Randomized Crossover Comparison of Proportional Assist Ventilation and Patient-Triggered Ventilation in Extremely Low Birth Weight Infants with Evolving Chronic Lung Disease

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Key Words
Extremely low birth weight infant \cdot Proportional assist ventilation \cdot Apnea

Abstract

Background: Refinement of ventilatory techniques remains a challenge given the persistence of chronic lung disease of preterm infants. Objective: To test the hypothesis that proportional assist ventilation (PAV) will allow to lower the ventilator pressure at equivalent fractions of inspiratory oxygen (FiO\textsubscript{2}) and arterial hemoglobin oxygen saturation in ventilator-dependent extremely low birth weight infants in comparison with standard patient-triggered ventilation (PTV).

Methods: Design: Randomized crossover design. Setting: Two level-3 university perinatal centers. Patients: 22 infants (mean (SD): birth weight, 705 g (215); gestational age, 25.6 weeks (2.0); age at study, 22.9 days (15.6)). Interventions: One 4-hour period of PAV was applied on each of 2 consecutive days and compared with epochs of standard PTV. Results: Mean airway pressure was 5.64 (SD, 0.81) cm H\textsubscript{2}O during PAV and 6.59 (SD, 1.26) cm H\textsubscript{2}O during PTV (p < 0.0001), the mean peak inspiratory pressure was 10.3 (SD, 2.48) cm H\textsubscript{2}O and 15.1 (SD, 3.64) cm H\textsubscript{2}O (p < 0.001), respectively. The FiO\textsubscript{2} (0.34 (0.13) vs. 0.34 (0.14)) and pulse oximetry readings were not significantly different. The incidence of arterial oxygen desaturations was not different (3.48 (3.2) vs. 3.34 (3.0) episodes/h) but desaturations lasted longer during PAV (2.60 (2.8) vs. 1.85 (2.2) min of desaturation/h, p = 0.049). PaCO\textsubscript{2} measured transcutaneously in a subgroup of 12 infants was similar. One infant met prespecified PAV failure criteria. No adverse events occurred during the 164 cumulative hours of PAV application. Conclusions: PAV safely maintains gas exchange at lower mean airway pressures compared with PTV without adverse effects in this population. Backup conventional ventilation breaths must be provided to prevent apnea-related desaturations.

Introduction

The search for alternatives to mechanical ventilation and for refinement of conventional ventilatory techniques has been fuelled by the persistence of a high incidence of chronic lung disease in the smallest preterm infants. Patient-triggered ventilation (PTV) modes such as synchronized intermittent mandatory ventilation...
(SIMV), assist/control ventilation (A/C), or pressure support ventilation typically synchronize one or two events of the ventilator cycle to certain points in the spontaneous respiratory cycle (start and end of inspiratory effort). Between these points in time, the applied ventilator pressure plateau and waveforms remain preset without adapting to the course of spontaneous breathing activity. The concept of proportional assist ventilation (PAV) is fundamentally different from this conventional perception of the ventilator being a ‘pump’ that releases bursts of air when triggered. During PAV, the applied ventilator pressure is servo-controlled based on a continuous input from the patient. This input signal alone controls the instantaneous ventilator pressure continuously, virtually without a time lag. The input signal is the modified tidal volume and/or airflow signal of the patient’s spontaneous breath. The ventilator pressure increases in proportion to the instantaneous tidal volume and/or inspiratory airflow generated by the patient. Applying such ventilator pressure waveforms proportionally enhances the effect of the respiratory muscle effort on ventilation. It enables the patient to fully control all variables of his/her respiratory pattern and thus express his/her endogenous breathing pattern while on the ventilator during PAV. Backup conventional mechanical ventilation must be initiated during episodes of decreased or absent respiratory drive.

It has been shown in preterm infants with acute moderate lung disease that PAV [1–7] has a potential to lower transpulmonary pressure requirements in comparison with standard modalities of assisted mechanical ventilation [8]. In this previous study, infants were exposed only to 45 min of PAV. No other studies comparing this new modality of assisted ventilation with standard modes of mechanical ventilation in premature infants have been published.

In contrast to the aforementioned study, this investigation tests whether PAV can support chronic ventilator-dependent preterm infants in a safe and effective way over longer periods of time.

We hypothesized that in comparison with a standard mode of assisted mechanical ventilation, PAV will reduce positive airway pressure without an increase in inspired oxygen requirements in extremely low birth weight infants with evolving chronic lung disease. To test this hypothesis, 8 h of PAV with settings chosen by the investigators were compared in a randomized crossover fashion to PTV. The positive airway pressure load was the predefined primary outcome criterion on which the study sample size calculation was based on. It was attempted to record a number of secondary outcome criteria such as minute ventilation and transcutaneously measured partial pressure of carbon dioxide (tcPCO₂).

