Central blood flow measurements in newborn infants

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CHAPTER 4

EFFECT OF LUNG RECRUITMENT ON PULMONARY, SYSTEMIC AND DUCTAL BLOOD FLOW IN PRETERM INFANTS

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ABSTRACT

Objective
To determine the effect of lung recruitment on pulmonary, systemic and ductal blood flow in preterm infants treated with primary high-frequency ventilation (HFV).

Study design
Thirty four infants (median gestational age 28 weeks) were included in this prospective cohort study. Changes in oxygenation in response to stepwise changes in the continuous distending pressure (CDP) were used to monitor lung recruitment during HFV. For each individual patient the opening pressure (CDPo), closing pressure (CDPc) and optimal pressure (CDPopt) were determined. Ultrasound measurements of right ventricular output (RVO), superior vena cava (SVC) and ductus arteriosus (DA) flow were performed at the start of recruitment (CDPs), CDPo, and CDPopt.

Results
Increasing the CDP from 8 (CDPs) to 20 (CDPo) cmH₂O resulted in a decreased RVO (mean difference -17%; 95%CI -24, -10%) and unchanged SVC flow and ductal shunting. Transient low RVO and SVC flow values at CDPo were seen in, respectively, 3 and 2 infants.

Conclusions
Individual lung recruitment during HFV in preterm infants does not seem to result in clinically relevant changes in pulmonary, systemic and ductal blood flow.
Introduction

Despite the increased use of early nasal continuous positive airway pressure (CPAP), a substantial number of preterm infants with respiratory distress syndrome (RDS) are still treated with mechanical ventilation. Although often lifesaving, mechanical ventilation can also damage the immature lung by alveolar overdistension and repetitive opening and collapse. This process of secondary lung injury is considered one of the major risk factors for the development of bronchopulmonary dysplasia (BPD).

In an attempt to lower the incidence of BPD, many clinicians use high-frequency ventilation as a lung protective ventilation mode in preterm infants. Randomized controlled trials, however, have shown that high-frequency ventilation (HFV) only results in a modest and inconsistent decrease in BPD. Some have suggest that this disappointing result is, in part, caused by the ventilation strategy used during HFV. Indeed animal studies have shown that the small tidal volumes used during HFV will only attenuate lung injury when combined with alveolar recruitment and stabilization (i.e. optimal lung volume or open lung strategy).

We recently showed that lung recruitment during HFV is also feasible in preterm infants with RDS using changes in intrapulmonary shunt and subsequent changes in oxygenation to guide alveolar recruitment. The relatively high mean airway pressures used during and after this recruitment procedure did not affect blood pressure and heart rate. However, these hemodynamic parameters may not always reflect the true changes in systemic blood flow. Studies in preterm infants have shown that high mean airway pressures are associated with low systemic blood flow and that the latter increases the risk for intraventricular haemorrhage and poor neurodevelopmental outcome. So far, two studies measured systemic flows during HFV and showed no difference compared with conventional ventilation. However, these studies did not measure the changes in blood flow during the actual recruitment procedure.

The objective of the present study is to assess the direct effect of lung recruitment with primary HFV on pulmonary and systemic blood flow in preterm infants with RDS.

Methods

Patients

This prospective observational cohort study was performed between June 2006 and January 2008 in the neonatal intensive care unit of Emma Children’s Hospital, Amsterdam, The Netherlands, where HFV is used as the primary mode of ventilation in preterm infants needing mechanical ventilation for a suspected diagnosis of RDS. Infants were eligible if they had a gestational age less than 35 weeks and were less than 48 hours old. Infants with major congenital malformations were excluded. Informed consent was obtained from the parents and the study was approved by the local ethics committee.
**Ventilation strategy**

