Differentiation between the sensory and affective aspects of histamine-induced bronchoconstriction in asthma

Steven De Peuter a, *, Valentine Lemaigre b, Ilse Van Diest a, Geert Verleden b, Maurits Demedts b, Omer Van den Bergh a

a Research Group for Stress, Health & Well-Being, Psychology Department, University of Leuven, Tiensestraat 102, B-3000 Leuven, Belgium
b Department of Pneumology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

Received 13 June 2006; accepted 14 September 2006
Available online 30 October 2006

KEYWORDS
Asthma; Dyspnea; Emotion; Histamine; Symptom perception

Summary
Respiratory symptom perception research has focused mainly on respiratory sensations. Because dyspnea is multidimensional, affective aspects should be investigated. Patients with asthma (N = 25) underwent a histamine provocation until a 20% fall in forced expiratory volume in 1 s (FEV1). After each dose level, 6 symptoms of dyspnea intensity and 6 symptoms of dyspnea affectivity were rated. Individual perceptual sensitivity was determined by calculating the linear slope between the fall in FEV1 and the increase in the total symptom score, and for affective and sensory symptoms separately [Bijl-Hofland, Folgering, van den Hoogen, et al. Perception of bronchoconstriction in asthma patients measured during histamine challenge test. Eur Respir J 1999;14:1049–54]. Trait anxiety, baseline state anxiety, daily asthma symptoms and catastrophizing during an asthma exacerbation were also assessed. Sensitivity was unrelated to physiological indices of disease severity (i.e., baseline FEV1 and histamine dose level at 20% fall in FEV1), whereas it was positively related to trait anxiety, state anxiety, daily asthma symptoms and catastrophic thinking during an asthma exacerbation in daily life. These relationships were overall much stronger for affective than for sensory symptom slopes. In stepwise multiple regressions, state anxiety was the best predictor of the affective symptom slopes, whereas catastrophic thinking during an asthma exacerbation was the best predictor for the sensory aspect.

Abbreviation: ANOVA, analysis of variance; ASC, asthma symptom checklist; CAS, catastrophizing about asthma scale; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; NA, negative affectivity; PANAS, positive and negative affect schedule; PC20, provocative concentration of histamine causing a 20% fall in FEV1; PS20, symptom scores corresponding to a 20% fall in FEV1; SD, standard deviation

* Corresponding author. Tel.: +32 16 32 60 38; fax: +32 16 32 60 55.
E-mail address: steven.depeuter@psy.kuleuven.be (S. De Peuter).

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doi:10.1016/j.rmed.2006.09.018
Introduction

Poor symptom perception puts patients with asthma at increased risk of severe attacks, because medication may be delayed or omitted.1,2 Poor symptom perception may cause mild asthma to deteriorate as inflammation stays undetected.3 Because bronchial provocation tests provide information on the relatively rapid development of bronchoconstriction, simultaneous symptom reports can provide information about patients’ perceptual sensitivity.

It is important to identify determinants of poor perception, such as age, gender, severity of bronchial responsiveness3,4 and temporal adaptation. Few studies, however, have investigated psychological variables. Spinhoven and colleagues5 reported that anxiety associated with increasing breathlessness led to more complaints at a reduction in lung function of 20%. In addition, anxious perceivers had a higher sensitivity for bronchoconstriction, despite similar airway responsiveness compared to low anxious patients.

We wanted to investigate how psychological variables influence breathlessness perception.

First, trait anxiety has been shown to be similar to negative affectivity (NA; the tendency to experience a broad range of negative emotions6,7). Research both in patients with asthma and healthy participants consistently found that persons with a high level of NA report more symptoms than persons with a low level of NA, without corresponding physiological differences.8,9 Also, high-NA persons are less accurate in perceiving respiratory symptoms than low-NA persons, especially in distressing situations.10,11

Because trait anxiety is used to describe a variety of negative emotional states, more specific components may distinctively influence symptom reporting and illness behavior in asthma. In pain research, patients with catastrophic thoughts about their pain report more pain, more intense pain, more disability from their pain, and more interference with their daily activities and other life domains.12,13

Recently, similarities between pain and dyspnea have been described14,15 and first findings about the effect of catastrophic thinking in asthma have been reported.16 Therefore, we included measures of trait and state anxiety, and of catastrophic thinking about asthma.

