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REVIEW

Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis

Sachin Sud
Jan O. Friedrich
Paolo Taccone
Federico Polli
Neill K. J. Adhikari
Roberto Latini
Antonio Pesenti
Claude Guérin
Jordi Mancebo
Martha A. Q. Curley
Rafael Fernandez
Ming-Cheng Chan
Pascal Beuret
Gregor Voggenreiter
Maneesh Sud
Gianni Tognoni
Luciano Gattinoni

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S. Sud · J. O. Friedrich · N. K. J. Adhikari
Interdepartmental Division of Critical Care,
University of Toronto, Toronto, Canada

J. O. Friedrich (✉)
Critical Care and Medicine Departments,
The Keenen Research Centre in the Li Ka Shing Knowledge Institute,
St. Michael's Hospital, 30 Bond Street,
Bond Wing, Room 4-015,
Toronto, ON M5B 1W8, Canada
e-mail: j.friedrich@utoronto.ca
Tel.: +1-416-8645559
Fax: +1-416-8646013

P. Taccone · L. Gattinoni
Dipartimento di Anestesia e Rianimazione,
Fondazione IRCCS – "Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena" di Milano, Milan, Italy

F. Polli · L. Gattinoni
Istituto di Anestesiologia e Rianimazione,
Università degli Studi di Milano,
Milan, Italy

N. K. J. Adhikari
Department of Critical Care Medicine,
Sunnybrook Health Sciences Centre,
Sunnybrook Research Institute,
Toronto, Canada

R. Latini
Department of Cardiovascular Research,
Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

A. Pesenti
Dipartimento di Medicina Perioperatoria e Terapie Intensive, Azienda Ospedaliera San Gerardo di Monza, Monza, Italy

A. Pesenti
Dipartimento di Medicina Sperimentale,
Università degli Studi Milano-Bicocca,
Milan, Italy

C. Guérin
Service de Réanimation Médicale et Assistance Respiratoire, Hôpital de la Croix-Rousse, Lyon, France

J. Mancebo
Servei de Medicina Intensiva,
Hospital de Sant Pau,
Barcelona, Spain

M. A. Q. Curley
School of Nursing,
University of Pennsylvania,
Philadelphia, USA

R. Fernandez
ICU Department, CIBERES,
Hospital Sant Joan de Deu-Fundacio Althaia, Manresa, Spain

M.-C. Chan
Section of Chest Medicine,
Department of Internal Medicine,
Taichung Veterans General Hospital,
Taichung, Taiwan

P. Beuret
Service de Réanimation, Centre Hospitalier,
Roanne, France

G. Voggenreiter
Department of Orthopaedic and Trauma Surgery, Hospitals in the Natureparc Altmühltal, Eichstätt, Germany

M. Sud
Faculty of Medicine,
University of Manitoba,
Winnipeg, Canada

G. Tognoni
Consorzio Mario Negri Sud,
Santa Maria Imbaro, Italy

Abstract *Background:* Prone position ventilation for acute hypoxemic respiratory failure (AHRF) improves oxygenation but not survival, except possibly when AHRF is severe. *Objective:* To determine effects of prone versus supine ventilation in AHRF and severe hypoxemia [partial pressure of arterial oxygen (PaO_2)/inspired fraction of oxygen (FiO_2) <100 mmHg] compared with moderate hypoxemia (100 mmHg ≤ PaO_2/

$FiO_2 \leq 300$ mmHg). *Design:* Systematic review and meta-analysis. *Data Sources:* Electronic databases (to November 2009) and conference proceedings. *Methods:* Two authors independently selected and extracted data from parallel-group randomized controlled trials comparing prone with supine ventilation in mechanically ventilated adults or children with AHRF. Trialists provided subgroup data. The primary outcome was hospital mortality in patients with AHRF and PaO_2/FiO_2 <100 mmHg. Meta-analyses used study-level random-effects models. *Results:* Ten trials ($N = 1{,}867$ patients) met inclusion criteria; most patients had acute lung injury. Methodological quality was relatively high. Prone ventilation reduced mortality in patients with PaO_2/FiO_2 <100 mmHg [risk ratio (RR) 0.84, 95% confidence interval (CI) 0.74–0.96; $p = 0.01$; seven trials, $N = 555$] but not in patients with $PaO_2/FiO_2 \geq 100$ mmHg (RR 1.07, 95% CI 0.93–1.22; $p = 0.36$; seven trials, $N = 1{,}169$). Risk ratios differed significantly between subgroups (interaction $p = 0.012$). Post hoc analysis demonstrated statistically significant improved mortality in the more hypoxemic subgroup and significant differences between subgroups using a range of PaO_2/FiO_2 thresholds up to approximately 140 mmHg. Prone ventilation improved oxygenation by 27–39% over the first 3 days of therapy but increased the risks of pressure ulcers (RR 1.29, 95% CI 1.16–1.44), endotracheal tube obstruction (RR 1.58, 95% CI 1.24–2.01), and chest tube dislodgement (RR 3.14, 95% CI 1.02–9.69). There was no statistical between-trial heterogeneity for most clinical outcomes. *Conclusions:* Prone ventilation reduces mortality in patients with severe hypoxemia. Given associated risks, this approach should not be routine in all patients with AHRF, but may be considered for severely hypoxemic patients.

Keywords Acute lung injury · Prone position · Hypoxia · Randomized controlled trial · Systematic review · Meta-analysis

Introduction

Acute lung injury (ALI) and the more hypoxemic subgroup of acute respiratory distress syndrome (ARDS) may occur after many primary or secondary pulmonary injuries, leading to a common syndrome characterized by hypoxemia, pulmonary congestion, and decreased pulmonary compliance. This syndrome is associated with substantial mortality [1, 2], morbidity [3, 4], and costs [5]. Mechanical ventilation usually corrects tissue hypoxemia [6] but also may be complicated by ventilator-induced lung injury. Although lower tidal volume [7] reduces ventilator-induced lung injury, mortality in patients with ARDS remains high [1, 2].

Mechanical ventilation of patients with ALI in the prone position, first suggested in 1974 [8], optimizes both lung recruitment and ventilation–perfusion matching [9]. Collapse due to gravity of ventral lung segments in the prone position is less than that of dorsal lung segments in the supine position [10, 11], while lung perfusion in the prone position is more evenly distributed [12]. Other potentially important improvements include enhanced postural drainage of secretions [13] and decreased alveolar overdistension [14], cyclic alveolar collapse, and ventilator-induced lung injury [15].

Multicenter randomized trials [16–18] and systematic reviews [19–23] have failed to demonstrate that prone ventilation improves overall mortality in patients with acute hypoxemic respiratory failure, despite the strong physiological rationale. Subgroup analyses have suggested a mortality benefit in patients with severe hypoxemia [16] or with higher severity of illness [16, 21, 22]. However, these analyses are limited by reporting bias due to lack of subgroup data from most trials [21, 22], limited numbers of patients and events [16, 21, 22], and omission of appropriate statistical tests to detect subgroup differences [24].

