ORIGINAL RESEARCH

Development of a questionnaire for the assessment of bronchial hyperresponsiveness

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Abstract

Introduction: Bronchial hyperresponsiveness (BHR) is a hallmark of asthma. Treatment approaches based on BHR severity have been shown to be effective. However, challenge tests are expensive, inconvenient to patients, time consuming, and not easily accessible to general practitioners. Assessment of BHR by a questionnaire would be advantageous in the diagnosis and management of asthma.

Aim: To select a set of respiratory symptoms and provoking stimuli related to BHR to compose a reliable Bronchial Hyperresponsiveness Questionnaire (BHQ).

Method: A list of 33 symptoms and 68 stimuli were selected by in-depth interviews, focus group discussions with asthma patients, and literature review. After a histamine challenge test patients (n=302) were asked to score each question on a 7-point scale (0=no; 6=severe complaints). Factor analysis was performed to identify clusters of interrelated symptoms associated with PC₂₀-histamine. The sensitivity to detect the presence of BHR was analysed by Receiver Operating Curves (ROC). The correlation between the PC₂₀-score and the scores on the questions was analysed.

Results: 15 symptoms and 19 provoking stimuli were ultimately selected for the BHQ.

Conclusion: The BHQ was developed according to FDA-approved standards and is a condition-specific questionnaire able to assess the presence of BHR.

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Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. This chronic inflammation is associated with airway hyperresponsiveness and leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with airway obstruction that is often reversible either spontaneously or with treatment.¹

The chronic inflammatory process of the airways in asthma can lead to structural changes in the bronchial wall, a process known as airway remodelling which may be accompanied by lung function loss.² Therefore, successful asthma management depends on effective suppression of inflammation and remodelling, generally by using inhaled corticosteroids (ICS).^{3,4} In daily clinical practice, asthma treatment decisions are usually based on patient-reported symptoms and simple measures of lung function. Since

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airway inflammation is only to a small extent associated with respiratory symptoms and lung function, symptom-based titration of the dose of ICS can be unreliable. Indeed, several studies have shown that the management of asthma improves and results in less exacerbations and better quality of life (QOL) with the provision of additional information about the severity of airway inflammation.^{5,6}

The gold standard for determining the severity of airway inflammation is a bronchial biopsy. Alternative methods have been sought over the years since biopsies are invasive, expensive and are therefore very impractical to use for a large number of subjects. Currently accepted and less invasive alternatives are the measurement of the level of exhaled nitric oxide, the number and type of inflammatory cells in induced sputum, and the severity of bronchial hyperresponsiveness (BHR). The latter has been shown to be associated with airway inflammation in several studies.⁷⁻⁹

Sont *et al* have shown that treatment adjustments aimed at reducing BHR lead to more effective control of symptoms, fewer exacerbations, and a reduction in airways remodelling.¹⁰ These results suggest that measuring BHR at regular intervals in clinical practice could benefit standard monitoring of patients with asthma. However, there are several drawbacks; challenge tests are expensive, time consuming, not very convenient to patients, and are often not directly accessible in primary care. If the presence of BHR could be determined with a questionnaire this would thus be cheaper, less time consuming and more convenient for both patients and doctors. Such a questionnaire could be of value in the management of asthma in primary care.

Although several attempts have been made to develop such a questionnaire, so far investigators have never applied structured patient interviews and proper questionnaire development rules as propagated (for instance) by the U.S. Department of Health and Human Services Food and Drug Administration (FDA).^{11,12} Thus these questionnaires were not specifically designed for the assessment of BHR but rather were modifications from other questionnaires. We hypothesised that it is crucial to pay detailed attention to the method of item selection in order to create a successful, condition-specific questionnaire. This article describes the methods of item collection and selection that we used to develop a questionnaire for the assessment of BHR in patients with asthma.