**Methods**

The study protocol and the parental consent form were approved by the Institutional Review Boards at the University of Miami, Florida, the University of Munich, Germany, and by the US Food and Drug Administration. The PAV device was approved under the investigator-initiated Investigational Device Exemption #G950100. Infants were enrolled after written parental consent had been obtained.

**Eligibility Criteria**

Ventilator-dependent infants with signs of evolving chronic lung disease who were difficult to wean and/or experienced frequent apneas and arterial oxygen desaturations were included in the study. Major congenital anomalies, grades III and IV intracranial hemorrhage, and major surgery except for a status post patent ductus arteriosus ligation, and an endotracheal tube leak >20% of the expiratory tidal volume were exclusion criteria.

**Sample Size Calculation**

In a previous within-infant comparison of PAV and conventional triggered ventilation [8], the standard deviation of the change in mean airway pressure (MAP) was 1.10 cm H₂O. Based on this data it was estimated that a sample size of 21 participants was required for the present study to detect an average change of 1 cm H₂O in MAP with an α error probability of 1% and a power of 90%.

**Endotracheal Tube Leak Effects during PTV and during PAV**

The endotracheal tube leak size was measured prior to the study as the difference in inspiratory and expiratory tidal volume during mechanical lung inflations. If it exceeded 20% of the expiratory tidal volume, the endotracheal tube was replaced for the next larger size, provided that the respiratory condition was unstable, and this was possibly related to the leak. Otherwise, the infant was ineligible.

An endotracheal tube leak flow mimics inspiratory airflow to a flow sensor probe that is mounted between the ventilator Y-piece and the endotracheal tube. If the leak is excessive, it may persist even with the low airway pressure during expiration and may then initiate the trigger before the infant commences a spontaneous inspiration. During PTV, this may cause autotriggering. Airflow leaks during expiration, however, did not occur during this study. The endotracheal tube leaks, if present, opened with the higher inspiratory ventilator pressures only.

An airflow leak around the endotracheal tube during inspiration signals a higher inspiratory flow and volume to the ventilator flow sensor than truly enters the lung. During PAV, this may cause an inspiratory rise in ventilator pressure that is out of proportion to the inspiratory airflow and volume entering the lung. Ventilator software algorithms for PAV can eliminate such leak effects to some extent, however a major leak may still derange the inspiratory ventilator pressure contour during PAV. Therefore, an excessive endotracheal tube leak precludes the application of PAV.
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**Protocol**

Each infant was studied during 2 consecutive days over a total of 16 h. PTV and PAV study periods of 4 h each were crossed over on each day. With the exception of the ventilatory mode, the remaining clinical management was kept unchanged during the entire study time, and the investigators did not participate in patient management. Signal recording for a study period was started when the infant fell in quiet sleep after completion of the nursing procedures including endotracheal tube suctioning. Recordings were then obtained over a total sampling time of 4 h per study period. This does not include the time during which sampling had to be halted in the presence of gross body movements or if major accumulation of airway secretions required additional endotracheal tube suctioning. In such event, sampling was resumed as soon as the infant went back to quiet sleep but not earlier than 15 min after a suctioning procedure. To rule out carry-over effects, a 1-hour interval for washout was guaranteed between modes. The ventilatory modality of the first study epoch was determined by randomization using sealed opaque envelopes. The order of the ventilatory modes was reversed on day 2.

PTV study modes and settings were those previously chosen by the clinical team. Modifications of the PTV settings during the study were at the discretion of the clinical attending. The A/C mode or the SIMV mode was used for PTV. It was applied in a pressure-controlled fashion throughout the study. The mechanical inflation time was set by the clinical team. A flow-derived signal was utilized to initiate a synchronized mechanical breath during PTV. Sufficient inspiratory and expiratory times were assured by observing the airflow signal in order to confirm that it returned to zero flow at end-inspiration and end-expiration, respectively. If this was not the case, inspiratory or expiratory times were prolonged. During A/C, each identified spontaneous inspiration triggered a mechanical inflation. If the patient was breathing faster than the (backup) control rate, decreasing the control rate had no effect on the mechanical breath rate. Therefore, the primary adjustment for hypocapnia was reduction in peak inflation pressure. During SIMV, adjustments could be made in either ventilatory rate or pressure according to clinical preference. In both PTV modes, the transition from mechanical inflation to expiration was time-cycled, not flow-cycled. The highest trigger sensitivity avoiding autotriggering was selected to minimize imposed additional work of breathing for initiating the trigger. Except for FiO2 adjustments, ventilator settings were not modified during the study. The end-expiratory pressure was identical during PTV and PAV periods.