The objective of this systematic review, performed in collaboration with prone ventilation trialists, was to determine whether prone ventilation reduces mortality compared with supine ventilation in patients with acute hypoxemic respiratory failure and severe hypoxemia. We reasoned that patients with severe hypoxemia would be the most likely to benefit from prone ventilation because the main effect of prone ventilation is to improve oxygenation [19], and clinicians use this technique primarily for refractory hypoxemia [25]. Furthermore, the proposed protective effects of prone ventilation occur due to lung recruitment, and patients with more severe hypoxia have more recruitable lung [26]. A priori, we hypothesized that prone ventilation would reduce mortality in severely hypoxemic patients, defined by baseline ratio of partial pressure of arterial oxygen (PaO_2) to inspired fraction of oxygen (FiO_2) <100 mmHg, but not in patients with moderate hypoxemia ($100 \text{ mmHg} \leq PaO_2/FiO_2 \leq 300$ mmHg). We chose a threshold PaO_2/FiO_2 of 100 mmHg to identify severe hypoxemia because this value was used to stratify patients in the most recent randomized controlled trial (RCT) of prone ventilation [27] and because bedside clinicians can readily determine whether a patient's PaO_2/FiO_2 is above or below this threshold.

Methods

Study identification

We updated our previous search [19] using systematic methods (Appendix) to identify RCTs of mechanical ventilation in the prone compared with supine position in patients with ALI, ARDS, and acute hypoxemic respiratory failure [28]. We identified all relevant trials using the following techniques: electronic searches of MEDLINE, EMBASE, and CENTRAL (from inception to November 2009); manual searches of reference lists from included studies and review articles; manual and electronic searches of conference proceedings of the American Thoracic Society (1994–2009), Society of Critical Care Medicine (1994–2009), European Society of Intensive Care Medicine (1994–2009), American College of Chest Physicians (1994–2009), and the International Symposium on Intensive Care and Emergency Medicine (1997–2009); and contact with primary investigators. Finally, we searched for unpublished and ongoing trials in clinicaltrials.gov and controlled-trials.com [29]. No language restrictions were applied [30].

Study eligibility

Two investigators independently evaluated retrieved studies for possible inclusion and resolved differences by consensus [31]. We included studies if they (1) enrolled mechanically ventilated adults or postneonatal children with acute hypoxemic respiratory failure (defined by $PaO_2/FiO_2 \leq 300$ mmHg); (2) randomly assigned patients to two or more groups, including a treatment group ventilated at least once in the prone position and a control group ventilated in the supine position, with an intervention period of at least 48 h in duration; and (3) reported any of our primary or secondary outcomes (see below).

Trials allocating patients in alternating fashion or by hospital registry number (quasirandomization) or trials with co-interventions (such as high-frequency oscillation or nitric oxide) specified as part of the intervention and applied equally to both groups were also eligible. We excluded randomized crossover trials in which patients received both treatment and control interventions in random order. We also excluded short-term trials in which the intervention was applied for $\leq$48 h, because we believed that outcomes would be minimally affected by applying the intervention for such a short duration.

We included trials in which prone positioning was used early (within 72 h after initiation of mechanical ventilation for acute hypoxemic respiratory failure) and as late or rescue therapy (72 h after initiation of mechanical ventilation), and trials in which prone ventilation was applied intermittently (for a predefined period of time each day) or continuously (without interruption for the duration of the study period).

Data extraction and study quality

Two reviewers independently abstracted data on study methods, details of prone ventilation (including duration of prone ventilation per day and total duration of the intervention period) and general mechanical ventilation, and study outcomes. Disagreements were resolved by consensus.

We abstracted data on: method of randomization and allocation concealment, number of postrandomization withdrawals and losses to follow-up, and crossovers between assigned groups [32]. Allocation concealment was assessed according to the criteria of the Cochrane Collaboration [33]. We also determined whether studies were stopped early for benefit [34] or for other reasons such as harm or futility. Since blinding of caregivers, patients, and family members is impossible in a trial evaluating prone ventilation, we determined whether outcome assessors were blinded to the diagnosis of ventilator-associated pneumonia (VAP) and whether important co-interventions such as weaning, sedation and paralysis, steroids, and use of rescue therapies for hypoxemia (inhaled nitric oxide, high-frequency oscillation, extracorporeal oxygenation) were standardized or equally applied in treatment and control groups.

The authors of included trials collaborated in this systematic review by reviewing original trial data, providing previously unpublished data for subgroups of patients, and clarifying data and methods.

Outcomes

The primary outcome was mortality in the subgroup of patients with severe acute hypoxemic respiratory failure, defined by baseline $PaO_2/FiO_2 < 100$ mmHg, compared with mortality in patients with $100 \text{ mmHg} \leq PaO_2/FiO_2 \leq 300$ mmHg. For each study, mortality was determined at hospital discharge or, if not available, at the longest duration of follow-up. Secondary outcomes included mortality stratified according to the same threshold PaO_2/FiO_2 but limited to patients with ALI/ARDS; and in all patients, duration of mechanical ventilation, ventilator-free days to day 28, and adverse events (VAP, pressure ulcers, endotracheal tube obstruction, unplanned extubation, unplanned removal of central venous catheters or arterial lines, unplanned removal of chest tubes, pneumothoraces, and cardiac arrests). We also considered the effect on PaO_2/FiO_2 ratio on the first, second, and third calendar day after randomization in all patients. We measured the oxygenation effect of prone positioning by comparing the mean PaO_2/FiO_2 ratio

measured in the prone group with the closest available recorded measurement in the supine group. Where more than one measurement was taken we chose the measurement closest to the end of the proning session on that day.

We analyzed patients according to assigned group for all outcomes.

Statistical analysis

We aggregated outcome data at the trial level and performed statistical calculations with Review Manager (RevMan) 5.0 (2009; The Cochrane Collaboration, Oxford, UK) and STATA 9.2 (2006; StataCorp, TX, USA) using random-effects models. Random-effects models incorporate both within-study and between-study variation and provide more conservative treatment estimates when heterogeneity is present. We reported continuous outcomes using mean differences (a measure of absolute change) and ratios of means (a measure of relative change [35]), and binary outcomes as risk ratios (RR). For the primary outcome, we performed a z test of interaction between the RR for mortality in the subgroup of patients with PaO_2/FiO_2 <100 mmHg and the RR in the subgroup of patients with $PaO_2/FiO_2 \geq 100$ mmHg, which tests the null hypothesis that the treatment effect in each subgroup is the same. In a post hoc analysis, we conducted similar comparisons of the more versus less hypoxemic subgroups using PaO_2/FiO_2 thresholds ranging from 80 to 200 mmHg, in increments of 10 mmHg. All statistical tests were two sided. We considered $p < 0.05$ as statistically significant in all analyses and report individual trial and summary results with 95% confidence intervals (CIs).

We assessed between-study heterogeneity for each outcome using the I^2 measure [36, 37]. We considered statistical heterogeneity to be low for $I^2 = 25$–49%, moderate for $I^2 = 50$–74%, and high for $I^2 \geq 75\%$ [37].

To assess publication bias we examined funnel plots of treatment effect versus study precision and assessed statistically using Begg's rank correlation test [38] and modified Macaskill's regression test [39]. Given the low power of these tests, we assumed a more liberal level of significance ($p < 0.10$) to indicate publication bias.

