The relative impact of respiratory muscle activity on tidal flow and lung volume in infants
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Respiratory muscle activity related to flow and lung volume in preterm infants compared to term infants

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Abstract

Introduction: Infants with chronic lung disease (CLD) have a high capacity to maintain normal functional lung volume despite their alterations in lung mechanics. We hypothesise that they achieve this by altering breathing pattern and dynamical elevation of lung volume, leading to differences in the relationship between respiratory muscle activity (rEMG), flow pattern and lung volume, whereby timing indices derived from rEMG could be new non-invasive bedside markers of altered lung mechanics in CLD.

Methods: Lung function and transcutaneous rEMG were measured simultaneously in 20 infants with CLD (median postconceptional age 45 wks) and 39 healthy age matched controls during quiet sleep. We compared amplitude and coefficient of variation (CV) of rEMG and their temporal relationship to flow and lung volume (FRC) between these two groups.

Results: The time between start of inspiratory muscle activity and resulting flow ($t_{ria}$) in relation to respiratory cycle time was significantly longer in infants with CLD. Although FRC was similar associations between FRC and $t_{ria}$ and post-inspiratory activity corrected for respiratory cycle time, the breath to breath variability (CV) of the diaphragm tEMG and the response to a resistive load significantly differed between groups.

Conclusion: The temporal relationship of rEMG to flow and the loss of adaptive variability provide additional information on coping mechanisms in infants with CLD not obvious in FRC measurements alone. This new technique could be used for non-invasive bedside monitoring of CLD as well as during EMG triggered ventilation in these infants in future trials.
Introduction

Chronic lung disease of infancy (CLD) represents the final common pathway of a heterogeneous group of pulmonary diseases that start in the neonatal period that usually evolves from acute respiratory disorders experienced by newborn infants. The pathogenesis of this condition can be multi-factorial. Prematurity, chorioamnionitis, oxygen toxicity and baro- and volutrauma as a result of neonatal ventilation as well as other risk factors contribute to the evolution of CLD. In current clinical practice, the functional monitoring of these infants in the post-acute phase is mainly limited to SaO2, 02 and pCO2 measurements. There is a need for non-invasive simple techniques, which provides information on alterations in lung mechanics in the unsedated infant during natural sleep.

Tidal breathing parameters, lung volume and ventilation homogeneity are affected by the morphologic changes in CLD and they can be measured by lung function studies in this age group. Some studies showed decreased end-expiratory volume (FRC) and lung clearance index (LCI) in sedated infants, while other studies in spontaneously breathing infants in natural sleep could not confirm these observed differences in FRC and LCI between healthy infants and infants with CLD. We and other authors pointed out that, the latter findings are in line with clinical observations that infants with CLD in natural sleep may have a high capacity to maintain relatively normal lung volume and relatively normal gas exchange despite their alterations in lung mechanics, whereas this capacity may be reduced during sedation.

Recently, we described the combination of matched tidal breathing measurements and electromyography of the respiratory muscles (rEMG) in healthy infants. Our findings suggested that the interaction of the respiratory muscles and lung mechanics are actively controlled breath to breath, and that simultaneous measurement of tidal breathing parameters and rEMG parameters potentially provide a more comprehensive picture of pulmonary mechanics in disease. We hypothesise that infants with CLD achieve to maintain a relatively normal lung volume by altering breathing pattern and dynamical elevation of lung volume, however at the cost of increased energy expenditure. These mechanism may be detected by differences in the temporal relationship between
respiratory muscle activity (rEMG), flow pattern and lung volume, whereby timing indices derived from rEMG could be new non-invasive bedside markers of altered lung mechanics in CLD.

The aim of the current study is to determine the temporal relationship between rEMG and tidal flow, the variability of these parameters, the relationship to lung volume and the response to a resistive/elastic load at the airway measured in infants with CLD in comparison age matched healthy controls during unsedated sleep.

