Central blood flow measurements in newborn infants

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CHAPTER 3

CARDIORESPIRATORY EFFECTS OF CHANGES IN END EXPIRATORY PRESSURE IN VENTILATED NEWBORNS

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ABSTRACT

Background
Positive pressure ventilation in premature infants can improve oxygenation, but may also diminish cerebral blood flow and cardiac output. Low brain and upper body flow (superior vena cava flow, SVC) increases the risk of intraventricular haemorrhage, with previous research showing that higher mean airway pressure is associated with low SVC flow. It is not known whether this is a direct effect of positive pressure ventilation or a reflection of severity of lung disease. The aim of this study was to determine whether positive end expiratory pressure (PEEP) in ventilated newborns could be increased without causing clinically relevant cardiorespiratory changes.

Methods
Ventilated newborns were studied before and 10 minutes after increasing PEEP from 5 to 8 cmH₂O, then again when returned to baseline. Simultaneous echocardiographic and respiratory function measurements were collected during the intervention.

Results
Fifty infants were studied. Overall, increased PEEP was associated with a non-significant difference in mean SVC flow of -5 ml/kg/min (95%CI -12 to 3) but a significant reduction in right ventricular output of 17 ml/kg/min (95%CI 5 to 28). There was a non-significant increase in lung compliance of (median difference 0.02 ml/cmH₂O/kg; p 0.093) and a significant decrease in lung resistance of 18 cmH₂O/L/s (95%CI 10 to 26). There was a positive association between % change in lung compliance and % change in SVC flow when corrected for paCO₂ changes (regression coefficient 0.4 % (95%CI 0.2 to 0.6)).

Conclusions
A short-term increase in PEEP does not result in a significant change in systemic blood flow, although 36% of infants had clinically important changes in flow (+/- 25%). The intervention can improve dynamic lung function, especially airway resistance. Improvements in compliance tend to be associated with improvements in blood flow.
Background

A low systemic blood flow state is common in babies born before 30 weeks and is associated with significant morbidity. Therefore an understanding of the factors that might affect blood flow in this population is essential.\(^1,2\) Previous studies have shown that higher mean airway pressure is a determinant of low superior vena cava (SVC) flow.\(^3\) It is not known whether this is a direct effect of positive pressure ventilation on reducing systemic venous return, as suggested by animal studies, or a reflection of severity of lung disease.\(^4,5\)

Positive end expiratory pressure (PEEP) is used to increase end-expiratory lung volume so as to improve arterial oxygen content, decrease the alveolar to arterial oxygen difference, and decrease shunt fraction by preventing alveolar collapse.\(^6,7\) Most neonatal intensive care units use a static level of PEEP, and levels may vary between 3 and 8 cmH\(_2\)O. The haemodynamic safety of different PEEP levels in a clinical setting has not been investigated yet. There is theoretical potential for higher PEEP, by opening up the lungs, it may reduce pulmonary vascular resistance and increase pulmonary and systemic blood flow. Our goal was to study whether end expiratory pressure in ventilated newborns could be increased from 5 to 8 cmH\(_2\)O without causing clinically relevant cardiorespiratory changes.

Methods

All newborn infants admitted to RPA Newborn Care between April 2005 and March 2006, who required assisted ventilation in the first 3 days, were eligible. Infants were excluded from the study if they had a major congenital malformation, severe perinatal asphyxia defined as a Sarnat score greater than 2 at any point, or severe hypoxia with a FiO\(_2\) more than 80%. Infants were also excluded if the peak inspiratory pressure was below 12 cmH\(_2\)O with a FiO\(_2\) of 21%, as increasing PEEP in these infants might compromise tidal volume. Informed consent was obtained from the parents of eligible infants, and the study was approved by the local ethics committee.

Infants received surfactant as soon as possible after birth on the basis of a surfactant function test (click test) performed on an early tracheal aspirate.\(^8\) Ventilator strategies included adjusting the peak inspiratory pressure to achieve an expiratory tidal volume of 4 ml/kg with the rate adjusted to achieve a paCO\(_2\) of 40 to 55 mmHg, and FiO\(_2\) was adjusted to maintain pre-ductal oxygen saturation between 88 to 95%. All infants in our institution are generally maintained at a PEEP of 5 cmH\(_2\)O. Morphine sedation is given selectively to babies considered to be uncomfortable on the ventilator. Circulatory support interventions were not changed during the time period of the studies.

