



Letter

Markers of small airway involvement and asthma control in patients with moderate to severe asthma

The role of airway inflammation that involves the entire bronchial tree, from proximal to distal airways, in the pathogenesis of asthma is well understood. Small airways are the most peripheral airways, with an inner diameter less than 2 mm; it is in this region that oxygen and carbon dioxide exchanges take place. The contribution of the small airways to the development of the clinical features and functional impairment in asthma is incompletely understood, possibly because of the lack of definite noninvasive techniques for the study of small airways. The single-breath nitrogen washout test can be used to evaluate the presence of uneven ventilation, and this test has been found to discriminate between patients with severe asthma with and without recurrent exacerbations.¹ This abnormal distribution of alveolar ventilation may result in a ventilation perfusion ratio ($\dot{V}/\dot{Q}$) imbalance, determining pulmonary gas exchange abnormalities that may reflect changes in the small airways.² Bronchoconstriction induced by both methacholine (with a direct mechanism on smooth muscular cells) and adenosine monophosphate (with an indirect mechanism determining an inflammatory process) induces pulmonary gas exchange abnormalities as assessed by $\dot{V}/\dot{Q}$.³ Interestingly, after inhaled salbutamol, which acts mainly on proximal airways, these disturbances persisted. Other indexes of abnormal distribution of ventilation, including multiple-breath nitrogen washout and impulse oscillometry, have been used to assess small airway involvement,⁴ with some positive results in terms of either a distinction between symptomatic and non-symptomatic patients or a correlation with other functional or inflammatory markers of airway involvement. Finally, biomarkers have also been used to detect small airway inflammation in asthma. Fractional exhaled nitric oxide (FENO) has been considered a marker of eosinophilic inflammation that involves small airways in asthma.

Some asthmatic patients have the same level of functional large airway impairment, as assessed by forced expiratory volume in 1 second (FEV₁), but with different clinical control of the disease in terms of symptoms and exacerbations. This different asthma control might be due to a different involvement of small airways. Even if this was the case, it would not be clear whether such involvement of small airways represents a different phenotype of asthma or just a marker of greater disease severity.

To test the hypothesis that patients with uncontrolled and controlled asthma are better distinguished by markers of small airway involvement than by markers of large airway involvement, we selected a homogeneous group of asthmatic patients under regular treatment and compared markers of involvement of large (FEV₁ and sputum eosinophil count) and small (single-breath test, alveolar-arterial gradients of oxygen and carbon dioxide, and

alveolar exhaled nitric oxide) airways between patients with controlled and uncontrolled asthma as assessed by Global Initiative for Asthma (GINA) guidelines.⁵

Thirty-one asthmatic (GINA steps 3–4) patients (13 men; mean [SD] age, 55.9 [10.7] years) with a postbronchodilator FEV₁ of 60% predicted or more were studied. To be included in the study, they needed to be clinically stable, to be without a history of recent (<4 weeks) exacerbations, and to have signed an informed consent form. Exclusion criteria included the frequent use of oral corticosteroids, severe comorbidities, or a history of brittle asthma. The observational study had been approved by the local ethic committee.

Each patient underwent (1) complete standard pulmonary function tests, including a single-breath nitrogen washout test, following American Thoracic Society recommendations⁶; (2) measurement of resting alveolar-arterial difference of oxygen (AaDO₂) and arterial-alveolar difference of carbon dioxide (aADCO₂); and (3) measurement of biomarkers of airway inflammation (exhaled nitric oxide and eosinophil percentages in the induced sputum). All measurements were performed after the patients had taken their regular morning drugs.

During the 4 weeks preceding the tests, patients monitored daytime and nighttime symptoms and rescue medication use and measured peak expiratory flow (Mini-Wright Peak Flow Meter;

Table 1

Comparison of the markers of small airway involvement between patients with controlled (well controlled and partly controlled) and not controlled asthma^a

Marker	Well or partly controlled asthma (n = 21)	Not controlled asthma (n = 10)
FEF _{25%-75%} , mean (SD), % predicted	49.0 (24.4)	38.9 (19.1)
CV/VC, median (range), %	0.0 (0.0–25.0)	0.0 (0.0–17.6)
ΔN_2 , median (range), %L ⁻¹	2.3 (0.9–7.7)	2.5 (0.9–4.8)
CalvNO, mean (SD), ppb	9.9 (5.8)	6.2 (4.3)
JawNO, mean (SD), mL/s ⁻¹	37.4 (78.7)	58.3 (92.5)
AaDO ₂ , mean (SD), mm Hg	22.3 (0.1)	30.3 (10.1) ^b
aADCO ₂ , mean (SD), mm Hg	1.9 (3.1)	3.4 (3.1)

Abbreviations: AaDO₂, alveolar-arterial difference of oxygen; aADCO₂, arterial-alveolar difference of carbon dioxide; CalvNO, alveolar concentration of exhaled nitric oxide; CV, closing volume; FEF_{25%-75%}, forced expiratory flow between 25% and 75% of forced vital capacity; JawNO, bronchial production of exhaled nitric oxide; ΔN_2 , the slope of phase 3 obtained by the single-breath nitrogen washout; VC, vital capacity.

^a*p* < .05.

