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Comparison of Two Lung Recruitment Strategies in Children with Acute Lung Injury

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Abstract

Background. Lung recruitment maneuvers are frequently used in the treatment of children with lung injury. Here, we describe a pilot study to compare the acute effects of two commonly used lung recruitment maneuvers on lung volume, gas exchange and hemodynamic profiles in children with acute lung injury (ALI).

Methods. In a prospective, non-randomized, cross-over pilot study, n=10 intubated pediatric patients with lung injury sequentially underwent (1) a period of observation, (2) a sustained inflation (SI) maneuver of 40 cm H_2O for 40 seconds and open lung ventilation, (3) a staircase recruitment strategy (SRS) which utilized 5 cm H_2O increments in airway pressure from a starting plateau pressure of 30 cm H_2O and PEEP of 15 cm H_2O, (4) a downwards PEEP titration and (5) a one hour period of observation with PEEP set 2 cm H_2O above closing PEEP.

Results. Arterial blood gases, lung mechanics, hemodynamics and functional residual capacity were recorded following each phase of the study and following each increment of the SRS. Both SI and SRS were effective in raising arterial oxygen tension and functional residual capacity. During the SRS maneuver, we noted significant increases in dead space ventilation, a decrease in CO_2 elimination, an increase in arterial carbon dioxide tension and a decrease in compliance of the respiratory system (Crs). Lung recruitment was not sustained following the decremental PEEP titration.

Conclusions. SRS is effective in opening the lung in children with early ALI, and is hemodynamically well tolerated. However, attention must be paid to carbon dioxide tension during the SRS. Even minutes following lung recruitment, lungs may derecruit when PEEP is lowered beyond the closing pressure.

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Keywords: acute lung injury, acute respiratory distress syndrome, recruitment maneuver, functional residual capacity, staircase recruitment strategy

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Introduction

Acute lung injury (ALI) is a heterogenous lung disease in which regions of diseased lung collapse in association with regional changes in lung surfactant, surface tension and lung water.[1] This leads to regions of intrapulmonary shunting and hypoxemia. Decreases in aerated lung tissue may result from the weight of edematous lung[2] or from alveolar flooding[3]. Regardless of mechanism, it is agreed upon that increasing airway pressures are required to recruit these regions. Because lung disease is heterogenous, compliant alveoli are aerated first, followed by diseased alveoli. Maneuvers designed to open the lung must be applied with sufficient pressure over sufficient time to reach diseased lung. Recruitment maneuvers (RMs) may be used to reverse episodes of profound hypoxemia, applied empirically following periods of derecruitment (e.g. suctioning)[4] or utilized as part of a ventilation strategy[5].

Two lung recruitment maneuvers have been commonly described: sustained inflation (SI) and the staircase recruitment strategy (SRS). SI is produced by applying high continuous positive airway pressures (40-50 cm H_2O) for a brief period of time (30-40 seconds). When combined with measures to maintain lung recruitment, SI raises arterial oxygen tension in patients with ALI[6], although this has not been shown to improve oxygen delivery or long term outcomes.[7-9] The SRS utilizes stepwise increases in plateau and positive end-expiratory pressures (PEEP) to recruit the lung gradually over time, and has demonstrated safety and efficacy in opening the lung in adult[10-12] and pediatric[13] patients with ALI. When compared to SI, SRS may impose less afterload on the right ventricle and less impairment of cardiac output.[14, 15] SI has been

associated with temporary hemodynamic instability, desaturation and agitation in pediatric patients[16], whereas SRS has been shown to be well tolerated in pediatric patients with ALI[13]. In our intensive care unit, patients with ALI are treated with sustained inflations at the provider's discretion, e.g. following suctioning or during a desaturation episode. We performed a pilot study of the safety and efficacy of SRS following SI in pediatric patients with ALI.

Methods

This study was approved by the Institutional Review Board (IRB) at Boston Children's Hospital. Our protocol was modified from that described by Borges[11], which included a sequential, non-randomized application of a sustained inflation and open lung approach (OLA), followed by application of a staircase recruitment strategy. Although this precluded direct comparison of the two maneuvers, we viewed this primarily as a safety and feasibility study, and therefore adopted similar methodology.

Patients and Monitoring

Patients admitted to the Medical Surgical Intensive Care Unit at Boston Children's Hospital between October 1, 2008 and January 1, 2011 were screened for this study. Inclusion criteria included patients age 44 weeks post conceptual age to 18 years meeting criteria for ALI[17] (PaO_2/FiO_2<300 on ABG obtained within 6 hours of screening, acute onset of bilateral infiltrates on chest radiograph, and no evidence of left atrial hypertension); demonstrated apnea due to neuromuscular blockade or deep sedation; indwelling arterial line in situ; cuffed endotracheal tube in situ; conventional mechanical

ventilation with current PEEP level between 5 and 15 cm H_2O; written parental consent obtained. Of note, we did not include spontaneously breathing patients in this study as our institution's review board disapproved of administering additional sedative or neuromuscular blocking (NMB) agents for this pilot study, stating that NMBs are not part of standard practice for lung recruitment maneuvers and therefore imposed an additional risks to patients. Exclusion criteria were patients meeting criteria for ALI for > 72 hours; active hemodynamic instability (defined as >50% change in vasopressor dosing over preceding 6 hours); history of prematurity (birth at post-conceptual age <37 weeks); clinically-recognized airway disease; known congenital heart disease; congenital diaphragmatic hernia; recent history of intrathoracic instrumentation (e.g., orthopedic instrumentation, cardiac pacemaker, thoracostomy); known restrictive lung disease, cystic fibrosis, or severe pulmonary hypertension (including patients on pulmonary vasodilator therapy); severe brain injury; or the use of extra-corporeal life support.

