"Effect of Mechanical Ventilation In The Prone Position …" A Research Review Report

This file contains a Research Review Report, its 5 appendices, and a related "Commentary" article published in the April 2008 issue of the

Canadian Medical Association Journal.

Sud S, Sud M, Friedrich JO, Adhikari NKJ.

Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis.

CMAJ Apr, 2008;178 (9); pgs 1153-1161.

Gattinoni L, Protti A.

Ventilation in the prone position: For some but not for all?

CMAJ Apr, 2008;178 (9); pgs 1174-1176.

This research review report (and its related Commentary article) is ***not*** related to the effects of prone restraint application in the field, primarily because ***all*** the reviewed studies' subjects were intubated and being mechanically ventilated.

In Appendix 2 (pages 14-18 of this file), the authors identify the ***manner*** of prone positioning employed for the studies "**where reported**." Some subjects were in a position where the abdomen was "**unrestrained, using cushions to support abdomen above bed surface**." Some subjects were in a position where the abdomen was "**restrained by direct contact with bed**." But, many of the studies did ***not*** report the manner of prone positioning employed! **[I cannot imagine WHY presumably "intelligent" researchers would fail to consistently report such a vitally important position-related ventilation factor.]**

This file does, however, include SUMMARIES of the several prone-positioned studies reviewed by these authors:

1. Leal RP, Gonzalez R, Gaona C, et al. Randomized trial compare prone vs supine position in patients with ARDS [abstract]. Am J Respir Crit Care Med 1997;155:A745.
2. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345:568-73.
3. Beuret P, Carton MJ, Nourdine K, et al. Prone position as prevention of lung injury in comatose patients: a prospective, randomized, controlled study. Intensive Care Med 2002;28:564-9.
4. Watanabe I, Fujihara H, Sato K, et al. Beneficial effect of a prone position for patients with hypoxemia after transthoracic esophagectomy. Crit Care Med 2002;30:1799-802.
5. Gaillard S, Couder P, Urrea V, et al. Prone position effects on alveolar recruitment and arterial oxygenation in acute lung injury [abstract]. Intensive Care Med 2003;29:S12.

6. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 2004;292:2379-87.
7. Curley MA, Hibberd PL, Fineman LD, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. JAMA 2005;294:229-37.
8. Papazian L, Gainnier M, Marin V, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. Crit Care Med 2005;33:2162-71.
9. Voggenreiter G, Aufmkolk M, Stiletto RJ, et al. Prone positioning improves oxygenation in post-traumatic lung injury — a prospective randomized trial. [discussion 341-343]. J Trauma 2005;59:333-41.
10. Mancebo J, Fernandez R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;173:1233-9.
11. Demory D, Michelet P, Arnal JM, et al. High-frequency oscillatory ventilation following prone positioning prevents a further impairment in oxygenation. Crit Care Med 2007;35:106-11.
12. Ibrahim TS, El-Mohamady HS. Inhaled nitric oxide and prone position: How far they can improve oxygenation in pediatric patients with acute respiratory distress syndrome? Journal of Medical Sciences 2007;7:390-5.
13. Chan MC, Hsu JY, Liu HH, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community-acquired pneumonia. J Formos Med Assoc 2007;106:708-16.
14. Murray JF, Matthay MA, Luce JM, et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138:720-3. [erratum in: Am Rev Respir Dis 1989;139:1065].
15. Slutsky AS. Consensus conference on mechanical ventilation — January 28-30, 1993 at Northbrook, Illinois, USA. Part I. European Society of Intensive Care Medicine, the ACCP and the SCCM. Intensive Care Med 1994;20:64-79 [erratum appears in Intensive Care Med 1994;20:378].
16. Slutsky AS. Consensus conference on mechanical ventilation — January 28–30, 1993 at Northbrook, Illinois, USA. Part 2. Intensive Care Med 1994;20:150-62.
17. Friedrich JO, Sud S, Sud M, et al. Prone position ventilation for community-acquired pneumonia [letter]. J Formos Med Assoc. 2008;107:191.
18. Chan MC, Hsu JY, Liu HH, et al. Reply to Friedrich et al [letter]. J Formos Med Assoc. 2008;107:192.
19. Bernard GR, Atigas A, Brigham KL, et al. The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:819-824.

YOURS, CHAS
(Ms. Charly D. Miller)

Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis

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Abstract

Background: Mechanical ventilation in the prone position is used to improve oxygenation in patients with acute hypoxemic respiratory failure. We sought to determine the effect of mechanical ventilation in the prone position on mortality, oxygenation, duration of ventilation and adverse events in patients with acute hypoxemic respiratory failure.

Methods: In this systematic review we searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Science Citation Index Expanded for articles published from database inception to February 2008. We also conducted extensive manual searches and contacted experts. We extracted physiologic data and clinically relevant outcomes.

Results: Thirteen trials that enrolled a total of 1559 patients met our inclusion criteria. Overall methodologic quality was good. In 10 of the trials (n = 1486) reporting this outcome, we found that prone positioning did not reduce mortality among hypoxemic patients (risk ratio [RR] 0.96, 95% confidence interval [CI] 0.84–1.09; p = 0.52). The lack of effect of ventilation in the prone position on mortality was similar in trials of prolonged prone positioning and in patients with acute lung injury. In 8 of the trials (n = 633), the ratio of partial pressure of oxygen to inspired fraction of oxygen on day 1 was 34% higher among patients in the prone position than among those who remained supine (p < 0.001); these results were similar in 4 trials on day 2 and in 5 trials on day 3. In 9 trials (n = 1206), the ratio in patients assigned to the prone group remained 6% higher the morning after they returned to the supine position compared with patients assigned to the supine group (p = 0.07). Results were quantitatively similar but statistically significant in 7 trials on day 2 and in 6 trials on day 3 (p = 0.001). In 5 trials (n = 1004), prone positioning was associated with a reduced risk of ventilator-associated pneumonia (RR 0.81, 95% CI 0.66–0.99; p = 0.04) but not with a reduced duration of ventilation. In 6 trials (n = 504), prone positioning was associated with an increased risk of pressure ulcers (RR 1.36, 95% CI 1.07–1.71; p = 0.01). Most analyses found no to moderate between-trial heterogeneity.

Interpretation: Mechanical ventilation in the prone position does not reduce mortality or duration of ventilation despite improved oxygenation and a decreased risk of pneumonia. Therefore, it should not be used routinely for acute hypoxemic respiratory failure. However, a sustained improvement in oxygenation may support the use of prone positioning in patients with very severe hypoxemia, who have not been well-studied to date.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/178/9/1153/DC1

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Patients with acute lung injury[1,2] and hypoxemic respiratory failure may require mechanical ventilation to maintain oxygenation. Persistent hypoxemia may entail additional treatments, such as inhaled nitric oxide[3] or high-frequency oscillation,[4–6] but these treatments are not universally available. In contrast, ventilation in the prone position, first recommended in 1974,[7] can be readily implemented in any intensive care unit (ICU), and clinicians should be familiar with its effects on patient outcomes.

Improved ventilation-perfusion matching is the major physiologic effect of prone positioning for ventilation in patients with acute lung injury.[8] In the supine position, the dependent dorsal lung regions (compared with nondependent regions) are atelectatic owing to decreased transpulmonary pressure and direct compression by the lungs, heart and abdominal contents (via pressure on a passive diaphragm). Gravity favours increased perfusion to these collapsed dorsal lung segments, which creates shunt conditions. In the prone position, lung compression is decreased, and chest-wall and lung mechanics create more uniform transpulmonary pressure. The previously atelectatic lung thus becomes aerated,

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and new atelectasis in the now dependent ventral regions is comparatively minor. In addition, lung perfusion in the prone position is more homogeneous. Shunt conditions are therefore reduced and ventilation is better matched to perfusion. Other clinical effects of prone positioning may include enhanced postural drainage of secretions,[9,10] decreasing the risk of ventilator-associated pneumonia. Effects may also include decreased alveolar overdistension, cyclic alveolar collapse and ventilator-induced lung injury.[11] For this reason, some investigators have recommended prone positioning for mechanical ventilation in the treatment of acute lung injury.[8,11]

Although ventilation in the prone position offers physiologic advantages and does not require specialized tools, one survey found that in most ICUs, 3 personnel (range 2–6) were required to turn an adult patient.[12] These caregivers must handle major safety challenges in putting patients with life-threatening hypoxemia in the prone position, including disconnection or removal of endotracheal tubes or intravascular catheters, and kinking or secretion-induced plugging of endotracheal tubes.[13]

Despite prone positioning's physiologic advantages, individual randomized controlled trials have not demonstrated its superior clinical outcomes compared with supine positioning. Consequently, we conducted a systematic review and meta-analysis to evaluate the effect of prone positioning on clinical outcomes, including mortality, oxygenation, ventilator-associated pneumonia, duration of ventilation and adverse events, in patients with acute hypoxemic respiratory failure.

Methods

Literature search

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Science Citation Index Expanded for articles published from database inception to February 2008. Our search strategy is outlined in Appendix 1, available at www.cmaj.ca/cgi/content/full/178/9/1153/DC2. We also searched supplementary data sources, including the "related articles" feature on PubMed; bibliographies of included studies and review articles; conference proceedings of the American Thoracic Society (1994–2007), the American College of Chest Physicians (1994–2007), the European Society of Intensive Care Medicine (1994–2007) and the Society of Critical Care Medicine (1994–2008); and clinical trial registries (www.clinicaltrials.gov, www.controlled-trials.com). We contacted clinical experts and the authors of all included studies for additional data. We did not impose language restrictions.

Study selection

We included studies that met 3 criteria. First, they enrolled adult or pediatric patients with acute hypoxemic respiratory failure (defined as the ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 300 mm Hg), including acute lung injury and acute respiratory distress syndrome, who received mechanical ventilation. Second, they randomly assigned patients to 2 or more groups, including a treatment group that received ventilation at least once in the prone position and a control group that received ventilation in the supine position. Third, they reported all-cause mortality, the ratio of partial pressure of oxygen to inspired fraction of oxygen, ventilator-associated pneumonia, the duration of ventilation, the number of ventilator-free days from randomization to day 28 or 30, or adverse events, including pressure ulcers, endotracheal tube obstruction, unplanned extubation, dislodgement of central venous catheters or thoracostomy tubes, pneumothoraces and cardiac arrests. Our quantitative analyses included trials that enrolled adults or postneonatal children. Excluding the pediatric trials did not change any results; therefore, we present only the combined results.