Settings during PAV were chosen as follows: The gain of resistive unloading was set to approximately compensate for the resistance of the endotracheal tube. To determine this gain, a 2.5-mm inner diameter endotracheal tube was connected to an elastic bag to simulate lung compliance. Resistive unloading was then applied and the gain or resistive unloading was increased gradually until the system began to oscillate. The resistance unloading gain at this point was considered to approximate the resistance of the endotracheal tube, i.e. fully compensate for its resistance. This gain was 20 cm H2O/l/s which was subsequently used for all study subjects who all had 2.5-mm inner diameter endotracheal tubes. The following procedure was used to determine an appropriate gain for the elastic unloading component of PAV: At the beginning of each PAV study period, the gain of elastic unloading was gradually increased from zero to a degree at which overcompensation of lung elastic recoil occurred. Overcompensation was identified during inspiration by the typical airway pressure waveform which rapidly increases to the set upper pressure limit (runaway phenomenon, fig. 1) [9]. The elastic unloading gain was then reduced below this threshold to a level at which the infant appeared to breathe comfortable with least chest wall distortion [10, 11]. The upper airflow pressure limits were set at 5 cm H2O above the peak inspiratory pressure (PIP) during PTV. Whenever cessation of spontaneous breathing for more than 10 s occurred during PAV, a backup mandatory ventilation was automatically started with the same PIP and control rate as used during PTV in each patient. This backup ventilation was immediately suppressed and PAV was resumed whenever a spontaneous breath was identified on the airflow signal by the respirator’s software. The time interval from cessation of spontaneous breathing to backup ventilation could be shortened to 3 s if the infant already developed oxygen desaturations after less than 10 s without breathing. The FiO2 was increased whenever pulse oximetry readings fell below 85% for
more than 30 s. It was decreased when readings above 96% occurred consistently over more than 5 min. Stephanie® Infant Ventilators (Stephan Biomedical Inc., Gackenbach, Germany) [4, 5, 12] were used for the study. If, however, an infant had been ventilated with a Babylong 8000® respirator (Software version 3, Draeger, Inc., Chantilly, Va., USA) prior to the study, he remained on this device during the PTV study periods. Thus in 10 patients the two comparison modes were applied by different respirator brands which used two different methods for airflow recording (anemometry during PTV and pneumotachography during PAV). The additional dead space introduced by the flow probes was 0.8 ml with the Draeger device and 0.9 ml with the Stephan ventilator. The Draeger anemometry sensor failed to detect very small airflows around zero flow, which occurred in particular with the unassisted spontaneous breath during PTV. Therefore a comparison of volumetric data between PTV and PAV was precluded in this center, all studied infants were on a Draeger Babylog respirator before the study and remained on this respirator during the PTV arm of the study (patient subgroup 1). Center 2 commonly used rapid rates and lower inflation pressures. They enrolled 12 patients of whom 4 received A/C, the remaining infants underwent SIMV. Among these 12 infants, the range of control rates was 40–78/min, peak inflation pressures ranged from 11 to 19 cm H2O. In this center, all studied infants were on a Stephan respirator before the study and remained on this respirator during the entire study (patient subgroup 2). For the entire study population, PTV settings as entered at the ventilator front panel and as noted in the charts were as follows (mean (SD)): peak inflation pressure, 15.7 cm H2O (2.6); control rate, 43.4 cycles/min (19.7); mechanical inflation time, 0.35 s (0.05); positive end-expiratory pressure, 3.95 cm H2O (1.43).

Ventilator settings for the experimental arm of the study (PAV) were: gain of volume-proportional assist (elastic unloading), 0.88 cm H2O/ml (0.18); the gain of flow-proportional assist (resistive unloading) was uniformly set at 20 cm H2O/l/s because all study infants had a 2.5-mm inner diameter endotracheal tube and the intention was to unload approximately the resistance of the endotracheal tube.

All but 3 infants fully completed the study protocol: Based on decisions of the clinical team, 2 infants were successfully extubated after completion of the first half of the protocol, and 1 infant met the prespecified failure criteria for PAV on her second day of study. Her FiO2 requirements increased by about 0.2, and she had prolonged oxygen desaturations in association with apneas while on PAV.

