ORIGINAL ARTICLE

Assessment of lung ventilation in infants with respiratory distress syndrome using electrical impedance tomography

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Abstract

Aim: The aim of the present study was to determine immediate changes of global and regional lung function after exogenous surfactant administration in mechanically ventilated infants with respiratory distress syndrome (RDS) using electrical impedance tomography (EIT) measurements.

Materials and Methods: A prospective study was conducted in a Neonatal Intensive Care Unit at a university hospital. Seventeen preterm infants (<12 hours old) suffering from RDS were included in this study. Interventions taken were low-pressure recruitment maneuver, surfactant administration and minimal adjustments in ventilator settings. Repeated EIT measurements (401 in total) were performed before and after (15 min - 30 min) surfactant administration. Global lung function changes were assessed with two markers, namely absolute resistivity (AbsR) and normalized impedance change (ΔZ); redistribution of regional lung ventilation was assessed as well. Airway pressure and arterial blood gases were recorded.

Results: Surfactant administration resulted in a statistically significant increase of both the AbsR and ΔZ markers. Moreover, there was a ventilation shift towards dorsal – dependent lung areas with less asymmetry in the right-to-left air distribution.

Conclusions: Surfactant administration in the recruited lung with RDS modifies regional ventilation, as assessed by EIT, contributing to a more homogeneous air distribution. Furthermore, significant changes in EIT markers reflect improvement of global lung function after surfactant administration. Hippokratia 2013, 17, 2: 115-119

Keywords: Infant, respiratory distress syndrome, surfactant, electrical impedance tomography

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Introduction

Infants with Respiratory Distress Syndrome (RDS) have surfactant-deficient lungs, often requiring mechanical ventilation and oxygen support. RDS has an approximate range of incidence of 12% to 88% at 26-34 weeks' gestation, inversely correlated to gestational age[1]. Surfactant replacement therapy (SRT) reduces surface tension and equalizes pressures in different parts of the lungs, therefore increasing lung residual functional capacity by allowing alveoli to inflate. Usage of natural porcine –derived surfactant improves oxygenation, lung function and reduces ventilatory requirements more rapidly than by the administration of any other kind of natural of currently available synthetic type[2]. There have been only a few studies that have evaluated immediate changes in lung function within minutes after natural surfactant instillation[3-5].

The respiratory status of these critically ill infants needs to be clinically examined on a regular basis and their vital functions evaluated. Arterial blood gas analysis, pulse oxymetry, transcutaneous monitoring of O_2/$PaCO_2$ are valuable tools in assessing pulmonary gas exchange. In mechanically ventilated infants, airway pressure measurements from the ventilator, as well as X-ray examination provide additional information[6]. These techniques provide information only on global lung function and may have complications[7]. Electrical impedance tomography (EIT) is a novel, non-invasive, bedside image-based technique that allows dynamic monitoring and a thorough insight of regional lung ventilation[7-10]. There are one human and two animal studies that have used EIT to determine regional lung ventilation changes after exogenous surfactant administration (SA)[7,10,11]. However, there is only one study, assessing with EIT immediate lung ventilation changes in high-frequency ventilated (HFOV) RDS infants[12].

Therefore, the aim of the present study was to determine global and regional lung function changes before and after exogenous surfactant administration in conventional ventilated preterm infants with RDS using repeated EIT measurements. We hypothesized that exogenous surfactant administration could rapidly improve global lung function, leading to an increased lung volume and a more homogeneous distribution of ventilation.

Methods

Subjects

The experimental protocol was approved by the scientific board of Papageorgiou hospital. Infants' parents included

in the study have given their written consent in advance.

Seventeen infants (<12 hours old) with RDS were included in the study. All infants had oxygen demands ≥30% and clinical signs of respiratory insufficiency or increased $PaCO_2$. An X-ray confirmed the diagnosis of RDS. Inserted catheters (intravenous-intraarterial) were used for blood sampling, monitoring pressures or drug administration. Exclusion criteria were: presence of congenital anomalies, congenital heart disease (regardless of being hemodynamically significant or not), serious intracranial hemorrhage (grade III/IV), sepsis, perinatal asphyxia, pneumothorax, pulmonary hemorrhage or lobar atelectasis.