Second, the perception of bronchoconstriction is generally measured in general terms of ‘dyspnea’ or ‘breathlessness’. However, dyspnea is not one-dimensional: clinical, experimental, and neuroimaging data suggest that a distinction between physical sensations and emotional reactions to dyspnea is clinically useful.17,18,19,21,22 By keeping symptom reports limited to physical sensations, important aspects of the subjective experience of bronchoconstriction/dyspnea may be overlooked.

In short, the aims of this study were (1) to investigate individual differences in patients with asthma’s perception of dyspnea induced by a standardized histamine provocation; (2) to test different aspects of dyspnea; and (3) evaluate the effect of anxiety and catastrophic thinking about asthma on dyspnea.

Methods

Participants

We invited patients with asthma who had been referred to the university hospital for a histamine provocation. Reasons for referral were: regular control measurements of airway reactivity—to assess the long-term development of the disease, or diagnostic purposes. Inclusion criteria were: a confirmed diagnosis of asthma (based on symptom reports, lung function data, a positive reaction to asthma medication, and a positive response to the bronchial provocation), age between 18 and 65, Dutch-speaking, baseline FEV1 >50% of the predicted value, a provocative concentration of histamine causing a 20% fall in FEV1 (PC20) <8 mg/ml, and at least two doubling doses of histamine (to be able to determine the patients’ sensitivity during the test; see further). Twenty-nine patients were invited to participate, two were excluded because they did not understand Dutch, one patient declined participation because of lack of time; another patient said she was too anxious and preferred not to answer any more questions. The final study sample consisted of 25 patients with asthma (13 male, 12 female; mean age = 38.5; SD = 13.6). According to GINA guidelines,23 18 patients had mild persistent asthma, 5 had moderate persistent asthma. For two more patients, we had insufficient data to determine asthma severity. Seven patients used inhaled corticosteroids (ICS) to control their disease. The Medical Ethical Board of the hospital approved of the study and all patients provided informed consent.

Subjective measures

We used the NA scale of the Positive and Negative Affectivity Schedule (PANAS26) to measure trait anxiety: Participants rated the degree to which 10 negative adjectives are applicable to themselves. End points are very little or not at all (scored 1) and very much (scored 5), resulting in a total score between 10 and 50.

We used the validated Dutch translation of the Asthma Symptom Checklist (ASC) to assess subjective asthma symptoms.27,28 The ASC is a 36 item-checklist, consisting of 6 subscales: symptoms of airway obstruction, dyspnea, symptoms of hyperventilation, fatigue, anxiety, and irritability. The first three subscales measure the sensory aspect of dyspnea, the latter three the affective aspect. Internal consistency for five of the six subscales is high (Cronbach’s α: ranging from 0.86 to 0.93) and acceptable for hyperventilation complaints (Cronbach’s α: 0.7628). At baseline (see Procedure section), patients rated how frequently they experience each symptom during a typical asthma
exacerbation on a scale from never (scored 1) to always (scored 5; “ASC-Exacerbation”). A second version of the ASC measured symptom intensity at baseline on an 11-point scale ranging from not at all (scored 0) to symptoms as bad as possible (scored 10; “ASC-Now”). To restrict completion time and not to interfere with the standardized histamine protocol, we constructed a third version, consisting of two items per subscale (“ASC-Short”). The ASC-Short was used during the histamine provocation to measure symptom intensity on an 11-point scale ranging from not at all (scored 0) to symptoms as bad as possible (scored 10).

The Catastrophizing about Asthma Scale (CAS) was used to measure catastrophic cognitions about asthma. Patients rated the extent to which 24 items expressing catastrophic thoughts and feelings about asthma are applicable to themselves. The scale has two subscales, one referring to the situation of an asthma exacerbation (the ‘exacerbation’ scale), one referring to the situation in general, whenever no exacerbation is present (‘general’ scale). The CAS has high internal consistency (Cronbach’s $\alpha = 0.93$), excellent test–retest reliability ($r = 0.94$), and good construct validity.29

