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REGIONAL VENTILATION DISTRIBUTION IN THE FIRST SIX MONTHS OF LIFE

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ABSTRACT
Electrical Impedance Tomography has been used to study regional ventilation distribution in neonatal and paediatric lung disease. Little information has been obtained in healthy newborns and infants.

Data on regional ventilation distribution and regional filling characteristics has been obtained with EIT in the neonatal period, at 3 and 6 months of age in spontaneously breathing infants during NREM sleep. Regional ventilation distribution was described with regional end-expiratory and end-inspiratory impedance amplitudes and geometric centre of ventilation. Regional filling characteristics were described with the phase lag or lead of the regional impedance change in comparison to global impedance change.

32 infants were measured in supine position. Regional impedance amplitudes increased with age but regional ventilation distribution remained unchanged in all infants at any age with the dependent (posterior) lung always better ventilated. Regional filling characteristics showed that the dependent lung filled during inspiration before the non-dependent lung during all follow up measurements.

Regional ventilation distribution and regional filling characteristics remained unchanged over the first 6 months of life and the results obtained on regional ventilation distribution are very similar found in adult subjects.

KEY WORDS
Electrical Impedance Tomography, Respiratory Mechanics, Ventilation Distribution, Infant, Sigh, Healthy Reference

INTRODUCTION

A better understanding of normality is needed for deriving thresholds of clinical significance for disease [1]. The rapid lung growth occurring over the first few years of life necessitates repeated measurements to understand the developmental changes of lung growth and physiological behaviour [2]. The ability to perform such measurements has been technically difficult due to the inability of infants and young children to cooperate in testing and the lack of repeatable non-invasive tests [3]. Whilst there is a sound body of literature describing the respiratory mechanics of neonates and infants in disease [3-5], much knowledge is yet to be obtained in spontaneously breathing healthy infants. In this age group, the traditional methods of measuring respiratory mechanics, in particular regional ventilation distribution, pose some difficulties [6-8]. Multiple breath inert gas washout techniques are commonly used to assess ventilation distribution but cannot provide information about regional ventilation distribution [5, 8]. Other methods, such as Computed Tomography (CT) and aerosol dispersion involve exposure to radiation [9, 10].

Electrical Impedance Tomography (EIT) has emerged as a non-invasive functional imaging modality that can be used to measure regional ventilation distribution [11]. EIT can be used repeatedly for extended periods of patient monitoring, without the need for sedation. One of the distinct advantages of EIT measurements is that data can be analysed over a given time period and be reported as an EIT image similar to a CT scan or EIT data can be analysed on a breath by breath basis to analyse the time course of regional filling [12, 13]. This aspect is important for lung function measurements in infants, where irregular breathing and sighs are a common finding [1]. This paper reports the results of follow-up EIT measurements from a small cohort of healthy newborns at 2 weeks, and at 3 and 6 months of life measured in non-rapid eye movement (NREM) sleep. The questions that have been addressed are (a) does regional ventilation distribution change within the first 6 months of life, (b) does regional filling change and (c) what is the impact of a sigh on regional ventilation distribution?

MATERIAL AND METHODS

Study design. This study was undertaken as part of a larger prospective healthy reference cohort study from birth to 2 years, in which healthy term neonates were enrolled following a normal delivery. Regional ventilation distribution with EIT was evaluated during regular quiet breathing in NREM sleep at 2 weeks, 3 months and 6 months of age.

Subjects. EIT measurements were taken in supine position at 2 weeks, 3 and 6 months of age in 32 term infants (17 male / 15 female) in the sleep laboratory of the Mater Children's Hospital, Brisbane, Australia. Inclusion criteria were: non-smoking families without history of allergies/pulmonary disease and without prenatal/perinatal maternal medical history. The study had the approval of the local research ethics committee and written informed consent was obtained. A polysomnography and sleep staging was performed according to recommendations [14].

Electrical Impedance Tomography. A Goe-MF II system (Cardinal Health, Germany) was used to perform EIT measurements in the supine position for durations of ten minutes. The principles of EIT systems have been published elsewhere [11, 12, 15, 16]. All EIT measurements were taken with electrodes at nipple level and were sampled at thirteen images per second (13 Hz) with a 50 kHz injection current of 5 $mA_{pk\text{-}pk}$. EIT data was referenced to a regular tidal breathing period during quiet NREM sleep. EIT data was analysed offline using a custom developed EIT Data Analyser program based in MATLAB v7.7 (The Mathworks, Inc.).