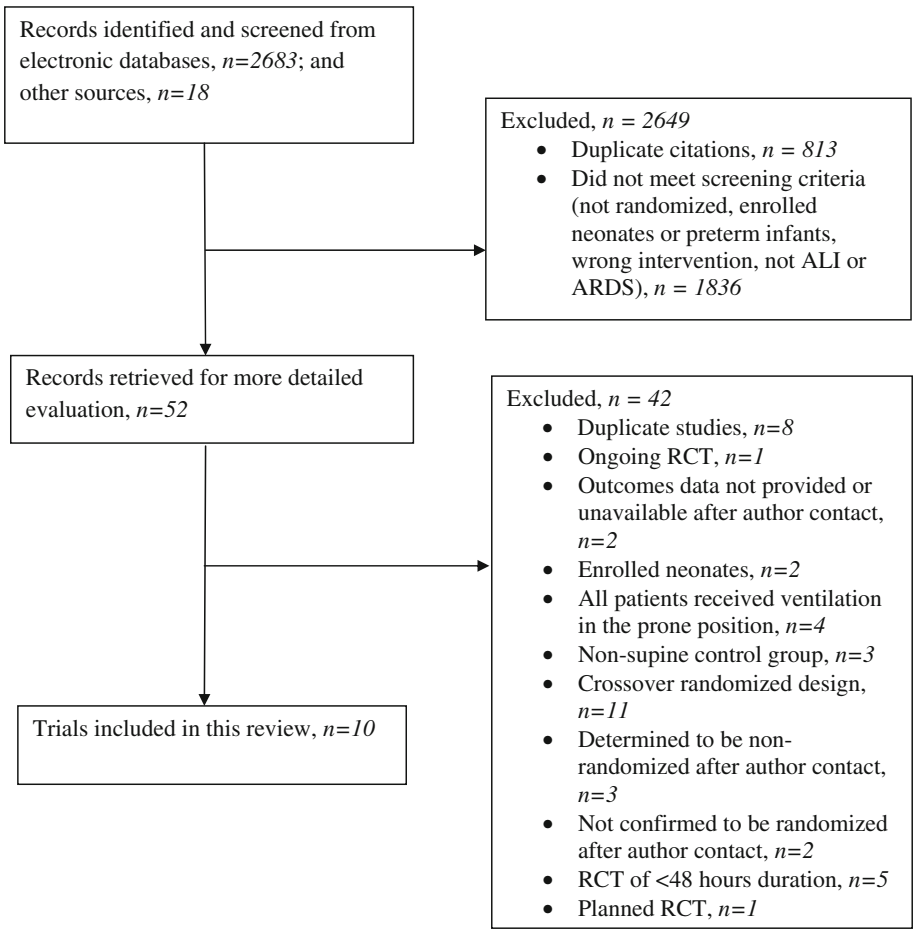

Fig. 1 Flow diagram for studies included in this review. *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *RCT* randomized controlled trial

Results

Literature search

We identified 2,683 citations from searches of electronic bibliographic databases and 18 citations from other sources. We retrieved 52 records for detailed evaluation, of which 10 trials [16–18, 27, 40–45] met criteria for inclusion in our review (Fig. 1). One study [40] was verified to be randomized after contacting authors [46, 47]. We identified eight publications [46–53] whose authors provided duplicate or supplementary data. We excluded five trials [54–58] in which the intervention period was less than 48 h and identified one ongoing study that would meet inclusion criteria [59]. Reviewers had perfect agreement for study inclusion. The largest trial ($n = 802$) [17] enrolled patients with acute hypoxemic respiratory failure ($PaO_2/FiO_2 \leq 300$ mmHg), including ALI/ARDS ($n = 413$). One other trial [45] enrolled patients requiring mechanical ventilation with Glasgow coma score ≤ 9, for which we included only patients with $PaO_2/FiO_2 \leq 300$ mmHg at baseline. All other trials reporting mortality enrolled exclusively patients with ALI/ARDS.

Study characteristics and methodological quality

The ten included trials (Table 1) [16–18, 27, 40–45] enrolled 1,867 patients (median 77 per trial, range 16–802). One trial ($n = 102$) enrolled children [41]. Most trials enrolled patients within 72 h after the development of hypoxemic respiratory failure [18, 27, 40–43, 45], but two studies did not limit the duration of acute hypoxemic respiratory failure prior to enrolment [16, 17]. The median PaO_2/FiO_2 at baseline was 122 (range 100–243) mmHg. Patients in the included trials were ventilated in the prone position for a median of 14 h per day (range 4–24 h), and prone ventilation was continued either for a prespecified duration [40, 44] or until prespecified clinical improvements [16–18, 27, 41–43, 45] (median duration of proning 4.7 days, range 4–10 days).

The included trials had relatively high methodological quality (Table 1). Eight trials concealed allocation [16–18, 27, 41–43, 45], one trial [40] did not conceal allocation [46, 47], and another enrolled alternating patients [44]. All trials analyzed outcomes for patients by assigned group. Seven studies were terminated prematurely after meeting prespecified criteria for futility [41] or because of slow recruitment [16, 18, 40, 42, 43, 45]. For the trials that reported mortality, vital status was known at the end of follow-up for all patients in three trials [40, 41, 43] and losses were less than 5% of those randomized in six trials (12/802 [17], 6/142 [18], 6/344 [27], 2/42 [42], 2/53 [45], 7/304 [16]). Seven trials reported crossovers between groups; these involved <6% of randomized patients for five trials (12/304 [16], 4/102 [41], 5/136 [18], 2/40 [42], 20/342 [27]), and 12% (6/51[45]) and 32% (251/791[17]) in two trials. Five trials mandated low-tidal-volume ventilation (6–8 ml/kg body weight) [27, 40–43], and five trials [18, 27, 40, 41, 43] used mechanical ventilation guidelines or protocols during the study period. Protocols for sedation [18, 41, 42, 44] and for weaning from mechanical ventilation [17, 18, 41, 42] were used in four trials each. Blinded assessment [45] or independent adjudication [17] for VAP was used in two of seven trials that reported this outcome [17, 18, 40, 42–45].

Quantitative data synthesis

Mortality

Seven [16–18, 27, 40–42] of ten trials provided mortality stratified by baseline PaO_2/FiO_2 and were included in the primary analysis. Two trials [43, 45] could not be included in the analysis because only one patient [43] or no patients [45] had PaO_2/FiO_2 <100 mmHg, and one trial did not report mortality [44]. The seven trials [16–18, 27, 40–42] in the primary analysis had the lowest baseline PaO_2/FiO_2 (median 113 mmHg, range 100–152 mmHg), and all but one trial [41] followed patients to hospital discharge [18, 40, 42, 43, 45] or at least 90 days [16, 17, 27]. Prone ventilation significantly reduced all-cause mortality (Fig. 2) in patients with baseline PaO_2/FiO_2 <100 mmHg (RR 0.84, 95% CI 0.74–0.96; $p = 0.01$; $N = 555$) but not in patients with baseline $PaO_2/FiO_2 \geq 100$ mmHg (RR 1.07, 95% CI 0.93–1.22; $p = 0.36$; $N = 1,169$). The test for interaction between these subgroups was statistically significant ($p = 0.012$), indicating that treatment effects differed significantly in subgroups with severe and moderate baseline hypoxemia.[1] Considering all patients together, regardless of severity of hypoxemia, there was no effect on mortality (RR 0.97, 95% CI 0.88–1.07; $p = 0.54$; $N = 1,786$). In the severely hypoxemic subgroup, the number of patients needed to prone to prevent one death was 11 (95% CI 6–50, calculated from a random-effects risk difference model).