Methods

Study design
At the postconceptional age of 44 weeks, transcutaneous rEMG was measured prior to the onset of the face mask and at three occasions in parallel to standardised lung function tidal flow and volume (refs) in infants with CLD in comparison to age matched healthy infants in natural quiet unsedated sleep. The measurements were followed by rEMG measurements during multi-breath FRC measurements shortly thereafter in the same sleep stage.

Subjects
Twenty infants with a history of mild to moderate chronic lung disease of infancy, defined according to the criteria of Jobe et al, were recruited for this study from the neonatal unit of the University Maternity Hospital (Bern, Switzerland). Thirty nine healthy term-born infants were recruited for an ongoing birth cohort study in Bern, Switzerland. Patient data are given in table 1. The study was approved by the Medical Ethics Committee of the University Hospital and the Canton of Berne and written informed consent was obtained from all parents. The parents were usually present during the measurements.
Table 1. Anthropometric data of the study infants.

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Chronic lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Gestational age at birth, wks</td>
<td>39.9 (37.0 - 41.7)</td>
<td>27.3 (24.0 – 36.7)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.4 (2.2 – 4.4)</td>
<td>0.95 (0.45 – 2.6)</td>
</tr>
<tr>
<td>Gestational age at study date, weeks</td>
<td>44.4 (41.9 – 48.1)</td>
<td>44.6 (43.4 – 51.1)</td>
</tr>
<tr>
<td>Weight at study date, kg</td>
<td>4.3 (3.1 – 6.4)</td>
<td>4.0 (2.6 – 5.4)</td>
</tr>
<tr>
<td>Height at study date, cm</td>
<td>54.2 (47.0 – 61.3)</td>
<td>52.1 (47.5 - 59)</td>
</tr>
</tbody>
</table>

Data is given as median (range)

Measuring procedure

Infants were studied during quiet sleep in supine position with the head in midline, and with a mask (size 1, Homedica, Cham, Switzerland). All measurements were done according to the standards of infant lung function testing which ensured that resistive properties or dead space of the equipment did not exceed the recommended limits 7-9. Sleep state was defined clinically by using the criteria of Prechtl 14.

Lung function

Flow was measured by using a prototype ultrasonic flowmeter (Exhalyzer®D, Eco Medics AG, Duernten, Switzerland). Main outcome tidal breathing parameters were respiratory frequency (f), inspiratory time (ti), expiratory time (te), ratio of time to peak tidal expiratory flow and te (tPTEF/te), tidal volume(V T), and minute ventilation (V’ E). Three series of multibreath SF6 washout procedures were performed and an average obtained for FRC was calculated using an optimized analysis method 12.

rEMG recordings

The electrical activity of the diaphragm and intercostal muscles were measured transcutaneously. The technical aspects of the measurements, measurement device and validation have been previously described 6,15,16. In order to obtain simultaneous
recordings of flow and rEMG activity, an extra isolated analogue output was created for the flow signal of the ultrasonic flow meter and synchronized with the rEMG measurements. Thirty breathing cycles of the rEMG-measurement were sampled before lung function measurements were started (T0). The rEMG-activity of the first 30 breaths was recorded in parallel to tidal flow measurements (T1), followed by a sequence of 30 breaths after two minutes (T2) and by a third sequence of 30 breaths after 8-10 minutes (T3).

Main outcome rEMG parameters were inspiratory time of the rEMG ($t_{I,rEMG}$), expiratory time of the rEMG ($t_{E,rEMG}$), post-inspiratory time ($t_{pia}$), and ramp inspiratory activity time ($t_{ria}$). The variability in the relative contribution of the respiratory muscles is expressed as the coefficient of variation (CV). To calculate the relative amplitude variations of the EMG signals, the logarithm of the EMG Activity Ratio (logEMGAR) was used as previously described.

