Gas exchange and lung inflammation using nasal intermittent positive-pressure ventilation versus synchronized intermittent mandatory ventilation in piglets with saline lavage-induced lung injury: An observational study*

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Objective: **Physiologic and pathologic comparison of two modes of assisted ventilation, nasal intermittent positive-pressure ventilation (NIPPV) and synchronized intermittent mandatory ventilation (SIMV), in spontaneously breathing term newborn piglets with saline lavage-induced lung injury.**

Design: **After inducing acute lung injury via repetitive saline lavage, piglets were randomized to NIPPV (n = 12) or SIMV (n = 11) and treated for 6 hrs.**

Setting: **Clinical laboratory.**

Subjects: **Spontaneously breathing term newborn piglets.**

Interventions: **Invasive (SIMV) or noninvasive (NIPPV) assisted ventilation for 6 hrs.**

Measurements: **Physiologic parameters and arterial blood gases were continuously monitored. At the conclusion of the study, lung tissue was obtained to analyze for evidence of inflammation, including myeloperoxidase, interleukin-8, and hydrogen peroxide levels, as well as for evidence of pathologic injury.**

Main Results: **Piglets treated with NIPPV demonstrated higher arterial blood gas pH ($p < .001$), lower $Paco_2$ ($p < .05$), and a lower set respiratory rate ($p < .0001$) as compared with the SIMV-treated piglets. The piglets in the SIMV group had higher Pao_2/PAO_2 ratio than those in the NIPPV group ($p = .001$). There was significantly more interstitial inflammation ($p = .04$) in the SIMV-treated piglets compared with the NIPPV-treated piglets. Total respiratory rate, heart rate, blood pressure, oxygen saturation, and biochemical markers of lung inflammation were not different between the groups.**

Conclusion: **In surfactant-deficient term newborn piglets, NIPPV offers an effective and noninvasive ventilatory strategy with the potential for less pathologic lung inflammation. (Crit Care Med 2008; 36:183–187)**

KEY WORDS: mechanical ventilation; continuous positive airway pressure; lung injury; animal model

The use of noninvasive ventilatory strategies in the treatment of respiratory distress syndrome may minimize lung inflammation and subsequent acute and chronic injury associated with mechanical ventilation. Increased early use of continuous positive airway pressure (CPAP) with avoidance of intubation has been shown to be an effective treatment for respiratory distress syndrome (1, 2). It also has been associated with a decreased incidence of chronic lung disease (2). However, for some preterm babies, CPAP does not offer sufficient ventilatory support to attain adequate ventilation. In these children, intubation and mechanical ventilation may be avoided and improved ventilation achieved by adding intermittent positive-pressure breaths to CPAP, a technique called nasal intermittent positive-pressure ventilation (NIPPV).

NIPPV is an intermediate form of ventilatory support. It is noninvasive, because an endotracheal tube is not required, but similar to mechanical ventilation in that intermittent breaths augment endogenous respiratory effort to improve minute ventilation. In a retrospective study, Dr. Villanueva and colleagues (3) found that NIPPV could be used to decrease respiratory distress and improve oxygenation in children with acute respiratory failure. In an observational study, synchronized NIPPV was used successfully after surfactant administration as an alternative to continued mechanical ventilation in selected babies (4). Additional studies in premature infants have demonstrated that NIPPV improves extubation success and decreases apnea of prematurity (4, 5, 6). However, to date, no studies have evaluated the physiologic and pathologic effects of NIPPV when used as a primary mode ventilation in a surfactant-deficient population. Therefore, we evaluated the effects of NIPPV vs. mechanical ventilation on markers of physiologic tolerance, inflammation, and lung injury in a saline washout model of acute lung injury in spontaneously breathing term newborn piglets.

MATERIALS AND METHODS

Twenty-five full-term, spontaneously breathing newborn piglets were studied. All animals were in their first week of life and of similar weight. Two piglets died before initiation of the study; one was not able to be successfully intubated, and the other died of a pulmonary hemorrhage during preparation.

