Efficacy and safety of lung recruitment in pediatric patients with acute lung injury

Juan P. Boriosi, MD; Anil Sapru, MD; James H. Hanson, MD; Jeanette Asselin, MS, RT; Ginny Gildengorin, PhD; Vivienne Newman, MD, FCP (SA), FAAP; Katie Sabato, MS, RT; Heidi R. Flori, MD

Objective: **To assess the safety and efficacy of a recruitment maneuver, the Open Lung Tool, in pediatric patients with acute lung injury and acute respiratory distress syndrome.**

Design: **Prospective cohort study using a repeated-measures design.**

Setting: **Pediatric intensive care unit at an urban tertiary children's hospital.**

Patients: **Twenty-one ventilated pediatric patients with acute lung injury.**

Intervention: **Recruitment maneuver using incremental positive end-expiratory pressure.**

Measurements and Main Results: **The ratio of partial pressure of arterial oxygen over fraction of inspired oxygen (Pao_2/Fio_2 ratio) increased 53% immediately after the recruitment maneuver. The median Pao_2/Fio_2 ratio increased from 111 (interquartile range, 73–266) prerecruitment maneuver to 170 (interquartile range, 102–341) immediately postrecruitment maneuver ($p < .01$). Improvement in Pao_2/Fio_2 ratio persisted with an increase of 80% over the baseline at 4 hrs and 40% at 12 hrs after the recruitment maneuver. The median Pao_2/Fio_2 ratio was 200 (interquartile range, 116–257) 4 hrs postrecruitment maneuver ($p < .05$) and 156 (interquartile range, 127–236) 12 hrs postrecruitment maneuver ($p < .01$). Compared with prerecruitment maneuver, the partial pressure of arterial carbon dioxide ($Paco_2$) was significantly decreased at 4 hrs postrecruitment maneuver but not immediately after the recruitment maneuver. The median $Paco_2$ was 49 torr (interquartile range, 44–60) prerecruitment maneuver compared with 48 torr (interquartile range, 43–50) immediately postrecruitment maneuver ($p = .69$), 45 torr (interquartile range, 41–50) at 4 hrs postrecruitment maneuver ($p < .01$), and 43 torr (interquartile range, 38–51) at 12 hrs postrecruitment maneuver. Recruitment maneuvers were well tolerated except for significant increase in $Paco_2$ in three patients. There were no serious adverse events related to the recruitment maneuver.**

Conclusions: **Using the modified open lung tool recruitment maneuver, pediatric patients with acute lung injury may safely achieve improved oxygenation and ventilation with these benefits potentially lasting up to 12 hrs postrecruitment maneuver. (Pediatr Crit Care Med 2011; 12:431–436)**

Key Words: ARDS; respiratory distress syndrome; adult; ALI; acute lung injury; positive end-expiratory pressure; pulmonary gas exchange

Acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS), account for 1–4% of all pediatric intensive care unit admissions. Estimated mortality is 8–28% in most patient groups (1–3). ALI is characterized by lung alveolar collapse, decreased compliance, and hypoxemia resulting from increased intrapulmonary shunt (4). Adult studies have demonstrated that a low tidal volume strategy significantly reduces mortality in ALI (5–8).

A low tidal volume ventilation strategy is associated with progressive lung collapse. Recruitment maneuvers (RMs) can prevent lung collapse by temporarily increasing transpulmonary pressure (9). Animal studies show that RMs improve oxygenation and may attenuate derecruitment-associated lung injury (10, 11). However, the efficacy of RMs in adults and pediatrics remains controversial (9). Some studies suggest a benefit in mortality and physiological parameters such as oxygenation and dynamic respiratory system compliance (6, 12–28). Other studies suggest only a transient benefit or no benefit at all (29, 30).

Diverse methods for lung recruitment have been described in the medical literature (9). RMs can be applied by increasing volume or pressure over time. A sustained high-pressure inflation technique uses pressures from 35 to 50 cm H_2O for a duration of 20–40 secs. The intermittent sigh technique uses three consecutive sighs set at 45-cm H_2O pressures. Other methods of recruitment are intermittent increase in positive end-expiratory pressure (PEEP) or peak inspiratory pressure for brief periods. There is no consensus on the optimal performance of RMs (31).

