

REVIEW ARTICLE

Diagnosis of asthma – a new approach

O. Löwhagen

Sahlgrenska Academy, Instit Medicine, University of Göteborg, Sweden

To cite this article: Löwhagen O. Diagnosis of asthma – a new approach. *Allergy* 2012; **67**: 713–717.

Keywords

asthma; basic mechanisms; dyspnea; hyperresponsiveness; physiology; sports.

Correspondence

Olle Löwhagen, Sahlgrenska Academy,
Instit Medicine, University of Göteborg,
411 15 Göteborg, Sweden.

Tel.: +46-708-272675

E-mail: olle.lowhagen@gu.se

Accepted for publication 2 March 2012

DOI:10.1111/j.1398-9995.2012.02821.x

Edited by: Marek Sanak

Abstract

Current definition of asthma involves four cornerstones: inflammation, hyperresponsiveness, bronchoconstriction, and symptoms. In research, the symptoms have had the slightest attention. According to international guidelines, the asthma symptoms are episodic breathlessness, wheeze, cough, tightness of the chest, and shortness of breath. As there are several symptoms, a primary question is how they are related to bronchoconstriction, the main clinical feature of asthma. Symptoms and lung function tests are regularly used for the evaluation of clinical health status and effect of treatment. However, there is no or poor correlation between these two variables, which means that they represent different mechanisms. Reduced lung function, such as a low FEV₁, represents bronchial constriction, what do the symptoms represent? Some symptoms such as breathlessness and shortness of breath seem not to be evidence-based asthma symptoms. Focusing on bronchial obstruction is important in view of the potential risk of asthma attacks, but nonobstructive symptoms occur frequently and may also cause severe discomfort and poor quality of life. Interpreting all symptoms as signs of bronchoconstriction (asthma) may lead to misinterpretation when assessing health status and effect of treatment. Although a 'soft' variable, the strength of symptoms is that they are representing various mechanisms. The physiological preconditions for control and defense of respiration must be considered in the diagnostic process, regardless of inflammation, allergy, psychology, or other etiological factors. Based on studies on dyspnea in cardiopulmonary diseases, including asthma and asthma-like disorders, there seems to be a continuous spectrum of symptoms and mechanisms integrated in a single asthma syndrome.

The cornerstones in current definition of asthma are inflammation, hyperresponsiveness, reversible airway obstruction, and respiratory symptoms (1–4). During the past decades, hospital care and mortality of asthma have decreased markedly; however, new clinical problems have been reported. One problem is the high percentage of uncontrolled or poorly controlled asthma (5–10). As effective treatment is available, these reports (5, 7, 11–17) have been frustrating for researchers and clinicians. Various causes have been discussed, lack of access to asthma clinics, low drug adherence, undertreatment, poor perception of asthma, phenotypes resistant to current medication, remodeling of the airways, and so on (17–25). Other asthma problems are the poor correlation between symptoms and other asthma tests, the observations that physician-diagnosed asthma sometimes cannot be verified and that different outcomes in asthma studies give differ-

ent results. Some of these problems may be explained by incomplete or incorrect asthma diagnosis. If the diagnosis is not 'right', the treatment will not be 'right.' Although it has been pointed out that differential diagnoses and comorbidity must be separated from asthma, the deeper aspects of this topic have only marginally been discussed in the literature. The need for critical discussion of diagnosis is underlined by the high prevalence of asthma-like disorders. These disorders may be confused with 'classical' asthma (26–28).

Aim

The aim is to discuss the diagnosis of adult asthma on the basis of existing control and defense mechanisms in the respiratory system, including not only bronchoconstriction but also other mechanisms. A new theory is presented.

