**Title:** Safety and efficacy of automated proning with review of the physiology, benefits and complications of prone positioning in the treatment of acute lung injury.

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Safety and efficacy of automated proning with review of the physiology, benefits and complications of prone positioning in the treatment of acute lung injury.

ABSTRACT

Title
Safety and efficacy of automated proning with review of the physiology, benefits and complications of prone positioning in the treatment of acute lung injury.

Objective
Review of the literature on prone positioning in treatment of ALI and to assess the utility and complications of automated prone positioning with lateral rotation in the treatment of acute lung injury (ALI) with

Design
Consecutive case series and review of the literature.

Setting
Multicenter

Patients
Sixty-four adult patients with ALI

Interventions
Nineteen patients assigned alternately to automated proning 12 or 19.5 hours/day, subsequently 45 patients assigned to 19.5 hours/day.

Measurements and Results
Adverse events, pulmonary variables, APACHE III scores, and mortality were collected in all patients. Chest CT scans were obtained at the time of device placement on the first 19 patients and repeated in 14 of the 19 at 48 hours. All CT scans showed recruitment of dorsal lung. Automated proning was not associated with more adverse events.

Medline database studies reporting physiology, benefits and complications of supine and manual prone positioning in ALI were reviewed. Numerous studies reported improved V/Q match, P/F ratios, pleural pressures and lung recruitment in prone compared to supine position in ALI. Two large randomized trials with 8 hours of proning/ day did not demonstrate benefit where a large randomized trial targeting 20 hours/day proning reported decreased mortality.

Conclusion

A number of ALI studies report improved pulmonary physiology associated with the prone position. One large randomized trial demonstrated improved mortality; it is possible that lack of benefit in two other randomized trials may be due to ineffective dose of this therapy, while a larger dose can be safely delivered by one RN using this automated lateral rotating proning unit.

Abbreviations:

ALI Acute lung injury
APACHE Acute physiology and chronic health evaluation
ARDS Acute respiratory distress syndrome
ICU Intensive care unit
Introduction

In acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) over distention of relatively normal lung units and shear forces associated with repetitive opening and closing of diseased units are thought to be major contributors to ventilator associated lung injury (VALI) and mortality. [1,2] Reduction of VALI by low tidal volume ventilation is the only therapy shown to reduce mortality in ALI and ARDS. Conservative fluid management has recently been shown to more rapidly improve lung injury scores, reduce ventilator time and ICU length of stay but not mortality. Ongoing trials in ARDS include use of surfactant, high frequency ventilation, immunomodulation, neutrophil elastase inhibitors, drotrecogin alfa, corticosteroids and prone positioning. Only high frequency ventilation and prone positioning are directed at further reduction of VALI.

VALI, due to over distention of normal and repetitively opening and closing of more compliant diseased lung segments, is exacerbated by the supine position which directs more ventilation to anterior lung while leaving the less compliant posterior lung atelectatic and/or consolidated [3,4]. This mal-distribution of tidal volume, in the supine position, is due an increase in dorsal pleural pressures from
the gravitational force of; the heart resting on the lungs, the weight of abdominal
organs pushing the diaphragm cephalad and the mass of the posterior lobe
resting against the dorsal pleura. (Figure 1A) [3-6]. The reverse is true in the prone
position where gravitational forces create a more negative and evenly distributed
pleural pressure by; the heart resting on the sternum unweighting the lungs and
dorsal pleura, the abdominal organs falling anteriorly pulling the diaphragm
caudally and the weight of the posterior lung falling away from the dorsal pleura
(Figure 1B). Additionally, in the prone position, the anterior chest wall and
adjacent lung is restricted, becoming less compliant. These prone position
related factors create a more negative and evenly distributed pleural pressures
and a decrease in anterior lung compliance both resulting in a more
homogeneously distributed tidal volume and associated lung strain [4,7-10].
Additional in the prone position as more tidal volume is distributed posterior, V/Q
match is improved since the majority of blood flow is maintained dorsally
regardless of body position. In ARDS/ALI these factors combined lead to
recruitment of dorsal lung, reduced VALI in the ventral lung and improved
oxygenation [3,6,8-16].