HFV was delivered with a SensorMedics 3100A oscillator (SensorMedics Critical Care, Yorba Linda, CA) using an open lung ventilation strategy as previously described. In short, this strategy aims to recruit and stabilize the majority of collapsed alveoli, using oxygenation as an indirect parameter for lung volume. Starting at 6 to 8 cmH₂O, the continuous distending pressure (CDP) was stepwise increased as long as transcutaneous oxygen saturation (SpO₂) and/or partial oxygen pressure improved. The fraction of inspired oxygen (FiO₂) was stepwise reduced keeping SpO₂ within the target range (86–94%). The recruitment procedure was stopped if oxygenation no longer improved or the FiO₂ was ≤ 0.25. The corresponding CDP was called the opening pressure (CDPo). Next, the CDP was stepwise reduced until the SpO₂ deteriorated. Deterioration of oxygenation was defined as sustained drop in SpO₂ of equal or more than 5% of the initial value at CDPo or an absolute SpO₂ value below 86%. The corresponding CDP was called the closing pressure (CDPc). Following a second recruitment maneuver with the known CDPo, the optimal CDP (CDPopt) was set 2 cmH₂O above the CDPc. The pressure amplitude was adjusted to maintain the transcutaneous partial carbon dioxide pressure between 40 and 60 mmHg. This approach ensured application of the lowest possible CDP to maintain an open lung for each individual patient. Ventilator settings and data on oxygenation were recorded at the start of the recruitment (CDPs), at CDPo, CDPc and at CDPopt. Following this first recruitment procedure patients were treated with exogenous surfactant according to the department protocol.

**Hemodynamic measurements**

Right ventricular output (RVO), superior vena cava flow (SVC) and ductus arteriosus (DA) flow were measured at CDPs, at CDPo and at CDPopt using a Sequoia ultrasound system (Siemens medical, Germany) with an 8 MHz vector array transducer incorporating colour flow and pulsed wave Doppler. RVO and SVC flow were measured according to previously published methodology, using thresholds of 150 and 45 ml/kg/min to define low RVO and low SVC flow respectively. For calculations of flow the following formula was used: Flow = \((\text{velocity time integral} \times \pi \times \text{diameter}^2/4) \times \text{heart rate}/\text{body weight.}\)

Ductal diameter was determined from the 2D image using a suprasternal or high parasternal position in a way that the whole length of the duct could be visualised. The diameter was taken at the smallest point (in the cardiac cycle) at the pulmonary side of the duct. The time of right-to-left ductal shunting was measured in the ductal flow pattern and expressed as a percentage of the total duration of the cardiac cycle measured between two consecutive R waves. A right-to-left ductal shunt percentage of more than 30% of the cardiac cycle was considered significant pulmonary hypertension (PH).

Since all measurements were done at a very early postnatal age, we visually analysed ductal flow for the presence of laminar flow. If laminar, ductal flow velocity was sampled by pulse doppler ultrasonography at the same position where 2D
measurements of the diameter were obtained according to the methodology described by Phillipos et al.\textsuperscript{15} Velocity time integrals (Vti’s) were determined by the average area under the curve of five consecutive Doppler waveforms. All upward and all downward Vti’s were averaged to determine right-to-left and left-to-right velocity time integrals over the DA. Averaged Vti’s were used with the 2D diameter of the duct in the aforementioned formula to determine right-to-left and left-to-right flow over the DA. The net ductal flow (DA flow) was calculated as the left-to-right flow minus the right-to-left flow. A negative net DA flow would therefore indicate a right-to-left shunt.

All measurements were performed by one investigator (KW). The scans were recorded on magnetic optical disks, and measurements were done as a batch away from the bedside at a later time.

Blood pressure and heart rate were recorded during the recruitment procedure. Blood pressure was measured by a non-invasive oscillometric device or an indwelling arterial line and this method was not changed during the recruitment procedure.

Statistics
The effect of lung recruitment on pulmonary and hemodynamic outcomes was evaluated with a General Linear Model with repeated measurements for normally distributed outcomes. A Friedman test was used for non-parametric outcomes. The association between the CDP and flow changes was evaluated with linear regression analysis. P-values smaller than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 12 (SPSS Chicago, IL).