Asthma symptoms

The medical history is the diagnostic base. However, the occurrence of several different symptoms in asthma may complicate the matter. In international guidelines, the listed symptoms are episodic breathlessness, wheeze, cough, tightness of the chest, and shortness of breath (1–4). A key question is how these symptoms are related to bronchial constriction, the cardinal clinical sign of asthma. The literature is unclear on this point. The first symptom mentioned in GINA's (Global Initiative for Asthma) chapter 'Diagnosis and Classification', (1) episodic breathlessness, seems not to be related to bronchoconstriction. By using factor analysis on questionnaire data in an epidemiological study (29), four different respiratory groups were identified: asthma, cough, breathlessness, and urgent medical visit (a subset of asthma). Breathlessness was not correlated with asthma (later established). The breathlessness group had normal lung function and normal airway responsiveness. In the same study, the factor analysis also showed that the degree of shortness of breath was similar in the asthma and the breathlessness groups, indicating that even shortness of breath is not related to bronchoconstriction. In a study comparing symptoms between one group with well-defined asthma and one group with asthma-like symptoms (no airway obstruction and no bronchial hyperresponsiveness), it was found that most symptoms were similar in the two groups (30). Of 14 lower airway/chest symptoms, only five were significantly different: 'difficulty in getting air', 'difficulty in taking deep breaths', 'wheezing', 'hissing', and 'feeling of sore throat'. Wheezing and hissing were significantly more common in the asthma group; the others were significantly more common in the asthma-like group. The tested symptoms were obtained from repeated qualitative surveys on patients admitted to an asthma-allergy clinic. Epidemiological studies have also shown that there is no quite typical symptom of asthma, but wheeze or the combination of wheeze and other symptoms seems to be the best available choice (29–32).

Dyspnea

Instead of symptoms, the term *dyspnea* (Greek for difficult breathing) is usually used in pulmonary, cardiovascular, neuromuscular, and other diseases with symptoms related to the respiration. The respiratory center receives projections from a variety of receptors: central and peripheral chemoreceptors, receptors in the airways, chest joints, tendons, and respiratory muscles that affect ventilation and may cause dyspnea. The current theory of dyspnea is that it arises as a result of a mismatch between incoming signals from the receptors and outgoing signals from the respiratory center to the respiratory muscles (motor command) (33–35). When propagated to the sensory area of the cortex, the mismatch is felt as dyspnea of varying type and degree. The qualitatively different types/sensations may be caused by different pathophysiological mechanisms (34–37).

Normal volunteers can distinguish sensations induced by breath holding, carbon dioxide inhalation, physical exercise,

and resistive respiratory loads (37–39). These sensations are caused by the activation of respiratory receptors. The best-described dyspneic sensations are effort/work, tightness of the chest, and air hunger (35). A bronchoconstriction induced by, for example, inhaled histamine and methacholine may be felt as an increased effort/work (35, 40). Effort/work may also be triggered if the respiratory muscles are weakened or if they are strained, for example, when lung volumes are increased because of hyperinflation (34, 41–43).

Several dyspneic sensations associated with bronchoconstriction have been described. When effort/work was induced by inhaled histamine and compared with an external resistance at a comparable magnitude, the histamine-induced dyspnea was greater (40). Inhaled lidocaine reduced the histamine-induced sensation, but had no effect on the effort caused by the external resistive load. Thus, histamine seems to have an effect besides the pure bronchoconstricting effect. Effort/work is probably associated with severe obstruction and the following dynamic hyperinflation (37, 43). In a study with inhaled methacholine, asthmatic patients reported dyspnea. When the effort to breathe was removed by mechanical ventilation, however, dyspnea remained and was expressed as tightness of the chest, indicating that tightness is not arising from the work of breathing but from airway receptors (44). Thus, stimulation of pulmonary sensory receptors, presumably vagal rapid-adapting receptors, could be the source of chest tightness that is experienced by many asthmatic patients. A simultaneous bronchial obstruction, however, is not necessary, as vagal afferents may be activated even when there is little or no airflow obstruction (45–47). During bronchoconstriction induced by inhaled methacholine in 232 patients referred to a pulmonary function laboratory, several expressions of dyspnea were observed (48). The authors explored the extent to which these symptoms were discriminated, finding that chest tightness, chest pain, wheeze, air hunger/breathlessness/inability to get air, and labored/obstructed breathing were well-separated clusters of symptoms, indicating corresponding, separated mechanisms.

Different stimuli may have different effects on the pulmonary receptors. Prostaglandin E₂, a mediator that increases sensory nerve excitability, exacerbates the dyspnea associated with exercise, despite the fact that it is a bronchodilator (49). Histamine inhalation leads to a more profound dyspnea than methacholine, despite a similar degree of bronchoconstriction (50, 51).