EIT Image Analysis. EIT data were band pass filtered, inclusive of the first and second harmonics of the respiratory rate [12, 17, 18], and a cut-off mask at 20% of the peak impedance signal applied [19]. EIT images were generated using the average end expiratory to end inspiratory impedance differences for each individual pixel time course array to describe the magnitude of the regional tidal volume change among individuals. Six slices from anterior to posterior (AP-axis) and from right to left (RL-axis) were defined as ROI_{1-6} for regional impedance amplitude analysis [15]. EIT images and regional amplitudes were obtained for a minimum of 10 consecutive breaths during quiet breathing. Additionally the regional impedance amplitudes were measured prior to, during and after a sigh in NREM sleep. The geometric centre of the EIT image was calculated for the entire image and for the right and left lung separately [20]. The geometric centre, based on the 32x32 matrix, defines the centre of ventilation using a balanced averaging of pixel values from anterior to posterior or from right to left.

EIT Time Course Analysis. Regional filling characteristics of the lung can be measured using the time course of the impedance measurements. A ROI impedance change may show a phase lead or lag in relation to the whole lung. Such phase shifts were described with phase angles [21]. If a ROI fills ahead of the rest of the lung, the phase angle is positive. If a ROI fills after the rest of the lung, the phase angle becomes negative. We used a cross correlation method to calculate the phase angles [12, 22].

Analysis of sighs. The regional impedance amplitudes were calculated for 10 breaths prior to and after a sigh and also during the sigh itself. The regional volume expansion of the tidal breaths and the sigh was compared to global volume expansion by plotting the impedance change of the anterior or posterior lung against that of the global signal forming a curve [13]. A linear relationship is found if the percentile degree of volume change of a ROI is the same as the global lung. If the rate of change in a ROI is initially less but then towards the end of the inspiratory effort greater than the global lung, then the curve has a concave shape. If the rate of expansion in a ROI during the initial phase of the inspiration is greater than the global lung but decreases towards the end, then the curve has a convex shape. To quantify this physiological behaviour a curve fit was performed [23]:

$$I(g) = a \cdot g^{FI} + c$$

where *I(g)* is the impedance change of the region of interest, g is the impedance change of the global signal, *FI* is the filling index of the region of interest, *a* and *c* are constants. *FI* describes the shape of the curve – where a convex curvature is evident when $FI < 1$ and a concave shape is evident when $FI > 1$ – and thus the physiological behaviour observed. To analyse the impact of a sigh on regional filling characteristics, the FIs of the anterior and posterior lung were calculated for ten breaths prior to, during and ten breaths after a sigh.

Statistics: Results were described using the mean and confidence intervals. A one-way ANOVA with a Bonferroni correction was applied for repeated measurements.
A multi-way ANOVA was performed to assess the effect of gender, age and region of interest on regional amplitudes, geometric centre and phase angles. A paired t-test was used for comparison of variables within different lung regions. For statistical analysis SPSS version 15.0 (SPSS Inc., Chicago, IL) was used.

RESULTS

Feasibility of Measurements

All enrolled 32 infants were assessed during NREM sleep with EIT at 13.7 ± 3 days (mean ± SD) of which 25 infants could be followed up and measured at 3 months (aged 97 ± 8 days) and 26 infants at 6 months of age (aged 187 ± 6 days). In each infant at least one 10 minute EIT measurement could be obtained at each recording session.

EIT Image Analysis. Overall there were significant increased regional amplitudes with age for any ROI investigated in the AP-axis and RL-axis (***P*** < 0.001, multi-way ANOVA , Figure 1). Inspection of regional differences showed that the measured ROI amplitudes in the gravity (AP) axis increased with the greatest change between 2 weeks and 3 months of age for all measured ROIs (*P* < 0.05, one-way ANOVA with Bonferroni correction) but then only a moderate increase was found between the age of 3 and 6 months (*P* = ns). The greatest regional amplitude change with growth was found in the posterior (dependent) lung with an average amplitude of 0.045 (CI 0.006) at 2 weeks, 0.055 (CI 0.006) at 3 months and 0.066 (CI 0.008) at six months of age (*P* < 0.001). In the anterior (non-dependent) lung the average amplitude increased similarly but to a lesser extent from 0.039 (CI 0.004) at 2 weeks to 0.054 (CI 0.004) at 3 months and to 0.060 (CI 0.007) at 6 months of age. In the RL- axis the regional amplitudes increased with age similar to the AP-axis with the greatest change between 2 weeks and 3 months but to a lesser degree between 3 and 6 months of age. The geometric centre remained, over the entire age range, in the centre of the chest with a slight trend in location toward the anterior lung (Figure 2).

