Complications From Recruitment Maneuvers in Patients With Acute Lung Injury: Secondary Analysis From the Lung Open Ventilation Study

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BACKGROUND: There are limited data on the safety and efficacy of recruitment maneuvers (RMs) in acute lung injury (ALI) patients. OBJECTIVE: To evaluate the frequency, timing, and risk factors for complications from RMs in adult ALI patients. METHODS: Secondary analysis of data from a randomized controlled trial of a lung open ventilation strategy that included sustained inflation RMs. RESULTS: Respiratory (eg, desaturation) and cardiovascular (eg, hypotension) complications from recruitment maneuvers were common (22% of all patients receiving RMs), and the majority occurred within 7 days of enrollment. New air leak through an existing chest tube was uncommon (< 5%). As compared to patients receiving 1 or fewer RMs, the number of RMs received was associated with increased risk in both younger (age ≤ 56 y) and older patients (age > 56 y): 2 RMs odds ratio [OR] 6.92 (95% CI 1.70–28.2), ≥ 3 RMs OR 15.4 (95% CI 4.77–49.6), and 2 RMs OR 5.43 (95% CI 1.76–16.8), ≥ 3 RMs OR 4.93 (95% CI 1.78–13.7), respectively. Patients with extrapulmonary ALI had decreased odds of developing complications (OR 0.42, 95% CI 0.22–0.80). CONCLUSIONS: Complications in adult ALI patients receiving RMs were common, but serious complications (eg, new air leak through an existing chest tube) were infrequent. There is a significant association between the number of RMs received and complications, even after controlling for illness severity and duration. Given their uncertain benefit in ALI patients, and the potential for complications with repeated application, the routine use of sustained inflation RMs is not justified. *Key words: critical care; lung recruitment; recruitment maneuvers; respiration; artificial; respiratory distress syndrome; adult.* [Respir Care 2012;57(11):1842–1849. © 2012 Daedalus Enterprises]

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This research was partly supported by a Fellowship Award from the Canadian Institutes of Health Research; Pathway to Independence Award K99-HL096955 from the National Heart, Lung, and Blood Institute; and a Clinician-Scientist Award from Johns Hopkins University. None of the funding organizations or sponsors had any role in the preparation, review, or approval of the paper. The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.01684

Introduction

Despite ongoing research into novel therapies, mortality from acute lung injury (ALI) remains high, ranging from 32–48% in recent studies.[1] The only intervention found to reduce mortality from ALI is a pressure- and volume-limited approach to mechanical ventilation[2] in ALI, and in ARDS patients possibly early short-duration neuromuscular blockade,[3] prone positioning,[4] and relatively high levels of PEEP.[5]

To improve lung volumes and oxygenation, recruitment maneuvers (RMs) may be an important component of a lung-protective ventilation strategy. Recruitment refers to the dynamic process of reopening collapsed lung units by transiently increasing transpulmonary pressure, leading to increased end-expiratory lung volume.[6] Increases in end-expiratory lung volume enlarge the surface area available for gas exchange and may attenuate ventilator-associated lung injury by reducing the repetitive opening and closing of unstable lung units.[6,7] Moreover, by increasing the number of available aerated lung units, recruitment may also reduce ventilator-associated lung injury by reducing the distention of individual aerated alveolar units for a given tidal volume.[8,9]

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In spite of their potential benefit, clinical studies of RMs in ALI have yielded variable results regarding their safety and efficacy.[10] Though transient hypotension and oxygen desaturation are the most common complications reported from RMs, serious side effects, such as barotrauma and arrhythmias, may also occur.[11-13] The duration and mechanism of pulmonary injury, whether direct or indirect, may be important determinants of alveolar recruitment, associated physiologic responses, and risk for complications.[14,15] In spite of the potential for complications from RMs, there is limited information regarding the safety of RMs in adults with ALI. To study this further, we examined the complications from sustained inflation RMs in patients with ALI enrolled in the multicenter Lung Open Ventilation Study.[12] Specifically, our objectives were to evaluate the frequency and timing of complications from RMs, compare complications among patients with pulmonary versus extrapulmonary ALI, and examine risk factors in patients who experienced complications from RMs.

QUICK LOOK

Current knowledge

Recruitment maneuvers are used to improve oxygenation in patients with acute lung injury. However, the literature has yielded variable results regarding safety and efficacy of these maneuvers.