Methods

Item collection for the preliminary questionnaire

An initial pool of items was generated by literature review,¹³⁻¹⁶ in-depth interviews, and a focus group discussion with asthma patients. The search programs PubMed and Medline were used for the literature review, and the search terms used were "bronchial", "airway", "hyperreactivity", "hyper-

responsiveness", "questionnaire", "stimuli", "triggers" and "triggering". Patients participating in the in-depth interviews and focus group discussion were selected from general practice. All participants had mild to moderately severe asthma as diagnosed by their general practitioner (GP) in agreement with the Dutch asthma guidelines¹⁷ (that are similar to the GINA-guideline¹⁸). The focus group discussion and single interviews began with open-ended questions followed by a semi-structured interview. Patients were asked to discuss the stimuli that provoked a deterioration of their asthma and the kind of symptoms that were experienced when asthma was not stable as opposed to when it was stable. The main goal was to collect as many different stimuli and symptoms related to BHR in daily life as possible. All interviews and focus group discussions were recorded on tape and transcribed. All mentioned stimuli and symptoms were listed in a questionnaire. The stem question of the symptom part of the questionnaire was; 'Did you experience "symptom X", during the past 3 months?', whereas the stem question of the stimuli part was; 'Did "stimulus X", bother you during the past 3 months?'

With these selected questions a pre-test was performed. Six asthma patients filled in the questionnaire in the presence of a researcher. They were asked to recapture the last three months in answering the questions and to identify and discuss unclear questions with the researcher. The main objective of this pre-test was to eliminate errors and clarify obscurities in the questions. The remaining questions were collected in a preliminary questionnaire.

Statistical analyses

Data analyses were performed using the SPSS version 12. Two of the four participating lung function centres assessed hyperresponsiveness by the 2-minute tidal breathing method (resulting in a PC₂₀), the other two by the dosimeter method (PD₂₀). Two groups of patients were identified: 1) a group with a 20% fall in FEV₁ (PD₂₀ <2.4mg ; PC₂₀ <32mg/ml) and 2) a group without a 20% fall in FEV₁.

Receiver Operating Curves (ROC) were made with all items of the preliminary questionnaire to investigate the sensitivity and specificity of each individual question to determine the presence or absence of BHR.

Factor analysis with no restriction on the number of factors was performed on all questionnaires completed by patients with BHR to identify clusters of interrelated questionnaire items. It was only performed on the symptom part of the preliminary questionnaire because questions pertaining to stimuli not encountered in the past three months could not be answered – thus these data could not be included for this type of analysis.

Spearman rank correlation tests were performed to investigate the relation between the level of PC₂₀-histamine

and the scores of each individual item in patients with doctor-diagnosed asthma (see Figure 1). For this analysis, we only used individuals who underwent BHR testing with the PC₂₀ histamine method, since this was used in the vast majority – and moreover, conversion of PC₂₀ into PD₂₀ is difficult and not 100% reliable.^{18,19} Patients subjected to the PD₂₀ measurement did not differ from those patients who were subjected to the PC₂₀ measurements.

Item generation

The preliminary questionnaire consisted of questions about stimuli and symptoms. These questions were scored on a 7-point Likert scale: 0 = no complaints, 6 = severe complaints. Questions about stimuli had “X” as an extra answering option which implied: ‘I have not been in contact with this stimulus during the past 3 months’. All patients who underwent a histamine challenge test were asked to complete the preliminary questionnaire directly after they had completed the challenge test. In this way the outcome of the challenge test (in this study used as the reference and gold standard for BHR) could be linked to the scores on the items of the preliminary questionnaire.

The investigator assigned each patient into one of the following diagnostic categories: 1. asthma; 2. COPD; 3. mixed asthma/COPD; 4. other diagnosis; and 5. not obtained (Figure 1). This allocation was based on the doctor's diagnosis, lung function scores and histamine scores collected from discharge letters and conforming to the Dutch asthma and COPD guidelines.

Cut-off values for the items to be included in the BHQ were a rho ≥ 0.2 with a significance level < 0.05 (Spearman rank correlation test) and/or an area under the curve ≥ 0.5 with a significance level < 0.05 (ROC). These cut-off values were determined by an expert panel consisting of a GP, a pulmonologist and a statistician.

