# Spontaneously Breathing Preterm Infants Change in Tidal Volume to Improve Lung Aeration Immediately after Birth

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**Objective** To examine the temporal course of lung aeration at birth in preterm infants <33 weeks gestation.

**Study design** The research team attended deliveries of preterm infants <33 weeks gestation at the Royal Alexandra Hospital. Infants who received only continuous positive airway pressure were eligible for inclusion. A combined carbon dioxide ($CO_2$) and flow-sensor was placed between the mask and the ventilation device. To analyze lung aeration patterns during spontaneous breathing, tidal volume ($V_T$), and exhaled $CO_2$ ($ECO_2$) were recorded for the first 100 breaths.

**Results** Thirty preterm infants were included with a total of 1512 breaths with mask leak <30%. Mean (SD) gestational age and birth weight was 30 (1) weeks and 1478 (430) g. Initial $V_T$ and $ECO_2$ for the first 30 breaths was 5-6 mL/kg and 15-22 mm Hg, respectively. $V_T$ and $ECO_2$ increased over the next 20 breaths to 7-8 mL/kg and 25-32 mm Hg, respectively. For the remaining observation period $V_T$ decreased to 4-6 mL/kg and $ECO_2$ continued to increase to 35-37 mm Hg.

**Conclusions** Preterm infants begin taking deeper breaths approximately 30 breaths after initiating spontaneous breathing to inflate their lungs. Concurrent $CO_2$ removal rises as alveoli are recruited. Lung aeration occurs in 2 phases: initially, large volume breaths with poor alveolar aeration followed by smaller breaths with elimination of $CO_2$ as a consequence of adequate aeration. *(J Pediatr 2015;167:274-8)*.

At birth, preterm infants have to facilitate the early development of an effective functional residual capacity (FRC), remove carbon dioxide ($CO_2$), and improve oxygenation in order to achieve the fetal-to-neonatal transition. The majority of infants achieve this without help;[1] however, a significant proportion of premature infants require breathing support at birth.[2] The cornerstone of respiratory support immediately after birth is positive pressure ventilation (PPV).[3] The purpose of PPV is to establish lung aeration, deliver an adequate tidal volume ($V_T$), initiate spontaneous breathing, and facilitate gas exchange.[4] Recent phase contrast X-ray imaging studies in spontaneous breathing term newborn rabbits and nonbreathing preterm rabbits demonstrate that lung liquid clearance and lung aeration occurs only during inspiration.[5-7] Lung aeration accumulates with each breath, and the FRC volume increase equals the volume of liquid leaving the airways.[7] Several studies have described how exhaled $CO_2$ ($ECO_2$) can be used to monitor lung aeration.[8-12] Kang et al[12] and Palme-Kilander et al[8] demonstrated that spontaneously breathing infants have higher $ECO_2$ values compared with infants receiving PPV. This is further supported by Hooper et al who described that $ECO_2$ levels in preterm infants at birth also are correlated with $V_T$, suggesting a correlation between change in $V_T$, minute ventilation (MV), and $ECO_2$.[10] To our knowledge, there is no information regarding the changes in lung aeration after birth in preterm infants who are breathing spontaneously. The aim of the study was to examine in detail how spontaneously breathing premature infants <33 weeks achieve lung aeration after birth.

## Methods

This study was carried out at The Royal Alexandra Hospital, Edmonton, Canada, a tertiary perinatal center admitting ∼350 infants with a birth weight of <1500 g annually to the neonatal nursery. The Royal Alexandra Hospital Research Committee and Health Ethics Research Board, University of Alberta, and the Health Ethics Research Board approved the study and granted deferred consent. After admission to the neonatal intensive

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| $CO_2$ | Carbon dioxide |
| CPAP | Continuous positive airway pressure |
| $ECO_2$ | Exhaled $CO_2$ |
| FRC | Functional residual capacity |
| MV | Minute ventilation |
| PPV | Positive pressure ventilation |
| $VCO_2$ | Amount of $CO_2$ elimination |
| $V_T$ | Tidal volume |

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care unit, parental consent was requested. Between June 2013 and July 2014, 297 deliveries of preterm infants were attended by the research team in addition to the Resuscitation-Stabilization-Triage team (usually a neonatal nurse, neonatal respiratory therapist, neonatal nurse practitioner or neonatal fellow, and a neonatal consultant). The research team was not involved in the clinical care of the infants.

The study was limited to infants <33 weeks gestational age who were spontaneously breathing and receiving continuous positive airway pressure (CPAP) immediately after birth for respiratory support as judged by the clinical team. Infants who did not need respiratory support at birth or received free-flow oxygen only, PPV, chest compressions, or epinephrine in the delivery room were excluded.