Air hunger/difficulty in getting air can be induced by the central and peripheral chemoreceptors in the presence of hypercapnia and hypoxia. The sense of air hunger appears to arise from an increased brain stem 'drive' to breathe (35, 36, 52, 53). Even patients with normal lung function and without signs of hypercapnia and hypoxia may suffer from air hunger (51, 54–57). Thus, activation of airway sensory nerves may lead to dyspnea, which need not necessarily be dependent on bronchial constriction (51).

Asthma-like disorders

Asthma-like, nonobstructive disorders have previously mainly been described as hyperventilation syndrome. However,

although hyperventilation of short duration has been clearly documented (58–62), the existence of a chronic hyperventilation state has been disputed as there is a lack of data on long-term disturbances of the blood gases (63, 64). Other asthma-like disorders described are nonasthmatic eosinophilic bronchitis (65, 66), functional breathing disorder (55), dysfunctional breathing (26, 67–70), multiple chemical sensitivity localized to the lower airways (71, 72), and sensory hyperreactivity (56, 73–77). The latter disorder is prevalent in patients hypersensitive to scents, and identified by a capsaicin inhalation cough test. Besides cough, other nonobstructive dyspneic reactions, such as heavy breathing and difficult in getting air, may be induced by capsaicin. The prevalence in the general population has been estimated to about 6% (28), which could be compared with a prevalence of about 8% in patients with physician-diagnosed asthma in the same country (78). Another asthma-like disorder reported in patients having an asthma diagnosis is dysfunctional breathing. It is reported to be common, 35% in asthmatic females and 20% in asthmatic males, mean 29% (26, 69, 70). The condition has been identified using the Nijmegen questionnaire, historically used for diagnosing hyperventilation syndrome (26, 69). The questionnaire includes 16 items. Symptoms directly related to asthma and asthma-like disorders are the following: fast or deep breathing, shortness of breathes, tight feeling in the chest, and cannot breath deeply/cannot sigh. The question is whether dysfunctional breathing is a disorder linked to asthma or whether it is an independent (psychological) state (70). As the condition is found in every third patient, it might be closely related to the primary disease. A discussion of inducing factors, however, is beyond the scope of this presentation. Asthma-like disorders have been observed in 42% of patients attending a hospital asthma clinic (79) and in 30% of patients referred to an asthma-allergy clinic for the investigation of suspected asthma (unpublished data).

The asthma syndrome

Several studies have shown that dyspneic sensations represent different respiratory mechanisms. Focusing on bronchial obstruction is important because of the potential risk of severe asthma attacks; however, other nonobstructive symptoms are frequent (28) and may also cause severe suffering and poor quality of life (60, 80, 81). Interpreting all symptoms as obstruction may lead to misinterpretations. The lack of a broader diagnostic approach may explain some of the current problems in the asthma area. For example, some uncontrolled asthma and 'difficult-to-treat asthma' may be explained by the fact that the patients do not have symptoms/mechanisms that are able to respond to the given treatment. Analyzing the causes of 'problematic' asthma, 'uncontrolled asthma', 'difficult-to-treat asthma', and 'severe refractory asthma' (82) is important, but of primary concern is the exploration of the mechanisms behind common symp-

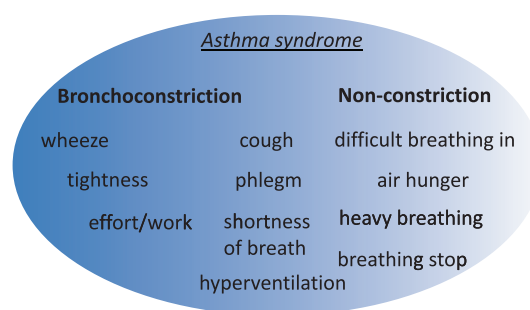


Figure 1 The asthma syndrome. A possible distribution of symptoms in relation to bronchoconstriction (asthma) and non-constriction (asthma-like disorder) illustrated by a gliding color scale.

toms like breathlessness, shortness of breath, tightness of the chest, difficult in getting air, air hunger, heavy breathing, and others.