**Histamine provocation**

All patients underwent spirometry according to ERS guidelines on a Mass-flow Sensor (Sensormedics, Vmax 20C, 2000). Non-specific airway responsiveness to histamine was measured according to the method described by Cockcroft and colleagues. After determination of baseline FEV$_1$ (expressed as the percentage of the predicted value) the patient inhaled saline (NaCl; 0.9%) followed by progressive doubling concentrations of histamine (0.25–8 mg/ml; prepared by the hospital pharmacy and stored at 4°C) until the FEV$_1$ had fallen at least 20% below participants’ baseline value or until the maximum concentration of 8 mg/ml was reached. Aerosols were generated by pressed air with a flow of 6 l/min via a System 22 Disposable Sidestream Nebulizer (Medic-Aid, Paghom, UK; mass median diameter 3 µm, respirable output 80%). Every aerosol pot contained 3 ml of test liquid (saline or histamine). Participants wore a nose clip and inhaled the aerosols quietly at tidal volume through a mouthpiece for 2 min at 5 min intervals. All substances were inhaled at room temperature. FEV$_1$ was measured 60 and 180 s after each inhalation, the lower value of both measurements was used for analyses.

On the day of the study, patients had not taken any short-acting $\beta_2$-agonists and anticholinergics for 8 h, long-acting $\beta_2$-agonists and theophyllines for 24 h and antihistaminics and long-acting anticholinergics for 48 h. Inhaled corticosteroids were allowed.

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Procedures

When patients registered at the nurse’s desk on the day and time of their scheduled appointment, they were invited to participate in the study. The purpose of the study was explained, patients who were willing to participate signed the informed consent form and completed the questionnaires in the waiting room (Baseline measures: PANAS, ASC-Exacerbation, CAS, ASC-Now). Next, they performed baseline spirometry and patients with an FEV$_1 > 50\%$ of predicted values continued with the histamine provocation. After each inhalation (starting with NaCl) and before the first FEV$_1$ measurement, symptoms were assessed with the ASC-Short. When participants’ FEV$_1$ had fallen at least 20% below baseline measures, participants received salbutamol (Ventolin® 400 µg, GlaxoSmithKline) to guarantee maximal reversion of the bronchoconstriction. Thereafter, they were debriefed.

**Data reduction and analysis**

We calculated Pearson’s product–moment correlations between symptom scores and lung function data both at baseline and at the maximal fall in FEV$_1$. We also correlated symptom scores with the subjective measures.

The provocative concentration of histamine causing a 20% fall in FEV$_1$ (PC$_{20}$) and the symptom scores corresponding to a 20% fall in lung function (PS$_{20}$) were determined by linear interpolation from the last two points on the log dose–response curve. We transformed all symptom scores to a scale ranging from 0 to 50 so that the range of symptom scores and the range of FEV$_1$ were similar. Next, the sensitivity of the perception of bronchoconstriction during the histamine challenge was calculated by regressing the changes in symptoms compared to the post-saline ratings on the reduction in FEV$_1$ as percentage of the post-saline value. The change in FEV$_1$ was placed on the $y$-axis as the independent variable and the linear regression coefficient ($B$) for symptoms was calculated. This slope is an index of the perceptual sensitivity of an individual; the steeper the slope, the more sensitive a person is. We performed this analysis first for the ASC-Short total scores, and subsequently for the affective (subscales anxiety, irritability, and fatigue) and sensory (subscales obstruction and dyspnea) groups of symptoms separately [exploratory factor analysis on data from a previous study (De Peuter et al., unpublished data) suggested a three-factor solution with an affective and a sensory factor as the first two factors; a third factor grouped the ‘hyperventilation’ complaints. Because the hyperventilation items had low factor loadings on this factor we decided not to use the ‘hyperventilation’ scale in the current analyses]. Slopes based on these different (sub)scorest are given a subscript in the text referring to the (sub)score they are based on, e.g. slope$_{Total}$.

Next, we compared the different slopes using $t$-tests and calculated Pearson’s product–moment correlations between the slopes and other patient characteristics. Partial correlations were used to control for differences in baseline FEV$_1$ and highest histamine dose where appropriate.
We used forward stepwise multiple regression analysis to assess the relative influence of the psychological variables on participants’ sensitivity.

Finally, because 10 patients had a flat slope_{Affective} and this constitutes 40% of our sample, we used 2-way ANOVA’s to compare the group with a flat slope with the group with a slope > 0.

All analyses were performed with STATISTICA 7.1 (StatSoft, Inc., Tulsa, USA).