Results

Item collection for the preliminary questionnaire

Eleven in-depth interviews and one focus group discussion were performed. After the pre-test procedure, 101 items remained for the preliminary questionnaire – 33 questions about symptoms and 68 about stimuli. This preliminary questionnaire was completed by 302 patients after BHR testing. Patient characteristics are presented in Table 1. Centres 1 and 2 (n=265) obtained PC₂₀ by the 2-minute tidal breathing method, centres 3 and 4 (n=37) PD₂₀ by the dosimeter method. Asthma was diagnosed in 172, COPD in 7, mixed asthma/COPD in 11, and other diagnoses in 85 cases. The last category consisted of patients who were referred to the lung function centre for additional diagnostic tests by dermatologists, ear nose and throat-specialists, or allergologists. In 28 cases no diagnosis could be obtained because no discharge letter was available. A PD₂₀ < 2.4 mg or a PC₂₀ < 32 mg/ml was obtained in 225 of the 302 patients.

Clustering of items in the preliminary questionnaire

Factor analysis on the scores of questionnaires from patients with BHR (n=225) showed eight clusters of symptoms. Five

Figure 1. Flowchart.

Table 1. Characteristics of the total group.

	n	%	
Hospital			
1	230	76.2	
2	35	11.6	
3	24	7.9	
4	13	4.3	
	302	100	
Sex			mean age (yrs)
male	115	38.1	43.6
female	187	61.9	37.2
Smoking			
yes	59	19.5	
no	213	70.5	
missing	30	10	
Hyperresponsiveness			
yes	225	74.5	
no	77	25.5	
Diagnosis			
asthma	172	57.0	
COPD	7	2.3	
mixed asthma/COPD	11	3.6	
other diagnosis	85	28.2	
diagnosis not obtained	27	8.9	

clusters were quite homogeneous, and were associated with the following domains: difficulty in breathing (e.g. asthma-like symptoms), allergic symptoms, fever/chest pain, COPD-

like symptoms, and systemic complaints/malaise. The other clusters were more difficult to identify specifically (Table 2).

Sensitivity of each item to predict BHR

Sensitivity to predict BHR was determined using Receiver Operating Curves (ROC). Analysis was performed on all 101 items of the preliminary questionnaire in the total group of patients (n=302). Each item was tested for its property to detect the presence of BHR. An item with an area under the curve of more than 0.5 is a potential indicator for the presence of BHR. The results of the ROC analysis are presented in Table 3.

Correlation of each item with PC₂₀-histamine score

A Spearman rank correlation test was conducted on the items of the preliminary questionnaires completed by the group of patients in centres 1 and 2 with doctor-diagnosed asthma (n=143). The investigated group consisted of 50 males, mean age 39.1 years and 99 females, mean age 34.4 years. Four patients had a PC₂₀-histamine of ≥ 32 mg/ml, one of them used salmeterol <12 hours before the provocation test and was therefore left out of the analysis. The other three performed a correct challenge test and stayed in the analysis. Breathlessness, waking up at night due to chest tightness, shortness of breath, sensation of pressure on the chest, acute breathlessness, wheeze, panting/gasping, palpitation/fast heart rate and hyperventilation/fast breathing were significantly associated with the level of PC₂₀ (see Table 3).

