Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure*

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Most patients with acute lung injury and the acute respiratory distress syndrome (ALI/ARDS) (1) require mechanical ventilation to reduce the work of breathing and ensure adequate gas exchange. Traditional mechanical ventilation techniques for ALI/ARDS use low to moderate levels of positive end-expiratory pressure (PEEP) to support arterial oxygenation by reversing or preventing some alveolar atelectasis and flooding (2, 3). With this approach, ventilation-associated lung injury may occur from repeated opening and closing of bronchioles and alveoli that are atelectatic at end-expiration, from excessive stress at the margins between aerated and nonaerated lung units, or from overdistention of aerated lung units (4–6). In several animal models of ALI/ARDS, higher PEEP levels attenuated lung injury, perhaps by reducing the proportion of alveoli that were atelectatic or flooded at end-expiration (4, 7–9). Higher PEEP, combined with lower tidal volumes, was associated with lower mortality rates (10) and lower concentrations of inflammatory cytokines and mediators in bronchoalveolar lavage fluid and blood in ALI/ARDS patients (11). Some investigators have suggested that ALI/ARDS patients should be ventilated with higher levels of PEEP to achieve lung protective effects from greater lung recruitment (10–12).

Lung recruitment also may be achieved by periodically briefly raising transpulmonary pressure to higher levels than are achieved during tidal ventilation (recruitment maneuvers [RMs]) (10, 13–17). In a trial of mechanical ventilation strategies in 53 ALI/ARDS patients, a lung protective ventilation strategy combined RMs with relatively high levels of PEEP and small tidal volumes (10). The conventional ventilation strategy used lower levels of PEEP and did not use RMs. The lung protective ventilation strategy resulted in better survival, but it was not clear that the RMs contributed substantially to lung recruitment, reduced ventilation-associated lung injury, or improved outcomes. Moreover, the frequency of RMs was not indicated.

More information is needed to define the role of RMs in ventilator management in ALI/ARDS patients. The potential for recruitment is substantial when relatively low levels of PEEP are used (16, 17), but there is little information regarding RM effects when higher levels of PEEP are used, as in some recent clinical studies (10, 11). Moreover, the duration of RM effects must be better defined. If RM effects are beneficial but brief, then frequent RMs would be necessary to maintain their effects. Therefore, this study was designed to assess effects of RMs in patients receiving mechanical ventilation with relatively high levels of PEEP and low tidal volumes. We conducted RMs like those used in the previous study of a lung protective ventilation strategy (10).

***See also p. 2701.**

Key Words: respiratory distress syndrome; adult; ventilators; mechanical; atelectasis; acute lung injury

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The objectives were to assess a) the magnitude of the immediate effects of RMs on arterial oxygenation; b) the duration of the effects of RMs on requirements for oxygenation support (F_{IO_2} and PEEP); and c) the immediate effects of RMs on blood pressure and heart rate and on frequency of barotraumas.

METHODS

This study of RMs was conducted as an ancillary study in ALI/ARDS patients enrolled in a multiple-center clinical trial conducted by the National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Clinical Trials Network (participating members and centers are listed in the appendix). This trial was designed to compare outcomes of ALI/ARDS patients supported with either a traditional lower PEEP mechanical ventilation strategy or a higher PEEP strategy. All patients received mechanical ventilation with small tidal volumes (18). The trial of lower vs. higher PEEP was initiated in October 1999 and enrolled 550 patients by February 2002. This ancillary study of RMs was conducted only in patients randomized to the higher PEEP arm of the main trial (Table 1) from October 1999 to June 2000. The study was approved by all institutional review boards. Informed consent was obtained from subjects or surrogates.