Data analysis and statistics

Dependent on the distribution of the group data, descriptive statistics, t-test and Non parametric tests, respectively were performed to compare tidal breathing parameters, FRC, and rEMG parameters between healthy infants and infants with CLD. Linear regression analysis was used to compare EMG –flow timing parameters and lung volume. Statistical analysis and graphics were performed with SPSS (SPSS Inc., Chicago, Illinois, USA) and SigmaPlot (Systat Software Inc., California, Richmond, USA). The data processing and analysis were done using the data acquisition and processing package Polybench (Applied Biosignals, Weener, Germany).

Results

Out of 20, data of one infant with CLD was excluded because of an insufficient period of quiet sleep. Data of 19 infants with CLD and all data from the healthy infants were used for tidal breathing analysis, Multi breath washout (MBW) analysis, and rEMG analysis.

Comparison between healthy infants and infants with CLD

Tidal breathing timing indices derived from airway opening flow and from rEMG
Group median values (range) of tidal breathing indices measured at the airway opening as and derived from rEMG, as well as lung volumes (FRC) of healthy infants and infants with CLD are summarized in table 2. Significant differences between both groups were found for \( t_I, t_{PTEF}/t_E, t_{rEMG}, \) and \( t_{ria}/t_{tot}. \) All other tidal parameters as well as FRC were not different between the groups.

Table 2. Comparison of tidal breathing parameters, FRC and rEMG parameters between healthy infants and infants with CLD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy</th>
<th>CLDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory rate (min⁻¹)</td>
<td>44.6 (27.5 – 63.2)</td>
<td>47.7 (35.9 – 100.6)</td>
</tr>
<tr>
<td></td>
<td>0.105</td>
<td></td>
</tr>
<tr>
<td>( t_I ) (ms)</td>
<td>599 (435 – 897)</td>
<td>564 (304 – 689)</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>( t_E ) (ms)</td>
<td>736 (501 – 1443)</td>
<td>721 (283 – 1000)</td>
</tr>
<tr>
<td></td>
<td>0.437</td>
<td></td>
</tr>
<tr>
<td>( t_{PTEF}/t_E ) (%)</td>
<td>33.1 (14.6 – 63.37)</td>
<td>24.4 (14.43 – 48.73)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( V_T ) (mL)</td>
<td>28.8 (20.0 – 45.0)</td>
<td>28.5 (17.0 – 38.0)</td>
</tr>
<tr>
<td></td>
<td>0.584</td>
<td></td>
</tr>
<tr>
<td>( V'_E ) (mL/min)</td>
<td>1262 (675 - 2039)</td>
<td>1269 (757 - 1937)</td>
</tr>
<tr>
<td></td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td>FRC (mL/kg)</td>
<td>25.4 (17.7 – 36.4)</td>
<td>24 (19.4 – 30.7)</td>
</tr>
<tr>
<td></td>
<td>0.575</td>
<td></td>
</tr>
<tr>
<td>( t_{rEMG} ) (ms)</td>
<td>604 (417 - 929)</td>
<td>573 (306 - 718)</td>
</tr>
<tr>
<td></td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>( t_{E,rEMG} ) (ms)</td>
<td>698 (481 - 1468)</td>
<td>645 (298 - 1005)</td>
</tr>
<tr>
<td></td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>( t_{ria} ) (ms)</td>
<td>218 (72 - 355)</td>
<td>237 (125 - 388)</td>
</tr>
<tr>
<td></td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>( t_{pia} ) (ms)</td>
<td>460 (203 - 1224)</td>
<td>425 (95 - 863)</td>
</tr>
<tr>
<td></td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>
Data is given as median (range) and p-value as determined by Mann-Whitney U test for unpaired measurements.

The mean breath by breath variability, expressed as CV, of the intercostals muscles and diaphragm of infants with CLD were 11.2% and 22.6%, respectively (table 2). The CV of the diaphragm was significantly lower (P<0.05) in comparison with healthy infants.