We also considered trials that assigned patients in alternating fashion or by hospital registry number (quasi-randomization), or involved cointerventions, such as high-frequency oscillation or nitric oxide, that were specified as part of the intervention and were applied equally to both groups. We used authors' definitions of acute lung injury and acute respiratory distress syndrome. We excluded randomized crossover trials that assigned patients to both treatment and control groups.

Data abstraction and validity assessment

Each of us independently evaluated studies for inclusion and abstracted data on study methods and outcomes; disagreements were resolved by consensus. Measures of study quality included method and concealment of allocation (adequate v. inadequate), postallocation withdrawals (yes v. no), patients with missing mortality status owing to loss to follow-up (yes v. no), crossovers between groups (yes v. no), analysis of data by group to which patients were originally assigned (yes v. no), blinding of outcome assessors for ventilator-associated pneumonia (blinded or centrally adjudicating assessors v. neither), cointerventions (standardization or equal application of mechanical ventilation, ventilator weaning, sedation and paralysis, and alternative treatments for hypoxemia), and early stopping of the trial before planned enrolment was completed (yes v. no).

We contacted authors of all included trials to clarify methodology and request data missing from prespecified analyses.

Statistical analysis

The primary outcome was all-cause mortality in the ICU at any time after randomization; if ICU mortality was not reported, we used mortality at 28 or 30 days after randomization or hospital mortality. A priori, we planned subgroup analyses based on patient population (acute lung injury or acute respiratory distress syndrome v. other) and duration of prone positioning (prolonged, which we defined as up to 24 hours daily for more than 2 days, v. short-term).

Secondary outcomes included ventilator-associated pneumonia, the number of days on mechanical ventilation and ventilator-free days, oxygenation on days 1–3 and adverse events. Oxygenation outcomes are presented only for days 1–3 because the extent of missing data for subsequent days (in trials reporting these outcomes) limits the interpretability of these analyses. To show the maximal effect of prone positioning on oxygenation, we compared the mean ratio of partial pressure of oxygen to inspired fraction of oxygen, measured in the prone group at the end of a prone manoeuvre,

with the simultaneously recorded measurement in the supine group for each day. For this measurement, day 1 refers to the end of the first proning session (for sessions lasting less than 24 hours) or the end of 24 hours (for continuous proning lasting longer than 24 hours). To measure the difference in oxygenation that remained after patients in the prone group were returned to the supine position, we compared the mean ratios of partial pressure of oxygen to inspired fraction of oxygen between the prone and supine groups that were measured in the morning (just before the subsequent proning manoeuvre in the prone group). Day 1 for this measurement refers to the measurement taken the morning after the first proning session and applies only to proning sessions that lasted less than 24 hours. Finally, in a post hoc analysis we compared the mean ratio of partial pressure of oxygen to inspired fraction of oxygen measured within 1 hour of patients being turned to the prone position with the near-simultaneous measurement in the supine group.

In our meta-analysis, all statistical tests were 2-sided, and we considered $p < 0.05$ to be statistically significant. We report continuous outcomes as weighted mean differences (a measure of absolute change) for number of days of mechanical ventilation and ventilator-free days, and as ratios of means (a measure of relative change)[14] for ratio of partial pressure of oxygen to inspired fraction of oxygen. We report binary outcomes (mortality, ventilator-associated pneumonia and adverse events) as risk ratios (RRs). All outcomes are presented with 95% confidence intervals (CIs). At least 2 of us independently conducted each analysis to minimize data management errors.[15]

We measured heterogeneity and expressed it as I^2, the percentage of total variation across studies owing to between-study heterogeneity rather than chance,[16,17] with suggested thresholds for low (I^2 = 25%–49%), moderate (I^2 = 50%–74%) and high ($I^2 \geq 75\%$) values.[17] A priori hypotheses to explain moderate to high heterogeneity in mortality and ventilator-associated pneumonia included study population and duration of prone positioning, and study quality (adequate v. inadequate concealment of patient assignment, including quasi-randomization, and blinded or centrally adjudicating assessors v. neither [for ventilator-associated pneumonia only]). We performed meta-analyses using a random-effects model, which incorporates within- and between-study variation and provides more conservative treatment estimates when heterogeneity is present.[18]

To assess publication bias, we visually examined the funnel plot for mortality (standard error of the natural logarithm of RR v. RR for each trial) and performed a Begg rank correlation test[19] and Macaskill regression test,[20] as modified by Peters and colleagues,[21] in which we considered $p < 0.10$ to be statistically significant.

Results

Literature search

Through the searches of bibliographic databases we identified 1676 citations. Of these citations and additional citations retrieved from other sources, we retrieved 50 studies for detailed evaluation and excluded 29. We selected 13 primary randomized and quasi-randomized trials for inclusion in our review and meta-analysis,[22–34] along with 8 citations providing duplicate or supplementary data (data from 4 of 13 primary trials were distributed among several additional publications)[35–42] (Figure 1). Reviewers had perfect agreement on study inclusion.

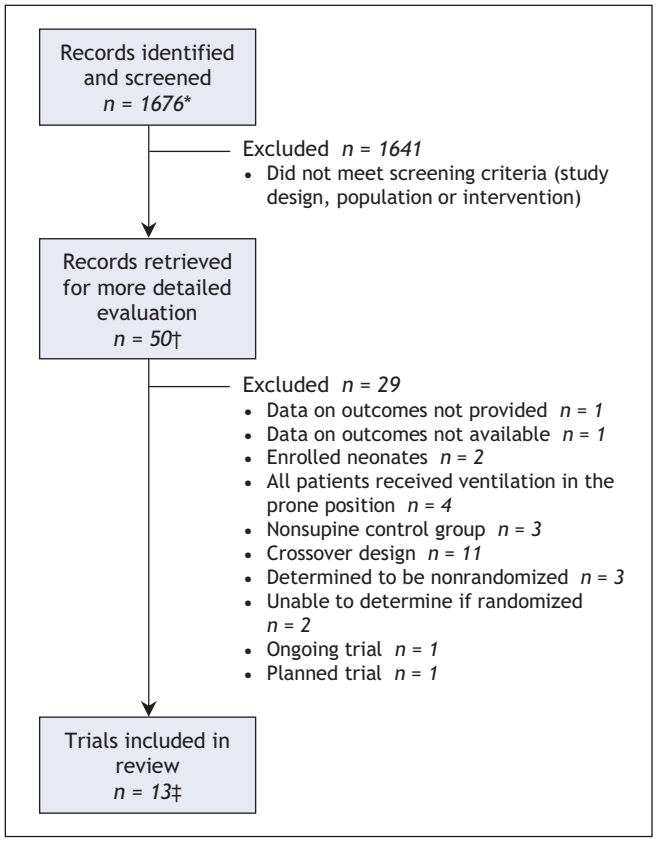

Figure 1: Flow of studies in the systematic review. *Records were identified in electronic database search. †The records retrieved for more detailed evaluation came from the electronic databases and other sources. ‡We included 13 primary trials and 8 references with duplicate or additional data. Of the studies retained for analysis, 12 trials contributed oxygenation data, 10 contributed data on adverse events, and 10 were included in our primary mortality analysis.

The authors of the included trials provided additional clinical[22,24,28,30,34] and physiologic[23,24,28–30,32,34] data or clarified data or methods.[22–25,28–34] The author of 2 of the trials[26,27] could not provide any additional information.

Study characteristics and methodologic quality

Appendix 2 (available at www.cmaj.ca/cgi/content/full/178/9/1153/DC2) describes the 13 included trials,[22–34] which enrolled a total of 1559 patients (median per trial 28, range 16–802) with acute lung injury,[23,26,28,30] acute respiratory distress syndrome,[22,29,31,32,34] or acute hypoxemic respiratory failure.[25,27,33] The largest trial (n = 802) enrolled patients with acute hypoxemic respiratory failure; 51% had acute lung injury or acute respiratory distress syndrome and 7% had cardiogenic pulmonary edema.[27] Most of the trials enrolled patients within

48 hours of diagnosis. One trial enrolled comatose patients (Glasgow coma score ≤ 9), who were not necessarily in acute hypoxemic respiratory failure, within 24 hours of mechanical ventilation.[24] Only data for subgroups of patients with hypoxemia (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 300 mm Hg), or acute lung injury or acute respiratory distress syndrome were used in our analyses. Two trials enrolled only children.[28,33]

Patients received mechanical ventilation in the prone position for a median of 12 hours per day (range 4–24 hours), and proning manoeuvres continued either for a prespecified period[22,25,26,29,32,33] or until prespecified clinical improvements occurred[23,24,27,28,30,31,34] (median duration of proning 4 days, range 1–10 days). About 2–6 clinical personnel[23,25,28,31] were required for each turning procedure (4–6 personnel were required in trials enrolling adults).[23,25,31] The turning procedure lasted a mean of 10 (standard deviation 12) minutes in the only trial that reported this information.[23]

All but 1 trial,[22] which was available only in abstract form, provided some description of mechanical ventilation. Five trials mandated low tidal volume ventilation (6–8 mL/kg body weight),[26,28,30,32,34] 4 trials used protocols to adjust positive end-expiratory pressure,[26,28,32,34] and 5 trials reported a mean positive end-expiratory pressure of 7–12 cm H_2O during the study period.[23,27,28,30,31] Additional cointerventions that were specified as part of the treatment and applied to all patients in both groups included use of nitric oxide[33] and high-frequency oscillation.[29]

The trials had high methodologic quality (Appendix 2). Most described adequate allocation concealment (9 trials).[22–24,27–32] Allocation was not concealed in 3 trials,[25,33,34] of which 2 assigned patients using alternate allocation.[25,33] Nine trials standardized or described at least 1 other cointervention such as sedation,[28,30,31] paralysis,[29–32] or ventilator weaning.[24,25,27,28,31,33] Four trials reported postrandomization withdrawals: less than 5% of enrolled patients in 3 trials (9/802,[27] 1/102,[28] 6/142[31]) and 8% in 1 trial[33] (2/24). Only 1 trial[27] reported any losses to follow-up (< 0.25% of patients or 2/802). However, only 2 of the 5 trials reporting ventilator-associated pneumonia[24,25,27,30,31] partially blinded outcome assessors to treatment group[24] or adjudicated the outcome,[27] and only 3 trials provided specific diagnostic criteria for ventilator-associated pneumonia.[24,27,30] One trial classified pressure ulcers using standardized criteria.[23] Five trials[23,24,27,28,31] reported crossovers between groups, which involved less than 10% of patients in 4 trials (12/304,[23] 2/21,[24] 4/102,[28] 5/142[31]). All trials analyzed data for patients by assigned group.[22–34] Five trials ended early, 1 after meeting prespecified futility criteria,[28] and 4 because of low or declining enrolment.[23,24,31,34]

