

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;■■■■:■■■-■■■.)

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
Scnd:	Ventilation heterogeneity generated in the conductive lung zone
TLC:	Total lung capacity

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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

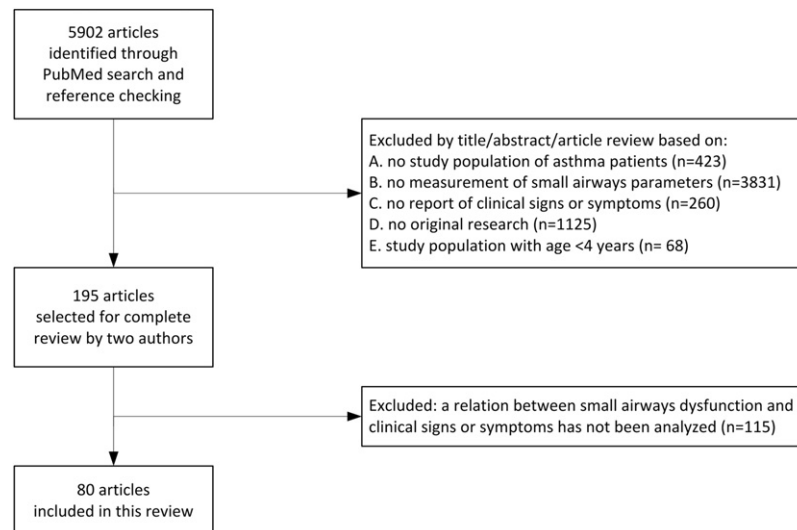


FIG 1. Flowchart of the literature search. A PubMed search resulted in 5902 articles using the term “Asthma AND (small airway* OR peripheral airway* OR distal airway* OR distal lung OR impulse oscillometry OR alveolar nitric oxide OR exhaled nitric oxide OR nocturnal OR residual volume OR montelukast 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 al¹⁵ 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

TABLE I. Parameters to assess small- or large-airways (dys) function or inflammation

Method	Parameters of small-airways (dys)function	Parameters of large-airways (dys)function
Flow		
Spirometry	FEF _{25%-75%} , FEF _{50%} , FVC/SVC	FEV ₁ , FEV ₁ /FVC ratio, PEF
Helium-oxygen flow-volume curves	FEF _{50%} (no increase)	FEF _{50%} (increase)
Resistance		
IOS	R5-R20, AX, X5, Fres	R20
Bronchoscopy	Peripheral resistance	
Ventilation heterogeneity		
SBNT	CV, CC; slope phase III	
MBNW-test	Sacin, Scond	
H ³ HeMRI	Regional ventilation defects	
Air trapping		
Body plethysmography	FRC, RV, RV/TLC	
HRCT	Air trapping	
Inflammation		
Bronchoscopic biopsy	Transbronchial biopsy	Endobronchial biopsy
Bronchoscopy	BAL	
Sputum induction	Late-phase sputum	Early-phase sputum
Exhaled NO	Alveolar NO	Bronchial NO
Additional		
Frequency dependence of dynamic compliance	Increased respiratory frequency Decreased dynamic compliance	

CC, Closing capacity; CV, closing volume; FRC, functional residual capacity; Fres, resonant frequency of reactance; FVC, forced vital capacity; H³HeMRI, Magnetic resonance imaging with inhaled hyperpolarized helium-3 gas; HRCT, High-resolution computed tomography; IOS, Impulse oscillometry; R5, Resistance of the respiratory system at 5 Hz; R20, Resistance of the respiratory system at 20 Hz; R5-R20, difference of R5 and R20; SVC, slow vital capacity; X5, Reactance of the respiratory system at 5 Hz.

associated with loss of asthma control. Shi et al¹⁶ additionally found that dysfunction of the small, but not the large, airways was associated with worse asthma control. They found that the R5-R20 and reactance area (AX) values were the only small-airways parameters that could discriminate between patients with controlled and uncontrolled asthma, with a high sensitivity and specificity of 84% and 86%, respectively.

Ventilation heterogeneity of the small airways can be investigated with a nitrogen washout test. A higher ventilation heterogeneity is reflected by an increase in the phase III slope. A limitation of this measurement is that the large airways can also contribute to an abnormal phase III slope.^{17,18} In this context the multiple-breath nitrogen washout (MBNW) test is an important improvement because it is able to distinguish between ventilation heterogeneity generated in the conductive lung zone (Scond) and ventilation heterogeneity generated in the acinar lung zone (Sacin), with a cutoff around the 15th generation.¹⁹ Farah et al²⁰ demonstrated that patients with poorly controlled asthma have higher Scond and Sacin values than patients with well-controlled asthma. These results are in line with those of Bourdin et al,²¹ who demonstrated that asthmatic patients with more alveolar heterogeneity, as determined with the phase III slope of the single-breath nitrogen test (SBNT), have worse asthma control (Fig 2, A).

