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The Risk of Hospitalization and Near-Fatal and Fatal Asthma in Relation to the Perception of Dyspnea*

Rasmi Magadle, MD; Noa Berar-Yanay, MD; and Paltiel Weiner, MD

Background: A life-threatening asthma attack is still of major concern. One of the main goals in treating patients with asthma is identification of the patients at risk of having these attacks. It has been shown that patients who have a near-fatal asthma attack have a blunted perception of dyspnea (POD). The purpose of this study is to measure the POD in patients with asthma, and to relate POD to life-threatening attacks within a 24-month follow-up period.

Methods: The POD was scored using the Borg scale during breathing against a progressive load at 1-min intervals, in order to achieve mouth pressure up to 30 cm H$_2$O, in 113 consecutive asthmatic patients with stable asthma attending an outpatient clinic. All patients were invited to regular follow-up every 3 months for up to 24 months, and all hospitalizations and near-fatal and fatal asthma attacks were recorded. The prebronchodilator morning peak expiratory flow rate (PEFR), daily regular treatment, and $\beta_2$-agonist consumption were recorded in a diary card for the first 4 weeks.

Results: Seventeen patients (15%) had high POD compared to the normal subjects, 67 patients (59%) had POD within the normal range, and 29 patients (26%) had lower-than-normal POD. In the patients with low POD, there was a tendency for higher age, higher female/male ratio, and a longer duration of disease. The rate of severe asthma was higher in the low-POD group than in the normal-POD group, but did not differ from the rate in the high-POD group. The mean daily $\beta_2$-agonist consumption in the patients with low POD was significantly lower ($p < 0.01$) than in the patients with high POD, although the mean PEFR was lower in the low-POD group. During the 2 years of follow-up, the patients in the low-POD group had statistically significantly more emergency department (ED) visits, hospitalizations, near-fatal asthma attacks, and deaths compared to the normal-POD and high-POD groups.

Conclusions: Approximately 26% of the referral subjects with asthma had low POD when compared to healthy matched subjects. Patients with low POD had statistically significantly more ED visits, hospitalizations, near-fatal asthma attacks, and deaths during the follow-up period. Reduced POD may predispose patients to a life-threatening attack.

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Key words: asthma; life-threatening asthma attack; perception of dyspnea

Abbreviations: ED = emergency department; PEFR = peak expiratory flow rate; POD = perception of dyspnea
and to hypoxic hypercapnia in 11 patients with near-fatal asthma. This observation that most patients with near-fatal asthma have blunted perception of dyspnea (POD) suggests that a dysfunction in these defense mechanisms may play a role in near-fatal asthma.

Fatal or near-fatal asthma is undoubtedly severe asthma, but it may not have been manifested in poor lung function or in terms of disturbing the patient very much, leading to consultation with a doctor. In the Barcelona soybean epidemic, patients with near-fatal asthma had fewer symptoms and had attended EDs significantly less than asthmatic patients who did not have near-fatal asthma.

The prognosis of patients with near-fatal asthma is not good. The in-hospital mortality rate is 16.5% in patients who require mechanical ventilation, and an additional 14% of patients die during the following period. We hypothesized that assessment of the POD in patients with asthma will identify patients at risk of having fatal or near-fatal asthma attacks.

**Materials and Methods**

One hundred thirteen patients with stable asthma attending an outpatient clinic (54 male and 59 female patients) were recruited for the study. Our outpatient clinic receives only patients who are referred by their primary physician, and therefore may have more complicated conditions than patients with asthma alone. All patients satisfied the American Thoracic Society definition of asthma, with symptoms of episodic wheezing, coughing, and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented in at least one previous pulmonary function study. Their characteristics are summarized in Table 1. All patients were tested at baseline and were followed up for at least 24 months. The severity of asthma was defined according to spirometric values. Patients with a history of near-fatal asthma attacks were excluded from the study, because these patients are known to have an excessive risk for further fatal or near-fatal attacks. Near-fatal attacks were defined as attacks of asthma requiring treatment with mechanical ventilation or resulting in unconsciousness and severe respiratory failure.

All patients were invited to have regular follow-up every 3 months and were required to be compliant with the recording of prebronchodilator morning peak expiratory flow rates (PEFRs), daily regular treatment, and β2-agonist consumption on a diary card for the first 4 weeks. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all the subjects.

**Table 1—Clinical Characteristics of the Patients With Low, Normal, and High POD**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low POD (n = 29)</th>
<th>Normal POD (n = 67)</th>
<th>High POD (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>42 ± 5.4</td>
<td>39 ± 4.8</td>
<td>32 ± 4.9</td>
</tr>
<tr>
<td>Male/female sex</td>
<td>11/18</td>
<td>37/30</td>
<td>7/10</td>
</tr>
<tr>
<td>Duration of asthma, yr</td>
<td>21 ± 5.0</td>
<td>15 ± 4.6</td>
<td>12 ± 4.1</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>93 ± 6.5</td>
<td>96 ± 6.8</td>
<td>96 ± 6.2</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>75 ± 4.5</td>
<td>85 ± 5.5</td>
<td>90 ± 5.0</td>
</tr>
<tr>
<td>Severity of asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Moderate</td>
<td>12</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Oral glucocorticosteroids</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inhaled glucocorticosteroids</td>
<td>27</td>
<td>67</td>
<td>16</td>
</tr>
<tr>
<td>History of ED visit</td>
<td>9</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>History of hospitalization</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No.

