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Response to $\beta_2$-agonist of respiratory muscle activity, flow and lung volume in wheezy infants

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Abstract

Introduction: Wheeze is a common symptom during infancy and the treatment of wheezy infants with bronchodilators remains controversial. We hypothesise that administration of \( \beta_2 \)-agonist may lead to differences in the relationship between respiratory muscle activity (rEMG), flow pattern and lung volume.

Methods: Simultaneous measurements of lung function and transcutaneous rEMG were performed in 25 sedated infants with recurrent wheeze before and after salbutamol inhalation. We compared the coefficient of variation (CV) of rEMG and its temporal relationship to flow and lung volume (FRC before and after inhalation of \( \beta_2 \)-agonist).

Results: The time between the start of inspiratory muscle activity and resulting flow (\( t_{\text{ia}} \)) in relation to respiratory cycle time was significantly shorter after administration of inhaled salbutamol. The breath to breath variability (CV) of the diaphragm was significantly increased after inhalation of the \( \beta_2 \)-agonist. Although FRC remained unchanged, tidal volume increased significantly after administration of salbutamol.

Conclusion: The temporal dynamic interaction between respiratory muscle activity, resulting flow and lung volume was altered after inhalation of salbutamol. The temporal relationship of rEMG to flow and the profit of adaptive breath to breath variability provide additional information on the response of wheezy infants to inhaled \( \beta_2 \)-agonist, which becomes not obvious from lung function measurements alone.
Paediatric Respiratory Medicine of the Emma Children’s Hospital. Infants were referred to the outpatient hospital by general practitioners for evaluation of their wheezing episodes. All infants received inhaled corticosteroids on a regular basis, prescribed by their general practitioner. Infants with other diseases, such as chronic pulmonary, cardiac, or neurological disease, were excluded from the study. The hospital’s medical ethics committee of the AMC approved the study and written informed consent was obtained from all parents.

Measuring procedure

Infants were free of acute respiratory symptoms and none had received bronchodilators at least 8 hours prior to the start of measurements. Chloral hydrate (75-100 ml/kg, rectally) was administered 30 minutes before the measurements to prevent the infants from waking up during the measurements. Infants were studied in supine position with the head in midline, and with the mask (size 2, Laerdal, New York, NY, USA) placed over the mouth and nose according to the standards for infant lung function testing 9-11. The rEMG measurements were synchronized with the flow signal and recorded simultaneously. The tidal flow-volume loops were checked for leaks and the rEMG signals were examined for quality: presence of clear electrical heart activity (ECG) and absence of mains interference. During measurements heart rate and oxygen saturation were monitored by pulse oximetry (Nellcor, Hayward, CA, USA).

Thirty breathing cycles of the rEMG-measurement were sampled without the face mask before baseline lung function measurements were started (Baseline-T0). The pre-warmed face mask was then set gently on the infant’s mouth and nose. The EMG-activity of the first 30 breaths was recorded in parallel to tidal flow measurements at the airway opening (Baseline-T1), followed by a sequence of 30 breaths after two minutes (Baseline-T2) and followed by a third sequence of 30 breaths after a time period of 8-10 minutes (Baseline-T3) whereby the face mask was not moved and the sleep stage did not change. At the end of this procedure, using the same measurement set-up we performed three measurements of lung volume using the multi-breath SF6 washout technique as previously described 12-14.
After the baseline measurement, 400 µg salbutamol was administered from a pressurised metered dose inhaler through a spacer (Babyhaler®). Lung function measurements were repeated after 10 minutes, using the same procedure as described above. 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\textsuperscript{9-11}.

\textit{Lung function measurements at airway opening}

Tidal flow and multi-breath inert gas washout measurements were performed using a modified commercially-available apparatus (Exhalyzer\textsuperscript{D}, Eco Medics AG, Duernten, Switzerland). This equipment is based on ultrasonic flow meter technology following the assessment of flow and molar mass at the same time as previously described\textsuperscript{13}. Main outcome tidal breathing were respiratory frequency (f\textsubscript{r}), inspiratory time (t\textsubscript{i}), expiratory time (t\textsubscript{e}), t\textsubscript{i} as a fraction of respiratory cycle time (t\textsubscript{i}/t\textsubscript{tot}), time to peak tidal expiratory flow (t\textsubscript{PTEF}/t\textsubscript{E}), tidal volume(V\textsubscript{T}), minute ventilation (V\textsuperscript{e} of 30 breaths at time points T1, T2 and T3 before and after inhalation of salbutamol. Lung volume and ventilation inhomogeneity were assessed by multi breath washout (MBW) procedure. Outcomes were end-expiratory volume (FRC) and lung clearance index (LCI), which were calculated using an optimized analysis method \textsuperscript{12}. This procedure is known not to disturb the breathing pattern of infants, since an inert gas is used.