Results

Baseline data

Means and standard deviations of the questionnaire data are presented in Table 1. At baseline, symptom scores were low (ASC-Now), although the value for dyspnea was well above 0.

Clinical characteristics are presented in Table 2. Baseline FEV_1 ranged from 69% to 127% of predicted values. In most patients, FEV_1 increased slightly after NaCl-inhalation (maximum increase = +7%; maximum fall = −4%). Accordingly, ASC-Short scores decreased from 1.6 (SD = 1.7) at baseline to 0.7 (SD = 1.0) after NaCl-inhalation.

The correlations between baseline FEV_1 values (before NaCl inhalation) and baseline symptom reports (ASC-Now) were of minor magnitude and not significant, with only the correlations for the anxiety and irritability scale exceeding |0.10| (r = 0.16, P = 0.47 and −0.13, P = 0.55, respectively).

Symptom perception

Absolute perceptual magnitude

The mean maximal reduction in FEV_1 was 26.8% (SD = 5.5; range 20–44%). The mean symptom score associated with this reduction in FEV_1 was 2.3 (SD = 2.0; range 0.2–8.5). The partial correlation controlling for histamine dose between these two variables was 0.40, P = 0.054. The mean symptom score at a reduction of 20% in FEV_1 (PS_{20}) was 1.9 (SD = 1.7; range 0.1–8.3).

Sensitivity

Two examples of individual slopes, one for a patient with a high sensitivity and one for a patient with very low sensitivity are presented in Fig. 1.

Means and standard deviations of the regression lines are presented in Table 2. There were no relations between participants’ sensitivity and subjective measures of disease severity: all the correlations between the slopes and baseline FEV_1 levels were <0.13 and not significant (all P’s > 0.5%). Similarly, the correlations between the slopes and the provocative dose of histamine causing a 20% fall in FEV_1 (PC_{20}) were not significant: r = −0.24; −0.15 and −0.41 for slope_{Total}, slope_{Sensory} and slope_{Affective}, respectively.

In contrast, we observed a relation between participants’ sensitivity and (subjective) symptom reports: there was a substantial correlation between the absolute perceptual magnitude (PS_{20}) and the slope_{Total}: r = 0.46, P < 0.05.

Similarly, the correlation between participants’ sensitivity and subjective symptoms at baseline (ASC-Now) was significant, r = 0.46, P < 0.05.

Table 1: Means (and standard deviations) from the questionnaires completed before the histamine provocation.

| Questionnaire data          |  
|------------------------------|--- |
| ASC-Exacerbation total       | 2.5 (0.6) |
| Obstruction                  | 2.7 (1.1) |
| Dyspnea                      | 3.6 (1.1) |
| Anxiety                      | 2.1 (0.9) |
| Irritability                 | 2.4 (0.7) |
| Fatigue                      | 2.9 (1.1) |
| Hyperventilation             | 1.8 (0.7) |
| ASC-Now total                | 1.5 (1.6) |
| Obstruction                  | 1.7 (2.5) |
| Dyspnea                      | 2.4 (2.8) |
| Anxiety                      | 1.1 (1.4) |
| Irritability                 | 1.6 (2.0) |
| Fatigue                      | 1.9 (2.6) |
| Hyperventilation             | 0.5 (0.8) |
| PANAS—Trait anxiety          | 23.5 (6.4) |
| ‘Exacerbation’ scale         | 17.9 (10.4) |
| ‘General’ scale              | 11.9 (11.7) |

Note: ASC-Exacerbation: frequency of symptoms during an exacerbation on a scale from 1 (‘never’) to 5 (‘always’); ASC-Now: intensity of symptoms before the histamine challenge on a scale from 0 to 10. The range of the triat anxiety scale was 10–50; Ranges for CAS scores are: CAS ‘exacerbation’: 0–52; CAS ‘general’: 0–44.

