Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: A systematic review

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Traditionally, asthma has been considered a disease that predominantly involves the large airways. Today, this concept is being challenged, and increasing evidence has become available showing that abnormalities in the small airways also contribute to the clinical expression of asthma. The small airways can be affected by inflammation, remodeling, and changes in the surrounding tissue, all contributing to small-airways dysfunction. In this article we have performed a systematic review of the literature on the association between small-airways dysfunction and clinical signs and symptoms of asthma. This review shows that small-airways dysfunction associates with worse control of asthma, higher numbers of exacerbations, the presence of nocturnal asthma, more severe bronchial hyperresponsiveness, exercise-induced asthma, and the late-phase allergic response. Importantly, small-airways dysfunction can already be present in patients with mild asthma. Our review provides suggestive evidence that a better response of the small airways to inhaled steroids or montelukast associates with better asthma control. For this reason, an early recognition of small-airways dysfunction is important because it enables the physician to start timely treatment to target the small airways. It is important to develop simpler and more reliable tools (eg, questionnaires or bronchial provocation tests with small-particle stimuli) to assess the presence and extent of small-airways dysfunction in daily clinical practice. (J Allergy Clin Immunol 2013;131:646-57.)

Key words: *Small-airways disease, asthma, phenotypes, asthma control*

Abbreviations used

ACQ:	Asthma Control Questionnaire
AX:	Reactance area
BAL:	Bronchoalveolar lavage
BDP:	Beclomethasone dipropionate
BHR:	Bronchial hyperresponsiveness
CFC:	Chlorofluorocarbon
DPI:	Dry powder inhaler
$FEF_{25\%-75\%}$:	Forced expiratory flow at 25% to 75% of forced vital capacity
$FEF_{50\%}$:	Forced expiratory flow at 50% of forced vital capacity
HDM:	House dust mite
HFA:	Hydrofluoroalkane
ICS:	Inhaled corticosteroid
MBNW:	Multiple-breath nitrogen washout test
MMAD:	Mass median aerodynamic diameter
NO:	Nitric oxide
PEF:	Peak expiratory flow
$PM_{2.5}$:	Particulate matter less than 2.5 μm in diameter
PM_{10}:	Particulate matter less than 10 μm in diameter
R5:	Resistance of the respiratory system at 5 Hz
R20:	Resistance of the respiratory system at 20 Hz
R5-R20:	Difference between R5 and R20
RV:	Residual volume
Sacin:	Ventilation heterogeneity generated in the acinar lung zone
SBNT:	Single-breath nitrogen test
Scond:	Ventilation heterogeneity generated in the conductive lung zone
TLC:	Total lung capacity

Asthma is a chronic inflammatory lung disease affecting the total bronchial tree from the large to the small airways. Four decades ago, it was already suggested that the small airways are involved in asthma. Hogg et al,[1] using a retrograde catheter, demonstrated that the resistance of the small airways is increased in patients with chronic obstructive lung disease compared with that seen in healthy control subjects. However, because the contribution of the small airways to total lung resistance was minimal, asthma was considered a disease mainly of the large airways, and the small airways were labeled the "quiet zone."[1-4]

During the last decade, there has been renewed interest in the role of small-airways disease in asthma. The small airways are usually defined as airways with an internal diameter of less than 2 mm, referring to the landmark study of Macklem and Mead,[2] who wedged a retrograde catheter with a diameter of 2 mm in the bronchi to measure airflow resistance. The definition is also in line

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Supported by Chiesi.

Disclosure of potential conflict of interest: D. S. Postma has received grants from the Dutch Asthma Foundation, NWO, ZonMw, SAB, AstraZeneca, and Chiesi and has received travel support from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Nycomed/Takeda. M. van den Berge has consulted for GlaxoSmithKline and Novartis and has received payment for a lecture for Nycomed. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication August 31, 2012; revised December 1, 2012; accepted for publication December 26, 2012.

Available online February 5, 2013.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2012.12.1567