Since two trials [17, 45] included patients with acute hypoxemic respiratory failure but without ALI/ARDS, we also analyzed mortality limited to patients with ALI/ARDS. Results were similar, although the interaction p value (0.06) was not statistically significant: RR 0.85, 95% CI 0.74–0.98, $p = 0.02$ in patients with baseline PaO_2/FiO_2 <100 mmHg ($N = 495$), and RR 1.04, 95% CI 0.89–1.22, $p = 0.60$ in patients with baseline $PaO_2/FiO_2 \geq 100$ mmHg ($N = 852$).

[1] Two trials were excluded from this subgroup analysis because only one patient [43] or no patients [45] had PaO_2/FiO_2 <100 mmHg. Adding data from these two trials to the $PaO_2/FiO_2 \geq 100$ mmHg subgroup caused small changes to the pooled effect estimate for this subgroup (RR 1.05, 95% CI 0.92–1.20, $p = 0.44$; $N = 1,230$) and test for subgroup interaction ($p = 0.019$).

Table 1 Characteristics of the randomized controlled trials included in the systematic review

	Guérin et al. [17] 2004	Taccone et al. [27] 2009	Gattinoni et al. [16] 2001	Mancebo et al. [18] 2006	Curley et al. [41] 2005
Population:					
Patients	802	344	304	142	102 children (age 2 weeks to 18 years)
Enrolment period	1998-2002	2004-2008	1996-1999	1998-2002	2001-2004
Enrolment criteria	Hypoxemic acute respiratory failure (413 ALI/ARDS patients)[a]	ARDS with PEEP ≥5 cmH_2O[a]	ALI/ARDS with PEEP ≥5 cmH_2O[a]	ARDS with four-quadrant infiltrates on CXR[a]	ALI/ARDS [a]
Mean enrolment PaO_2/FiO_2 (mm Hg)	152	113	127	105	100
Mean enrolment PEEP (cmH_2O)	8	10	10	7	9
Stratified randomization by severity	No	Yes (by PaO_2/FiO_2)	No	No	No
Time after meeting enrolment criteria	>12-24 h	<72 h	Not prespecified	<48 h	<48 h
Last follow-up	90 days	6 months	6 months	Hospital discharge	Hospital discharge or 28 days
Prone positioning:					
Planned duration	≥8 h/day until weaning criteria	20 h/day for 28 days	6 h/day for 10 days	20 h/day until weaning criteria	20 h/day until weaning criteria (max. 7 days)
Actual duration (average)	9 h for 4.1 days	18 h for 8.3 days	7 h for 4.7 days	17 h for 10.1 days	18 h for 4 days
Prone discontinuation criteria	Clinical improvement [b]	FiO_2 ≤40% and PEEP ≤10 cmH_2O	None	FiO_2 ≤45% and PEEP ≤5 cmH_2O	Spontaneous breathing and OI <6
Crossover criteria (supine to prone)	PaO_2/FiO_2 <100 for 12 h	PaO_2 ≤55 mmHg on FiO_2 = 1.0 and PEEP ≥15 cmH_2O	No	PaO_2 ≤60 mmHg on FiO_2 = 1.0 and PEEP = 20 cmH_2O	No
Co-interventions:					
Protective mechanical ventilation	No	Yes (*i.e.*, Vt ≤ 8ml/kg of PBW [c])	Consensus conference guidelines[a]	Yes (*i.e.*, Vt ≤10ml/kg of PBW[c] or ABW)	Yes (*i.e.*, Vt 6-7 ml/kg of IBW[h])
Weaning protocol	Yes	No	No	Yes	Yes
Pre-defined sedation targets	No	No	No	Yes	Yes
Concealment of allocation	Sealed opaque envelopes	Central	Central	Sealed opaque envelopes	Sealed opaque envelopes
Randomized patients excluded for all mortality analyses [f]	7/385 supine, 4/417 prone	1/175 supine, 1/169 prone	No	2/62 supine, 4/80 prone	No
Crossover (supine to prone group)	81/378	20/174	12/152	5/60	0/51
Crossover (prone to supine group) [i]	170/413	0/168	0/152	0/76	4/51
Trial ended early	No	No	Yes (slow enrolment)	Yes (slow enrolment)	Yes (futility stopping rule)

Table 1 continued

	Fernandez et al. [42] 2008	Voggenreiter et al. [43] 2005	Chan et al. [40] 2007	Beuret et al. [45] 2002	Watanabe et al. [44] 2002
Population:					
Patients	42	40	22	53	16
Enrolment period	2003-2004	1999-2001	2002-2003	1997-2000	1995-1999
Enrolment criteria	ARDS[a]	ALI (for at least 24h)/ARDS (for at least 8h) PEEP ≥5 cmH_2O[a]	ARDS secondary to community-acquired pneumonia[a]	Intubated coma [21 hypoxemic (PaO_2/FiO_2 <300) and 7 ALI/ARDS patients][a]	PaO_2/FiO_2 <200 with PEEP >5 cmH_2O
Mean enrolment PaO_2/FiO_2 (mm Hg)	118	221	109	326 (243 in 21 hypoxemic and 238 in 7 ALI/ARDS patients)	166[g]
Mean enrolment PEEP (cmH_2O)	11	11.5	13	n/a	n/a
Stratified randomization by severity	Yes (by SAPS II)	No	No	No	No
Time after meeting enrolment criteria	<48 h	<48 h	<72 h	<24 h	5 days post esophagectomy
Last follow-up	Hospital discharge	Hospital discharge	Hospital discharge	Hospital discharge	4 days
Prone positioning:					
Planned duration	20 h/day until weaning criteria	8-23 h/day until weaning criteria	24 h/day continuous for at least 72 h	4 h/day until weaning criteria	6 h/day for 4 days (fixed duration)
Actual duration (average)	18 h[d]	11 h for 7 days	24 h for 4.4 days	4 h for 6.0 days	6 h for 4 days
Prone discontinuation criteria	PaO_2/FiO_2 >250 and PEEP ≤8 cmH_2O for 12 h	PaO_2/FiO_2 >300 for 48 h	SpO_2 >90%, FiO_2 <60% for >24 h (after 72 h)	Able to sit in chair	Not applicable
Crossover criteria (supine to prone)	FiO_2 =1.0 and PEEP =24 cmH_2O for 6 h	No	No	PaO_2/FiO_2 <150	No
Co-interventions:					
Protective mechanical ventilation	Yes (*i.e.*, Vt 6-8ml/kg of PBW [c])	Yes (*i.e.*, Vt 6-8ml/kg of BW)	Yes (*i.e.*, Vt 6-8ml/kg of IBW[e])	No	No
Weaning protocol	Yes	No	No	No	No
Pre-defined sedation targets	Yes	No	No	No	Yes
Concealment of allocation	Central	Central	No	Sealed opaque envelopes	No (alternate allocation)
Randomized patients excluded for all mortality analyses[f]	1/20 supine, 1/22 prone	No	No	2/28 supine, 0/25 prone	Not applicable
Crossover (supine to prone group)	2/19	0/19	0/11	3/26 (1/9 hypoxic)	0/8
Crossover (prone to supine group)[i]	0/21	0/21	0/11	3/25 (1/12 hypoxic)	0/8
Trial ended early	Yes (slow enrolment)	Yes (slow enrolment)	Yes (slow enrolment)	Yes (slow enrolment)	Not reported

Abbreviations: ABW, actual body weight; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CXR, chest x-ray; FiO_2, fractional concentration of inspired oxygen; IBW, ideal body weight; OI, oxygenation index; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; Vt, tidal volume.