A theory that is strongly supported is that symptoms/sensations with underlying mechanisms form a spectrum of reactions depending on which receptors in the respiratory system are activated. Thus, different mechanisms may be integrated in one single asthma syndrome (Fig. 1). If this theory turns out to be correct, it will have crucial implications for the diagnostic process. To establish a reliable diagnosis, it may not be enough to assess bronchial obstruction (lung function, hyperresponsiveness, etc.). For a complete diagnosis, the whole symptom picture must be analyzed. This requires a new symptom questionnaire, as the list of symptoms described in GINA and other consensus reports is incomplete and not evidence-based. A new list is in progress (own data). Substantially increased research is needed to evaluate which symptoms reflect bronchial constriction and which reflect other mechanisms. The most likely obstructive symptoms are wheezing, tightness of the chest, and cough. Other symptoms such as breathlessness, shortness of breath, heavy breathing, difficult in getting air, air hunger, and difficult in taking deep breaths probably reflect nonobstructive dyspnea. Symptoms are 'soft' variables that primarily have to be measured by subjective scales. However, as the underlying mechanisms become known, it will be possible to develop objective tests. This has long been the case with bronchial constriction (lung function tests) and hyperresponsiveness (methacholine test, mannitol test, etc.). Other examples of developed objective tests are the voluntary hyperventilation test for diagnosing hyperventilation syndrome (58–60) and the capsaicin inhalation test for diagnosing sensory airway hyperreactivity (56, 83).

Conflict of interest

There is no conflict of interest.