A recent multicenter randomized study, which targeted 20 hours of proning
per day, showed a 25% relative reduction in mortality, which reached statistical
significance after adjusting for increased severity of illness in the proned group.
Two other randomized ARDS proning trials failed to demonstrate benefit but were
weakened by short duration of proning (8 hours/day), crossovers to the proned group and missed episodes of proning in the treatment group. [17,18]

For proning to be studied and applied to a large number of patients with ARDS, it must be safe, efficient, and in sufficient dose (time spent prone) to be effective. Manual proning is difficult, labor-intensive, requiring up to five health care professionals for turning and has been associated with increased pressure sores. [19-21] As a result, proning has been used mainly as a rescue intervention outside a few ICUs in the United States. [18] Even without proning, continuous lateral rotation of > 40° (Kinetic Therapy) has been shown to recruit consolidated lung, reduce need for bronchoscopy and reduce ventilator associated pneumonia along with the benefit of reduced skin breakdown. [22-25]. It is likely that valid evaluation of prone positioning treatment of ARDS and ALI will require a longer duration of proning. It is possible that a sufficient dose of proning, combined with frequent turning to deliver routine nursing care, decrease facial edema, skin breakdown, ventilator associated pneumonia and increased mobilization of secretions would demonstrate benefit. [22,23,26] The technology studied in this trial addresses many of these issues.

**Materials and Methods**

A single center two-group comparison of 12 verses 19.5 hours/24 hours of proning in the treatment of ARDS and ALI using an automated kinetic therapy proning unit. (Figure 2A, 2B) This was followed by four center consecutive case
series to evaluate device safety and efficacy in treatment of ALI utilizing the 19.5 hours/24 hour proning dose. Adverse events were collected each 12 hours. Adverse events were compared to historical event rates reported in the literature of patients with ALI/ARDS.

The primary measure was number of adverse events with the automated kinetic therapy proning unit, with a nursing/patient ratio of 1:1. (With increased familiarity the ratio decreased to 1:2 for some patients on the device.) Secondary measures were PaO₂/FiO₂ ratio, compliance (in first 19 patients), lung injury score (LIS)¹ [27] and mortality. Chest CT’s were evaluated before and after device placement in 14 of the first 19 patients.

All patients were screened for ARDS and ALI by the European/North American consensus criteria of inclusion and exclusion (Table 1) and were managed with low tidal volume, volume control ventilation, sedation, and weaning protocols. [28] The first 19 patients were alternately assigned to 12 hours/day of proning (Group One) or 19.5 hours/day (Group Two). Baseline characteristics were collected on ICU admission (Table 2). Chest CT scans were obtained at the time of device placement and again at 48 hours of therapy for those patients who could be safely transported. Adverse events, pulmonary variables, hemodynamic

¹ LIS measures four variables, P/F ratio, PEEP required, lung compliance and number of quadrants involved on chest x-ray. The scale for each component ranges from 1-4 with 1 being normal and 4 representing the most severe abnormality. The components are summed then divided by 4 to produce a final score.
status and daily chest x-ray appearance were recorded every 12 hours for all 64 patients. Hospital mortality was documented.

Medline database from 1963 through 2008 was searched; articles and studies reporting physiology, benefits, complications and outcomes of supine and prone positioning were reviewed. These included the physiology of pleural pressures, lung recruitment, V/Q match, PaO₂/FiO₂ ratios, lung compliance and complications of supine and prone position. The study was approved by the Institutional Review Board at each site and informed consent was obtained.

Interventions

Sixty-four patients with ARDS and ALI were placed on the automated kinetic therapy proning unit; one patient (who survived) was excluded from data analysis due to age < 18 years. The first 19 patients were allocated to two groups. Group One was to receive 12 hours proning/day with supine and prone periods of two hours each. Group Two was to receive 19 hours 30 minutes proning/day with supine periods of 45 minutes and prone periods of 3 hours 15 minutes. No increase in adverse events was seen with the longer proning interval; therefore, the subsequent 40 patients were to receive 19.5 hours proning/24 hours. All patients received 62° lateral rotation, supine and prone. Patients were removed from the automated kinetic therapy proning unit when positive end expiratory pressure was < 10 cm H₂O and FiO₂ < 50% for 24 hours.
Low tidal volume, volume-controlled mechanical ventilation, sedation and weaning protocols were continued.