Doppler echocardiographic measurements were performed using a Siemens Aspen ultrasound system with a 7 MHz vector array transducer incorporating colour flow and pulsed wave Doppler. SVC flow, Doppler measurement of right ventricular output (RVO), left pulmonary artery velocity (LPA), colour Doppler diameter of ductus arteriosus shunt and size, and Doppler of the middle cerebral arteries (MCA) were performed according to previously published methodology.\(^9,10\) Doppler
assessment of pulmonary artery pressure was also performed using the time to peak velocity divided by the right ventricular ejection time (TPV/RVET). All measurements were performed by one investigator (KW). Blinding at the time of measurement was achieved by allocating each study a random number drawn from a sealed envelope. This number was the only identifier on the ultrasound screen. The scans were recorded to different magnetic optical disks, and measurements were done as a batch away from the bedside at a later time.

The intervention and data collection was performed, if possible, between 3 and 9 hours of age. Echocardiographic and other parameters were recorded at the initial setting of 5 cmH₂O PEEP, then after an increase of PEEP to 8 cmH₂O for 10 minutes, and again 10 minutes after PEEP was returned to 5 cmH₂O. An arterial blood gas was drawn just before the start of the protocol and before the intervention measurement. If no arterial line was in place, transcutaneous measurements of paCO₂ and paO₂ were noted. Respiratory function parameters were measured using the Dräger 8000 ventilator (dynamic lung compliance, mean airway pressure, minute volume, FiO₂) and were collected together with physiological parameters (heart rate, blood pressure) from the Phillips Agilent monitor. Average respiratory function parameters were calculated from 30-second interval measurements. Respiratory function measurements were excluded if the tube leak was more than 25%. Exit criteria to stop the intervention were an increase in FiO₂ more that 30% from baseline or a drop in mean blood pressure of 20% from baseline.

Statistics
Our hypothesis was that an increase in PEEP would not result in a significant change in SVC flow of more than 25% from baseline. The cut-off of 25% was chosen to allow for measurement error that was documented in previous studies and to allow for clinically unimportant changes in SVC flow. Statistical analysis was performed using a computer statistics package (SPSS 12.0 for windows). General linear models with repeated measurements were performed for normally distributed outcomes to tests the within-subjects effects at the three measurement time points. A Friedman test was used for non-parametric outcomes. A paired t-test was used to estimate mean differences in normally distributed outcomes and a Wilcoxon signed rank test for non-parametric outcomes after the increase in PEEP compared to baseline.

Linear regression was used to identify risk factors for changes in flow before and after the increase in PEEP and to evaluate the possible interaction or confounding effect of gestational age, postnatal age and paCO₂ on the relation between PEEP increase and flow changes. Statistical significance was set at 5%. One way analysis of variance was used to identify risk factors for changes in compliance. Groups were divided based on a clinically relevant change in compliance of 10% (no clinically relevant change, difference > 10% or < -10%).
The association between severity of lung disease (Mean airway pressure, Compliance, Resistance, FiO₂) and flow changes was evaluated with linear regression analysis.

Results
Fifty infants with a median gestational age of 30 weeks and a median weight of 1612 g were included. There were 40 preterm and 10 term infants included in the study. Twenty two of the preterm infants were less than 30 weeks in gestation. All preterm infants were ventilated because of respiratory distress syndrome (RDS) and received surfactant. Of the term infants, 2 infants were ventilated for meconium aspiration, 5 for non-specific lung disease with a positive click test for surfactant function, 2 for pneumonia/sepsis and one infant for mild perinatal asphyxia.