Results:
Patient characteristics
Thirty four infants with a median (inter quartile range, IQR) gestational age of 28 weeks (26-29) and a median birth weight of 1060 grams (760-1300) were included in this study. The median postnatal age at start of the recruitment was 5 hours (1-10). Eleven infants (32%) had received a complete course of antenatal steroids. There were 4 infants (12%) with a low SVC flow at the start of the recruitment procedure and 2 (6%) of these infants also had a low RVO. Nine infants (26%) received hemodynamic support before the recruitment procedure, based on their clinical condition and blood pressure. All 9 received volume expansion, 3 infants also received dopamine and 1 infant received dopamine and dobutamine before lung recruitment was started. None of the patients required additional hemodynamic support during the recruitment procedure.

Effect of lung recruitment on RVO and SVC flow
As shown in table 1, the mean CDPo was 20 cmH\textsubscript{2}O, resulting in a significant decrease in the median FiO\textsubscript{2} from 0.70 to 0.25. This lung volume could thereafter be maintained at a mean CDPopt of 14 cmH\textsubscript{2}O.
The RVO was significantly lower at CDPo compared with CDPs (mean difference -51 ml/kg/min; 95% CI -73, -29 or -17%; 95% CI -24, -10%) and this remained unchanged after reaching CDPopt. The SVC flow, however, remained stable during all stages of lung recruitment (Table 1, Figure 1).

Table 1: Pulmonary and hemodynamic response to lung recruitment in 34 infants as mean ± SD or median (IQR) where appropriate. Ductal flows are reported for 30 infants. CDP: continuous distending pressure, FiO\textsubscript{2}: fractional inspired oxygen, RVO: right ventricular output, SVC: superior vena cava, %RL: percentage of cardiac cycle with right to left shunt, R-L: right to left, L-R: left to right, DA Vti: Ductal velocity time integral, HR: heart rate; SBP: systolic blood pressure, DBP: diastolic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Start (CDPs)</th>
<th>Open (CDPo)</th>
<th>Optimal (CDPopt)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>time (min)</td>
<td>0 ± 0</td>
<td>28 ± 11</td>
<td>50 ± 18</td>
<td>&lt;0.001</td>
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<tr>
<td>CDP (cmH\textsubscript{2}O)</td>
<td>8 ± 1</td>
<td>20 ± 4</td>
<td>14 ± 3</td>
<td>&lt;0.001</td>
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<td>Amplitude (cmH\textsubscript{2}O)</td>
<td>22 ± 5</td>
<td>24 ± 5</td>
<td>23 ± 5</td>
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<td>FiO\textsubscript{2}</td>
<td>0.70 (0.50 - 1.00)</td>
<td>0.25 (0.23 - 0.35)</td>
<td>0.28 (0.23 - 0.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Saturation (%)</td>
<td>86 ± 11</td>
<td>90 ± 4</td>
<td>91 ± 4</td>
<td>0.030</td>
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<tr>
<td>RVO (ml/kg/min)</td>
<td>318 ± 101</td>
<td>267 ± 106</td>
<td>266 ± 85</td>
<td>&lt;0.001</td>
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<td>SVC flow (ml/kg/min)</td>
<td>79 ± 30</td>
<td>78 ± 34</td>
<td>72 ± 27</td>
<td>0.239</td>
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<tr>
<td>Duct diameter (mm)</td>
<td>2.5 ± 0.7</td>
<td>2.5 ± 0.9</td>
<td>2.5 ± 0.8</td>
<td>0.896</td>
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<td>Ductal shunt (%R-L time)</td>
<td>21 ± 14</td>
<td>23 ± 16</td>
<td>22 ± 18</td>
<td>0.846</td>
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<td>R-L DA Vti (cm/s)</td>
<td>2.3 (0.5 - 4.5)</td>
<td>2.4 (0.7 - 5.1)</td>
<td>2.3 (0.7 - 4.0)</td>
<td>0.927</td>
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<td>L-R DA Vti (cm/s)</td>
<td>13.6 (5.0 - 24.0)</td>
<td>12.8 (4.1 - 22.4)</td>
<td>12.6 (5.1 - 20.1)</td>
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<td>HR (beats/min)</td>
<td>151 ± 14</td>
<td>145 ± 15</td>
<td>144 ± 14</td>
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<td>SBP (mmHg)</td>
<td>46 ± 10</td>
<td>46 ± 8</td>
<td>44 ± 8</td>
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<tr>
<td>DBP (mmHg)</td>
<td>27 ± 8</td>
<td>27 ± 7</td>
<td>27 ± 7</td>
<td>0.592</td>
</tr>
</tbody>
</table>