What this paper contributes to our knowledge

Complications associated with recruitment maneuvers are common, but serious complications are rare. Complications are more frequent with repetitive maneuvers. Patients with extrapulmonary lung injury are less likely to experience a complication during a recruitment maneuver.

Methods

Study Population and Design

The details of the original study have been previously described.[12] In brief, patients with ALI and a P_{aO_2}/F_{IO_2} ≤ 250 mm Hg during invasive mechanical ventilation were included in the study. Patients were excluded if they had evidence of left atrial hypertension as the primary cause of respiratory failure, anticipated duration of mechanical ventilation < 48 hours, inability to wean from experimental strategies (eg, inhaled nitric oxide), severe chronic respiratory disease, neuromuscular disease that would prolong mechanical ventilation, intracranial hypertension, morbid obesity, pregnancy, lack of commitment to life support, premorbid conditions with an expected 6-month mortality risk exceeding 50%, greater than 48 hours of eligibility, and participation in a confounding trial. At study initiation, all patients randomized to the experimental strategy (n = 475) received an RM, applying continuous positive airway pressure of 40 cm H_2O for 40 seconds, with F_{IO_2} of 1.0. Patients in this group could then subsequently receive up to 4 RMs daily, following ventilator disconnects. RMs were withheld when mean arterial pressure was < 60 mm Hg, F_{IO_2} was ≤ 0.4, and for untreated (eg, subcutaneous emphysema) or unresolved barotrauma (eg, active air leak through existing chest tube).

Outcome

The primary outcome was complications during RMs. These were classified as respiratory (ie, desaturation to an S_{pO_2} < 85%), cardiovascular (ie, heart rate < 60 or > 140 beats/min, mean arterial pressure < 60 mm Hg, new arrhythmia), or new air leak through an existing chest tube. The duration of these events was not explicitly recorded.

Risk Factors

Potential risk factors studied included: patient demographics (ie, age, sex); baseline severity of illness (ie, Acute Physiology and Chronic Health Evaluation [APACHE] II score, non-pulmonary multiple organ dysfunction score[16]) and severity of oxygenation failure in ALI (ie, oxygenation index = [mean airway pressure × F_{IO_2} × 100]/P_{aO_2}); ventilator settings (ie, applied PEEP, plateau pressure); physiologic parameters (ie, P_{aO_2}/F_{IO_2}, minute ventilation); and clinical factors. The contributing causes of ALI were recorded at study baseline. We further classified patients as having primarily pulmonary (eg, pneumonia) or extrapulmonary (eg, nonpulmonary sepsis) ALI. For the purpose of this analysis, we classified patients with mixed pulmonary and extrapulmonary causes as having pulmonary ALI. As a sensitivity analysis, we re-categorized all mixed causes of ALI as extrapulmonary in random subsets of 10% and performed the regression analyses explained below to test the robustness of our assumption.

Biostatistical Methods

We report descriptive statistics using median and interquartile range (IQR) for continuous data, and proportions for categorical data, and performed formal comparisons using Wilcoxon rank-sum and chi-square tests, respectively. We modeled risk factors based on prespecified thresholds that are clinically relevant or previously reported. In the absence of such information, we derived thresholds from a locally weighted scatter plot smoother.[17,18] Age was dichotomized at its median value. We classified patients as having 0–1, 2, or at least 3 RMs. To identify potential risk factors associated with complications from RMs, we conducted univariable logistic regression analyses. Univariables achieving significance at $P < .20$ were then included in a multivariable logistic regression analysis. We assessed for linear relationships between continuous risk factors and the log odds of complications from RMs using graphical methods. Two patients with some missing data were excluded from all analyses. To test the robustness of our findings, we performed a second sensitivity analysis using a composite outcome of complications from RMs or death in the ICU in a separate multivariable model. Multicollinearity, evaluated using variance inflation factors,[17] was not detected among any pairs of covariates included in the multivariable models. We tested for goodness of fit of final logistic regression models using the Hosmer-Lemeshow test.[19] All analyses were performed with statistics software (Stata 11.0, StataCorp, College Station, Texas).

