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Regional and overall ventilation inhomogeneities in preterm and term-born infants

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Abstract *Objectives:* We compared ventilation inhomogeneity assessed by electrical impedance tomography (EIT) and multiple breath washout (MBW) in preterm and term-born infants. We hypothesised that EIT measurements in spontaneously breathing infants are repeatable and that differences in regional ventilation distribution measured by EIT can distinguish between preterm and term-born infants. *Design:* Cross-sectional group comparison study. *Setting:* Lung function laboratory at a University Children's Hospital. *Participants:* Seventeen healthy term-born and 15 preterm infants at a matched postmenstrual age of 44 weeks. *Measurements and results:* We concurrently measured ventilation inhomogeneity by EIT, ventilation inhomogeneity (LCI) and functional residual capacity (FRC) by MBW and tidal breathing variables during unsedated quiet sleep. EIT measurements were highly repeatable (coefficient of variation 3.6%). Preterm infants showed significantly more ventilation of the independent parts of the lungs compared to healthy term-born infants assessed by EIT (mean difference 5.0, 95 CI 1.3–8%). Whereas the two groups showed no differences in lung volumes or ventilation inhomogeneities assessed by MBW, EIT discriminated better between term and preterm infants. (FRC/kg: mean difference 1.1 mL, 95% CI −1.4–3.8 mL; LCI: mean difference 0.03, 95% CI −0.32–0.25). *Conclusions:* EIT shows distinct differences in ventilation distribution between preterm and term-born infants, which cannot be detected by MBW. Although preterm infants are capable of dynamically maintaining overall functional residual volume and ventilation distribution, they show some spatial differences from fullterm infants.

Keywords Infant lung function · Ventilation distribution · Prematurity · Electrical impedance tomography

Introduction

Lung development is interrupted in preterm-born infants and therefore alveolar and vascular growth is disturbed leading to impaired alveolar function [1]. Other factors such as mechanical ventilation (volutrauma) and hyperoxia can aggravate this impairment and the combination may lead to chronic lung disease of infancy (CLDI) [2, 3]. These changes in development have an impact on lung function with respect to lung volume, ventilation inhomogeneity and lung mechanics [4–6].

Different techniques are being used to assess the above mentioned alterations by measuring multiple variables

related to lung structure (computer tomography), lung mechanics (bodyplethysmography, forced flows), lung volumes (multiple breath washout, bodyplethysmography), overall ventilation inhomogeneity (multiple breath washout), gas exchange (transcutaneous oxygen saturation, carbon dioxide partial pressure) and resultant tidal breathing variables, probably a combination of the above and the control of breathing [7–10]. All these techniques are either invasive with the need for sedation (computer tomography, forced flows) or only show overall lung function changes (bodyplethysmography, multiple breath washout, tidal breathing variables). In contrast, a promising technique emerging over the last years, electrical impedance tomography (EIT), is able to detect regional ventilation differences and has the advantage of a high temporal resolution [11–13]. This leads to the possibility of dynamic assessment of spatial and temporal ventilation inhomogeneities. EIT measurements in infants can be performed without any sedation and are therefore optimal for clinically relevant situations [6, 14, 15].

Several studies comparing functional residual capacity (FRC) and lung clearance index (LCI)—as measure of overall ventilation inhomogeneity—derived from multiple breath washout (MBW) and other techniques show distinct differences between term and preterm born infants. In preterm infants FRC has been shown to be diminished and ventilation inhomogeneity is increased, evident via an increase in LCI [8, 16]. Other studies in spontaneously breathing infants question these findings and show no differences between term and preterm infants measured at a comparable postmenstrual age [17]. The discrepancy between the results may have different reasons. Standards for lung function testing in this age group have only been published a few years ago and the results of the older studies might be influenced by either sedation of the infants, changed breathing pattern or differences in measurement techniques [18–21]. More recent studies show differences in other variables, mainly tidal breathing characteristics [9, 22]. These findings suggest the presence of compensating mechanisms in preterm born infants to maintain lung volume and overall ventilation homogeneity. EIT may be useful in visualising these mechanisms by showing regional differences in ventilation.