Several studies have demonstrated that higher alveolar nitric oxide (NO) concentrations are associated with the presence of

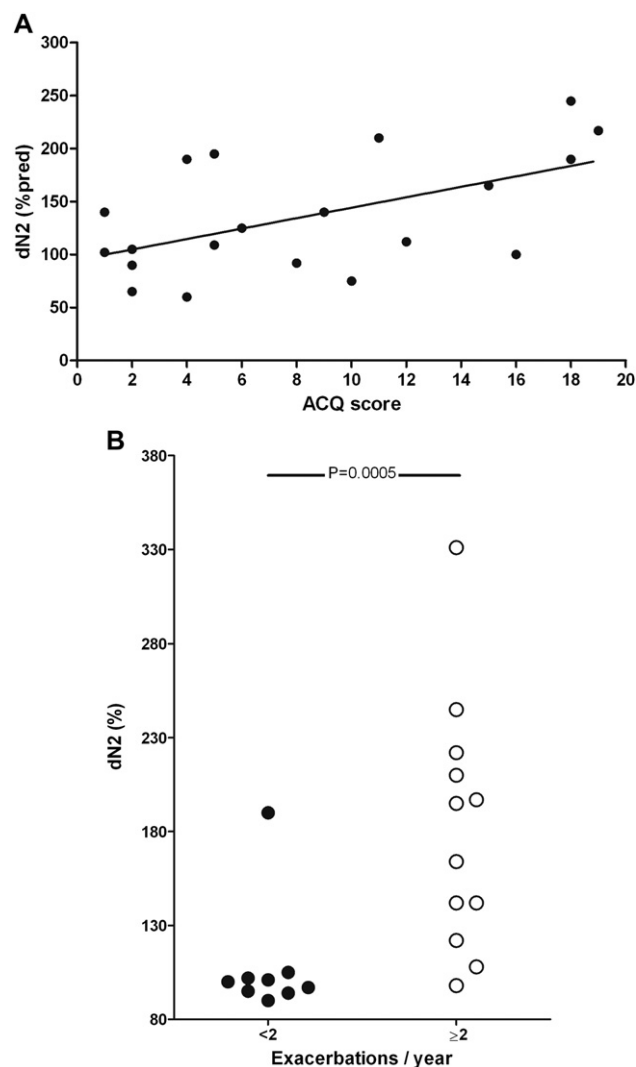


FIG 2. A, Significant correlation between the percent predicted slope of phase III of SBNT (dN2) and the ACQ score (Spearman correlation coefficient: $\rho = 0.62$, $P = .003$). B, Significant differences in dN2 values between frequent and infrequent exacerbators ($P = .0005$). Reproduced with permission from Bourdin et al.²¹

symptoms and worse asthma control.²²⁻²⁵ Exhaled NO can be divided into bronchial and alveolar NO based on a mathematic model, assuming that bronchial NO is derived from the proximal large airways and alveolar NO reflects inflammation in the distal small airways.²⁶ Puckett et al²⁷ divided 179 asthmatic children 6 to 17 years of age into 4 groups based on the concentration of alveolar and bronchial NO: (1) normal alveolar and bronchial NO levels; (2) increased bronchial NO levels only; (3) increased alveolar NO levels only; and (4) both increased bronchial and alveolar NO levels. Interestingly, even though FEV₁ percent predicted did not differ between the groups, patients with increased alveolar NO levels (groups 3 and 4) had worse asthma control, as assessed by the Asthma Control Test, than patients with normal alveolar and bronchial NO levels or those with increased bronchial NO levels only (groups 1 and 2). In addition, patients with increased alveolar NO levels more frequently had a severe exacerbation. In contrast with these findings, Mahut et al²⁸ did not observe an association between changes in alveolar or bronchial NO levels over a period

of 1 to 12 weeks and change in asthma control in adults and children with asthma. In addition, Berry et al²⁹ investigated asthmatic patients using high doses of oral corticosteroids or inhaled corticosteroids (ICSs) and did not observe an association between alveolar NO levels and asthma control. A possible explanation for the lack of an association between NO levels and asthma control in the latter 2 studies might have been that the majority of patients used high-dose ICSs, which are especially effective in suppressing exhaled NO levels.³⁰ In conclusion, there is some evidence that alveolar NO levels are associated with asthma symptoms. However, it has to be taken into account that both alveolar and bronchial levels are affected by the use of inhaled or oral corticosteroids. Finally, Van Vyve et al³¹ investigated inflammation in bronchoalveolar lavage (BAL) fluid in relation to the severity of asthma, as defined by the Aas score.³² A higher Aas score (ie, more severe asthma) was associated with a higher eosinophil percentage in BAL fluid, suggesting involvement of the small airways.

OCCURRENCE OF AN ASTHMA EXACERBATION

Bourdin et al²¹ showed that frequent ($\geq 2/y$) exacerbators have a higher degree of small-airways dysfunction as reflected by the SBNT phase III slope than infrequent exacerbators ($< 2/y$), whereas FEV₁ percent predicted values were comparable between these 2 groups (Fig 2, B). These findings are in line with those of in't Veen et al,³³ who demonstrated that frequent exacerbators have a higher SBNT closing volume and closing capacity than infrequent exacerbators.

Air trapping can be assessed by using body plethysmography or computed tomographic scanning, which are indirect parameters, to assess small-airways dysfunction. Mahut et al³⁴ have compared the presence of air trapping between children with and without a severe asthma exacerbation and with and without symptoms. The 108 asthmatic children with a severe exacerbation had more air trapping (ie, a higher residual volume [RV] and RV divided by total lung capacity [TLC; RV/TLC]) than children without exacerbations and mild or no symptoms. In addition, more air trapping, as assessed by using computed tomographic scanning in another study, was associated with asthma-related hospitalizations and a history of pneumonia.³⁵

Alveolar NO levels were shown to increase during an exacerbation and to subsequently decrease during resolution, additionally suggesting involvement of the small airways.³⁶ Furthermore, Gelb et al³⁷ showed that an increased alveolar NO level predicts increased asthma exacerbations independently of FEV₁. However, the same was observed with an increased bronchial NO level, and it is questionable whether this finding suggests small-airways involvement. In a later study, Gelb et al³⁸ did not find an increase in alveolar NO levels during an exacerbation when they corrected for NO back diffusion from the central to the peripheral airways.

In summary, the balance of evidence in the abovementioned studies suggests that a higher degree of small-airways dysfunction is associated with more frequent asthma exacerbations, although an influence of large-airways dysfunction on these results will also likely play a role.