Study protocol

Mechanical ventilation was provided by a time-cycled pressure limited infant ventilator (Babylog 8000 SC, Dräger Medical Inc., Telford, Pennsylvania, USA). A recruitment maneuver was performed before administering surfactant by increasing stepwise end-expiratory pressure to a level of 6-8 cmH_2O until oxygenation no longer improved. This ventilation strategy intended to recruit and stabilize collapsed alveoli at the lowest possible airway pressure (PEEP). After a stabilization period of 5-10 minutes, followed by surfactant administration, interventions and maneuvers were applied. In particular, fraction of inspired oxygen (FiO_2) and ventilator settings were reduced when hyperoxia or hypocapnia occurred. FiO_2 was adjusted to keep the oxygen saturation measured by pulse oxymetry above 88 %. Peak inspiratory pressure (PIP) and breath rate were adjusted as necessary to maintain $PaCO_2$ at less than 55 mmHg and the tidal volume (Vt) in the range of 4 to 6 ml/kg. None of the above adjustments were carried out during EIT recordings. Infants received an initial dose of 200 mg/kg poractant alfa. Poractant alfa was supplied within a few seconds after disconnection of the endotracheal tube (closed lung) from vials containing 1.5 ml (120 mg phospholipids) of surfactant (Curosurf, Chiesi Pharmaceuticals, Parma, Italy). All infants were mechanically ventilated in the supine position. Measurements were recorded exactly before (phase A) and after administering the surfactant at 15 min (phase B) and 30 min (phase C).

Arterial blood samples, alveolar-arterial difference ($AaDO_2$), arterial to alveolar ratio (a/A ratio) were recorded at phases A, B and C using a data acquisition system (Rapidlab 1265, Siemens AG, Erlangen, Germany). Peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), tidal volume (Vt), minute volume (MV), dynamic compliance (C_{dyn}) and pulmonary resistance were also recorded.

Data collection

By placing a number of electrodes in the perimeter of the thorax and by injecting an alternating current in two of them, electric potential differences between the rest of the electrodes were measured[13]. The data collected was used to calculate the electrical impedance of the tissues in the cross section area under study, leading to the reconstruction of two dimensional images. The equipment used in the current study was a PulmonaryScan Mark 3.5 EIT system (Maltron International Ltd., Rayleigh, Essex, UK) equipped with eight electrodes placed equidistantly in an anti-clockwise pattern on the circumference of the neonate's thorax, just above the nipple line. The system is multi-frequency, applying 30 frequencies from 2 kHz to 1.6 MHz. However, the lower and upper frequencies of this range were excluded from data analysis, therefore only measurements at 24 frequencies (4 - 812.75 kHz) were used. The data acquisition rate was 25 Hz, i.e. 25 frames/sec. The reciprocity value of all measurements was at least 0.8[14].

Data analysis

No major problems in EIT data collection were observed. Time duration for each EIT measurement was 10 sec. EIT data collected were used to calculate two quantities (markers), namely, absolute resistivity (AbsR) and normalized relative impedance change (ΔZ). AbsR is the mean absolute resistivity of all frequencies and is given in Ohm-meters (Ω m)[15]. Its value was obtained from the software of the equipment (Maltron International Ltd., Rayleigh, Essex, UK). ΔZ was calculated as a normalized ratio of relative impedance change ventilation between end inspiration and end expiration according to the procedure described by Frerichs, from an image obtained with the Electrical Impedance Tomography and Diffuse Optical Tomography Reconstruction Software (EIDORS, free software, version 3.2)[7,16]. The image consisted of 576 triangular pixels and was reconstructed from the data collected at the frequency of 50.8 kHz. The picture was then transformed into one of 1024 (32×32) square pixels and analysis for regional ventilation was performed by calculating right and left lung fractional ventilation (RL--FV and LL--FV, respectively) and determining the center of ventilation (CG%) along the gravitational axis from ventral to dorsal position following the procedure described in[10].

Statistical analysis

The volume of air in the lungs is the major determinant of thoracic impedance change. Therefore, the two null hypotheses, tested statistically, were that the AbsR and ΔZ values and regional ventilation do not differ before and after the administration of the surfactant. Repeated measures ANOVA were conducted for the assessment of the significance of AbsR and ΔZ evolution during the three phases of the study. Paired samples t-tests using a Bonferroni correction were further used in a post-hoc fashion. The Pearson correlation coefficient was used for the assessment of pair-wise correlations. Normality assumption was assessed using the Shapiro-Wilk test for normality. Data conformed to normality except for FiO_2 which was assessed using respective non-parametric methodology. P-values less than 0.05 were considered statistically significant. JMP 8.0 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis.

Results

Subjects

Seventeen infants of gestational age (GA) 30.94 ± 2.38 weeks and birth weight (BW) 1585.3 ± 542.5 gr

were included in the study. All infants received surfactant within 12 hours of age and three infants (C1, C2 and C6) received an additional dose of surfactant because of continuously high oxygen demands. Characteristics of the seventeen infants are shown in Table 1.