Clinical outcomes

Mortality

In the primary analysis (10 trials, $n = 1486$),[22–24,27–32,34] ventilation in the prone position had no effect on mortality (RR 0.96, 95% CI 0.84 to 1.09; $p = 0.52$) (Figure 2). Three trials provided no mortality data.[25,26,33] In the subgroup analysis, we found no significant difference in mortality between trials of short-term prone positioning[22,29,32] (RR 0.77, 95% CI 0.46 to 1.28) and those of prolonged prone positioning[23,24,27,28,30,31,34] (RR 0.97, 95% CI 0.85 to 1.11; $p = 0.39$ for comparison of RRs

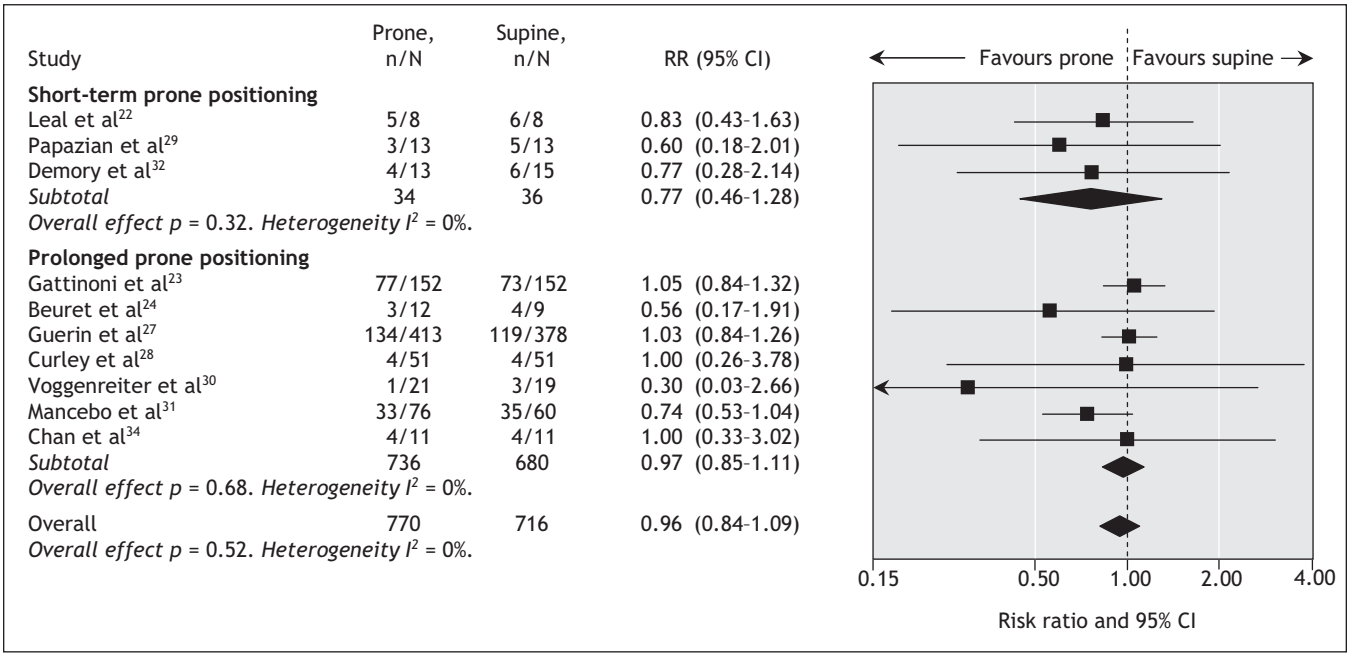

Figure 2: Effect of ventilation in the prone position on mortality. We used a random-effects model in our analysis. The duration of prone positioning was up to 24 hours for 1–2 days in the short-term trials and up to 24 hours daily for more than 2 days in the prolonged-duration trials. One trial[24] included data only for patients with acute hypoxemic respiratory failure. Including all patients from this trial (7/25 deaths in the prone group and 14/28 deaths in the supine group) did not change the result (RR 0.95, 95% CI 0.83 to 1.08; $p = 0.41$). I^2 = percentage of total variation across studies owing to between-study heterogeneity rather than chance. CI = confidence interval, RR = risk ratio.

using *z* score) (Figure 2). However, a single trial investigating an extended proning strategy (mean of 17 hours per day for 10 days) for acute respiratory distress syndrome showed a trend toward reduced mortality (RR 0.74, 95% CI 0.53 to 1.04; $p = 0.08$).[31] The effect of prone positioning on mortality was also similar (nonsignificant *z* scores for differences in RRs) in 9 trials ($n = 681$) among patients with acute lung injury or acute respiratory distress syndrome[22–24,28–32,34] (RR 0.92, 95% CI 0.78 to 1.09; $p = 0.35$) and in 6 trials ($n = 611$) in the subset of these patients who had prolonged duration of prone positioning (RR 0.94, 95% CI 0.79 to 1.13; $p = 0.53$).[23,24,28,30,31,34] Additional subgroup analyses to explore the effects of study quality and age (children v. adults) were limited because, in each case, one of the subgroup pairs included only a single randomized controlled trial (Appendix 3, available at www.cmaj.ca/cgi/content/full/178/9/1153/DC2). All mortality analyses showed little to no statistical heterogeneity beyond that expected by chance ($I^2 < 10\%$).

Visual inspection of a funnel plot revealed asymmetry, which suggested under-reporting of smaller trials showing excess mortality in the prone group. However, results of statistical tests did not confirm publication bias (Appendix 4, available at www.cmaj.ca/cgi/content/full/178/9/1153/DC2).

Oxygenation

Relative to supine patients, prone ventilation increased the ratio of partial pressure of oxygen to inspired fraction of oxygen by 23%–34% on days 1–3 after randomization, measured at the end of the prone manoeuvre (Table 1 and Figure 3). Post-hoc analysis revealed that most of this improvement occurred within 1 hour of the patients being turned to the prone position. The ratio of partial pressure of oxygen to inspired fraction of oxygen remained 6%–9% higher in patients in the prone group after they were returned to the supine position after a prone manoeuvre (Table 1) (Appendix 5, available at www.cmaj.ca/cgi/content/full/178/9/1153/DC2).

Ventilator-associated pneumonia and duration of ventilation

In 6 trials ($n = 1026$),[24,25,27,30,31,34] ventilation in the prone position reduced the risk of ventilator-associated pneumonia (RR 0.81, 95% CI 0.66 to 0.99, $p = 0.04$), with no statistical heterogeneity beyond that expected by chance ($I^2 = 0\%$) (Figure 4). One of the 6 trials ($n = 22$) recorded no cases of ventilator-associated pneumonia.[34] The effect was similar in trials that blinded ventilator-associated pneumonia assessors[24] or adjudicated the outcome[27] ($p = 0.89$ for comparison of RRs in these v. other trials). Although in 6 trials ($n = 992$)[24,25,27–30] patients who received ventilation in the prone position generally had shorter durations of ventilation (weighted mean difference –0.9 days, 95% CI –1.9 to 0.1; $p = 0.06$, $I^2 = 3\%$), in 4 trials ($n = 148$),[23,24,28,29] the number of ventilator-free days in the prone group was not significantly greater than the number in the supine group (weighted mean difference 3.7 days, 95% CI –1.8 to 9.3; $p = 0.19$, $I^2 = 67\%$).

Adverse events

In 6 trials ($n = 504$),[22–24,28,30,34] ventilation in the prone position increased the risk of pressure ulcers (RR 1.36, 95% CI 1.07 to 1.71; $p = 0.01$, $I^2 = 0\%$). Between 5 and 8 trials contributed data to analyses of other adverse events; these analyses showed no increased risks (Figure 5, Table 2). When data

Table 1: Effect of ventilation in the prone position on oxygenation, by timing of measurement of ratio of partial pressure of oxygen to inspired fraction of oxygen*

Timing of oxygenation measurement; day since randomization	No. of trials (patients)	Ratio of means† (95% CI)	*p* value	I^2, %‡
1 hr after start of proning manoeuvre				
Day 1	4 (434)	1.31 (1.12-1.53)	< 0.001	76
Day 2	3 (379)	1.25 (1.09-1.43)	0.001	55
Day 3	3 (330)	1.24 (1.05-1.46)	0.01	68
At the end of proning manoeuvre				
Day 1	8 (633)	1.34 (1.23-1.45)	< 0.001	29
Day 2	4 (379)	1.30 (1.15-1.46)	< 0.001	42
Day 3	5 (445)	1.23 (1.15-1.32)	< 0.001	0
Just before subsequent proning manoeuvre§				
Day 1	9 (1206)	1.06 (1.00-1.12)	0.07	19
Day 2	7 (1106)	1.09 (1.04-1.14)	< 0.001	0
Day 3	6 (1045)	1.09 (1.04-1.14)	< 0.001	0

Note: CI = confidence interval.
*The author of 1 trial[33] confirmed that the published error terms for ratios of partial pressure of oxygen to inspired fraction of oxygen were standard deviations rather than standard errors of means. Meta-analyses of oxygenation index (defined as 100 × mean airway pressure/ratio of partial pressure of oxygen to inspired fraction of oxygen) are not shown because only 3 trials[28,29,33] reported these data at any time, with only 1 trial[28] providing data beyond day 1. These 3 trials all reported the ratio of partial pressure of oxygen to inspired fraction of oxygen and oxygenation index simultaneously.
†Ratio of means is the mean ratio of partial pressure of oxygen to inspired fraction of oxygen in the prone group divided by that in the control group. Random-effects models were used in all analyses.
‡I^2 = percentage of total variation across studies owing to between-study heterogeneity rather than chance.
§Data were recorded in the morning, just before the subsequent proning manoeuvre, when patients in the prone group were in the supine position. On day 1, patients in the prone group had already completed 1 manoeuvre.

from one trial[27] reporting the number of occurrences of adverse events instead of the number of patients who experienced adverse events per group were included, the risk of endotracheal tube obstruction became statistically significant (RR 2.46, 95% CI 1.33 to 4.55; $p = 0.004$, $I^2 = 0\%$).[27–29]

Interpretation

Our systematic review suggests that mechanical ventilation in the prone position does not improve survival for patients with acute hypoxemic respiratory failure, including acute lung injury and acute respiratory distress syndrome, despite improved oxygenation and a reduced risk of ventilator-associated pneumonia. Prone positioning increased the risk of pressure ulcers and possibly endotracheal tube obstruction, but otherwise it was safe. Despite variable duration of ventilation in the prone position and clinically diverse populations in the included trials, pooled clinical outcomes had little statistical heterogeneity, which strengthens our findings. These results do not justify the routine use of prone positioning during mechanical ventilation in patients with acute hypoxemic respiratory failure.