Statistical analysis

Simple comparisons between the groups were evaluated using Fisher’s exact test for binary outcomes (e.g. mortality) and the t-test or Kruskal-Wallis test for quantitative outcomes (e.g. LIS). The former parametric tests were used whenever appropriate. When confounders were included in quantitative outcome models (e.g. LIS) after accounting for severity of injury analysis of variance techniques were used. When necessary, transformations were performed to accommodate the assumption of normality. [29]

Results

Chest CT scans were obtained on the first 19 patients at the time of therapy placement and in 14 (who could be safely transported) of these patients again 48 hours later. All 14 of the post therapy placement CT scans showed less density in the dorsal lung after proning. (Figure 3A - 3J) PaO₂/FiO₂ ratio improved in all patients in both groups after proning.

The target time prone/day was 12 hours in Group 1 and 19.5 hours in Group 2. In Group 1 and Group 2 we achieved respectively a mean prone duration of 10 hours/24 hours (range 7:51-13:00/24 hours) and 15.2 hours/24 hours (range 8:40-19:30/24 hours).
Adverse events in all 64 patients were similar to rates reported in the literature for ALI/ARDS patients treated supine and proned manually. (Table 3) Although facial edema occurred in all patients, it improved during the supine interval and did not interfere with eye or oral assessment. Increased sedation requirement was common with the automated kinetic therapy proning unit. One full thickness skin breakdown occurred, which led to a change in the device configuration, and there was one corneal abrasion. There was a significant decrease in endotracheal tube problems (p= 0.048), an increase in gastric tube dislodgment (p= 0.006) and a trend for fewer pressure sores (p= 0.058). (Table 3)

In ARDS patients with pneumonia, we observed, but did not quantify, an increase in the secretions mobilized in the prone period compared with supine position. Six patients with initial pleural effusion had follow up CTs. Five of these patients' effusions were smaller by CT within 48 hours.

LIS significantly improved from baseline at day one and at day four. By day four only 36 of the 64 patients still met criteria for continued prone therapy. (Figure 4)

Hospital mortality was 31.3% with a mean APACHE III score of 90 (n =20). Mean APACHE III score of survivors was 70 (n = 44). (Table 4)
Discussion

Animal studies show a reduction in VALI in the prone compared to supine position and data in animals and humans demonstrate the prone position produces improved V/Q match, oxygenation, pleural pressures, reduced dorsal atelectasis and consolidation. [7,10,15,30-34] Whether these will result in improved outcomes is a matter of substantial debate. The two largest randomized trials of proning in humans for treatment of ARDS did not show benefit and were limited by proning for only 8 hours per day with missed episodes of proning and crossover from supine to prone treatment. A third trial suggested that proning for 20 hours per day improved outcomes in ARDS. In this trial after adjusting for severity of illness, mortality improvement reached statistical significance. [19,20] Prone positioning in severe ARDS is often delayed and used in the United States as a rescue intervention, partly due to the difficulty and complications of manually proning patients which could be overcome by this device.

In our trial, adverse events related to automated kinetic therapy proning, with the exception of gastric tube dislodgment, were equal to or less frequent than that previously reported with supine or manual prone positioning in treatment of ALI/ARDS. This suggests that the device is safe as used in our patients. Since our study was designed to look specifically for adverse events it is unlikely that we captured fewer than the comparison groups, reinforcing that the device is safe.
This automated unit allowed one nurse to achieve the prone position up to 19.5/24 hours using a proning interval of 3 hours 15 minutes and a supine interval of 45 minutes. This dose of proning improved pulmonary pathophysiology (LIS) without increasing complications or disruption of routine nursing care delivery.

Benefits of prone position with Kinetic Therapy in ARDS patients include increased mobilization of secretions, improved lung compliance, LIS, lung recruitment and decreased FiO₂ requirement.

All patients received kinetic therapy to 62° lateral rotation. Therefore we were unable to separate the contribution of proning from kinetic therapy. However, we felt it unethical to keep the patient either supine or prone without frequent body movement, given the known benefit in prevention of skin breakdown, mobilization of pulmonary secretions, lung recruitment and reduction of ventilator associated pneumonia. [22-25,35] The only significant adverse events attributed to the device or the position was a corneal abrasion which healed and a full-thickness skin breakdown on one patient which was due to movement of a bed pad; this device problem was promptly corrected.