EIT Time Course Analysis. The phase angles for the anterior (non-dependent) lung were predominately negative and for the posterior (dependent) lung were positive indicating that during spontaneous breathing the dependent lung filled temporally before the non-dependent lung (*P* < 0.05). A similar filling pattern was found at 3 and 6 months of age (*P* < 0.05). The comparison of the filling pattern between right and left showed that the right lung filled before the left lung in all age groups (*P* < 0.05).

Analysis of sighs. For each infant at least two sighs were considered at each age for analysis. The measured regional impedance amplitudes of tidal breaths before and after a sigh were not different (*P* = ns) for all age groups. The regional impedance amplitude of the sigh was significantly greater than the tidal breaths but showed a similar regional distribution with the posterior lung showing the greatest impedance amplitudes. The FI of the posterior and anterior lung showed a very characteristic behaviour in all investigated infants prior to and after a sigh. The FIs of the posterior lung were significantly less than 1.0 indicating that the rate of volume change in the dependent lung is greater at the beginning of the inspiration in comparison to the rest of the lung. The FIs of the anterior lung before and after the sigh were greater than 1.0 showing a reduced initial rate of volume change in the non-dependent lung. The FI of the sigh itself showed the opposite value to the tidal breaths before and after the sigh. This pattern was similar for all age groups (Table 1).

DISCUSSION

Electrical impedance tomography has emerged as a new non-invasive lung function monitoring tool but its role in assessing the progression of lung disease remains unclear and is a topic of many recent studies [11]. Most published studies present data obtained in mechanically ventilated subjects or patients with lung disease. Few reports document EIT measurements in healthy subjects and none yet exist for follow up studies. We investigated healthy newborn infants and followed them up with EIT measurements to provide normal data.

EIT Image Analysis

The investigation of the change in regional ventilation over the first 6 months of age along the gravity (AP) axis showed that the posterior (dependent) lung was slightly better ventilated than the anterior (non-dependent) lung, irrespective of age. Figure 1 shows that the greatest increase in ventilation between 2 weeks and 3 months of age occurred in the posterior lung. In the RL-axis a similar increase in regional ventilation could be observed with both lungs contributing a similar amount. Two aspects of these findings need to be discussed. First, age specific normal values for the magnitude of regional ventilation were found with the dependent lung preferentially better ventilated in all age groups. Brown et al [24] described similar maturational changes in absolute lung resistivity with serial EIT measurements and has shown that resistivity increases with age. Second, there is a proportionally larger increase in the magnitude of regional ventilation in the posterior (dependent) than in the anterior (non-dependent) lung with growth. These findings contradict conventional teaching of neonatal ventilation distribution which states that the non-dependent lung is preferentially ventilated. Heaf et al investigated a small cohort of infants and children with lung disease using a radio labelled tracer gas (krypton-81m) method and found that infants and children have the reverse ventilation pattern to adults [25]. Frerichs et al were the first to challenge these findings and could demonstrate with EIT measurements that ventilation in infants is more centrally located [15]. We have previously described a similar ventilation distribution in a small cohort of newborn infants [18]. EIT and krypton-81m ventilation scanning have some distinct differences in the way they measure lung volume and regional ventilation. In healthy subjects, the alveolar lung volume remains almost constant during tidal breathing and most of the volume changes (convection) during tidal breathing occur in the central, peripheral airways and alveolar ducts [26]. EIT measurements are based on tidal volume change. Since the alveolar volume in healthy subjects is hardly changing, EIT can not identify these regions unless alveolar recruitment occurs during tidal breathing. Krypton-81m ventilation scanning investigates steady-state ventilation images based on the inhalation of the tracer gas. Hence images obtained with krypton-81 scanning are both convection and diffusion dependent. Infants tend to breath near the closing volume of the lung and regional differences in the distribution of the closing volume exist causing partial atelectasis of the dependent lung in spontaneously breathing and sedated infants [2, 27]. In the study by Heaf the investigated subjects were sedated and had lung disease [25]. Therefore their findings of preferential ventilation of the non-dependent lung may not apply for healthy non-sedated infants. The differences in regional amplitudes between the anterior and posterior compartments can further be explained by the artificial division of the chest into two compartments. The anterior chest compartment contains the heart as a ‘non-lung’ structure. In supine position, gravity causes the heart to be suspended from the sternum occupying a larger space in the anterior compartment, whereas in prone the heart is resting on the sternum allowing more anterior lung expansion. Our EIT data set will provide a valuable comparison for future studies in subjects with lung disease or during mechanical ventilation where alveolar recruitment and de-recruitment during tidal breathing can occur [26, 28-30].