Table 1: Demographic data of the 17 infants studied by electrical impedance tomography (EIT).

Neonate	Sex	BW (g)	GA (wk)	Surfactant doses	Mode of Ventilation
C1	M	750	27	2	SIPPV
C2	M	720	29	2	SIPPV
C3	F	920	28	1	SIPPV
C4	F	1150	30	1	SIMV
C5	F	1380	32	1	SIMV
C6	F	1220	30	2	SIPPV
C7	M	1820	31	1	SIMV
C8	F	2580	35	1	SIMV
C9	M	2090	35	1	SIMV
C10	F	1110	28	1	SIMV
C11	M	1980	31	1	SIMV
C12	F	1840	33	1	SIMV
C13	M	1600	29	1	SIMV
C14	F	1820	33	1	SIMV
C15	F	1700	30	1	SIMV
C16	M	2270	33	1	SIMV
C17	F	2000	32	1	SIPPV
Mean		1585.3	30.94		

M: male, F: female, SIPPV: synchronized intermittent positive pressure ventilation, SIMV: synchronized intermittent mandatory ventilation.

Ventilation parameters

At phase A (baseline), PIP, PEEP and breaths/min were at 18 ± 2.5 cmH_2O, 6 ± 1 cmH_2O and 35 ± 10, respectively. At the end of the study (phase C) the parameters were similar except in cases where hypocapnia or hyperoxia had occurred. Within 30 min (phase C) the delivered Vt and MV reached the values of 4.7 ± 1 ml/kg and 0.3 ± 0.08 ml/kg/min from 3.5 ± 1.1 ml/kg and 0.19 ± 0.09 at phase A ($p = 0.005$ and $p = 0.001$, respectively). At this time period, C_{dyn} increased from 0.31 ± 0.17 to 0.52 ± 0.19 ml/cmH_2O/kg ($p = 0.01$), whereas pulmonary resistance was reduced from 128.2 ± 62.7 to 71.8 ± 48 cmH_2O/lt/sec ($p = 0.022$).

Blood gas values

Throughout the 30 min period after SA, the SaO_2 remained at 88 % or higher. The FiO_2 (%) was gradually reduced from 35.9 ± 10.3 (phase A) to 28.7 ± 13.13 at 15min (phase B) and 25.9 ± 7.3 at 30 min (phase C). The FiO_2 trend to decrease between phases A and C, reached a statistically significant difference ($p = 0.021$). The $AaDO_2$ was also significantly reduced from 133.2 ± 82 mmHg to 70.3 ± 50.5 mmHg at 30 min ($p = 0.015$) while a/A ratio significantly increased from 32.2 ± 13.4 to 52.9 ± 20.1 ($p = 0.003$) at 30 min. During the 30 min time period $PaCO_2$ gradually reduced from 49.5 ± 9 mmHg to 38.4 ± 6.2 mmHg ($p = 0.001$). Regarding pH, a significant increase from 7.28 ± 0.08 to 7.38 ± 0.07 was observed ($p < 0.001$).

Electrical impedance data

A total of 401 measurements were performed before and after SA. The calculated mean values for AbsR and ΔZ at phases A, B and C are shown in Table 2.

Table 2: Absolute resistivity **(**AbsR) and normalized relative impedance change (ΔZ) values obtained before (A) and after (B and C) surfactant administration.

Neonate	AbsR (Ω m)			ΔZ		
	A	B	C	A	B	C
C1	3.17	3.80	3.87	0.60	0.65	0.86
C2	4.00	6.00	6.00	0.42	0.99	0.92
C3	4.16	4.10	4.70	1.06	1.31	1.40
C4	4.12	4.00	3.50	1.05	1.22	1.16
C5	3.03	3.00	3.23	0.88	1.22	1.15
C6	2.93	3.00	3.20	1.16	1.24	1.15
C7	1.70	2.60	3.20	1.08	1.05	1.11
C8	2.63	2.77	2.87	0.17	1.00	0.95
C9	3.80	4.80	4.98	0.35	0.57	0.75
C10	2.64	3.84	3.93	0.88	1.07	1.13
C11	2.98	3.32	2.78	0.64	0.97	1.3
C12	3.03	3.28	3.84	0.73	1.07	1.25
C13	2.50	2.82	2.88	0.64	1.03	1.05
C14	3.40	4.60	4.60	0.98	1.35	1.38
C15	5.40	6.00	6.24	0.89	1.17	1.09
C16	5.55	5.70	8.22	0.24	0.24	0.88
C17	2.26	2.30	2.80	1.03	1.25	1.20

A: before surfactant administration, B: 15 min after surfactant administration, C: 30 min after surfactant administration.