***See also p. 349.**

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Animal Preparation. This study was approved by the Institutional Animal Care and Use Committee of Children's Hospital of Minnesota—St. Paul. Animal care was conducted in accordance with the National Institutes of Health guidelines (7). Each piglet was sedated with intramuscular ketamine (50 mg/kg) before preparation. Intubation was performed using a 3.5-mm internal diameter endotracheal tube. During the remainder of the preparation period, the piglets were mechanically ventilated using synchronized intermittent mandatory ventilation (SIMV) plus volume guarantee mode (Dräger Babylog 8000, Dräger America, Telford, PA). The ventilator settings during the preparation period were as follows: rate, 20 bpm (breaths per minute); F_{IO_2}, 1.0; maximal peak inspiratory pressure (PIP), 40 cm H_2O; peak end-expiratory pressure, 5 cm H_2O; inspiratory time. 0.35 secs; and tidal volume, 8 mL/kg.

After subcutaneous injection of 2% Xylocaine over the medial border of the sternocleidomastoid, the right lateral neck space was dissected to isolate the carotid artery and external jugular vein. The external jugular vein was catheterized and utilized for intravenous fluid and medication administration, including sedation via continuous ketamine infusion (5 mg/kg per hr) and respiratory augmentation with doxapram infusion (4 mg/kg per hr). A central arterial catheter was placed in the carotid artery and was used for continuous arterial blood gas and blood pressure measurements (Paratrend-7, Diametrics Medical, St. Paul, MN).

Experimental Protocol. Surfactant-deficient lung injury was achieved by repetitive saline lavage (40 mL/kg) via the endotracheal tube (8). The piglet was deemed surfactant deficient when, on a F_{IO_2} of 1.0, the Pa_{O_2} was <100 torr (<13,332 Pa) for 15 consecutive mins. Once the injury criteria were met, piglets were randomized via sealed envelope shuffle to NIPPV or SIMV for 6 hrs. If the piglet was randomized to NIPPV, it was extubated and placed on NIPPV with handmade nasal prongs (Airlife cannula, Cardinal Health, McGaw Park, IL). The piglet's mouth was taped shut and the NIPPV prongs were placed through Duoderm occlusive tape onto the snout to minimize air leaks. The average preparation time before randomization to SIMV was 120 ± 43 mins. The average preparation time before randomization to NIPPV was 145 ± 59 mins.

The SIMV parameters were as follows: rate 20 bpm, PIP 30 cm H_2O, peak end-expiratory pressure 5 cm H_2O, inspiratory time 0.35 secs, and tidal volume 8 mL/kg. The NIPPV parameters were as follows: rate 20 bpm, PIP 30 cm H_2O, peak end-expiratory pressure 5 cm H_2O, and inspiratory time 0.35 secs. The Dräger Babylog 8000 was used to provide NIPPV by disengaging the flow sensor, turning off the minute ventilation and apnea alarms, and setting the mode to conventional mechanical ventilation.

Arterial blood gas measurements and vital signs were obtained hourly throughout the 6-hr study period (SpaceLabs, Redmond, WA). F_{IO_2} was adjusted to maintain a target Pa_{O_2} of 80–100 torr (10,666–13,332 Pa). Initially, ventilator rate was adjusted to maintain a goal Pa_{CO_2} of 35–55 torr (4666–7333 Pa) with the protocol-stating to go up by 2 bpm to a maximum of 30 bpm and down by 1 bpm to a minimum of 15 bpm for persistent (>5 min) Pa_{CO_2} values outside of the goal parameters. If adjustments in the rate did not allow the goal Pa_{CO_2} to be achieved, then the PIP (if on NIPPV) or volume guarantee (if on SIMV) were adjusted to maintain a goal Pa_{CO_2} of 35–55 torr (4666–7333 Pa). The PIP was adjusted in increments of 2 cm H_2O and the volume guarantee was adjusted in 0.5 mL/kg increments when necessary. At the end of the 6-hr study period, the piglets were given a bolus of ketamine (200 mg) and then euthanized with a lethal dose of potassium chloride.