EIT Time Course Analysis

Forty years ago regional filling characteristics of the lung were first described in healthy adults using radio-labelled isotopes [10]. Theoretically, if lung regions fill homogeneously, the degree of expansion will be consistent throughout the entire lung. It was found that in an upright position the change in lung volume (expressed as a percentage of total lung capacity) observed during an inspiratory vital capacity (VC) manoeuvre was greater in the lower regions than in the upper lung regions and that the right lung filled earlier during a deep inhalation. Asynchrony in regional lung filling was found by Koler et al. [31] using differential bronchospirometers in animal experiments, confirming that lung regions may not fill synchronously. EIT allows the measurement of the asynchronous filling and emptying of different lung regions [12]. In our study we demonstrated that the dependent lung filled before the non-dependent lung, which is consistent with the lung model proposed by Milic-Emili [10] which models the lung as a suspended spring in gravity with the dependent parts of the spring showing easier expansion. Milic-Emili showed that during the initial phase of a VC manoeuvre the rate of volume change was greatest in the non-dependent lung, whereas during the end-phase of the inspiration the greatest volume change was found in the dependent lung. In our cohort of infants we found a similar regional rate of impedance change for all analysed sighs. During tidal breathing the opposite behaviour was found, with the greatest rate of impedance change during the initial phase of the inspiration in the posterior lung and the greatest rate of impedance change during the end-phase of the inspiration in the anterior lung. To explain these differences one must consider the mechanism of lung expansion during a VC manoeuvre and the contribution of the diaphragm during tidal breathing. In infants most of the tidal volume during spontaneous breathing is generated by diaphragm excursion [32] and to a lesser degree by the chest wall [33]. During tidal breathing the posterior part of the diaphragm shows the greatest shortening of muscle fibres and hence the rate of change in lung volume in these regions will be greater than in the anterior parts of the lung [34]. During a sigh the contribution of the chest wall will proportionally increase to generate the large inspiratory effort [35]. The posterior part of the chest will experience proportionally less excursion than the anterior as the posterior chest wall is splinted by the surface the infant is lying on in supine position [36]. The greater change of the anterior lung volume at the beginning of a sigh is caused by chest wall geometry and compliance in supine position.

Limitations. The observed changes in impedance both during tidal breathing as well as an effect of growth may not be only contributed by change in air volume, but also by change in blood volume and lung tissue characteristics. The separation of several tissue impedance characteristics can only be obtained with a multi-frequency EIT equipment, which currently is not yet available for clinical use. In theory with a multi-frequency EIT the tissue to air ratio of the lung could be separated and lung growth documented.

CONCLUSION

Regional ventilation distribution measurements with EIT at 2 weeks, 3 and 6 months of age showed that the dependent lung is preferentially ventilated and is filling ahead of the rest of the lung; a breathing pattern that is similar to adults.

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Figure Legends

Figure 1
Regional impedance amplitudes increased overall from at 2 weeks to 6 months of age ($\boldsymbol{P} < 0.001$) with the greatest increase in regional amplitudes between 2 weeks and 3 months of age. Mean and CI are indicated.

Figure 2
Geometric centre of the left, the right and the global lung. The geometric centre remained centrally located for all age groups. Mean and CI are indicated. The X-axis represents the right to left direction and the Y-axis the anterior to posterior axis of the EIT image.

Figure 3
Regional filling characteristics described with phase angles. A positive value indicates that a ROI fills ahead of the rest of the lung while a negative value indicates that a ROI fills after the rest of the lung. Mean and CI are indicated.