References

- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (update 2010), 2010. Available at www.ginasthma.org. Last accessed date 20 March 2012.
- National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007;**120**(5 Suppl):S94–S138.
- Levy ML, Fletcher M, Price DB, Hausen T, Halbert RJ, Yawn BP. International Primary Care Respiratory Group (IPSRG) Guidelines: diagnosis of respiratory diseases in primary care. *Prim Care Respir J* 2006;**15**:20–34.
- British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. *Thorax* 2008;**63**(Suppl 4):iv1–iv121.
- Chapman KR, Boulet LP, Rea RM, Franssen E. Suboptimal asthma control: prevalence, detection and consequences in general practice. *Eur Respir J* 2008;**31**:320–325.
- Stanford RH, Gilsenan AW, Ziemiecki R, Zhou X, Lincourt WR, Ortega H. Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies (ACCESS). *J Asthma* 2010;**47**:257–262.
- Vermeire PA, Rabe KF, Soriano JB, Maier WC. Asthma control and differences in management practices across seven European countries. *Respir Med* 2002;**96**:142–149.
- Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national Web-based survey. *J Allergy Clin Immunol* 2007;**119**:1454–1461.
- Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007;**120**:1360–1367.
- Carlton BG, Lucas DO, Ellis EF, Conboy-Ellis K, Shoheiber O, Stempel DA. The status of asthma control and asthma prescribing practices in the United States: results of a large prospective asthma control survey of primary care practices. *J Asthma* 2005;**42**:529–535.
- Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802–807.
- Chapman KR, Ernst P, Grenville A, Dewland P, Zimmerman S. Control of asthma in Canada: failure to achieve guideline targets. *Can Respir J* 2001;**8**(Suppl A):35A–40A.
- Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;**114**:40–47.
- Luskin AT. Achieving asthma control: the need for risk assessment. *Manag Care* 2005;**14**(8 Suppl):12–15; discussion 25–27.
- FitzGerald JM, Boulet LP, McIvor RA, Zimmerman S, Chapman KR. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. *Can Respir J* 2006;**13**:253–259.
- McIvor RA, Boulet LP, FitzGerald JM, Zimmerman S, Chapman KR. Asthma control in Canada: no improvement since we last looked in 1999. *Can Fam Physician* 2007;**53**:673–677.
- Holgate S, Bisgaard H, Bjermer L, Haahela T, Haughey J, Horne R et al. The Brussels Declaration: the need for change in asthma management. *Eur Respir J* 2008;**32**:1433–1442.
- Cypcar D, Busse WW. Steroid-resistant asthma. *J Allergy Clin Immunol* 1993;**92**:362–372.
- Nimmagadda SR, Spahn JD, Leung DY, Szeffler SJ. Steroid-resistant asthma: evaluation and management. *Ann Allergy Asthma Immunol* 1996;**77**:345–355; quiz 355–356.
- Kay AB. Pathology of mild, severe, and fatal asthma. *Am J Respir Crit Care Med* 1996;**154**(2 Pt 2):S66–S69.
- Barnes PJ. Corticosteroid resistance in airway disease. *Proc Am Thorac Soc* 2004;**1**:264–268.
- Adcock IM, Ito K. Steroid resistance in asthma: a major problem requiring novel solutions or a non-issue? *Curr Opin Pharmacol* 2004;**4**:257–262.
- Wenzel S. Severe asthma in adults. *Am J Respir Crit Care Med* 2005;**172**:149–160.
- Adcock IM, Ford PA, Bhavsar P, Ahmad T, Chung KF. Steroid resistance in asthma: mechanisms and treatment options. *Curr Allergy Asthma Rep* 2008;**8**:171–178.
- Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;**66**:910–917.
- Thomas M, McKinley RK, Freeman E, Foy C. Prevalence of dysfunctional breathing in patients treated for asthma in primary care: cross sectional survey. *BMJ* 2001;**322**:1098–1100.
- Johansson A, Bramerson A, Millqvist E, Nordin S, Bende M. Prevalence and risk factors for self-reported odour intolerance: the Skovde population-based study. *Int Arch Occup Environ Health* 2005;**78**:559–564.
- Johansson A, Millqvist E, Nordin S, Bende M. Relationship between self-reported odor intolerance and sensitivity to inhaled capsaicin: proposed definition of airway sensory hyperreactivity and estimation of its prevalence. *Chest* 2006;**129**:1623–1628.
- Bai J, Peat J, Berry G, Marks G, Woolcock A. Questionnaire items that predict asthma and other respiratory conditions in adults. *Chest* 1998;**114**:1343–1348.
- Ringsberg KC, Bjarneman P, Löwhagen O, Oden A, Toren K. Differences in trigger factors and symptoms between patients with asthma-like symptoms and patients with asthma: development of a basis for a questionnaire. *Respir Med* 2002;**96**:305–311.
- Sistek D, Tschopp JM, Schindler C, Brutsche M, Ackermann-Liebrich U, Perruchoud AP et al. Clinical diagnosis of current asthma: predictive value of respiratory symptoms in the SAPALDIA study. Swiss Study on Air Pollution and Lung Diseases in Adults. *Eur Respir J* 2001;**17**:214–219.
- Pekkanen J, Pearce N. Defining asthma in epidemiological studies. *Eur Respir J* 1999;**14**:951–957.
- Schwartzstein RM, Simon PM, Weiss JW, Fencel V, Weinberger SE. Breathlessness induced by dissociation between ventilation and chemical drive. *Am Rev Respir Dis* 1989;**139**:1231–1237.
- Manning HL, Schwartzstein RM. Respiratory sensations in asthma: physiological and clinical implications. *J Asthma* 2001;**38**:447–460.
- Nishino T. Dyspnoea: underlying mechanisms and treatment. *Br J Anaesth* 2011;**106**:463–474.
- Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. *N Engl J Med* 1995;**333**:1547–1553.
- Scano G, Stendardi L, Grazzini M. Understanding dyspnoea by its language. *Eur Respir J* 2005;**25**:380–385.
- Simon PM, Schwartzstein RM, Weiss JW, Lahive K, Fencel V, Teghtsoonian M et al. Distinguishable sensations of breathlessness induced in normal volunteers. *Am Rev Respir Dis* 1989;**140**:1021–1027.
- Simon PM, Schwartzstein RM, Weiss JW, Fencel V, Teghtsoonian M, Weinberger SE. Distinguishable types of dyspnea in patients with shortness of breath. *Am Rev Respir Dis* 1990;**142**:1009–1014.