Differentiation between sensory and affective aspects of dyspnea

Overall, slope_{Sensory} was significantly higher than slope_{Affective}; t(47) = 3.88, P < 0.001. This difference was also significant when only the patients with a slope_{Affective} > 0 were included, t(37) = 2.34, P < 0.05. The correlation between PS_{20} and slope_{Affective} was high (r = 0.50, n = 15, P = 0.055), whereas the correlation for slope_{Sensory} was much lower (r = 0.27, n = 24, n.s.). So, especially those patients who reported more

A comparison between the patients who used Inhaled Corticosteroids to control their disease and the remainder of the group revealed that there were no significant differences in the mean slopes between the groups, all P’s < 1.
Sensory/affective aspects of bronchoconstriction

Two examples of linear regression slopes. The left panel shows the data of a patient with a high sensitivity for changes in lung function (patient 20; slope = 1.49); the right panel shows the data of a patient with a very low sensitivity for changes in lung function (patient 23; slope = 0.07). The X-axis shows the percentage decline in lung function compared to post-saline values, the Y-axis shows the increase in symptoms compared to post-saline values.

Affective complaints as their lung function decreased reported more complaints at a 20% fall in lung function.

A similar pattern was observed for asthma complaints during an exacerbation in daily life, although the correlations were not significant ($r = 0.26$, $n = 13$ and $0.02$, $n = 21$ for $slopes_{Affective}$ and $slopes_{Sensory}$ respectively, n.s.).

Psychological variables and symptom perception

Anxiety

The partial correlation (i.e., controlled for baseline FEV$_1$) between trait anxiety and PS$_{20}$ was 0.23, $n = 25$, n.s. The partial correlation between trait anxiety and the $slope_{Total}$ was 0.30, $n = 25$, n.s. In contrast, there was a strong effect of baseline (state) anxiety: patients who reported more anxiety before the start of the histamine provocation (ASC-Now), also reported more complaints in general ($slope_{Total}$) as their lung function decreased, $r = 0.55$, $n = 24$, $P < 0.01$. The correlation between baseline anxiety symptoms and $slope_{Affective}$ was slightly lower but still significant, $r = 0.55$, $n = 15$, $P < 0.05$, whereas the correlation with $slope_{Sensory}$ was only 0.31, $n = 23$, n.s. This pattern of results was even more obvious when we controlled for baseline FEV$_1$: $r = 0.55$, $n = 24$, $P < 0.01$; $r = 0.57$, $n = 15$, $P = 0.05$; and $r = 0.29$, $n = 23$, n.s. for $slope_{Total}$, $slope_{Affective}$, and $slope_{Sensory}$, respectively.

Nevertheless, the partial correlation between baseline anxiety (ASC-Now) and PS$_{20}$ was small and not significant, $r = 0.19$, $n = 24$, n.s.

Catastrophizing about asthma

The correlations between CAS scores and the slopes are presented in Table 3. In contrast to anxiety ratings, catastrophic thoughts and feelings during an asthma exacerbation were more strongly related to the reporting of sensory complaints than to the reporting of affective complaints during histamine induced bronchoconstriction.

Moreover, we observed strong partial correlations (controlled for baseline FEV$_1$) between the ‘general’ scale and symptom reports at baseline (ASC-Now; all $r'$s $>0.30$) with significant correlations for anxiety and dyspnea symptoms.

Relative weight of psychological variables

Forward stepwise multiple regression analysis with the slopes as dependent variables and anxiety scores at baseline and CAS ‘exacerbation’ scores in the model for $slope_{Total}$, $eta$'s $= 0.48$ and 0.29, respectively, adj. $R^2 = 0.34$, $F(2, 20) = 6.62$, $P < 0.01$. For $slope_{Affective}$, only anxiety scores at baseline were retained, $\beta = 0.55$, explaining 24% of the variance, $F(1, 12) = 5.22$, $P < 0.05$, whereas for $slope_{Sensory}$ only CAS ‘exacerbation’ scores were retained, $\beta = 0.54$, explaining 23% of the variance $F(1, 20) = 7.49$, $P < 0.05$.

Comparison between patients with a ‘flat’ $slope_{Affective}$ and a $slope_{Affective} > 0$

There were no significant differences between the 10 patients with a flat $slope_{Affective}$ and the other patients in terms of baseline FEV$_1$, change in FEV$_1$ after NaCl inhalation.

Table 2 Clinical characteristics of the study population and mean slopes.