In the 22 study subjects, the primary study outcome variables, i.e. PIP and MAP were statistically significantly lower during PAV compared with PTV at equivalent exposure to inspired oxygen and arterial hemoglobin oxygen saturation (table 1, fig. 2). While the incidence of arterial oxygen desaturation events was not statistically different, their average duration was longer during PAV than during PTV (n = 22 infants). Though statistically significant, this difference was small in size.

In terms of the secondary outcome variables, a comparison between PTV and PAV with respect to the aver-
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Table 1. Breathing pattern and gas exchange. Comparison of 8 h of PAV to standard PTV in 22 extremely low birth weight infants with evolving chronic lung disease

<table>
<thead>
<tr>
<th></th>
<th>PTV</th>
<th>PAV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean airway pressure, cm H₂O</td>
<td>6.59 ± 1.26</td>
<td>5.64 ± 0.81</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Peak airway pressure, cm H₂O</td>
<td>15.1 ± 3.64</td>
<td>10.3 ± 2.48</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minute ventilation, ml/kg/min⁴</td>
<td>496.4 ± 135.1</td>
<td>469.1 ± 133.9</td>
<td>0.038</td>
</tr>
<tr>
<td>Respiratory rate/min⁴</td>
<td>68.2 ± 8.4</td>
<td>66.5 ± 8.06</td>
<td>0.64</td>
</tr>
<tr>
<td>Expiratory tidal volume, ml/kg⁴</td>
<td>7.60 ± 1.87</td>
<td>7.27 ± 1.64</td>
<td>0.29</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.34 ± 0.14</td>
<td>0.34 ± 0.13</td>
<td>0.70</td>
</tr>
<tr>
<td>SpO₂</td>
<td>92.9 ± 1.8</td>
<td>92.6 ± 1.8</td>
<td>0.28</td>
</tr>
<tr>
<td>SpO₂ &lt; 85%, n/h</td>
<td>3.34 ± 3.0</td>
<td>3.48 ± 3.2</td>
<td>0.70</td>
</tr>
<tr>
<td>SpO₂ &lt; 85%, min/h</td>
<td>1.85 ± 2.2</td>
<td>2.60 ± 2.8</td>
<td>0.049</td>
</tr>
<tr>
<td>Transcutaneous PCO₂, mm Hg (n = 12)</td>
<td>53.2 ± 5.7</td>
<td>55.1 ± 7.9</td>
<td>0.09</td>
</tr>
</tbody>
</table>

FiO₂ = Fraction of inspired oxygen; SpO₂ = arterial hemoglobin oxygen saturation as measured by pulse oximetry.

¹ Subgroup of 12 infants, data represent total ventilation, i.e. ventilator-generated and spontaneous breaths.

No acute adverse events occurred in any of the infants during the study.

Discussion

By exposing extremely low birth weight infants with evolving chronic lung disease to PAV in a clinical routine setting over a cumulative time of 196 h without untoward effects, this study supports the safety of PAV in this population. Of importance is the result that PAV appears to apply positive airway pressure in a more effective way al-

Fig. 2. Peak and mean airway pressure (MAP). During PAV, PIP (left) was 32% lower and MAP (right) 14% lower than during PTV in 22 low birth weight infants. * Different from SIMV, p < 0.05.
lowing for a decrease in airway pressure load compared with standard assisted ventilation. Mean PIP and MAP were lower at equivalent oxygen exposure and similar arterial hemoglobin oxygen saturation, however, the mean duration of oxygen desaturation episodes was longer during PAV.

It was a major study objective to emulate clinical practice in the control arm of the study. Mechanical ventilator device brands and ventilator settings that had been in use for the individual infants before the study were therefore intentionally retained for ventilation during the study control arm. Variability between centers with respect to device brands and with respect to preferences for PTV settings reflects common differences in clinical practice. In this study this led to two subgroups: subgroup 1 was on a Draeger ventilator and subgroup 2 was on a Stephan machine during PTV. Also, in the former group, attendings preferred lower rates and higher peak pressures; in the latter group, more rapid rates and lower peak pressure settings were applied. Both subgroups showed trends towards differences in outcome variables in the same direction as in the entire study population. Therefore, the PAV effects shown in this study appear to be specific for PAV. Differences to conventional PTV remain, irrespective of device brands or preferences for certain settings.