NOCTURNAL ASTHMA

We identified several studies investigating the association between small-airways dysfunction and nocturnal asthma. First, Kraft et al³⁹ showed that peripheral airways resistance, as measured with a wedged bronchoscope, is increased in patients with

nocturnal compared with nonnocturnal asthma. A further study investigated both endobronchial and transbronchial biopsy specimens at daytime (4 AM) and nighttime (4 PM) in 11 patients with nocturnal asthma, which was defined as a 15% or greater decrease in peak expiratory flow (PEF) rate at night, and 10 patients without nocturnal asthma.⁴⁰ Although there were no differences in inflammation between day and night in endobronchial biopsy specimens of the large airways, a significant nighttime increase in eosinophil counts was observed in the transbronchial biopsy specimens, specifically in patients with nocturnal asthma. These findings suggest that inflammation of the small airways contributes to asthma symptoms and the decrease in lung function at night in patients with nocturnal asthma (Fig 3).⁴⁰

This is in line with the findings of Martin et al,⁴¹ who also observed an increased inflammation of the small airways during the night in the BAL fluid of patients with nocturnal asthma. In contrast to the findings of the latter study, Oosterhoff et al⁴² and Jarjour et al⁴³ did not find an overnight increase in the number of eosinophils in BAL fluid in patients with nocturnal asthma. A possible explanation for this discrepancy might be the difference in asthma severity. Martin et al⁴¹ investigated predominantly patients with severe asthma (mean FEV₁, 74% of predicted value), whereas Oosterhoff et al⁴² and Jarjour et al⁴³ investigated patients with milder asthma with a mean FEV₁ of 88% and 89% of predicted value, respectively. Taken together, it has been shown that peripheral airways resistance increased during the night in patients with nocturnal asthma in parallel with an increased small-airways inflammation and the occurrence of nocturnal symptoms.

One study compared patients with nocturnal symptoms with patients without symptoms at night by using alveolar NO levels.⁴⁴ All patients had a recent diagnosis of asthma, were steroid naive, and had a comparable lung function and bronchial NO concentration. Interestingly, patients with nocturnal symptoms had higher alveolar NO values than patients without nocturnal symptoms, suggesting that even in patients with mild asthma, nocturnal symptoms are associated with small-airways inflammation.

BHR

Change of small-airways function during a provocation test

Two studies have used the wedged bronchoscope technique to investigate the response of the small airways to a provocation test.^{45,46} In one study peripheral airways resistance increased faster in patients with asthma than in healthy control subjects after local application of histamine.⁴⁵ The other study demonstrated that greater peripheral airways resistance is associated with more BHR to methacholine.⁴⁶ Together, these results confirm the sensitivity of the small airways to nonallergic stimuli in asthmatic patients.

This is in line with the findings of Segal et al,⁴⁷ who performed a methacholine provocation test with both FEV₁ and impulse oscillometry. It was found that both total and small-airways resistance increased in patients with BHR (PC₂₀ ≤ 16 mg/mL) compared with that seen in patients without BHR (PC₂₀ > 16 mg/mL), whereas large-airways resistance was comparable between the groups. Additionally, 9 of 33 patients had symptoms during the challenge, even though their FEV₁ did not decrease. In these patients the total respiratory resistance (R5) increased significantly, predominantly because of an increase in R5-R20 and AX values. The latter suggests that the increase in

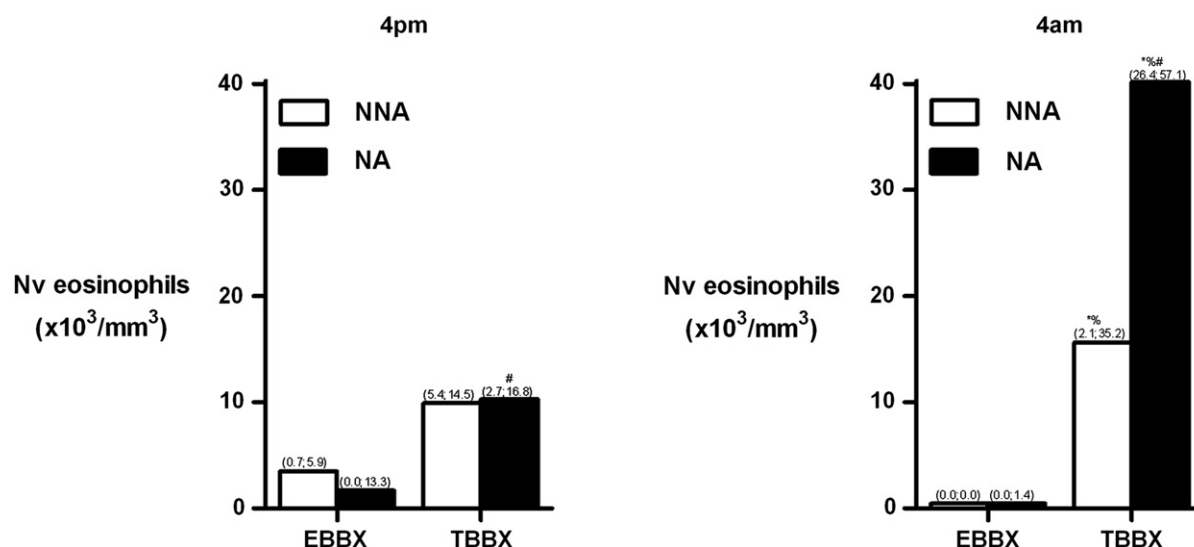


FIG 3. Number per volume (*Nv*) of eosinophils in patients with nonnocturnal asthma (*NNA*) and nocturnal asthma (*NA*) is shown in the endobronchial biopsy specimens (*EBBX*) and transbronchial biopsy specimens (*TBBX*) at 4 AM and 4 PM. The *open bars* represent the nonnocturnal asthma group (*n* = 10), and the *solid bars* represent the nocturnal asthma group (*n* = 11). Values are expressed as medians with the 25th to 75th interquartile range in parentheses above each bar. #*%*P* ≤ .05. The transbronchial biopsy specimens of patients with nocturnal asthma show a significant increase in eosinophil numbers overnight. Reproduced with permission from Kraft et al.⁴⁰

