4A Randomized Trial of Prolonged Prone Positioning in Children With Acute Respiratory Failure*

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Study objective: To compare the effect of the prone position (PP) vs supine position (SP) on oxygenation in children with acute respiratory failure (ARF).

Design: Prospective, randomized controlled trial.

Setting: A 36-bed pediatric critical-care unit in a tertiary-care, university-based children’s hospital.

Patients: Ten children (mean [SD] age, 5 ± 3.6 years) with ARF with a baseline oxygenation index (OI) of 22 ± 8.5.

Interventions: Following a period of stabilization in the SP, baseline data were collected and patients were randomized to one of two groups in a two-crossover study design: group 1, supine/prone sequence; group 2, prone/supine sequence. Each position was maintained for 12 h. Lung mechanics and acute response to inhaled nitric oxide were examined in each position.

Measurements and main results: OI was significantly better in the PP compared to the SP over the 12-h period (analysis of variance, p = 0.0016). When patients were prone, a significant improvement in OI was detected (7.9 ± 5.3; p = 0.002); this improvement occurred early (within 2 h in 9 of 10 patients) and was sustained over the 12-h study period. Static respiratory system compliance and resistance were not significantly affected by the position change. Inhaled nitric oxide had no effect on oxygenation in either position. Urine output increased while prone, resulting in a significantly improved fluid balance (+ 6.6 ± 15.2 mL/kg/12 h in PP vs + 18.9 ± 13.6 mL/kg/12 h in SP; p = 0.041). No serious adverse effects were detected in the PP.

Conclusion: In children with ARF, oxygenation is significantly superior in the PP than in the SP. This improvement occurs early, remains sustained for a 12-h period, and is independent of changes in lung mechanics.

Key words: acute respiratory failure; children; lung mechanics; nitric oxide; oxygenation; oxygenation index; prone position; supine position

Abbreviations: ANOVA = analysis of variance; ARF = acute respiratory failure; Cst,w = thoracoabdominal cage compliance; Fio2 = fraction of inspired oxygen; iNO = inhaled nitric oxide; NO = nitric oxide; OI = oxygenation index; Paw = mean airway pressure; PEEP = positive end-expiratory pressure; PP = prone position; Ppl = pleural pressure; ppm = parts per million; PSS = prone/supine sequence; SP = supine position; SPS = supine/prone sequence

The positive effect of the prone position (PP) on oxygenation has been known for about 25 years. In 1974, Bryan¹ was the first investigator to suggest the use of the PP in patients receiving mechanical ventilation. Subsequent CT studies demonstrating heterogeneous distribution of disease in ARDS, generally limited to dependent zones with sparing of nondependent zones, have stimulated increased attention to positioning.² Adult studies have demonstrated that the rotation of selected patients with acute respiratory failure (ARF) from a supine position (SP) to a PP is associated with improved oxygenation.³–⁸ The existing literature consists of case reports or case series, and randomized controlled trials or outcome studies are not available at this

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time. Most reports are limited to short-term prone positioning (4 h), with only two studies evaluating the longer-term effect of the PP, but in selected adult patients. It has not been established whether the improved oxygenation is related to the PP itself, the act of rotating position, or both. Currently, the PP is used more as a transient rescue maneuver rather than a primary modality of treatment.

Prone positioning is an attractive therapy in children because of its relative simplicity and ease due to small patient size. The reported use of the PP in children is limited to only two studies, both of short duration (30 min and 1 h, respectively) and with contradicting results. This randomized controlled study was designed to compare the effect of prolonged prone to supine positioning on oxygenation in children with moderate to severe ARF.

Materials and Methods

During a 12-month period (July 1997 through June 1998), consecutive children aged 8 weeks to 16 years requiring mechanical ventilation for moderate to severe ARF were potential candidates for the study. For the purpose of this study, ARF was defined as the acute presentation of lung disease with bilateral radiologic infiltrates without clinical evidence of cardiogenic shock. Consecutive children aged 8 weeks to 16 years requiring mechanical ventilation for moderate to severe ARF were potential candidates for the study. The reported use of the PP in children is limited to only two studies, both of short duration (30 min and 1 h, respectively) and with contradicting results. This randomized controlled study was designed to compare the effect of prolonged prone to supine positioning on oxygenation in children with moderate to severe ARF.