Measured endpoints included heart rate, saturations, invasive arterial blood pressure and central venous pressure, which were continuously monitored. At the end of each increment, vital signs, arterial blood gas (iStat CG8$^+$, Abbott Point of Care, Princeton, New Jersey), functional residual capacity by multiple breath nitrogen washout[18, 19] (GE Engstrom Carestation, GE Healthcare, United Kingdom), static compliance of the respiratory system (Crs), and tidal volume were recorded. Dead space ventilation and elimination of carbon dioxide (VCO_2) were also measured using a mainstream breath

analyzer (CO2SMO® Plus, Respironics Corporation, Amsterdam, Netherlands).

Experimental Protocol

All patients were in the supine position, sedated, and received 100% oxygen except where specified. Prior to initiation of the study, intravascular volume status was assessed by plethysmoghraphic variability index (PVI, Radical 7 pulse oximeter, Masimo Corporation, Irvine, California).[20, 21] Patients with high variability (PVI>15%) received a 5 mL/kg, one-time fluid bolus prior to subsequent interventions. PVI was followed but not intervened upon thereafter. Patients then underwent three pressure-volume curve determinations (Avea, VIASYS Healthcare, CardinalHealth, Yorba Linda, California) for identification of upper and lower inflection points. When identified, the upper inflection point was set as the upper pressure limit for the subsequent phases of the study. Complete lung opening was defined as the sum of PaO_2 and $PaCO_2$ exceeding 400 mm Hg on an arterial blood sample. In adults with ARDS undergoing lung recruitment maneuvers, Borges et al[11] found that patients meeting this endpoint exhibited <5% collapse of total lung mass when studied by multislice CT scan. All arterial blood gases were performed on FiO_2 of 1.0. Study phases are outlined in Figure 1.

1. *Baseline Ventilation*. Patients were observed on their baseline PEEP (i.e. the set PEEP level at study enrollment) with volume control ventilation to achieve a tidal volume of 6 mL/kg ideal body weight (IBW)[22] for 10 minutes, followed by measurements described above.

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2. *Sustained inflation followed by open lung ventilation strategy (SI)*. A continuous positive airway pressure of 40 cm H_2O was applied for 40 seconds using a ventilator-delivered inspiratory hold maneuver. Upon completion of this maneuver, PEEP was set 2 cm H_2O above the lower inflection point (LIP) as previously identified on the pressure-volume curve. When a LIP was not identified, PEEP was set 2 cm H_2O above baseline PEEP. Patients were ventilated using volume-controlled ventilation (VCV) using a tidal volume of 6 mL/kg IBW. Respiratory frequency was adjusted to ensure that measured minute ventilation was maintained as measured at baseline. This ventilation strategy was continued for 10 minutes followed by measurements.
3. *Staircase recruitment strategy (SRS)*. Patients were then placed in pressure-controlled ventilation (PCV) with a plateau pressure (Pplat) of 15 cm H_2O above PEEP. Inspiratory time remained unchanged from baseline. PEEP was initially set at 15 cm H_2O, which was maintained for 5 minutes, followed by the measurements described above. If PaO_2 plus $PaCO_2$ was less than 400 mm Hg, Pplat and PEEP were immediately increased by 5 cm H_2O and ventilation continued for another 5 minutes, followed by repeated measurements. Measured minute ventilation was continually monitored, and respiratory frequency was adjusted to achieve the baseline measured minute ventilation as closely as possible. Inspiratory to expiratory (I:E) ratio was continuously monitored to ensure that it did not decrease below 1; if it did, inspiratory time was adjusted to maintain I:E ratio of 1. Spirometry was also examined to ensure that expiratory flow reached zero following each breath. Following each arterial blood

gas, respiratory frequency was further titrated as needed to maintain arterial pH >7.25. The process was continued until either (a) PaO_2 plus $PaCO_2$ exceeded 400 mm Hg, which represented complete lung opening, or (b) Pplat reached either 50 cm H_2O or the measured upper inflection point (from the initial pressure-volume curve).

4. *PEEP Titration*. Following SRS, PEEP was instantaneously decreased to 20 cm H_2O with tidal volumes of 6 mL/kg in VCV. Following ventilation for 5 minutes, endpoints were measured. Whenever the sum of PaO_2 and $PaCO_2$ exceeded 400 mm Hg, PEEP was decreased by 2 cm H_2O for 5 minutes, followed by repeated measurements. Downward PEEP titration was continued until PaO_2 + $PaCO_2$ was less than 380 (suggesting that the lung had reached a closing pressure and begun the process of derecruitment[11]), at which point PEEP was increased and maintained 2 cm H_2O above closing PEEP for the one hour followup period. No attempts at repeating lung recruitment were made prior to this change.
5. *Observation and Followup*. PEEP was maintained at 2 cm H_2O above closing PEEP for 60 minutes, with measurements taken at 30 and 60 minutes to evaluate maintenance of lung recruitment. Patients were followed after completion of the protocol for 24 hours to monitor for development of pneumothorax or subcutaneous emphysema. Patient disposition was determined by subsequent chart review.