This study’s data do not provide an explanation as to why the ventilator pressure cost for CO₂ removal appears to be lower with PAV compared to conventional ventilatory assist. There was a concomitant reduction in minute ventilation in this study during PAV which, although small in magnitude, did reach statistically significance. This latter finding must be interpreted with much caution, because it represents a secondary outcome variable with a borderline level of statistical significance only. It may be speculated that there was less respiratory muscle activity wasted with breathing out of phase with the inspirator during PAV leading to a lower level of oxygen consumption and CO₂ production. It is of interest that the infants elected to breathe small tidal volumes during PAV although this mode enabled them to do otherwise with the positive feedback between the inspiratory activity and ventilator pressure delivery. PAV proportionally enhances the ventilatory effect of the patient’s respiratory muscle effort. The magnitude of the diaphragmatic effort during PAV, however, is apparently adjusted by the subject’s central respiratory control to target small tidal volumes. During PAV, this typically results in a spontaneous breathing pattern with high rates and shallow tidal volumes in preterm infants. Currently, this is regarded a protective ventilatory strategy which avoids pulmonary volutrauma. In this context, the findings of our present study on PAV in preterm infants are in line with previous results.

Theoretically, PAV should allow for more respiratory pattern variability compared to pressure-controlled ventilation. It is therefore surprising that the standard deviation for tidal volumes and for respiratory rates were not higher during PAV in comparison to pressure-controlled ventilation (table 1). The fact that the control arm of the study was a patient-triggered mode, and not just a fully controlled mechanical ventilation, may have contributed to this result. It, however, also shows that the infants expressed a quite and regular breathing pattern without major periodicity while on PAV in this study.

Gain settings for the resistive and the elastic unload components of PAV can be based on individual measurements of pulmonary mechanics and may thus be tailored precisely to the type and degree of lung mechanics derangement [8, 13]. This may achieve the largest possible airway pressure reduction with PAV. However, lung mechanics measurements are difficult to obtain and their precision may be limited. Our study demonstrates that appropriate gain settings for PAV may be chosen in a clinical setting without precise knowledge of lung compliance and airway resistance. While gradually increasing the elastic unloading gain, we identified the gain above which overcompensation developed and subsequently used a setting below this threshold. Visual assessment of the degree of chest wall distortion may also assist in selecting appropriate gains for clinical purposes [10, 11].

We did not find any evidence in this study that lower airway pressures were achieved by increased work of breathing. All infants were breathing in a stable way and did not show signs of discomfort such as increased chest wall distortion or visually deeper and prolonged inspiration. Esophageal pressures were not measured in this study, but were shown to be lowest during PAV in comparison to A/C and IMV in infants with acute lung disease [8].

All enrolled infants had a previous history of frequent apneas and arterial oxygen desaturations. As PAV allows the infant to breathe ‘freely’ without imposing any preset cycling of the machine, one might expect that infants feel less disturbed and develop fewer restlessness-related oxygen desaturations than under PTV. This was not corroborated in our study. The incidence of desaturations during PAV and PTV was almost identical. The slightly, though statistically significantly longer average duration of desaturations during PAV may be related to the time allowed to elapse during an apnea before backup ventilation starts. The Stephanie® Infant Ventilator software al-
allows the clinician to select a lag time of 3–15 s between the points in time when the ventilator software identifies cessation of breathing and the onset of backup mechanical ventilation. We initially used 10 s for some infants during the study which in light of our results appears to be too long, particularly for the smallest infants who are more prone to have long apneic episodes. However, the backup ventilation settings may not have been sufficiently effective to quickly resolve a desaturation. On the other hand, excessive backup ventilation may suppress the infant’s spontaneous respiratory activity so that ventilation may not revert to proportional assist. Further study is required on this issue.

The tcPCO$_2$ data did not reach a statistically significant level of difference between the two modes in this study, and we cannot rule out that a larger sample size might demonstrate higher tcPCO$_2$ during PAV. Still, these data are of interest since it now appears very unlikely that PAV leads to lower tcPCO$_2$ levels (the opposite trend), i.e. spontaneous hyperventilation. Spontaneous hyperventilation and possibly associated increased pulmonary barotraumas was a theoretical concern about PAV in preterm infants who often have borderline metabolic acidosis and might therefore hyperventilate when enabled to do so by PAV.

In conclusion, chronically ventilator-dependent preterm infants undergoing routine clinical care may benefit from lower airway pressures and possibly less barotrauma during PAV compared to standard mechanical ventilation techniques. We speculate that the reduction in airway pressure load during PAV is related to improved matching between the ventilator pressure waveform and the individual derangement in lung elastance and airway resistance. Early initiation of effective conventional backup ventilation during apneas and hypoventilation is essential during PAV. Whether these lowered pressure requirements are associated with longer-term benefits such as earlier weaning from the ventilator, a lower incidence of chronic lung disease or an improved neurological outcome remains subject to further study.

Acknowledgements

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