Figure 4
Filling indices averaged for all newborns (2 weeks of age) calculated for the anterior and posterior lung for the 10 breaths prior, for the sigh and 10 breaths after the sigh. * The FI for the sigh was significantly different to the FI obtained from the tidal breaths prior to and after the sigh ($P < 0.05$). Mean and CI are indicated.

Table 1

	pre sigh		**sigh**		**post sigh**	
	anterior	posterior	anterior	posterior	anterior	posterior
2 weeks	1.063 (0.010)	0.966 (0.005)	0.953 (0.044)	1.034 (0.020)	1.087 (0.014)	0.957 (0.007)
3 months	1.092 (0.008)	0.931 (0.007)	0.927 (0.045)	1.072 (0.036)	1.098 (0.010)	0.930 (0.007)
6 months	1.153 (0.031)	0.912 (0.020)	0.960 (0.051)	1.053 (0.046)	1.174 (0.031)	0.901 (0.015)

Filling Indices (FI) for the anterior and posterior lung of 10 breaths prior to and after a sigh as well as for the sigh itself. The FI was significantly different between lung anterior and posterior regions as well as during the sigh ($P < 0.001$).

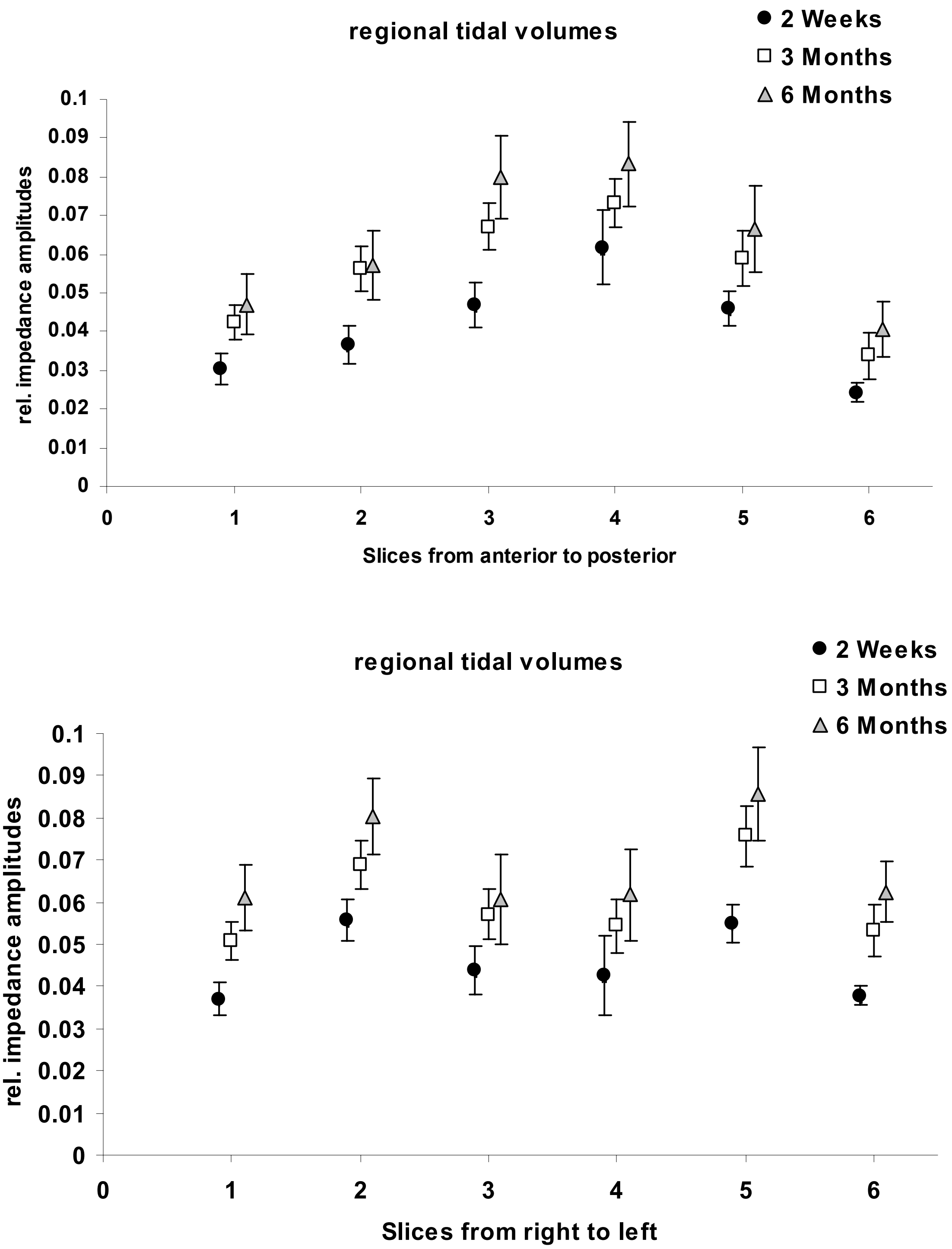

regional tidal volumes
2 Weeks
3 Months
6 Months
rel. impedance amplitudes
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
1
2
3
4
5
6
Slices from anterior to posterior
regional tidal volumes
2 Weeks
3 Months
6 Months
rel. impedance amplitudes
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
1
2
3
4
5
6
Slices from right to left

Figure 1

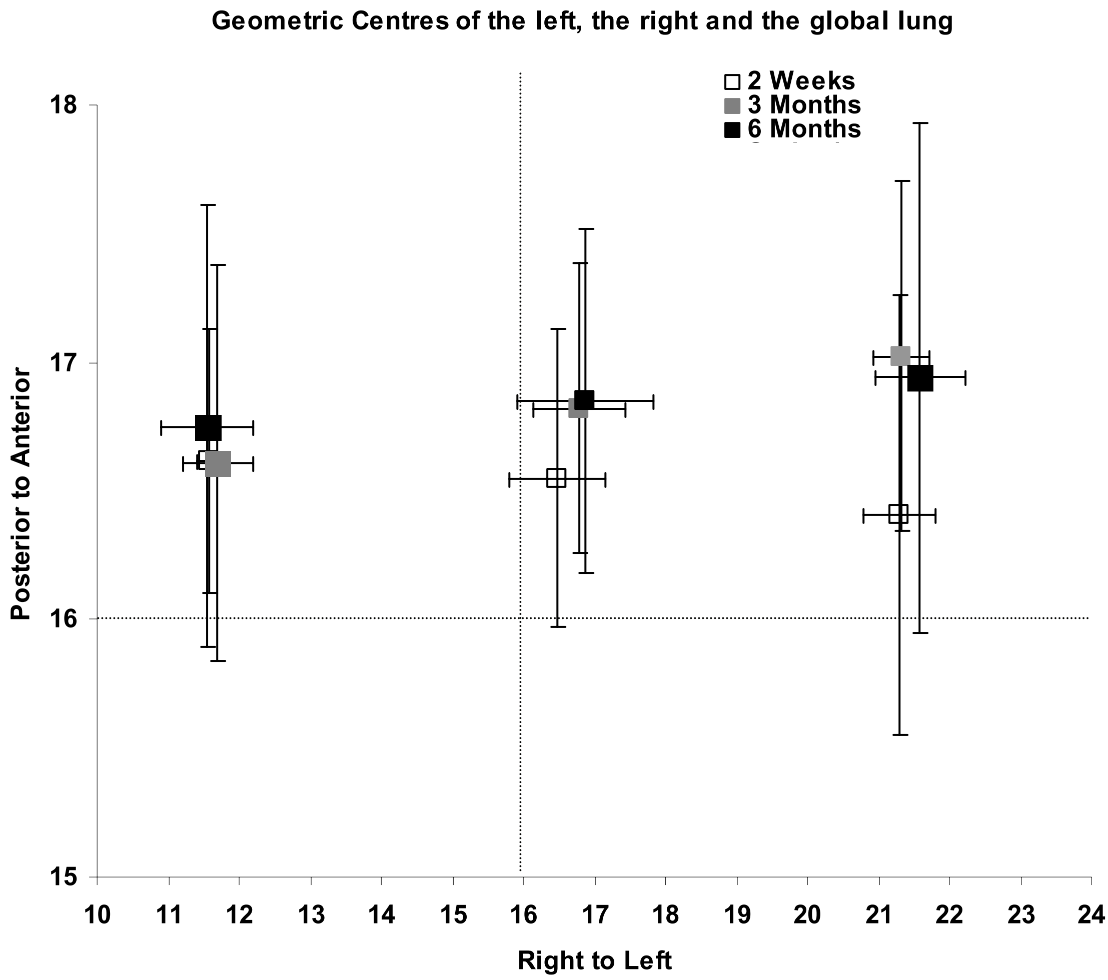
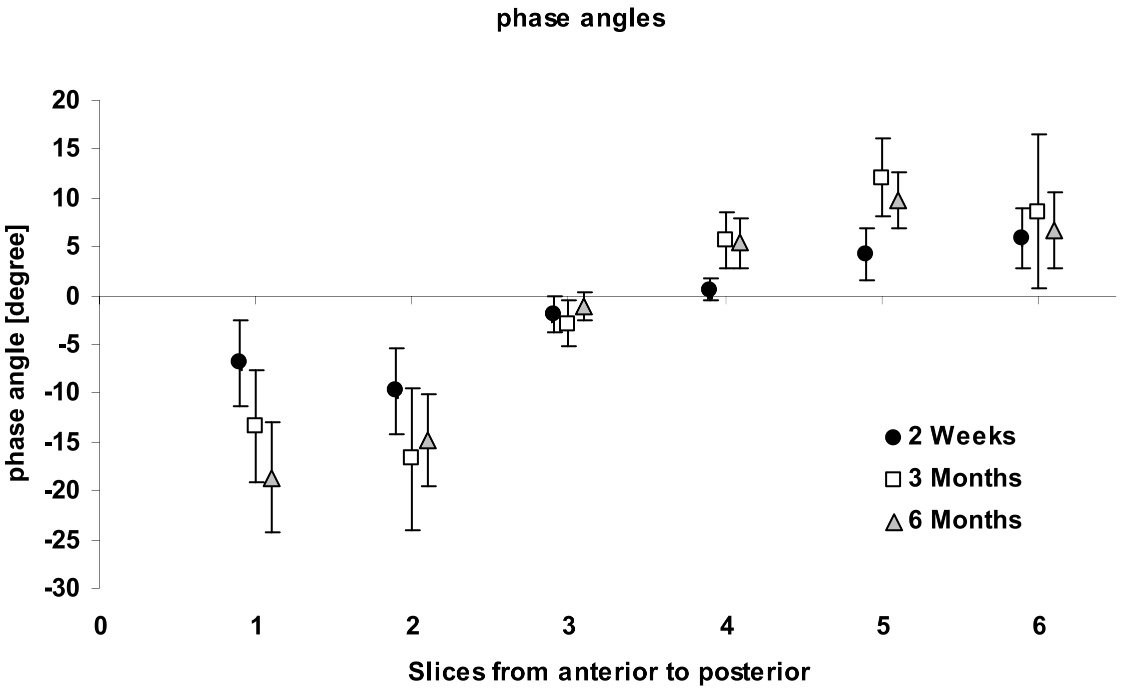