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Criteria for aborting the study at any phase included arterial pH below 7.00, decrease in mean arterial blood pressure by 20% or more, increase in vasoactive support by more than 50%, an arterial lactate greater than 2 mg/dL, or a decrease in arterial saturations below 80%.

Data Management. All ventilator data, arterial blood gases values, pulmonary mechanics, and functional residual capacity were hand recorded on data collection forms in real-time, and subsequently entered into GraphPad Prism (Prism 5, Version 5.0b, GraphPad Software, Inc, LaJolla, California) for analysis. Vital signs were stored by the hospital's electronic medical record system, and collected off-line for analysis. Arterial oxygen tension, functional residual capacity and lung mechanics (as shown in Figure 4) following each phase were compared to baseline values using a Wilcoxon matched pairs test, except as noted. IBW was used for all weight-based calculations.

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Results

During the study period, 58 patients with a definitive diagnosis of ALI (i.e. had an ABG demonstrating $PaO_2/FiO_2<300$) were assessed for eligibility. Of these patients, 46 were excluded and 12 were enrolled. One of these patients was then excluded due to the development of heart block during baseline observations and a second was excluded because we discovered a small pneumothorax on the most recent CXR during the timeout immediately prior to the protocol. Therefore, 10 patients completed the protocol (Table 1). The primary reason for exclusion was that patients were spontaneously breathing (n=12). Others included prematurity (<37 weeks gestational age, n=6), known restrictive lung disease (n=4), severe reactive airways disease (n=4), age >18 years (n=4), airleak or presence of a thoracostomy tube (n=4), team member inavailability (n=4), hemodynamic criteria (n=2), unilateral pneumonia (n=2), pleural or pericardial effusions, PEEP > 16 cm H_2O, primary pulmonary hypertension and tracheomalacia.

Of the 10 patients completing the protocol, all completed step 1 of the SRS (PEEP 15 cm H_2O, delta P 15 cm H_2O). Subsequently, one patient exited the protocol due to severe respiratory acidosis, which was a stopping criteria for the study, and two others met criteria for lung opening (i.e. $PaO_2 + PaCO_2 \geqq 400$ mmHg). Seven patients completed step 2 of the SRS (PEEP 20 cm H_2O), and one of these subsequently met criteria for lung opening. Six patients completed step 3 (PEEP 25 cm H_2O), none of whom then met criteria for lung opening. Six patients completed step 4 (PEEP 30 cm H_2O), two of whom subsequently met criteria for lung opening, and one did not go on to step 5 because this would have exceeded the measured upper inflection point. Three

patients completed step 5 (PEEP 35 cm H_2O), two of whom subsequently met criteria for lung opening and the third did not. Therefore, of the 10 children studied, 7 achieved complete lung recruitment, and all of these were discharged from the hospital. Three remaining patients failed to achieve complete lung recruitment: the patient who completed the 5 steps of the SRS without achieving lung opening was discharged from the hospital. The patient who exited the protocol following step 4 due to the measured upper inflection point died several days later. The third patient who exited the SRS following step 1 due to severe respiratory acidosis died several days later. Except for the patient who met stopping criteria (respiratory acidosis), all patients (n=9) completed the PEEP titration and observation phases of the protocol.

Efficacy of RMs. Arterial oxygen tension at the end of the SRS phase (383 [95% confidence interval, 247-519] mm Hg) was significantly higher than baseline values (226 [113-339] mm Hg, *P*=0.0195), and non-significantly higher than following SI (261 [128-395] mm Hg, *P*=0.0547). PaO_2 following SI was also significantly higher than baseline values (*P*=0.0128). Following the decrease in airway pressures at the end of SRS, PaO_2 increased further during the first several steps of the PEEP titration phase (Figure 2). PaO_2 subsequently decreased with downward titration of PEEP throughout the PEEP titration phase, and was not different from baseline values during the observation phase.

Functional residual capacity following SI was non-significantly higher than baseline values (18.6 mL/kg IBW during SI vs 14.6 mL/kg IBW at baseline, *P*=0.0547), but increased significantly to 34.8 mL/kg IBW at the end of SRS (*P*=0.0156). In contrast to the increase

in PaO_2 during the initial steps of the PEEP titration, FRC decreased to a plateau early in the PEEP titration phase which was not significantly different from baseline values.

Safety of RMs. Three patients received a one-time, 5 mL/kg fluid bolus for PVI>15% prior to entering the protocol. One patient exited the protocol due to severe respiratory acidosis and mild hypotension during the first step of the SRS phase. This patient was placed on HFOV, then ECMO support and subsequently died of respiratory failure. Two patients experienced desaturation at the end of the sustained inflation procedure, which resolved spontaneously upon the release of the maneuver. Two patients exhibited tachycardia without hypotension during the SI, which resolved at the end of the maneuver. There were no episodes of desaturation, tachycardia or hypotension associated with SRS. There were no statistically significant differences in heart rate and mean arterial blood pressure during the recruitment protocol (Figure 3). Central venous pressure transiently increased during the later phases of the SRS. There were no episodes of pneumothorax or subcutaneous emphysema.