Chest CT scans showed recruitment of dorsal consolidated lung and decrease in the size of pleural effusions within 48 hours. (Figure 3 A-D) Dorsal lung recruitment in the prone position is facilitated by resting the heart on the sternum, moving its weight off the lung, lowering the diaphragm as the abdominal contents fall ventrally, and suspending the dorsal lung from the pleura. These
factors result in lower and more evenly distributed pleural pressures and ventilator stress forces while expanding rather than compressing the dorsal lung. [3,4,10] Additionally, the anterior chest wall and lung are restricted in the prone position. These factors, along with mobilization of secretions, result in dorsal lung recruitment, protection of the ventral lung from VALI and improved oxygenation. [8,12-14,16]

Our study is limited by a number of factors: a) The use of historical control groups; however, the low rates of significant adverse events that we report in this study specifically designed to look at complications of proning a patient with one nurse suggest that our safety and efficiency conclusions are correct. b) Our case report forms for the second group of 45 patients did not break out the individual components of LIS. Therefore we do not know which parameter or parameters contributed most to the improved score. c) Data was not collected on fluid balance so CT scan improvement in pleural effusions could be multifactorial; however, it is possible that a mechanism of decreased pleural effusion observed with proning is improved lymphatic drainage of the lung and pleura, since the majority of the lung is above the heart in the prone position were as the reverse is true in the supine position [9]. In addition, proning shifts pleural fluid to areas with less adjacent consolidated lung and inflammation, possibly increasing absorption. In future proning trials, evaluation of pleural effusion should be considered.
Our study was not designed nor powered to evaluate the effect of this
device on ARDS mortality. Mortality of 31.2% (Table 4 and Figure 5) is consistent
with outcome of the ARDS NET low tidal volume trial. As expected, patients who
died had higher APACHE scores than survivors (Table 4). This pilot trial suggests
this device is safe, based on the incidence of adverse events reported and
mortality consistent with best practice.

In the 12 hour proning group, we achieved an average of 10 hours/24
hours prone and in the 19.5 hour group an average of 15.2 hours/24 hours, the
reduction due to time supine for transport and procedures. Increased sedation
was required with this proning device.

The low number of adverse events with 1:1 or 1:2 nurse/patient ratio
achieved proning up to 19.5 hours/day, suggest that this modality, with up to 19.5
hours/day, should be considered when comparing proning to standard care for
ARDS and ALI. Other possible effects of proning need to be studied, including the
effect on pleural effusions, sinus drainage, gastric drainage and intra-abdominal
pressure.

Conclusion

There are substantial data in animals and humans which support improved
pulmonary pathophysiology with prone positioning in ALI/ARDS, including rapid
mobilization of secretions, improved oxygenation, recruitment of dorsal
consolidated lung and reduction of VALI. It is possible that benefit from proning in ALI/ARDS was not demonstrated in two of three large randomized studies due to ineffective dosing and difficulty of administering prone therapy. Increased proning can be accomplished safely, with one nurse, using this technology. These findings will likely broaden the application of an automated laterally rotating proning device in the study and treatment of ALI/ARDS.
Figure 1 A, An example of pleural pressures in the supine (A) and prone (B) position in cm H2O.
Figure 2 A, 2B. Automated Kinetic Therapy Proning Unit. (A) Prone position; (B) Supine position at 40°
Figure 3.  (A) Patient #1 at therapy-unit placement (B) Patient #1 at therapy-unit placement at 48 hours (C) Patient #13 at therapy-unit placement (D) Patient #13 at therapy-unit placement at 48 hours (E) Patient #15 at therapy-unit placement; homogeneous ARDS (F) Patient #15 at therapy-unit placement at 48 Hours; homogeneous ARDS (G) Patient #20 at therapy-unit placement (This patient was excluded from the study due to age, but had a dramatic response and survived) (H) Patient #20 at therapy-unit placement at 48 Hours (I) Patient #20 at therapy-unit placement (J) Patient #20 at therapy-unit placement at 48 Hours at 48 Hours
Figure 4. Lung physiology parameters

Figure 5. Mortality with Exact 2-Sided 95% Binomial Confidence Limits
Table 1  Patient Selection

Inclusion Criteria

Acute onset of:

- \( \text{PaO}_2 / \text{FiO}_2 \leq 300 \)
- Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric
- Requirement for positive pressure ventilation via endotracheal tube
- No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure \( \leq 18 \text{ mmHg} \)
- Criteria must coexist within a 24-hour interval