This was a crossover study in which patients were randomized to receive single RMs on either the first and third or the second and fourth mornings after enrollment in the main trial. To control for effects of time during the period of observation after RMs, single sham recruitment maneuvers (sham RMs) were conducted on the alternate days (second and fourth or first and third days after enrollment). Sham RMs were conducted by assigning an initial time in the morning and then recording respiratory, hemodynamic, and radiographic data while patients continued on mechanical ventilation without conducting a RM. There were "wash-out" periods of approximately 24 hrs between RMs and sham RMs. RMs and sham RMs were not conducted if patients were weaning, if systolic blood pressure was <100 mm Hg or >200 mm Hg, or if heart rate was <70/min or >140/min. No additional sedatives or neuromuscular blocking agents were required. All patients were supported with volume-assist/control ventilation before RMs or sham RMs. RMs were conducted by changing the ventilator mode to continuous positive airway pressure (CPAP) and gradually raising the CPAP over 5–10 secs to 35 cm H_2O (40 cm H_2O if measured weight exceeded 150% predicted body weight). This level of CPAP was maintained for 30 secs unless systolic blood pressure decreased to ≤90 mm Hg or by >30 mm Hg, heart rate increased to ≥140/min or by >20/min, oxyhemoglobin saturation measured by pulse oximetry (SpO_2) was <90% and had decreased by ≥5%, or a cardiac dysrhythmia occurred. The CPAP level then was decreased over 5–10 secs, and previous ventilator settings (mode, PEEP, and F_{IO_2}) were resumed.

Magnitude and Duration of RM Effects on Arterial Oxygenation. We monitored SpO_2 continuously. To assess immediate effects of RMs, we compared greatest increments in SpO_2 during the first 10 mins after initiating RMs or sham RMs. After the first 10 mins, F_{IO_2} and PEEP were adjusted in discrete steps according to an explicit protocol (F_{IO_2}/PEEP-step, Table 1) to maintain SpO_2 of 88–95%. To assess duration of RM effects, we recorded changes in F_{IO_2}/PEEP-step at 30 mins and 1, 2, 4, and 8 hrs after RMs or sham RMs (a decrease in F_{IO_2}/PEEP-step is a favorable change). In some instances, SpO_2 was >95% or <88% at the specified times for comparison of F_{IO_2}/PEEP-step changes, but the F_{IO_2}/PEEP-step had not yet been changed according to the protocol rules. For analysis, these F_{IO_2}/PEEP-step values were adjusted up by one step if SpO_2 was <88% and adjusted down by one step if SpO_2 was >95% (adjusted F_{IO_2}/PEEP-step), according to the protocol. We also measured respiratory system compliance (Crs) as tidal volume/[plateau pressure − PEEP] at 1, 4, and 8 hrs after initiating RMs and sham RMs.

Safety of RMs. We recorded lowest blood pressure, highest and lowest pulse rate, and lowest SpO_2 during the 10 mins after initiating RMs and sham RMs. We examined the first chest radiographs obtained after RMs and sham RMs for pneumothorax, pneumomediastinum, and pneumatoceles.

Statistics. Changes in requirements for oxygenation support (F_{IO_2}/PEEP-step) were used to estimate changes in lung recruitment after the initial 10 mins after RMs and sham RMs. We reasoned that the duration of beneficial effects must be ≥2 hrs for regularly scheduled RMs to become a practical aspect of ventilator management. Therefore, the primary outcome variable for the RM study was the difference between the changes in F_{IO_2}/PEEP-step 2 hrs after RMs and sham RMs. To estimate the sample size required for this RM study, we analyzed 840 intervals of 1–3 hrs in a recent trial in ALI/ARDS in which similar F_{IO_2}/PEEP-steps were used (18). In that earlier trial, F_{IO_2}/PEEP-step was decreased by one or more steps (because of improving arterial oxygenation) in 17% of instances, was unchanged in 73%, and was increased by one or more steps (because of worsening arterial oxygenation) in 9%. We designed the present study to show the following favorable shifts in F_{IO_2}/PEEP-steps 2 hrs after RMs: 56% decreased, 42% unchanged, and 2% increased. These favorable shifts would be equivalent to an average RM-induced improvement in F_{IO_2}/PEEP-step of 0.46 steps (a decrease in F_{IO_2} of 0.046 or a decrease in PEEP of 0.92 cm H_2O). The study would have 84% power to show this difference by comparing F_{IO_2}/PEEP-step changes after RMs and sham RMs in 30 patients.