Nine infants had their first study done after 24 or 48 hours of life, because they were transported to our centre or they were not ventilated in the first 24 hours of life. Cardiovascular and pulmonary function measurements before, during and after the increase in PEEP are shown in tables 1 and 2. In 8 infants, some indices of flow were not measurable due to poor windows, but SVC flow was always measurable. Pathologically low measures of SVC and RVO are defined as less than 40 and 120 ml/kg/min, respectively.13 No infant met the exit criteria during the study.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Intervention</th>
<th>Return to</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP 5 cmH₂O</td>
<td>PEEP 8 cmH₂O</td>
<td>PEEP 5 cmH₂O</td>
<td></td>
</tr>
<tr>
<td>RVO (ml/kg/min)</td>
<td>234 ± 103</td>
<td>216 ± 95</td>
<td>224 ± 87</td>
</tr>
<tr>
<td>SVC (ml/kg/min)</td>
<td>92 ± 36</td>
<td>87 ± 36</td>
<td>86 ± 34</td>
</tr>
<tr>
<td>SVC d (mm)</td>
<td>3.7 ± 1.0</td>
<td>3.6 ± 1.1</td>
<td>3.6 ± 1.0</td>
</tr>
<tr>
<td>SVC Vt (m/s)</td>
<td>0.093 ± 0.032</td>
<td>0.097 ± 0.035</td>
<td>0.090 ± 0.029</td>
</tr>
<tr>
<td>LPA mean (m/s)</td>
<td>0.33 ± 0.11</td>
<td>0.32 ± 0.13</td>
<td>0.32 ± 0.12</td>
</tr>
<tr>
<td>DAd (mm)</td>
<td>2.2 (1.6 - 3.0)</td>
<td>2.2 (1.9 - 2.8)</td>
<td>2.1 (1.8 - 3.1)</td>
</tr>
<tr>
<td>Ductal shunt (%RL)</td>
<td>14 (0 - 25)</td>
<td>12 (0 - 27)</td>
<td>15 (0 - 28)</td>
</tr>
<tr>
<td>MCA mean (m/s)</td>
<td>0.13 (0.09 - 0.17)</td>
<td>0.14 (0.10 - 0.18)</td>
<td>0.12 (0.09 - 0.16)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>143 ± 17</td>
<td>141 ± 20</td>
<td>143 ± 19</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>47 ± 9</td>
<td>48 ± 9</td>
<td>47 ± 9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>30 ± 7</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
</tr>
</tbody>
</table>

Table 1: Cardiovascular response to an increase in PEEP in all 50 infants as mean ± SD or median (IQR) where appropriate. RVO: right ventricular output; SVC: superior vena cava flow; Vt: velocity time integral; LPA: left pulmonary artery velocity; MCA: middle cerebral artery; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure, %RL: percentage of cardiac cycle with right to left shunt.

Effect of higher PEEP on SVC flow and RVO
A change in SVC flow of more than 25% from baseline was found in 18 (36%) infants, with 9 infants having increased flows and 9 decreased flows (figure 1). Overall, there was a non-significant difference in SVC flow after the increase in PEEP of -5 ml/kg/min (95%CI -12 to 3) or -0.7% (95% CI -10.7 to 9.2%) due to a small but significant decrease in SVC diameter of 1.6 mm (95%CI 0.3 to 2.9 mm). The intervention caused a significant reduction in RVO with a mean of 17 ml/kg/min (95%CI 5 to 28) or 5 % (95%CI 0 to 10).

Gestational age was not found to be an interaction factor or confounding factor in these analyses.
Gestational age, birth weight, baseline RVO, mean airway pressure, FiO₂, lung compliance or resistance did not predict the direction of the change in SVC flow or RVO. There was a negative association between baseline SVC flow and change in SVC flow after the increase in PEEP; linear regression coefficient -0.3 ml/kg/min (95%CI -0.5 to -0.1). Postnatal age (hours) was positively associated with change in RVO after the increase in PEEP; regression coefficient 0.8 ml/kg/min (95%CI 0.1 to 0.5).

Figure 1. % change in SVC flow with the intervention. Black lines show more than 25% change at 8 cmH₂O of PEEP compared to baseline.