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The hospital Research Ethics Board approved the study protocol, and families were approached for informed consent.

Mode of Ventilation

Management of ventilation and oxygenation remained at the discretion of the attending physician. In general, this unit employs a lung protective strategy with high PEEP level, low tidal volumes (5 to 10 mL/kg), and permissive hypercapnea. Synchronized intermittent mandatory ventilation with pressure or volume control (Siemens Servo 300 C; Elema AB; Solna, Sweden) was applied to nine patients, and high-frequency oscillation (model 3100A; SensorMedics; Yorba Linda, CA) in one patient. The general approach to improving oxygenation was the initial weaning of FIO₂ to 0.5 followed by reduction in PEEP or peak inspiratory pressure, maintaining PaO₂ >60 mm Hg.

Study Protocol

A randomized controlled trial comparing supine to prone positioning was performed with a two-crossover study design, in order to control for the natural history of the disease over time and the position sequence effect. Following a period of stabilization in the steady-state SP, baseline data were collected and patients were randomized to one of two groups. Group 1 was the supine/prone sequence (SPS): subjects remained in SP for 12 h followed by PP for 12 h. Group 2 was the prone/supine sequence (FSS): patients were placed in PP for 12 h followed by SP for 12 h. The total study duration was 24 h.

All patients were sedated with a continuous infusion of morphine and/or midazolam. Five patients who were paralyzed with pancuronium bromide remained so for the duration of study. Diuretic treatment, if instituted before the study, was unchanged over the study period.

Data (hemodynamic parameters, arterial blood gas analysis, and respiratory parameters) were collected at baseline SP and then at 30 min and at 2, 4, 6, 8, and 12 h for each position. Fluid balance (in milliliters per kilogram) was calculated at the end of each position (total fluid intake minus total urine output). Total static respiratory system compliance and total respiratory system resistance were performed at the end of the first position and within the third hour of the second position. Any changes in inotropic support, sedation, or clinical side effects were recorded.

A challenge with inhaled nitric oxide (iNO) was performed in each position (30 parts per million [ppm] for 40 min) and then discontinued regardless of effect. Mechanical ventilation settings and vasoactive agents were kept constant during this period. Arterial blood gases and ventilatory and hemodynamic parameters were collected before iNO, and 40 min after iNO was commenced.

Lung Mechanics

Airflow was measured with a low-dead space thermistor pneumotachograph (Bear NVM-1; Bear Medical Systems; Riverside, CA) inserted between the endotracheal tube and the ventilator Y piece. A change in lung volume was obtained by integration of the flow signal. Airway opening pressure was measured at the proximal end of the endotracheal tube using a pressure transducer (Validyne MP45; Validyne Engineering, Northridge, CA). Both flow and pressure signals were recorded on-line by a personal computer using analog-to-digital conversion at a sampling rate of 250 Hz (DT2801A; Data Translation; Marlborough, MA) and specially designed software allowing data acquisition, valve control, and final analysis. For measurement of the compliance and resistance of the respiratory system, the pressure signal during occlusion and the flow signal during exhalation were used, based on the principle described by Lesouef et al.

Nitric Oxide Administration

Nitric oxide (NO) was released from a tank containing NO in nitrogen at a concentration of 500 ppm. NO was delivered into the inspiratory limb of the patient ventilator circuit, just distal to the humidifier. Flow was titrated into the circuit to deliver the prescribed level of NO. Inspired gas was continuously sampled from the inspiratory limb close to the patient endotracheal tube. Both NO and NO₂ concentration were analyzed with a SensorNOx analyzer (SensorMedics).