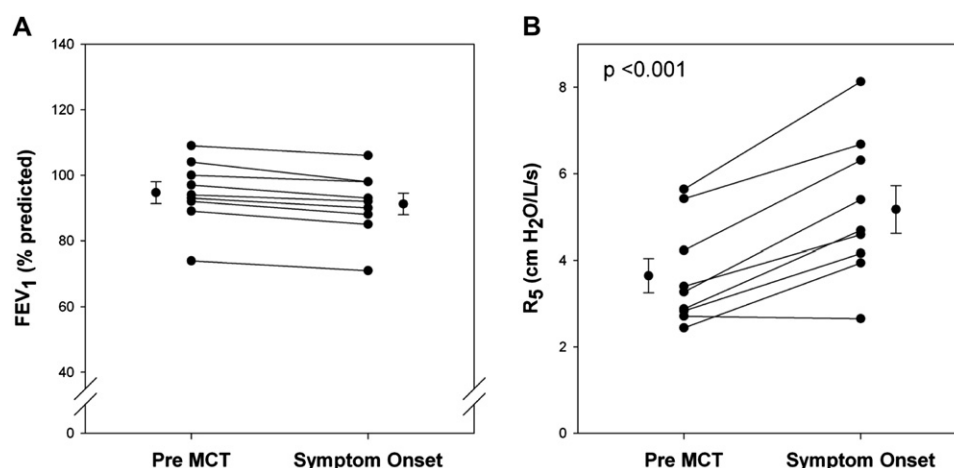


FIG 4. Relationship between onset of respiratory symptoms and changes in FEV₁ (**A**) and R5 (**B**) values. Data are illustrated for the 9 of 33 subjects who developed symptoms with minimal change in FEV₁ during the provocation test (mean change, −3.4%). *MCT*, Methacholine provocation test. Adapted from Segal et al.⁴⁷ Disparity between proximal and distal airway reactivity during methacholine challenge, COPD, ©2011, Informa Healthcare. Reproduced with permission of Informa Healthcare.

small-airways resistance was responsible for the onset of symptoms in these subjects (Fig 4).⁴⁷ These findings are in line with those of Mansur et al,⁴⁸ who showed that a higher small-airways reactance is associated with more severe dyspnea, wheezing, and chest tightness after provocation. Together, these studies show that the small airways are involved in BHR and that the response in the small airways is associated with the development of symptoms during a provocation test.

Furthermore, several studies have shown that air trapping can occur during methacholine-induced bronchoconstriction.^{49–53} For example, Loughheed et al⁴⁹ showed that 66% of asthmatic patients hyperinflate to greater than 300 mL at the PC₂₀ level, as reflected by a decrease in their inspiratory capacity. Moreover, a higher

degree of air trapping was related to increased symptoms of chest tightness and dyspnea. These findings are in line with several other studies showing that a higher degree of air trapping during a methacholine provocation test associates with the severity of dyspnea, even in a multivariate regression analysis, after adjusting for the decrease in FEV₁.^{50–52} *Vice versa*, the reduction in air trapping after administration of 200 µg of salbutamol at the end of the provocation test was associated with the decrease in the intensity of dyspnea.⁵¹ The mechanism for the increase in air trapping during acute bronchoconstriction is controversial. Possible mechanisms might be expiratory flow limitation of the larger airways, significant intrinsic positive end-expiratory pressure, or closure of the small airways during expiration.^{51,54}

Association between small-airways dysfunction and severity of BHR

In a retrospective study Drewek et al⁵⁵ showed that asthmatic patients with BHR to methacholine have a lower forced expiratory flow at 25% to 75% of forced vital capacity (FEF_{25%-75%}). This is in line with the findings of Currie et al,⁵⁶ who compared asthmatic patients with moderate-to-severe (PC₂₀ ≤ 1 mg/mL) and borderline (PC₂₀ ≥ 8 mg/mL) BHR to methacholine. Although patients were matched for FEV₁ percent predicted, patients with moderate-to-severe BHR had significantly lower FEF_{25%-75%} values. In addition, Lang et al⁵⁷ observed a lower forced expiratory flow at 50% of forced vital capacity (FEF_{50%}) and increased BHR in children with severe asthma compared with those with nonsevere asthma, whereas the FEV₁ percent predicted value was comparable between both groups. Furthermore, Backer and Mortensen⁵⁸ investigated the airways distribution of radioactive aerosol in children and adults in relation to lung function and BHR. Patients with an irregular deposition of the aerosol had a significantly lower FEF_{75%} value and more severe BHR. Downie et al⁵⁹ analyzed BHR with the MBNW test in asthmatic patients. They demonstrated that Scond is associated with the severity of BHR to methacholine. Finally, Pliss et al⁶⁰ showed that more severe BHR is associated with more severe small-airways inflammation, as reflected by a higher percentage of eosinophils in BAL fluid.