Changes from baseline after RMs or sham RMs were compared by repeated measures analysis of covariance, controlling for treatment order, day, and baseline values. Generalized estimating equations were used for repeated measures polychotomous logistic regression to estimate odds ratios of improved F_{IO_2}/PEEP-step 2 hrs after RMs vs. sham RMs. Both methods of analysis account for the potential correlation from repeated measures on the same individuals.

We used SAS version 8.1 (SAS Institute, Cary NC). The procedures (MIXED and GEN-

Table 1. Higher PEEP Ventilation Strategy Summary

Mode: Volume assist/control
Tidal volume/plateau pressure goals: Initial tidal volume = 6 mL/kg PBW. Tidal volume reduced further to 5 or 4 mL/kg PBW if necessary to achieve plateau pressure <30 cm H_2O.
Inspiratory flow and I/E: Any inspiratory flow or inspiratory flow waveform allowed to achieve target I/E = 1:1-1:3.
Arterial oxygenation goal: Spo_2 = 88–95% or Pao_2 = 55–80 mm Hg.
F_{IO_2} and PEEP: The following discrete F_{IO_2}/PEEP settings were allowed:

F_{IO_2}	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.9	1.0	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	20	20	20	20	20	22	24

PEEP, positive end-expiratory pressure (cm H_2O; PEEP may be increased to 34 cm H_2O if necessary to achieve arterial oxygenation goal; PBW, predicted body weight, calculated from these equations: male PBW (kg) = 50 + 0.91 [(height in cm) − 152.4]; female PBW (kg) = 45.5 + 0.91 [(height in cm) − 152.4]; I/E, ratio of the duration of inspiration to the duration of expiration; Spo_2, pulse oximetry.

MOD) use all data, paired and unpaired. Values shown are mean ± standard error unless stated otherwise. Two sided p values ≤.05 were required for statistical significance.

RESULTS

Data were available for 370 instances in 96 patients in which RMs or sham RMs could have been conducted from days 1 to 4 after randomization. There were 66 RMs and 70 sham RMs in 43 patients in whom at least one RM and one sham RM were conducted. There were 14 RMs and 15 sham RMs in patients without paired RMs and sham RMs. Of the 370 instances, neither RMs nor sham RMs were conducted because patients were weaning or extubated (37%), were hypo- or hypertensive (9%), had tachy- or bradycardia (2%), or were withdrawn from the study (2%), or for reasons that were not specified (5%).

Characteristics of all patients in whom at least one RM or one sham RM were conducted are shown in Table 2. The mean PEEP, tidal volume, and plateau pressure immediately before RMs and sham RMs were 13.8 ± 3.0 (SD) cm H_2O, 6.0 ± 0.8 (SD) mL/kg predicted body weight, and 26.4 ± 4.7 (SD) cm H_2O, respectively. The most common cause of ALI/ARDS was pneumonia (43%).

Magnitude and Duration of RM Effects on Arterial Oxygenation. Increments from baseline SpO_2 were greater within 10 mins after RMs than after sham RMs (1.7 ± 0.2% vs. 0.6 ± 0.3%, $p <$ .01). The responses to RMs were highly variable (Fig. 1). In ten instances, SpO_2 increased by 5–9% during the first 10 mins. However, in 14 instances, SpO_2 decreased by 1–4% after initiating RMs and did not increase back to baseline SpO_2 levels within 10 mins. In patients with pulmonary (pneumonia and aspiration) and extrapulmonary causes of ALI/ARDS, there were similarly greater increments in SpO_2 during the first 10 mins after RMs than after sham RMs (1.2% and 1.0%, respectively). The interaction between treatment effect (RM vs. sham RM) and cause of ALI/ARDS (pulmonary vs. extrapulmonary) was not significant (p = .72). Changes in SpO_2 were greater 60 mins after RMs (0.21 ± 0.26 vs. −0.51 ± 0.26, $p <$ .05), but differences at the other time points (10, 30, 120, 240, and 480 mins) were not significant.

