Effect of Minimally Invasive Surfactant Therapy on Lung Volume and Ventilation in Preterm Infants

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Objective To assess the changes in (regional) lung volume and gas exchange during minimally invasive surfactant therapy (MIST) in preterm infants with respiratory distress syndrome.

Study design In this prospective observational study, infants requiring a fraction of inspired oxygen (FiO_2) ≥0.30 during nasal continuous positive airway pressure of 6 cmH_2O were eligible for MIST. Surfactant (160-240 mg/kg) was administered in supine position in 1-3 minutes via an umbilical catheter placed 2 cm below the vocal cords. Changes in end-expiratory lung volume (EELV), tidal volume, and its distribution were recorded continuously with electrical impedance tomography before and up to 60 minutes after MIST. Changes in transcutaneous oxygen saturation (SpO_2) and partial carbon dioxide pressure, FiO_2, respiratory rate, and minute ventilation were recorded.

Results A total of 16 preterm infants were included. One patient did not finish study protocol because of severe apnea 10 minutes after MIST. In the remaining infants (gestational age 29.8 ± 2.8 weeks, body weight 1545 ± 481 g) EELV showed a rapid and sustained increase, starting in the dependent lung regions, followed by the nondependent regions approximately 5 minutes later. Oxygenation, expressed as the SpO_2/FiO_2 ratio, increased from 233 (IQR 206-257) to 418 (IQR 356-446) after 60 minutes ($P < .001$). This change was significantly correlated with the change in EELV ($\rho = 0.70$, $P < .01$). Tidal volume and minute volume decreased significantly after MIST, but transcutaneous partial carbon dioxide pressure was comparable with pre-MIST values. Ventilation distribution remained unchanged.

Conclusions MIST results in a rapid and homogeneous increase in EELV, which is associated with an improvement in oxygenation. *(J Pediatr 2016;170:67-72)*.

Respiratory distress syndrome (RDS) is the most common cause of respiratory failure in preterm infants.[1,2] It is characterized by structural immaturity of the lung and a lack of endogenous surfactant.[3] Treatment consists of respiratory support and exogenous surfactant. Until recently, surfactant was administered via an endotracheal tube during mechanical ventilation; however, this mode of respiratory support is considered an important risk factor for developing bronchopulmonary dysplasia, and for this reason, preterm infants are managed increasingly on nasal continuous positive airway pressure (nCPAP) directly after birth.[4,5] Recent studies have therefore investigated less-invasive methods for surfactant therapy via the use of a semirigid or flexible catheter placed just below the vocal cords to administer surfactant during spontaneous breathing on noninvasive respiratory support.[6-8] The results of this so-called minimally invasive surfactant therapy (MIST) have been promising, demonstrating less need for mechanical ventilation and shorter duration of oxygen therapy.[9,10]

The effect of exogenous surfactant on lung function during invasive mechanical ventilation has been studied extensively in animal models[11-13] and preterm infants.[14-16] The most prominent and consistent finding in these studies is a surfactant-induced increase in end-expiratory lung volume (EELV), resulting in an improved oxygenation. Studies in animals and humans also have shown that this increase in EELV after surfactant treatment favors the dorsal (dependent) lung regions, suggesting a gravity-dependent distribution of exogenous surfactant.[15,17] Whether these effects on EELV also are applicable to MIST remains unclear, because to date only one study, performed in animals, has investigated the effect of MIST on lung function, but this study did not explore the impact on EELV.[18]

AU	Arbitrary unit	nCPAP	Nasal continuous positive airway pressure
EELV	End-expiratory lung volume	RDS	Respiratory distress syndrome
ΔEELV	Relative changes in EELV	SpO_2	Transcutaneous oxygen saturation
EIT	Electrical impedance tomography	$TcPCO_2$	Transcutaneous partial carbon dioxide pressure
fEIT	Functional electrical impedance tomography	ΔZ	Impedance changes
FiO_2	Fraction of inspired oxygen		
MIST	Minimally invasive surfactant therapy		

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Supported by Chiesi Pharmaceutical, Rijswijk, The Netherlands. The EIT device was provided by CareFusion, Yorba Linda, CA. I.F. has received reimbursement for congress and travel expenses and speaking fees from Dräger and Swisstom. A.v.K. has received travel expenses and speaking fees from CareFusion, Yorba Linda, CA. The other authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.11.035

Therefore, we measured the changes in lung volume and its distribution before, during, and after MIST in preterm infants with RDS, using electrical impedance tomography (EIT). EIT is a noninvasive, radiation-free tool that measures (regional) changes in impedance in a cross-sectional slice of the lung, which correlate well with actual changes in aeration and are representative for the changes in the whole lung in preterm infants.[19,20] We hypothesized that MIST would lead to an increase in EELV favoring the more dependent lung regions.