All infants received respiratory support by a round silicone facemask (Fisher and Paykel Healthcare, Auckland, New Zealand). Respiratory support was provided with a T-piece device (Giraffe Warmer, GE Health Care, Burnaby, Canada), a continuous flow, pressure-limited device with a built-in manometer and a positive end expiratory pressure valve. The default settings were a gas flow of 8 L/min and positive end expiratory pressure of 6 cm $H_2O$.

A respiratory profile monitor (NM3; Philips Healthcare, Electronics Ltd, Markham, Ontario, Canada) was used to continuously measure $V_T$, airway pressures, gas flow, and $ECO_2$. Airway pressure and gas flow are measured with a fixed orifice differential pressure pneumotachometer. $V_T$ was calculated by integrating the flow signal. $ECO_2$ was measured by a nondispersive infrared absorption technique.[11] The accuracy for the gas flow is $\pm0.125$ L/min and for $ECO_2$ $\pm2$ mm Hg. In the delivery room, the respiratory profile monitor and the computer screen were not visible to the resuscitation team and the monitor alarm was disabled.

IntelliVue MP50 (Philips Healthcare, Philips Electronics Ltd) was used to continuously measure heart rate and oxygen saturation. A Masimo Radical pulse oximeter (Masimo Corporation, Irvine, California) probe set at maximum sensitivity and 2-second averaging was placed around the infant's right wrist to measure systematic oxygen saturation. Heart rate was measured using three Micro-Premie Leads (Vermed, Bellows Falls, Vermont).

An Invos Cerebral/Somatic Oximeter Monitor (Invos 5100, Somanetics Corporation, Troy, Michigan) with the neonatal sensor was used to measure cerebral regional tissue oxygenation. A transducer contains a light emitting diode and 2 sensors at different distances. The InvosCerebral/Somatic Oximeter Monitor calculates the cerebral regional tissue oxygenation, which is expressed as the percentage of oxygenated hemoglobin (oxygenated hemoglobin/total hemoglobin). The transducer was positioned on the left frontoparietal forehead in each infant regardless of mode of delivery. The sensor on the forehead was secured with a wrap.[13]

All variables were stored continuously in a multichannel system "alpha-trace digital MM" (B.E.S.T. Medical Systems, Vienna, Austria) for subsequent analysis. Values of gas flow, $V_T$, airway pressure, and $ECO_2$ were recorded at 200 Hz; arterial and regional oxygen saturation and heart rate were stored every second, and the sample rate of cerebral regional tissue oxygenation was 8 seconds (0.13 Hz).

### Statistical Analyses

Demographics of study infants were recorded. A breath-by-breath analysis of airway pressure, gas flow, $V_T$, and $ECO_2$ was performed for the first 100 breaths for each infant. Mask leak was calculated by expressing the volume of gas that did not return through the flow sensor during expiration as a percentage of the volume that passed through the flow sensor during inflation.[10] Spontaneous breaths with a mask leak >30% were excluded from further analysis as this had the potential to underestimate measured expired $V_T$ and $ECO_2$.[12] MV was calculated for each breath using the $V_T$ and respiratory rate. Data of $V_T$, $ECO_2$, and MV were combined to 5 breaths (1-5 breaths, 5-10 breaths, and so on) for further analysis. The data are presented as mean (SD) for normally distributed continuous variables and median (IQR) when the distribution was skewed. For all respiratory variables, the median value for each infant was calculated first and then either the mean or median of the median was calculated. Data were compared using repeated measures ANOVA with Bonferroni post-test. *P* values are 2-sided and $P < .05$ was considered statistically significant. Statistical analyses were performed with Stata (Intercooled 10; StataCorp, College Station, Texas). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines.[14]

## Results

The clinical team attended a total of 436 deliveries, and the research team attended 297 deliveries. Twenty-five infants were excluded because parents did not consent to use the recorded data. A total of 242 infants were excluded because 47 did not require any respiratory support, 12 received only free-flow oxygen, and 183 received PPV at any given time leaving 30 infants eligible for this study (**Table**). A total of 3200 breaths were analyzed (1688 [53%] were excluded with mask leak >30%), leaving 1512 breaths for analysis. None of the infants had delayed cord clamping.

### $V_T$, $ECO_2$, and MV

The range of $V_T$ during the first 30 breaths was 5-6 mL/kg, as $ECO_2$ increased from 15-22 mm Hg (**Figure 1**). Over the next 20 breaths, we observed increases in $V_T$ and $ECO_2$ to 7-8 mL/kg and 25-32 mm Hg, respectively. For the remaining observation period, $V_T$ decreased to 4-6 mL/kg, and $ECO_2$ continued to increase to 35-37 mm Hg. The change in MV was similar, with an initial increase in MV from 130-135 mL/kg/min to 164-184 mL/kg/min, which coincided with an increase in $V_T$. Thereafter, MV plateaued at around 150 mL/kg/min (**Figure 1**). Overall, $V_T$ was significantly higher within the first 30 breaths compared with the end of