Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children

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1Beatrix Children’s Hospital, University Hospital Groningen, 9700 RB Groningen; 2Department of Medical Physiology, University of Groningen, 9700 RB Groningen; and 3Emma Children’s Hospital, Academic Medical Center/University of Amsterdam, 1105 AZ Amsterdam, The Netherlands

Sprikkelman, Aline B., Leo A. Van Eykern, Marlies S. Lourens, Hugo S. A. Heymans, and Wim M. C. Van Aalderen. Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children. J. Appl. Physiol. 84(3): 897–901, 1998.—We investigated whether an increase in transcutaneous electromyographic (EMG) activity of the diaphragm and intercostal muscles corresponds to the concentration of histamine that induces a 20% fall in the forced expiratory volume in one second (FEV1; PC20). Eleven asthmatic children (mean age 11.9 yr) were studied after they were given histamine challenge. EMG activity at PC20 or at the highest histamine concentration was compared with activity at baseline by calculating the ratio of the mean peak-to-peak excursion at the highest histamine dose to that at baseline [EMG activity ratio (EMGAR)]. In all children reaching PC20, an increase in diaphragmatic and intercostal EMGAR was observed. No increase was found at the dose step before PC20 was reached. In six challenges, no fall in FEV1 was induced, and no increase in EMGAR was seen. In two challenges, no fall in FEV1 was induced, but increase in diaphragmatic or intercostal EMGAR was observed. Increase in the electrical activity of the diaphragm and intercostal muscles in asthmatic children corresponds closely to a 20% fall in FEV1 induced by histamine challenge.

MATERIALS AND METHODS

Subjects. Eleven children (4 boys) with mild to moderate asthma (7a), without concomitant diseases, aged 9–15 yr (mean 11.9 yr), were recruited from the outpatient clinic of Beatrix Children’s Hospital in Groningen, The Netherlands. All children had a concentration of histamine that induces a 20% drop in FEV1 (PC20) <8 mg/ml in the year before this pilot study was performed. All children used daily inhaled corticosteroids, with a dosage ranging from 200 to 400 µg twice daily and used bronchodilator therapy on demand. None of the children used oral corticosteroids. The mean baseline Tiffeneau index (FEV1/vital capacity) before the histamine inhalation challenge test was 85% of predicted (range 76–97%). Four children performed one histamine challenge test. Seven children performed two histamine challenge tests on 2 days, at the same time of day, and separated by 24 h to 1 wk. The repeated challenge tests were part of a more extended study that aimed to investigate the reproducibility of the appearance of lung sounds during the histamine challenges (results will be published elsewhere). All consecutive subjects who performed repeated histamine-challenge tests in the extended study were included in the present study. The first challenge with histamine was requested as part of the children’s routine evaluation. No child had a history of a respiratory tract infection for at least 1 mo before the challenge tests or between the 2 test days.

Bronchodilator therapy was withheld for at least 8 h (short acting) or 24 h (long acting) before testing to allow histamine-induced bronchoconstriction to occur. Inhaled corticosteroids were continued. Informed consent of the child and parents was obtained. The study was approved by the Medical Ethics Committee of the University Hospital Groningen.

Inhalation-challenge test. The children performed spirometric tests by using a water-sealed spirometer (Lode, Groningen, The Netherlands). The best result of three FEV1 attempts was used for analysis. Histamine inhalation was preceded by baseline lung function measurements, followed immediately by the inhalation of phosphate-buffered saline as a control. After inhalation of the phosphate-buffered saline, doubling concentrations of histamine (beginning with 0.03 mg/ml to a maximum of 16.0 mg/ml) were administered during four inhalations through the Asthma Provocation System nebulizer (version SA, Jæger), with a calibrated output of 5 µl per puff. The aerosol was delivered into the mouthpiece while the children were wearing a nose clip.
During each inhalation, a deep breath was taken and held for 10 s. Three minutes after the fourth inhalation of the aerosol, FEV₁ measurements were performed. Successive concentrations of histamine solutions were given at 5-min intervals. The provocation tests were discontinued if the FEV₁ decreased by 20% or more from the baseline or when the maximum dose of histamine was reached. Bronchial responsiveness was defined as the total cumulative concentration of histamine inducing a fall of 20% or more in FEV₁, i.e., PC₂₀.