[a] according to the criteria of the American-European Consensus Conference[69]

[b] Defined by 1 major (relative improvement of PaO_2/FiO_2 ≥30% after randomization, with FiO_2 ≤60%) and at least 1 minor criterion (PEEP ≤8 cmH_2O, no sepsis, cause of acute respiratory failure under control, stable or improving chest x-ray, and <3 organ dysfunctions, including lung dysfunction).

[c] predicted body weight was calculated as 50 + 0.91 · (height in centimeters - 152.4) for male patients and as 45.5 + 0.91 · (height in centimeters - 152.4) for female patients [7].

[d] average over first 2 days only; average number of days proned not available

[e] ideal body weight was calculated as (height in centimeters – 80)· 0.7 for male patients and as (height in centimeters – 70)· 0.6 for female patients

[f] lost to follow up (Guérin [17] - 1 prone and 1 supine); withdrawal of consent (Guérin[17] – 1 prone and 4 supine); inclusion mistake (Taccone [27] – 1 prone and 1 supine ; Guérin [17] – 2 prone and 2 supine); missing data (Mancebo [18] – 3 prone and 2 supine; Fernandez[42] – 1 prone and 1 supine); transfer out of study ICU (Mancebo [18] – 1 prone patient); died within first 24 hours (Beuret [45] – 2 supine).

[g] prone group only (baseline PaO_2/FiO_2 in supine group not reported)

[h] ideal body weight was determined for sex and recumbent length to 3 years of age using the National Center for Health Statistics growth charts. Predicted weight charts for sex/stature beyond 3 years of age was generated by identifying the 50th percentile weight associated with age then linking that data to the 50th percentile height. See http://www.cdc.gov/nchs/nhanes/growthcharts/clinical_charts.htm.

[i] Refers to patients randomized to receive prone position ventilation and either never proned or prone position changes were discontinued prior to meeting prone weaning criteria. In addition, 41/152 patients in Gattinoni [16] and 34/168 patients in Taccone [27] randomized to receive prone ventilation missed one or more sessions. The number of sessions missed per patient in these studies is unavailable.

[j] Additional partial loss to follow up after hospital discharge but prior to 6 months or 90 days, respectively: Gattinoni [16] 4/152 prone and 3/152 supine all with enrolment $PaO_2/FiO_2 \geq$100 mm Hg; Guérin [17] 1/378 supine with $PaO_2/FiO_2 \geq$100 mm Hg; and Taccone [27] 2/168 prone and 2/174 supine with enrolment $PaO_2/FiO_2 \geq$100 mm Hg (1 prone and 2 supine) and PaO_2/FiO_2 <100 mm Hg (1 prone).

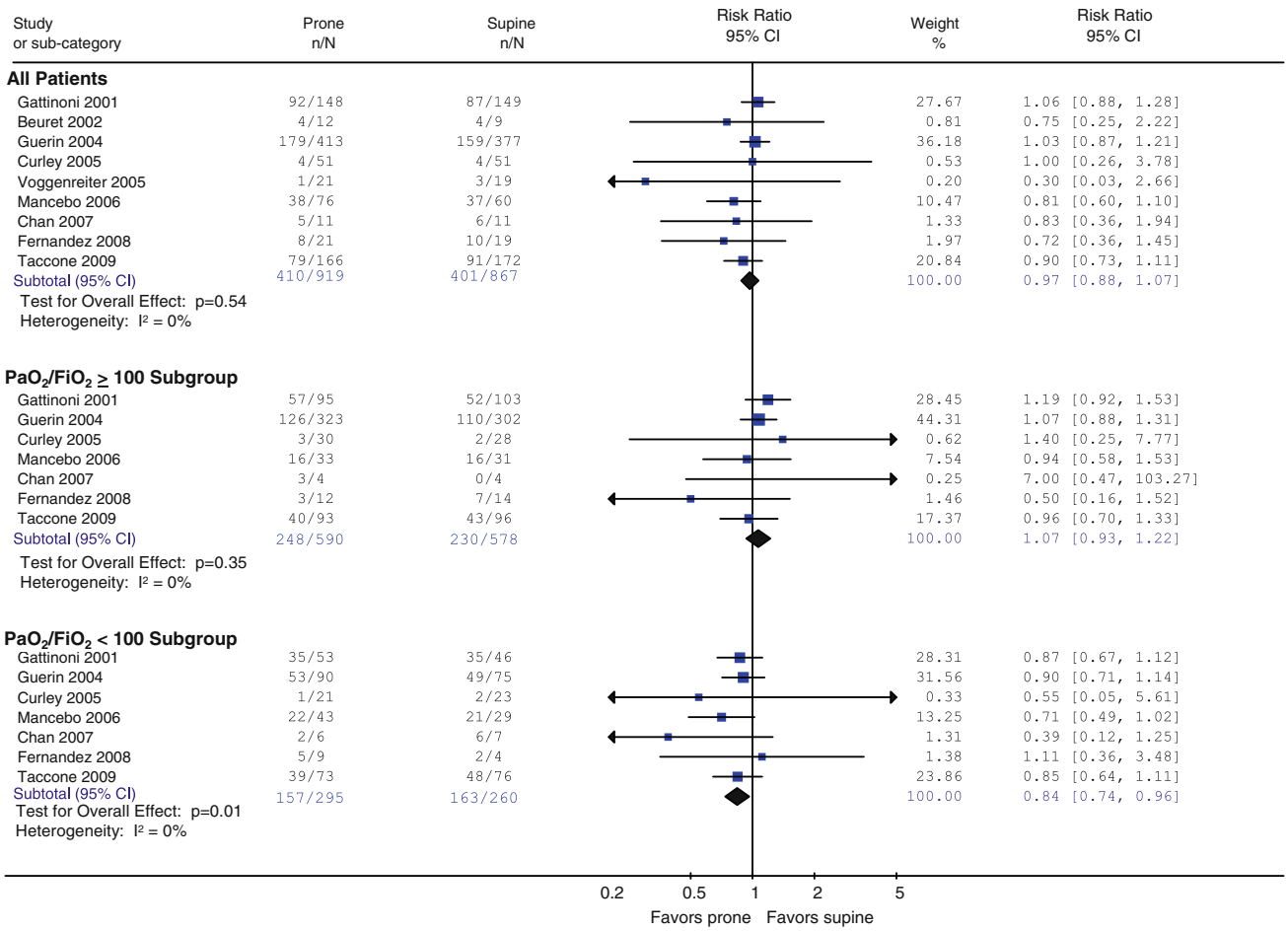

Fig. 2 Effect of prone ventilation on mortality (at hospital discharge or longest duration of follow-up). The *z* test for subgroup interaction was statistically significant ($p = 0.012$). Trialists verified all overall and subgroup mortality data; overall mortality data differed from the original publication in one case [16]. Patients lost to follow-up were removed from the denominator. Results are unchanged if these patients are retained in the denominator and assumed to be alive at the end of the follow-up period, as done in two trials that followed up patients for 6 months [16, 27]. Baseline PaO_2/FiO_2 values were unavailable for one patient in the prone group in one trial [40] and one patient in the supine group in another trial [42]. Weight is the contribution of each study to the overall risk ratio. *CI* confidence interval, I^2 percentage of total variation across studies from between-study heterogeneity rather than chance, *n/N* = number of deaths/number of patients randomized