EXERCISE-INDUCED ASTHMA SYMPTOMS

Involvement of the small airways in the response to exercise

Fonseca-Guedes et al⁶¹ found a significant correlation between the exercise-induced decrease in FEF_{25%-75%} and FEV₁, particularly in patients with moderate-to-severe asthma. Interestingly, in patients with mild asthma, a significant decrease in FEF_{25%-75%} (≥26%) was observed, whereas FEV₁ did not decrease by more than 10%. In addition, Rundell et al⁶² analyzed lung function and asthma symptoms in ice hockey players before and after exercise and observed a significantly lower baseline FEF_{25%-75%} in subjects with asthma symptoms during or after exercise than subjects without. Kaminsky et al⁶³ performed a bronchoscopy to challenge the small airways locally with cold, dry air. This induced an increase in peripheral airways resistance in asthmatic patients but not in healthy control subjects. In line with this, Decramer et al⁶⁴ showed that peripheral resistance, as measured with the forced oscillation technique, increases after a hyperventilation test with cold, dry air. Together, these findings suggest that the small airways are involved in the response to exercise.

Kiers et al⁶⁵ investigated the role of air trapping in asthmatic patients with a history of exercise-induced asthma. The increase in functional residual capacity was significantly correlated with the exercise-induced decrease in FEV₁. Kosmas et al⁶⁶ studied the presence of air trapping during exercise in 20 patients with stable asthma and normal lung function at baseline. Exercise-induced asthma, based on a 15% or greater decrease in FEV₁, was only observed in 3 patients, whereas 13 patients had air trapping during exercise. Importantly, the presence of air trapping was associated with reduced exercise capacity. The latter suggests that small-airways collapse can occur during and after exercise in patients with stable asthma without a response in the large airways.

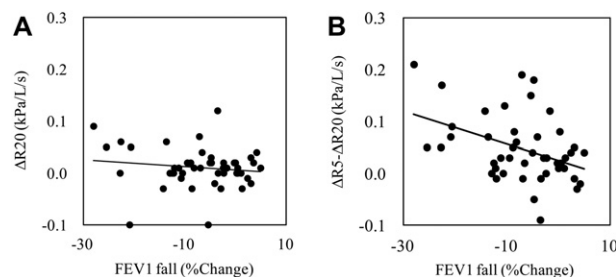


FIG 5. Correlations between the decrease in FEV₁ versus the increasing resistance (R20 [A] and R5-R20 [B]) at 5 minutes after exercise challenge. R5-R20, reflecting resistance of the small airways, is correlated with FEV₁ ($\rho = -0.375$, $P = .009$), whereas R20, reflecting resistance of the large airways, did not correlate with FEV₁ ($\rho = -0.104$, $P = .487$). Adapted with permission from Lee et al.⁶⁸

Association between small-airways dysfunction and the severity of exercise-induced asthma

Several studies have suggested that small-airways dysfunction is associated with more severe exercise-induced bronchoconstriction.^{63,67-71} Aronsson et al⁷² divided 34 asthmatic patients into 2 groups, one with no response and another with a positive response to mannitol, which is another indirect stimulus to measure BHR and closely related to exercise.⁷³ Patients with BHR to mannitol had higher R5-R20 and AX values than patients without BHR. In line with this, Lee et al⁶⁸ observed that more severe exercise-induced bronchoconstriction is associated with a higher increase in peripheral airways resistance (R5-R20) but not with an increase in large-airways resistance (R20, Fig 5).⁶⁸

Two studies investigated the phase III slope of the single-breath helium and sulfur hexafluoride washout test before and after a cold, dry air hyperventilation test.^{69,70} Both studies demonstrated that an increase in the helium and sulfur hexafluoride phase III slopes were associated with the decrease in FEV₁.^{69,70} In addition, Ljungberg and Gustafsson⁷⁰ showed in asthmatic children that the phase III slope at baseline was correlated with the decrease in FEV₁ after challenge. In contrast, FEV₁ at baseline did not correlate with the decrease in FEV₁ after challenge. This is in line with the findings of Keen et al,⁷¹ who showed that a higher Scond value, as measured with the MBNW test, is associated with the severity of the response to cold, dry air.

EFFECTS OF ALLERGEN EXPOSURE ON SMALL-AIRWAYS DYSFUNCTION

Asthma and allergies are strongly associated, and allergen exposure can provoke asthma symptoms in sensitized subjects. Allergen exposure can result in an immediate airways response, the so-called early asthmatic response, followed by a late-phase response in a subset of asthmatic patients.⁷⁴

The role of the small airways in the allergic response has been investigated by the change in the FEF_{50%} after breathing a mixture of helium-oxygen compared with room air.^{75,76} Because of the lower gas density of helium, it can be assumed that a higher increase in FEF_{50%} will indicate obstruction in the more proximal airways, which are flow dependent. Metzger et al⁷⁵ studied the helium-oxygen flow-volume curves in 12 asthmatic patients with both an early- and late-phase allergic response based on a 20% and 10% decrease in FEV₁, respectively. Immediately after allergen challenge, FEF_{50%} increased, suggesting involvement of

mainly the large airways. Of interest, FEF_{50%} gradually decreased 6 and 24 hours after the allergen challenge, suggesting that the small airways contribute importantly to the late-phase asthmatic response. This is in agreement with the findings of Machado et al,⁷⁶ who similarly showed an immediate increase in FEF_{50%} after an allergen provocation, followed by a decrease in FEF_{50%} 6 hours later. Ahmed et al⁷⁷ studied the early asthmatic response to ragweed provocation, distinguishing reactors and nonreactors based on a 35% decrease in specific airway conductance. There were no differences between the 2 groups in terms of spirometric results or the phase III slope of the SBNT at baseline. Still, 6 of 10 reactors had an abnormal phase III slope in contrast to 1 of 6 of the nonreactors suggestive for small-airways involvement.