There are several hypotheses that may explain the neutral effect of ventilation in the prone position on mortality. First, short- to medium-term improved oxygenation may not increase survival[43] because of poor correlation between oxygenation and severity of lung injury. Indeed, patients with acute respiratory distress syndrome die more often of multiple organ failure than hypoxemia.[44,45] Although prone positioning improves oxygenation within 1 hour and to a greater extent than inhaled nitric oxide,[3] such improvements may help only the most severely hypoxemic patients to survive. Gattinoni and colleagues[23] reported a post hoc analysis showing a significantly lower 10-day mortality rate with prone positioning in the subgroup of patients with the lowest ratio of partial pressure of oxygen to inspired fraction of oxygen. In contrast, Mancebo and colleagues[31] did not find the initial ratio of partial pressure of oxygen to inspired fraction of oxygen to be a significant predictor of mortality in a multivariable logistic regression model. Neither study reported a statistical test of the interaction between treatment group and initial ratio of partial pressure of oxygen to inspired fraction of oxygen. No randomized controlled trials have investigated prone positioning during ventilation as rescue therapy for critical hypoxemia. Prone positioning in such patients may prevent imminent death and allow time for other treatments to help.

Second, the broad nature of selection criteria in the in-

Study	Prone, N	Supine, N	Ratio of means (95% CI)
Day 1			
Gattinoni et al[23]	147	148	1.28 (1.15-1.42)
Watanabe et al[25]	8	8	1.39 (1.16-1.66)
Curley et al[28]	45	49	1.14 (0.95-1.37)
Papazian et al[29]	13	13	1.64 (1.29-2.10)
Mancebo et al[31]	71	59	1.27 (1.09-1.49)
Chan et al[34]	11	11	1.53 (1.00-2.33)
Demory et al[32]	13	15	1.69 (1.28-2.24)
Ibrahim et al[33]	11	11	1.30 (1.02-1.66)
Overall	319	314	1.34 (1.23-1.45)
Overall effect $p < 0.001$. *Heterogeneity* $I^2 = 29\%$.			
Day 2			
Gattinoni et al[23]	121	139	1.25 (1.13-1.39)
Watanabe et al[25]	8	8	1.38 (1.16-1.65)
Curley et al[28]	41	47	1.19 (1.00-1.41)
Chan et al[34]	8	7	2.09 (1.26-3.47)
Overall	178	201	1.30 (1.15-1.46)
Overall effect $p < 0.001$. *Heterogeneity* $I^2 = 42\%$.			
Day 3			
Gattinoni et al[23]	95	132	1.20 (1.07-1.34)
Watanabe et al[25]	8	8	1.46 (1.21-1.76)
Curley et al[28]	29	41	1.16 (0.96-1.41)
Mancebo et al[31]	65	52	1.22 (1.06-1.40)
Chan et al[34]	8	7	1.08 (0.66-1.77)
Overall	205	240	1.23 (1.15-1.32)
Overall effect $p < 0.001$. *Heterogeneity* $I^2 = 0\%$.			

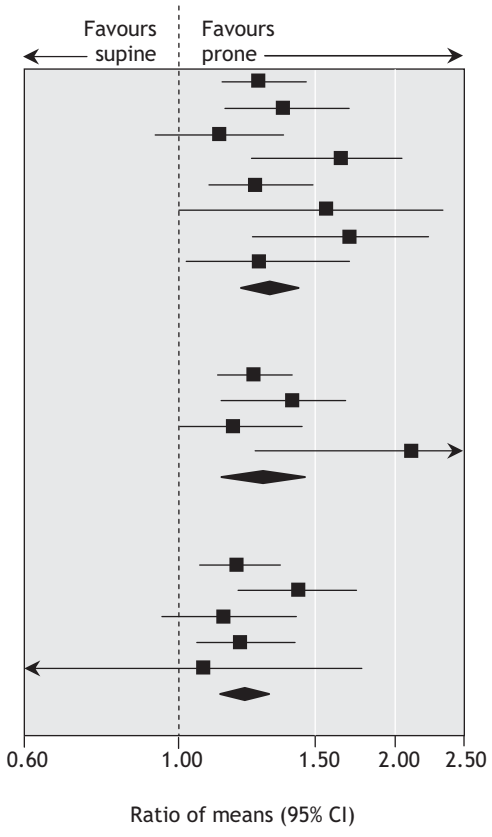

Figure 3: Effect of ventilation in the prone position on daily ratio of partial pressure of oxygen to inspired fraction of oxygen. We used a random-effects model in our analysis. Values were recorded at the end of the period of prone positioning (prone group) and simultaneously in the supine group. Ratio of means = mean ratio of partial pressure of oxygen to inspired fraction of oxygen in the prone group divided by that in the supine group. I^2 = percentage of total variation across studies owing to between-study heterogeneity rather than chance. CI = confidence interval.

cluded trials may have failed to identify a particular population that would benefit from ventilation in the prone position. Several trials enrolled patients with diverse types of respiratory failure.[24,25,27,30] In the largest trial, only 51% of the 802 patients had acute lung injury or acute respiratory distress syndrome.[27] Although meta-analysis restricted to patients with acute lung injury or acute respiratory distress syndrome did not show a mortality benefit, physiologic variables (other than oxygenation response) may identify a subgroup of these patients who might benefit from ventilation in the prone position. For example, Gattinoni and colleagues[36] reported in a post hoc analysis that decreased partial pressure of carbon dioxide after an initial 6-hour prone period, which likely reflected a lower fraction of minute ventilation delivered to nonperfused lungs (dead space), was associated with improved survival.

Third, the duration of prone positioning may have been insufficient. Our subgroup analysis did not show benefit among all prolonged-duration trials; however, the most intensive proning regimen studied (17 hours daily for 10 days) was shown in an adjusted analysis to reduce mortality.[31] An ongoing randomized controlled trial of mechanical ventilation with an intensive proning regimen (20 hours daily for up to 28 days) involving 340 patients with acute respiratory distress syndrome (the Prone–Supine Study II [www.clinicaltrials.gov/ct2/show/NCT00159939?term=NCT00159939&rank=1]) may provide valuable additional data regarding this issue.

Finally, it is possible that the benefits of ventilation in the prone position were overshadowed by a mechanical ventilation strategy that injured the lungs and perpetuated multiple organ failure. The ongoing Prone–Supine Study II mandates lung-protective mechanical ventilation, which may resolve this issue. Another planned randomized controlled trial[46] would add to current knowledge by enrolling patients with severe acute respiratory distress syndrome (ratio of partial pressure of oxygen to inspired fraction of oxygen no greater than 100 mm Hg and high severity of illness) and mandating prolonged prone positioning and lung-protective ventilation.

Our meta-analysis demonstrated a reduced risk of ventilator-associated pneumonia associated with prone positioning. Some small nonrandomized studies suggested better drainage of respiratory secretions with this technique,[9,10] which may prevent aspiration. However, our finding is limited by potential ascertainment bias because most of the trials lacked standard diagnostic criteria and blinding of outcomes assessors. Furthermore, the clinical importance of reduced ventilator-associated pneumonia with prone positioning is

Study	Prone, n/N	Supine, n/N	RR (95% CI)
Beuret et al[24]	2/12	4/9	0.38 (0.09-1.62)
Watanabe et al[25]	1/8	2/8	0.50 (0.06-4.47)
Guerin et al[27]	85/413	91/378	0.85 (0.66-1.11)
Voggenreiter et al[30]	13/21	17/19	0.69 (0.48-1.00)
Mancebo et al[31]	14/76	9/60	1.23 (0.57-2.64)
Chan et al[34]	0/11	0/11	NA
Overall	541	485	0.81 (0.66-0.99)

Overall effect $p = 0.04$. *Heterogeneity* $I^2 = 0\%$.

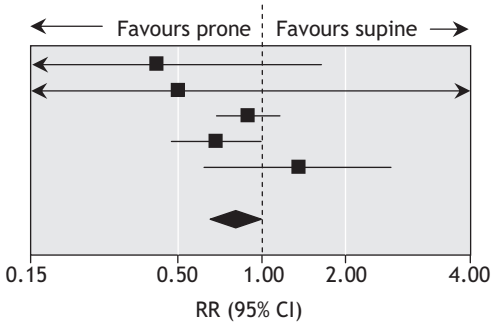

Figure 4: Effect of ventilation in the prone position on risk of ventilator-associated pneumonia. We used a random-effects model in our analysis. One trial[24] included data only for patients with acute hypoxemic respiratory failure. I^2 = percentage of total variation across studies owing to between-study heterogeneity rather than chance. CI = confidence interval, NA = not applicable, RR = risk ratio.

Study	Prone, n/N	Supine, n/N	RR (95% CI)
Leal et al[22]	1/8	0/8	3.00 (0.14-64.26)
Gattinoni et al[23]	55/152	42/152	1.31 (0.94-1.83)
Beuret et al[24]	2/12	2/9	0.75 (0.13-4.36)
Curley et al[28]	10/51	8/50	1.23 (0.53-2.85)
Voggenreiter et al[30]	19/21	12/19	1.43 (0.99-2.07)
Chan et al[34]	2/11	0/11	5.00 (0.27-93.55)
Overall	255	249	1.36 (1.07-1.71)

Overall effect $p = 0.01$. *Heterogeneity* $I^2 = 0\%$.