We are not aware of any published studies of RMs in ventilated pediatric patients with ALI. The objective of this study is to assess the safety and efficacy of

From the Department of Pediatrics (JPB), University of Wisconsin, Madison, WI; the Department of Pediatrics (AS), University of California, San Francisco CA; Kaiser Permanente Group (JHH), Oakland, CA; Children's Hospital and Research Center Oakland (JA), Oakland, CA; Children's Hospital Oakland Research Institute (GG), Oakland, CA; and Pediatric Critical Care (VN), Respiratory Care (KS), and Pediatric Critical Care (HRF), Children's Hospital and Research Center Oakland, Oakland, CA.

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For information regarding this article, E-mail: jpboriosi@pediatrics.wisc.edu

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a RM, the Open Lung Tool (OLT), in pediatric patients with ALI. The OLT has been recently shown to be useful in selecting the PEEP that prevents end-expiratory alveolar collapse (optimal PEEP) in animal and adult human studies (32, 33). We hypothesized that lung recruitment may result in an improvement in oxygenation and ventilation without complications in pediatric patients with ALI.

MATERIALS AND METHODS

The Institutional Review Board at Children's Hospital and Research Center Oakland as well as the Committee on Human Research at the University of California San Francisco Medical Center approved the study. A data safety monitoring board was established to assure the continuing safety of research participants. An interim analysis was planned to ensure safety of participants after the first ten subjects have been enrolled or fewer if concerns arouse.

Consecutive patients in the pediatric intensive care unit at Children's Hospital and Research Center Oakland were prospectively screened for the study. Informed consent was obtained for all participants in the study. The inclusion criteria were: pediatric patients from 1 month to 18 yrs of age within 72 hrs of meeting the American–European Consensus Conference criteria definitions of ALI or ARDS (34). Initial exclusion criteria were: recent pulmonary resection surgery (<7 days), hemodynamic instability (defined as need for dopamine >20 μg/kg/min or epinephrine >0.1 μg/kg/min or refractory metabolic acidosis), endotracheal tube air leak >25% of inspiratory tidal volume, pneumothorax without a chest tube in place, bronchopleural fistula, increased intracranial pressure (>20 mm Hg), severe head injury, cyanotic congenital heart disease, clinician team deemed the patient unacceptable candidate, or the family did not consent. The primary outcome was improvement in oxygenation as measured by the Pao_2/Fio_2 ratio. Secondary outcomes were: improvement in ventilation as measured by $Paco_2$, air leak, hypotension (systolic blood pressure <55 mm Hg in neonates, <65 mm Hg in infants, <70 mm Hg in those 1–4 yrs, <80 mm Hg in those 5–12 yrs, and <90 mm Hg in those >12 yrs), hypoxemia (oxygen saturation <84%), bradycardia (heart rate <60 beats/min), hypercapnia ($Paco_2$ >80), or arrhythmias.

A data safety monitoring board was established *a priori* with the plan to review the safety profile of the RM after the first ten subjects have been enrolled or fewer if concerns arouse.

There was transient hypercapnia associated with the RM in three of the first five patients enrolled in the study. The study was temporary halted and the data safety monitoring board convened. As a result of the interim review we modified the protocol as follows: 1) increased ventilator rate during the RM (see subsequently); 2) exclude patients with severe acidosis (start arterial pH <7.25, see subsequently); 3) stop the RM if there was an increase in end tidal carbon dioxide; and 4) assure a tidal volume of at least 4 mL/kg during the RM. These changes were reviewed and approved by the Institutional Review Board at Children's Hospital and Research Center Oakland.