\textit{rEMG recordings}

The electrical activity of the diaphragm and intercostal muscles were measured transcutaneously from paired electrodes. The technical aspects of the measurements, measurements device and validation have been previously described \textsuperscript{8,15-17}. 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. The accuracy of the signal was tested and the channels were matched according to the standards for data acquisition in infant lung function testing \textsuperscript{10,11}. Main outcome rEMG parameters were the inspiratory time of the rEMG (t\textsubscript{r,EMG}), the expiratory time of the rEMG (t\textsubscript{E,EMG}), the post-inspiratory time (t\textsubscript{psa}), and the ramp
inspiratory activity time ($t_{ria}$). The variability in the relative contribution of intercostal muscles and diaphragm is expressed as the coefficient of variation (CV). To calculate the relative amplitude variations of the EMG signal, the logarithm of the EMG Activity Ratio (logEMGAR) was used as previously described 18.

**Data analysis and statistics**

Descriptive statistics were performed to compare tidal breathing parameters, FRC and rEMG parameters between baseline lung function measurements and measurements after bronchodilation. Statistical analysis and graphics were performed with SPSS (SPSS Inc., Illinois, Chicago, 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**

25 infants with a history of recurrent wheeze (at least 3 periods) were referred to our outpatient clinic of Paediatric Respiratory Medicine for evaluation. The infants had a median (range) age of 11.7 (6.2 – 23.0) months, and had a body weight and length of 10.1 (8.0 – 12.0) kg and 75.7 (67 – 90) cm, respectively. All infants tolerated the lung function and the rEMG measurements; two infants woke up after the nebulisation of salbutamol and before FRC measurements could be performed.

**Comparison between baseline and post salbutamol measurements**

**Tidal breathing and rEMG parameters**

Median (range) of tidal breathing, multi breath washout, and rEMG parameters are summarized in table 1. There was a significant increase for $V_T$ and $t_{ria} / t_{tot,EMG}$ and a significant decrease for $t_{PTFE} / t_{E}$, $t_{ria}$, $t_{plia}$, $t_{ria} / t_{tot,EMG}$. 137
Table 1. Comparison of tidal breathing parameters, FRC and rEMG parameters between baseline and after inhalation of salbutamol.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Salbutamol</th>
<th>After Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>f (breaths/min)</strong></td>
<td>28.6 (18.9 – 43.0)</td>
<td>28.7 (19.7 – 38.3)</td>
</tr>
<tr>
<td><strong>t I (ms)</strong></td>
<td>850 (603 - 1239)</td>
<td>886 (640 - 1116)</td>
</tr>
<tr>
<td><strong>t E (ms)</strong></td>
<td>1164 (770 - 1961)</td>
<td>1148 (934 - 1975)</td>
</tr>
<tr>
<td><strong>tI/ttot (%)</strong></td>
<td>42.4 (35 – 50)</td>
<td>40.0 (36 – 49)</td>
</tr>
<tr>
<td><strong>tPEF/tE (%)</strong></td>
<td>24.7 (14.6 – 50.6)</td>
<td>21.8 (10.2 – 44.02)*</td>
</tr>
<tr>
<td><strong>VT (mL/kg)</strong></td>
<td>10.1 (7.1 – 14)</td>
<td>10.3 (7.4 – 15.4) *</td>
</tr>
<tr>
<td><strong>V’E (mL/min)</strong></td>
<td>2909 (2237 – 4066)</td>
<td>3017 (2360 - 4254)</td>
</tr>
<tr>
<td><strong>FRC (ml)</strong></td>
<td>223 (146 – 298)</td>
<td>205 (126 – 297)</td>
</tr>
<tr>
<td><strong>T IrEMG (ms)</strong></td>
<td>828 (622 - 1041)</td>
<td>825 (625 - 1168)</td>
</tr>
<tr>
<td><strong>T EirEMG (ms)</strong></td>
<td>1123 (594 - 2079)</td>
<td>1073 (823 - 1942)</td>
</tr>
<tr>
<td><strong>t ria (ms)</strong></td>
<td>328 (112 - 439)</td>
<td>293 (119 – 382)*</td>
</tr>
<tr>
<td><strong>t pia (ms)</strong></td>
<td>811 (356 - 1752)</td>
<td>809 (564 - 1684)*</td>
</tr>
<tr>
<td><strong>t ria / Ttot (%)</strong></td>
<td>16.2 (4.0 – 24.0)</td>
<td>13.6 (4.0 – 21.0) *</td>
</tr>
<tr>
<td><strong>t pia / Ttot (%)</strong></td>
<td>38.3 (25.0 – 57.0)</td>
<td>42.1 (34.0 – 55.0) *</td>
</tr>
<tr>
<td><strong>CV dia (%)</strong></td>
<td>48.9 (27.9 – 72.9)</td>
<td>46.2 (28.0 – 70.3)</td>
</tr>
<tr>
<td><strong>CV int(%)</strong></td>
<td>22.3 (9.1 - 35.0 )</td>
<td>23.6 (8.99 – 37.5)</td>
</tr>
</tbody>
</table>