Response to the onset of the elastic and compliant face mask load

Breathing frequency and tidal volume measured at the airway opening changed in both groups in response to the face mask load, however, there was a large variability within the groups and an overlap of the 95% group confidence intervals. Nevertheless, we found a significant decrease (P<0.05) of the $f$ and $V'_E$ between T2 and T3 in healthy infants, whereas in contrast in infants with CLD there was a significant increase (P<0.05) of the $f$ between T1 and T2. Furthermore, $V'_E$ significant decreased between T2 and T3 in infants with CLD.

Measured from rEMG, in the infants with CLD the amplitude of the electrical activity of the diaphragm increased significantly (p < 0.05) when the face mask was placed (T1) compared to T0. This was expressed in a 20% increase in mean diaphragmatic logEMGAR at T1 and T3 (0.08) compared to baseline (T0, logEMGAR=0). The increase in diaphragmatic rEMG electrical activity in response to the face mask load was similar in both group.
Regarding the rEMG timing indices, we found a significant increase (P<0.05) of $t_{\text{pia}}/t_{\text{tot,EMG}}$ between T2 and T3 and a significant decrease in $t_{\text{rta}}/t_{\text{tot,EMG}}$ between T2 and T3 in infants with CLD but not in healthy infants. Fig 1 shows the group mean response of the tidal breathing parameters ($f, V_T, V'E$) and rEMG parameters ($t_{\text{pia}}/t_{\text{tot,EMG}}, t_{\text{rta}}/t_{\text{tot,EMG}}$) in response to the face mask load in healthy infants and infants with CLD at the three time points T1, T2 and T3.

**Figure 1**

The response of the tidal breathing parameters ($f, V_T, V'E$) and rEMG parameters ($t_{\text{pia}}/t_{\text{tot,EMG}}, t_{\text{rta}}/t_{\text{tot,EMG}}$) to the onset of the elastic and compliant face mask load of the three sequence of thirty breaths (T1, T2, T3) in healthy infants and infants with CLD. * p < 0.05 with Mann-Whitney U test for unpaired measurements (between T1 and T2). ** p < 0.05 with Mann-Whitney U test for unpaired measurements (between T2 and T3). Arrow-line p < 0.05 with Wilcoxon Test of the paired measurements
Relationship between FRC and rEMG

Although there was no significant difference in FRC corrected for bodyweight between healthy infants and infants with CLD (table 2), the relationship between respiratory muscle activity and FRC was different between the group. Although the relationship between muscle activity and FRC was weakly correlated and showed large intrasubject, intersubject variability and overlap between the groups, we nevertheless found a significant positive correlation between $t_{ria}/t_{tot,EMG}$ (means of 30 breaths) and FRC(mL/kg) ($r=0.39$, $r^2=0.15$, $P<0.001$) (Fig 2a) and a significant negative relation between $t_{pia}/t_{tot,EMG}$ and FRC expressed in mL/kg ($r=-0.33$, $r^2=0.11$, $P<0.001$) (figure 2b) in infants with CLD.

In healthy infants, we determined a significant positive correlation between $t_{pia}/t_{tot,EMG}$ (means of 30 breaths) and FRC expressed in mL/kg ($r=0.34$, $r^2=0.12$, $p<0.001$) (Fig 2b) and no correlation between the FRC and the ratio $t_{ria}/t_{tot,EMG}$ (Fig 2a). This cross-sectional analysis was performed in all measurements per group.

We furthermore investigated the influence of bodyweight (explanatory variable) on the relationship between rEMG and FRC using multivariable regression models. The $R^2$ value of the multivariable regression gives a measure how much the variability in the outcome is determined by the body weight. We found a better correlation between FRC and bodyweight for infants with CLD in comparison with healthy infants ($R^2$ value of 19% for healthy infants and 43.9% for infants with CLD). The association significant improved by additionally including $t_{ria}/t_{tot,EMG}$ ($R^2$ 49%, $p< 0.001$) in infants with CLD. There was no significant improvement in healthy infants by including $t_{ria}/t_{tot,EMG}$ ($R^2$ 22%, $p < 0.04$). These findings indicate that the FRC is determined by two components, first by body size (expressed by body weight) and by some adaptive mechanism where muscle activity plays an important role. In infants with CLD, FRC is more determined by body size and infants with CLD have less degree of freedom to dynamically regulate the FRC by adapting respiratory muscle activity, and they dominantly do this by activation ramp inspiratory muscle activity $t_{ria}/t_{tot,EMG}$. 