EMG recordings. The electrical muscle activity (EMG) of the diaphragm and intercostal muscles was derived transcutaneously from electrodes [disposable electrocardiogram (ECG)/respiratory impedance-type electrodes; 3M red dot] placed bilaterally in the second intercostal space and below the costal margin in the nipple line, respectively. The electrodes were connected to a preamplifier based on the reference amplifier (Twente Medical Systems, Enschede, The Netherlands) by means of shielded cables to avoid interference pickup. 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 QRS complexes of the ECG are detected easily and stretched to a standard pulse with a width of 100 ms (QRS). During this pulse, a cut is made in the slightly delayed (40 ms) EMG signal, with the purpose of gating out the QRS complex completely (gated EMG). Next, the gated EMG is rectified and averaged with a moving time window of t = 200 ms. Finally, the missing signal in the gate is filled with the ongoing average showing good interpolation during gating, which leads to an almost ECG-free averaged EMG signal (Avg Dia in Fig. 1). The excursions in the averaged diaphragm EMG are of inspiratory nature, and the amplitude changes suggest a form of airflow control (10). For comparison, an indication of the airflow at one of the nostrils is shown, measured by means of a thermistor (see Fig. 1).

In our study, the 1-min EMG measurements were started 2 min after administration of each dose of histamine during quiet respiration and before FEV₁ measurements were performed. During the EMG recordings, the children were asked to sit in an upright position with their hands resting on their legs. EMG activity at PC₂₀ for histamine or at the highest histamine concentration was compared with EMG activity at the baseline by means of calculating the ratio of the mean peak-to-peak excursion at the highest histamine dose to that at baseline, the EMG activity ratio (EMGAR). An increase in EMG activity is denoted by an EMGAR > 1, no increase in EMG activity is denoted by an EMGAR ≤ 1.

The correlation between the maximum fall in FEV₁ and the logarithm of the EMGAR of the diaphragm and intercostal...
The intercept, with unrestricted variance matrix, and assuming independent within-person errors with constant variance.

### RESULTS

The results of the study are presented in Table 1.

Seven children performed two histamine challenge tests on 2 days, and four children performed one challenge test. Six children had a positive histamine challenge test (PC20 < 16.0 mg/ml) on 1 test day, one child on 2 test days. Three children had a negative histamine challenge test on both test days, one child on 1 test day. In Fig. 2, an example of the diaphragm and intercostal EMG recordings during a histamine challenge test is shown (patient 3). In eight challenges, an increase in diaphragmatic and intercostal EMG was detected at the dose step that induced a fall in FEV1 of at least 20%. No increase in EMG was observed in the dose step before the PC20-histamine was reached. In one challenge, an increase in diaphragmatic and intercostal EMG was observed at a fall in FEV1 of 17% (patient 4). In another challenge, an increase in intercostal EMG was observed at a fall in FEV1 of 17% was observed (patient 5). In six challenges, no fall in FEV1 was induced, and no increase in EMG of the diaphragm and/or intercostal muscles was detected. In the other two challenges, no fall in FEV1 was induced, but an increase in both diaphragmatic and intercostal EMG (patient 1) and only intercostal EMG (patient 9) was observed, respectively.

In Fig. 3, the correlation between the maximum fall in FEV1 and the logarithm of the EMGAR is shown. The correlation coefficient for the diaphragmatic EMGAR was 0.65 (P = 0.05) and for the intercostal EMGAR was 0.72 (P = 0.01).

### DISCUSSION

We found that an increase of the transcutaneous diaphragmatic and intercostal EMGAR corresponds closely to a histamine-induced 20% fall in FEV1 in asthmatic children. In all children reaching a 20% fall in FEV1 after histamine challenge, an increase in the EMG activity of the diaphragm and intercostal muscles was observed. In these children, no increase in diaphragmatic and/or intercostal EMGAR was found at the dose step before the PC20-histamine was reached. Our observation that EMG activity in asthmatic children increases after histamine-induced bronchoconstriction is in accordance with Haxhiu et al. (4) and Van Lunteren et al. (15, 16), who found an increase in diaphragmatic and intercostal EMG activity after histamine- and methacholine-induced bronchoconstriction in dogs, and with Trippenbach and Kelly (14), who made the same observation in rabbits.

