Histamine induced airway response in pre-school children assessed by a non-invasive EMG technique

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Summary The aim of the study was to investigate the association between surface electromyographic (EMG) activity of the diaphragm and intercostal muscles, and clinical symptoms (wheeze, cough, increased respiratory rate and prolonged expiration) during bronchial challenge testing and after administration of salbutamol in asthmatic pre-school children.

A histamine challenge test was performed in 20 asthmatic pre-school children. The histamine dose at the appearance of 1 or more clinical symptoms was defined as the maximum histamine provocation dose (PDcs). The clinical symptoms were recorded with a microphone over the trachea. The logarithm of the EMG-Activity-Ratio (log EMGAR; mean peak activity ratio to baseline of respiratory muscles during tidal breathing) was used as EMG parameter.

In both the diaphragmatic and the intercostal log EMGAR values a linear increase was observed in the four histamine dose-steps prior to PDcs. At PDcs the mean log EMGAR of the diaphragm (di) and intercostal muscles (int) was significantly increased as compared to the baseline values. After administration of salbutamol the log EMGARDi and log EMGARint returned to baseline values and the clinical symptoms normalized in all children. At PDcs, no significant differences in the log EMGAR values could be detected at the appearance of the distinctive clinical symptoms, which suggests that wheezing is not the only indicator for the detection of airway responsiveness in young children.

We found a linear association between histamine dose and the increase in surface diaphragmatic and intercostal respiratory EMG activity during a bronchial challenge test in pre-school asthmatic children, which returned to baseline values after inhalation of salbutamol. These findings support the idea that EMG measurements of the diaphragm and intercostal muscles may offer an opportunity to estimate airway response in young children in an alternative way.

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Introduction

The accumulating evidence of an increased incidence of asthma in early childhood and the impact of early treatment on pulmonary function...
outcome both justify the development of reliable methods to evaluate airflow limitation and bronchial responsiveness in the pre-school child.\textsuperscript{1,2} Several methods have been used to assess bronchial responsiveness in this age group.\textsuperscript{3} However, most of the methods are not used routinely because none of them are easily applicable.

A method to assess bronchial responsiveness is based on detecting audible clinical symptoms over the chest or trachea.\textsuperscript{4-7} In earlier studies we found in asthmatic school children that the appearance of wheeze, cough, a prolonged expiration, and an increased respiratory rate corresponded well with a 20% fall in FEV\textsubscript{1} during a bronchial challenge test.\textsuperscript{8,9} Wheeze by itself was found to be an insensitive indicator for assessing bronchial responsiveness.

In the process of a study for a method to assess airway response in an indirect way, allowing for a minimum of co-operation from the child, we developed a non-invasive technique for monitoring respiratory muscle activity.\textsuperscript{10,11} In recent studies we found that the respiratory EMG method correlated with the maximum fall in FEV\textsubscript{1} during a histamine challenge in asthmatic school children.\textsuperscript{10,11} Moreover, the respiratory EMG method correlated well at different degrees of airflow limitation and the signal appeared to be reproducible during tidal breathing with and without airflow limitation in school children with asthma.\textsuperscript{11,12} In pre-school children we showed that the respiratory EMG method was reproducible during tidal breathing without airflow limitation.\textsuperscript{12}

The aim of the study was to investigate the association between surface electromyographic (EMG) activity of the diaphragm and intercostal muscles, and clinical symptoms (wheeze, cough, increased respiratory rate and prolonged expiration) during bronchial challenge testing and after administration of salbutamol in asthmatic pre-school children.

**Methods**

**Patients**

A histamine challenge was performed in 20 pre-school children (8 males, 12 females), between the ages of 2 and 6. The children were diagnosed as having asthma according to the International Consensus Report on Diagnosis and Management of Asthma\textsuperscript{13} and attended the outpatient clinic of the Emma Children’s Hospital at the University Hospital of Amsterdam. All suffered from recurrent periods of coughing, wheezing and dyspnoea. Children with lung diseases other than asthma were excluded from participation in the study. All children were free of complaints and symptoms of pulmonary origin on the day of the measurements. All children reacted well on \( \beta \)-adrenergic drugs and used these drugs on demand. Thirteen children were treated with inhaled corticosteroids. The children avoided short and long acting bronchodilator therapy 8 and 24h, respectively, before the measurements. Inhaled corticosteroid therapy was continued during the study. The children were measured in an upright sitting position with their hands resting on their legs. The Medical Ethics Committee of the University Hospital of Amsterdam approved the study. Informed consent from the parents was obtained prior to inclusion in the study.