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Figure 2a)
Relationship between $t_{ria}/t_{tot, rEMG}$ and FRC (mL/kg) in infants with CLD (black points) ($r=0.39$, $r^2=0.15$, $P<0.001$) and healthy infants (grey points) (no significant relation).
Figure 2b)
Relationship between \( t_{\text{pia}} / t_{\text{tot,REMG}} \) and FRC (mL/kg) \((r=-0.33, \ r^2=0.11, \ P<0.001)\) in infants with CLD (black points) and healthy infants (grey points) \((r=0.34, \ r^2 0.12, \ p<0.001)\) .
Table 3. Tidal flow parameters and indices of rEMG of the diaphragm (Mean (±SD) of three different sequences.

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory rate (min⁻¹)</td>
<td>49.8 (11.6)</td>
<td>51.8 (15.2)*</td>
<td>50.3 (15.5)</td>
</tr>
<tr>
<td>t₁ (ms)</td>
<td>558 (84)</td>
<td>538 (98)*</td>
<td>556 (93)</td>
</tr>
<tr>
<td>tₑ (ms)</td>
<td>732 (185)</td>
<td>697 (182)</td>
<td>715 (189)</td>
</tr>
<tr>
<td>t_{PTEF/ₑ} (%)</td>
<td>25.0 (9.1)</td>
<td>27.8 (9.8)*</td>
<td>29.4 (8.3)</td>
</tr>
<tr>
<td>Vₑ (mL)</td>
<td>28.5 (5.3)</td>
<td>28.1 (5.8)</td>
<td>27.0 (6.6)</td>
</tr>
<tr>
<td>Vₑ' (mL/min)</td>
<td>1357 (250)</td>
<td>1373 (285)</td>
<td>1299 (272)**</td>
</tr>
<tr>
<td>t_{LE,EMG} (ms)</td>
<td>551 (86)</td>
<td>546 (96)</td>
<td>577 (93)**</td>
</tr>
<tr>
<td>t_{E,EMG} (ms)</td>
<td>649 (179)</td>
<td>646 (175)</td>
<td>679 (189)**</td>
</tr>
<tr>
<td>t_{dia} (ms)</td>
<td>243 (56)</td>
<td>245 (54)</td>
<td>223 (49)**</td>
</tr>
<tr>
<td>t_{pia} (ms)</td>
<td>430 (151)</td>
<td>412 (163)</td>
<td>461 (180)**</td>
</tr>
<tr>
<td>CV dia (%)</td>
<td>25.4 (8.6)</td>
<td>24.6 (9.6)</td>
<td>24.5 (9.1)</td>
</tr>
<tr>
<td>CV int (%)</td>
<td>11.1 (3.4)</td>
<td>10.7 (3.3)</td>
<td>10.9 (3.5)</td>
</tr>
</tbody>
</table>

* p < 0.05 with Wilcoxon Test of the paired measurements (between T1 and T2)
** p < 0.05 with Wilcoxon Test of the paired measurements (between T2 and T3)
Discussion
In this present study, comparison of tidal breathing and rEMG parameters between healthy infants and infants with CLD showed significantly longer delay between start of inspiratory muscle activity and resulting flow corrected for the respiratory cycle time and a significantly shorter \( t_i \) and \( t_{PTEF}/t_E \) in the CLD group, indicating longer inspiratory muscle efforts already during expiration before flow at the airway opening can occur. Although FRC was similar in healthy infants and in infants with CLD, FRC and \( t_{ria}/t_{tot,EMG} \) or \( t_{pia}/t_{tot,EMG} \) FRC were found be weak but on a group level positively correlated to \( t_{pia}/t_{tot,EMG} \) in healthy infants and negatively correlated in infants with CLD. Unlike in healthy infants, we found a positive relation between \( t_{ria}/t_{tot,EMG} \) and FRC in infants with CLD. However, the relationship respiratory muscle activity and FRC was highly variably in the spontaneously breathing unsedated healthy as well as CLD infant.