* P < 0.05 with Wilcoxon test for paired measurements compared to baseline measurement
The mean breath by breath variability, expressed as CV, of the diaphragm at baseline lung function measurement and post-salbutamol lung function measurement. 1 rEMG-measurement without the face mask before baseline lung function measurements was started. 2 lung function measurement with face mask was started. 3 rEMG measurement without face mask 10 minutes after administration of a β₂-agonist. 4 lung function measurement with face mask was started 10 minutes after administration of a β₂-agonist.

Electrical activity

The electrical activity of the diaphragm increased significantly (P < 0.05) when the face mask was placed (Baseline-T1) compared to Baseline-T0. The same significant increase (P < 0.05) in electrical activity was found when the face mask was placed after salbutamol inhalation (post-salbutamol-T1) compared to post salbutamol-T0. There was no significant differences between the Baseline-T0 and post-salbutamol-T0 (P = 0.07)
Variability

The mean breath by breath variability, expressed as CV of the intercostal muscles and diaphragm were 22.3% and 48.9%, respectively at baseline measurement, and 23.6% and 46.3%, respectively at post-salbutamol measurement. Post-salbutamol-T0 (CV 55 %) was significantly higher (P < 0.05) compared to baseline-T0 (CV 48.8%) (figure1).

Response to the onset of the face mask load

Fig 2 shows the response of the tidal breathing parameters (f, V_T, V_E, t_PTEF/te) and rEMG parameters (t_ria/t_tot,EMG and t_pia/t_tot,EMG) to the elastic and compliant face mask load of the three sequences of thirty breaths (T1, T2, T3) at baseline measurement and post-salbutamol measurement. There is a significant difference between both measurement sequences for f, t_ria/t_tot,EMG and t_pia/t_tot,EMG at T1 and for t_PTEF/te at T2 and T3. We found a significant increase (P < 0.05) of V_T and V_E between T1 and T2 at baseline measurement and post-salbutamol measurement. There was also a significant increase of t_PTEF/te between T1 and T2 at baseline measurement.

Relationship between FRC, tidal volume and rEMG

We found no significant difference in FRC between baseline lung function measurement and post-salbutamol measurement. We determined no relation between FRC and t_ria/t_tot,EMG or t_pia/t_tot,EMG in infants with recurrent wheeze before and after administration of a β2-agonist. Tidal volume (mL/kg) was negatively related to t_ria/t_tot,EMG (r=0.67, r²=0.45, P < 0.05) at baseline lung function measurement. After salbutamol inhalation, this negative relationship became weaker, but still significant (r=0.55, r²=0.3, P < 0.05).
Figure 2)

The response of the tidal breathing parameters \( (f, V_T, V'_E) \) and rEMG parameters \( (t_{ria}/t_{tot,rEMG}, \ t_{pia}/t_{tot,rEMG}) \) to the onset of the elastic and compliant face mask load at three sequences of thirty breaths at baseline lung function measurement and post-salbutamol measurement. 

**Solid black line**: baseline lung function measurement; **solid grey line**: post-salbutamol lung function measurement

* \( P < 0.05 \) with the Wilcoxon test of the paired measurements (between Baseline-T1 and Post-salbutamol-T1)
Discussion

Using lung function measurements according to recently defined standards, we observed a significant reduction in $t_{PEF}/t_E$ and $t_{dia}/t_{tot,EMG}$ and a significant increase of the $T_V$ and $t_{pia}/t_{tot,EMG}$ after administration of salbutamol in infants with recurrent wheeze. Furthermore, we found a significant increase in the breath by breath variability after salbutamol. There was a difference in response of tidal breathing parameters and rEMG parameters to the onset of the face mask after inhalation of salbutamol in comparison to baseline lung function values. FRC remained similar before and after administration of a $\beta_2$-agonist. We found no correlation between FRC and $t_{dia}/t_{tot,EMG}$, or $t_{pia}/t_{tot,EMG}$. We found a negative significant association between $t_{dia}/t_{tot,EMG}$ and $T_V$.

Comparison with other studies

In addition to our studies in healthy infants and infants with CLD (Hutten 2x), this is the first study in wheezy infants that investigates bronchodilating properties of a $\beta_2$-agonist measured with combined rEMG measurements and matched tidal breathing measurements at airway opening adhering the new standards 9-11. There are studies that show a positive effect of a $\beta_2$-agonist 2-3 but also studies that found no effect 4-5 for tidal breathing parameters and lung volume. These latter observations are in line with our observation that the use of $\beta_2$-agonist did not improve tidal breathing parameters and FRC.