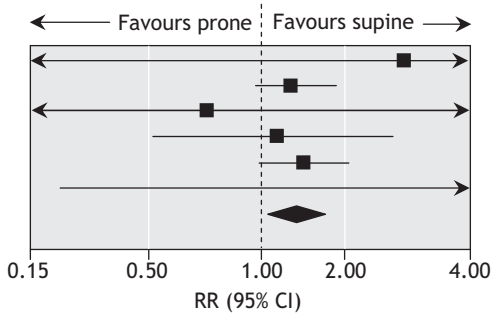

Figure 5: Effect of ventilation in the prone position on risk of pressure ulcers. We used a random-effects model in our analysis. One trial[24] included data only for patients with acute hypoxemic respiratory failure. I^2 = percentage of total variation across studies owing to between-study heterogeneity rather than chance. CI = confidence interval, RR = risk ratio.

unclear given similar duration of ventilation, ventilator-free days and mortality among patients who received ventilation in the prone and supine positions.

We found mechanical ventilation in the prone position to be generally safe, at least in centres participating in clinical trials. However, the procedure was labour-intensive, requiring 4–6 personnel to turn an adult patient, and it increased the risk of pressure ulcers. In contrast, with the exception of possible endotracheal tube blockage, prone positioning did not increase the risk of potentially life-threatening complications such as accidental extubation and dislodgement of central catheters or thorocostomy tubes. Nevertheless, some trials reported airway obstruction, accidental extubation and dislodgement of central catheters directly related to the turning procedure,[23,31] which led to cardiac arrest in one instance.[31] Such complications, although infrequent, could be catastrophic in patients with critical hypoxemia. Less experienced centres may face more life-threatening complications, but turning protocols and nursing care guidelines may mitigate the risk.[13,38,47]

A recent survey of 702 (predominantly adult) ICUs in Germany[48] reported more complications during various forms of positioning therapy than recorded in randomized controlled trials. These included hemodynamic instability (reported by 74% of ICUs), accidental removal of tubes or catheters (50%), worsening gas exchange (45%), patient intolerance owing to inadequate sedation (41%) and cardiac arrhythmias (22%). Moreover, many respondents believed that successful application of positioning therapy forced clinicians to compromise other aspects of critical care by requiring them to deepen sedation (77% of ICUs) and to stop (16%) or at least reduce (33%) enteral feeds. Another survey of proning practices in 25 ICUs in Belgium reported similar rates of serious complications, in addition to increased workload (owing to increased suctioning and eye care), which contributed to the reluctance of nurses in 9 ICUs (36%) to use the technique.[12]

Strengths of our review include methods to reduce bias and analysis of a comprehensive set of prespecified clinical and physiologic outcomes. Our study had a number of limitations, including variability in the selection criteria of individual trials (including author definitions of acute lung injury and acute respiratory distress syndrome) and reduced sample size in 5 trials that ended early because of futility or declining enrolment. Both factors may have diluted our ability to detect a survival benefit through meta-analysis. In addition, although the mortality funnel plot suggested publication bias (Appendix 4, available at www.cmaj.ca/cgi/content/full/178/9/1153/DC2), results of statistical tests did not confirm the presence of publication bias. Statistical tests may fail to detect publication bias, but the assumption of such bias in our meta-analysis would imply that small unpublished randomized trials have shown higher rates of mortality in the prone group than the supine group. Data from such trials would only move the estimated pooled RR for mortality closer to no effect. Another limitation is that supplementary information was not available for all trials, 2 of which were published only as abstracts. In addition, the small number of trials included in our review reduced the precision of the pooled estimates for some clinical and physiologic analyses and may have underestimated heterogeneity. Finally, findings from the largest trial[27] dominated the meta-analysis of ventilator-associated pneumonia and endotracheal tube obstruction.

In summary, our systematic review found that ventilation in the prone position in patients with acute hypoxemic respiratory failure improved oxygenation and reduced the risk of ventilator-associated pneumonia, but it did not improve survival. The technique appeared safe in expert centres; however, serious airway, catheter and tube complications may occasionally occur, and the technique increased the risk of pressure ulcers. Consequently, we do not recommend the routine use of prone positioning for patients with hypoxemic respiratory failure. Despite the neutral effect on mortality, clinicians may still consider

Table 2: Risk of adverse events in 12 trials of prone positioning for mechanical ventilation included in our systematic review*

Adverse event	No. of trials (patients) contributing data†	No. (%) of patients with adverse event‡	RR (95% CI)	*p* value	I^2, %§
Pressure ulcers*	6 (504)	153/504 (30.4)	1.36 (1.07–1.71)	0.01	0
Endotracheal tube obstruction*	5 (204)	3/204 (1.5)	1.32 (0.09–18.50)	0.84	33
Accidental extubation*	8 (662)	44/662 (6.6)	0.88 (0.48–1.60)	0.67	0
Loss of central venous or arterial access	7 (526)	25/526 (4.8)	0.67 (0.31–1.44)	0.31	0
Thorocostomy tube dislodgement	6 (504)	7/504 (1.4)	6.00 (0.73–49.24)	0.10	NA
Pneumothorax*	6 (336)	16/336 (4.8)	0.93 (0.35–2.45)	0.89	0
Cardiac arrest*	5 (230)	0/230 (0)	NA	NA	NA

Note: CI = confidence interval, NA = not applicable, RR = risk ratio. Random-effects models were used in all analyses.
*We excluded the trial by Guerin et al[27] from the analysis because it reported the number of occurrences of adverse events rather than the number of patients with adverse events. Assuming a similar distribution of occurrences per patient in the prone and supine groups, when we included these data, the risk of endotracheal tube obstruction became statistically significant (RR 2.46, 95% CI 1.33–4.55; $p = 0.004$; $I^2 = 0\%$) and the risk of pressure ulcers became more significant (RR 1.25, 95% CI 1.10–1.43; $p < 0.001$; $I^2 = 0\%$). This trial contributes heavily to the pooled RRs when its data are included (92% weighting in the endotracheal tube obstruction analysis and 70% in the pressure ulcer analysis).
†We counted trials that collected data on the adverse event, regardless of whether an event occurred.
‡This is the unweighted proportion of patients in the prone and supine groups (in trials collecting data on adverse events) who experienced an adverse event.
§I^2 = percentage of total variation across studies owing to between-study heterogeneity rather than chance.

prone positioning for life-threatening hypoxemia, along with other supportive therapies. Current data for such patients are limited, and early termination of several published trials owing to slow enrolment suggests that additional studies, although highly desirable, will be challenging to complete.

This article has been peer reviewed.

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Appendix 1: Search strategy

The following databases were searched in OVID on Feb. 2, 2008: MEDLINE (1950 to week 4, January 2008), EMBASE (1980 to week 5, 2008), Evidence-Based Medicine Reviews (fourth quarter 2007), Cochrane Central Register of Controlled Trials (fourth quarter 2007).

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.

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 and EMBASE (lines 2 and 5) are based on published sensitive strategies for retrieving randomized trials.[1,2] References from these 3 databases were combined and duplicates removed using OVID software.

We also separately searched ISI Science Citation Index Expanded (1945 to present) using the following strategy:

1. TS=prone
2. TS=prone position*
3. TS=prone ventilation
4. 1 or 2 or 3
5. TS=acute respiratory distress syndrome
6. TS=adult respiratory distress syndrome
7. TS=acute lung injury
8. TS=hypox*
9. TS=acute respiratory failure
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10
12. TS=randomized controlled trial
13. TS=controlled clinical trial
14. TS=clinical trial
15. 12 or 13 or 14
16. 11 and 15

Notes: '*' retrieves unlimited suffix variations; TS denotes topic.

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Ongoing randomized controlled trial (n=1)
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Randomized controlled trial with outcomes data not provided after author contact (n=1)
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Randomized controlled trial with outcomes data not available after author contact (n=1)
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Randomized controlled trial enrolling neonates (n=2)
4. Kumar P, Steele AM. Effect of prone positioning on oxygenation and pulmonary mechanics in preterm infants with acute respiratory distress syndrome [abstract]. Am J Respir Crit Care Med. 2003;167:A509.
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Randomized controlled trial where all patients received ventilation in the prone position (n=4)
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Randomized controlled trial with non-supine control group (n=3)
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Appendix 2: Characteristics of randomized trials of prone versus supine positioning for mechanical ventilation included in our systematic review

Study	Patient population*†	Details of prone ventilation‡	General mechanical ventilation and cointerventions (both groups)	Concealment of patient assignment	Unplanned crossovers (assigned group)§	Trial ended early
Leal et al[1]	16 patients at 1 centre who had acute respiratory distress syndrome (ratio of partial pressure of oxygen to inspired fraction of oxygen < 150 mm Hg and lung injury score[14] > 2.5); time from diagnosis to enrolment ≤ 24 h	24 h (fixed duration)	No information on ventilation parameters No high-frequency oscillation or nitric oxide	Sealed opaque envelopes (sequentially numbered)	None	No
Gattinoni et al[2]	304 patients older than 15 yr at 30 centres who had acute lung injury (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 200/300 mm Hg with positive end-expiratory pressure ≥ 5/10 cm H_2O)	Abdomen restrained; planned duration ≥ 6 h/d for up to 10 d if hypoxemia criteria met; actual duration 7.0 (SD 1.8) h/d for 4.7 d; 4.6 (SD 0.9) people required per turn; 10 (SD 12) min per turn	1994 American–European mechanical ventilation guidelines[15,16] Baseline tidal volume 10.3 (SD 2.8) mL/kg predicted body weight and positive end-expiratory pressure 9.6 (SD 3.1) cm H_2O Little change in tidal volume or positive end-expiratory pressure over 10 d	Central (randomization independent of centre enrolling patients)	12/152 (supine)	Yes (slow enrolment)
Beuret et al[3]	53 adults at 1 centre who had a Glasgow coma score < 9 and needed mechanical ventilation; 7 of 21 patients with hypoxemia (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 300 mm Hg) had acute lung injury or acute respiratory distress syndrome; time from intubation to diagnosis ≤ 24 h	Planned duration 4 h/d until patient sitting up in chair; actual duration 6.0 (SD 3.6) d	Initial tidal volume 10 mL/kg body weight, then adjusted to keep partial pressure of carbon dioxide 35–40 mm Hg Initial positive end-expiratory pressure 5 cm H_2O, increased for hypoxemia Pressure support weaning in both groups	Sealed opaque envelopes	1/12 (prone); 1/9 (supine)	Yes (slow enrolment)

Appendix 2 to Sud S, Sud M, Friedrich JO, et al. Prone ventilation improves oxygenation but not mortality in acute hypoxemic respiratory failure: systematic review and meta-analysis. *CMAJ* 2008: 178(9): 1153–1161.

