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Research letter

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FORCED OSCILLATION TECHNIQUE FOR OPTIMISING PEEP IN VENTILATED EXTREMELY PRETERM INFANTS

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To the Editor,

Ventilatory settings are critical in mechanically ventilated extremely preterm newborn infants due to the risk of ventilation induced lung injury (VILI) and subsequent development of bronchopulmonary dysplasia (BPD) [1]. The positive end-expiratory pressure (PEEP) settings usually rely on blood gases, oxygen requirement, lung auscultation, evaluation of chest radiograph, and assessment of pressure-volume curves provided by the ventilators. Studies of optimal PEEP settings in the surfactant treated preterm infant in need of mechanical ventilation are limited and evidence based clinical guidelines are sparse [2,3]. A bedside method identifying the PEEP value that comprises maximal lung volume recruitment and minimizing tissue overdistension could improve real-time optimisation of PEEP and potentially minimize the risk of VILI and BPD [4,5].

The respiratory input reactance measured by the forced oscillation technique (FOT) has been shown to be feasible bedside in premature infants at different maturational and postnatal ages [6,7], and in animal models it has been shown to identify the lowest PEEP at which lung recruitment is most optimal during a decreasing PEEP trial [8,9].

Our aim was to investigate the relationship between lung mechanics and PEEP during the first week of life using FOT, and to characterize the mechanical optimal PEEP ($\mathrm{PEEP_{FOT}}$) settings in ventilated extremely preterm infants in comparison to the clinically set PEEP ($\mathrm{PEEP_{CLIN}}$).

Patients and Methods

Study population

Infants born < 28 weeks of gestational age were eligible if intubated and mechanically ventilated during the first day of life, and if no congenital abnormalities or other malformations relevant to lung function were present. During the study period 22 patients met the inclusion criteria, but 8 were excluded as they were extubated and remained so after day 1. Fourteen extremely preterm infants (mean gestational age 24.4 +/- 1.7 weeks; birth weight 612±132g) were included after informed parental consent. All measurements were performed at the Neonatal Intensive Care Unit, University Children´s Hospital in Uppsala, Sweden, between June 2011 and May 2014. All infants received prenatal steroids and early surfactant. Median duration of mechanical ventilation was 38 days (range 12-239). One infant died before 36 weeks and 7 of the remaining 13 patients (54%) were diagnosed with severe BPD. The study was approved by the Regional Ethical Review Board (Dnr:99092).

Study protocol

Infants were intubated with uncuffed endotracheal tubes (ETT; 2.0– 2.5mm) and ventilated by assist/control ventilation (Stephanie Ventilator, Fritz Stephan GmbH, Germany), enabling the patients to get support during spontaneous breaths. PEEP was chosen by the attending clinician, and the peak inspiratory pressures were set according to predefined pCO_2 targets. During the intervention ventilatory parameters except PEEP were kept constant, with fraction of inspired oxygen (FiO_2) adjusted to maintain oxygen saturation according to institutional guidelines. The infants were studied on the 1st, 3rd and 7th day of life. Lung mechanics were measured using FOT by a 5, 10, and 15 Hz over-imposed sinusoidal pressure signal on the ventilation pressure waveform. PEEP was increased 2 cmH_2O above the clinically set PEEP ($PEEP_{CLIN}$) then decreased by four 5-minute steps of 1 cmH_2O, and finally restored to $PEEP_{CLIN}$. Registration periods were held short as to not interfere with the on-going ventilatory assistance**.**

Pressure was measured at the inlet of the ETT and the flow signal was obtained from the ventilator. All signals were sampled at 300Hz by a custom-made digitizer and stored on a laptop for subsequent analysis. Reliable impedance-data were obtained from all frequencies without interference by ventilator frequency, but only data measured at 10 Hz is presented as 5 and 15 Hz did not provide more information on lung mechanics. All calculations were made after each registration, and the attending clinicians were blinded for the results in all instances.