Although our observations are in accordance with observations in animal studies, before this study was performed we were not sure whether the observations in animal studies could be extrapolated to humans. The investigated animals breathe in a supine position and, therefore, might have a different physiological diaphragm mechanism. It should be mentioned that, in contrast to our study, invasive electrodes inserted in the diaphragm and intercostal muscles were used in these animal studies.

To our knowledge, no data have been published on the use of diaphragmatic and intercostal EMG after

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**Table 1. Characteristics of patients and results of lung function testing**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Test</th>
<th>FEV1/VC, %</th>
<th>Histamine PC20, mg/ml</th>
<th>Maximum Fall in FEV1, %</th>
<th>EMG (Ratio)</th>
<th>Respiratory Rate</th>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline PC20</td>
</tr>
<tr>
<td>1</td>
<td>14 M</td>
<td>1</td>
<td>78</td>
<td>9.40</td>
<td>35.0</td>
<td>1.4</td>
<td>1.4</td>
<td>18 17</td>
</tr>
<tr>
<td>1</td>
<td>15 F</td>
<td>1</td>
<td>81</td>
<td>&gt;16.0</td>
<td>0.0</td>
<td>1.3</td>
<td>1.6</td>
<td>18 17</td>
</tr>
<tr>
<td>1</td>
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<td>1</td>
<td>89</td>
<td>&gt;16.0</td>
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<td>0.9</td>
<td>0.6</td>
<td>15 14</td>
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<tr>
<td>1</td>
<td>13 F</td>
<td>1</td>
<td>88</td>
<td>8.00</td>
<td>20.0</td>
<td>1.4</td>
<td>2.4</td>
<td>13 14</td>
</tr>
<tr>
<td>2</td>
<td>10 F</td>
<td>1</td>
<td>95</td>
<td>8.77</td>
<td>41.7</td>
<td>2.2</td>
<td>2.0</td>
<td>16 16</td>
</tr>
<tr>
<td>2</td>
<td>9 M</td>
<td>1</td>
<td>90</td>
<td>&gt;16.0</td>
<td>18.1</td>
<td>1.2</td>
<td>1.3</td>
<td>16 18</td>
</tr>
<tr>
<td>5</td>
<td>10 F</td>
<td>1</td>
<td>90</td>
<td>9.72</td>
<td>43.3</td>
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<td>2.0</td>
<td>21 24</td>
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<tr>
<td>6</td>
<td>9 F</td>
<td>1</td>
<td>92</td>
<td>&gt;16.0</td>
<td>17.1</td>
<td>2.8</td>
<td>0.9</td>
<td>17 17</td>
</tr>
<tr>
<td>7</td>
<td>15 F</td>
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<td>97</td>
<td>&gt;16.0</td>
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<td>0.3</td>
<td>1.0</td>
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<tr>
<td>7</td>
<td>9 F</td>
<td>1</td>
<td>98</td>
<td>&gt;16.0</td>
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<td>0.9</td>
<td>12 12</td>
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<tr>
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<td>88</td>
<td>8.93</td>
<td>34.0</td>
<td>5.0</td>
<td>4.5</td>
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<tr>
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<td>12 M</td>
<td>1</td>
<td>85</td>
<td>&gt;16.0</td>
<td>0.0</td>
<td>1.6</td>
<td>1.1</td>
<td>23 19</td>
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<tr>
<td>11</td>
<td>10 F</td>
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<td>5.76</td>
<td>31.2</td>
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<td>1.3</td>
<td>20 20</td>
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<tr>
<td>11</td>
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<td>1</td>
<td>78</td>
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<td>21.2</td>
<td>3.3</td>
<td>1.8</td>
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</tr>
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</table>

M, male; F, female; FEV1, forced expiratory volume in 1 s; VC, vital capacity; PC20, concentration of histamine causing a 20% fall in FEV1; EMG, transcutaneous diaphragmatic and intercostal electromyographic activity. EMG activity ratio (EMGAR) = (mean peak value highest concentration – base-level value highest concentration)/(mean peak value baseline – mean base-level value baseline).