Two hours after sham RMs, adjusted F_{IO_2}/PEEP-step had been decreased by one or more steps in 23% of instances, was unchanged in 65%, and had been increased in 12% (Table 3). Two hours after RMs, adjusted F_{IO_2}/PEEP-step had been decreased in 34% of instances, was unchanged in 56%, and had been increased in 10%. Improvement by one or more adjusted F_{IO_2}/PEEP-steps at 2 hrs after RMs was not significantly greater than after sham RMs (odds ratio, 1.54, p = 0.21; confidence interval, 0.78–3.02).

None of the differences between the changes in adjusted F_{IO_2}/PEEP-step after RMs and sham RMs were significant (Fig. 2). The mean decrease in adjusted F_{IO_2}/PEEP-step 2 hrs after RMs was 0.19 ± 0.14 (SEM) steps greater than the mean decrease in adjusted F_{IO_2}/PEEP-step 2 hrs after sham RMs (p = .18). This is equivalent to a difference in PEEP of 0.36 cm H_2O or a difference in F_{IO_2} of 0.018. Adjusted F_{IO_2}/PEEP-step at 2 hrs had been decreased more after RMs than after sham RMs by similar amounts in patients with pulmonary (pneumonia and aspiration) and with extrapulmonary causes of ALI/ARDS (0.19 and 0.18 steps, respectively). The interaction between treatment effect (RM vs. sham RM) and cause of ALI/ARDS (pulmonary vs. extrapulmonary) was not significant (p = .98). Crs increased significantly more at 240 mins after sham RMs than after RMs (Fig. 3). Changes in compliance at other times were not significantly different.

Safety of RMs. Decreases in systolic blood pressure were significantly greater after RMs than after sham RMs (Table 4). Decreases in SpO_2 during the first 10

Table 2. Characteristics of Patients

Age, yrs	53 ± 17
F_{IO_2}	0.39 ± 0.10
PEEP, cm H_2O	13.8 ± 3.0
Respiratory system compliance, mL/cm H_2O	35.4 ± 19.4
Tidal volume, mL/kg predicted body weight	6.0 ± 0.8
Plateau pressure, 0.5-sec pause	26.4 ± 4.7
Causes of ALI/ARDS, %	
Pneumonia	43
Sepsis	18
Aspiration	22
Trauma	7
Other causes	10

PEEP, positive end-expiratory pressure; ALI/ARDS; acute lung injury and acute respiratory distress syndrome. Values are mean ± SD immediately before all recruitment maneuvers and sham recruitment maneuvers.