40. Taguchi O, Kikuchi Y, Hida W, Iwase N, Satoh M, Chonan T et al. Effects of bronchoconstriction and external resistive loading on the sensation of dyspnea. *J Appl Physiol* 1991;**71**:2183–2190.
41. Gandevia SC, Killian KJ, Campbell EJ. The effect of respiratory muscle fatigue on respiratory sensations. *Clin Sci (Lond)* 1981;**60**:463–466.
42. Loughheed D, Webb K, O'Donnell D. Breathlessness during induced lung hyperinflation in asthma: the role of the inspiratory threshold load. *Am J Respir Crit Care Med* 1995;**152**:911–920.
43. Loughheed M, Fisser T, O'Donnell D. Dynamic hyperinflation during bronchoconstriction in asthma. Implication for symptom perception. *Chest* 2006;**130**:1072–1081.
44. Binks AP, Moosavi SH, Banzett RB, Schwartzstein RM. "Tightness" sensation of asthma does not arise from the work of breathing. *Am J Respir Crit Care Med* 2002;**165**:78–82.
45. Moy ML, Woodrow Weiss J, Sparrow D, Israel E, Schwartzstein RM. Quality of dyspnea in bronchoconstriction differs from external resistive loads. *Am J Respir Crit Care Med* 2000;**162**(2 Pt 1):451–455.
46. Manning HL, Mahler DA. Pathophysiology of dyspnea. *Monaldi Arch Chest Dis* 2001;**56**:325–330.
47. Undem BJ, Carr MJ. Pharmacology of airway afferent nerve activity. *Respir Res* 2001;**2**:234–244.
48. Killian KJ, Watson R, Otis J, St Amand TA, O'Byrne PM. Symptom perception during acute bronchoconstriction. *Am J Respir Crit Care Med* 2000;**162**(2 Pt 1):490–496.
49. Taguchi O, Kikuchi Y, Hida W, Iwase N, Okabe S, Chonan T et al. Prostaglandin E2 inhalation increases the sensation of dyspnea during exercise. *Am Rev Respir Dis* 1992;**145**:1346–1349.
50. Tetzlaff K, Leplow B, Ten Thoren C, Dahme B. Perception of dyspnea during histamine- and methacholine-induced bronchoconstriction. *Respiration* 1999;**66**:427–433.
51. Undem BJ, Carr MJ. The role of nerves in asthma. *Curr Allergy Asthma Rep* 2002;**2**:159–165.
52. Banzett RB, Lansing RW, Reid MB, Adams L, Brown R. 'Air hunger' arising from increased PCO2 in mechanically ventilated quadriplegics. *Respir Physiol* 1989;**76**:53–67.
53. Banzett RB, Lansing RW, Brown R, Topulos GP, Yager D, Steele SM et al. 'Air hunger' from increased PCO2 persists after complete neuromuscular block in humans. *Respir Physiol* 1990;**81**:1–17.
54. Lowhagen O. [Functional respiratory disorders as significant differential diagnosis in asthma]. *Lakartidningen* 1989;**86**:57–59.
- Funktionella andningsbesvar viktig differentialdiagnos vid astma.
55. Ringsberg KC, Lowhagen O, Sivik T. Psychological differences between asthmatics and patients suffering from an asthma-like condition, functional breathing disorder: a comparison between the two groups concerning personality, psychosocial and somatic parameters. *Integr Physiol Behav Sci* 1993;**28**:358–367.
56. Millqvist E, Bende M, Lowhagen O. Sensory hyperreactivity—a possible mechanism underlying cough and asthma-like symptoms. *Allergy* 1998;**53**:1208–1212.
57. Lowhagen O. Asthma and asthma-like disorders. *Respir Med* 1999;**93**:851–855.
58. Grossman P, de Swart JC. Diagnosis of hyperventilation syndrome on the basis of reported complaints. *J Psychosom Res* 1984;**28**:97–104.
59. Gardner WN. The pathophysiology of hyperventilation disorders. *Chest* 1996;**109**:516–534.
60. Folgering H. The pathophysiology of hyperventilation syndrome. *Monaldi Arch Chest Dis* 1999;**54**:365–372.
61. Lowhagen O, Arvidsson M, Bjarneman P, Jorgensen N. Exercise-induced respiratory symptoms are not always asthma. *Respir Med* 1999;**93**:734–738.