Methods

The prospective observational study was performed in the level III neonatal intensive care unit of the Emma Children's Hospital, Academic Medical Center (Amsterdam, The Netherlands). Preterm infants were considered eligible for MIST if they fulfilled all of the following criteria: (1) gestational age ≥26 weeks; (2) birth weight of ≥750 g; (3) fraction of inspired oxygen (FiO_2) ≥0.30 while supported with a nCPAP of 6 cmH_2O; (4) clinical and radiological signs of RDS; and (5) adequate respiratory drive. All infants with a gestational age <28 weeks received prophylactic caffeine treatment started within the first hour after life. Infants receiving MIST were included in the study if the procedure was performed within 72 hours after birth and written informed consent was obtained from both parents. The study was approved by the institutional review board.

The protocol was based on the MIST procedure described by Göpel et al.[9] Infants were placed in supine position. With the use of a laryngoscope and a Magill forceps, a marked 3.5-5 Fr catheter was placed 2 cm below the vocal cords and, based on the whole content of a vial, a dose of 160-240 mg/kg porcine-derived surfactant (Curosurf; Chiesi Pharmaceuticals, Parma, Italy) was administered slowly (1-3 minutes). During the pilot phase of implementation, a considerable proportion of infants showed loss of surfactant via the nose and mouth. For this reason, we decided to administer surfactant under continuing visual inspection of the vocal cords to avoid reflux of surfactant as much as possible. nCPAP was continued during this procedure. After surfactant administration, the infants were placed in supine 12° reverse Trendelenburg position for 60 minutes. Transcutaneous oxygen saturation (SpO_2) values were targeted between 86% and 94% throughout the study.

Patient characteristics, including gestational age, birth weight, Apgar scores, and postnatal age at MIST, were collected. In addition, nCPAP settings, FiO_2, heart rate, SpO_2, and transcutaneous partial carbon dioxide pressure levels ($TcPCO_2$) were recorded throughout the study.

Lung impedance changes (ΔZ) were measured continuously from 10 minutes before until 60 minutes after the MIST procedure. Sixteen hand-trimmed electrodes (Blue Sensor, BRS-50-K; Ambu Inc, Linthicum Heights, Maryland) were placed equidistantly on the thorax circumference, just above nipple line and connected to the Goettingen Goe-MF II EIT system (CareFusion, Yorba Linda, California). Repetitive electrical currents (5 mA, 100 kHz) were injected cyclically (scan rate 13 Hz) through adjacent electrode pairs. Voltage changes were registered in all other passive electrode pairs. A back-projection algorithm generated a series of 32 × 32-pixel matrices of relative ΔZ by comparing these voltage changes to a reference period. ΔZ values were recorded with a custom-designed Polybench-based software package (Applied Biosignals, Weener, Germany).

Analyses

EIT data analysis was performed off-line with AUSPEX version 1.6 (VUmc, Amsterdam, The Netherlands). The change in EELV was calculated by selecting a stable 30-second period just before the start of the MIST procedure, which was used as reference. Next, the relative ΔZ at the troughs of the breaths in the stable 30-second was used to calculate the relative changes in EELV (ΔEELV) in arbitrary units (AUs) after MIST, by comparing it with the average ΔZ at the troughs at 5-minute intervals during the first 60 minutes after surfactant administration. The ΔEELV were then normalized for body weight, expressed in AU/kg.

The same 30-second recordings used for ΔEELV analysis also were used for calculating changes in EIT-derived tidal volume; however, tidal volume changes at each time point were now referenced to the average ΔZ in that same interval. The EIT waveforms of relative ΔZ values were band-pass filtered in the band of spontaneous breathing rate (10/min below the actual breathing frequency and 10/min above its second harmonic). The peak and trough signal values were identified and averaged over the selected period. The average amplitude was normalized for body weight.

Regional (tidal) ventilation distribution of the spontaneous breaths was assessed by means of functional EIT (fEIT) images. fEIT images were generated by calculating the SD of the impedance waveforms in each individual pixel within the 32 × 32-pixel matrix. A ventilation profile was derived from each fEIT image showing the distribution of ventilation in 32 anteroposterior slices, as described previously.[11] Subsequently, the areas under the curve for the anterior (slice 1-16) and posterior (slice 17-32) regions were calculated. Finally, the geometrical center of ventilation was determined as an additional measure describing the ventilation distribution in relation to the ventral-to-dorsal chest diameter, as described previously.[11,21]

Statistical analysis was performed with GraphPad Prism 5.0 (GraphPad Software Inc, San Diego, California) and SPSS version 20.0 (SPSS Inc, Chicago, Illinois). Data were expressed as mean with SD or median with IQR, as appropriate. Comparative analysis was performed with the Friedman test for repeated measures for skewed data and one-way ANOVA for repeated measures for normally distributed data, followed by post hoc testing. Correlations were expressed as Spearman