**Histamine challenge**

For histamine inhalation we used a calibrated De Villbiss 646 nebulizer (De Villbiss, Somerset, MA, USA) with an output of 0.13 ml/min. The aerosol was delivered into a soft clear plastic facemask (Vital Signs, Inc., Totowa, USA) to provide a good seal on the patients, and inhaled through the mouth. In order to avoid an effect of histamine on nasal resistance all children wore a small nose clip, so that the dead space was not increased. The children inhaled an aerosol of 0.9% phosphate-buffered saline solution (PBS) during 2 min of tidal breathing, as a control for the histamine-challenge test. Subsequently, at 5-min intervals, doubled histamine aerosol concentrations were administered from 0.03 mg/ml up to a maximum of 8 mg/ml during 2 min of tidal breathing as well. In between dose steps, clinical symptoms were recorded over the trachea for 2 min, starting 1 min after administration of each dose of histamine during quiet respiration. The provocation test was terminated when 1 or more of the following clinical symptoms were observed: (1) wheeze, (2) persistent cough, (3) prolonged expiration, (4) increased respiratory rate, or (5) when the maximum dose of histamine was reached. For definition of the criteria see ‘Tracheal auscultation’. Bronchial responsiveness was defined as the histamine provocation dose at which 1 or more of these clinical symptoms was observed (PDCs). After reaching the PDCs and/or the maximum dose of histamine, 4 puffs of 100\( \mu \)g salbutamol dose-aerosol were administered with a Babyhaler. A 2-min recording of the lung sounds was repeated 10 min after inhalation of salbutamol to make sure that the clinical symptoms normalized.
Trachea auscultation

A microphone (Wip & Broos, Groningen, The Netherlands) was placed in the suprasternal notch and attached to the skin with two-sided adhesive tape rings. The clinical symptoms were stored on tape (DT-120 Rn, Sony), using a digital audio tape recorder (DTC-59 ES, Sony). The clinical symptoms were analysed directly by the investigator (E.M.) and classified as wheeze, persistent cough, prolonged expiration, and increase in the respiratory rate. Cough was scored when it appeared and was persistent, defined as during 1 min or more continuously coughing after inhalation of histamine. Prolonged expiration was scored when the duration of expiration exceeded the duration of inspiration. An increase in the respiratory rate was defined as an increase of 50% or more from the baseline respiratory rate. As a control, a second analysis of the clinical symptoms was performed from the audio tape recordings. During this second analysis the investigator was unaware of patient characteristics and histamine concentrations.

Electromyographic recordings

A schematic presentation of the equipment used in the study is shown in Fig. 1. Respiratory electromyographic (EMG) signals were recorded continuously. Surface EMG of the diaphragm and intercostal muscles was derived from pairs of single electrodes (disposable Neotrode, ConMed Corporation, New York, USA). To obtain electrical activity from the diaphragm, 2 electrodes were placed bilaterally below the costal margin in the nipple line. To obtain electrical activity from the intercostal muscles, 2 electrodes were placed bilaterally, 1 each in the second intercostal space left and right. A common electrode was placed at the height of the sternum.

The electrodes were connected to a portable Porti-16 front-end (TMS International, Enschede, The Netherlands) by means of shielded cables to avoid interference pick-up. To prevent loss of electrode signal to the cable capacity, a low impedance version of this electrode signal was fed back to the shield (guarding). The front-end measured, conditioned and digitized the analog signals, and pre-processed the digital signals. The Porti-16 front-end configuration comprises 8 bipolar electro-physiological (EXG) channels and 8 differential physical (AUX) channels. The bipolar EXG channels have high input impedances (> 2 GΩ). The common mode signal range is 6 V, the differential signal range is 300 mV and the common mode rejection ratio is > 100 dB at 50–60 Hz. Analogue high-pass or low-pass filters are absent so that the analogue signals cannot be degraded before sampling. Firstly, a surface EMG signal is not a periodic signal but more or less random noise modulated by muscle activity, so in principle an AA filter was not needed. Secondly, the A–D converter as used was of
the sigma-delta type. The principle of this method is in short that at a very high sample frequency (570 kHz) a numeric representation of the signal (sigma) is made by updating sigma with the difference (delta) of the input signal and the previous sigma. This updating is performed by means of a high order digital low-pass (decimation) filter. The data stream of the decimation filter is sub-sampled with the output sample frequency. The cut-off frequency of the digital filter is automatically set to 0.34* the output sample frequency, so acting as an inherent AA filter. To prevent aliasing at the 570 kHz primary sample frequency a simple first order low-pass analogue filter at 5 kHz was sufficient. Although the maximum sample frequency of the front-end is 2 kHz, the sensitivity for the detection of respiratory muscle activity during tidal breathing was optimal at a sample frequency of ~400 Hz. The ADC puts out samples with a resolution of 22 bits, resulting in a least significant bit of 71.5 nV for the differential signal. The total amplifier and ADC noise is <2 μVpp. The EXG signal was transformed into an EMG signal by means of a digital first-order high-pass filter (time constant = 0.01 s), as an electro-physiological signal is characterized by the position of the electrodes in relation to the electrically active tissue and its signal properties.