We have previously shown (Hutten, PP2008) that infants are likely to adapt their tidal flow and volume breath by breath by activating dominantly diaphragmatic but also intercostal muscle activity. The relative contribution of the diaphragmatic muscle activity in infants is highly variable, but this variability was significantly lower in CLD in comparison to the healthy infants at similar sleep stage. Adding the resistive and elastic mechanical load to the face mask to infant respiratory system may be seen as a model of the response to changes in mechanical demands imposed on the respiratory system. Respiratory rate, \( V_T \), \( t_{ria}/t_{tot,EMG} \), \( t_{pia}/t_{tot,EMG} \) and the amplitude of respiratory EMG muscle activity (logEMGAR) responded differently the onset of the face mask in the CLD group.

Interpretation of the findings and possible mechanism
A previously reported in a large cohort of unsedated infants with of infants with CLD, we found no differences between FRC corrected for bodyweight in infants with CLD in comparison to healthy infants. These findings are consistent with previous observations that infants have a high capacity to dynamically maintain their lung volume. Post-inspiratory muscle activity and ramp inspiratory muscle activity during expiration are
important to actively control end expiratory level and FRC in infants 20-22. Our current findings suggest that infants with CLD achieve to control their end expiratory level by using different breathing strategies and different respiratory muscle activation pattern than healthy infants. Infants with CLD start their inspiratory muscle activity much earlier in the expiratory phase than healthy infants, and multi-variable analysis indicates that this muscle activity is a strong and positively correlated determinant of FRC in disease but not in healthy infants. This has likely to do with their obstructive and restrictive lung mechanics in CLD, which force these infants to overcome a large intrathoracic pressure by activating their diaphragmatic ramp inspiratory muscle activity prior to the resulting flow at the airway opening. In contrast, healthy infants seem not have to such restrictions, moreover as known from the literature (refs), they have a relatively low elastic equilibrium volume in comparison to adults. In healthy infants ramp inspiratory muscle activity was not positively correlated to FRC, but longer post-inspiratory muscle activity was correlated with FRC. Our findings are consistent with the hypothesis that healthy infants dynamically elevate their endexpiratory volume by activating their post-inspiratory muscle activity. We speculate that these breathings strategies are energetically less demanding than the breathing strategies which are needed in restrictive and obstructive lung mechanics in CLD. However, the relationship between these timing indices and FRC are very weak and highly variable on a group level, indicating that these muscular mechanism are just one of a network of components influencing FRC in health and disease. These changes in timing indices of the muscle-flow interaction must be seen as indirect markers of how neuro-respiratory control reacts on changes in lung mechanics.

Variability and adaptive capacity

Neuro-respiratory control works based on a feedback loop system influenced by many factors. These feedback loops consist of the respiratory oscillator in the brainstem, efferent neural activity, muscle characteristics and their activation pattern, lung and upper airway mechanics and afferent mechano- and chemoreceptor activity23. Most of these components can adapt breath by breath resulting in a highly variable breathing pattern in infants 24-26. If one of this components are altered or restricted (e.g. lung mechanics), then the system looses degrees of freedom and likely variability. In our
previous work in healthy infants, we found that breath to breath variability is mostly seen in diaphragmatic muscle activity. In disease this variability is decreased, consistent with a loss of breath to breath adaptive capacity of the respiratory system in disease, the control system becomes more deterministic.