Lung Tissue Analysis. The lungs and heart were dissected *en bloc* immediately after each animal was euthanized. The lungs were perfused via the pulmonary artery with cold Millonig's phosphate buffer (9). The left lung was uniformly inflated three times by application of 30 cm H_2O pressure via bag valve mask, with sustained inflation before tying off the lung. The left lung was then formalin-fixed and embedded in paraffin. Five-micrometer sections from four consistent regional samples, including two samples each from the craniodorsal (nondependent) and caudal ventral (dependent) lobes of the left lung, were analyzed qualitatively with gross light microscopy at 4× and 40× magnification. Slides from each section were stained with hematoxylin and eosin and scored using a semiquantitative scoring system by a pediatric pathologist blinded to treatment group. Pathologic variables of lung injury—including alveolar and interstitial inflammation, alveolar and interstitial hemorrhage, edema, atelectasis, and necrosis—were each scored on a 0- to 4-point scale: no injury scored 0, injury in 25% of the field scored 1, injury in 50% of the field scored 2, injury in 75% of the field scored 3, and injury throughout the field scored 4 (10).

Consistent regional samples of the right lung were dissected with clean technique. Fresh samples weighing 300 mg were dried at 60°C for 84 hrs to obtain wet/dry ratios. The remaining samples were snap-frozen in liquid nitrogen, and stored at −80°C for subsequent analysis of interleukin-8, hydrogen peroxide (H_2O_2), and myeloperoxidase (MPO). Supernatants from lung tissue homogenates were used in all of the inflammatory marker assays. Supernatant recovery for the interleukin-8 and MPO enzyme-linked immunosorbent assays were performed as previously delineated (9, 11). The interleukin-8 enzyme-linked immunosorbent assay was performed on duplicate samples using porcine-specific capture and detection antibodies with recombinant porcine cytokine protein as positive controls (DuoSet Porcine IL 8, R&D Systems, Minneapolis, MN). The MPO assay was a "sandwich" enzyme-linked immunosorbent assay using human MPO antibodies for capture and goat anti-MPO antibodies for detection (Bioxytech MPO-EIA, Oxis Research, Portland, OR). H_2O_2 was assessed by a colorimetric, quantitative assay based on the oxidation of ferrous ions (Fe^{+2}) to ferric ions (Fe^{+3}) by hydrogen peroxide under acidic conditions (Bioxytech H2O2–560, Oxis Research, Portland, OR).

Statistical Analysis. Physiologic variables included respiratory rate, heart rate, mean blood pressure, arterial pH, Pa_{CO_2}, Pa_{O_2}, and oxygen saturations. Pathologic variables included scored microscopic evidence of lung injury, wet/dry ratios, and inflammatory marker levels (myeloperoxidase, interleukin-8, hydrogen peroxide) in the lung tissue. Data were analyzed using statistical software (Statview, SAS Institute, Cary, NC). Physiologic data were analyzed using analysis of variance for repeated measures. Inflammatory marker data were analyzed using the Mann-Whitney U test. Lung injury scores were analyzed using the Kruskal-Wallis test and Wilcoxon's rank-sum test, as appropriate. $p < .05$ was accepted as statistically significant.

RESULTS

Physiologic Data. Animals in each group were similar in size (SIMV group, 1.56 ± 0.14 kg; NIPPV group, 1.56 ± 0.20 kg). All animals had similar blood gases, heart rates, blood pressures, and oxygen levels after induction of lung injury (baseline) (Table 1). Throughout the study, NIPPV-treated piglets had higher pH ($p < .001$) and lower arterial partial pressure of carbon dioxide (Pa_{CO_2}) levels ($p < .05$) than those treated with SIMV. These differences in ventilation were significant, and increased over time during the experiment (Table 1). Piglets in the NIPPV group also had significantly fewer mechanically supported breaths per minute than those in the SIMV group ($p = .0001$). However, the piglets' intrinsic respiratory rates were not significantly different between the two groups ($p = .09$) (Fig. 1). Arterial-alveolar oxygen tension ratio, or Pa_{O_2}/P_{AO_2} ratio, defined as the arterial partial pressure of oxygen divided by the alveolar partial pressure of oxygen, were used to assess oxygenation status in each group, because Pa_{O_2}/P_{AO_2} ratio is known to decrease with pulmonary disease and is relatively unaffected by increasing supplemental oxygen. The piglets in the SIMV group had higher Pa_{O_2}/P_{AO_2} ratio than those in the NIPPV group ($p = .001$) (Table 1). However, there were no significant differences in the arterial Pa_{O_2} values ($p = .11$) in each group. For the