Prone Positioning

The patient was placed in the PP with head placed in a lateral position with the elbows flexed or extended. The pelvis was supported with a small pillow and a folded sheet was placed under the chest to allow the abdomen to be suspended. Abdominal suspension was considered an important factor in the effectiveness of prone positioning and was confirmed by the ability to pass a hand between the abdomen and the bed.
Data Analysis

Data are expressed as the mean \pm SD. Statistical calculations were performed using a software package (BMDP Statistical Software; Los Angeles, CA). Analysis of variance (ANOVA) for repeated measurements was performed in order to compare the OI in different positions. Paired samples, where variables were measured only twice in each individual, were compared with paired Student’s t test. The other statistical evaluations were made according to Student’s t test. A p value of 0.05 was considered statistically significant. A 20% change in OI was considered to be clinically significant.

RESULTS

Twelve patients were enrolled and 10 patients concluded the study. Two patients were excluded after enrollment due to physical restrictions preventing prone positioning (abdominal burns, cervical collar). Patient demographics are reported in Table 1. Infection-related respiratory failure was the primary etiology in 8 of 10 cases.

Patients’ mean baseline data (Table 1) were as follows: OI, 22 \pm 8.5; \text{PaO}_2/\text{FiO}_2, 97 \pm 29 \text{ mm Hg}; and PEEP, 11.2 \pm 2.2 \text{ cm H}_2\text{O}. Prior to enrollment, the mean duration of respiratory illness was 6.4 \pm 3 days and patients received mechanical ventilation for 3.0 \pm 1.8 days.

Mean values of OI by position at the different time points for the 10 patients are reported in Figure 1, and for single patient in position-sequence subgroups in Figures 2, 3. Comparison of OI in PP vs SP demonstrates significant superiority in the PP (ANOVA, p = 0.0016). When children were prone, oxygenation improvement appeared within 30 min, and was well established by 2 h (Fig 4). The mean improvement of OI was evaluated after 2 h in the PP and compared to baseline supine data (PSS group) or the last supine measurement (SPS group; Fig 2, 3). The improvement in OI was 7.9 \pm 5.3 \text{ U}(34 \pm 17\%; p = 0.002) and was considered clinically significant in 9 of 10 patients, as defined \textit{a priori} by a change in OI of > 20\%. Patient 7 (with aspergillosis pneumonia after bone marrow transplantation) showed a smaller improvement within the first 2 h (17\%), but the OI improved by 30\% after 4 h in the PP. The improvements were sustained over the 12-h period, with a mild deterioration that was transient in three patients (Fig 2, 3).

Hemodynamic and ventilation parameters were not affected by position change. There were no significant changes in mean heart rate, mean arterial pressure, and \text{PaCO}_2 (data not shown). PEEP levels were not significantly altered after position change (10.9 \pm 2.3 \text{ cm H}_2\text{O} in SP vs 10.2 \pm 2.3 \text{ cm H}_2\text{O} in PP).

Lung mechanics were performed in nine patients and showed no differences (data not shown). Mean total respiratory system static compliance in SP and PP was 0.42 \pm 0.16 mL/cm H\text{2}O/kg and 0.49 \pm 0.22 mL/cm H\text{2}O/kg, respectively.

<table>
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<th>Patient No.</th>
<th>Group</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Gender</th>
<th>Baseline OI</th>
<th>Baseline \text{PaO}_2/\text{FiO}_2</th>
<th>Intubation Before Study, d</th>
<th>Outcome</th>
<th>Diagnosis</th>
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<td>21.3 ± 7.9</td>
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<td>22 ± 8.5</td>
<td>97 ± 29</td>
<td>3 ± 1.8</td>
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*M = male; F = female; S = survived; D = died; BMT = bone marrow transplantation; RSV = respiratory syncytial virus.

†Mean ± SD of each group.
‡Mean ± SD of all patients.
Resistance in SP and PP was $0.058 \pm 0.053$ cm H$_2$O/mL/s and $0.057 \pm 0.05$ cm H$_2$O/mL/s, respectively ($p = 0.6$).