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histamine- or methacholine-induced bronchoconstriction in the assessment of bronchial responsiveness in humans. Muller et al. (7) found an increase in tonic activity of the diaphragm and intercostal muscles after histamine-induced hyperinflation in adult asthmatic patients. Tonic activity was defined as electrical activity in the EMG present at the end of expiration. In this study, intercostal EMG was recorded with surface electrodes and diaphragmatic EMG with esophageal electrodes. Using esophageal electrodes, Gandevia and McKenzie (2) observed changes in the diaphragmatic EMG activity when posture or lung volume was changed.

The application of surface electrodes is sometimes criticized for possible contamination by the activity of other muscles and for possible effects of variation in posture. However, it has been shown in earlier studies that the electrical activity of the diaphragm detected by surface electrodes is comparable to the activity detected by esophageal electrodes (3, 13). To avoid these contaminations, the children in our study were placed in a sitting position with their hands resting on their legs and they were asked not to move or talk during the recordings. Besides these precautionary measures, we found in two patients (patients 1 and 9) an increase in the EMG activity of the diaphragm and intercostal muscles without a fall in FEV₁ after histamine challenge. Possible causes of these false positives could be changes in posture not observed by us, movement of electrodes over the skin, or changes in lung volume (hyperinflation) not noticed by the investigator. It is likely that children use various breathing strategies during histamine-induced bronchoconstriction, and because of this changes in posture or lung volume may occur, causing an increase in EMGAR. Different breathing strategies such as chest breathing, abdominal

Fig. 2. Diaphragm and intercostal EMG recordings during a histamine-challenge test. Averaged diaphragm and intercostal EMGs are shown at baseline and at dose steps of 2, 4, and 8 mg/ml histamine.

Fig. 3. Correlation between fall in forced expiratory volume in 1 s (FEV₁) and EMG activity ratio (EMGAR) (at a logarithmic scale) of diaphragm and intercostal muscles.

\[ \text{BASELINE} \]

\[ \begin{array}{l}
\text{INTERCOSTAL} \\
\text{DIAPHRAGM}
\end{array} \]

\[ \begin{array}{l}
\text{2 mg/ml} \\
\text{INTERCOSTAL} \\
\text{DIAPHRAGM}
\end{array} \]

\[ \begin{array}{l}
\text{4 mg/ml} \\
\text{INTERCOSTAL} \\
\text{DIAPHRAGM}
\end{array} \]

\[ \begin{array}{l}
\text{8 mg/ml} \\
\text{INTERCOSTAL} \\
\text{DIAPHRAGM}
\end{array} \]

\[ 10 \mu V \]

\[ 10 \text{ s} \]
breathing, or a combination of both are possible and were observed in all patients. An example is shown in Fig. 2. These various breathing strategies result in changes in diaphragmatic and intercostal EMGAR. At baseline, there is mainly intercostal activity, whereas after inhalation of 2 mg/ml histamine, the breathing strategy changes toward more diaphragmatic activity, suggesting a shift from chest to abdominal breathing. After inhalation of 4 mg/ml histamine, the abdominal breathing shifts back to chest breathing again, but after inhalation of 8 mg/ml a strong combination of abdominal and chest breathing is present at first, and both diaphragmatic and intercostal EMGAR are clearly increased.

In conclusion, increase in the EMGAR as a parameter for increased electrical activity of the diaphragm and intercostal muscles in asthmatic children is easy to detect and corresponds closely to a histamine-induced 20% fall in FEV1. In the present study, we initiated the development of an alternative method to recognize the fall in FEV1 of 20% or more, at a certain dose of inhaled histamine, in the assessment of bronchial responsiveness in asthmatic children. The assessment of bronchial responsiveness by measuring the transcutaneous diaphragmatic and intercostal muscle activity during the inhalation challenge could be a method used in younger children who are not able to perform spirometry reliably.

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