Table 1. Physiologic and arterial blood gas variables

Time	Groups	FIO_2	RR	HR	MBP	pH[a]	$PaCO_2$[b]	PaO_2	$P(A\text{-}a)O_2$[c]
Baseline	SIMV	1.0	49 ± 21	170 ± 26	61 ± 3.1	7.35 ± 0.06	45 ± 9.1	86 ± 9.3	0.12 ± 0.02
	NIPPV	1.0	47 ± 17	160 ± 21	64 ± 5.4	7.35 ± 0.07	44 ± 3.9	83 ± 9.2	0.12 ± 0.02
Hr 1	SIMV	0.83 ± 0.19	80 ± 47	144 ± 27	69 ± 16	7.32 ± 0.04	43 ± 4	82 ± 16	0.17 ± 0.1
	NIPPV	0.90 ± 0.19	73 ± 21	166 ± 38	87 ± 12	7.31 ± 0.08	45 ± 10	79 ± 17	0.16 ± 0.1
Hr 2	SIMV	0.60 ± 0.25	75 ± 44	155 ± 26	77 ± 12	7.33 ± 0.05	42 ± 6	88 ± 13	0.29 ± 0.1
	NIPPV	0.85 ± 0.23	83 ± 14	178 ± 34	81 ± 8	7.38 ± 0.05	40 ± 6	81 ± 11	0.17 ± 0.1
Hr 3	SIMV	0.50 ± 0.21	79 ± 45	178 ± 38	78 ± 11	7.35 ± 0.06	41 ± 7	88 ± 14	0.36 ± 0.2
	NIPPV	0.69 ± 0.28	75 ± 9	192 ± 44	79 ± 9	7.38 ± 0.05	39 ± 7	84 ± 7	0.24 ± 0.1
Hr 4	SIMV	0.45 ± 0.22	78 ± 40	189 ± 36	80 ± 11	7.35 ± 0.07	40 ± 7	89 ± 15	0.43 ± 0.2
	NIPPV	0.62 ± 0.3	75 ± 13	196 ± 47	80 ± 12	7.40 ± 0.04	37 ± 3	84 ± 10	0.29 ± 0.2
Hr 5	SIMV	0.42 ± 0.24	78 ± 41	198 ± 31	80 ± 11	7.35 ± 0.07	40 ± 7	89 ± 14	0.49 ± 0.2
	NIPPV	0.53 ± 0.30	73 ± 12	201 ± 47	76 ± 8	7.43 ± 0.04	36 ± 4	85 ± 12	0.37 ± 0.2
Hr 6	SIMV	0.41 ± 0.26	77 ± 42	203 ± 31	77 ± 10	7.36 ± 0.07	39 ± 7	85 ± 14	0.5 ± 0.3
	NIPPV	0.51 ± 0.3	78 ± 21	205 ± 42	78 ± 10	7.42 ± 0.03	34 ± 3	84 ± 12	0.39 ± 0.2

RR, intrinsic respiratory rate (breaths per minute); HR, heart rate (beats per min); MBP, mean blood pressure (mm Hg); SIMV, synchronized intermittent mandatory ventilation; NIPPV, nasal intermittent positive pressure ventilation.

[a] $p \leq .001$; [b] $p < .05$; [c] $p = .001$ (analysis of variance). Data are shown as mean ± SD of time-averaged hourly points.