Carbon dioxide tension increased throughout the SRS phase (46.1 [41.09-51.24] mm Hg during the first increment of SRS to 64.33 [48.6-80.0] mm Hg during maximal lung opening, *P*=0.0120, Mann Whitney), but was not associated with a significant change in arterial pH (*P*=0.3510, Figure 4a). As patients progressed through the SRS phase, there were significant increases in dead space fraction (Figure 4b). Immediately upon release of airway pressures at the end of SRS (mean PEEP decreased from 27 to 18 cm H_2O), dead space fraction decreased to values similar to baseline. Similarly, CO_2 elimination (VCO_2)

decreased significantly as patients progressed through SRS (*P*=0.0074, linear regression), and was lower during the final phase of SRS (67.9 [28.4-107.4] mL CO_2/min/kg IBW) than following SI (109.4 [68.5-150.4] mL CO_2/min/kg, *P*=0.0273, Wilcoxon signed rank test) (Figure 4c). VCO_2 during the SRS reached as low as 2 mL/min/kg in one patient, and 11 mL/min/kg in another, both during the final phase of SRS. These changes were paralleled by a decrease in respiratory system compliance (Figure 4d) and tidal volume (Figure 4e) throughout the SRS phase, all of which normalized with release of airway pressures during the PEEP titration phase. In response to decreases in tidal volume, respiratory frequency was significantly increased to 124% [112%-135%] of baseline by the end of the SRS.

Discussion

Our results suggest that in ventilated pediatric patients with ALI: (1) both SI and SRS effectively raise arterial oxygen tension and functional residual capacity; (2) SI may be associated with temporary desaturation in children; (3) SRS is associated with an increase in carbon dioxide tension during the maneuver; (4) both SI and SRS are hemodynamically well tolerated.

Several studies have noted that both SI and SRS are effective in raising arterial oxygen tension in adults and children with ARDS.[7, 11, 13, 23] When an SRS was applied following a SI in non-randomized fashion, Borges[11] noted that arterial oxygen tension raised further following SRS. When assessed using computed tomography, Borges also noted regions of lung collapse which had not opened following SI became aerated following SRS. This is consistent with the increase in FRC we demonstrated following SRS compared to

following SI. However, in both Borges' and our study, the non-randomized, sequential application of SRS after a SI precludes any conclusions regarding the efficacy of one maneuver over the other; it is possible that serial applications of SI could have a similar effect.

The increase in oxygen tension following lung recruitment was not sustained in our study using a modification of the PEEP titration described by Borges[11]. It has been demonstrated in both adults[24] and children[13] that in order to sustain improvements in oxygenation following recruitment maneuvers, PEEP must be optimized following the completion of the recruitment maneuver. In our protocol, we weaned PEEP following SRS until we found evidence on arterial blood gas of partial lung 'closing', i.e. that the PaO_2 plus $PaCO_2$ decreased below 380 mmHg, which most likely represented a decrease in PEEP below the critical closing pressure of the lung. Because we did not then take measures to re-recruit the lung following this step, it was not surprising that the improvement in oxygenation was no longer sustained. Following a similar stepwise recruitment maneuver followed by downward PEEP titration, Boriosi[13] found that the addition of a 're-recruitment' maneuver (ventilation at 'opening pressures for 2 minutes', i.e. the highest step used during the SRS) afforded an improvement in PaO_2/FiO_2 ratio which persisted up to 12 hours post RM.

Consistent with prior reports[13, 25], patients tolerated the sustained inflation with only transient desaturation, and did not exhibit significant hemodynamic changes during SRS. However, one very important potential adverse effect of SRS is severe hypercarbia during

the maneuver itself. Boriosi[13] described a protocol in children similar to the SRS described here, though they utilized similar airway pressures (peak pressures of 45 versus 50 cm H_2O) over significantly shorter periods of time (1 minute versus 10 minutes per step), and did not measure arterial blood gases during the SRS itself. They described an initial cohort of patients who developed hypercarbia following the SRS, and they modified the SRS to include a minimum tidal volume of 4 mL/kg, increased respiratory frequency during the maneuver, and a stopping rule for increases in end tidal CO_2. They also excluded patients with pre-existing respiratory acidosis from enrollment. With these modifications, the authors did not report significant changes in carbon dioxide tensions immediately following the SRS. Our protocol did not include such modifications, though we carefully monitored arterial blood gases, minute ventilation and carbon dioxide elimination during each increment of the SRS. Although respiratory frequency was increased in most patients as they progressed through the SRS to maintain near-baseline measured minute ventilation, we still noted significant increases in arterial CO_2 and decreases in CO_2 elimination during the SRS. However, only two patients (one patient with hypercarbia and one patient with an upper inflection point boundary) met predefined stopping rules which precluded completion of the SRS maneuver. In patients in whom arterial carbon dioxide tensions are not closely monitored, the safety of SRS may be compromised. Because the mechanism of hypercarbia in this setting may be an increase in dead space ventilation, it is possible that monitoring of end-tidal CO_2 alone may be insufficient. Safety of the maneuver may be further enhanced by utilizing regular recovery periods at lower pressures (as utilized by Borges)[11], utilizing lower airway pressures for shorter durations[13, 26], or by use of larger driving pressures (PIP minus PEEP) during the maneuver. The use

of esophageal pressure monitoring to quantify transpulmonary pressure[27] may also enhance the safety profile of SRS.