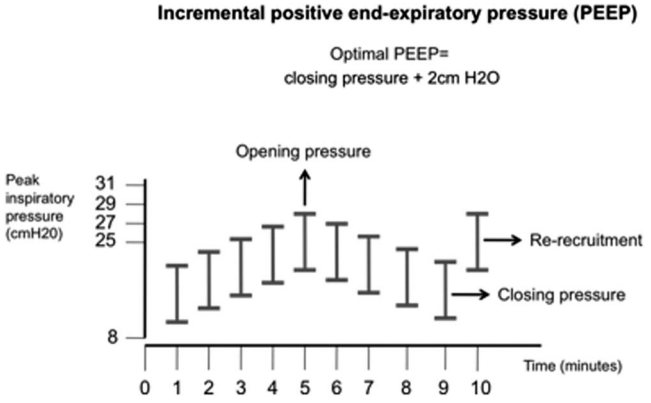

Figure 1. Study protocol. Each vertical bar represents a protocol step of 1 min duration at the end of which a data set was obtained.

Patients enrolled in the study were mechanically ventilated using the Servo-I ventilator (Servo-I; Maquet Critical Care, Solna, Sweden). The OLT software available on the Servo-I ventilator was used to display real-time dynamic compliance (Cdyn) during the application of a RM (35). The original OLT algorithm was not designed to be used in children. Therefore, we decided to use a modified OLT program during the application of our RM. We used a lung protective ventilation strategy to limit peak pressures to <35 cm H_2O and tidal volume to 6–8 mL/kg of ideal body weight. PEEP was adjusted to keep an oxygen saturation of 88–93%.

Recruitment Maneuver. A respiratory therapist with attending and/or fellow investigator supervision performed the RMs (Fig. 1). Patients were given analgesia, sedation, and muscle relaxed with vecuronium before the RM. Vital signs were continuously monitored during the maneuver. The RM was divided into two distinct parts. The first part of the maneuver consisted of finding the critical opening pressure. Critical opening pressure was defined as the PEEP yielding highest Cdyn. The RM was performed in assist-control/pressure control mode. The pressure above PEEP was set at 15 cm H_2O and Fio_2 at 100%. Inspiratory/expiratory ratio was set at 1:1. Ventilator rate stayed unchanged if the patient's respiratory rate before the maneuver was less than 30 breaths/min or ventilator rate set at 30 breaths/min if the patient's respiratory rate before starting the maneuver was >30 breaths/min. PEEP was set at 8 cm H_2O and increased by 2 cm H_2O every 1 min until a drop in Cdyn or peak pressure reached 45 cm H_2O, whichever occurred first. The second part of the RM consisted of a decremental PEEP titration to find the critical closing pressure. We defined critical closing pressure as the PEEP yielding highest Cdyn during the decremental PEEP trial. We defined optimal PEEP as the critical closing pressure plus 2 cm H_2O. Starting at critical opening pressure, we reduced PEEP by 2 cm H_2O every 1 min until a drop in Cdyn was identified. After finishing the decremental PEEP titration, we re-recruited the lung for 2 mins at opening pressure and adjusted the ventilator with the same parameters used at the beginning of the RM but changing to the optimal PEEP determined during the maneuver. We did one recruitment maneuver per patient in all the study subjects. After the RM, Fio_2 was adjusted to keep Spo_2 88–93% and optimal PEEP was set on the ventilator. The clinical team was notified of the optimal PEEP determination. Arterial blood gases were collected before, immediately after the RM, at 4 hrs, and at 12 hrs after the RM.

The RM was terminated immediately if the patient developed hypotension (systolic blood pressure <55 mm Hg in neonates, <65 mm Hg in infants, <70 mm Hg in those 1–4 yrs, <80 mm Hg in those 5–12 yrs, and <90 mm Hg in those > 2 yrs), hypoxemia (oxygen saturation <84%), bradycardia (heart rate <60 beats/min), if the first arterial blood gas after the patient was placed on initial RM settings showed severe acidosis (arterial pH <7.25), or if the end-tidal CO_2 increased significantly from the premaneuver value: >20 torr if arterial pH 7.25–7.35, >30 torr if arterial pH 7.36–7.45, and >40 torr if arterial pH >7.46. If the RM was stopped secondary to an unacceptably high increase in end-tidal CO_2, an arterial blood gas was drawn immediately to

Table 1. Demographic and clinical characteristics

Clinical Characteristics	No. (%)
Age, yrs, median (IQR)	4.8 (1–14)
Male gender	11 (52)
Race	
White	6 (28)
Black	3 (14)
Native American	10 (47)
Asian	1 (5)
Other	1 (5)
Latino ethnicity	10 (47)
Diagnosis	
Primary ARDS	15 (71)
Aspiration pneumonia	2 (13)
Infectious pneumonia	11 (73)
Near-drowning	2 (13)
Secondary ARDS	6 (29)
Sepsis	4 (66)
Cardiopulmonary bypass	2 (33)

IQR, interquartile range; ARDS, acute respiratory distress syndrome.