With the present work we aimed to (1) determine short-term repeatability of EIT measurements in term and preterm infants and (2) compare EIT variables with other variables of lung function, namely FRC as an estimate of lung volume, LCI as an estimate of overall functional ventilation inhomogeneity, minute ventilation as an estimate of respiratory need and tidal breathing variables in preterm and term-born infants at the same postmenstrual age.

Materials and methods

Subjects

Fifteen preterm infants of less than 37 weeks gestational age hospitalised at the University Children's Hospital Bern were recruited during their initial hospital stay. Seventeen term-born infants were recruited as part of a prospective birth cohort study within the same time period and the same region [23].

The study protocol was approved by the ethics committee of the canton of Bern, Switzerland. Written informed parental consent was obtained at enrolment.

Measurements

One 10-min tidal breathing measurement and repetitive recordings of EIT and MBW were performed simultaneously during quiet natural sleep in a supine position with the head midline according to the standards of infant lung function testing [18, 19]. Data were only included if at least two (MBW) or three (EIT) technically acceptable measurements without evidence of sighs or irregular breathing were available.

Data acquisition and processing

EIT: A Goettingen GoeMF II EIT tomograph (VIASYS Healthcare, The Netherlands) was used with a frame rate of 44 Hz and a 60 s recording time in combination with self-adhesive electrodes for infants (Blue Sensor, BR-50-K, Medicotest, Olstykke, DK). EIT scans were generated from the collected potential differences and the known excitation currents using weighted back-projection in a 32×32 pixel matrix [24]. Anterior to posterior (φAP) phase angle, as a measure of asynchronous filling and emptying of the lungs, reflecting temporal inhomogeneity, and the proportion of ventilation distributed into the anterior parts of the lung (AUC_{ant}), reflecting spatial inhomogeneity, were calculated adapted to previously published methods using Matlab 7.0.4 (The MathWorks Inc., Nattick, MA, USA) [13]. Briefly, a positive φAP reflects a phase lead of the anterior to the posterior parts of the lung, whereas a negative φAP represents a phase lag of the anterior parts. The EIT signal was high- and low-pass filtered around the frequency domain of the respiratory rate as described by Dunlop at al [11].

MBW: Data were obtained by the sulfur-hexafluoride (SF_6) MBW method with an Exhalyzer_D ultrasonic flowmeter (Ecomedics, Duernten, Switzerland) via an infant face mask size 1 (Homedica AG, Cham, Switzerland) and analysed using an optimised temperature and dead space correction as previously validated [25].

Tidal breathing: Data were obtained with an Exhalyzer_D ultrasonic flowmeter (Ecomedics, Duernten, Switzerland) via an infant face mask size 1 (Homedica AG, Cham, Switzerland). 100 consecutive breaths without evidence of sighs or irregular breathing were analysed with respect to minute ventilation and the ratio of time to peak tidal expiratory flow to total expiratory time (t_{PTEF}/t_E) [18].

Statistics

Short term repeatability

Repeatability was assessed using intra-subject coefficient of variation (CV) from all EIT measurements available and Bland-Altman plots from the first and the last available measurement of each subject. The mean of the difference, the 95% limits of agreement and the number of outliers are reported for the Bland-Altman plots [26].

Association with biometric and tidal breathing variables

Regression analysis was performed with φAP and AUC_{ant} as outcomes and biometric, MBW and tidal breathing variables as exposures, in order to assess the influence of the different factors. φAP was normally distributed, so that we used linear regression analysis, whereas AUC_{ant} was not normally distributed within the whole group of 30 subjects, so that we used a logistic regression analysis partitioning AUC_{ant} by above and below mean. Multivariable analysis was not performed because of the small sample size.

Comparison between groups

t-Tests, taking into account unequal variances were used for comparison of EIT and MBW between groups (term vs. preterm) after testing for normality (Shapiro-Wilk *W*-test) within groups. Results are presented as mean (standard deviation) unless stated otherwise.

All data analyses were performed using StatsDirect 2.6.5 (StatsDirect Ltd, Cheshire, UK) and STATA 10 (STATA Corporation, College Station, TX, USA).