The sensation of dyspnea was measured while the subject breathed through a device similar to that proposed by Nickerson and Keens. Subjects inhaled through a two-way valve (Hans-Rudolph; Kansas City, MO), the inspiratory port of which was connected to a chamber and plunger to which weights could be added externally. The subjects breathed against a progressive load at 1-min intervals, in order to achieve mouth pressures of 0 (no load), 5, 10, 20, and 30 cm H2O. After breathing for 1 min at each level of threshold load, in a protocol similar to the one previously described by Kikuchi and coworkers, with resistive loads, using a method recently published by Larson and associates with the same device as ours, using threshold loads, the subjects rated the sensation of difficulty in breathing (dyspnea) using the modified Borg scale. This is a linear scale of numbers ranking the magnitude of difficulty in breathing, ranging from 0 (none) to 10 (maximal).

**Data Analysis**

Normal POD was defined as mean ± 1 SD of 100 age- and sex-matched normal subjects. Comparisons of dyspnea score and follow-up hospital visits were carried out using the two-way repeated-measures analysis of variance.

**Results**

The data of the POD in the patients with asthma were compared to the data received from 100 age- and sex-matched normal subjects. Seventeen patients (15%) had high POD compared to the mean ± 1 SD POD of normal subjects. 67 patients (59%) had POD within the normal range, and 29 patients (26%) had lower-than-normal POD. The mean Borg scores during breathing against load in the normal subjects was 0.2, 1.7, 2.7, 3.8, and 4.8 while breathing against loads of 0, 5, 10, 20, and 30 cm H2O, respectively (Fig 1). The mean Borg score during breathing against load in
The asthma patients with within-normal POD was somewhat lower than in normal subjects, but with no statistical significance. The mean Borg score during breathing against a load in the asthma patients with low POD was significantly lower \((p < 0.005)\) than in the normal subjects \((0.1, 0.9, 1.2, 1.8, \text{and} 2.4\) while breathing against loads of 0, 5, 10, 20, and 30 cm \(H_2O\), respectively). The mean Borg score during breathing against a load in the asthma patients with high POD was also significantly higher \((p < 0.001)\) than in the normal subjects \((0.5, 2.8, 4.0, 5.8, \text{and} 6.4\) while breathing against loads of 0, 5, 10, 20, and 30 cm \(H_2O\), respectively).

There was a tendency for higher age, higher female/male ratio, and a longer duration of asthma in the patients with low POD (Table 1). The rate of severe asthma was higher in the low-POD group than in the normal-POD group, but did not differ from that in the high-POD group \((15\% \text{ and} 24\%, \text{respectively})\). However, no correlation was found in the whole group for POD vs FEV1 \(\%\) (Fig 2), POD vs age, and POD vs duration of asthma. In addition, it could be suggested that low POD was associated with a history of ED visits and hospitalizations.

During the 4 weeks of follow-up, the mean daily \(\beta_2\)-agonist consumption in the patients with low POD was significantly lower \((p < 0.01)\) than in the patients with high POD, although the mean PEFR was lower in the low-POD group. It was also lower than that in the normal-POD group, but it did not reach statistically significance (Table 2).

During the 2 years of follow-up, the patients in the low-POD group had statistically significantly more ED visits \((p < 0.001 \text{ and} p < 0.01)\), hospitalizations \((p < 0.001 \text{ and} p < 0.001)\), near-fatal asthma \((p < 0.001 \text{ and} p < 0.001)\), and deaths \((p < 0.001 \text{ and} p < 0.001)\), compared to the normal-POD and the high-POD groups, respectively (Table 3). Three patients died at home. One patient died during an asthma attack, the second patient was found dead in his bed and no autopsy was performed, and the cause of death for the third patient could not be determined. The three remaining patients in the low-POD group died during hospitalization for acute asthma, with mechanical ventilation. It was also noticed that the patients with high POD had signif-

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**Table 2—Morning PEFR and Daily \(\beta_2\)-Agonist Consumption During the First 4 Weeks of Follow-up**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low POD ((n = 29))</th>
<th>Normal POD ((n = 67))</th>
<th>High POD ((n = 17))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta_2)-agonist consumption, puffs/d</td>
<td>1.7 ± 0.2</td>
<td>2.4 ± 0.3</td>
<td>4.1 ± 0.7</td>
</tr>
<tr>
<td>Morning PEFR, L/min</td>
<td>293 ± 31</td>
<td>325 ± 34</td>
<td>334 ± 33</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM.