Nine patients had an iNO challenge in the PP and SP. No significant changes in oxygenation were detected in individual patients as well as the overall group. The mean OIs in the PP before and after iNO were 12 ± 6.6 and 11.8 ± 6.7, respectively. The mean OIs in the SP before and after iNO were 16.6 ± 8.2 and 16.9 ± 9.5, respectively.
In nine patients, fluid balance was calculated for the 12-h period in each position. The mean fluid balance over the 12-h period was significantly less positive in PP than in SP (6.6 ± 15 mL/kg/12 h vs 18 ± 13.6 mL/kg/12 h, respectively; p = 0.041; Fig 5).

The only minor adverse effect of PP was facial edema, which occurred in three patients. No increments in sedation or analgesia were required.

Figure 3. Individual patient oxygenation expressed as OI in group 2 (PSS). Baseline OI is in SP on recruitment. OI values at different time points are given in Table 1.

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Figure 4. Individual patient oxygenation response in the first 2 h of PP. The improvement in OI was 7.9 ± 5.3 (34 ± 17%; p = 0.002).
This study demonstrates that oxygenation in children with ARF is significantly better in the PP. Improvement in oxygenation is achieved within 2 h after position change, and is sustained over the 12-h period. Position change was not associated with changes of lung mechanics and does not result in any change in responsiveness to iNO. Patients in the PP tend to improve their urinary output.

Comparisons over six time points in the 12-h period shows dramatically better oxygenation in the PP compared to SP (ANOVA, p = 0.0016; Fig 1). Considering the study was conducted as a crossover study, the increased and sustained oxygenation in PP should be attributed to the position itself and not to the natural history of the disease. This is also supported by the deterioration in OI in all PSS patients on return to the SP.

A great variability in oxygenation response in adults has been described by previous investigators, ranging from dramatic improvement, to no improvement, to deterioration. While a small sample size in the present study may limit generalization, all children experienced clinically significant improvement in oxygenation in the PP, compared to the 45 to 90% response reported in adults.

Previous studies have shown that if an improvement in oxygenation does occur, it appears within the 30 min, or at least in the first 2 h. We confirmed this finding in children; 9 of 10 patients improved within the first 2 h (Fig 4), and except for 3 patients with a transient mild deterioration, this improvement persisted over time (Fig 2, 3). The fact that oxygenation continues to improve over time may suggest that the PP has a prolonged beneficial effect.

Most studies are limited to the short-term effect of the PP in its use as a transient rescue maneuver, rather than a modality of care. Only two studies evaluated PP beyond 4 h in a relatively large number of selected patients, but both studies have methodologic flaws.

The effect of PP in children has been evaluated in two previous studies with conflicting results. Murdoch and Storman reported a significant improvement in hemoglobin saturation, which appeared in seven of seven patients within 30 min. However, Numa et al. failed to show such improvement in 30 children. The lack of improvement in the study by Numa et al. may be attributed to the short time that the children were in PP (1 h) as well as to the position itself; children were put prone without a pillow beneath the pelvis, which may reduce the pressure of the abdominal contents on the diaphragm. Although improved oxygenation has been reported in adults without the use of pelvic support, abdominal suspension may have more significance in children.

iNO has been shown to improve oxygenation and decrease pulmonary arterial pressure in adults and children with ARDS. This effect is due to its selective vasodilator effect on the ventilated regions of the lung. Since one of the speculated mechanisms by which PP improves oxygenation is alveolar recruitment in the dependent zones, PP may enhance the effect of iNO, as shown by Papazian et al. In order to reevaluate this hypothesis, we compared the effect of iNO in SP to PP. No improvement in oxygenation in response to iNO was manifested in any patient regardless of position. As the response to iNO in ARDS is quite variable and unpredictable, this finding is not unusual and may have been influenced by the short duration of exposure (40 min) and/or the dose (30 ppm) of iNO. Since pulmonary vascular resistance or pulmonary arterial pressures were not evaluated, we cannot exclude a hemodynamic effect.