Our study has several limitations. (1) It is a single institution study, and our sample size was significantly restricted by the requirements for indwelling arterial lines and for apnea due to sedation or neuromuscular blockade. During the study period, most intubated patients with ALI were kept spontaneously breathing and were monitored non-invasively (i.e. without an arterial line), thus excluding them from study. (2) Because our patients were heavily sedated or receiving neuromuscular blockade, we did not experience problems with agitation or ventilator dyssynchrony during either SI or SRS. Therefore, the safety of the SRS maneuver described here cannot be applied broadly to patients who are less sedate and/or breathing spontaneously. This represents one important area of future research before SRS can be applied broadly to the pediatric population. (3) As mentioned above, the study protocol was modified from one previously described[11] in which patients were exposed first to a sustained inflation followed by 'open lung approach (OLA)' and then to a similar SRS (which utilized higher airway pressures). Although the authors concluded that 'the proposed maximum-recruitment strategy recruited the lung significantly better than the OLA,' the sequential, non-randomized fashion in which both experiments were performed precludes any conclusions regarding the efficacy of one technique over the other. In our protocol, patients received several recruitment maneuvers in series (including three PV curve measurements, SI and SRS), which likely had a cumulative hysteretic effect. As the SRS was performed last in the experimental protocol, the positive results may be biased by this sequence effect. Further, the

measurements of lung opening following the SI were performed following a 5 minute period of 'open lung ventilation.' Although this approach (at least theoretically) prevented lung derecruitment during OLA ventilation by maintaining PEEP above the lower inflection point, the measurements were completed on ventilating settings (rather than recruitment settings, as in the SRS), which precludes comparison of the two maneuvers. (4) We examined only for short term hemodynamic effects. If RMs are performed regularly, e.g. as part of a ventilation protocol, they may lead to cumulative air trapping that could cause hemodynamic compromise. (5) Our inclusion criteria excluded patients not adequately resuscitated or with active hemodynamic instability. Our protocol also included steps to optimize intravascular volume using an objective monitor of intravascular volume status. The safety of SI or SRS in hemodynamically unstable patients is, therefore, unknown. (6) The presence of ventilator associated lung injury associated with the protocol cannot be completely ruled out, though the absence of air leak as a result of the protocol was reassuring. (7) Finally, we studied the efficacy of lung opening in patients within 72 hours of the diagnosis of ALI. Several authors have suggested that lung recruitment in later stages may be less effective.[28-30]

In the majority of our patients, we noted a sequence of events associated with lung recruitment. As patients approached the critical opening pressure during SRS, tidal volumes decreased, compliance of the respiratory system decreased and carbon dioxide elimination decreased, at times dramatically. It is possible that in order to recruit densely consolidated lung, compliant alveoli must be markedly overdistended (and thus rendered less compliant) in order to open less compliant regions. In doing so, perfusion to more

compliant regions decreases[31], which increases dead space ventilation and carbon dioxide elimination, and decreases Crs.[32] This phenomenon also shunts pulmonary blood flow from compliant alveoli towards less compliant regions (which presumably exhibit a higher alveolar-arterial oxygen gradient), which may further increase intrapulmonary shunting. We hypothesize that oxygenation improves when diseased, poorly compliant regions are recruited during the SRS, and improves further as airway pressures are released and perfusion to healthy alveoli is restored.

Many questions remain regarding the utility of RMs in the care of patients with ALI. The ability of RMs to impact patient outcome (e.g. ventilator-free days or mortality) has not been demonstrated in either adult or pediatric populations.[33] Before these clinical trials can be appropriately designed, the safety of the SRS should be studied in a larger cohort of children (ideally stratified by severity of lung injury), and the SRS and SI should be compared in randomized fashion. Finally, the ability of RMs to achieve significant lung recruitment in the later stages of ALI should be examined.

Conclusions

In heavily sedated, volume-replete pediatric patients, both SI and SRS appear to be hemodynamically well-tolerated. Both SRS and SI are effective in immediately raising arterial oxygen tension. Hypercarbia is an important risk of SRS which requires caution in clinical use and merits further study. When followed by decremental PEEP titration without attempts a lung re-recruitment, the lung recruiting effects of the SRS were transient.

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Figure Legends

Figure 1. Study protocol

Ventilation in phases 1, 2, 4 and 5 was performed using volume controlled (VC) ventilation. Phase 3 used pressure control (PC) ventilation with a plateau pressure 15 cm H_2O above PEEP and an inspiratory time that was the patient's baseline. Endpoints were measured following each increment of each phase (see arrows). 'P380' denotes the PEEP increment at which PaO_2 + $PaCO_2$ was less than 380 mmHg.