Table 2. Results factor analysis of the symptoms.

	coefficient		coefficient
cluster 1: difficulty with breathing		cluster 4: COPD- like symptoms	
breathing consciously and with difficulty	0.84	Coughing	0.80
shortness of breath	0.82	phlegm, excess mucus	0.79
inability to breathe deeply	0.80	to have a "frog" in one's throat	0.64
trouble walking uphill	0.71	cluster 5: systemic complaints/malaise	
breathlessness	0.70	Headache	0.75
panting, gasping	0.66	Fatigue	0.66
avoid more situations/activities than usual	0.66	Dizziness	0.66
waking up at night due to chest tightness	0.48	trouble concentrating on tasks	0.64
acute breathlessness	0.47		
Wheeze	0.42	cluster 6: ?	
cluster 2: allergic symptoms		hyperventilation, fast breathing	0.91
watery, itchy or red eyes	0.85	palpitation, fast heart rate	0.89
Sneeze	0.84		
hay fever	0.81	cluster 7: ?	
nasal catarrh	0.81	unconsciousness, memory loss	0.72
irritated mucous membranes	0.62	Panic	0.55
cluster 3: fever/chest pain		cluster 8: ?	
Fever	0.69	Hoarseness	0.68
pain in the chest	0.59	Nervousness	0.60
feeling ill	0.59		
chest tightness	0.58		
sensation of pressure on the chest	0.49		

? = no proper clustername could be determined

Table 3. Results of ROC analysis and Spearman rank correlation test.