Data and Statistical analysis

The respiratory system resistance (Rrs) and reactance (Xrs) were obtained by computing the transfer function between pressure and flow at the stimulus frequencies and correcting for the ETTs contribution. Xrs accounts for the elastic and inertial properties of the system [10]. For each protocol step 10 breaths were automatically selected for each frequency and their end-expiratory Rrs and Xrs values were averaged to have one data point for each PEEP level.

Optimal PEEP ($PEEP_{FOT}$) was defined as the pressure associated to the maximum value of Xrs during a decreasing PEEP trial [6,8,11].

Two-way (days of life and PEEP) ANOVA for repeated measurements was used to test differences in the measured parameters. Tukey test was used as a post hoc test after ANOVA. A $p<0.05$ was considered statistically significant.

Results

$PEEP_{FOT}$ was lower than $PEEP_{CLIN}$ on day 1 and 7; $PEEP_{FOT}$ was higher on day 3 and 7 compared to day 1 while $PEEP_{CLIN}$ did not show statistical changes with time (Figure 1). Xrs at $PEEP_{FOT}$ was higher than Xrs at $PEEP_{CLIN}$ (mean difference (95%CI) of Xrs at $PEEP_{FOT}$ compared to $PEEP_{CLIN}$ was 4.7 (1.4;8.0) cmH_2O*s/L on day 1, 2.5 (0.4;4.6) cmH_2O*s/L on day 3, and 5.2 (0.04;10.3) cmH_2O*s/L on day 7.

Xrs decreased significantly when PEEP was increased by 2 cmH_2O from $PEEP_{CLIN}$ (mean difference (95%CI): 11.7 (8.3;15.2) cmH_2O*s/L on day 1; 10.0 (5.7;14.4) cmH_2O*s/L on day 3; and 9.1 (4.7; 13.5) cmH_2O*s/L on day 7) indicating that the lungs were easily overdistended. Oxygen need did not differ between the days, or between $PEEP_{FOT}$ and $PEEP_{CLIN}$ (Figure 1), and FiO_2 was low on all days during the time of the trial (0.23±0.05, 0.27±0.9 and 0.26±0.06 respectively on day 1, 3 and 7; NS) resulting in non-significant changes in the SpO_2/FiO_2 rates (Figure 1). Clinically set peak inspiratory pressures were lower on the first day of life compared to the third and seventh day (15±2 vs 18±4 and 19±3 cm H_2O; $p<0.05$), but with no differences in tidal volumes (4.4±0.9 vs 4.7±0.8 and 5.2±1.1 ml) or respiratory rates (59±8 vs 59±4 and 58±9 breaths/min) between the study days.

Discussion

In this cohort of extremely preterm infants the optimal PEEP as identified by FOT were lower than the clinical set PEEP on day 1 and 7. The lower optimal PEEP settings were not associated with changes in oxygenation or other clinical measurements compared to the clinically set PEEP. Our data suggests that clinically set PEEP levels might be too high, implying that the surfactant-treated lung is highly compliant and easily overdistended by the PEEP during mechanical ventilation. Our data indicated overdistension of the lung despite the limited increase in PEEP during the trial (+2 cmH_2O), and although only a small, but significant, mean difference was noted between $PEEP_{CLIN}$ and $PEEP_{FOT}$ on day 1 and 7, this represented a range of 0 to +2 and -1 to +2 cmH_2O on these respective days. Also on day 3, the individual differences between $PEEP_{CLIN}$ and $PEEP_{FOT}$ ranged from -1 to +2 cmH_2O. Thus, PEEP settings may be especially critical on the first day of life as we observed larger differences in Xrs during PEEP titration at the beginning than at the end of the first week of life.

The differences between PEEP derived from clinical data compared to PEEP-derived from lung mechanical measurements by FOT, illustrates the limitation of the available bedside information for tailoring individualized PEEP, and the need for more accurate assessments of lung mechanics during the first initial phase of life. The lower $PEEP_{FOT}$ was not associated with any changes in FiO_2 suggesting the uncertainty of using oxygen requirements to guide PEEP settings bedside in extremely preterm newborn infants. Our data also suggests that in the absence of lung mechanical measurements, clinically set PEEP might be biased toward higher values leading to potentially harmful overdistention of the immature lung. Moreover, $PEEP_{CLIN}$ showed lower sensitivity to evolving lung conditions, without differences in $PEEP_{CLIN}$ during the study period.