Substantial heart activity (mainly QRS complexes) interferes with the diaphragmatic and intercostal EMG signals measured at the trunk. This heart activity was removed from the respiratory muscle activity as described by O’Brien et al. In short, the QRS complexes were detected and stretched to a standard pulse width of 100 ms. During this pulse a cut was made in the slightly delayed (40 ms) EMG signal in order to filter out the QRS complexes completely (so-called ‘gated EMG’). Next, the gated EMG was rectified and averaged with a moving time window of T = 200 ms. Finally, the missing signal in the gate was filled with the running average resulting in a fairly good interpolation during the gate and an almost QRS-free averaged EMG signal. More detailed technical aspects of the measurements and measurement devices were described in a recent paper.

The EMGAR method is based on the relation of the inspiratory neural drive needed to reach a certain lung volume at a given test moment with that at a reference moment, acting as baseline. The peak in the averaged electrical activity of the respiratory muscle represents the end of increasing lung volume, the peak amplitude represents the amount of neural drive necessary to reach end-inspirational lung volume. To avoid contamination of the peak values by tonic activity and instrumental noise, especially at low peak values, the tonic activity was eliminated by the vectorial subtraction of the bottom activity (containing the vectorial sum of the tonic activity and the instrumental noise) from the peak values.

Data analysis and statistics

During the histamine challenge test, the respiratory EMG signals were recorded continuously. To be able to compare both methods, we selected the part of the continuous EMG registration during tracheal auscultation (2 min in between histamine dose steps, starting 1 min after administration of each dose of histamine) for data analyses. Cough periods were isolated and eliminated from EMG recordings used for calculating the EMGAR. For analysis of the EMG signals we calculated the EMG-Activity-Ratio (EMGAR), which can be represented as the ratio of the mean peak-to-bottom averaged EMG value during airway response and the mean peak-to-bottom averaged EMG value at baseline. A logarithmic conversion (log EMGAR) was used to make the relative change in EMG activity symmetric around the unity value. For example, a log EMGAR of 1 means an increase in EMG activity with a factor of 10, a log EMGAR of −1 means a decrease with a factor of 10, compared to the baseline value. For the calculation of the mean peak-to-bottom value a minimum of 6 tidal breaths was used, as described in detail in a recent paper. A two-tailed paired t-test was used for statistical analysis. A p ≤ 0.05 was considered to be statistically significant.

Results

The characteristics of the children and results of the bronchial challenge tests are presented in Table 1. All children had a positive challenge test (PDcs). In all but 1 (child 11) challenges an increase in diaphragmatic and intercostal EMG activity was detected at the dose step at which 1 or more clinical symptoms appeared (PDcs).

In Fig. 2, an example of the averaged diaphragmatic EMG recording during a bronchial challenge test is shown (child 5). Both the diaphragmatic and the intercostal EMGAR values increased in association with the appearance of clinical symptoms during the process of an increasing airway response. However, during this process of airway response alternating activity of the diaphragm and intercostal muscles was observed in nine individuals.
<table>
<thead>
<tr>
<th>Child No.</th>
<th>Age (years)</th>
<th>Histamine PDCs (mg/ml)</th>
<th>Log EMG-activity-ratio</th>
<th>Clinical symptoms</th>
<th>Additional symptoms</th>
<th>After salb.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diaphragm</td>
<td>At PDCs</td>
<td>After salb.</td>
<td>At PDCs</td>
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<td>2</td>
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<td>0.13</td>
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<td>3</td>
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<td>0.03</td>
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<td>0.57</td>
<td>-0.04</td>
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<td>-</td>
<td>0.31</td>
<td>-</td>
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<tr>
<td>20</td>
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<td>4.0</td>
<td>0.31</td>
<td>0.12</td>
<td>0.50</td>
<td>-0.43</td>
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</table>