Results

From the 32 infants enrolled, MBW and EIT measurements of 30 subjects were analysed. Demographic data of the two groups are shown in Table 1. Reasons for exclusion were irregular breathing pattern in one infant and an insufficient number of EIT measurements in another infant. From a mean of 18 measurements per subject we excluded an average of eight because of irregular breathing and sighs. We neither found interference with external power sources nor skin irritations from the electrodes.

Table 1 Demographic data of the study infants

	Preterm ($n = 14$)	Term ($n = 16$)
Female sex	4	5
Birth weight (kg)[a]	0.82 (0.45–1.77)	3.42 (2.45–4.37)
Gestational age (weeks)[a]	26.4 (24.3–33.1)	39.9 (37.0–41.3)
Postmenstrual age (weeks)[b,c]	45.2 (1.6)	44.9 (1.5)
Postnatal age (days)[a,c]	130 (84–160)	35 (30–55)
Weight (kg)[b,c]	4.04 (0.80)	4.48 (0.72)
Length (cm)[b,c]	52.4 (3.6)	56.0 (2.2)
z-Score weight[a]	−0.78 (−3.90–0.63)	−0.08 (−2.08–2.32)
z-Score length[a]	−1.01 (−3.79–0.65)	0.57 (−2.66–1.75)
z-Score weight/length[a]	−0.33 (–3.81–1.33)	−0.38 (−4.07–1.03)

[a] Data is given as median (range)
[b] Data is given as mean (standard deviation)
[c] At study date
z-Score standard deviation score derived from Anthro, Anthropometric calculator v2.0.2 (World Health Organization)

Short-term repeatability of EIT measurements

The mean (SD) number of analysed measurements per subject was 9.9 (3.7) with a range of 3–16. Mean (SD) coefficient of variation (CV) for all 30 subjects with a total of 199 measurements was 3.60% (2.26%) for AUC_{ant}. CV results for term-born and preterm infants did not differ from each other. Furthermore we found no differences in CV between subjects with more than seven measurements ($n = 23$) and subjects with three to seven measurements ($n = 7$). The median (range) time between the first and the last measurements was 75 (5–227) min. Mean (SD) difference between the first and last measurement of each subject was 0.89% (4.95) and 1.93° (9.77) for AUC_{ant} and φAP, respectively. Some infants were repositioned and/or breastfed in between measurements. No differences in CV were observed in these infants.

Association of EIT and MBW with biometric and tidal breathing variables

Table 2 shows an overview of all the tested variables and the results of the EIT data. In summary, φAP was positively associated with gestational age, tidal volume corrected for body weight and t_{PTEF}/t_E and negatively to postnatal age. AUC_{ant} was only associated positively with preterm birth. In our small study population neither FRC

Table 2 Odds ratio derived from logistic regression (AUC_{ant}) and univariable regression coefficients (φAP) of EIT variables of ventilation inhomogeneity with demographic and tidal breathing variables

	Exposure	Spatial heterogeneity			Temporal heterogeneity		
		AUC_{ant} (%)			φAP (°)		
		Odds ratio	CI 95%	*P*	Coefficient	CI 95%	*P*
Demographics	Female sex	2.67	0.52–13.65	0.239	−6.347	−14.574 to 1.880	0.125
	Gestational age (weeks)	0.91	0.81–1.03	0.130	0.656	0.098 to 1.214	**0.023**
	Postmenstrual age (weeks)	1.23	0.75–2.01	0.411	1.097	−1.289 to 3.683	0.392
	Postnatal age (days)	1.01	0.99–1.03	0.107	−0.079	−0.157 to −0.001	**0.049**
	Preterm birth	5.5	1.15–26.41	**0.033**	−5.857	−13.411 to 1.697	0.124
	Weight (kg)	0.90	0.35–2.30	0.820	−1.190	−6.328 to 3.947	0.639
	Length (cm)	0.92	0.73–1.15	0.453	−0.477	−1.503 to 0.549	0.349
Tidal breathing	Tidal volume (mL/kg)	0.96	0.46–2.01	0.916	3.837	0.036 to 7.599	**0.046**
	t_{PTEF}/t_E (%)	0.93	0.85–1.02	0.137	0.455	0.079 to 0.831	**0.020**
	Minute ventilation (mL/kg)	1.01	0.99–1.03	0.122	0.005	−0.082 to 0.0.091	0.908