We have previously shown that bedside FOT is well tolerated in this population of extremely preterm infants during their first day of life [7]. This study adds information about evolving lung mechanics during the first postnatal week as measured by FOT, and we believe that Xrs changes with PEEP might provide useful information for real-time individualization of PEEP repeatedly and at daily basis.

Limitation of our study is the low number of patients included, the limited range of PEEP covered by the trial, and the fixed inspiratory pressures (chosen to prevent changes in peak inspiratory pressures). In our study the impedance data were measured only at end-expiration, i.e. at PEEP, and ~~as~~ it has been shown that optimal PEEP assessed by FOT minimizes intra-tidal recruitment (9). However, if the use of other ventilation approaches results in different applied tidal volumes, the degree of lung volume recruitment and, consequently, also $PEEP_{FOT}$, may change. Additionally, studies are needed to explore the effects of repeatedly adjusted PEEP settings according to FOT measurements on ventilation and oxygenation.

In summary, we have found that the optimal PEEP during mechanical ventilation of extremely preterm infants, as evaluated by FOT in the first week of life, is lower than the clinically set PEEP and that it changes over time. The lower $PEEP_{FOT}$ identified on day 1 compared to day 3 and 7, together with the low FiO_2 and PIP, suggests that the surfactant treated lungs of extremely preterm infants can be easily overdistended even at low PEEP.

FOT might be a valuable bedside tool for assessment of lung mechanics for adjustments of PEEP over time and as part of a protective ventilation strategy to these vulnerable patients, especially during the first days of life. Further studies are needed to evaluate the possible long-term benefits of adjusting clinical PEEP by FOT, in this population of the most preterm infants.

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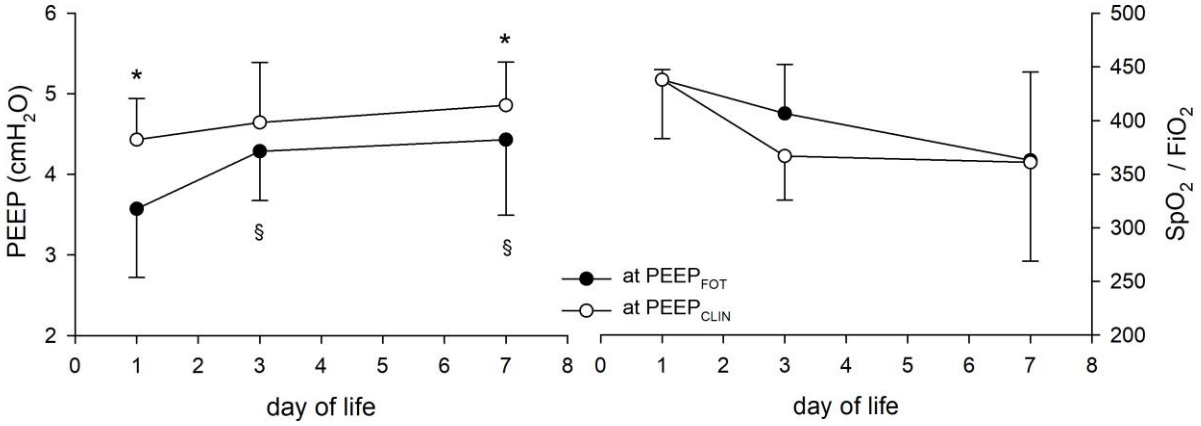

Figure 1. PEEP (left panel) when PEEP was optimised by clinical parameters (PEEPCLIN) and by FOT (PEEPFOT) on the 1st, 3rd and 7th day of life; and oxygen saturation (SpO2) and fraction of inspired oxygen (FiO2) ratio (right panel). § p<0.05 comparison to day 1; *p<0.05 comparison between PEEPCLIN and PEEPFOT; at day 3 PEEPCLIN and PEEPFOT did not reach statistical difference (p=0.10).