Figure 2. Efficacy of Recruitment Maneuvers

Arterial oxygen tension (PaO_2, as measured on FiO_2 of 1.0) is plotted throughout the phases of study. PaO_2 increased relative to baseline measurements (BL) following a single sustained inflation (SI). As patients progressed through the staircase recruitment strategy (SRS) consisting of sequentially increasing airway pressures, PaO_2 decreased initially then increased significantly as patients progressed through the SRS. **Of note, in Figures 2-4 the data within the SRS phase is organized such that the final SRS step for each patient is aligned to the solid gray bar, with preceding increments being shown progressively leftward**. PaO_2 increased even further during the first three steps of the PEEP titration phase, then decreased to near-baseline levels as PEEP was weaned beyond the closing pressure, and maintained there during the observation (Obs) phase. Comparisons drawn between phase shown and baseline using Wilcoxon matched pairs test. Dotted line represents quadratic polynomial regression line. *, $P<0.05$, **, $P<0.01$, error bars = SEM.

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Figure 3. Vital sign changes during each phase of study

Changes in heart rate (HR), mean arterial blood pressure (MABP) and central venous pressure (CVP) plotted as percent change relative to baseline. There were no significant differences in HR or MABP during any phase of the study. CVP increased during the latter increments of the SRS, which correlated with a similar trend in mean airway pressure. Of note, only the first two increments of the PEEP titration phase are shown for simplicity. Line within each box represents median value, box = interquartile range, whiskers = range.

Figure 4. Safety of Lung Recruitment Maneuvers

(**a**) Arterial pH and arterial carbon dioxide tension ($PaCO_2$) during each phase of study. $PaCO_2$ was noted to increase during the SRS phase (*P*=0.0127, linear regression) but arterial pH did not decrease significantly. As patients progressed through the SRS, (**b**) dead space fraction increased (*P*=0.0136, linear regression), (**c**) elimination of carbon dioxide decreased (*P*=0.0074, linear regression), (**d**) respiratory system compliance decreased (*P*=0.0006, linear regression), and (**e**) tidal volume decreased (*P*=0.0048, linear regression) and respiratory frequency (expressed as a percentage of baseline respiratory rate) was increased (*P*=0.0264, linear regression). (**a-e**) Differences between baseline, SI and the final phase of SRS were assessed by Wilcoxon matched pairs tests, the results denoted by asterisks. Changes during SRS were determined by linear regression. *, *P*<0.05, **, *P*<0.01, error bars = SEM, dotted line = linear regression line.

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Table 1. Patient factors upon meeting inclusion criteria

Pt	Sex	Age (yr)	IBW (kg)	Diagnosis	Etiology[a]	FiO2	P/F Ratio[b]	PEEP (cm H_2O)	Crs[c]	OI
1	F	5.9	20	Parainfluenza pneumonia	P	0.7	87	12	0.71	16.1
2	M	4.2	16.2	Kawasaki Syndrome	NP	1	65	12	0.37	27.7
3	F	10.2	13.9	Sepsis, ascites	NP	0.6	192	12	0.45	8.9
4	F	5.6	34	Sepsis	NP	0.5	224	8	0.44	6.7
5	F	10.4	38.5	Necrotizing pneumonia	P	0.6	123	14	0.21	17.0
6	F	13.9	54.7	Sepsis	P	0.6	123	14	0.33	22.7
7	F	17.3	73.1	MAS	NP	0.7	201	10	0.47	7.0
8	F	4.9	18.2	RSV pneumonitis[d]	P	1	60	15	0.50	30.0
9	M	11.7	43.1	Sepsis	NP	0.4	268	12	0.47	6.4
10	F	9.4	38.5	Trauma	NP	0.4	188	10	0.36	8.0

IBW = ideal body weight, OI = oxygenation index (FiO_2 x mean airway pressure/PaO_2), MAS = macrophage activation sydrome.
[a]Etiology of ALI: P = pulmonary, NP = non-pulmonary.
[b]P/F ratio upon meeting inclusion criteria
[c]Crs = compliance of the respiratory system (mL/cm H_2O/kg IBW)
[d]This patient with RSV did not exhibit signs of airways disease by spirometry.

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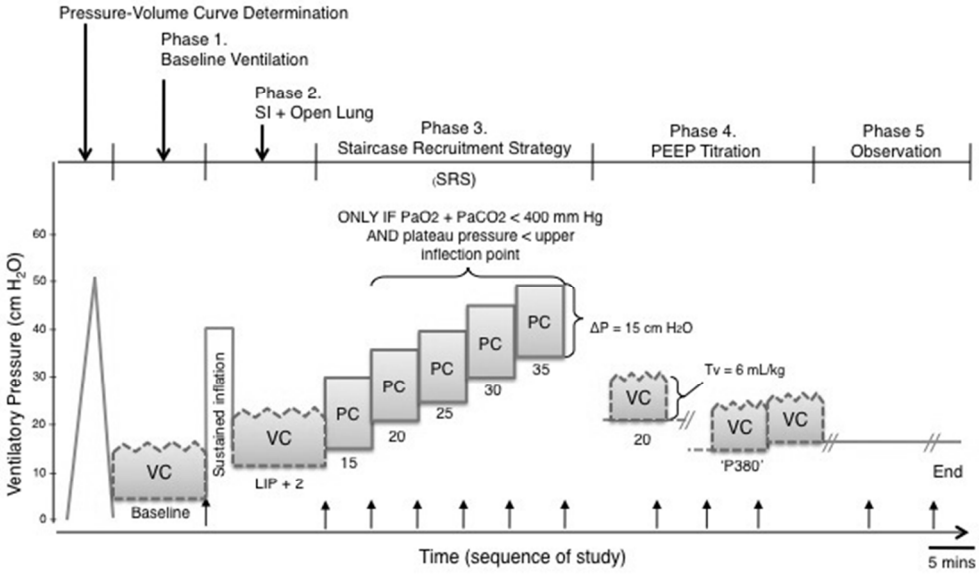