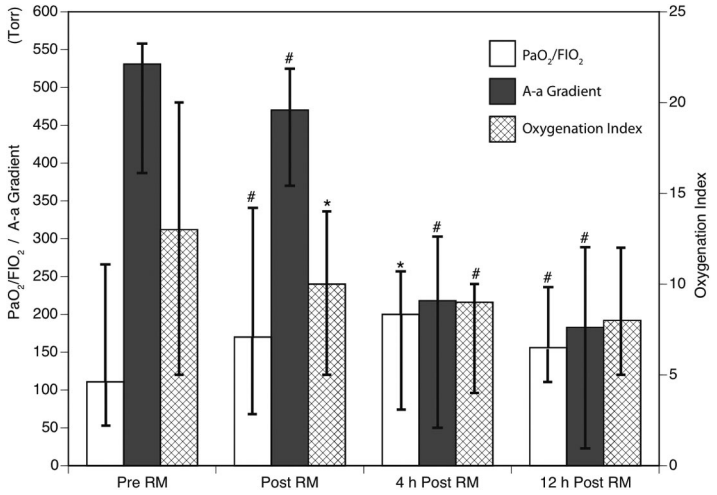

Figure 2. Effect of the recruitment maneuver (*RM*) on partial pressure of arterial oxygen over fraction of inspired oxygen (Pao_2/Fio_2), alveoloarterial oxygenation gradient (*A-a gradient*), and oxygenation index. Median (interquartile range). *$p < .05$ compared with pre-RM maneuver. #$p < .01$ compared with pre-RM maneuver.

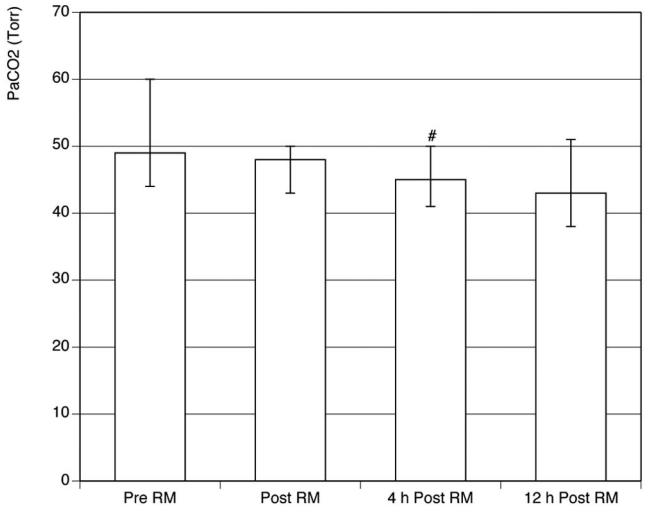

Figure 3. Effect of the recruitment maneuver (*RM*) on partial pressure of arterial carbon dioxide ($Paco_2$). Median (interquartile range). #$p < .01$ compared with pre-RM.

document partial pressure of arterial carbon dioxide ($Paco_2$).

Based on $Paco_2$ and Pao_2/Fio_2 ratio data obtained from Gattinoni et al (36), a power analysis was conducted before collecting the data, using a paired *t* test, with a .05 two-sided significance level.

We estimated a sample size of 22 patients would have 80% power to detect a difference from one time point to another in mean Pao_2/Fio_2 of 22 torr and a difference in mean $Paco_2$ of 2.9 torr assuming a SD of 68 torr and 9 torr, respectively.

Data Analysis. The statistical analysis was performed using SAS (version 9.2, Cary, NC). Descriptive statistics were computed on the patient characteristics and clinical and physiological data, including means, medians, and percentages. We used nonparametric tests to compare changes over time resulting from small sample sizes. Wilcoxon rank sum tests and Friedman's test for repeated measures with multiple comparisons were applied to examine changes over time—pre-RM, post-RM, 4 hrs post-RM, and 12 hrs post-RM—in the physiological variables. A significance level of .05 was used for all statistical tests.