Geometric Centres of the left, the right and the global lung
2 Weeks
3 Months
6 Months
18
17
16
15
Posterior to Anterior
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
Right to Left

Figure 2


phase angles
phase angle [degree]
20
15
10
5
0
-5
-10
-15
-20
-25
-30
0
1
2
3
4
5
6
Slices from anterior to posterior
2 Weeks
3 Months
6 Months

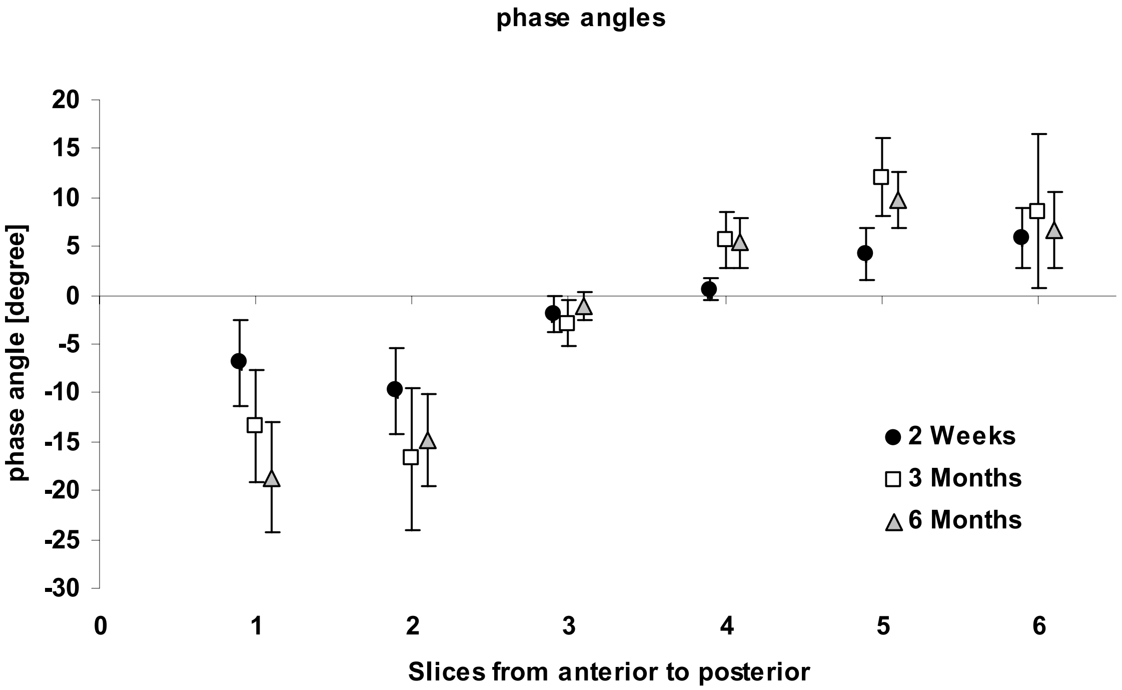

phase angles
phase angle [degree]
20
15
10
5
0
-5
-10
-15
-20
-25
-30
0
1
2
3
4
5
6
Slices from anterior to posterior
2 Weeks
3 Months
6 Months

Figure 3

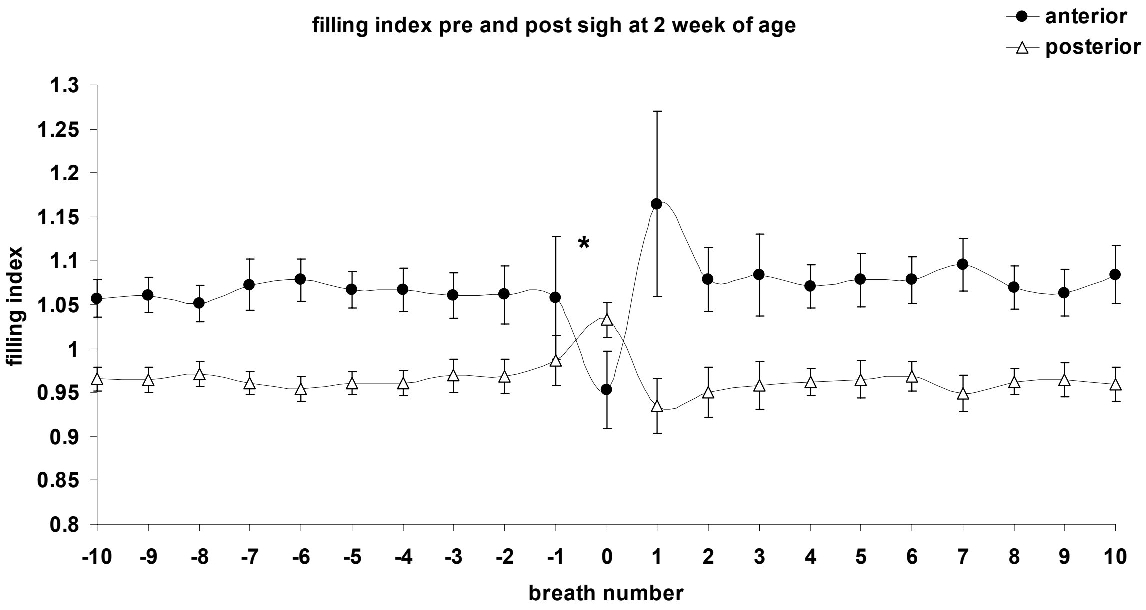

filling index pre and post sigh at 2 week of age
anterior
posterior
filling index
1.3
1.25
1.2
1.15
1.1
1.05
1
0.95
0.9
0.85
0.8
*
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10
breath number

Figure 4