The coefficients refer to the change in the respective EIT variables per unit change in the exposure

Table 3 Comparison of EIT, MBW and tidal breathing variables between groups

		Preterm ($n = 14$)	Term ($n = 16$)	*P*
EIT	φAP (°)	5.6 (10.2)	11.5 (10.0)	0.12
	AUC_{ant} (%)	56.9 (5.7)	51.9 (4.4)	**0.01**
MBW	FRC (mL)	94.3 (15.7)	109.4 (11.1)	**0.05**
	FRC (mL/kg)	23.7 (3.5)	24.8 (3.5)	0.37
	LCI	6.54 (0.49)	6.51 (0.27)	0.80
	M2/M0	6.6 (1.8)	5.7 (0.8)	0.10
Tidal breathing	Tidal volume (mL/kg)	7.3 (1.1)	7.7 (0.9)	0.27
	Minute volume (mL/kg)	330 (54)	331 (43)	0.93
	t_{PTEF}/t_E (%)	26.3 (5.8)	37.6 (9.3)	<0.01

Data is given as mean (standard deviation) and *P*-value determined by an unpaired *t*-test

nor LCI derived from MBW showed significant association with any of the tested variables.

Comparison between groups

Results of EIT, MBW and tidal breathing are summarised in Table 3.

EIT variables

The proportion of ventilation distributed to the anterior parts of the lung (AUC_{ant}) was significantly larger in preterm infants (Fig. 1). No differences were found for φAP. Figure 2 shows a plot of AUC_{ant} against gestational age to illustrate the overlap between the two groups.

MBW and tidal breathing variables

Preterm infants had a lower total FRC but this difference disappeared when corrected for body weight; same was true for tidal volume. None of the other MBW variables showed a significant difference between preterm and term-born infants.

Discussion

Summary

With the present study we demonstrate that EIT measurements show an excellent short-term repeatability over hours. We further show that EIT can detect differences in ventilation inhomogeneity in preterm and term-born infants more sensitively than SF_6 MBW. In this study variables assessing spatial ventilation differences were more discriminative of ventilation inhomogeneity in preterm infants than variables of temporal or overall ventilation inhomogeneity derived from EIT and MBW.

Comparison with other studies

Multiple studies have been performed to evaluate the value of EIT in assessing regional differences of

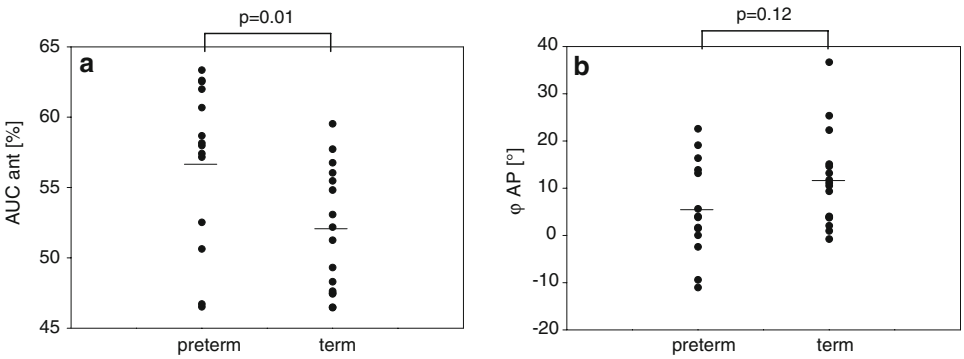

Fig. 1 **a** Point plot showing AUC_{ant} in preterm versus term-born infants (*line*: mean), *P*-value derived from paired *t*-test. **b** Point plot showing φAP in preterm versus term-born infants (*line*: mean), *P*-value derived from paired *t*-test