RESULTS

Twenty-one patients were entered in the study between December 2007 and March 2009 (Table 1). The RM was performed once in each patient and within 72 hrs of meeting ALI/ARDS criteria.

Effect of the Lung Recruitment Maneuver on Oxygenation. The Pao_2/Fio_2 ratio increased 53% immediately after the RM ($p < .01$; Fig. 2). Improvement in Pao_2/Fio_2 ratio persisted with an increase of 80% over the baseline at 4 hrs ($p < .05$) and 40% at 12 hrs after the RM ($p < .01$). The alveoloarterial oxygenation gradient decreased by 12% immediately after the RM ($p < .01$, Fig. 2), by 59% at 4 hrs, and by 66% at 12 hrs after the RM ($p < .01$). Compared with baseline, the oxygenation index improved by 24% immediately after the RM ($p < .05$, Fig. 2) and by 31% at 4 hrs after the RM ($p < .05$).

Effect of the RM on Ventilation. Compared with baseline, the $Paco_2$ was not significantly changed immediately after the RM and 12 hrs after the RM, but it was significantly decreased 4 hrs post-RM ($p < .01$; Fig. 3).

Effect of the RM on Respiratory Variables. Peak inspiratory pressure decreased by 17% below the baseline at 4 hrs and 12 hrs after the RM ($p < .05$; Table 2). Fraction of inspired oxygen was not significantly changed at 4 hrs and 12 hrs after the RM. Dynamic compliance and mean airway pressure were not significantly changed after the RM.

The optimal PEEP found by the RM was statistically different from the PEEP selected by the clinician to keep Spo_2 88–93%. PEEP increased from a median of 8 cm H_20 (interquartile range, 6–8) pre-RM to 10 cm H_20 (interquartile range, 8–12) post-RM ($p = .02$).

Safety. All patients tolerated the RM without hemodynamic compromise (hypotension and/or bradycardia) (Figs. 4 and 5). We found no statistically significant difference in heart rate at selected time points during the RMs compared with pre-RM. We found a statistically sig-

Table 2. Respiratory variables at selected time points

	Prerecruitment Maneuver	Postrecruitment Maneuver	4 Hrs Postrecruitment Maneuver	12 Hrs Postrecruitment Maneuver
Mean airway pressure, cm H_2O[a]	14 (11–17)	13 (10–19)	13 (11–17)	13 (11–15)
Peak inspiratory pressure, cm H_2O[a]	31 (25–36)	29 (23–33)	26 (21–30)[b]	26 (21–29)[b]
Dynamic compliance, mL/cm H_2O[a]	8 (3–12)	9 (2–11)	5 (2–14)	5 (3–14)
Respiratory rate, breaths/min[a]	24 (20–29)	21 (18–28)	29 (27–35)[c]	29 (25–33)[c]
Fraction of inspired oxygen[a]	0.6 (0.45–0.65)	0.6 (0.5–1)[b]	0.5 (0.45–0.6)	0.5 (0.4–0.6)

[a]Data are median (interquartile range); [b]$p < .05$ vs. prerecruitment maneuver; [c]$p < .01$ vs. prerecruitment maneuver.

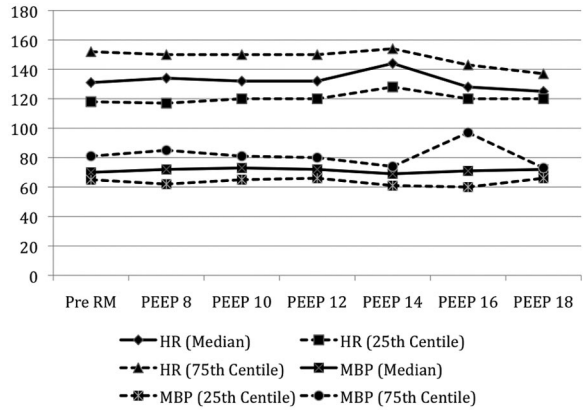

Figure 4. Heart rate (*HR*) and mean arterial blood pressure (*MBP*) during recruitment maneuver (*RM*) upward positive end-expiratory pressure (*PEEP*) titration. $p < .05$: MBP PEEP 12 compared with pre-RM. $p < .01$: MBP PEEP 8 and MBP PEEP 10 compared to pre-RM.