Note: Log EMG-Activity-Ratio = logarithm of the ratio of the current mean peak-to-bottom value of EMG activity, to that at baseline; PDCs = histamine provocation dose at which the appearance of clinical symptoms was observed; prol. expir. = prolonged expiration; respir. rate = respiration rate. There are 3 missing values because of technical problems.
Figure 3 shows the mean ± standard deviation of the log EMGAR values of the diaphragm and intercostal muscles for all children. In both the mean diaphragmatic and intercostal EMG activity a linear increase was observed in the 4 histamine dose steps prior to PDcs. At PDcs, the mean log EMGAR of the diaphragm and intercostal muscles was increased with a factor 2.7 (0.43 ± 0.18, $P = 0.004$) and with a factor 3.2 (0.51 ± 0.34, $P = 0.005$), respectively, as compared to the mean baseline values. Ten minutes after administration of salbutamol the diaphragmatic and intercostal log EMGAR returned to baseline values in all challenges.

In 10 out of 20 children the challenge test was terminated because of wheezing, in eight because of persistent cough and in two children because a prolonged expiration was observed. In 15 of 20 positive challenges a combination of wheeze, persistent cough, a prolonged expiration or an increased respiration rate was detected. Most children (85%) coughed at the histamine dose at which one or more of the four clinical symptoms were observed (PDcs). The clinical symptoms used in the present study, for determining the PDcs, do not necessary reflect the same degree of response. However, no significant differences in diaphragmatic and intercostal log EMGAR values could be detected at the appearance of the different clinical symptoms at PDcs.

### Discussion

This study shows an increase in the mean surface diaphragmatic and intercostal log EMG-Activity-Ratio in association with the appearance of clinical symptoms during a bronchial challenge test in asthmatic pre-school children. Ten minutes after administration of salbutamol the diaphragmatic and intercostal log EMGAR returned to baseline values in all challenges.

The applicability of the respiratory EMG technique has been described in patients of all ages for monitoring disordered respiratory behaviour, including diaphragmatic inactivity from phrenic nerve injury, augmented expiratory muscle activity, diaphragmatic activity in the presence of a tension pneumothorax, weaning infants from ventilators, neural drive and inspiratory neuromuscular coupling in patients with asthma. Although the transcutaneous EMG technique could serve as a useful tool in assessing breathing patterns and airways obstruction (indirectly) in asthmatic patients, this method is still controversial. It has been argued that with this technique, difficulties arise in maintaining electrode orientation with respect to the muscle fibres and in controlling for influences of variable muscle-to-electrode distance, because of variations in the amount of subcutaneous fat. However, we minimized the above mentioned influence by using the ratio of the averaged electrical muscle activity at a given level of airflow limitation in relation to the baseline (EMG Activity Ratio). Using this ratio, constant factors that influence the amount of electrical activity measured at both instances will be reduced to unity and after logarithmic transformation (log EMGAR) to zero, in fact correcting the actual value for the baseline value. In the present study there were three missing values because of technical problems. However, the assessment of airway response in an indirect way by measuring the surface diaphragmatic and intercostal muscle
activity during bronchial challenge testing in pre-school children is innovative. With the development of new software, we hope to reduce the amount of missing values in future studies.

The diaphragmatic and intercostal EMGAR values increased in association with the appearance of clinical symptoms during airway response. A larger variability in intercostals EMG activity was found compared to diaphragm EMG activity, as can be seen in Fig. 3. This difference in variability may be explained in the functional characteristics of the respiratory muscles. As the diaphragm is the
principal inspiratory muscle, the main function of the intercostal muscles during tidal breathing is rib stabilization. When ventilation needs increase, for example during histamine challenge in asthmatic patients, the accessory inspiratory muscles are recruited. However, during the process of airway response, alternating activity of the diaphragm and intercostal muscles was observed in some individuals (Table 1). For example, we found in 2 challenges (patients 2 and 16) a more pronounced increase in EMGAR of the diaphragm at PDcs, while in two other challenges (patients 8 and 13) a more pronounced increase in EMGAR of the intercostal muscles was observed at PDcs. The activity of the diaphragm and the intercostal muscles appeared to alternate at the different histamine dose steps, suggesting a shift from chest to abdominal breathing. Some children may respond with a more expressed abdominal breathing pattern while others prefer chest breathing or the combination of both. However, in spite of these possible different breathing strategies, we found a linear increase in both diaphragmatic and intercostal mean log EMGAR values in the four histamine dose steps prior to PDcs. Therefore, monitoring both the diaphragm and the intercostal muscle activity could provide additional information in the process of estimating airway response in pre-school children. As the histamine dose-steps increased exponentially, it may be concluded that the increase in peak respiratory EMG activity bears a linear relation with the administered histamine dose in asthmatic children.