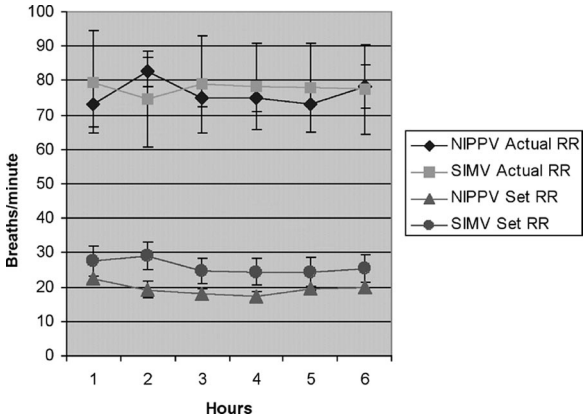

Figure 1. Summary of intrinsic respiratory rates and mechanical breaths, showing mean ± SE of the time-averaged hourly points. Each group's average intrinsic respiratory rate (*RR*) is noted in the upper half of the graph. The number of mechanical breaths in each group is noted in the lower half of the graph. While the intrinsic respiratory rate of each group was not significantly different, there were significantly fewer mechanically supported breaths delivered to the nasal intermittent positive-pressure ventilation (*NIPPV*)-treated group compared with the synchronized intermittent mandatory ventilation (*SIMV*)-treated group ($p = .0001$).

duration of the study, the mean blood pressures ($p = .09$) and heart rates ($p = .17$) were not significantly different in either group.

Inflammatory Markers. There were no significant differences in myeloperoxidase ($p = .83$), interleukin-8 ($p = .55$), or hydrogen peroxide ($p = .48$) levels between the SIMV- and NIPPV-treated groups.

Lung Injury. Pathologic lung injury scores included assessment of alveolar and interstitial inflammation, alveolar and interstitial hemorrhage, edema, atelectasis, and necrosis. The lung injury scores from all four lung sections were summed for an assessment of total lung injury per pathologic variable. Individual scores from all four sections were not different. The SIMV-treated piglets had increased interstitial inflammation compared with those treated with NIPPV ($p = .04$) (Table 2). There were no significant differences between the groups when comparing alveolar inflammation, alveolar hemorrhage, interstitial hemorrhage, edema, atelectasis, or necrosis. Further assessment of lung tissue edema using wet to dry ratios demonstrated no significant difference in wet/dry ratios between the two groups ($p = .66$).

DISCUSSION

In this comparison of NIPPV to intubated SIMV in surfactant-deficient term newborn piglets, we saw improved ventilation and a trend toward less lung inflammation during the noninvasive form of treatment, NIPPV. Even with active weaning of respiratory support, the NIPPV-treated piglets maintained the same average respiratory rate as those treated with SIMV, yet had higher pH and lower $PaCO_2$ values. Oxygenation, as reflected by the PaO_2/PAO_2 ratio, was better in the SIMV animals, suggesting more uniform transmission of mean airway pressure via the endotracheal tube compared with the nasal prong system. We also saw lower PIPs in the SIMV group; this group was managed with volume-targeted ventilation; thus, the PIP was servo-controlled and varied with each breath. With the ventilator used for NIPPV in this study, we were unable to synchronize or target tidal volume for technical reasons. Therefore, NIPPV delivered pressure-targeted breaths and the peak inspiratory pressure was fixed unless manually adjusted. We concede that without direct measurement of the delivered tidal volumes when using NIPPV there is a potential for larger tidal volume delivery than with SIMV. However, one would assume that if this were the case, hypocarbia would prevail and the NIPPV settings would need to be modulated to a greater extent than what we saw in our study. Nonetheless, the evidence of improved ventilation, combined with the stable vital signs and the trend toward decreased pathologic lung inflammation seen in the NIPPV-treated group, suggests that NIPPV may be an alternative to more invasive ventilatory support in some situations and offer potential improvements in outcomes.

Few data exist regarding the use of NIPPV in the laboratory or in the care of premature infants with surfactant deficiency and respiratory distress syndrome.