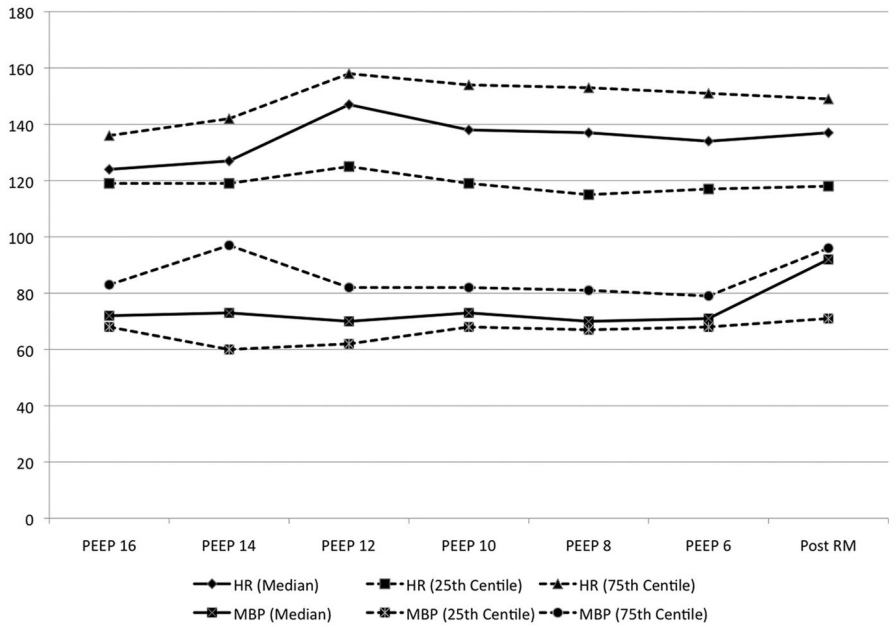

Figure 5. Heart rate (*HR*) and mean arterial blood pressure (*MBP*) during recruitment maneuver (*RM*) downward positive end-expiratory pressure (*PEEP*) titration. $p < .05$: MBP PEEP 12 and MBP PEEP 8 compared with pre-RM. $p < .01$: MBP PEEP 10, MBP PEEP 6, and MBP post-RM compared with pre-RM.

nificant difference in mean arterial blood pressure at selected time points during the RMs compared with pre-RM. The difference in mean arterial blood pressure was not clinically significant and no RM was terminated early secondary to hypotension. There were no cases of barotrauma, hypoxemia, or arrhythmias. There were three cases of transient hypercapnia that occurred during the RM and were entirely resolved by the end of the maneuver. One of these three RMs was terminated early secondary to transient hypercapnia. The protocol and exclusion criteria were changed accordingly (see "Methods").

DISCUSSION

Our study shows that in a selected group of ventilated pediatric patients with ALI/ARDS, the modified OLT RM: 1) improves oxygenation persisting up to 12 hrs after the RM; 2) has no clinically significant effect on ventilation; and 3) is safe and well tolerated.

Given the paucity of pediatric studies, the method of recruitment that we chose was based on adult literature, animal studies, and the Servo-I manufacturer recommendation (12, 32, 35, 37, 38). The continuous monitoring of dynamic compliance using the OLT program was a useful tool to identify the beginning of lung collapse after a RM in an animal model of ARDS (32). Adult studies showed improved oxygenation and respiratory system compliance using the OLT program during a RM in patients with ARDS (33). The original OLT algorithm was not designed to be used in children (35). Therefore, we decided to use a modified OLT program for continuous monitoring of Cdyn to identify the beginning of lung overdistention and collapse in pediatric ALI/ARDS.