Results

Patient Characteristics

Table 1 summarizes the baseline characteristics of the study patients. Of the 475 patients assigned to the experimental strategy, 366 (77%) received at least 1 RM after study initiation. In the remaining 109 (23%) patients who did not receive RMs after randomization, 15 (3%) did not meet the criteria for an RM, and 94 (20%) had a contraindication. Of those receiving RMs, 81(22%) patients developed at least 1 complication during an RM. Apart from a greater proportion of extrapulmonary ALI in the group that did not develop complications from RMs (41% vs 24%, $P = .006$), there were no significant differences in any baseline characteristics between the patients who did and did not develop complications from RMs.

Frequency and Timing of Recruitment Maneuvers and Subsequent Complications

A total of 1,351 RMs followed 1,596 ventilator disconnects. A significantly greater number of RMs were performed in patients who developed complications from RMs, as compared to those who did not (4 [2–7] vs 2 [1–3], $P < .001$). There was no significant difference in the timing of the first RM among patients with and without complications (day 1 [1–1] vs day 1 [1–1], $P = .75$).

Table 2 summarizes the frequency and timing of complications from RMs. Desaturation and hypotension were the most common complications, while new arrhythmias and new air leak through an existing chest tube were relatively infrequent. Most complications (68%) occurred early in the course of disease (ie, within 7 d of study initiation). There was a nonsignificant increase in both ICU mortality (41% vs 33%, $P = .21$) and hospital mortality (47% vs 40%, $P = .25$) in patients who developed complications from RMs, but no difference in the rates of unassisted breathing (85% vs 85%, $P = .98$), as compared to those who did not develop complications from RMs.

There was a significantly greater proportion of complications among patients with pulmonary versus extrapulmonary ALI (26% vs 14%, $P = .006$), even when we excluded patients with mixed causes of ALI from the analysis (29% vs 18%, $P = .02$). Other outcomes, including ICU and hospital mortality and rates of unassisted breathing, were not significantly different by ALI type.

Risk Factors for Complications From Recruitment Maneuvers

Risk factors for complications from RMs are shown in Table 3. On multivariable analysis, the number of RMs received was significantly associated with increased odds of developing a complication from RMs. Moreover, there was a dose-response effect among younger (ie, age ≤ 56 y) patients, with a greater risk of complications associated with a greater number of RMs received. With 0–1 RM as the reference, for 2 RMs the odds ratio (OR) was 6.92

Table 1. Baseline Characteristics

Characteristic	Complications From RM ($n = 81$)	No Complications From RM ($n = 285$)	P*	Overall LOVS Group† ($n = 475$)
Age, y	56 (41–71)	54 (41–67)	.30	55 (42–67)
Female sex, no. (%)	25 (31)	117 (41)	.13	193 (41)
Body mass index, kg/m^2	27 (24–31)	27 (25–33)	.36	27 (24–33)
Hospital stay, d	3 (1–5)	3 (2–6)	.18	3 (1–6)
Mechanical ventilation, d	2 (1–2)	2 (1–3)	.29	2 (1–3)
APACHE II score	25 (20–29)	26 (20–31)	.19	25 (19–30)
Nonpulmonary MOD score	5 (4–8)	7 (4–9)	.09	6 (4–9)
P_{aO_2}/F_{IO_2}, mm Hg	100 (76–125)	104 (78–148)	.14	108 (80–149)
$P_{aO_2}/F_{IO_2} < 200$ mm Hg, no. (%)	77 (95)	271 (95)	.36	451 (95)
Oxygenation index	13 (10–20)	12 (9–18)	.24	12 (9–17)
Set PEEP, cm H_2O	10 (10–14)	12 (10–14)	.13	12 (10–14)
Plateau pressure, cm H_2O	30 (28–34)	30 (27–35)	.77	30 (27–34)
Tidal volume, mL/kg PBW	8.3 (7.1–9.8)	8.2 (6.8–9.8)	.55	8.2 (6.8–9.8)
Minute ventilation, L/min	11.5 (9.0–14.0)	11.2 (9.0–13.9)	.48	11.1 (8.9–13.5)
Total respiratory rate, breaths/min	22 (17–27)	22 (17–26)	.90	22 (17–26)
Barotrauma, no. (%)	1 (1)	14 (5)	.15	17 (4)
Cause of ALI, no. (%)				
Sepsis	29 (36)	139 (49)	.06	248 (49)
Pneumonia‡	42 (52)	114 (40)	.04	233 (46)
Gastric aspiration	18 (22)	48 (17)	.23	106 (21)
Multiple transfusions	5 (6)	28 (10)	.34	40 (8)
Prolonged shock	8 (10)	21 (7)	.42	24 (5)
Pulmonary contusion	5 (6)	9 (3)	.20	26 (5)
Multiple major fractures	4 (5)	13 (5)	.85	27 (5)
Acute pancreatitis	1 (1)	10 (4)	.30	27 (5)
Drug overdose	3 (4)	10 (4)	.90	19 (4)
Pneumocystis jiroveci	1 (1)	8 (3)	.44	15 (3)
Burn injury	4 (5)	9 (3)	.42	8 (2)
Inhalation injury	2 (2)	3 (1)	.32	5 (1)
Other	1 (1)	9 (3)	.36	11 (2)
Extrapulmonary ALI, no. (%)	19 (23)	117 (41)	.006	176 (37)