<table>
<thead>
<tr>
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<th>Patients ($n = 25$)</th>
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<tbody>
<tr>
<td>PC$_{20}$ (mg/ml)*</td>
<td>1.57 (1.51–2.75)</td>
</tr>
<tr>
<td># Histamine inhalations</td>
<td>4.2 ± 1.4</td>
</tr>
<tr>
<td>Baseline FEV$_1$ (% pred)</td>
<td>96.6 ± 13.9</td>
</tr>
<tr>
<td>FEV$_1$ change after NaCl (% pred)</td>
<td>1.7 ± 2.5</td>
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</tbody>
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| Slopes of the regression line between change in FEV$_1$ and |            |
| ASC-Short Total ($n = 25$) | 0.32 (0.30) |
| ASC-Short Sensory ($n = 24$) | 0.58 (0.45) |
| ASC-Short Affective ($n = 15$) | 0.26 (0.36) |

Note: Data are presented as Mean ± SD, except for: *: geometric mean (95% confidence interval). PC$_{20}$: provocative concentration of histamine causing a 20% fall in FEV$_1$; % pred: percentage of predicted value.
or baseline symptom reports. Patients with a flat slope\textsubscript{Affective} showed a tendency to have more severe airway reactivity, however; they reached a 20% fall in FEV\textsubscript{1} at 1.5 mg/ml histamine (PC\textsubscript{20}) on average, compared to 2.6 mg/ml for the other group, \(F(1, 23) = 3.80, P = 0.06\).

The group with a flat slope\textsubscript{Affective} scored significantly lower on trait anxiety (\(M = 19.4, \text{SD} = 5.5\)) compared to patients with a higher slope\textsubscript{Affective} (\(M = 26.2, \text{SD} = 5.5\)), \(F(1, 23) = 9.18, P < 0.01\); they had significantly lower baseline anxiety levels (ASC-Now) than the group with a higher slope\textsubscript{Affective}, \(M \pm SD = 0.3 \pm 0.5 \) and \(1.5 \pm 1.6\), respectively (Mann–Whitney U-test: 2 \times 1 sided exact \(P < 0.05\)); and they had a tendency to report less anxiety during an exacerbation in daily life, \(M \pm SD = 1.7 \pm 0.6\) and \(2.4 \pm 1.0\), respectively, \(F(1, 20) = 3.13, P = 0.09\). Finally, patients with a flat slope\textsubscript{Affective} also had lower slope\textsubscript{Sensory} (\(M = 0.40, \text{SD} = 0.14\)) than patients with a higher slope\textsubscript{Affective} (\(M = 0.70, \text{SD} = 0.12\)), although this difference was not significant, \(F(1, 22) = 2.70, P = 0.11\).

**Discussion**

We investigated symptom perception in patients with asthma during a histamine provocation. The slope of the regression line between the decrease in lung function and the increase in subjective symptoms was used as a measure of overall perceptual sensitivity and for sensory and affective symptoms separately.

There was no relation at baseline between subjective symptoms and lung function, probably due to temporal adaptation to pre-existing obstruction:\cite{3, 11}: at the end of the histamine provocation there was a correlation between changes in subjective symptoms and lung function. In contrast to previous findings, we found no relation between the participants’ perceptual sensitivity for dyspnea and physiological measures of disease severity such as FEV\textsubscript{1} and histamine dose level at 20% decrease of FEV\textsubscript{1}.

The distinction between sensory and affective aspects of dyspnea proved to be clinically relevant. Slopes for sensory symptoms were much higher than slopes for affective symptoms. Whereas all patients reacted to the histamine challenge with sensory symptoms, 10 out of 24 patients showed no affective response at all. Nevertheless, especially those patients whose affective symptoms increased as their lung function decreased ended up reporting more symptoms. Patients with higher trait anxiety reported a stronger increase in symptoms with decreasing lung function and, specifically for affective symptoms, patients with higher baseline anxiety were significantly more sensitive compared to patients with low baseline anxiety. In contrast, the relation between state anxiety and sensory symptoms was not significant.

A relation between depression/anxiety and symptom reports in asthma has been reported before and emotional status is a determinant of clinical dyspnea scores. However, Spinhoven and colleagues did not observe effects of baseline anxiety. They suggested a curvilinear relation between anxiety and symptom reporting and reported that their study group had an average of 5.7 previous histamine provocations, probably putting them at ease. We did not record the number of previous histamine provocations our participants had experienced, but most patients indicated that the procedure was new to them and that they did not know what to expect. This uncertainty may have induced anxious expectancies and, consequently, baseline anxiety.