questions about symptoms (n=33)	area (sig)	rho (sig)		area (sig)	rho (sig)
* breathlessness	.62 (.002)	.28(.001)	Headache	.53 (.329)	.16(.067)
* waking up at night due to chest tightness	.66 (.000)	.20(.017)	Dizziness	.55 (.196)	.16(.070)
* shortness of breath	.57 (.083)	.29(.001)	unconsciousness or memory loss	.54 (.266)	.05(.563)
* trouble walking uphill	.60 (.011)	.14(.096)	trouble concentrating on tasks	.52 (.568)	.02(.821)
decrease in maximum possible exercise	.52 (.593)	.05(.599)	* hoarseness	.59 (.019)	.12(.181)
* sensation of pressure on the chest	.60 (.011)	.23(.007)	Fatigue	.53 (.445)	.10(.247)
* chest tightness	.61 (.003)	.19(.024)	Panic	.50 (.933)	.09(.299)
* pain in the chest	.59 (.023)	.21(.013)	Nervousness	.46 (.284)	.10(.264)
* inability to breathe deeply	.63(.001)	.17(.050)	* palpitation, fast heart rate	.56 (.128)	.28(.001)
* breathing consciously and with difficulty	.61 (.006)	.16(.058)	* hyperventilation, fast breathing	.53 (.459)	.22(.010)
* acute breathlessness	.59 (.015)	.26(.002)	hay fever	.58 (.053)	.18(.044)
* wheeze	.69 (.000)	.32(.000)	Sneeze	.52 (.543)	.13(.181)
* panting, gasping	.53 (.377)	.24(.006)	runny nose	.49 (.856)	.02(.829)
cough	.53(.401)	.18(.037)	irritated mucous membranes	.50 (.915)	.09(.279)
phlegm, excess mucus	.54 (.284)	.12(.160)	watery, itchy or red eyes	.51 (.795)	.15(.074)
feeling ill	.50 (.954)	.16(.060)	Fever	.48 (.618)	.19(.021)
to have a frog in one's throat	.51 (.665)	.02(.856)			
questions about stimuli (n=68)	area (sig)	rho (sig)		area (sig)	rho (sig)
Dog	.58 (.071)	.162(.124)	vapor of cleaning product	.51(.751)	.05(.582)
* cat	.59 (.050)	.18(.081)	perfumed candles	.58(.061)	.04(.699)
bird	.55 (.335)	.08(.569)	ordinary candle	.54 (.280)	.06(.542)
* rodents	.60 (.050)	.21(.120)	puffed out candle	.55 (.263)	.08(.412)
* household dust, mite	.58 (.055)	.33(.000)	Cooking	.55(.167)	.13(.130)
* mould	.59 (.048)	.21(.053)	* scent of building materials	.60 (.018)	.21(.048)
* wool	.59(.033)	.31(.002)	* scent of petrol	.61 (.016)	.12(.265)
* down (pillow)	.56 (.065)	.34(.001)	choke (car)	.54 (.323)	.07(.496)
* grass, hay	.59 (.027)	.28(.002)	exhaust fumes (specially diesel)	.54 (.339)	.05(.572)
* pollen	.59 (.035)	.21(.028)	industrial areas	.58 (.078)	.12(.263)
flowers or plants in general	.57(.098)	.11(.250)	scent of paint or varnish	.58 (.055)	.09(.365)
* trees like, asp, birch, poplar, elm, pine	.57 (.138)	.23(.018)	scent of glue	.57(.083)	.09(.334)
smell of the woods	.53 (.441)	.15(.152)	newspaper ink	.53 (.455)	.02(.849)
Food in general	.49 (.815)	.13(.180)	scent of cleaning products	.55 (.217)	.02(.793)
synthetic materials, fibers	.53 (.493)	.04(.667)	* scent of ammonia	.60 (.019)	.00(.990)
tobacco smoke, cigar, cigarettes	.52 (.555)	.04(.658)	scent of chlorine	.53 (.407)	.05(.603)
smoky places	.52 (.551)	.04(.672)	scent of alcohol, other methylated spirits	.56 (.158)	.02(.855)
incense	.59(.074)	.07(.499)	other chemicals	.53 (.666)	.08(.586)
smoke from fireplace (indoors)	.56 (.210)	.17(.153)	peppermint (oil)	.54 (.435)	.21(.088)
smoke from fireplace (outdoors)	.56(.194)	.08(.502)	chewing gum	.53 (.505)	.05(.605)
* dusty places	.55 (.242)	.20(.028)	* lavatory air freshener	.60 (.015)	.03(.778)
vacuum cleaning	.57 (.074)	.15(.111)	inhalation powder (medication)	.543(.343)	.10(.319)
wood dust, sawdust	.54 (.432)	.11(.289)	spray cans	.58 (.054)	.10(.288)
water vapor, shower	.55 (.251)	.00(.986)	* hair spray	.58 (.044)	.07(.459)
aspiration of water	.54 (.336)	.03(.751)	deodorant, perfumes, after shaves	.52 (.426)	.09(.306)
* moist places	.65 (.001)	.08(.437)	air fresheners	.58 (.083)	.00(.975)
High atmospheric humidity	.58 (.056)	.12(.189)	alcohol consumption	.49 (.872)	.09(.368)
* fog	.61 (.007)	.16(.069)	exercise, e.g. cycling, ascending stairs	.56 (.143)	.19(.019)
Cold air, cold wind	.54 (.265)	.02(.280)	emotional stress	.51 (.782)	.14(.129)
* change from warm to cold environment	.58 (.037)	.08(.385)	excitation, arousal	.53 (.520)	.19(.033)
change from cold to warm environment	.57 (.067)	.08(.356)	laughing, speaking, anger	.58 (.053)	.09(.327)
* change of weather	.59 (.025)	.20(.022)	hyperventilation, fast breathing	.54 (.292)	.09(.372)
air conditioning	.55 (.279)	.04(.669)	Panic	.51 (.799)	.16(.110)
cosmetics, make-up powder	.55 (.270)	.04(.754)	respiratory tract infection, common cold	.59 (.141)	.06(.126)

Explanation of Table 3:

Rho = Spearman rho; area = area under the curve of the ROC analysis; sig = significance

Values with an area under the curve ≥ 0.5 and a significance level ≤ 0.05 are printed boldValues with a rho ≥ 0.2 and a significance level ≤ 0.05 are printed bold

* grey and printed bold = questions selected for the BHQ

Stimuli with significant associations with the level of PC₂₀ were: household dust/mite; wool; down (pillow); grass/hay; pollen; trees like aspen/birch/poplar/elm/pine; dusty places; a change of weather; and the scent of building materials.

Item generation for the BHR questionnaire

Table 3 shows the results of the Spearman rank correlation test and the ROC analysis used to select items for the BHR Questionnaire (BHQ). The selection criteria for the correlation test were a $\rho \geq 0.2$ and $p \leq 0.05$, and an area under the curve ≥ 0.5 and $p \leq 0.05$ for the ROC analysis. Using these criteria, 34 items were selected for the BHQ, 15 from the symptom domain and 19 from the provoking stimulus domain.