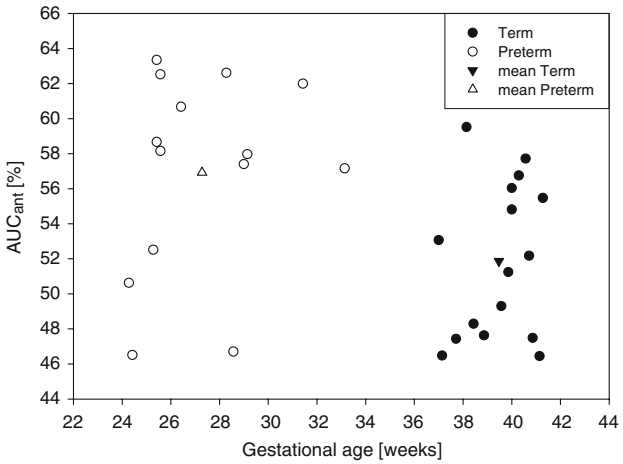

Fig. 2 AUC_{ant} plotted against gestational age

ventilation in animals, infants and adults in different clinical and experimental situations [27–30]. Different authors investigated EIT as a tool to optimise lung recruitment during conventional mechanical ventilation and high-frequency oscillatory ventilation [31–33]. The technique has been validated against computer tomography and ventilation scintigraphy in several studies [14, 34]. While the temporal resolution of EIT is much higher than with computer tomography, its spatial resolution is lower. In our study we only looked at the anterior-posterior in ventilation distribution, which might have led to loss of spatial information. Nevertheless, we were able to detect differences between preterm and term-born infants using AUC_{ant}.

In ventilated animals EIT has been shown to be highly reproducible [35], but no data on reproducibility or repeatability has been published so far for spontaneously breathing infants. We can clearly show an excellent short-term repeatability making EIT a robust technique in the assessment of spontaneously breathing infants. Given that there is no difference in CV between infants with three to seven and more than seven measurements we recommend to perform at least three measurements of high quality. To achieve this number it is necessary to perform at least six measurements during quiet sleep to allow strict quality control criteria. The time needed to perform a sufficient number of measurements mainly depends on the sleep stage of the infant and therefore shows a wide range.

Neither lung volume (FRC) nor ventilation inhomogeneity (LCI) was different between term-born and preterm infants in our cohort. This is in contrast to the work of Hjalmarson and Sandberg who showed clear differences in FRC and LCI [8, 16]. Note that they studied healthy infants at the age of 24–72 h, in a phase of high transitional changes of lung mechanics and lung perfusion, with a nitrogen washout using 100% oxygen, known to induce atelectasis, both of which may explain this disparity [36, 37]. However our results are in line with the work of another group using similar equipment and with the results of a larger cohort study from our group [21, 22]. We could show that due to a high capacity to adapt their breathing pattern preterm infants are capable of elevating their end-expiratory level and thus to normalise their FRC and LCI despite known structural inhomogeneities of their lung development.

Association of EIT with biometric and tidal breathing variables

We assessed two different EIT variables to determine regional differences between dependent (posterior) and independent (anterior) parts of the lung of infants in supine position. The phase angle φ is a measure of asynchronous filling and emptying and therefore predominantly indicates a temporal inhomogeneity of ventilation. AUC_{ant} on the other hand is independent of time and reflects regional or spatial differences in tidal volume distribution. The association of φAP with different 'timing' variables such as tidal rate constant and t_{PTEF}/t_E may be explained with the 'timing' nature of φAP itself. The association with tidal volume corrected for body weight confirms that ventilation distribution can be affected by tidal volume [38]. AUC_{ant} is not associated with any of the tested variables except preterm birth, making it a promising independent measure for the assessment of infant lung function.

Regional ventilation inhomogeneity: comparison between groups

In our group of patients we could only demonstrate a difference in spatial distribution (AUC_{ant}) but not in temporal distribution (φAP). This could partially explain why measures of overall ventilation inhomogeneity, such as LCI do not show a difference between term-born and preterm infants, since LCI is more dependent on the distribution of different time constants than on spatial tidal volume distribution. Also LCI only includes ventilated parts of the lung whereas EIT also allows visualisation of non-ventilated lung areas.