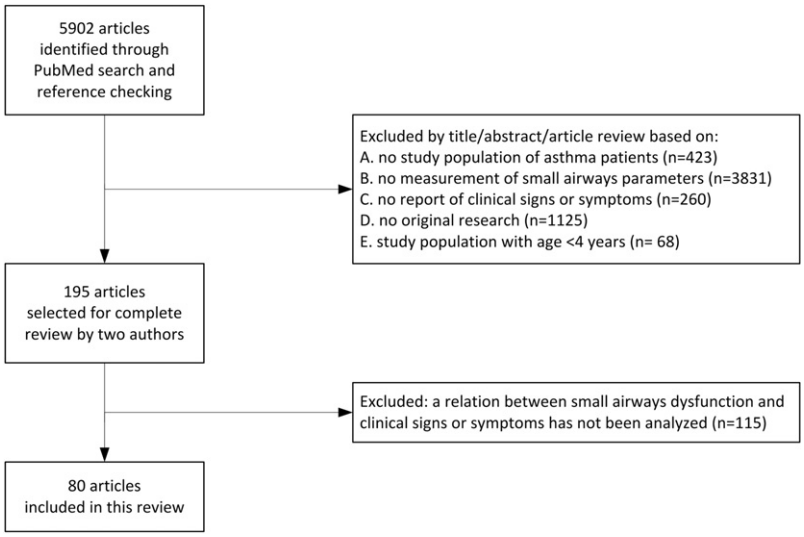

FIG 1. Flowchart of the literature search. A PubMed search resulted in 5902 articles using the term "Asthma AND (small airway* OR peripheral airway* OR distal airway* OR distal lung OR impulse oscillometry OR alveolar nitric oxide OR exhaled nitric oxide OR nocturnal OR residual volume OR montelukast OR HFA OR hydrofluoroalkane OR extra fine OR transbronchial OR closing volume OR closing capacity OR air trapping OR hyperinflation OR nitrogen OR HRCT OR high resolution CT OR MRI)" limited to the English language and human subjects. Hand searching of the reference lists of retrieved articles and reviews was also undertaken. Titles and/or abstracts and/or full articles were reviewed during the initial search, and 195 articles were selected according to the following criteria: A, a study population of asthmatic patients; B, measurement of small-airways parameters; C, reporting clinical signs or symptoms. An article was excluded if it met criteria D (ie, no original research [review, editorial, or case report]) or E (ie, a study population with age <4 years to exclude transient wheezing). According to these criteria, the relevance of these 224 articles were reviewed by 2 authors considering whether the relation between small-airways dysfunction and clinical signs or symptoms had appropriately been analyzed (clinical symptoms or severity of symptoms were not based on lung function or steroid use). Discrepancies were resolved by means of open discussion with all authors. Using this method, 80 articles were finally selected for extensive review in this article. The search was conducted in October 2012.

with the findings of Weibel,[5] who found that the total cross-sectional area of the bronchial tree increases exponentially after around the eighth-generation airways, which have an internal diameter of approximately 2 mm. The small airways are difficult to investigate because they are relatively inaccessible. Currently, several tests are available to assess small-airways dysfunction. The value and limitations of each test have been extensively reviewed elsewhere.[6-8] The conclusion of these reviews is that there exists no gold standard to assess small-airways dysfunction, and therefore all parameters are indicative rather than conclusive.[6-8]

Recent studies suggest that abnormalities in the small airways can contribute to the clinical expression of asthma.[8-10] The small airways can be affected by inflammation, remodeling, and changes in the surrounding tissue, all contributing to small-airways dysfunction.[9,11-14] The aim of this systematic review is to investigate the association between small-airways dysfunction on the one hand and clinical signs and symptoms of asthma on the other hand. To this end, we performed a PubMed search and selected relevant articles based on the following criteria: study population of patients with asthma, measurement of a small-airways parameter, and clinical signs or symptoms of asthma (Fig 1). Table I shows the small-airways parameters that were selected in the current review.[6] We did not include magnetic resonance imaging and frequency dependence compliance because they have not been used in clinical studies relating small-airways function to clinical parameters.

We divided the relevant articles in 8 domains possibly associated with small-airways dysfunction: symptoms and asthma control, exacerbations, nocturnal asthma, bronchial hyperresponsiveness (BHR), exercise-induced bronchoconstriction, allergen exposure, air pollution, and medication. For each of these domains, relevant articles are further subdivided based on the test used to measure small-airways dysfunction according to the following categories: flow, resistance, ventilation, heterogeneity, air trapping, and inflammation.[6]

ASTHMA SYMPTOMS AND CONTROL

Several studies have investigated the association between asthma symptoms or control and small-airways dysfunction, as reflected by different parameters of the small airways. Symptoms were assessed with asthma questionnaires or self-reported by the patient.

Takeda et al[15] measured large- and small-airways function with impulse oscillometry in 65 patients with stable asthma and assessed associations with health status, dyspnea, and asthma control using the St George's Respiratory Questionnaire, the Baseline Dyspnea Index, and the Asthma Control Questionnaire (ACQ), respectively. An increase in small-airways resistance, as reflected by the total resistance of the respiratory system at 5 Hz (R5) minus the resistance of the respiratory system at 20 Hz (R20; R5-R20), and an increase in large-airways resistance, as reflected by the R20 value, were independently associated with a lower health status and more dyspnea. Interestingly, greater small-airways reactance (ie, reactance of the respiratory system at 5 Hz) was