Figure 1. Mean(SD) right ventricular output (RVO) and superior vena cava (SVC) flow during lung recruitment. CDPs: continuous distending pressure at start of the recruitment procedure, CDPo: opening pressure, CDPopt: optimal pressure.
In 2 and 3 patients, respectively, the SVC flow and RVO dropped below the predefined low blood flow threshold values at CDPo, but returned to normal after reaching CDPopt. There was no significant association between the pressure difference between CDPs and CDPo and the decrease in RVO (regression coefficient -3.4 ml/kg/min per cmH\(_2\)O; 95% CI -10, 3).

**Effect of lung recruitment on DA shunt**
The DA was found to be patent in 32 infants with a median ductal diameter of 2.5 mm. In 30 infants the flow pattern in the duct was laminar, allowing for DA shunt measurements (Table 1). At the start of lung recruitment the shunt direction in these patients was right-to-left in 21% of the cardiac cycle and left-to-right in 79% of the cardiac cycle. In 9 infants (26%) the right-to-left shunt was more than 30% (definition of PH).
Overall, maximum lung recruitment did not produce significant changes in ductal shunt. As shown in figure 2, maximum lung recruitment did not produce a major change in the right-to-left flow (median difference 2 ml/kg/min, 95% CI 0, 7) over the DA. The left-to-right flow, however, decreased at CDPo compared to CDPs (median difference -20 ml/kg/min, 95% CI -54, 35) and returned to baseline values after reaching CDPopt. (Figure 2)

![Figure 2: Median (IQR) ductal left-to-right (L-R) and right-to-left (R-L) flow during lung recruitment. CDPs: continuous distending pressure at start of the recruitment procedure, CDPo: opening pressure, CDPopt: optimal pressure.](image-url)
In 3 infants the net DA flow velocity changed from positive (more left-to-right) at CDPs to negative (more right-to-left) at CDPO and returned to positive again at CDPopt. In 2 infants the net flow over the DA was negative at CDPs and changed to positive at CDPO and CDPopt. Only 2 of the 9 patients with PH (22%) reached a FiO2 ≤ 0.25 at CDPO, compared with 16 of the 25 infants (65%) without predominantly right-to-left shunt.

**Effect of lung recruitment on other hemodynamic parameters**
Heart rate decreased during the lung recruitment procedure (mean difference -6 beats/min; 95% CI -9, -2), but there were no significant changes in blood pressure (Table 1).

**Discussion:**
This study shows that a lung recruitment procedure during HFV in preterm infants with RDS results in a reduction in RVO with no changes in SVC flow. Furthermore, this study shows that right-to-left shunt over the DA is often present in ventilated infants with RDS and that lung recruitment has a variable effect on the shunt direction.

Although experimental and human studies have indicated that HFV is only lung protective when combined with an optimal lung volume or open lung strategy, the effect of this strategy on the hemodynamic stability of preterm infants has been poorly studied.6,17 The present study is, to our knowledge, the first that looked at the changes in pulmonary and systemic blood flow in response to lung recruitment in preterm infants. Despite the fact that the mean airway pressure increased almost 12 cmH2O during the initial recruitment, the RVO decreased only 17%. Although this reduction was statistically significant, we feel the clinical relevance of this change is questionable because in all but 3 infants, the absolute RVO value remained well above the lower threshold of 150 ml/kg/min. Furthermore, in these 3 infants RVO returned to normal values after reaching CDPopt.