Statistical analysis showed that AbsR and ΔZ increased to 4.16 ± 1.49 Ω m and 1.06 ± 0.27 at phase C from 3.37 ± 1.03 Ω m and 0.79 ± 0.28 at phase A, respectively. AbsR and ΔZ increased significantly through all phases ($p = 0.003$ and $p = 0.012$, respectively). However, only ΔZ had a significant correlation with Vt ($r > 0.7$ for phases A through C, $p < 0.001$). No further significant consistent correlations were found throughout all phases.

The re-distribution of regional ventilation, as assessed by comparing RL--FV and LL--FV after SA, was indicative of a more homogenous air distribution from phase A to phase C. Before SA, RL--FV was 51.23 ± 4.44 % and LL--FV 48.16 ± 4.33 %, while 30 min after SA the values were 50.47 ± 2.64 % and 49.35 ± 2.61 %, respectively (p NS) (Figure 1).

Additionally, the center of ventilation (CG) of the RL (RL-CG %) and LL (LL-CG %) was displaced along the gravitational axis (ventral-anterior to dorsal-posterior lung regions) from phase A to phase B (Figure 2). The shift of CG, consistent with recruitment of posterior--atelectatic lung regions, was more intense for the RL from phase A to phase B. From phase B to phase C, the center of ventilation moved slightly towards the anterior lung regions.

Conventional ventilation before surfactant administration indicated a slight asymmetry in lung volume distribution in

favor of the right lung (horizontally) and ventral lung regions (vertically). After surfactant administration, a more homogenized pattern of ventilation occurred between Right – Left Lung along the horizontal axis. A marginal shift to dorsal-posterior regions occurred at phase B, followed by a smaller shift towards ventral - anterior lung regions at phase C.

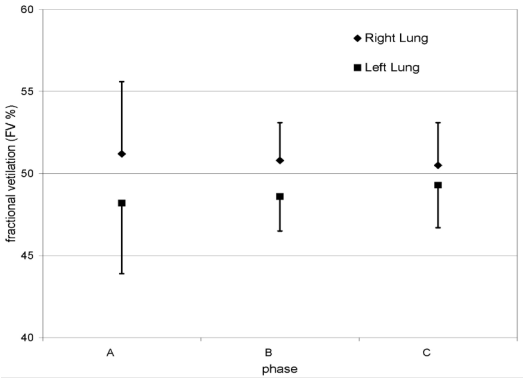

Figure 1: Fractional volume (FV) changes in right (RL-FV) and left (LL-FV) from phase A (before surfactant administration) to phases B and C (15 and 30 min after surfactant administration, respectively) showing a more homogeneous ventilation.

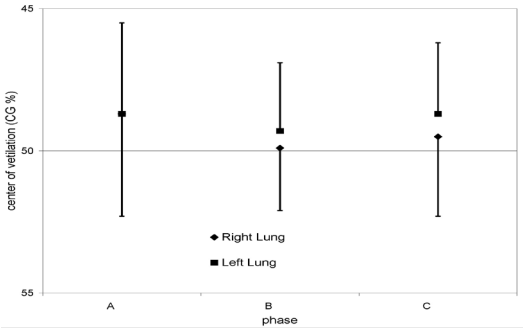

Figure 2: The location of center of ventilation (normalized position in percentage along the gravitational axis) for the right (RL) and left (LL) lung shows only a slight displacement to dorsal areas at phase B (15 min after surfactant administration) and to anterior areas at phase C (30 min after surfactant administration).

Discussion

This is the first study that continuously recorded immediate regional and global lung function changes using EIT in preterm infants with RDS on conventional ventilation (CV). The immediate effect of exogenous surfactant on lung function in CV patients has been evaluated with several methods[12,17,18]. However, the existing methods (e.g. blood gas analysis, $satO_2$, Vt, C_{dyn}) provide information on global lung function only and their application may be associated with undesired side-effects (e.g. chest x-ray).