We found no evidence of statistical heterogeneity for all mortality analyses ($I^2 = 0\%$). Neither Begg's rank correlation test ($p = 0.52$) nor the modified Macaskill's regression test ($p = 0.37$) suggested publication bias.

Post hoc analyses using varying PaO_2/FiO_2 thresholds (Fig. 3) suggested improved mortality in the more severely hypoxemic subgroup using PaO_2/FiO_2 thresholds up to approximately 140 mmHg to define this subgroup.

Oxygenation and nonmortality clinical endpoints

On days 1–3 after randomization, prone ventilation increased PaO_2/FiO_2 ratio in seven trials [16, 18, 27, 40–42, 44], by 27–39% (Fig. 4). Prone ventilation also reduced VAP (RR 0.81, 95% CI 0.67–1.00, $p = 0.05$; eight trials [17, 18, 40, 42–45], $N = 1{,}066$). Despite these improvements, there was no effect on duration of mechanical ventilation (mean difference −0.70 days, 95% CI −2.01 to +0.62 days, $p = 0.30$; eight trials [16, 17, 27, 41–45], $N = 1{,}588$) or ventilator-free days to day 28 (mean difference −0.88 days, 95% CI −2.14 to +0.37 days, $p = 0.17$; five trials [16, 27, 41, 42, 45], $N = 771$). Statistical heterogeneity was low to moderate for physiologic and clinical endpoints ($I^2 = 0$–35%).

Adverse events (Table 2)

Prone positioning increased the risk of pressure ulcers (RR 1.29, 95% CI 1.16–1.44, $p < 0.00001$; seven trials [16, 18, 40, 41, 43, 45], $N = 1{,}279$), endotracheal tube obstruction

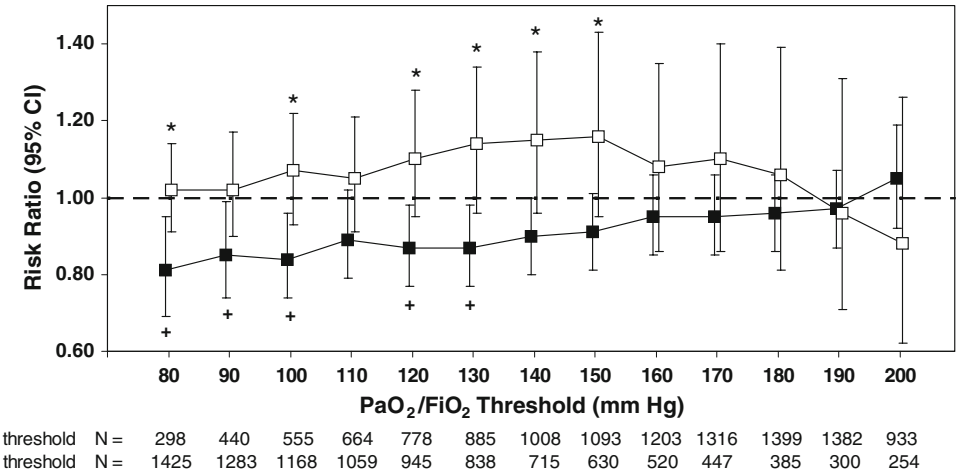

Fig. 3 Effect of prone ventilation on mortality in severe and moderate baseline hypoxemic subgroups for a range of PaO_2/FiO_2 threshold values. *Error bars* indicate width of 95% confidence interval of relative risk in the severe (*black squares*) and moderate (*white squares*) baseline hypoxemic subgroups. * Interaction *p* value <0.05, indicating that treatment effects differed significantly in subgroups with severe and moderate baseline hypoxemia at the PaO_2/FiO_2 threshold. $^+$ Treatment effect *p* value <0.05, indicating that prone ventilation significantly decreased mortality in the subgroup with severe baseline hypoxemia defined using the PaO_2/FiO_2 threshold. *p*-Values were not corrected for multiple comparisons. Trials with no or all patients with events (i.e., risk ratio not calculable) in either the severe or moderate baseline hypoxemia subgroup were excluded from both subgroups at each PaO_2/FiO_2 threshold. If the data from these trials are included in the subgroup in which the trial has some patients with events, there are no significant changes to the results. *CI* confidence interval, *N* number of randomized patients included for each subgroup at the PaO_2/FiO_2 threshold