Figure 1. Study protocol

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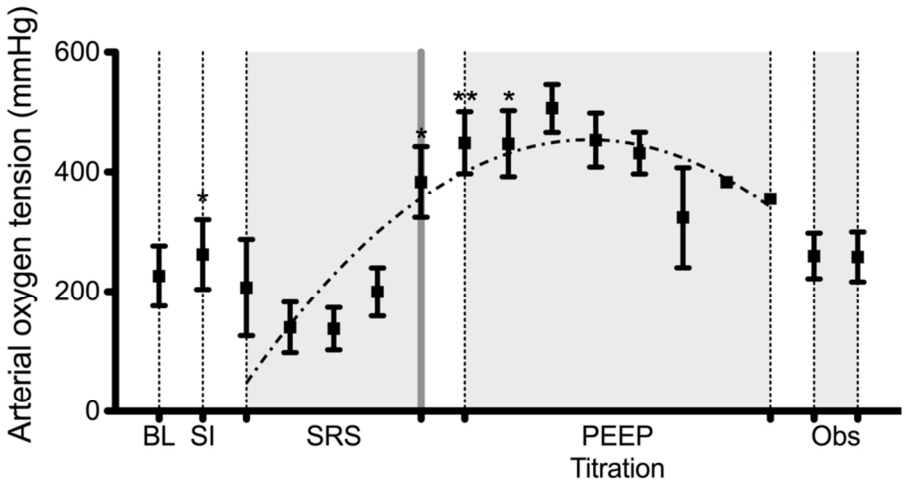

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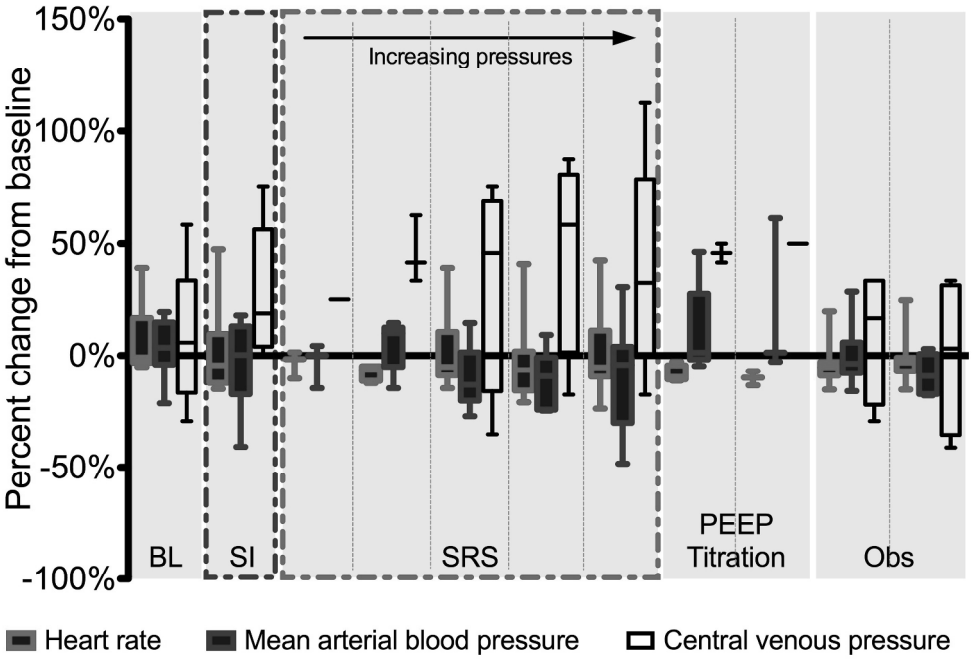