**Table 3—ED Visits, Hospitalizations, Near-Fatal Asthma, and Death in 113 Patients With Asthma**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low POD ((n = 20))</th>
<th>Normal POD ((n = 67))</th>
<th>High POD ((n = 17))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED visits</td>
<td>32</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>22</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Near-fatal asthma</td>
<td>13</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are presented as No.; patients may had more than one episode.
icantly more ED visits (p < 0.05) than the patients with normal POD, but not hospitalizations, near-fatal asthma attacks, or deaths.

**Discussion**

In this study, we found that approximately 60% of patients with asthma referred to our outpatient clinic had normal POD, approximately 26% of the patients had low POD, and the rest of the patients had high POD, when compared to healthy matched subjects. Patients with low POD tend to be older, have a longer duration of asthma, a higher female/male ratio, a low daily β2-agonist consumption, and statistically significantly more ED visits, hospitalizations, near-fatal asthma attacks, and deaths during the follow-up period.

In the management of bronchial asthma, the subject’s POD serves as one of the most important indexes used to guide treatment. It is well documented that large variations in perception of respiratory symptoms may be observed from one asthmatic patient to another; in 60% of asthma patients, there is no correlation between the POD and simultaneous peak flow measurements. Among the factors that can affect POD related to bronchoconstriction are changes in lung volume, speed of bronchoconstriction, anxiety level, duration of asthma, and age. Low POD may result in undertreatment of asthma, delay modification in treatment, and even predispose patients to fatal asthma attacks. One might think that the severity of the airway obstruction caused the patient’s death. However, death occurred in patients with FEV1 measurements from 53 to 77% of predicted normal values.

The low-POD patients tended to be older and female, and to have more airway obstruction than patients in the other groups. The latter accentuates how low the POD actually was, because usually patients have more dyspnea when they have more airway obstruction.

To investigate the ability of patients to perceive respiratory sensation, either bronchoprovocation testing or resistance/threshold load testing have been used. We prefer the latter test because very often only a few concentrations can be administered during the bronchoprovocation test, whereas assessment of the relation between respiratory sensation and the physical change requires an adequate number of observations over a wide range of stimulus intensity.

It has been shown that there is a close relationship between the sensation of breathlessness and respiratory muscle strength, both in normal subjects and in patients with severe lung function impairment. Thus, it could be argued that our assessment of POD, which compares breathlessness to absolute load rather than that relative to strength, might underestimate POD in subjects with strong respiratory muscles while overestimating POD in subjects with weak respiratory muscles. Furthermore, since our technique does not take intrinsic positive end-expiratory pressure into account, it might overestimate POD in severely obstructed, dynamically hyperinflated subjects. Since our low-POD patients tended to be older and female, and have more airway obstruction than our normal-POD or high-POD patients, we believe that any error resulting from variations in respiratory muscle strength and dynamic hyperinflation would only tend to bring POD estimates closer to normal.

There are relatively few assessments of mortality from asthma in the general population. Although fatal asthma is, almost by definition, difficult, approximately half of those who die have mild or moderate disease on postmortem review. Campbell and associates found that those who died were more likely to be women, to have more comorbidities, to have made more visits to the doctor in the 12 months prior to the attack, to have better self-management skills, and more likely to be receiving nebulized β-agonists. Suggestions also have been made that near-fatal asthma attacks are associated with previous hospital admissions for asthma, increased airway responsiveness and poor control, poor compliance, and a hyperacute form of attack.

The observation made by Kikuchi et al. that most patients with near-fatal asthma had a decreased hypoxic response accompanied by a blunted POD, suggested that a dysfunction in these defense mechanisms may play a role in near-fatal asthma. A blunted POD also was detected by others in association with fatal asthma. Published data suggest that blunted POD is found in patients with stable and unstable asthma and is correlated with the degree of sputum eosinophilia. Although the factors that influence perception of asthma are poorly understood, it seems that low POD is not usually an inborn defect but an acquired and changeable defect.

Although there have been many epidemiologic studies of fatal or near-fatal asthma, the precise mechanisms of life-threatening attacks were not completely elucidated, and concerns about deaths from asthma still exist. Most of the deaths are avoidable if the patients are adequately followed up and treated. To prevent death from asthma, it is important to identify patients who may be at risk of a fatal attack. Unfortunately, a history of a near-fatal asthma attack that required hospitalization and mechanical ventilation is the strongest single predictor
of subsequent death from asthma. The present study shows that patients with low POD, even without a history of near-fatal asthma, are at an increased risk of future hospitalization, a near-fatal asthma attack, or even death from an asthma attack.

The POD is not readily measured in patients with asthma. However, the findings of previous studies and ours have important implications for the prevention of death from asthma. Patients with a low POD should be monitored carefully and more often, and should be educated in self-management. Measurement of the POD should be performed at least once in all asthma patients, to identify those at high risk for a fatal attack. Either technique, the method of breathing against added resistance or added threshold loads, or the methacholine bronchoprovocation test, may be used to identify these patients.

REFERENCES

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