Zeidler et al⁷⁸ investigated 10 asthmatic patients who were exposed to cats until their FEV₁ decreased by 20%. At 6 and 23 hours after this natural cat allergen challenge, FEV₁ had returned to its baseline value. However, they still showed increased levels of air trapping, as measured by using high-resolution computed tomography and SBNT closing volume at both time points. In addition, 6 hours after allergen provocation, FEF_{25%-75%} was decreased compared with baseline values. Together, these observations indicate that the small airways contribute importantly to the late-phase asthmatic response.

Peroni et al⁷⁹ analyzed air trapping in 18 asthmatic children allergic to house dust mite (HDM). After prolonged HDM avoidance during a stay at high altitude, RV and RV/TLC values decreased significantly, yet after subsequent HDM exposure at home, these values increased toward baseline levels, suggesting a small-airways response on allergen exposure.

In theory, most particles larger than 10 μm will not enter the airways, and only particles smaller than 5 μm will enter the alveoli.^{80,81} Most particles of pollen are large, with a size of approximately 22 to 100 μm ; however, there are also smaller particles, such as ragweed, with a size of 0.2 to 5.25 μm , which causes symptoms of hay fever.^{82,83} Interestingly, pollen can fragment into small respirable particles on hydration by rain or conditions of higher humidity, resulting in an increased number of allergenic aerosols of paucimicronic size that penetrate deep in the lower airways.^{82,84} In this context it is noteworthy that epidemics of asthma attacks have been observed after thunderstorms, especially during the pollen season, suggesting that the small fragments of pollen induce a severe small-airways response.⁸⁵⁻⁸⁸ Another example of allergens with a small size are cat allergens, of which 40% are smaller than 5 μm .⁸⁹ Lieutier-Colas et al⁸⁹ evaluated the effect of provocation with either small-particle cat allergens (mass median aerodynamic diameter [MMAD], 1.4 μm) or large-particle cat allergens (MMAD, 10.4 μm) on the early- and late-phase response. Interestingly, the provocative dose inducing early bronchial symptoms was 20 times smaller for the large than for the small particles. In contrast, 24 hours after provocation with small particles, FEF_{25%-75%} values were significantly lower compared with those after provocation with large particles, with the latter being compatible with the notion that the late-phase response is predominantly mediated by the small airways.

ASSOCIATION OF SMALL-AIRWAYS DYSFUNCTION AND EXPOSURE TO PARTICULATE AIR POLLUTION

Both in children and adults with asthma, higher levels of particulate air pollution have been associated with an increase in

respiratory symptoms and use of rescue medication and a decrease in lung function.⁹⁰⁻⁹⁴ Particulate air pollution can be categorized according to particle size. Particulate matter larger than 10 μm in diameter (PM₁₀) reflects the coarse particle fraction that will mainly deposit in the larger airways, particulate matter of less than 2.5 μm in diameter (PM_{2.5}) is referred to as the fine-particle fraction, and particles with a diameter of less than 0.1 μm are labeled as ultrafine particles. Fine and ultrafine particles originate to a large extent from incomplete combustion processes, such as those resulting from road traffic and industry. Several studies have investigated the effects of different particulate matter size fractions on respiratory symptoms, medication use, and lung function.⁹⁵⁻¹⁰⁰

It has been shown by Penttinen et al⁹⁶ that a higher daily concentration of ultrafine particles, but not PM_{2.5} and PM₁₀, is associated with a decrease in PEF. These findings are in line with the study of von Klot et al,⁹⁷ who found that exposure to a higher concentration of ultrafine particles, but not coarse particles (PM_{2.5-10}), during 5 and 14 days is associated with increased asthma symptoms, such as wheezing. In addition, the level of exposure to fine and ultrafine particles was associated with increased use of bronchodilators, whereas this association was not found for the level of exposure to coarse particles. In contrast, Maestrelli et al⁹⁸ observed an association between a higher exposure to coarse particles (PM₁₀) and worse asthma control and quality of life, whereas exposure to fine particles (PM_{2.5}) was not related to these clinical parameters. Small airways function has not been measured in these studies and the contrast in outcomes can perhaps be explained by differences in small airways dysfunction. Taken together, predominantly, the fine and ultrafine fractions contribute to the adverse respiratory health effects of particulate air pollution, probably because of their higher peripheral lung deposition.^{101,102} Once deposited in the small airways, fine and ultrafine particles can induce oxidative stress and increase the asthmatic inflammatory response.^{103,104} This might explain why Iskandar et al¹⁰⁵ did not find an association between ultrafine-particle air pollution and hospital admission in the same week in a group of asthmatic children because it could be speculated that ultrafine-particle air pollution rather induces an effect in the long term than the short term.

Two studies have assessed the effects of particulate air pollution on parameters of small-airways dysfunction. First, Trenga et al⁹⁹ found that a higher exposure to fine particles during 24 hours was associated with decrements in FEF_{50%}, but not FEV₁ or PEF, in asthmatic children without anti-inflammatory medication. Next, McCreanor et al¹⁰⁰ compared the effects of high exposure to road traffic-related air pollution during a 2-hour walk on Oxford Street in London versus low exposure when subjects walked for 2 hours through Hyde Park on a separate occasion. A higher exposure to road traffic-related air pollution, especially the fine- and ultrafine-particle fractions, was accompanied by significant decreases in FEV₁, forced vital capacity, and FEF_{25%-75%}. In summary, especially the fine and ultrafine fractions of particulate air pollution are associated with worsening of asthma control and decreases in parameters of both large- and small-airways function.

EFFECT OF ASTHMA TREATMENT ON SMALL-AIRWAYS FUNCTION AND SYMPTOMS

Several studies have investigated the effect of treatment targeting the small airways on asthma control. In a recent study Farah et al¹⁰⁶ investigated the predictive value of the change in

asthma control after either ICS up-titration in patients with poorly controlled asthma (ACQ >1.5) or those with steroid-naïve asthma or ICS down-titration in the case of patients with well-controlled asthma. A higher level of small-airways dysfunction, as reflected by higher Sacin and Scnd values, was the only independent predictor for either improvement of asthma control after ICS up-titration or loss of asthma control after ICS down-titration. These findings are in agreement with the conclusion that small-airways dysfunction is present in asthmatic patients, is related to symptoms, and might require targeted treatment.

