CHEST

Objective Cough Frequency, Airway Inflammation, and Disease Control in Asthma

Paul A. Marsden, MD, PhD; Imran Satia, MD; Baharudin Ibrahim, PhD; Ashley Woodcock, MD; Lucy Yates, BSc (Hons); Iona Donnelly, BSc; Lisa Jolly, BSc; Neil C. Thomson, MD, PhD; Stephen J. Fowler, MD; and Jaclyn A. Smith, MD, PhD

BACKGROUND: Cough is recognized as an important troublesome symptom in the diagnosis and monitoring of asthma. Asthma control is thought to be determined by the degree of airway inflammation and hyperresponsiveness but how these factors relate to cough frequency is unclear. The goal of this study was to investigate the relationships between objective cough frequency, disease control, airflow obstruction, and airway inflammation in asthma.

METHODS: Participants with asthma underwent 24-h ambulatory cough monitoring and assessment of exhaled nitric oxide, spirometry, methacholine challenge, and sputum induction (cell counts and inflammatory mediator levels). Asthma control was assessed by using the Global Initiative for Asthma (GINA) classification and the Asthma Control Questionnaire (ACQ). The number of cough sounds was manually counted and expressed as coughs per hour (c/h).

RESULTS: Eighty-nine subjects with asthma (mean ± SD age, 57 ± 12 years; 57% female) were recruited. According to GINA criteria, 18 (20.2%) patients were classified as controlled, 39 (43.8%) partly controlled, and 32 (36%) uncontrolled; the median ACQ score was 1 (range, 0.0-4.4). The 6-item ACQ correlated with 24-h cough frequency ($r = 0.40$; $P < .001$), and patients with uncontrolled asthma (per GINA criteria) had higher median 24-h cough frequency (4.2 c/h; range, 0.3-27.6) compared with partially controlled asthma (1.8 c/h; range, 0.2-25.3; $P = .01$) and controlled asthma (1.7 c/h; range, 0.3-6.7; $P = .002$). Measures of airway inflammation were not significantly different between GINA categories and were not correlated with ACQ. In multivariate analyses, increasing cough frequency and worsening FEV_1 independently predicted measures of asthma control.

CONCLUSIONS: Ambulatory cough frequency monitoring provides an objective assessment of asthma symptoms that correlates with standard measures of asthma control but not airflow obstruction or airway inflammation. Moreover, cough frequency and airflow obstruction represent independent dimensions of asthma control. CHEST 2016; 149(6):1460-1466

KEY WORDS: airway inflammation; asthma; cough

ABBREVIATIONS: ACQ = Asthma Control Questionnaire; BHR = bronchial hyperresponsiveness; eNO = exhaled nitric oxide; GINA = Global Initiative for Asthma

AFFILIATIONS: From the Centre for Respiratory Medicine and Allergy (Drs Marsden, Satia, Ibrahim, Woodcock, Fowler, and Smith and Ms Yates), University of Manchester, and Manchester Academic Health Science Centre, Manchester, England; University Hospital of South Manchester NHS Foundation Trust (Drs Marsden, Satia, Woodcock, and Smith), Manchester, England; Institute of Infection Immunity and Inflammation (Mss Donnelly and Jolly, and Dr Thomson), University of Glasgow, Glasgow, Scotland; Lancashire Teaching Hospitals NHS Foundation Trust (Drs Marsden and Fowler), Preston, England; and the School of Pharmaceutical Sciences (Dr Ibrahim), Universiti Sains Malaysia, Penang, Malaysia.

Part of this article has been presented in abstract form (Marsden PA, Ibrahim B, Woodcock AA, Fowler SJ, Smith JA.

Asthma is a chronic inflammatory disease of the airways, estimated to affect 300 million people worldwide.[1] The aim of asthma treatment is to achieve and maintain control of the clinical manifestations of the disease; this approach includes managing current symptoms but also reducing the risk of future exacerbations. However, despite an increase in our understanding of the mechanisms underlying asthma and the availability of effective treatments, optimal asthma control is often not achieved.[2] Several tools are currently in use for describing asthma control; a categorical classification based on expert opinion has been suggested by the Global Initiative for Asthma (GINA), and clinical trials have commonly used the Asthma Control Questionnaire (ACQ),[3] which gives a numerical score and is responsive to treatment.[4-6] These tools rely on patient recall of symptom frequency, severity, and medication use over several weeks. Such reporting is inevitably influenced by a range of external factors unrelated to asthma, such as vigilance, mood, and social interactions, as well as memory. A more objective measure of asthma symptoms may therefore be a useful tool for assessing control and treatment responses.