Both, healthy and infants with CLD change their minute ventilation in response to the resistive and elastic mechanical load of a face mask and flowsensor to the infant respiratory system, which may also be seen as a model of the adaptive response. Both groups first increased their respiratory rate and decreased their VT. Then, healthy infants are capable to lift up their VT and decreased their respiratory rate. Infants with CLD compensated with a further decrease of their VT and a stabilised respiratory rate. Thus, infants with CLD compensate with different strategies to achieve optimal ventilation. We hypothesise, that a possible explanation for this difference is the low compliance of the lung in infants with CLD, whereby the muscle activity to increase pressure needed to generate higher tidal volumes may use more energy than the muscle activity needed to increase breathing rate. Also ramp inspiratory activity prolongs in response to the load. This is theoretically consistent with increase in expiratory pressure or with higher lung volumes.

Clinical relevance
Recently, long term outcome studies of preterm children without and with CLD showed an impaired lung function and increasing respiratory morbidity at older age. Such alterations are often not easy to identify in newborn infants with CLD due to the adaptive mechanism which can play when infants are not sedated. Combined rEMG-measurements with matched tidal flow will improve the understanding of changes in lung function and physiological development in infants with CLD and will enlarge the knowledge about the pathophysiology of CLD. Our findings demonstrate that this combination of measurements may help to understand why these infants with CLD can maintain relative normal lung volume and gas exchange if they are spontaneously breathing, but not when their neurorespiratory control is damped during sedation. To monitor lung disease in this cohort it may not enough to measure tidal flow and lung
volume alone. rEMG measurements in combination with tidal breathing measurements and FRC measurements may give a more comprehensive picture of the lung disease and the influence on the lung physiology.

Alterations in muscle activity possibly result in increased energy consumption in infants with CLD. The latest in combination with a decreased adaptive capacity may explain why infants with CLD are more prone to become respiratory distressed by external influences. However, future prospective studies have to investigate whether infants with CLD with a decreased adaptive variability and adaptive capacity to respond to a mechanical load are more prone decompensate in response to changes in lung mechanics e.g. during the first viral infections.
**Methodological aspects**

The transcutaneous way of assessing electrical activity of the respiratory muscles is favorable in infants with CLD since it is non-invasive. Although verified in a previous publication, one critical point of the EMG analysis may be the gating and filtering process, which may lead to problems of measuring the exact time indices in the breathing cycle. However, this study shows once again an optimal filtering procedure by an excellent correlation of time indices in EMG and flow, not only in healthy infants but also infants with CLD. Furthermore, transcutaneous recordings of the electrical activity of the respiratory muscles have been criticized, especially because of contamination of the signals by electrical activity of other muscles. In an earlier case report we clearly showed the absence of contamination of abdominal muscle activity during the measurements during quiet sleep. This is in the line with the observation of Praud et al. who reported no activity of abdominal muscles during quiet sleep. All together, the transcutaneous rEMG is an easy to handle and non invasive method to obtain indirect information about the respiratory neural drive.

A further limitation of the study is that the relationship between rEMG-flow time indices and lung volume is based on intra-individual and inter-individual data. Since infants have to be studied during their natural sleep, there is no other possibility to get this information other than by observational studies. Nevertheless, if multivariable analysis is performed to correct for dependent variables and biometric data, the findings remain robust. The advantage of the observational approach is the fact that the findings represent the real life situation.

**In summary**

Although minute ventilation and FRC were similar in infants with CLD, the temporal dynamic interaction between respiratory muscle activity, resulting flow and lung volume was altered. The temporal relationship of rEMG to flow and the loss of adaptive variability provide additional information on coping mechanisms in infants with impaired lung mechanics which is not obvious in tidal breathing and lung volume measurements alone. This information is easy to obtain with rEMG measurements with matched tidal breathing measurements at airway opening adhering the new standards.
and may be useful as non-invasive clinical monitoring tools for disease progression in the future. Furthermore, with the increasing interest in rEMG triggered artificial ventilation of infants with lung disease, our findings are crucial since the timing relationship between muscle activity and resulting flow, tidal volume and lung volume is different in health and disease. An even more important for rEMG triggered ventilation is finding that the timing of ramp inspiratory muscle activity strongly determines lung volume.

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References