62. Ternesten-Hasseus E, Johansson EL, Bende M, Millqvist E. Dyspnea from exercise in cold air is not always asthma. *J Asthma* 2008;**45**:705–709.
63. Bass C. Hyperventilation syndrome: a chimera? *J Psychosom Res* 1997;**42**:421–426.
64. Hornsveid H, Garssen B. Hyperventilation syndrome: an elegant but scientifically untenable concept. *Neth J Med* 1997;**50**:13–20.
65. Brightling CE. Cough due to asthma and nonasthmatic eosinophilic bronchitis. *Lung* 2010;**188**(Suppl 1):S13–S17.
66. Brightling CE. Eosinophils, bronchitis and asthma: pathogenesis of cough and airflow obstruction. *Pulm Pharmacol Ther* 2011;**24**:324–327.
67. Keeley D, Osman L. Dysfunctional breathing and asthma. It is important to tell the difference. *BMJ* 2001;**322**:1075–1076.
68. Thomas M, McKinley RK, Freeman E, Foy C, Prodder P, Price D. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 2003;**58**:110–115.
69. Thomas M, McKinley RK, Freeman E, Foy C, Price D. The prevalence of dysfunctional breathing in adults in the community with and without asthma. *Prim Care Respir J* 2005;**14**:78–82.
70. Thomas M, Bruton A, Moffat M, Cleland J. Asthma and psychological dysfunction. *Prim Care Respir J* 2011;**20**:250–256.
71. Ternesten-Hasseus E, Bende M, Millqvist E. Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity. *J Occup Environ Med* 2002;**44**:1012–1017.
72. Holst H, Arendt-Nielsen L, Mosbech H, Vesterhauge S, Elberling J. The capsaicin cough reflex in patients with symptoms elicited by odorous chemicals. *Int J Hyg Environ Health* 2010;**213**:66–71.
73. Millqvist E. Cough provocation with capsaicin is an objective way to test sensory hyperreactivity in patients with asthma-like symptoms. *Allergy* 2000;**55**:546–550.
74. Johansson A, Lowhagen O, Millqvist E, Bende M. Capsaicin inhalation test for identification of sensory hyperreactivity. *Respir Med* 2002;**96**:731–735.
75. Nordin S, Millqvist E, Lowhagen O, Bende M. A short Chemical Sensitivity Scale for assessment of airway sensory hyperreactivity. *Int Arch Occup Environ Health* 2004;**77**:249–254.
76. Andersson L, Johansson A, Millqvist E, Nordin S, Bende M. Prevalence and risk factors for chemical sensitivity and sensory hyperreactivity in teenagers. *Int J Hyg Environ Health* 2008;**211**:690–697.
77. Johansson A, Millqvist E, Bende M. Relationship of airway sensory hyperreactivity to asthma and psychiatric morbidity. *Ann Allergy Asthma Immunol* 2010;**105**:20–23.
78. Lotvall J, Ekerljung L, Ronmark EP, Wennergren G, Linden A, Ronmark E et al. West Sweden Asthma Study: prevalence trends over the last 18 years argues no recent increase in asthma. *Respir Res* 2009;**10**:94.
79. McClean PA, Howells JCG, Boyd G. Use of Nijmegen hyperventilation questionnaire and hyperventilation provocation in a hospital asthma clinic. *Am J Respir Crit Care Med* 1999;**159**:A652.
80. Ternesten-Hasseus E, Lowhagen O, Millqvist E. Quality of life and capsaicin sensitivity in patients with airway symptoms induced by chemicals and scents: a longitudinal study. *Environ Health Perspect* 2007;**115**:425–429.
81. Ringsberg KC, Segesten K, Akerlind I. Walking around in circles—the life situation of patients with asthma-like symptoms but negative asthma tests. *Scand J Caring Sci* 1997;**11**:103–112.
82. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;**66**:910–917.
83. Ternesten-Hasseus E, Larsson C, Bende M, Millqvist E. Capsaicin provocation using two different inhalation devices. *Respir Med* 2008;**102**:1784–1790.