Values are median (IQR) unless otherwise stated.
* Using Wilcoxon rank-sum test for continuous variables and chi-square test for proportions.
† Not all patients in the Lung Open Ventilation Study (LOVS) group received recruitment maneuvers (RMs) following randomization.
‡ Excluding *Pneumocystis jiroveci* pneumonia.
APACHE = Acute Physiology and Chronic Health Evaluation
MOD = Multiple Organ Dysfunction
PBW = predicted body weight
ALI = acute lung injury

(95% CI 1.70–28.2), and for ≥ 3 RMs the OR was 15.4 (95% CI 4.77–49.6). However, this dose-response effect was somewhat attenuated among older (ie, age > 56 y) patients. With 0–1 RM as the reference, for 2 RMs the OR was 5.43 (95% CI 1.76–16.8), and for ≥ 3 RMs the OR was 4.93 (95% CI 1.78–13.7). Patients with extrapulmonary ALI (OR 0.42, 95% CI 0.22–0.80) and/or lower baseline set PEEP (OR 0.89, 95% CI 0.81–0.98) had significantly decreased odds of complications from RMs. When patients with mixed causes of ALI (pulmonary and extrapulmonary) were excluded from the analyses, patients with extrapulmonary ALI had nonsignificant decreased odds of complications from RMs (OR 0.61, 95% CI 0.34–1.12).

In a sensitivity analysis using a multivariable model with a composite outcome of complications from RMs or ICU mortality (Table 4), there was a significant association between the number of RMs received and the risk of death or complications. With 0–1 RM as the reference, for 2 RMs the OR was 2.12 (95% CI 1.13–3.98), and for ≥ 3 RMs the OR was 1.58 (95% CI 1.00–2.49). Older age (> 56 y) and higher APACHE II score at baseline were associated with greater odds of the composite outcome, while female sex was associated with decreased odds of death or complications. Extrapulmonary ALI and baseline set PEEP were no longer significantly associated with the outcome.

Table 2. Frequency and Timing of Complications From Recruitment Maneuvers

Complication	Frequency, no. (%) (n = 366)*	Timing, no. (%) (≤ 7 d)†
Respiratory		
Desaturation (S_{aO_2} < 85%)	36 (10)	32 (64)
Cardiovascular		
Heart rate < 60 or > 140 beats/min	19 (5)	10 (45)
Hypotension (mean arterial pressure < 60 mm Hg)	40 (11)	37 (71)
New arrhythmia	3 (1)	3 (75)
New air leak through an existing chest tube	4 (1)	3 (75)

* Frequency of complications from recruitment maneuvers are reported per patient. Patients may have experienced more than one complication.
† Timing of complications from recruitment maneuvers are reported per episode. Percentages (in parentheses) represent proportion of total complications that occurred within 7 days of recruitment maneuvers. Patient may have experienced more than one complication per episode.

Table 3. Risk Factors for Complications From Recruitment Maneuvers

Risk Factor	Odds Ratio (95% CI)*	
Age		
≤ 56 y	Reference	
> 56 y	2.19 (0.56–8.54)	
Female sex	0.67 (0.38–1.23)	
Hospital stay prior to study enrollment (per day)	0.95 (0.90–1.00)	
Baseline APACHE II score	0.97 (0.92–1.02)	
Baseline nonpulmonary MOD score	1.01 (0.90–1.14)	
Baseline P_{aO_2}/F_{IO_2} (per mm Hg)	1.00 (0.99–1.00)	
Extrapulmonary acute lung injury	0.42 (0.22–0.80)	
Baseline set PEEP	0.89 (0.81–0.98)	
Number of recruitment maneuvers	Age ≤ 56 y	Age > 56 y
0–1	Reference	Reference
2	6.92 (1.70–28.2)	5.43 (1.76–16.8)
≥ 3	15.4 (4.77–49.6)	4.93 (1.78–13.7)
ICU stay (per day)	1.00 (0.99–1.02)	