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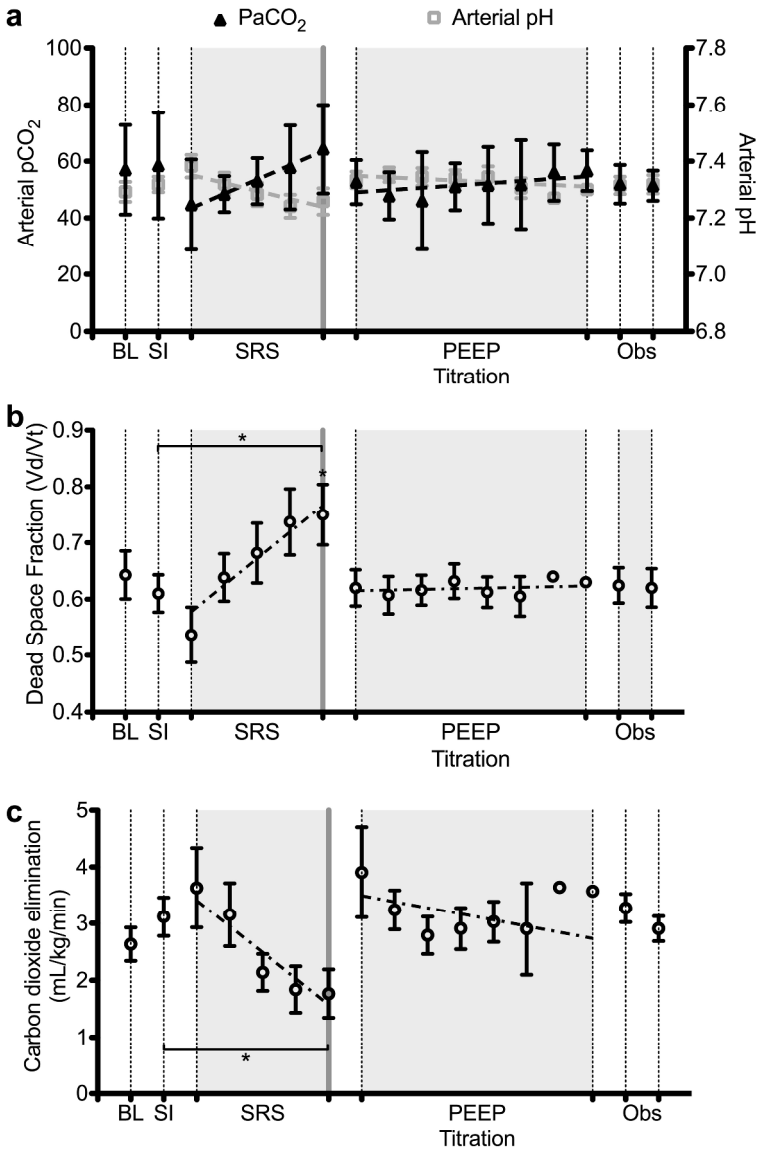

Figure 4. Safety of Lung Recruitment Maneuvers

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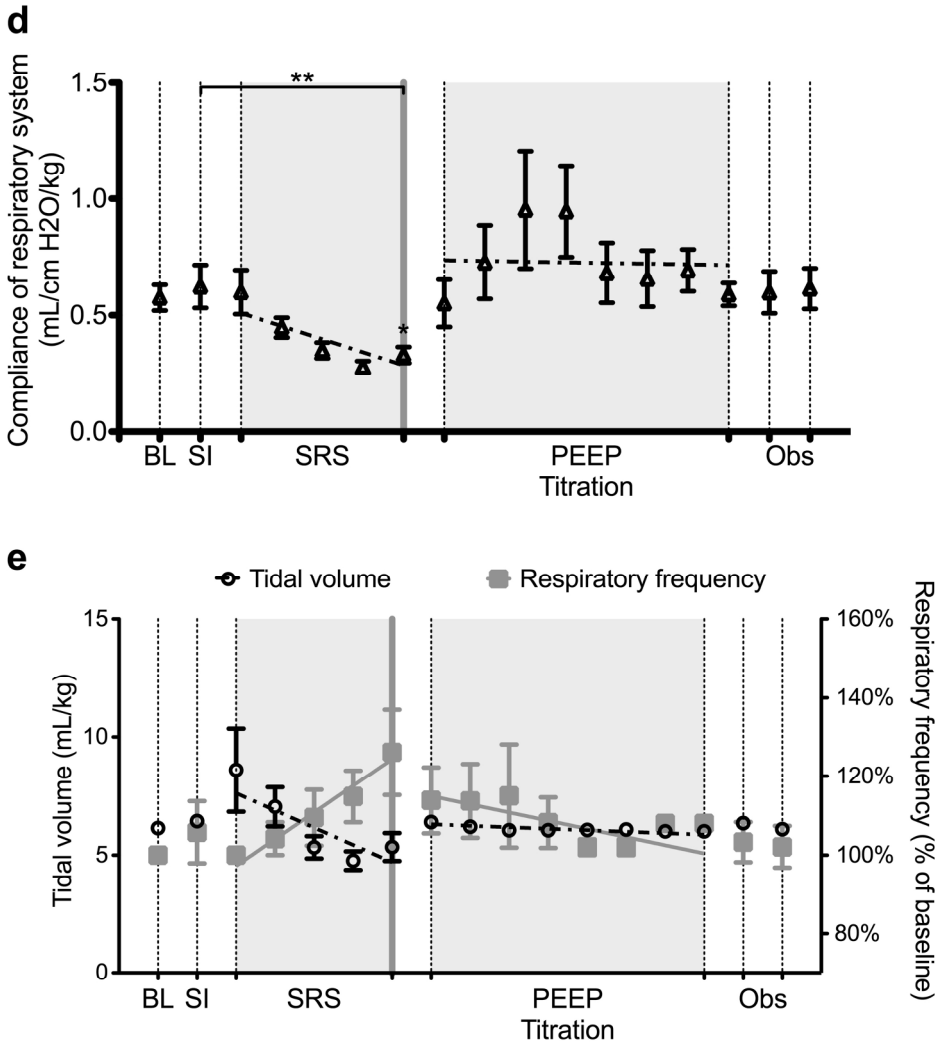

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