Watanabe et al[4]	16 adults at 1 centre who had hypoxemia (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 200 mm Hg) after 5 d of mechanical ventilation postesophagectomy	6 h/d for 4 d (fixed duration); 6 people required per turn	Tidal volume and respiratory rate adjusted to keep partial pressure of carbon dioxide 35–45 mm Hg Standard criteria for initiating weaning All patients paralyzed No high-frequency oscillation or nitric oxide during intervention period	No (alternate allocation)	None	Not reported
Gaillard et al[5]	16 patients at 1 centre who had "direct acute lung injury" (no further details provided)	12 h/d for 2 d (fixed duration)	Tidal volume 6–8 mL/kg body weight Positive end-expiratory pressure set at 2 cm H_2O above lower inflection point of pressure-volume curve	Not reported	None	Not reported
Guerin et al[6]	802 adults at 21 centres who had acute hypoxemic respiratory failure (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 300 mm Hg), including acute lung injury and acute respiratory distress syndrome (*n* = 413), cardiogenic pulmonary edema (*n* = 56), other¶	Planned duration ≥ 8 h/d until clinical improvement criteria met; actual duration 8.6 (SD 6.6) h for 4.1 (SD 4.7) d; abdomen restrained	No ventilation protocol Mean tidal volume 8.1-8.7 mL/kg body weight and mean positive end-expiratory pressure 7.2-7.8 cm H_2O over first 7 d Weaning protocol	Sealed opaque envelopes (sequentially numbered)	176/417 (prone); 81/385 (supine)	No
Curley et al[7]	102 children at 7 centres who had acute lung injury; time from diagnosis to enrolment ≤ 48 h	Planned duration 20 h/d until extubation readiness criteria met; actual duration 18 (SD 4) h for 4 d (range 1–7 d); 2-4 people required per turn; abdomen unrestrained	Tidal volume 6 mL/kg body weight Positive end-expiratory pressure and inspired fraction of oxygen adjusted according to chart Positive end-expiratory pressure 7.4 (SD 2.5) cm H_2O during trial Protocols for high-frequency oscillation, weaning and sedation	Sealed opaque envelopes (sequentially numbered)	4/51 (prone)	Yes (statistical stopping rule for futility met)

Appendix 2 to Sud S, Sud M, Friedrich JO, et al. Prone ventilation improves oxygenation but not mortality in acute hypoxemic respiratory failure: systematic review and meta-analysis. *CMAJ* 2008: 178(9): 1153–1161.

Papazian et al[8]	26 adults at 1 centre who had acute respiratory distress syndrome (ratio of partial pressure of oxygen to inspired fraction of oxygen < 150 mm Hg with positive end-expiratory pressure ≥ 5 cm H_2O); time from diagnosis to enrolment ≤ 24 h	12 h (fixed duration); abdomen unrestrained	All patients received high frequency oscillation and paralysis during 12-h study period No nitric oxide or steroids	Sealed opaque envelopes	None	No
Voggenreiter et al[9]	40 adults at 2 centres who had traumatic injury with acute lung injury (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 300 mm Hg with positive end-expiratory pressure ≥ 5 cm H_2O) and persistent hypoxemia; time from diagnosis to enrolment about 1–2 d	Planned duration 8–23 h/d until oxygenation improvement criteria met; actual duration 11 (SD 5) h for 7 (SD 4) d	Tidal volume 6–8 mL/kg body weight and peak inspiratory pressure < 35 cm H_2O Suggestion for positive end-expiratory pressure adjustment Baseline positive end-expiratory pressure 12 (SD 4) cm H_2O and similar during trial Sedation similar, trend to more days of paralysis in prone group No nitric oxide	Central (randomization independent of centre enrolling patients)	None	Not reported
Mancebo et al[10]	142 adults at 13 centres who had acute respiratory distress syndrome with diffuse bilateral infiltrates on chest radiograph; time from meeting inclusion criteria to enrolment ≤ 48 h	Planned duration 20 h/d until "weaning oxygenation threshold" met; actual duration mean 17 h/d for 10.1 (SD 10.3) d; ~5 persons took ~5–10 min per turn; abdomen restrained	Maximum tidal volume 10 mL/kg and positive end-expiratory pressure 10-15 cm H_2O, both adjusted to plateau pressure ≤ 35–40 cm H_2O Mean positive end-expiratory pressure 7–12 cm H_2O during trial Weaning protocol No nitric oxide or steroids Sedation and paralysis similar between groups	Sealed opaque envelopes (sequentially numbered)	5/62 (supine)	Yes (slow enrolment)

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Demory et al[11]	28 adults at 1 centre who had acute respiratory distress syndrome (ratio of partial pressure of oxygen to inspired fraction of oxygen < 150 mm Hg, positive end-expiratory pressure ≥ 5 cm H_2O); time from diagnosis to enrolment ≤ 24 h	12 h (fixed duration)	Tidal volume 6–7 mL/kg body weight and plateau pressure ≤ 35 cm H_2O while in prone position Positive end-expiratory pressure adjusted according to chart All patients received paralysis during study period and high-frequency oscillation while supine for 12 h after study period No nitric oxide or steroids	Sealed opaque envelopes	None	Not reported
Ibrahim et al[12]	24 children** at 1 centre who had acute hypoxemic respiratory failure (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 200 mm Hg); median 24 h (range 10–60 h) of mechanical ventilation before enrolment	20 h (fixed duration); abdomen unrestrained	Tidal volume 5-10 mL/kg body weight Positive end-expiratory pressure not described All patients received nitric oxide for 20 h	No (alternate allocation)	None	Not reported
Chan et al[13]	22 adults at 1 centre who had acute respiratory distress syndrome (ratio of partial pressure of oxygen to inspired fraction of oxygen ≤ 200 mm Hg) because of community-acquired pneumonia; time from diagnosis to enrolment ≤ 72 h	Planned duration ≥ 72 h (continuous) in prone position until oxygenation improvement criteria met; actual duration 4.4 (SD 2.8) d	Protocol with tidal volume 6–8 mL/kg body weight and positive end-expiratory pressure adjusted according to inspired fraction of oxygen No high-frequency oscillation or nitric oxide	No (entire randomization table visible to person enrolling patients in advance)[17,18]	None	Yes (slow enrolment due to outbreak of severe acute respiratory syndrome)

Note: SD = standard deviation.
*Mortality evaluated for all assigned patients (in trials reporting this outcome) except for 11/802 (4 assigned to prone, 7 assigned to supine; of these 11 patients, 9 were withdrawn from the study and 2 were lost to follow-up) patients in Guerin et al,[6] 1/101 (assigned to supine) in Curley et al,[7] and 6/142 (4 assigned to prone, 2 assigned to supine) in Mancebo et al.[10]
†Unless otherwise specified, patients with acute lung injury or acute respiratory distress syndrome met the American–European consensus definition.[19] In 3 trials[8,11,12] patients were also randomized to a third group. In our analyses of these trials, we included 2 groups: the treatment group and the control group, which differed only by the application of mechanical ventilation in the prone position.
‡We note abdominal position (unrestrained, using cushions to support abdomen above bed surface, or restrained by direct contact with bed) and personnel and time required for turning procedures where reported.
§Crossovers are listed as number of patients crossing over/number of patients initially assigned to treatment group.
¶Other (not mutually exclusive) causes of acute hypoxemic respiratory failure included pneumonia, shock, aspiration, septic shock, acute on chronic respiratory failure, coma, postoperative state and nonpulmonary sepsis.
**Two children were withdrawn from the trial and did not have oxygenation measured.

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Appendix 2 to Sud S, Sud M, Friedrich JO, et al. Prone ventilation improves oxygenation but not mortality in acute hypoxemic respiratory failure: systematic review and meta-analysis. *CMAJ* 2008: 178(9): 1153–1161.

Appendix 3: Additional subgroup analyses

Additional subgroup analyses to explore the effects of study quality and age (children v. adults) are limited because in each case, one of the subgroup pairs includes a single trial. There was no difference in mortality between the following pairs of subgroups:

1. adults (risk ratio [RR] 0.96, 95% confidence interval [CI] 0.84–1.09, 9 studies) v. children (RR 1.00, 95% CI 0.26–3.78, 1 study[1]); $p = 0.95$ for comparison of RRs using z-score
2. adequate allocation concealment (RR 0.96, 95% CI 0.84–1.09, 9 studies) v. no or unclear allocation concealment (RR 1.00, 95% CI 0.33–3.02, 1 study[2]); $p = 0.94$ for comparison of RRs using z-score
3. no loss to follow-up and less than 10% crossovers (RR 0.91, 95% CI 0.77–1.08, 9 studies) v. any loss to follow-up or at least 10% crossovers (RR 1.03, 95% CI 0.84–1.26, 1 study[3]); $p = 0.36$ for comparison of RRs using z-score

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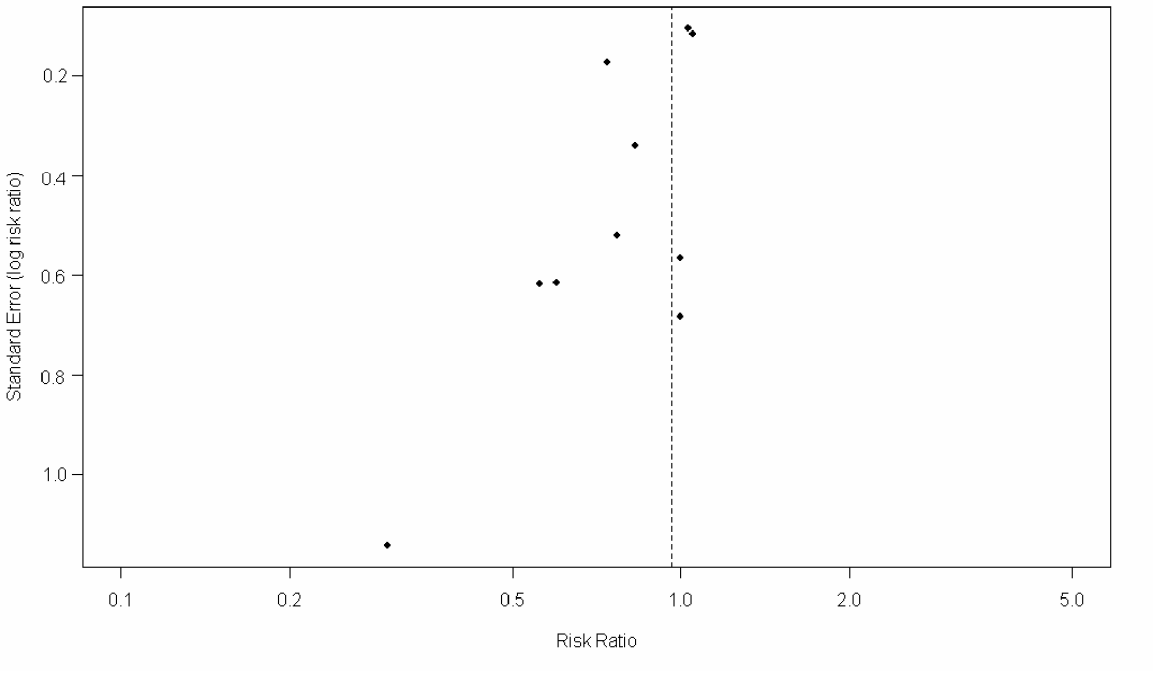
Appendix 3 to Sud S, Sud M, Friedrich JO, et al. Prone ventilation improves oxygenation but not mortality in acute hypoxemic respiratory failure: systematic review and meta-analysis. *CMAJ* 2008: 178(9): 1153–1161.