In the present study we used the method as based on detecting audible clinical symptoms over the trachea. As most of the methods to assess the bronchial responsiveness in this specific age group in clinical practice are not easily applicable or less reliable, we did not attempt to measure FEV\(_1\) values or other flow measures. In an earlier study we found that lung sounds obtained with a microphone placed on the trachea corresponded well with a 20% fall in FEV\(_1\) after methacholine challenge in school children. However, in the latter study wheeze by itself was found to be not sensitive for bronchial responsiveness. A persistent cough, an increased respiratory rate, and a prolonged expiration were more frequently found during bronchial provocation testing. In contrast, Springer et al. and Noviski et al. found that only the occurrence of wheeze correlated well with a decrease in FEV\(_1\). In addition, Noviski et al. observed the occurrence of cough and increased respiration rate, but found no association with either the methacholine concentration causing wheeze or the concentration causing a fall in FEV\(_1\) of 20% (19). Springer et al. found that cough was not helpful in determining the end point (PDcs). Considering these contradictory results it may be possible that the clinical symptoms used in the present study, for determining this end point of provocation, do not necessarily reflect the same degree of response. In addition, it is possible that histamine or methacholine may stimulate irritant receptors in the airways, resulting in cough rather than inducing bronchoconstriction. Cough is only an indirect consequence of bronchoconstriction mediated by irritant receptor stimulation. As monitoring the activity of the diaphragm and intercostal muscular system is the most direct way to obtain information on respiratory muscle function, this inter-individual difference in response to histamine could be detected by measuring the EMGAR of the diaphragm and intercostal muscles. However, when comparing the respiratory EMGAR values of the children who responded to histamine with different clinical symptoms, we could not find a significant difference in EMGAR of the diaphragm and intercostal muscles at the moment that these different clinical symptoms appeared (at PDcs). Although larger sample sizes would be preferable,

### Table 2

<table>
<thead>
<tr>
<th>Clinical symptom</th>
<th>N</th>
<th>Log EMGAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Diaphragm</td>
</tr>
<tr>
<td>Wheeze</td>
<td>10</td>
<td>0.44 ± 0.24</td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>0.44 ± 0.14</td>
</tr>
<tr>
<td>Prol. expiration</td>
<td>2</td>
<td>0.39 ± 0.09</td>
</tr>
<tr>
<td>Increased respir. rate</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Diaphragmatic and intercostal log EMGAR was not significantly different at the appearance of the different clinical symptoms at PDcs.

N = number of patients.
the findings in the present study makes it likely that wheezing is not the only indicator for the detection of airway responsiveness in asthmatic pre-school children. Our observation is supported by Guirau and colleagues, who investigated the correlation of airway responsiveness in asthmatic pre-school children under 2 years of age, and the clinical evaluation of these children at admission and at follow-up. They found a significant inverse gradient between PCwheeze and the severity of clinical symptoms obtained during clinical evaluation.

The use of EMG recordings to evaluate diaphragmatic activation during tidal breathing and histamine-induced airflow limitation has recently been criticized because an artefact might occur, created by changes in lung volume. It is well established that functional residual capacity (FRC) often increases, accompanied by an increase in tonic activity of the diaphragm and intercostal muscles during spontaneous breathing or during a histamine-induced airflow limitation. In the EMG curves in the present study we noticed that the tonic activity, defined as electrical activity in the EMG present at end expiration, slightly increased during histamine induced airway response (results not shown). Although others have described that voluntary diaphragm EMG is systematically affected by changes in lung volume, Beck et al. demonstrated that the diaphragm EMG was not artifactually influenced by lung volume at submaximal contraction levels. It should be mentioned that, in contrast to our study, an oesophageal electrode was used in these studies to measure diaphragm activity. Moreover, in a previous study we observed that histamine-induced changes in tonic activity of the respiratory muscles did not modify the association between the FEV1 and the EMG of the diaphragm and intercostal muscles.

In conclusion, we found an increase in surface diaphragmatic and intercostal log EMGAR values in association with the appearance of clinical symptoms during bronchial challenge testing in asthmatic pre-school children. After administration of salbutamol the diaphragmatic and intercostal log EMGAR returned to baseline values in all challenges. These observations indicate that in preschool children histamine induced airway response and reversibility after inhalation of salbutamol may be well reflected in the amplitudes of the diaphragm and intercostal muscles.

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References