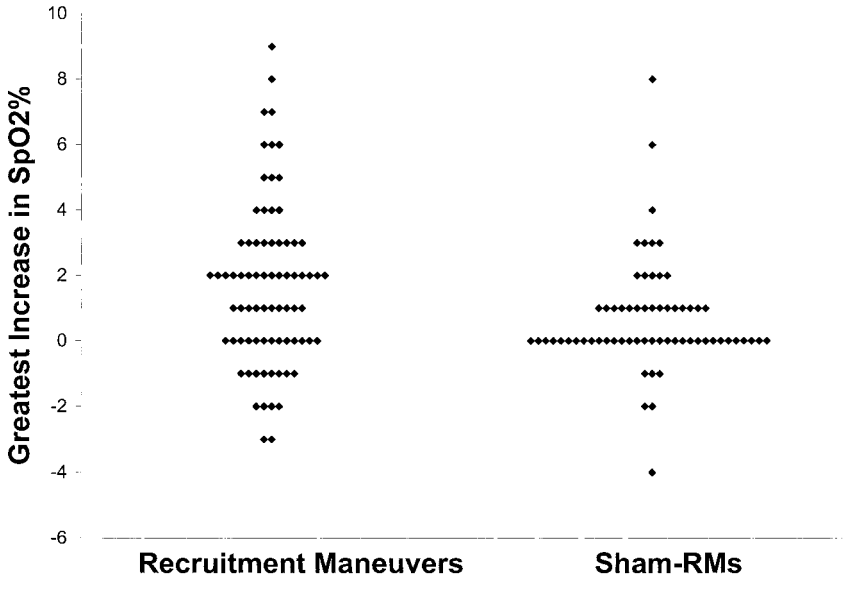

Figure 1. Greatest increments in oxyhemoglobin saturation within 10 mins after recruitment maneuvers (*RMs, left)* and sham RMs. *SpO_2,* oxyhemoglobin saturation measured by pulse oximetry.

Table 3. Adjusted FIO_2/Positive End-Expiratory Pressure-Step Changes 2 hrs After Recruitment Maneuvers (RMs) and Sham RMs

Step Changes	After RMs	After Sham RMs
−4	2	0
−3	0	1
−2	5	4
−1	18	12
0	41	49
+1	6	8
+2	1	1
Totals		
Improved	25	17
Unchanged	41	49
Worse	7	9

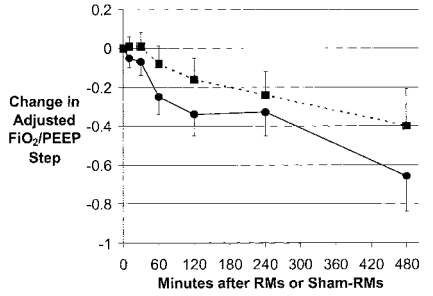

Figure 2. Effects of recruitment maneuvers (*RMs*; *circles*) and sham RMs (*squares*) on adjusted FIO_2/positive end-expiratory pressure-step. None of the differences between the changes that occurred after RMs and sham RMs were significant. *PEEP*, positive end-expiratory pressure.

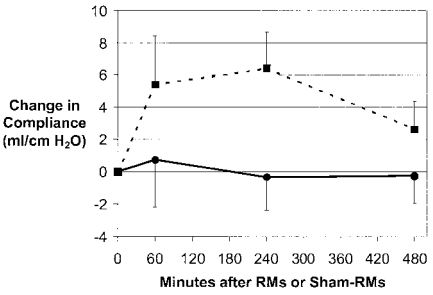

Figure 3. Effects of recruitment maneuvers (*circles*) and sham recruitment maneuvers (*RMs*; *squares*) on respiratory system compliance. The changes in respiratory system compliance at 240 mins were significantly different ($p = .04$).

mins were also significantly greater after RMs than after sham RMs (Table 4). RMs were terminated early in three instances because of hypotension or low SpO_2. There were no apparent sequelae from these events, which were transient and self-limited. New barotrauma was evident on the first chest radiographs after one RM and after one sham RM.

Table 4. Recruitment Maneuver Safety: Changes Within 10 mins of Initiating Recruitment Maneuvers (RMs) and Sham Recruitment Maneuvers

	RM	Sham RM	*p*
Lowest SBP, mm Hg	−9.4 ± 1.1	−3.1 ± 1.1	<.01
Lowest DBP, mm Hg	−1.9 ± 1.2	−0.8 ± 1.2	.33
Lowest HR, beats/min	−3.7 ± 0.8	−2.9 ± 0.9	.52
Highest HR, beats/min	5.1 ± 1.1	2.5 ± 1.1	.11
Lowest Spo_2, %	−2.3 ± 0.3	−0.9 ± 0.3	<.01

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; Spo_2, oxyhemoglobin saturation measured by pulse oximetry. Values shown are least squares mean ± SEM from repeated-measures analysis of covariance changes from values immediately before RMs or sham RMs. *p* values shown are for the comparison of the changes that occurred within 10 mins after initiating recruitment maneuvers vs. the changes that occurred after sham recruitment maneuvers.