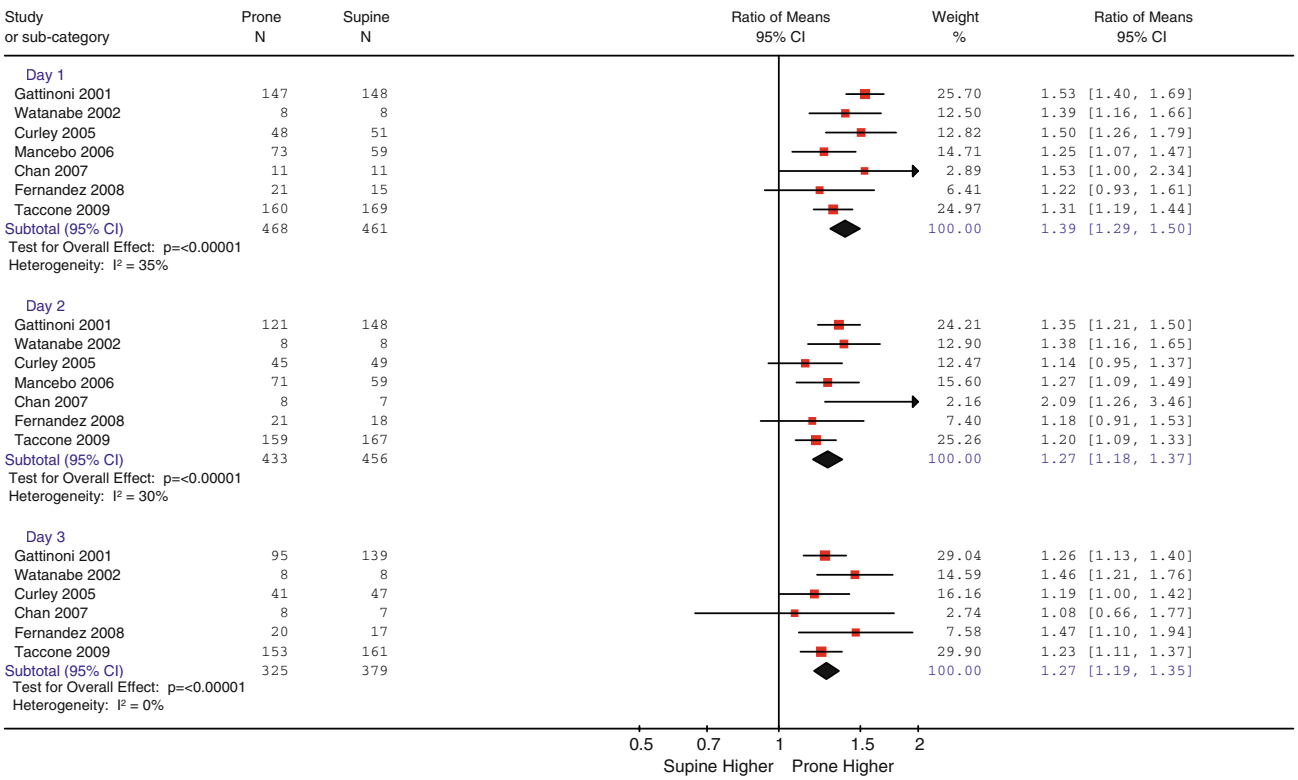

Fig. 4 Effect of prone ventilation on PaO_2 (partial pressure of arterial oxygen)/FiO_2 (inspired fraction of oxygen) on postrandomization calendar days 1–3. Ratio of means = mean PaO_2/FiO_2 in the prone group (in the prone position)/mean PaO_2/FiO_2 in the supine group (at the closest available time). Weight is the contribution of each study to the overall ratio of means. *CI* confidence interval, I^2 percentage of total variation across studies due to between-study heterogeneity rather than chance

Table 2 Adverse events

Adverse events	Trials (patients, events)	Treatment effect		Heterogeneity
		Risk ratio [95% CI]	*p*-Value	I^2 (%)
Ventilator-associated pneumonia	7 (1,066, 242)	0.81 [0.67, 1.00]	0.05	0
Pressure ulcers	6 (1,279, 620)	1.29 [1.16, 1.44]	<0.00001	0
Endotracheal tube obstruction	7 (1,351, 184)	1.58 [1.24, 2.01]	<0.001	0
Unplanned extubation or endotracheal tube dislodgement[a]	10 (1,813, 155)	1.07 [0.69, 1.65]	0.77	25
Unplanned removal of central or arterial lines	8 (886, 59)	1.49 [0.42, 5.27]	0.54	67
Thoracostomy tube dislodgement	8 (886, 17)	3.14 [1.02, 9.69]	0.05	0
Pneumothorax	7 (1,167, 67)	0.75 [0.47, 1.20]	0.23	0
Cardiac arrests	7 (1,031, 164)	0.96 [0.73, 1.26]	0.77	Not applicable[b]

Random-effects models were used for all analyses

CI confidence interval, I^2 percentage of total variation across studies from between-study heterogeneity rather than chance

[a] One trial [27] included all endotracheal tube dislodgement events (not just unplanned extubations). Excluding the results of this trial from the meta-analysis changes the risk ratio for unplanned extubation to 0.86 (95% CI 0.62–1.20, $p = 0.38$, $I^2 = 0\%$, nine trials, 1,471 patients, 129 events)

[b] Meta-analysis was not performed because all events occurred in the same trial

(RR 1.58, 95% CI 1.24–2.01, $p = 0.0002$; seven trials [17, 27, 41–45], $N = 1{,}351$), and inadvertent chest tube removal (RR 3.14, 95% CI 1.02–9.69, $p = 0.05$; eight trials [16, 27, 40–45], $N = 886$, of which only two trials [16, 27] reported any events). We found no significant differences in the risk of unplanned extubation, unplanned removal of central venous or arterial lines, pneumothoraces, and cardiac arrests. There was no statistical heterogeneity for adverse event analyses ($I^2 = 0\%$), except for the outcomes of unplanned extubations or endotracheal tube dislodgements ($I^2 = 25\%$) and unplanned removal of central venous or arterial lines ($I^2 = 67\%$). For both of these latter two adverse events, the most recent trial [27] found statistically significantly increased risks.

Post hoc mortality analysis comparing short versus long duration of prone ventilation

In another post hoc analysis, we compared mortality in trials with a mean duration of prone ventilation above the median of 14 h per day (RR 0.86, 95% CI 0.73–1.01; $p = 0.07$; five trials [18, 27, 40–42], published in 2005 or later, $N = 638$) with trials with duration of prone ventilation below the median (RR 1.04, 95% CI 0.92–1.17; $p = 0.57$; four trials [16, 17, 43, 45], published in 2005 or earlier, $N = 529$). There was a trend to different treatment effects between these longer- versus shorter-duration trials, but the interaction p value was not statistically significant (0.06).

Discussion

The main finding of our systematic review is that mechanical ventilation in the prone position has a different impact on mortality in patients with acute hypoxemic respiratory failure depending on the extent of hypoxemia: it reduces mortality in those with severe hypoxemia, defined by baseline PaO_2/FiO_2 <100 mmHg, but not in those with less severe hypoxemia. Post hoc analysis demonstrated that the statistically significant difference between the relative risk of death in the more severely hypoxemic subgroup compared with the less severely hypoxemic subgroup was robust across several PaO_2/FiO_2 thresholds up to approximately 140 mmHg. Other benefits of prone ventilation included significant improvements in oxygenation on days 1–3 and reduced VAP, although there was no decrease in duration of ventilation. The risks of pressure ulcers, endotracheal tube obstruction, and possibly line and tube dislodgement were increased. Results were consistent among trials for mortality and most other clinical outcomes, with low to moderate between-trial differences for oxygenation outcomes, strengthening our findings.

The 16% reduction in the relative risk of death among patients with PaO_2/FiO_2 <100 mmHg was consistent with our a priori hypothesis that improved oxygenation during prone ventilation would be clinically important in patients at high risk of death from profound hypoxemia. In a post hoc analysis, the first multicenter RCT of prone ventilation [16] showed improved mortality in the quartile of patients with the most severe hypoxemia. The treatment effect, however, did not significantly differ from that in less hypoxemic patients, possibly due to inadequate statistical power. In our meta-analysis, we analyzed mortality stratified by severity of hypoxemia for all trials of prone ventilation which measured this outcome, thereby providing a more robust and powerful analysis.

A physiologic explanation for our finding is that ventilation in the prone position recruits collapsed regions [10, 11] of the lung without increasing airway pressure

[16, 18, 41, 42] or hyperinflation [14]. Thus, the delivered tidal volume and peak pressure are dispersed to more alveoli, decreasing the risk of alveolar injury from stretch and strain forces [15]. This lung-protective effect of prone ventilation may be less important in patients with less severe hypoxemic respiratory failure, but appears to be highly relevant for patients with severe hypoxemia (mostly due to ARDS) who are most at risk for alveolar injury from shear and strain forces due to the low ratio of normal to collapsed lung [60]. In severely hypoxemic patients, prone ventilation may provide additive benefit to the lung-protective strategy of lowering delivered tidal volumes [7].