Other studies investigated the effect of $\beta_2$-agonist on pulmonary mechanics and found a positive effect of salbutamol on airway mechanics 19,20. A more comprehensive picture of the changes that occur in pulmonary mechanics after exposure of $\beta_2$-agonist can be achieved when lung mechanics are measured in relation to changes in respiratory muscle activity. We found significant differences in respiratory muscles activity after inhalation of salbutamol expressed by an increase in the variability of respiratory muscle activity, changes in the delay between start of inspiratory muscle activity and the resulting flow and changes in respiratory muscle activity during expiration. All these changes in infants with recurrent wheeze indicate that breathing becomes easier after inhalation of salbutamol.
Interpretation of the findings and possible mechanism

Lung mechanics are a dynamic equilibrium of the complex interaction between control of breathing, respiratory muscles and the mechanical properties of the respiratory system. It is likely that such a system shows large fluctuations in its behaviour and behaves like a dynamical nonlinear system. Not only tidal volume shows fluctuations over time, but also the relative contribution of the respiratory muscles to flow fluctuates over time. These fluctuations may be part of the adaptive capacity of the respiratory system to external influences like drugs.

The delay between the start of the respiratory muscles activity and resulting flow appeared to be significantly shorter after bronchodilation. In adults with chronic obstructive pulmonary disease, albuterol enhances respiratory muscle activity by improving length-tension relationship of the diaphragm rather than by improving contractility of the diaphragm. An improvement of the length-tension relationship ensures that the diaphragm needs less power to overcome the inertial forces to generate inspiratory flow. Although, the difference in end-expiratory volume was not significant in our study, a decrease of the FRC may cause a less flattened diaphragm at the end of expiration leading to an improved length-tension relationship.

Unlike in healthy infants and infants with CLD, we found no relation between FRC and $t_{rih}/t_{tot,EMG}$ or $t_{pia}/t_{tot,EMG}$. We propose that this can be explained by the stiffness of the chest wall. In younger infants, end-expiratory volume level is not only determined by passive mechanical factors such as thoracic and pulmonary elastic properties, but also by active control mediated through intercostals and diaphragmatic muscle activity. Transition from the breathing strategy of a dynamically maintained FRC to a more adult strategy of a passively maintained FRC occurred at the end of the first year. The median age of the infants measured grouping this study was almost one year, which means that the compliance of the chest wall is lower than the infants with a post-
menstrual age of 45 weeks measured in the two earlier studies. Chest wall stiffness relative to the lung may have profound significance regarding changes in respiratory system function with age, such as an improved ability to maintain adequate end-expiratory volume.

Clinical relevance

The evidence of benefit of β₂-agonist in the management of recurrent wheeze in the first two years of life is conflicting. To monitor effectiveness of β₂-agonist it may not enough to measure tidal flow and lung volume alone. In order to obtain additional information on the underlying response, our findings demonstrate that combined rEMG measurements with matched tidal flow can improve the understanding of changes in lung function and neural drive in infants with recurrent wheeze before and after administration of a β₂-agonist.

The transcutaneous way of assessing electrical activity of the intercostals muscle and diaphragm is favourable in infants with recurrent wheeze since it is non-invasive. Furthermore, it is possible to measure the electrical activity without sedation. In conclusion, rEMG measurements are suitable and capable of measuring a positive response on β₂-agonist, it can be done non-invasively and without the requirement the infant to be sedated.

Methodological strengths and limitations

To our knowledge, the interaction between muscle activity, flow and lung volume in sedated infants with recurrent wheeze before and after bronchodilation has never been studied according the recently defined standards of lung function testing. Sedation was administered by means of chloral hydrate. Information regarding the effects of chloral hydrate on tidal breathing parameters and respiratory control in infants is limited and conflicting in nature. Mallol et al described that wheezy infants with baseline arterial oxygen saturation less than or equal to 94% are more susceptible to central respiratory depression following sedation with chloral hydrate. In our group the arterial oxygen saturation remained always higher than 95% during the complete sedation period. In healthy infants, Lees et al have not identified an effect of chloral
hydrate on the ventilatory drive. There is also no effect of chloral hydrate on the activity of the diaphragm.

**In summary**

Although tidal volumes and FRC were similar in infants with recurrent wheeze before and after administration of salbutamol, the temporal dynamic interaction between respiratory muscle activity, resulting flow and lung volume was altered. The temporal relationship of rEMG to flow and the increase of adaptive variability after bronchodilation provide additional information on coping mechanisms in infants with recurrent wheeze treated with a β2-agonist which is not obvious in tidal breathing and lung volume measurements alone.

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References