* Hosmer-Lemeshow goodness of fit test (P = .83).
APACHE = Acute Physiology and Chronic Health Evaluation
MOD = Multiple Organ Dysfunction

Table 4. Risk Factors for Complications or ICU Mortality From Recruitment Maneuvers

Risk Factor	Odds Ratio (95% CI)*
Age	
≤ 56 y	Reference
> 56 y	2.11 (1.40–3.20)
Female	0.65 (0.43–0.97)
Hospital stay prior to study enrollment (per day)	1.01 (0.99–1.03)
Baseline APACHE II score	1.06 (1.02–1.10)
Baseline MOD score	1.04 (0.96–1.13)
Baseline P_{aO_2}/F_{IO_2} (per mm Hg)	0.99 (0.99–1.00)
Extrapulmonary acute lung injury	0.67 (0.44–1.04)
Baseline set PEEP	0.97 (0.91–1.03)
Number of recruitment maneuvers	
0–1	Reference
2	2.12 (1.13–3.98)
≥ 3	1.58 (1.00–2.49)
ICU stay (per day)	1.00 (0.99–1.01)

* Hosmer-Lemeshow goodness of fit test (P = .18).
APACHE = Acute Physiology and Chronic Health Evaluation
MOD = Multiple Organ Dysfunction

Discussion

This study of over 1,300 RMs performed on 366 patients in a randomized controlled trial of ventilation strategies for adult patients with ALI represents the largest clinical study of RMs to date. Complications from RMs were common, with desaturation and hypotension being the most frequent. Patients with complications from RMs received significantly more RMs than those without complications, and the majority of complications from RMs occurred early in the course of the study. A greater number of RMs received was a significant risk factor for increased odds of complications, although this association may be confounded by the severity and duration of ALI. Interestingly, patients with extrapulmonary ALI and/or lower baseline set PEEP (a marker for less severe lung injury), had significantly decreased odds of complications from RMs. In the subsequent analysis of risk factors using the composite outcome of complications from RMs or death in the ICU, the number of RMs received was still significantly associated with the outcome, but the magnitude of the association was attenuated.

In a recent systematic review of RMs in adult patients with ALI, we found that their use was associated with significant, albeit transient, increases in oxygenation.[10] The methods of the RM (eg, sustained inflation vs incremental PEEP) may influence both the efficacy and potential for complications.[20] Furthermore, the optimal pressure, duration, and frequency of RMs have not been determined or tested in large clinical trials. Given the uncertain importance of transient oxygenation benefits derived from RMs, any important risks would be critical in decision-making around their use in ALI patients. The results of this study are consistent with the systematic review, demonstrating that certain complications (eg, desaturation and hypotension) were common during the performance of RMs, but that serious complications (eg, new arrhythmia, barotrauma) were uncommon.[10] While these results suggest that RMs are generally well tolerated, the risks and sequelae of RMs may differ substantially between patients, as even transient events may be detrimental in some critically ill patients.

A number of preclinical and human studies have suggested greater physiologic improvements and potentially fewer complications in subjects with extrapulmonary ALI,[20-26] although there have been conflicting reports.[15,27-32] There may be many reasons for the observed variations in response, including differences in study populations, RM techniques, ventilator management, and definitions of response. The underlying pathophysiologic explanation may be the differences in the recruitability of the injured lung; specifically, there may be marginal lung recruitment from an RM when the underlying pathology is primarily focal consolidation (ie, pulmonary ALI from pneumonia), whereas there may be marked recruitment when the prevalent underlying pathology is diffuse interstitial edema and atelectasis (ie, extrapulmonary ALI from abdominal sepsis).[23,33] Indeed, Grasso and colleagues reported a significant decrease in cardiac output and mean arterial pressure from RMs in nonresponders (ie, poor recruitability) whereas hemodynamics were not significantly altered in responders.[31] Lower chest wall compliance in nonresponders leads to greater transmission of higher airway pressures during RMs to pleural pressure, resulting in greater impairment of venous return, cardiac filling, and cardiac output.[31] Moreover, when RMs do not result in significant aeration of atelectatic lung units, they may worsen oxygenation by causing regional alveolar overdistention, resulting in an increased amount of pulmonary blood flow that is shunted to non-aerated regions.[34,35] Thus, our data are consistent with the hypothesis that patients with pulmonary ALI may have been less responsive to recruitment, perhaps due to primarily less diffuse disease, and thus were at greater risk of developing complications from RMs.