The specific relationship between anxiety and affective sensitivity was supported by the results of the linear regression analyses, whereas sensitivity for physical symptoms was best predicted by catastrophic thinking during an asthma exacerbation. Spinhoven et al. did not observe this relation between catastrophic thoughts and symptom perception. However, they used a general measure of catastrophic thinking, assessing catastrophic thoughts about everyday situations, whereas the current study included a disease-specific measure.

The current study has some limitations. First, patients’ asthma was not well controlled and for some patients we were not able to determine asthma severity according to GINA guidelines. This may restrict the generalizability of our results to the broader asthma population. Furthermore, our sample was selected from patients referred for histamine challenge. As the majority of persons with asthma do not undergo histamine or other challenge procedures, the same critique applies. Second, the validity of bronchial provocation tests for examining perceptual sensitivity has been

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<thead>
<tr>
<th>Table 3 Correlations between CAS scores on the one hand and slopes and symptoms at baseline on the other hand.</th>
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<tr>
<td>Slope\textsubscript{Total} ((n = 24))</td>
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<tr>
<td>Slope\textsubscript{Sensory} ((n = 23))</td>
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<tr>
<td>Slope\textsubscript{Affective} ((n = 14))</td>
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<tr>
<td>ASC-Now*</td>
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<td>Obstruction*</td>
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<td>Dyspnea*</td>
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<td>Fatigue*</td>
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<td>Hy perventilation*</td>
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*Partial correlations (controlled for baseline FEV\textsubscript{1} values), \(n = 23\).  
**\(P < 0.05\).
criticized, as they do not reflect the real life situation of episodes of spontaneous bronchoconstriction. Patients will probably be more focused on their respiratory sensations in the laboratory compared to daily life. In addition, the laboratory setting with medical staff present may reduce or increase anxiety and influence symptom perception. Nevertheless, our results support the validity of histamine provocations: the relations between the patients’ perceptual sensitivity and the levels of symptoms at a 20% fall in lung function were similar to the relations between patients’ perceptual sensitivity and their symptom reports during an asthma exacerbation in daily life.

These results have important clinical implications. A high sensitivity seems favorable, because it allows the early detection of deteriorating lung function and quick medical relief. However, a high sensitivity is often associated with overperception of symptoms and it is unclear at which level sensitivity becomes maladaptive. To investigate this, two problems have to be solved: First, overperception should be defined. A variety of methods is used to measure the perception of dyspnea/bronchoconstriction, such as Borg scales, visual analogue scales and symptom ratings, either or not calculating slopes, complicating comparison across studies. Second, normative data are needed to determine (mal)adaptive levels of perceptual sensitivity.

We have argued before that a moderate degree of asthma-specific anxiety is adaptive because it is a good incentive to take action when symptoms emerge and may be associated with enhanced perception of bronchoconstriction. In contrast, the absence of anxiety may lead to indifference and neglect of symptoms; high illness-specific anxiety may lead to overperception. Again, this ‘optimal level of anxiety’ should be determined.

The relationship between sensitivity and perception should be extended to include disease outcome variables such as long-term development of the disease, medication compliance and self-management of asthma. Bijl-Hofland and colleagues reported that the 25% worst perceivers of their patient sample reported very little symptoms in combination with a more severe degree of asthma. In the current study, 40% of the sample did not react emotionally to the histamine inhalation. These patients were less anxious and tended to have higher airway reactivity than the patients who reacted emotionally. In addition, they showed somewhat lower sensitivity for sensory symptoms, suggesting a possible link between the absence of an affective response and underperception. Bijl-Hofland and colleagues suggest that these patients should receive more supervision from physicians, with treatment plans that may consist of training for peak flow monitoring. Our results further suggest that the treatment plan of over perceivers may best be aimed at reducing anxiety and, by extension, coping with the emotional impact of the disease.

Acknowledgements

The authors would like to express their gratitude to K. P. Van de Woestijne for his valuable comments on our data. We also would like to thank Felicien Rochette for his respiratory DIY-knowledge; and Marleen and Monique for the assistance in the data collection process.

References


24. Nouwen A, Freeston MH, Cournoyer I, Deschesnes F, Boulet LP. Perceived symptoms and discomfort during induced bronchos- 