Exclusion Criteria

- Inability to obtain informed consent
- Intracranial hypertension
- Open abdomen or recent median sternotomy
- Weight \(< 100 \text{ lbs or } > 400 \text{ lbs.} \)
- Height \(< 4' 6'' \text{ or } > 6' 6'' \)
- Unstable fracture
- Pregnancy
- Nasal tracheal intubation

Precautions

- Hemodynamic instability
- Uncontrolled agitation or severe claustrophobia
- Wounds at risk of dehiscence
- Implants susceptible to tissue erosion or skin breakdown (e.g., breast, penile, pacemaker)
### Table 2  Baseline Characteristics Comparing the First 19 Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1 12 hours of proning</th>
<th>Group 2 19.5 hours of proning</th>
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<tr>
<td>Patients</td>
<td>10</td>
<td>9</td>
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<tr>
<td>Age</td>
<td>61</td>
<td>57.8</td>
<td>.70</td>
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<tr>
<td>Acute Physiological Score -Day 1</td>
<td>60.9</td>
<td>54.3</td>
<td>.52</td>
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<tr>
<td>APACHE III-Day1</td>
<td>72.7</td>
<td>64.7</td>
<td>.49</td>
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<tr>
<td>LIS</td>
<td>3.2 (10)</td>
<td>3.1 (9)</td>
<td>.58</td>
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<td>PaO₂/FiO₂ ratio (mm/Hg)</td>
<td>125.5 (10)</td>
<td>131.0 (9)</td>
<td>.77</td>
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<tr>
<td>Compliance (ml/mbar)</td>
<td>33.7 (10)</td>
<td>35.3 (9)</td>
<td>.77</td>
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### Baseline Characteristics of All Patients 64

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<table>
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<tbody>
<tr>
<td>Age</td>
<td>52.8</td>
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<tr>
<td>Female</td>
<td>28(44%)</td>
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<tr>
<td>Male</td>
<td>38(66%)</td>
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<tr>
<td>Heart rate (BPM)</td>
<td>100.9</td>
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<td>Mean arterial pressure (mm Hg)</td>
<td>79.46</td>
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<td>Respiratory rate (BPM)</td>
<td>22.59</td>
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<td>Initial pO₂ / FiO₂ ratio</td>
<td>117.65</td>
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<td>Lung Injury Score</td>
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<td>Lung compliance</td>
<td>32.56</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.55</td>
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<tr>
<td>Bilirubin</td>
<td>1.37</td>
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<tr>
<td>APACHE III</td>
<td>76.45</td>
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<td>Studies</td>
<td>Study A</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>N</td>
<td>Supine</td>
</tr>
<tr>
<td></td>
<td>(n=378)</td>
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<tr>
<td>Hours Proned/24 hrs</td>
<td>0</td>
</tr>
<tr>
<td>Scleral Hemorrhage/Corneal Abrasion</td>
<td>N/A</td>
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<tr>
<td>New or Worsening Pressure Sores</td>
<td>42%</td>
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<td>Kinked / Obstructed/ loss of Endotracheal Tube or Selective Intubation</td>
<td>16%</td>
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<tr>
<td>Loss of functioning Vascular Access</td>
<td>N/A</td>
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<tr>
<td>Obstructed or Displacement Chest Tube or Pneumothorax</td>
<td>8%</td>
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<td>Loss of Oral Nasal Gastric Tube of Foley Catheter</td>
<td>N/A</td>
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<td>Increased Need for Muscle Relaxants</td>
<td>0%</td>
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<tr>
<td>Hemodynamic Instability or Dysrhythmia</td>
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7 F. Current study
Table 4. Mortality vs. APACHE III Score

<table>
<thead>
<tr>
<th>HOSPITAL DISCHARGE</th>
<th>N</th>
<th>APACHE SCORE MEAN</th>
<th>APACHE SCORE MEDIAN</th>
<th>P VALUE</th>
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<tr>
<td>ALIVE</td>
<td>44</td>
<td>70.23</td>
<td>66.50</td>
<td>0.006</td>
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<tr>
<td>DEAD</td>
<td>20</td>
<td>90.30</td>
<td>82.50</td>
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</tbody>
</table>
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