Interestingly, we found that the fluid balance was
less positive in the PP than in the SP (p = 0.041). Since diuretic treatment was unchanged during the study, we attributed the improvement in urinary output to the PP itself. Although cardiac output has not been measured in this study, previous studies in adults as well as in children have not shown changes in cardiac output during PP.\(^4\,11\,20\) We speculate that a reduction in intra-abdominal pressure during the PP, or the relief of direct compression on the kidney, vessels or urinary tract by the abdominal contents, may have been responsible for this improvement in urinary output. Previous studies failed to show changes in intra-abdominal pressure during the PP.\(^20\) We believe that the method (by which we performed the PP) ensuring abdominal suspension may have a major impact on decreasing the intra-abdominal pressure. The adverse effect of elevated intra-abdominal pressure and urinary output has been well documented.\(^21,\,22\) This observation is provocative and should be confirmed. Since the precise mechanism by which the PP improves oxygenation has not been well established, the “diuretic” effect of prone positioning may play a role.

Pellosi et al\(^23\) reported that improved oxygenation in the PP is directly correlated with a reduction in thoracoabdominal cage compliance (Cst,w). The greater the decrease in the compliance in PP, the greater the improvement in oxygenation. The greater the baseline Cst,w in the SP, the greater the improvement in oxygenation in the PP. In the SP, the more compliant sternal part of the chest wall is free to move, while when in PP, this part is compressed and less mobile. This may contribute to an overall uniform compliance in PP and, as a result, more uniform ventilation. Gattinoni et al\(^24\) have observed that Cst,w is primarily decreased in adult extrapulmonary/extrinsic ARDS, compared to intrinsic ARDS. The fact that children have higher chest wall compliance than adults and our study patients largely had intrinsic ARDS (Table 1) may explain why our study population showed a more dramatic and persistent improvement compared to adult reports.

As in the previous two studies,\(^12,\,23\) we failed to show a correlation between changes in lung compliance or resistance and the position change. It is likely that the primary mechanism of improved oxygenation in PP is related to regional changes that are not detectable when total lung or total respiratory system parameters are measured. Studies in animal models\(^25\) and humans\(^26\) show that the gravitational pleural pressure (Ppl) is more uniform in PP than in SP (ie, less gravitational gradient). In SP, the Ppl in the dependent regions is more positive (less negative), which exposes this part of the lung to closing pressure and results in alveolar collapse. In PP, the Ppl become more negative (the transpulmonary pressure increases), potentially allowing previously atelectatic regions to reopen. This could result in more uniform ventilation. CT studies at end-expiration support this premise.\(^2\)

The available data on lung perfusion in PP are inconsistent but suggest that gravity has a very limited effect on its general distribution.\(^27\) Nyren et al\(^28\) has shown that PP may affect perfusion in a similar way to ventilation: perfusion becomes more uniformly distributed. More uniform regional ventilation and perfusion contributes to improving ventilation-perfusion matching and thereby improves oxygenation.

Turning children in the PP is logistically a simple maneuver, compared to adults, for obvious size and weight reasons. Potential risks of the PP include accidental extubation, dislodgment of vascular lines, pressure sores including corneal abrasions, traction injuries to the brachial plexus, and spinal injury.\(^7\) In the present study, no significant complications were detected and no increments in sedation were required. However, physical restrictions may prevent the use of PP as shown by two patients who were excluded on this basis (cervical collar, extensive abdominal burns). Patient 10 required continuous venovenous hemofiltration via femoral venous access without compromise. We should emphasize that the preference for nasal intubation in children may decrease the risk of spontaneous extubation.

Although overall outcome was not evaluated, the persistently improved oxygenation of this magnitude in the PP may potentially be translated into a reduction of pressure and oxygen requirements in the management of these patients, thereby limiting the risk of secondary lung injury and potentially improving outcome in large-scale clinical trial.

Prone positioning in children is effective, easy to perform, and safe. Although the physiologic basis for PP and the effect on outcome require further investigation, we suggest that PP should be the preferred position for the management of oxygenation failure in children.

**References**