arguably more importantly, bedside interpretability. Our data suggest that without robust, relevant and consistent evidence and guidelines, we are unlikely to witness a significant departure from current practice.

This study has several limitations. The practice patterns we observed may not reflect 'usual practice', to the extent that Intensive Care Units' participation in the constituent trials is likely to have influenced usual care for potentially eligible patients. Additionally, assessment of the impact of fluid management strategies on ventilation was not feasible.

Whilst it is possible that gradual incorporation of research findings into practice demonstrated here is linked to the improved outcomes from ARDS observed over a similar time period [34–36], validating this assertion is not possible owing to its multifactorial nature. Additionally, literature, and likely practice, has continued to advance since completion of the constituent trials herein. However, this study provides a key benchmark for the evolution of clinical practice and thus an opportunity to guide future practice guidelines and research in this field.

5. Conclusions

This international analysis of more than 2000 patients over a 12-year period, demonstrates several key trends in the management of ARDS patients over time. As predicted, a significant reduction in V_T and P_{Plat} , along with a concomitant increment in PEEP, was observed over this time course. Likewise, volume-controlled ventilation and PAC use decreased, whilst use of pharmacological interventions (corticosteroids, iNO, NMED) significantly increased. Despite the probable multifactorial influences behind these trends, they are likely to correspond to the concurrent evolution, publication and awareness of ARDS literature. More work is required to support timelier implementation of the numerous new ARDS evidence-based management guidelines, which have been published since these data were generated.

In summary, this secondary analysis of clinical trial data indicates that intensive care clinicians appear to modify their practice in response to evolving evidence.

Author statement

Kate C. Tatham: Writing- original draft, review and editing; Visualization, **Niall D. Ferguson:** Conceptualization, Methodology, Investigation, Writing (all stages), Visualization, Supervision; **Qi Zhou:** Formal analysis; Writing (reviewing/editing); **Lori Hand:** Investigation, Writing (reviewing/editing); **Peggy Austin:** Investigation, Writing (reviewing/editing); **Ravi Taneja:** Investigation, Writing (reviewing/editing); **Alejandro C. Arroliga:** Investigation, Writing (reviewing/editing); **Juan F. Sanchez:** Investigation, Writing (reviewing/editing); **Edgar J. Jimenez:** Investigation, Writing (reviewing/editing); **Brandon P. Staub:** Investigation, Writing (reviewing/editing); **Michelle E. Kho:** Investigation, Writing (reviewing/editing); **J. Guillermo Domínguez-Cherit:** Investigation, Writing (reviewing/editing); **Adam Mullaly:** Investigation, Writing (reviewing/editing); **Yaseen M. Arabi:** Investigation, Writing (reviewing/editing); **Maureen O. Meade:** Conceptualization, Methodology, Investigation, Writing (all stages), Visualization, Supervision.

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Declaration of Competing Interest

All the other authors declare no conflicts of interest.

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Appendix A. Supplementary data

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