DISCUSSION

This was a multiple-center, randomized, crossover study to assess effects of RMs in ALI/ARDS patients receiving a lung protective mechanical ventilation strategy that combined smaller tidal volumes and higher PEEP levels than are used in traditional ventilation approaches. Systolic blood pressure and SpO_2 decreased significantly after RMs, but these effects were self-limited and without apparent long-term sequelae. SpO_2 increased significantly more within 10 mins after RMs than after sham RMs. The initial SpO_2 responses were highly variable (Figs. 1). In some patients there were substantial increases in SpO_2, whereas in others there was little or no positive response during the first 10 mins. Subsequent data showed small increases in mean SpO_2 only at 1 hr after RMs but not at other time points. Effects of RMs on requirements for FIO_2/PEEP-step were not significant at any time point, and respiratory system compliance did not increase more after RMs than after sham RMs.

Critique. We compared changes in SpO_2 within the first 10 mins after RMs or sham RMs to estimate immediate effects of RMs. Changes in SpO_2 do not directly reflect lung recruitment because SpO_2 may be affected by changes in other variables such as cardiac output. However, cardiac output did not change substantially during RMs in a recent study, and changes in venous admixture varied inversely with changes in PaO_2/FIO_2 (19). Since shunt from atelectasis and alveolar flooding are the main causes of elevated venous admixture in ALI/ARDS (20), RM-induced recruitment is the most likely cause of the improved venous admixture and oxygenation observed in this and the previous studies. Moreover, hemodynamic effects were unlikely to be present at 10 mins to 2 hrs after RMs, when the variables of interest were measured.

We used changes in Crs measured during tidal ventilation to estimate RM effects on lung compliance. Changes in Crs also could be caused by changes in thoracic compliance. Moreover, changes in tidal Crs could vary inversely with lung recruitment (17, 21). However, there were no changes in Crs after RMs. The apparent increase in Crs after sham RMs is unexplained.

The study was originally designed to include 30 patients, each with two RMs and two sham RMs. This would allow analysis using standard crossover design methods. However, many patients had incomplete information (fewer than four of the planned RMs and sham RMs). Therefore, we used a different method of analysis that incorporated the data from all patients who had at least one trial. Before the final analysis, we conducted simulations to ensure that this different method would have sufficient power. The method used is not biased by the missing data if the missing data points are random (22). This allows a dependency of the probability of missing a trial on the observed data from prior trials but not on the data that would have been observed in missed trials. This assumption is justified because the reasons that most patients missed trials were that they were weaning or were hypotensive.

There are several possible explanations why RMs did not cause greater and more sustained improvements in SpO_2 and FIO_2/PEEP-step in this study. First, the higher PEEP levels used in these patients may have achieved greater levels of recruitment than are usually achieved with more traditional PEEP levels (18). This could have reduced the potential for