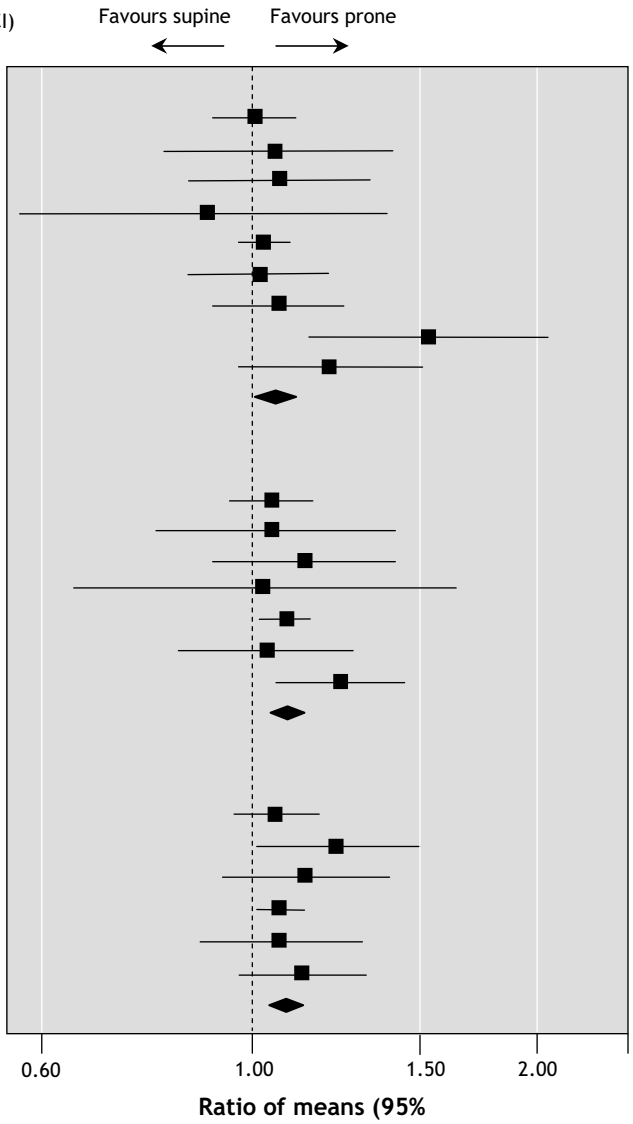
Appendix 4: Funnel plot for outcome of mortality in trials of mechanical ventilation in the prone v. supine position for acute hypoxemic respiratory failure. Each point represents 1 trial; the dashed vertical line is the overall estimated risk ratio (RR) assuming a fixed-effects model. Statistical tests were nonsignificant ($p = 0.53$ for Begg rank correlation test and $p = 0.14$ for the modified Macaskill regression test); however, these tests are underpowered because of the small number of trials. Given that the meta-analysis of published trials showed no benefit for prone positioning, any additional unpublished small trials showing excess mortality in the prone group would only move the pooled estimate for mortality even closer to no effect.



Appendix 4 to Sud S, Sud M, Friedrich JO, et al. Prone ventilation improves oxygenation but not mortality in acute hypoxemic respiratory failure: systematic review and meta-analysis. *CMAJ* 2008: 178(9):1153–1161.

Appendix 5: Effect of mechanical ventilation in the prone v. supine position for acute hypoxemic respiratory failure on the daily ratio of partial pressure of oxygen to inspired fraction of oxygen. Values are recorded in the morning just before the next proning manoeuvre in the prone group and at the corresponding morning time in the control (supine) group. The ratio of means measures the oxygenation difference between groups remaining after proned patients were returned to the supine position. Day 1 for this measurement refers to the measurement taken the morning after the first proning session and applies only to proning session durations of less than 24 hours. Data from one trial (Beuret et al.) includes only patients with acute hypoxemic respiratory failure. Ratio of means is the mean value in the prone group divided by the mean value in the supine group. I^2 is the percentage of total variation across studies due to between-study heterogeneity rather than chance. Complete citations of included studies are available in Appendix 2 at www.cmaj.ca/cgi/content/full/178/9/1153/DC2. Note: CI, confidence interval.

Study	Prone, N	Supine, N	Ratio of means (95% CI)
Day 1			
Gattinoni et al[2]	147	148	1.01 (0.91–1.11)
Beuret et al[3]	12	9	1.06 (0.81–1.40)
Watanabe et al[4]	8	8	1.07 (0.86–1.34)
Gaillard et al[5]	10	6	0.90 (0.57–1.39)
Guerin et al[6]	305	365	1.03 (0.97–1.10)
Curley et al[7]	50	49	1.02 (0.86–1.20)
Voggenreiter et al[9]	20	19	1.07 (0.91–1.25)
Demory et al[11]	13	15	1.54 (1.15–2.05)
Ibrahim et al[12]	11	11	1.21 (0.97–1.52)
Overall	576	630	1.06 (1.00–1.12)
Overall effect p = 0.07. Heterogeneity I^2 = 19%.			
Day 2			
Gattinoni et al[2]	141	139	1.05 (0.95–1.16)
Beuret et al[3]	12	9	1.05 (0.79–1.41)
Watanabe et al[4]	8	8	1.14 (0.91–1.42)
Gaillard et al[5]	10	6	1.03 (0.65–1.65)
Guerin et al[6]	317	338	1.09 (1.02–1.16)
Curley et al[7]	41	47	1.04 (0.84–1.28)
Voggenreiter et al[9]	21	19	1.24 (1.06–1.45)
Overall	550	556	1.09 (1.04–1.14)
Overall effect p < 0.001. Heterogeneity I^2 = 0%.			
Day 3			
Gattinoni et al[2]	132	132	1.06 (0.96–1.18)
Beuret et al[3]	10	8	1.23 (1.01–1.50)
Watanabe et al[4]	8	8	1.14 (0.93–1.39)
Guerin et al[6]	310	325	1.07 (1.01–1.14)
Curley et al[7]	31	41	1.07 (0.88–1.31)
Voggenreiter et al[9]	21	19	1.13 (0.97–1.32)
Overall	512	533	1.09 (1.04–1.14)
Overall effect p < 0.001. Heterogeneity I^2 = 0%.			



Appendix 5 to Sud S, Sud M, Friedrich JO, et al. Prone ventilation improves oxygenation but not mortality in acute hypoxemic respiratory failure: systematic review and meta-analysis. *CMAJ* 2008: 178(9): 1153–1161.

Research

Ventilation in the prone position: For some but not for all?

Luciano Gattinoni MD, Alessandro Protti MD

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Shortly after acute respiratory distress syndrome was first described, it was soon realized that mechanical ventilation, aside from being essential for the treatment of the disease, can also harm the lungs by increasing the stress and strain applicable to the parenchyma. Stress is the tension developed in the lungs' fibrous skeleton when a distending force is applied, and strain is the volume increase caused by the applied force relative to the resting volume of the lungs. Supporting a patient's diseased lung with very high airway pressures can rupture alveoli, causing pneumothoraces and pneumomediastinum. This stress is referred to as barotrauma. In much the same way, very high tidal volumes distend and strain alveoli, causing volutrauma. Remaining normal portions of the lungs are especially vulnerable to this effect. Secondary lung injury can be induced by mechanical ventilation. Increased inflammation as a result of positive-pressure ventilation has recently been termed biotrauma. Repetitive opening and closing of collapsed parts of the lung can amplify local stress and produce damage (atelectrauma).[1] The major mechanisms in the pathogenesis of ventilator-induced lung injury are summarized in Figure 1.

Indeed, the focus of mechanical ventilation has progressively shifted from ensuring normal gas exchange to protecting the lungs from excessive stress and strain. Any survival advantage resulting from the way mechanical ventilation is delivered is likely to depend on a decrease in ventilator-induced lung injury.[3] If correctly performed, mechanical ventilation "buys time" to allow other therapies to take effect; if performed incorrectly, it may kill the patient.

Why should ventilation in the prone position compared to the supine position improve survival? Physiologically, for ventilation in the prone position to increase survival, it must be less harmful than in the supine position. More specifically, the stress and strain induced by ventilation in the prone position must be lower relative to the supine position. Does prone positioning ensure lower pulmonary stress and strain? If so, why have no major trials demonstrated any survival benefit associated with ventilation in the prone position?

Inflammatory pulmonary edema that occurs during acute lung injury and acute respiratory distress syndrome increases lung weight. As a consequence, if a patient is in a supine position, the dorsal regions of the lungs collapse under the weight of the ventral regions, and the gas contents of the dorsal regions are squeezed out (compression atelectasis) (Figure 2). During mechanical ventilation, most of the air goes to the ventral, open parts of the lungs, increasing their stress and strain. A minor part of the tidal volume goes to the dorsal parts of the lungs, causing their cyclic opening and closing, thus amplifying the local stress and strain. In contrast, if the patient is in a prone position, the ventral regions become dependent and collapse under the weight of the dorsal regions, which inflate to a different extent. Because of their shape, more parts of the lungs are open to ventilation in the prone position than in the supine position (Figure 2).[4] Therefore, in the prone position, air is distributed more homogeneously throughout the lungs, and stress and strain are decreased. This is the main reason why prone positioning can delay the appearance of ventilator-induced lung injury and increase survival, as suggested by animal studies.[5]

Key points

- Prone ventilation is not recommended in the routine management of acute lung injury and acute respiratory distress syndrome, but it can be used as a rescue manoeuvre in cases of severe hypoxemia.
- Experimental evidence suggests that prone ventilation can prevent or attenuate ventilator-induced lung injury.
- The possible survival benefit of prone ventilation in subgroups of patients with acute lung injury or acute respiratory distress syndrome remains to be determined.