We can only speculate on the underlying mechanisms leading to the presented differences between term-born and preterm infants. In healthy lungs, the gravity-dependent strain on the independent (anterior) parts of the lungs may lead to a decrease in compliance (corresponding to a shift towards the right, flatter part on the pressure-volume curve). This decrease in compliance would tend to reduce local tidal volume in these parts of the lungs [39]. Furthermore, FRC in infants is close to the closing volume, i.e. the volume of the lung where alveoli collapse and no longer take part in gas exchange [40]. Thus, gravity-dependent compression of the posterior parts of the lungs may lead to closure and loss of aerated lung and again tendency towards reduced local tidal volume [39]. Crawford et al. also showed that distribution of tidal volume ventilation is influenced by tidal volume itself [38].

In preterm infants more of the tidal volume was distributed to the anterior parts of the lung. This may be explained by either less over-distension of the anterior parts of the lung because of relatively stiffer lungs (lower compliance) [8], or more lung collapse of the posterior parts due to a smaller difference between FRC and closing volume or, most likely, both mechanisms. The significantly lower t_{PTEF}/t_E in preterm infants supports this theory as a lower overall compliance will decrease t_{PTEF}/t_E [22]. The difference in t_{PTEF}/t_E (influenced by the overall respiratory system time constant), but not in LCI (influenced by the distribution of regional time constants) between the two groups again supports this assumption. Other factors that may contribute to the lower t_{PTEF}/t_E are postnatal age or obstruction of the airways. An effect of tidal volume on spatial distribution in our study is very unlikely as tidal volume corrected for body weight and tidal volume corrected for FRC was the same in both groups.

Strength and weaknesses of the study

To our knowledge this is the first study assessing EIT in comparison to MBW in preterm compared to healthy term-born infants. The groups were matched for postmenstrual age at time of study, measurements were performed according to the ERS/ATS standards and MBW analysis included the latest recommendations [18, 25]. In the presence of sighs or breathing irregularities the whole EIT measurement was excluded leaving us with high quality measurements of equal length. Frerichs and Heinrich showed distinct differences in regional ventilation after postural changes and also after changes in head position [14, 34]. These studies indicate that comparisons between different groups of patients can only be valid if measurements are performed under standardised postural conditions. All subjects in our study were lying supine with the head in midline position.

Our study has some weaknesses. First, as the duration of EIT measurements was fixed at 1 min for all infants, the number of breaths included in the analysis was variable. We cannot exclude this as a possible source of error, although the number of breaths corresponds to the standards of tidal breathing analysis [18]. Second, the EIT signal was not matched with the flow signal. Thus, regional differences in tidal breathing variables could not be determined simultaneously. Finally, in the present study we only investigated the differences between term-born and preterm infants regardless of the presence and severity of chronic lung disease of infancy. The relatively small number of preterm infants does not allow subgroup analysis or stratification. Thus, we are unable to comment on whether our results are attributable to severity of disease. However, we are able to show feasibility and repeatability as well as significant differences in EIT but not MBW parameters despite this small mixed population. A possible explanation may be that disturbed lung development is closely associated with gestational age, and prematurity is the main causative factor [1].

Clinical relevance

Given the high number of preterm infants and the possible impact of chronic lung disease of infancy on long-term morbidity it is important to understand and assess disturbances of lung development early in life [1]. We have shown that a non-invasive technique, which does not influence the breathing pattern of unsedated infants, can demonstrate differences in ventilation heterogeneity between term-born and preterm infants, where other techniques cannot. The addition of EIT to conventional lung function tests will help to better understand physiological mechanisms underlying the respiratory problems of premature infants.

Conclusion

In conclusion, EIT measurements during unsedated quiet sleep are highly repeatable. There is evidence that preterm

infants show distinct differences compared to term-born infants with respect to spatial ventilation distribution, namely increased ventilation of the anterior parts of the lungs. These differences cannot be detected with variables of temporal or overall functional ventilation inhomogeneity. Whether or not these differences are clinically relevant needs to be explored in a larger group appropriately combined with other lung function techniques. EIT may provide additional insights into lung physiology and developmental differences in preterm infants, and thus as a non-invasive and radiation free tool, it could have considerable potential in future clinical trials.

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