^bThe comparison between patients with controlled and noncontrolled asthma were performed by a 1-way analysis of variance comparison or by Mann-Whitney or Kruskal Wallis tests for normally and nonnormally distributed parameters, respectively.

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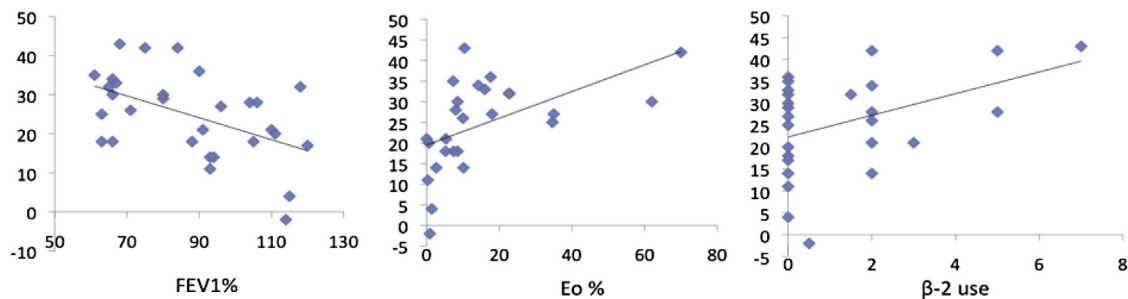


Figure 1. Correlations between alveolar-arterial difference of oxygen and forced expiratory volume in 1 second (FEV₁), sputum eosinophil count (Eo), and use of β_2 -agonist (β_2) (by the Pearson or Spearman test).

Clement Clarke International Ltd, Essex, United Kingdom). Asthma control was assessed according to the GINA guidelines.

The AaDO₂ aADCO₂ were measured by a mass spectrometer (Collins-Morgan-Ferraris, Pisa, Italy) according to published methods. This technique allows the assessment of the AaDO₂ and aADCO₂ by measuring simultaneously the Pao₂ and the Paco₂ in the arterial blood (by arterial blood gas analysis) and their medium alveolar pressures, breath by breath, when the instantaneous respiratory quotient equals the mean within each tidal volume (Rahn definition). In addition, analysis of arterial tension of carbon dioxide and its mean expiratory pressure can estimate the physiologic dead space (expressed as the ratio of tidal volume) index of effective ventilation for gas exchange using the Enghoff equation ($Paco_2 - PEco_2 / Paco_2$, where $PEco_2$ is the expiratory arterial pressure of carbon dioxide).^{7,8} In our experience, this technique allows the separation of symptomatic asthmatic patients from healthy controls (Malagrino et al, unpublished data, 2013).

FENO was measured in real time with a NOA Sievers analyzer (NOA 280; Sievers, Boulder, Colorado).⁹ Sputum was induced and analyzed as previously described.¹⁰

Patients were divided in those with controlled ($n = 21$) and not controlled ($n = 10$) asthma. The Table 1 gives a comparisons between the 2 groups for all the tested variables. AaDO₂ is the only variable statistically different between the 2 groups. In particular, 11 of 21 patients with controlled asthma had a mean (SD) AaDO₂ higher than 95th percentile of healthy controls (17.9 [2.7]),¹¹ whereas 7 of 10 patients with uncontrolled asthma had an AaDO₂ higher than the cutoff limit. Figure 1 shows the correlation between AaDO₂ and traditional markers of large airways involvement (FEV₁, sputum eosinophils, and exhaled nitric oxide).

This preliminary study found that the measurement of AaDO₂ distinguishes between patients with uncontrolled and controlled asthma regardless of their baseline FEV₁ values and of other markers of large airway inflammation (such as sputum eosinophil count and FENO). Small airway dysfunction in asthma contributes only marginally to total airway resistance, whereas it strongly influences the peripheral distribution of ventilation and the efficiency of gas exchange. Because AaDO₂ is an indirect measurement of $\dot{V}/\dot{Q}$ inequality related to a heterogeneous peripheral distribution of the alveolar ventilation, this finding supports the hypothesis that involvement of small airways is associated with poor asthma control.

To our knowledge, this is the first study to use this specific measurement of $\dot{V}/\dot{Q}$ inequality as a test of involvement of small airways in asthma, showing an association with poor asthma control. The possibility of distinguishing patients with controlled from not controlled asthma according to AaDO₂ and not to FEV₁, sputum eosinophil count, and FENO suggests that small airway involvement may be another independent factor that contributes to a poorer asthma control.

In conclusion, our study suggests that $\dot{V}/\dot{Q}$ inequality as measured by AaDO₂ may be a marker of small airway involvement in patients with moderate to severe asthma using inhaled corticosteroids and long-acting β -agonists and that this measurement may reflect different levels of asthma control better than more traditional markers of large airway involvement.

Laura Malagrino, MD*

Giosuè Catapano, MD†

Federica Novelli, MD*

Elena Bacci, MD*

Francesco Costa, MD*

Federico L. Dente, MD*

Antonella Di Franco, MD*

Manuela Latorre, MD*

Barbara Vagaggini, MD*

Alessandro Celi, MD*

Pierluigi Paggiaro, MD*

*Department of Surgery, Medicine
Molecular Biology, and Critical Care

University of Pisa

†CNR Institute of Clinical Physiology Pisa

Pisa, Italy

lauramalagrino@yahoo.it

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