We can only speculate on the possible mechanisms for this reduction in RVO. Based on studies performed in adults, application of high mean airway pressures leading to increased intrathoracic pressures can reduce cardiac output via [1] an increased right atrial pressure leading to a reduced cardiac input, [2] an increased right ventricular afterload due to an increased pulmonary vascular resistance as the lung is distended and, [3] a decreased ventricular filling due to ventricular interdependence.17-19 The slight changes in DA velocity time integrals seem to suggest that an increased right ventricular afterload due to an increase in pulmonary vascular resistance is one of the mechanisms for this reduction in RVO. This is consistent with fetal lamb studies showing that right ventricular stroke volume progressively decreases with an increase in afterload.20 However, other mechanisms cannot be ruled out by the present study because we did not measure other ultrasound parameters like flow over the foramen ovale, right ventricular
function and size, and/or left ventricular function. More invasive hemodynamic monitoring is currently not feasible in extremely low birth weight infants. The present study shows that the mean SVC flow does not change during the different stages of lung recruitment during HFV. In addition, only 2 infants showed a drop in absolute SVC flow below the critical value of 45 ml/kg/min, returning to normal values after reaching CDPopt. We feel this is an important observation considering the reported association between low SVC flow and intracranial haemorrhages.\(^8\)

We do not know if total cardiac input and lower body blood flow is not influenced by lung recruitment, because we did not measure flow in the inferior vena cava (IVC). Flow in the IVC represents 2/3 of the cardiac input, but it is difficult to measure via a trans-thoracic approach due to the small common confluence and its anatomical position for flow velocity determinations.

Hemodynamic stability is considered an important determinant of how a patient will respond to changes in ventilation.\(^21\) Some of the patients included in this study were hemodynamically instable at the start of lung recruitment having either low systemic flows or needing volume expansion and/or inotropes. Although the response to lung recruitment was sometimes variable, most of the patients tolerated lung recruitment on an individual basis well. Whether these finding are also applicable to patients with more severe hemodynamic instability needs further studying.

The present findings on RVO and SVC flow seem to be consistent with previous studies exploring the effect of increased mean airway pressures during conventional mechanical ventilation. Hausdorf and colleagues reported a 30% decrease in RVO when increasing the PEEP level from 0 to 8 cmH\(_2\)O in preterm infants.\(^22\) The inclusion of infants in the postacute phase of RDS who often showed signs of lung over-distension at a PEEP of 8 cmH\(_2\)O probably explains the fact that the decrease in RVO was almost twice the decrease reported in the present study. De Waal and colleagues reported the effect of much smaller changes in mean airway pressures by increasing PEEP 3 cmH\(_2\)O in ventilated preterm infants which led to a 5% reduction in RVO with no change in SVC flow.\(^23\) This seems to indicate that the effect of higher mean airway pressures on pulmonary and systemic blood flow is dependent on lung compliance.

We found a relatively high percentage (26%) of infants with PH at the start of lung recruitment. Walther and colleagues have reported similar results and suggested that the presence of PH reflects the severity of RDS.\(^24\) As expected, the patients with PH were less likely to reach the FiO\(_2\) target of 0.25 during lung recruitment compared with the patient without PH. This is probably explained by the fact that part of the hypoxemia in the PH patients is caused by extrapulmonary right-to-left shunt via the DA. This finding emphasizes the importance of stopping the stepwise increase in airway pressure as soon as oxygenation no longer improves, thereby minimizing the risk for lung over-distension.

There are several limitations to this study. The patients included in this study were all preterm infants with suspected RDS treated with nasal CPAP as initial form of treatment. No prophylactic surfactant was given, and the measurements were
performed during their initial lung recruitment. The results from this study may not be applicable to a population who received prophylactic surfactant or have other causes of respiratory failure with non-homogeneous lung disease. Future studies are needed to confirm or refute our findings in these different clinical conditions. In conclusion, the present study shows that individual lung recruitment during open lung HFV does not result in a clinical relevant reduction in RVO or SVC flow in most preterm infants. Furthermore, this study shows that PH is present in some infants with RDS. This should be taken into account when using oxygenation as an indirect parameter to guide to process of lung recruitment.
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