**Effect of higher PEEP on other haemodynamic measurements**

The ductus arteriosus was found to be patent in 40 infants with a median ductal diameter of 2.2 mm. The increase in PEEP had no significant effect on the ductal size or the percentage of ductal flow going right to left, a marker of relative pressure between the systemic and pulmonary system. LPA mean velocity was also not significantly changed by the intervention. As an assessment of pulmonary pressure, the time to peak velocity divided by the right ventricular ejection time (TPV/RVET) was calculated. It showed no significant change with the intervention and there was no association found between the change in RVO or LPA mean velocity and the change in TPV/RVET. The change in MCA mean velocity after the increase in PEEP was not significant (median difference 0.003 m/s; p 0.337).
Effect of higher PEEP on respiratory function
Valid analysis of respiratory outcomes was possible in 36 infants who had a tube leak less than 25%. Results are presented in table 2. Dynamic lung compliance showed a non-significant increase (median difference 0.02 ml/cmH\textsubscript{2}O/kg; p 0.093), but lung resistance was significantly decreased after 10 minutes of higher PEEP (mean difference at 10 minutes -18 cmH\textsubscript{2}O/L/s (95%CI -26 to -10)). Both compliance and resistance returned to their baseline values within 10 minutes of the PEEP returning to 5 cmH\textsubscript{2}O.
Significant associations were found between the following baseline characteristics and change in compliance with the intervention: mean airway pressure (F(2;35)=3.3, p 0.049), minute volume (F(2;27)=6.3, p 0.006) and resistance (F(2;35)=3.8, p 0.032). Infants who showed a decrease of more than 10% with the intervention had a higher mean airway pressure, higher minute volume and a lower resistance. This may point to overdistention as the cause for the decrease in compliance with an increase in PEEP.
An increase in PEEP resulted in a significant increase in paCO\textsubscript{2} (mean difference 3.0 mmHg; 95%CI 1.2 to 4.8). Linear regression showed no significant effect of paCO\textsubscript{2} changes on changes in RVO, MCA mean velocity or ductal shunting. An increase in paCO\textsubscript{2} was, however, associated with a small but significant increase in SVC flow (regression coefficient 1.3 ml/kg/min (95%CI 0.0 to 2.5).

<table>
<thead>
<tr>
<th>Baseline PEEP 5 cmH\textsubscript{2}O</th>
<th>Intervention PEEP 8 cmH\textsubscript{2}O</th>
<th>Return to PEEP 5 cmH\textsubscript{2}O</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP cmH\textsubscript{2}O</td>
<td>8.5 (7.3 - 10.0)</td>
<td>11.0 (9.6 - 12.3)</td>
<td>8.6 (7.2 - 10.0)</td>
</tr>
<tr>
<td>TV ml/kg</td>
<td>4.1 (3.4 - 4.9)</td>
<td>3.3 (2.7 - 4.3)</td>
<td>4.1 (3.5 - 5.3)</td>
</tr>
<tr>
<td>C\textsuperscript{*} ml/cmH\textsubscript{2}O/kg</td>
<td>0.43 (0.36 - 0.69)</td>
<td>0.53 (0.33 - 0.81)</td>
<td>0.45 (0.30 - 0.67)</td>
</tr>
<tr>
<td>R\textsuperscript{*} cmH\textsubscript{2}O/L/s</td>
<td>86 ± 41</td>
<td>78 ± 33</td>
<td>93 ± 40</td>
</tr>
<tr>
<td>paCO\textsubscript{2} mmHg</td>
<td>44 ± 12</td>
<td>47 ± 11</td>
<td>na</td>
</tr>
<tr>
<td>paO\textsubscript{2} mmHg</td>
<td>75 (63 - 99)</td>
<td>80 (63 - 99)</td>
<td>na</td>
</tr>
<tr>
<td>FiO\textsubscript{2} %</td>
<td>25 (21 - 34)</td>
<td>25 (21 - 31)</td>
<td>25 (21 - 30)</td>
</tr>
</tbody>
</table>

Table 2. Pulmonary response to an increase in PEEP in all 50 infants as mean ± SD or median (IQR) where appropriate. *Tidal volume (TV), compliance (C) and resistance (R) are reported for 36 infants with less than 25% tube leak. MAP: mean airway pressure; paCO\textsubscript{2}: partial carbon-dioxide pressure; paO\textsubscript{2}: partial oxygen pressure; FiO\textsubscript{2}: fractional inspired oxygen. na: not available.

Respiratory function and flow
We explored the relationship between changes in respiratory function and changes in flow and found two weak associations. An increase of 1 % in compliance is associated with a 0.4 % (95%CI 0.1 to 0.6) increase in SVC flow. (figure 2)
Second, a positive association between paCO\textsubscript{2} and MCA mean velocity was found (regression coefficient 0.002 m/s (95%CI 0.001 to 0.004), but the association between changes in paCO\textsubscript{2} and MCA mean velocity with the intervention was not statistically significant (regression coefficient 0.001 (95%CI -0.001 to 0.003).
Figure 2. Partial regression scatterplot of % change in SVC flow and % change in lung compliance if corrected for paCO\textsubscript{2} changes with 8 cmH\textsubscript{2}O of PEEP compared to baseline.