RM-induced improvements in gas exchange, as it did in animal models of ALI (16). Greater RM effects on arterial oxygenation occurred in previous studies when ALI/ARDS patients were ventilated with lower PEEP levels (13, 17, 23, 24). In one of these studies, there were significant effects on arterial oxygenation and recruited volume in responders within 2 mins after RMs (CPAP of 40 cm H_2O for 40 secs), but these effects had mostly reversed within 20 mins after the RMs. When ALI/ARDS patients were ventilated with PEEP set above the lower inflection point on individual pressure-volume curves, RM effects on arterial oxygenation were not significant 15 mins after the maneuvers (19). Second, all patients in this study were supported with a volume and pressure-limited mechanical ventilation strategy to reduce ventilation-associated lung injury from overdistention (18). There is a greater tendency for atelectasis to occur with this approach (25–27). Effects of RMs might have lasted longer if we used higher tidal volumes with higher inspiratory pressures between RMs. Third, the RM pressures used in this study were not as high as in some other studies of RMs in ALI/ARDS patients (17, 28) and in animal models of ALI (15, 29). Our RM pressures were chosen to assess safety and potential value of RMs conducted in a manner that was similar to the technique used in a previous trial of a lung protective ventilation approach (10). The mean difference between plateau pressures during tidal ventilation and the RM pressures used in this study was approximately 9 cm H_2O. In approximately 15% of patients, the difference was <5 cm H_2O. Higher RM pressures may have greater effects on gas exchange. However, RMs with inspiratory pressures of 50 cm H_2O did not have sustained effects on oxygenation when patients were ventilated with higher PEEP (19). Fourth, favorable effects of RMs on gas exchange might have been lost quickly in some patients if they were not relaxed after the RMs. Variable amounts of motor activity could account for some of the variability in responses to RMs in this study. In a previous study, significant effects of RMs with pressures $\sim$33–35 cm H_2O persisted for $\geq$1 hr in ALI/ARDS patients receiving neuromuscular blocking agents during and after the RMs (23). Fifth, favorable effects of RMs at time points after the first 10 mins could have been reversed in some patients if PEEP was decreased after RM-induced improvements in arterial oxygenation, according to the study protocol.

Most patients in this study had ALI/ARDS from pneumonia or aspiration. There may be greater potential for lung recruitment in sepsis- or trauma-induced ALI/ARDS (30). However, significant RM effects on oxygenation at 1 hr were observed in a different study in which 16 of 20 patients had pneumonia or aspiration (23) (when lower PEEP levels and neuromuscular blockade were used). In our study, effects of RMs on SpO_2 and on subsequent requirements for oxygenation support were similar in patients with ALI/ARDS from pulmonary and extrapulmonary causes. Nonetheless, inclusion of many patients with relatively low recruitment potential may have obscured RM effects in other patients. It is possible that greater and more sustained effects of RMs would be apparent in patients with indirect lung injury if the study had larger subsets for comparison.

RM pressures were sustained for only 30 secs in this study, whereas they were sustained for $\sim$40 secs in a previous study in ALI/ARDS patients (10). Times required for airway opening may be highly variable, but most airways open within several seconds when their transmural pressures are raised to sufficiently high levels (31, 32). Although it seems unlikely that RMs of 40 secs will be substantially more effective than RMs of 30 secs duration, we cannot rule out this possibility.

There are several alternative techniques for conducting RMs. One technique involves a series of higher tidal volumes and end-inspiratory airway pressures over several seconds (15). This approach may be more effective for recruitment and may have fewer adverse hemodynamic effects than a single sustained increase in airway pressure. However, controlled clinical evaluations are needed to demonstrate the value of this or other RM approaches.

Although RM effects appear to have been sustained in animal models of ALI (14, 15), the duration of effect may be shorter in ALI/ARDS patients because of differences in character and volume of respiratory secretions, bronchial smooth muscle tone, and surface tension properties. Moreover, neuromuscular activity in some ALI/ARDS patients, especially those who cough frequently, may rapidly reverse RM effects. In a recent study in ALI/ARDS patients, frequent sighs (three large mechanical ventilation breaths per minute) caused improvements in arterial oxygenation and respiratory system compliance, but these effects disappeared within 30 mins when the sighs were discontinued (33). This suggests that the duration of RM-induced recruitment is brief. Greater and more sustained effects are likely with higher RM pressures and with improved RM techniques. Also, effects of RMs may be greater in patients in whom there is greater potential for recruitment. More information regarding efficacy and safety is needed from clinical studies before RMs can be recommended as part of standard ventilator management in ALI/ARDS patients.

In acute lung injury/acute respiratory distress syndrome patients receiving mechanical ventilation with low tidal volumes and high positive end-expiratory pressure, short-term effects of recruitment maneuvers as conducted in this study are variable.

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