Several studies have investigated the efficacy of extrafine-particle pressurized metered-dose inhalers with respect to improvement of symptoms and asthma control.¹⁰⁷⁻¹¹³ Extrafine-particle ICSs with an MMAD of approximately 1 μ m have a higher lung deposition (50% to 60%) than coarse particle ICSs with an MMAD of 3 to 4 μ m (10% to 20%).¹¹⁴⁻¹¹⁶ Boulet et al¹⁰⁷ compared 3-month treatment with 320 μ g of hydrofluoroalkane (HFA)–ciclesonide administered once daily with 200 μ g of dry powder inhaler (DPI)–fluticasone administered twice daily in patients with asthma. Although no differences in FEV₁ improvement were observed, improvement in health-related quality of life was significantly higher with HFA-ciclesonide than fluticasone. This is in line with the study of Ohbayashi and Adachi,¹⁰⁸ showing an improvement in the Asthma-related Quality of Life Questionnaire after 3 months' treatment with HFA-beclomethasone compared with DPI-fluticasone together with a decrease in late-phase sputum eosinophil counts. Furthermore, Huchon et al¹⁰⁹ compared the efficacy of 24 weeks' treatment with extrafine fixed combination 200/12 μ g of HFA-beclomethasone dipropionate (BDP)/formoterol twice daily versus 500 μ g of chlorofluorocarbon (CFC)-BDP twice daily and 24 μ g of DPI-formoterol once daily. Although both treatments were equally effective in improving FEV₁, the extrafine-particle HFA-BDP/formoterol combination treatment resulted in better asthma control with less symptoms and a fewer asthma exacerbations.

More evidence in support of better asthma control with extrafine-particle treatment are derived from a retrospective, observational, real-life study comparing the efficacy of extrafine-particle HFA-beclomethasone (QVAR) with coarse-particle treatment with CFC-beclomethasone.¹⁰⁹ A primary care database was used to identify asthmatic patients who were prescribed either extrafine-particle HFA-beclomethasone or CFC-beclomethasone. Asthmatic patients receiving their first ICS prescription ($n = 11,528$) or their first increase in ICS dose ($n = 774$) were included. Extrafine-particle treatment more often resulted in good asthma control, which was defined as no recorded hospital admission or emergency department visits for asthma and no use of oral corticosteroids or antibiotics for respiratory tract infections of the airways. These results are strengthened by a similar study showing that asthmatic patients treated with extrafine-particle HFA-beclomethasone more frequently achieve asthma control than those treated with coarse-particle treatment with either CFC- or HFA-fluticasone.¹¹¹ This is in line with results of 2 further real-life cross-sectional studies showing that the use of extrafine-particle HFA-beclomethasone/formoterol was associated with a higher percentage of patients with well-controlled asthma based on their Asthma Control Test and ACQ scores than the use of fluticasone/salmeterol or budesonide/formoterol combination treatment.^{112,113} Taken together, these studies show that extrafine-particle pressurized metered-dose inhalers might have additional clinical benefits in the treatment of asthma compared with coarse-particle treatment.

Several studies investigated the effects of montelukast on the small airways, together with the effects on symptoms or clinical signs. Montelukast is a systematically administered leukotriene receptor antagonist that reaches the small and large airways. Receptors for leukotrienes are expressed at higher levels in fibroblasts derived from the small airways than the large airways, possibly resulting in a predominant effect of montelukast on the small airways.¹¹⁷ Kraft et al¹¹⁸ studied asthmatic patients with air trapping (RV, >140% of predicted value) and observed a significant improvement in symptoms of wheezing, dyspnea, and cough after treatment with montelukast.¹¹⁸ Treatment with montelukast resulted in improvements in several lung function parameters; however, only the improvement in RV was associated with less wheezing and chest tightness. These results are similar to those of Zeidler et al,¹¹⁹ evaluating lung attenuation areas with high-resolution computed tomography. An increase in lung attenuation was associated with an improvement in the overall mini-Asthma-related Quality of Life Questionnaire.

Spahn et al¹²⁰ investigated the effect of montelukast on the small airways in children with asthma. RV/TLC improved after treatment with montelukast compared with placebo, whereas FEV₁, FEV₁/forced vital capacity ratio, and FEF_{25%-75%} values did not differ between the groups. These studies demonstrate an association between improvements in symptoms and small-airways function after treatment with montelukast, whereas no relation existed with FEV₁ improvement, suggesting that montelukast has beneficial effects, particularly on the small airways.

CONCLUSIONS

This systematic review demonstrates that small-airways dysfunction is associated with clinical features of asthma: worse control of asthma,^{15,16,20,21} higher numbers of exacerbations,^{21,27,33} nocturnal asthma,^{40,41,44} more severe BHR,^{55,56,59,60} exercise-induced asthma,^{61,64,67-71} and the late-phase allergic response (Table II).*

It is important to mention that the data for this review are limited because most of the studies are small and not primarily designed to answer our research question. Another limitation is the lack of a gold standard to assess small-airways dysfunction, which made it necessary to mention many types of tests in this review. Obviously, all these tests have specific shortcomings, and they frequently cannot rule out an influence of large-airways dysfunction. For these reasons, the exact role of the small airways in asthmatic patients remains to be elucidated, and more research is necessary to obtain more conclusive evidence.