In our study, parameters of global lung function increased (pH, $AaDO_2$) or decreased (a/A ratio, PaCO2) from phase A to phase C. Parameters of lung ventilation (MV, Vt, C_{dyn}) also increased after SA. The increase in C_{dyn} is explained by SA and lung recruitment maneuver before SA[19]. The rationale for recruiting lungs by using high PEEP was the prevention of cyclic opening and closing of airspaces, to improve surfactant response and optimize lung mechanics in order to prevent ventilation-induced injury at the pre-surfactant period[10]. Experimental studies have shown that the combination of recruitment maneuvers and SA produce significant effects on lung mechanics and improve Functional Residual Capacity (FRC)[10,11,19]. The improvement of respiratory status after the instillation of surfactant is reflected also by the increase of AbsR and ΔZ from phase A to B and C in agreement with the observed changes in the established parameters for assessing global lung function. Treatment responses to surfactant can be divided into immediate response within minutes, intermediate over hours, and late onset after days or perhaps weeks[4]. The immediate treatment response investigated in the present study results from the biophysical properties of surfactant and depends on its rapid distribution in the lung. This early response of surfactant has been confirmed by our EIT deduced markers. ΔZ appeared to be a more sensitive marker than AbsR, since it was highly correlated with tidal volume changes, showing a statistically significant increase between phases A and C, i.e. even 30 min after surfactant administration.

EIT is a unique bedside technique that can detect and monitor regional ventilation changes. Regional ventilation was assessed by calculating the fractional ventilation of right and left lung at the horizontal axis and also by detecting the center of ventilation location along the gravitational (anterior-posterior) axis.

Regional ventilation analysis showed that before SA ventilation was more prominent in the right and ventral lung region, a finding supported by Miedema et al[12] who studied RDS neonates on HFOV. This finding can be attributed both to infants' prematurity, as well as to the anatomical position of the heart.

A ventilation shift with less asymmetry, towards a more uniform air distribution during the post-surfactant period (phases B and C) from RL to LL, took place. The effect of SA in fractional ventilation should be considered marginal, because of a non- statistically significant effect towards a more homogenous pattern. In animal models, it was also found that SA achieved a more homogenous distribution of ventilation between right and left lung[10,11]. This finding could also be explained by the fact that no major changes in ventilator settings occurred during our study.

The center of ventilation before SA was anteriorly located, as ventral-nondependent areas receive a larger portion of air than dorsal-dependent lung areas during mechanical ventilation[7]. This more pronounced distribution of tidal volume to anterior lung areas is also consistent with the fact that our group of patients was preterm infants[8]. The center of ventilation was displaced towards posterior areas after SA (phase B), thus reflecting a better ventilation of dorsal-dependent areas. This displacement was caused by a decrease in non-ventilated dorsal lung areas and it was more pronounced for the right than for the left lung[9]. The fact that oxygenation improved further after SA supports that the displacement of CV was consistent with lung recruitment and not distension of alveoli because of CV[12]. Subsequently, from phase B to phase C, the center of ventilation was displaced slightly

towards ventral areas, most likely reflecting hyper-inflation of ventral-nondependent areas. Since lung areas of RDS neonates are either collapsed, hyperinflated or appropriately ventilated, optimal pressures (PIP, PEEP) application during mechanical ventilation, should be in balance between recruitment and lung over-inflation. This displacement of center of ventilation at phase C, as seen in our study, indicated a need for reduction of pressure.

After SA, homogeneity of ventilation between lungs and recruitment of dorsal-dependent areas increased lung volume and were reflected in better gas exchange parameters and lung mechanics. Surfactant treatment also resulted in a statistically significant increase of C_{dyn} because of increased lung volume. Many studies have shown conflicting results on compliance changes after SA[10,20,21].

The limitations of the study should also be discussed. Firstly, for the instillation of surfactant we used a closed lung approach and PEEP titration for recruitment was guided by global indexes such as gas exchange. A large body of experimental evidence supports the open lung approach for the mechanically ventilated diseased lung and also global lung indexes are not reprensentive of regional ventilation changes during PEEP titration[22,23]. Secondly, EIT determines lung volume changes only in one transversal slice of the lung and handling of neonates with electrodes was sometimes difficult. It is the first time that an 8 electrode multifrequency EIT device was used in RDS infants on CV support, although a better image-resolution could have been obtained with a 16 -electrode device[24]. However the latter would result in more difficulties with electrode placement. Our intention was to facilitate neonatologists with the further management of RDS in infants because of its major clinical importance. Our study has indicated that RDS is an inhomogeneous disease. However, it has also proved that administration of porcine exogenous surfactant in CV infants with RDS increases lung volume and leads to ventilation homogeneity. These changes take place within a short period of time and, thus, neonatologists should reduce ventilatory settings as soon as they observe improvement of global lung markers (ΔZ, compliance) or regional ventilation shift along the gravitational axis to avoid overdistension. The fact that after SA in CV infants with RDS, global as well regional changes in lung function can be observed by Electrical Impedance Tomography gives the intensivist an additional non- invasive bedside tool towards the optimal management of these patients.

Conflict of Interest

The authors declare no conflicts of interest.

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