Discussion

We developed a questionnaire in order to assess the presence and severity of BHR in asthma according to FDA-approved standards for the development of questionnaires.²⁰ This BHR Questionnaire (BHQ) is a condition-specific questionnaire, consisting of 34 items – 15 regarding symptoms and 19 regarding provoking stimuli. As far as we are aware this is the first questionnaire specifically developed for the assessment of BHR in asthma. By using the PC₂₀-histamine as the main reference we selected items for the BHQ thereby expecting the BHQ to be a condition-specific instrument.

Various attempts have been made in the past to find a relationship between symptoms and/or stimuli that provoke respiratory symptoms on the one hand, and the severity or presence of BHR on the other. Studies investigating this subject used questionnaires such as the International Union against Tuberculosis and Lung Disease (IUATLD) questionnaire, the Medical Research Council (MRC) questionnaire, the American Thoracic Society-Division of Lung Diseases (ATS-DLD) questionnaire, or a subset of questions from these questionnaires. Although some questions derived from these questionnaires show a relation with BHR, so far no specific instrument has been developed to measure patient-perceived BHR.

Items related to BHR were generated by asthma patients. The expert panel decided to choose mild criteria for the item reduction. In this way they wished to prevent loss of possible predictive items. A disadvantage of this method is the relatively large number ($n=34$) of questions selected for the BHQ. Completing the questionnaire takes about 10-15 minutes which may be too long to be suitable for use in daily clinical practice although it is less time consuming than a challenge test.

An interesting finding in this study is that even though the selection criteria were mild, some questions about stimuli that are intuitively related with BHR were not included in the BHQ. For example, questions about contact with smoke from fire places or tobacco smoke proved to have little relation with

PC₂₀-histamine in our sample and were excluded. We can only speculate as to the reasons for this finding. It may well be that (tobacco) smoke is not specific enough to discriminate. This could mean that it is only a useful question in people not currently smoking.

Another remarkable finding is that hyperventilation as a symptom was selected for the BHQ whilst hyperventilation as a stimulus did not pass the selection criteria. Perhaps the way of asking the question explains the difference; as a symptom the question about hyperventilation was: "Did you experience hyperventilation / fast breathing during the last 3 months?" As a stimulus the question was: "Did hyperventilation / fast breathing bother you during the last 3 months?"

Symptoms like cough, phlegm, and excess mucus occur in asthma but are more often associated with COPD. Questions about these symptoms were not selected for the BHQ. This may have been due to the fact that the item generation was performed in predominantly asthmatic patients (Table 1). Of interest, allergic symptoms like nasal catarrh, watery, itchy or red eyes, hay fever and an irritated mucous membrane (Table 2, cluster 2) also showed little relation with PC₂₀-histamine and therefore were not included in the BHQ. This is remarkable because there is a close relation between allergic rhinitis and asthma. Epidemiological studies show that up to 60-78% of patients with asthma have coexisting allergic rhinitis, whereas 20-38% of patients with allergic rhinitis have asthma.^{21,22} Because the inflammatory processes involved in both diseases show large similarity some authors even speak of "one airway, one disease".²³ For the selection of questions we mainly focused on respiratory symptoms which is one explanation for our finding. The second explanation is the use of PC₂₀-histamine as the gold standard. This test is not exclusively sensitive to allergic triggers but also detects the BHR to non-allergic triggers.

In summary, we performed an active and systematic search for questions related to the presence and/or severity of BHR. By doing so according to FDA-proposed rules for the development of questionnaires, we created a condition-specific questionnaire that adds information about the presence of BHR in patients with asthma. Further research is necessary to check the predictive value of the questionnaire against the gold standard PC₂₀ to warrant its value and its accuracy in the management of asthma.

Conflict of interest

None.

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