Notwithstanding these shortcomings, results of the literature provide supportive evidence for a contribution of small-airways dysfunction to the clinical expression of asthma. Interestingly, a few studies have shown that small-airways dysfunction is not only a feature of severe asthma but can also be present in patients with mild asthma who have a low level of symptoms and FEV₁ values in the normal range.^{15,47,55,61,68} This indicates that the possibility of small-airways dysfunction should be considered in the complete spectrum of asthma severity. The latter might be of clinical importance because a better small-airways response to treatment with extrafine-particle ICSs or montelukast is accompanied by better asthma control.^{112,113,119} For this reason, further research is needed to develop simpler and more reliable tools

*See references 15, 16, 20-25, 27-29, 31, 33-53, 55-72.

TABLE II. Summary of studies investigating the association of small-airways dysfunction with the clinical expression of asthma

	Symptoms and asthma control	Exacerbations	Nocturnal asthma	BHR	Exercise
Flow				• FEF_{25%-75%} is lower in patients with BHR.^{55,56} • Children with severe asthma have a lower FEF_{50%} and severe BHR.⁵⁷ • Patients with an irregular aerosol deposition have a lower FEF_{75%} and more severe BHR.⁵⁸	• The decrease in FEF_{25%-75%} is correlated with the decrease in FEV₁ in response to exercise.⁶¹ • FEF_{25%-75%} was lower in subjects with symptoms in response to exercise than in subjects without symptoms.⁶²
Resistance	• A higher R5-R20 value is associated with a higher BDI score.¹⁵ • A higher X5 value is associated with a higher ACQ score.¹⁵ • R5-R20 and AX values are discriminating parameters for control of asthma.¹⁶		• Rp values are increased in patients with nocturnal asthma.³⁹	• Rp values increased more in asthmatic patients compared with healthy control subjects.⁴⁵ • A higher Rp value is associated with severe BHR.⁴⁶ • R5-R20 values increased more in patients with PC₂₀ ≤16 mg/mL than PC₂₀ >16 mg/mL during a methacholine provocation test.⁴⁷ • An increase in X5 value is associated with an increase in symptoms of dyspnea, wheezing, and chest tightness.⁴⁸	• Rp values increased in patients with asthma in response to cold, dry air.⁶³ • A higher Rp value is associated with more severe BHR.^{63,67} • Peripheral resistance measured with FOT increases after a provocation with cold, dry air.⁶⁴ • R5-R20 and AX values are increased in patients with BHR to mannitol.⁷² • An increase in R5-R20 values is associated with a more severe decrease in FEV₁ in response to exercise.⁶⁸
Ventilation heterogeneity	• Sacin and Scond values are increased in patients with ACQ scores ≥1.5.²⁰ • An increased dN2 value is associated with a higher ACQ score.²¹	• dN2 values are increased in patients with ≥2 exacerbations/y.²¹ • CV/VC and CC/TLC values are increased in patients with ≥2 exacerbations/y.³³		• An increased Scond value is associated with more severe BHR.⁵⁹	• A higher helium and SF6 phase III slope value is associated with a more severe response to exercise.^{69,70} • A higher Scond value is associated with a more severe response to cold, dry air.⁷¹
Air trapping		• RV/TLC values are increased in children with a severe exacerbation.³⁴ • CT-determined air trapping is related to indicators of exacerbation.³⁵		• FRC values are increased in patients with chest tightness after a methacholine provocation test.⁴⁹ • The increase in IC values is correlated with a higher Borg score during a provocation test.⁵⁰ • Air trapping (ΔIC or ΔRV) predicts the occurrence of dyspnea during a provocation test.⁵¹⁻⁵³	• An increased FRC value is associated with a more severe response to exercise.⁶⁵ • An increased IC value is associated with reduced exercise capacity.⁶⁶

(Continued)

TABLE II. (Continued)

	Symptoms and asthma control	Exacerbations	Nocturnal asthma	BHR	Exercise
Inflammation	• A higher alveolar NO value is associated with more asthma symptoms.²²⁻²⁵ • Patients with an increased alveolar NO value have worse asthma control, as reflected by a lower ACT score.²⁷ • Greater eosinophil numbers are associated with a higher asthma severity score.³¹	• Alveolar NO values increase during an asthma exacerbation.³⁶ • A higher alveolar NO value predicts the occurrence of asthma exacerbation.³⁷	• Eosinophil numbers in transbronchial biopsy specimens increase overnight in patients with nocturnal asthma.⁴⁰ • Eosinophil numbers in BAL fluid increase overnight in patients with nocturnal asthma.⁴¹ • Alveolar NO values are increased in patients with nocturnal symptoms.⁴⁴	• A higher percentage of eosinophils is associated with more severe BHR.⁶⁰	

One study found no increased alveolar NO levels during an exacerbation.³⁸ Two studies demonstrated no association between alveolar NO values and ACQ scores.^{28,29} The studies of Oosterhoff et al⁴² and Jarjour et al⁴³ did not observe an increase in eosinophil numbers overnight measured with BAL in patients with nocturnal asthma.

ACT, Asthma Control Test; BDI, Baseline Dyspnea Index; CC, closing capacity; CT, computed tomography; CV, closing volume; *dn2*, slope of phase III of SBNT; FOT, forced oscillation technique; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; R5, resistance of the respiratory system at 5 Hz; R20, resistance of the respiratory system at 20 Hz; R5-R20, difference of R5 and R20; Rp, peripheral lung resistance; SF6, sulfur hexafluoride; VC, vital capacity; X5, reactance of the respiratory system at 5 Hz.

(eg, questionnaires or bronchial provocation tests using small-particle stimuli) for assessment of the presence and extent of small-airways dysfunction in clinical practice. An early recognition of small-airways dysfunction enables the physician to start treatment targeting the small airways.

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