There are few studies involving RMs in children. Marcus and colleagues demonstrated that a RM improves Cdyn in children receiving general anesthesia (39). Two studies performed in children with no known lung disease undergoing general anesthesia for either computed tomography or magnetic resonance imaging showed a decrease in atelectasis as measured by thoracic computed tomography or magnetic resonance imaging with intermittent RMs (40, 41). Duff et al (42) showed a significant reduction in oxygen requirements lasting up to 6 hrs after RMs in ventilated pediatric patients in the pediatric intensive care unit. We

demonstrated early and lasting improvement in oxygenation up to 12 hrs after a RM in pediatric patients with ALI.

A sustained improvement in oxygenation after RMs depends on PEEP optimization once the RM is completed (15). In an earlier study by ARDSNet, RMs improved oxygenation, although the improvements in oxygenation lasted only 1 hr after the RMs (29). The ARDSNet study called for a weaning of PEEP if oxygenation improved post-RM, which may have negated a benefit from recruitment in some patients and produced only a brief improvement in oxygenation in the responders. Borges and colleagues (21), using higher RM pressures, were able to recruit the lung in the majority of patients with ALI/ARDS. Furthermore, using high levels of PEEP after the PEEP trial was completed allowed the oxygenation benefit to be maintained at least 6 hrs after the RM. Other studies have maintained significant oxygenation benefits for at least 4 hrs using a decremental PEEP trial to identify an "optimal" level of post-RM PEEP (20). It is possible that the clinician-selected optimal PEEP in some studies might have been insufficient to sustain the oxygenation benefits of the RM. This possibility is suggested by Sivan et al (42) who found that clinically chosen PEEP in children with acute respiratory failure secondary to restrictive lung disease is related to a pulmonary volume below functional residual capacity; increasing PEEP levels until functional residual capacity was reached resulted in improved compliance suggesting recruitment. We also found that the pre-RM PEEP was significantly lower than the post-RM PEEP, suggesting that clinicians underestimate PEEP requirements in children with restrictive lung disease.

Overall, RMs were well tolerated in our study. There were no cases of hypoxemia, barotrauma, arrhythmias, or hemodynamic compromise. In the only published study of RMs in ventilated supine patients in the pediatric intensive care unit, 14% of RMs had to be stopped secondary to agitation and bradycardia, both of which resolved immediately after the RM was discontinued (42). In our study, patients were sedated and paralyzed before the RM. There were no changes in heart rate or blood pressure during any part of the RM that would suggest that the patients experienced discomfort with the RM. We had three cases of transient $Paco_2$ retention associated with the RM. Only one of these three RMs was terminated early secondary to transient hypercapnia. Other authors have also reported transient $Paco_2$ retention associated with RMs without clinically significant implications (21, 30). Both in our study and others, these changes were not sustained after finishing the RM. These changes are expected as the RM involves lung expansion, therefore temporarily affecting perfusion. Patients who are potentially sensitive to these ventilation abnormalities may not be good candidates for a RM.

Our study has several limitations. This is a single-center study involving a small number of patients. Therefore, we were able to only examine short-term physiological outcomes and cannot determine the effect on long-term outcomes such as ventilator-free days and survival. A change in oxygenation, our primary outcome measure, may be influenced by both actual lung recruitment as well as other factors such as cardiac output or blood flow redistribution within the injured lung (37, 43) Both a RM and PEEP optimization can improve oxygenation by recruiting collapsed alveoli. Because we did both, whether the RM and/or the change in PEEP contributed to alveolar recruitment and oxygenation improvement cannot be determined. We studied the effects of a RM in pediatric patients with early (eg, $<$72 hrs) ALI/ARDS. RMs were not repeated in late ALI/ARDS. This should be considered in future trials.

CONCLUSIONS

The modified OLT RM and PEEP optimization strategy may improve oxygenation and appears to be safe for use in most pediatric patients with ALI/ARDS. The oxygenation benefit may last up to 12 hrs post-RM. It is possible that this benefit depends on determination and maintenance of optimal PEEP after the RM. Further studies need to elucidate which of these two aspects is more important for lung recruitment. Correlation with computed tomographic scans may help elucidate this question. Finally, future investigations should evaluate the potential benefit or harm of repeated RMs. Clinicians must be careful to review suggested computerized ventilator algorithms because they may not be designed for or tested in children.

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