We found that the majority of complications from RMs occurred within 7 days of study enrollment. This is contrary to our hypothesis that complications from RMs may be more apparent late in the course of illness when the injured lung transitions from an inflammatory to fibroproliferative phase, and may become less recruitable. A possible explanation is that since a large proportion of our patients had (pulmonary or nonpulmonary) sepsis, the early application of RMs in patients who had not achieved durable clinical stability (eg, suboptimal volume/hemodynamic status) may have contributed to the occurrence of cardiovascular complications.[36] There was no explicit protocol for fluid management in the randomized trial, but patients who were hypotensive (ie, mean arterial pressure < 60 mm Hg) did not receive an RM. Finally, the majority of RMs were performed within 7 days of study enrollment, and thus may have coincided with the more frequent occurrence of early complications.

We found that the risk of complications was increased with increased number of RMs. The incremental risk associated with each RM, even if small, should accrue as more RMs are performed. However, in a study of a recruitment strategy that utilized a stepwise approach with increasing airway pressure to maximize recruitment (essentially a number of RMs performed in series), nearly all patients completed the recruitment protocol (approximately 4–5 RMs) with only transient hypercapnia and hemodynamic effects.[32] Importantly, this study also demonstrated a bimodal distribution of threshold opening pressures, with more than half the patients requiring airway pressures > 40 cm H_2O to obtain maximal recruitment. This may be crucial when using a strategy with static inflation pressures: once lung units with threshold opening pressures below the applied pressure have been recruited, any subsequent RMs at the same airway pressure will presumably not lead to further benefits, but only the potential for adverse events through overdistention of more compliant lung units (eg, barotrauma) and/or increased intrathoracic pressure (eg, hypotension).

Our study has some potential limitations. First, the nonexperimental nature of our study does not allow us to draw causal inferences between risk factors and the subsequent development of complications from RMs. It is possible that sicker patients have unmeasured, or incompletely measured, factors that predispose them to receiving more RMs, as well as a greater propensity to develop post-RM complications (eg, lower respiratory system compliance). Although baseline characteristics, including a number of different measures of illness severity, were similar at baseline between patients who did and did not have complications from RMs, their lung injury may have evolved differently over time or independently from RMs, confounding the causal association between the number of RMs and the risk of subsequent complications. Thus, the finding of any associations between RMs and subsequent complications is hypothesis-generating, and requires further assessment. Similarly, we were unable to evaluate any causal association between RMs, their complications, and patient-important outcomes such as mortality.

Second, the present study employed only a single type of RM (ie, sustained inflation). Other types of RMs (eg, incremental increases in PEEP, extended/periodic sighs) may be associated with different risks for subsequent complications. Finally, since an early death as a consequence of RMs may prevent the observation of complications, we used a composite end point that included both ICU mortality and complications from RMs. However, this type of composite end point is problematic since equal weights are assigned to both death and complications.[37] While more sophisticated and robust analytical techniques may be employed to account for competing risks,[38,39] we elected to use a relatively simple technique to assess whether our "crude" association analysis was sensitive to the inclusion (or exclusion) of death within the context of the hypothesis-generating nature of our analysis.

Conclusions

In conclusion, while complications in adult patients with ALI receiving RMs were relatively common, serious adverse events were infrequent. We found a significant association between the number of RMs received and complications, although these findings require confirmation in future clinical trials. Consistent with prior mechanistic studies of alveolar recruitment in different models of ALI, patients with extrapulmonary ALI may be less likely to develop complications from RMs. Given their uncertain benefit in ALI patients, and the potential for complications with repeated application, we cannot recommend routine use of sustained inflation RMs at this time. However, these data can provide clinicians with a risk assessment of the potential for complications when deciding whether or not to perform an RM. For instance, RMs may be considered in patients with ALI (particularly those from an extrapulmonary etiology) with life-threatening refractory hypoxemia on an individualized basis. Future studies should compare the safety and efficacy of other types of RMs with interventions such as prone positioning and/or high-frequency oscillation, which may improve outcomes in patients with ARDS.

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