To detect any advantage of ventilation in the prone position, the pulmonary inflammatory edema must be severe enough to, in the supine position, produce an abnormally heterogeneous distribution of air and considerably increase the interface between the open and collapsed regions, which are possibly undergoing repetitive, cyclic opening and closing. It is obvious that without these conditions, such as in patients with only minimal inflammatory edema, we cannot expect any increased benefit from prone positioning.

In this issue of *CMAJ*, Sud and colleagues[6] report the results of their meta-analysis of 13 randomized or quasi-randomized controlled trials (1559 patients) comparing ventilation in the prone and supine positions in acute hypoxemic respiratory failure, including acute lung injury and acute respiratory distress syndrome. Mechanical ventilation for patients assigned to the prone group lasted a median of 12 hours per day (range 4–24) for 4 days (range 1–10). Sud and colleagues conclude that prone positioning cannot be recommended in the routine management of acute lung injury and acute respiratory distress syndrome because, despite improv-

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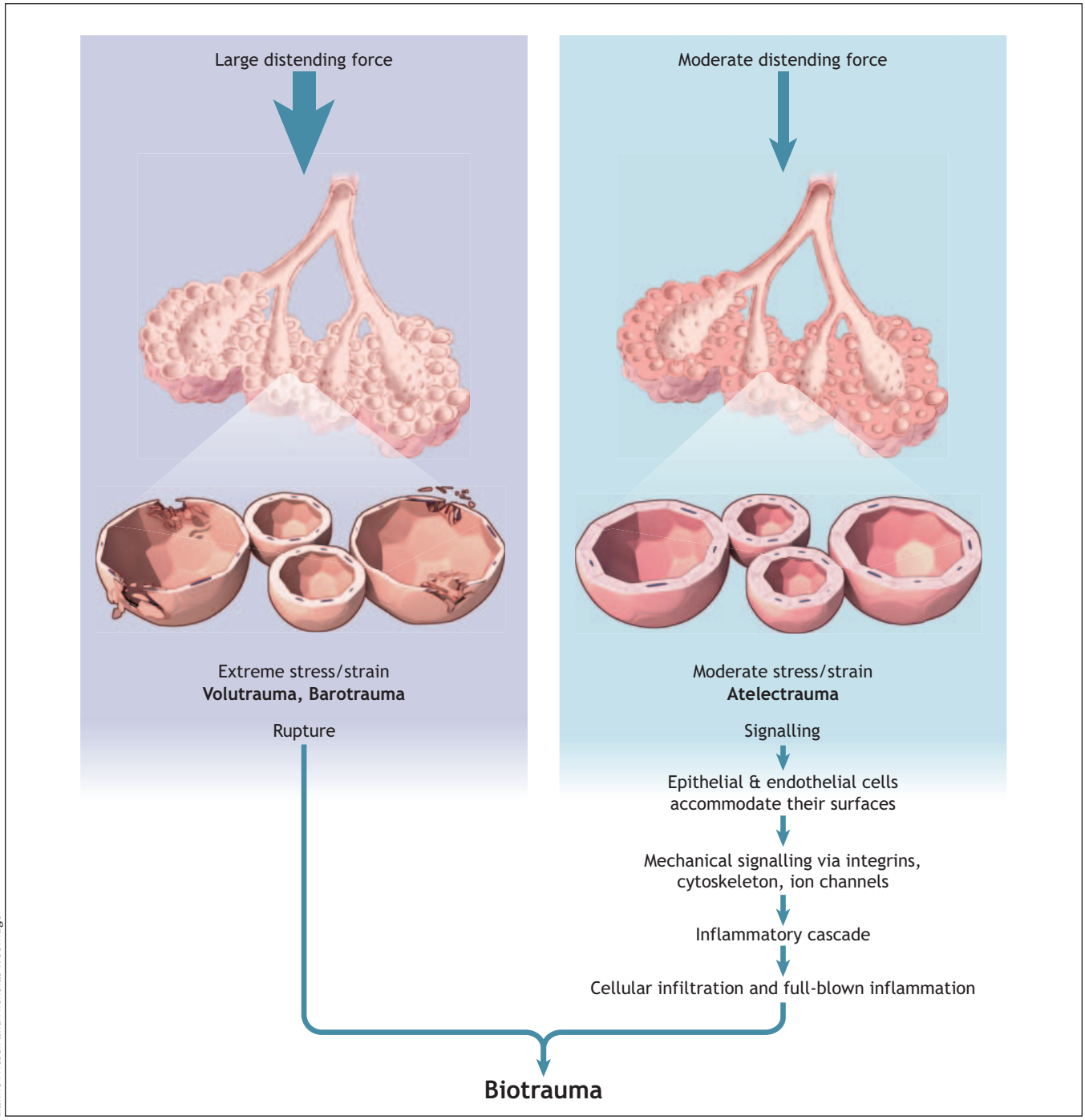
ing oxygenation, they found no evidence of improved survival. We feel that this conclusion is appropriate based on the results of all the major studies of ventilation in the prone position published to date. However, were those studies designed in the most appropriate way to detect a possible survival advantage of prone positioning?

Let us examine, from a physiological perspective, the largest trials included in the meta-analysis by Sud and colleagues. In a study previously performed by one of us (L.G.) involving 304 participants, patients remained in the prone position for an average of 7 hours per day.[7] There was no control for mechanical ventilation because, at that time, conclu-



Lianne Friesen and Nicholas Woolridge

Figure 1: Ventilator-induced lung injury is initiated by the application of excessive stress and strain to the lung. High levels of mechanical stress and strain that occur when high airway pressures and volumes are delivered can disrupt the pulmonary fibroelastic skeleton (barotrauma and volutrauma) and trigger a secondary inflammatory response (biotrauma). Moderate degrees of stress and strain related to the cyclic opening and closing of parts of the lung (atelectrauma) may directly induce the release of inflammatory mediators and noxious proteinases. Modified from Marini and Gattinoni.[2]

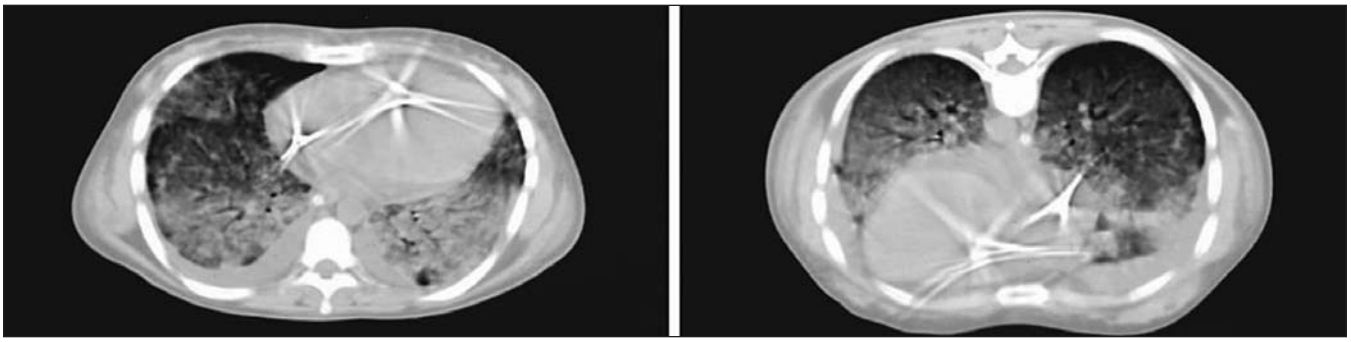


Figure 2: Computed tomography scan of the lungs showing acute respiratory distress syndrome when the patient is lying supine (left) and prone (right). Note the density redistribution in the prone compared with the supine position.

sive data supporting the delivery of low tidal volumes were not available. Despite the possibility of reduced pulmonary stress or strain, we limited the use of prone positioning to 7 hours per day. Moreover, the use of tidal volumes higher than those currently recommended could have eliminated any possible beneficial effect of prone positioning in some patients. Finally, only a small proportion of patients with acute lung injury or acute respiratory distress syndrome actually have a lung edema severe enough to expect an advantage from ventilation in the prone position.[8] Any beneficial effect of prone positioning in this subgroup could have been masked by the enrollment of patients lacking the physiological characteristics that warrant the use of the technique. Similarly recruitment of patients with different characteristics may have also affected the results of 2 other recent trials investigating the impact of high and low positive end-expiratory pressure on survival in patients with acute lung injury or acute respiratory distress syndrome.[9,10] It is possible that there may have been a significant benefit in a subgroup of patients, but this was not detected because of the enrollment of patients who did not warrant the use of positive end-expiratory pressure.[11]

These limitations are present at an even greater extent in the study by Guerin and colleagues,[12] who enrolled patients with inflammatory or cardiogenic lung edema ($n = 791$). Conversely, Mancebo and colleagues[13] enrolled 136 patients with relatively severe acute respiratory distress syndrome, used strictly controlled mechanical ventilation and maintained patients in the prone position for most of the day, reporting a strong, but nonsignificant ($p = 0.12$), tendency toward improved survival among patients in the prone group.

Although meta-analyses are fascinating, we must always remember that the final result strictly depends on the value of the studies retained for analysis. All of the randomized clinical trials studying ventilation in the prone position that have been published to date have been conducted without a clear understanding of the reason why prone positioning should improve patient outcomes. To correctly investigate the survival benefits associated with prone positioning, future studies will need to be designed in a way that considers the rationale behind the use of the technique, and researchers will need to appropriately select the study population and the timing of the intervention. We can conclude from the meta-analysis by Sud and colleagues that ventilation in the prone position for a few hours each day is very effective in relieving severe hypoxemia, but has no impact on survival in heterogeneous populations of patients with acute lung injury or acute respiratory distress syndrome — which is considerably different from concluding that ventilation in the prone position can never improve patient outcomes.

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