**Discussion**

This study showed that an increase of PEEP 5 to 8 cmH\textsubscript{2}O during 10 minutes did not lead to a clinically relevant change in upper body and brain blood flow (SVC flow) in the majority of infants. It was associated with a significant decrease in RVO but there were no clinically relevant changes in any of the other haemodynamic measurements. Improvements in SVC flow were associated with improvements in lung compliance, although this analysis is sensitive to the method of analysis. In contrast to the literature, our study found relatively little consistent change in hemodynamic parameters overall\textsuperscript{13,14}. Potential reasons for this include our heterogeneous study population, or the impact of our intervention. Possibly an increase of 5 to 8 cmH\textsubscript{2}O in PEEP was not large enough to cause consistent negative effects on blood flow as reported in the literature. Few infants had low systemic blood flows. We expected that infants with low baseline flow would show a larger decrease in flow with the intervention, but they were more likely to have an increase in SVC flow at 8 cmH\textsubscript{2}O of PEEP. This may be a regression to the mean. The decrease in RVO of -17 ml/kg/min was statistically significant, but we are not sure if this is of clinical significance considering the normal baseline RVO in this population. In 6 of the 7 patients with low baseline RVO (<120 ml/kg/min) the intervention resulted in no detectable change, but a potential adverse effect of
higher PEEP should be evaluated more thoroughly with further research, especially in infants with low flow. Probably the most important haemodynamic effect of PEEP in preterm infants with RDS is through the direct effect on alveoli. When PEEP is set too low, blood will be shunted away from collapsed alveoli which produce a regional increase in pulmonary vascular resistance. With optimal lung volume, lung vascular resistance will be at its lowest point, thus maximising RVO and cardiac input. PEEP is capable of optimising lung volume by keeping open (partially) collapsed alveoli. The intervention performed in this study is not considered a lung recruitment manoeuvre, and we can only speculate about lung volumes in the studied infants. Lung volume is also related to airway resistance. At low lung volumes due to insufficient PEEP, airway resistance is high and the work of breathing is high. The effect of PEEP on compliance in this study showed an increased compliance with a maximum increase after 10 minutes of PEEP 8 cmH\textsubscript{2}O. Stabilisation of alveoli after a change in PEEP has been shown to take up to 14 minutes. However, the evidence on the effect of PEEP on compliance is conflicting. Compliance can only be used as a measurement to optimize ventilation without decreasing blood flow, if it is combined with information on lung volume. Two previous studies investigating lung compliance and blood flow simultaneously in newborn infants showed a progressive decrease in cardiac output with less decrease in the infants with low compliance. We demonstrated a reduction in RVO, but found no significant positive association between an increase in compliance and an increase in RVO as we did for SVC flow. This could be caused by differences in flow measurements. In RVO, we looked at the change in velocity and assumed the diameter did not change, whereas change in SVC was very dependent on change in diameter. This suggests that RVO, though perhaps not such a consistent measure of systemic blood flow compared to SVC, is less vulnerable to measurement error if only change in velocity is assessed and may be a better method to detect short term changes such as in this study. Although our intervention seems to be only a minor increase in mean airway pressure, modest changes in PEEP can result in a clinically important decrease in tidal volume or functional residual capacity. This could explain the increase in \textit{paCO}_2 found in our study. Other studies suggest that the increase in \textit{paCO}_2 is responsible for an increase in cerebral blood flow (CBF). The relationship between \textit{paCO}_2 and CBF is exponential and a normal \textit{paCO}_2 - CBF reactivity is about 4% per mmH\textsubscript{g}. In this study, the increase in \textit{paCO}_2 was associated with an increase in SVC flow, but not with an increase in RVO or MCA mean velocity which makes the \textit{paCO}_2-SVC flow relationship difficult to interpret. The potential negative effect of PEEP on RVO could have been balanced by the potential positive effect of a higher \textit{paCO}_2 on CBF and SVC flow.

**Conclusion**

A short-term modest increase in PEEP reduces RVO, but does not lead to a clinically significant change in systemic blood flow in the majority of the infants.
Clinically significant changes (both positive and negative) in systemic blood flow were found in 36% of the infants. Improvements in lung compliance were associated with improvements in SVC flow. The association between ventilation and blood flow is a complex one that needs more study. Future research should focus on more sick infants, especially those with low blood flows, and on the effect of a larger intervention, such as lung recruitment manoeuvres.
References