Cough is an important symptom in asthma because it predicts disease severity,[7,8] poor prognosis,[9] and is a common,[10] troublesome symptom.[11] Unlike wheezing, breathlessness, and chest tightness, coughing is readily objectively quantified by using ambulatory monitoring systems.[12] We have previously shown that objective cough counts are elevated in patients with asthma compared with healthy control subjects but are poorly represented by patient reports of cough.[13] However, it is unknown whether the objective measurement of cough frequency is a useful marker of asthma control. Furthermore, it is unknown whether cough frequency is related to elements of asthma pathophysiology such as airflow obstruction and inflammation. Therefore, the aim of the current study was to examine, in a group of patients with asthma not selected for cough, the relationships between objective cough frequency, asthma control (using the GINA classification and the ACQ), and measures of airway obstruction and inflammation.

Subjects and Methods

Subjects

We studied subjects with asthma recruited from a longitudinal cohort of adult patients with asthma that had been established in 1997.[14,15] Inclusion criteria were: physician diagnosis of asthma, age ≥ 16 years, symptoms of asthma in the preceding 12 months, and minimum treatment with a short-acting bronchodilator. Ethical approval was obtained from the regional Research Ethics Committee (06/Q1403/110), and subjects provided written informed consent.

Study Procedures

All subjects attended the North West Lung Research Centre, University Hospital of South Manchester, on two occasions, at least 1 week apart and within a 2-week period. Prior to both visits, subjects withheld medication as follows: short-acting bronchodilators for 6 h; long-acting bronchodilators, theophyllines, and leukotriene receptor antagonists for 12 h; and antihistamines and inhaled steroids for 48 h.

At visit 1, subjects performed exhaled nitric oxide (eNO) testing (NIOX, Aerocrine Inc) followed by spirometry (Jaeger, Viasys Healthcare) and reversibility of FEV_1 to 400 μg of salbutamol determined according to American Thoracic Society criteria.[16] Reversible airflow obstruction was defined by an increase in FEV_1 of ≥ 12%. Sputum was induced by using 3%, 4%, and 5% saline sequentially via an ultrasonic nebulizer (Sonix 2000, Clement Clarke). Samples were processed as previously described.[17] A total of 400 nonsquamous cells were counted by a fully trained observer and were expressed both as a percentage and as a number of cells per gram of selected sputum. Competitive or sandwich enzyme-linked immunosorbent assays were performed to measure inflammatory mediators; leukotriene B_4, prostaglandin E_2, 8-isoprostane, leukotriene C_4, IL-8, myeloperoxidase, and eosinophilic cationic protein. Subjects completed the 7-item Asthma Control Questionnaire (ACQ-7).[3] The subjects were categorized into levels of asthma control according to GINA guidelines by using information given in questionnaires, clinical history, and pulmonary function. Finally, subjects underwent ambulatory 24-h cough monitoring by using the VitaloJAK cough recorder (Vitalograph Ltd) as previously described.[18,19] Recordings were analyzed by using an audio editing package (Audition 3.0, Adobe Systems Inc). The number of cough sounds was manually counted and expressed as coughs per hour (c/h).

At visit 2, bronchial hyperresponsiveness (BHR) was assessed by using the 5-breath dosimeter method (KoKo, Ferraris Respiratory, Inc) according to published guidelines, and it was defined by the dose causing a 20% drop from baseline FEV_1 in response to methacholine.[20] Skin prick testing was performed, and atopy was defined by the presence of at least one positive skin prick test result to common inhaled allergens (eg, house dust mite, cat, dog, grass, mixed molds).

Statistical Analysis

Data were analyzed by using SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation). Overall 24-h and daytime cough rates were log transformed prior to analysis and geometric mean (95% CI)

Am J Respir Crit Care Med. 2009;179:A5757 and *Thorax*. 2009; 64(suppl iV): A15).

FUNDING/SUPPORT: This research was funded by the North West Lung Research Centre Endowment Fund.

CORRESPONDENCE TO: Jaclyn A. Smith, MD, PhD, Education and Research Centre, 2nd Floor, University of Manchester, University Hospital of South Manchester, Southmoor Rd, Manchester, M23 9LT England; e-mail: jacky.smith@manchester.ac.uk

DOI: http://dx.doi.org/10.1016/j.chest.2016.02.676