Table 2. Summary of lung injury scores

Pathologic Variables	SIMV		NIPPV		*p* Value
	Injury Score	Rank	Injury Score	Rank	
Alveolar inflammation	1.3	12	0.7	9.9	.42
Interstitial inflammation	**2.8**[a]	**13.7**[a]	**1.7**	8	**.04**
Alveolar hemorrhage	1.6	12.5	0.7	9.4	.25
Interstitial hemorrhage	0.9	13.3	0.1	8.5	.08
Edema	0.91	11.5	0.7	10.4	.67
Atelectasis	4.8	12	4.3	9.9	.42
Necrosis	1.1	12.5	0.4	9.4	.24
Total score	13.5	13.2	8.7	8.6	.08

SIMV, synchronized intermittent mandatory ventilation; NIPPV, nasal intermittent positive pressure ventilation.

[a]$p < .05$. Seven pathologic variables of lung injury were assessed. Total lung injury score is the sum of the mean scores for each variable. There was significantly more interstitial lung inflammation in the SIMV-treated piglets compared with the NIPPV-treated piglets. Mean injury scores and mean ranks shown.

Dr. Jobe and colleagues (12) studied surfactant-deficient lambs treated with CPAP or mechanical ventilation and saw evidence of decreased inflammation with noninvasive ventilation, similar to our findings. However, their CPAP group did not have added mechanical breaths like our NIPPV group did. Dr. Moretti and colleagues (13) studied a group of 11 preterm infants, extubated after recovering from respiratory distress syndrome. In this crossover study comparing NIPPV with conventional CPAP, they saw increases in tidal volume and minute ventilation with concurrent decreases in transcutaneous P_{CO_2}, respiratory rate, and esophageal pressure during NIPPV. In other studies in infants, NIPPV has been shown to be a safe and effective mode of ventilation in the postextubation setting and in the treatment of apnea of prematurity (3, 4, 5, 6).

No previous studies have used NIPPV as an initial mode of ventilation in an animal model of surfactant deficiency. To date, only one pilot study in neonates has investigated NIPPV as an initial mode of ventilation. Dr. Manzar and colleagues (14) treated 16 neonates using an "avoid intubation" protocol; 13 never required intubation, and no NIPPV-related complications were seen. Our data provide additional information regarding the effectiveness and impact of NIPPV. Taken together, the limited information regarding the use of NIPPV as a primary mode of noninvasive ventilatory support is encouraging, and justifies further study.

Limitations of this study include small sample size, differences in piglet vs. human airway anatomy, short study time, and the difficulties associated with producing significant lung injury compatible with spontaneous breathing in an animal model. Steps were taken to minimize air leak from the piglets' airways by closing the mouth and occluding the space around the cannula and snout. However, the snout and upper airway of the piglet are convoluted and clearly different from those of a human, a known variable when using an animal model.

At 6 hrs, our study time was relatively short in duration. Dr. Jobe and colleagues (12) found inflammatory changes in an animal model of surfactant deficiency in as little as 2 hrs. Indicators of lung injury have been shown to be measurable within 2 hrs of preterm birth (15). Similarly, in previous studies performed in our laboratory, we have been able to detect evidence of early lung inflammation within 4 hrs (16). In this study, we were unable to show differences using biochemical evidence of inflammatory changes, although we did see changes in lung pathology. A longer study time in this model may have produced greater changes. Finally, our study was limited by the piglets' tolerance of the saline lavage procedure. Two unique aspects of this study contributed to these limitations: lack of exogenous surfactant administration after injury and maintenance of continuous spontaneous respirations at all times. Future studies could include other animal models, longer experimental times, a larger scope of investigation for acute lung injury, and an increased variety of pathologic specimens and biological markers.

CONCLUSION

In surfactant-deficient term newborn piglets with acute lung injury, NIPPV offers an effective and noninvasive ventilatory strategy with the potential for less pathologic lung inflammation than invasive mechanical ventilation. The current information regarding the use of NIPPV as a primary mode of noninvasive ventilatory support, although limited in nature, is encouraging and warrants further study both in the laboratory and clinical settings.

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