A practical question facing clinicians using this intervention is the optimal duration of prone positioning. This issue is difficult to address with the available data. Our post hoc analysis did not show a significant difference in effect on mortality between trials implementing longer versus shorter daily duration of prone ventilation. Furthermore, the analysis was based on subgroups of trials rather than subgroups of patients within trials, and these subgroups differed in several other important ways. Trials using shorter-duration prone ventilation were published earlier (up to 2005), whereas trials using longer-duration prone ventilation were published since 2005. Consequently, the longer-duration trials were more likely to implement treatments such as low-tidal-volume mechanical ventilation [7] that may have contributed to a reduction in mortality. In addition, the more recently completed trials attempted to enrol patients with more severe hypoxemia and earlier in the course of ARDS [18, 27, 40–42]. Finally, performing trial-level subgroup analysis using the mean overall duration of daily prone ventilation in each trial may lead to ecological bias [61], since it cannot be ascertained whether individuals within each trial who received longer durations of prone ventilation actually benefited more than individuals with shorter durations. In contrast, in the primary subgroup comparison of hypoxemia severity, groups of patients with severe and moderate hypoxemia within each trial were analyzed, limiting the potential for ecological bias.

Prone ventilation tended to reduce VAP, possibly through improved drainage of secretions [13]. Nonetheless, the observed reduction in VAP did not hasten weaning from mechanical ventilation. Moreover, as discussed previously [19], most trials did not blind outcome assessors or mandate duplicate independent VAP adjudication [18, 40, 42–44], and did not use protocols for sedation [16, 17, 27, 40, 43, 45] or ventilator weaning [16, 27, 40, 43–45]. Thus, the finding of reduced VAP must be interpreted cautiously.

Unlike other interventions for ARDS, such as high-frequency oscillation [62] and inhaled nitric oxide [63], prone ventilation is readily implemented in any intensive care unit. However, we found that prone ventilation was not without harm, significantly increasing the risks of pressure ulcers, endotracheal tube obstruction, and chest tube dislodgement. Although we did not find differences in pooled outcomes of other adverse events, one multicenter trial [27] found significantly increased rates of endotracheal tube and intravenous line dislodgements. Such events can have catastrophic effects in such critically ill patients. For example, in another trial [18] cardiac arrest resulted from dislodgement of a pulmonary artery catheter, which was directly attributed to a prone manoeuvre, highlighting that great care and experienced personnel are required when performing this intervention. Indeed, some ICU personnel remain reluctant to use this technique given its risks and perceived effects on other care practices, such as increased sedation needs and reduced enteral feeding [25, 64]. Our finding that prone ventilation benefits primarily the most severely hypoxemic patients, who are uncommonly cared for in many ICUs, challenges caregivers to implement this infrequently performed technique safely [64]. Such patients might be optimally served in higher-volume centres with more experience [65].

Our review has several strengths, including methods to reduce bias and a comprehensive set of relevant clinical and physiological outcomes. Trialists confirmed the primary data, which were analyzed using a predefined statistical plan. The primary hypothesis, that prone ventilation would be of benefit to patients with more severe hypoxemia, was prespecified, biologically plausible, and analyzed using appropriate tests for subgroup effects [66, 67]. However, subgroup analysis should, in general, be hypothesis-generating and confirmed in adequately powered randomized trials, and an ongoing trial targeting the enrolment of 500 patients with PaO_2/FiO_2 <150 mmHg [59] may provide more definitive data. Unfortunately, over half of the included trials to date were terminated due to slow enrolment. The trials included in this meta-analysis exhibited some methodological diversity (different inclusion criteria, different intervention intensity, etc.); however, for our primary comparison we used patient-level subgroup data, which helps balance out this diversity by producing similar distributions of these trial-specific characteristics in the severe and moderate hypoxemic subgroups. In some trials, some of the patients crossed over from the supine to the prone ventilation group or from the prone to the supine group (either missing one or more prone ventilation sessions or discontinuing prone ventilation prior to meeting prone weaning criteria). For example, in the largest trial [17] many patients randomized to the supine ventilation group whose PaO_2/FiO_2 decreased to <100 mmHg were treated with prone position ventilation. With our intention-to-treat analysis (i.e., analyzing patients by the group to which they were randomized), such crossovers would tend to reduce measured treatment effects, particularly in the severely hypoxic subgroup. Despite this type of analysis, we still found a significant treatment effect in this subgroup, which strengthens the findings.

Our review has other limitations. First, most trials reported PaO_2/FiO_2 ratio, which is influenced by ventilator

settings and many other factors that are difficult to standardize. An alternative measure, oxygenation index, which incorporates mean airway pressure as a marker of the intensity of mechanical ventilation, was not measured in most trials. However, the finding that a PaO_2/FiO_2 threshold identifies patients whose survival improves with prone ventilation provides predictive validity to this measure and at a minimum demonstrates that prone ventilation may have different effects on patients with more severe hypoxemia compared with less severe hypoxemia. Our post hoc analysis suggested a PaO_2/FiO_2 threshold at which prone ventilation begins to be beneficial of approximately 140 mmHg. However, individual patient data meta-analysis [68] would be a more robust method for identifying such a threshold, since it can adjust for patient-level confounders. Individual patient data meta-analytic techniques would also permit the conduct of time-to-event analyses and exploratory analyses of the optimal intervention duration for prone ventilation. Finally, the small number of available trials, many of which accrued fewer than 30 events, reduced the precision of our pooled effect estimates and may have underestimated heterogeneity.

In summary, our systematic review and meta-analysis found that prone ventilation significantly reduced mortality in patients with severe acute hypoxemic respiratory failure but not in patients with less severe hypoxemia. Prone ventilation improved oxygenation but also increased the risk of adverse events. Although the finding of improved mortality in severely hypoxemic patients is based on a subgroup analysis, clinicians may justifiably consider prone ventilation in these patients.

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Conflict of interest statement Dr. Gattinoni received a fee of 1,500 USD 5 years ago for one meeting at KCI Medical Products headquarters, as a member of an advisory board. The other authors declare no financial or other conflicts of interest to disclose. None of the funding agencies had any involvement in the study. The authors declare that they had full control of all primary data and that they agree to allow the journal to review their data if requested.

Appendix: Literature search

The following databases were searched in OVID on November 14, 2009: MEDLINE (1950 to present), EMBASE (1980 to week 46, 2009), and Cochrane Central Register of Controlled Trials (fourth quarter 2009).

MEDLINE

1. (pron$ adj4 position$).mp.
2. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
3. 1 and 2

EMBASE

4. (pron$ adj4 position$).mp.
5. random:.tw. or clinical trial:.mp. or exp health care quality/
6. 1 and 2

Cochrane Central Register of Controlled Trials

7. (pron$ adj4 position$).mp.

MEDLINE, 1,491 records
EMBASE, 807 records
CENTRAL, 385 records
Total records retrieved, 2,683
Number after duplicates manually removed, 1,870
Retrieved for more detailed evaluation, 52

Notes: "$" retrieves unlimited suffix variations. The ".mp." extension includes the title, original title, and abstract fields in all databases, in addition to the subject heading of "prone position" in MEDLINE. Filters for MEDLINE [70] (line 2) and EMBASE [71] (line 5) are based on published sensitive strategies for retrieving randomized trials.

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