

Lung Function Abnormalities and Their Correlation With Clinical Characteristics and Inflammatory Markers in Adult Asthma

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Asthma is a chronic inflammatory disorder of the airways that affects about 300 million individuals worldwide [1]. Different phenotypes and endotypes of the disease are used to determine variations in severity, clinical course, and treatment, especially in severe asthma. However, little is known about functional abnormalities and their correlation with the inflammatory subtypes, especially in nonsevere disease.

Air trapping is a prominent functional characteristic of severe uncontrolled asthma [2-6]. However, its clinical implications and pathophysiological causes are unclear.

The MEGA study analyzes the largest prospective cohort of Spanish asthma patients with varying degrees of severity recruited from 8 Spanish university hospitals to evaluate the natural history of and pathobiological mechanisms underlying the disease [7,8]. Based on data from this cohort, Rial et al [7] showed a significant relationship between the obstructive spirometry pattern and age, chronic rhinosinusitis with nasal polyps (CRSwNP), and severe asthma. Severe asthma was also associated with more severe symptoms and exacerbations, poorer asthma control, severe rhinitis, and bronchiectasis [7,8].

In the present study, we used spirometry and plethysmography data to describe the characteristics of asthma patients with different lung function patterns. As a secondary objective, we examined agreement between air trapping diagnosed using spirometry criteria and plethysmography.

A retrospective observational study was conducted by reviewing the MEGA cohort electronic database. A total of 445 asthma patients with complete data were selected and classified according to their functional pattern as defined by Sorkness et al [4] and Stocks et al [9] (see Supplementary I for further detail).

The mean age was 48.5 years, and 66.2% were women. A normal lung function pattern was detected in 56.8%, followed by obstruction (23.6%) and air trapping, as determined by spirometry (22.5%) and plethysmography (19.5%).

Age and the frequency of bronchiectasis and nasal polyps were higher in the obstructive group. Atopy and higher education level were significantly associated with air trapping. No other characteristics had significant effects on the spirometry-based classification. Details are given in Table I.a (Supplementary II).

The number of patients receiving long-term oral corticosteroids, biological treatment, and inhaled corticosteroids/long-acting β -agonists was significantly higher in the obstructive group (all $P < .05$). Severe asthma was significantly associated with air trapping and obstruction, while moderate asthma was associated with a normal and obstructive functional status. Asthma Control Test scores showed that uncontrolled asthma was associated with the obstructive pattern. In addition, a significant association was found between more frequent exacerbations and emergency room visits and the obstructive pattern.

There were no significant differences in diffusing capacity or bronchial hyperresponsiveness to methacholine in the functional patterns ($P < .05$). Lung function patterns are shown in Table I.b (Supplementary II).

Higher FeNO values were found in the normal pattern, while higher total IgE was found in the obstructive pattern. No statistically significant changes were observed for the other inflammatory biomarkers (Table I.c [Supplementary II]).

Air trapping was diagnosed in 100 patients (22.5%) using spirometry criteria and in 75 based on plethysmography (18.5%). No significant correlation was found between the 2 tests. The κ index was 0.056 (95%CI, 0.004-0.108), indicating slight agreement. Spirometry overestimated 4% of diagnoses compared to plethysmography. Significant differences were obtained between the 2 classifications in

terms of demographic and clinical characteristics. Details are provided in Supplementary III.

Multiple studies of lung function in severe asthma have been published to date. A greater prevalence of air trapping over airflow obstruction has been found in severe disease when measured using spirometry [3], plethysmography [5], and imaging techniques [6]. In our cohort, air trapping was only associated with severe asthma, while airway obstruction was also related to uncontrolled asthma, more intensive treatment, more emergency department visits, and a greater number of exacerbations.

Air trapping has been proposed as a late effect of small and large airway remodeling resulting from airway submucosal hypertrophy, mucosal thickening, and fibrosis [3,6]. This remodeling has been demonstrated to be irreversible in many cases [6]. In our study, the lack of an association between air trapping and other clinical parameters of severe asthma could be explained by a potential type II error, since air trapping was reported in only 20% of the patients studied. Gelb et al [10] reported the presence of mild emphysema as a cause of loss of elastic recoil in autopsied asthmatic lungs. Although our study did not use imaging procedures to rule out emphysema, DLCO was normal and not associated with any spirometry pattern.

We demonstrated overestimation of a diagnosis of air-trapping by comparing spirometry with plethysmography, the gold standard. The absence of a correlation between the 2 tests contrasts with some data [3] but supports other data [11].

Clinical characteristics such as age, CRSwNP, and bronchiectasis have been closely related to severe and uncontrolled asthma [3,4,7,12], as in our results. No association was found between asthma severity and sex or atopy. This observation is consistent with our previous findings [7] and those of other studies [5], although it contrasts with data reported elsewhere [13]. Smoking has been associated with severe asthma [12,13], increased exacerbation rate, and hospital admission. Of note, this study showed that both are independent factors for severity of asthma.

Higher FeNO and sputum eosinophilia are present in poorly controlled and severe asthma [14,15]. ten Brinke et al [5] related sputum eosinophilia to persistent airflow limitation. Despite the inclusion of different degrees of severity in the present study, only FeNO and IgE levels were significantly associated with severity. No other measures of airway inflammation demonstrated a significant difference in any functional pattern, suggesting that clinical asthma expression is well defined by the functional pattern, and even more so than by the inflammatory profile.

In conclusion, our study suggests that some abnormalities in lung function, such as airway obstruction, are good predictors of asthma severity and other clinical characteristics and, as such, may be used as complementary inflammatory markers, although air trapping was only associated with severe asthma. Moreover, we observed that spirometry overestimated the diagnosis of air trapping compared with plethysmography. This finding highlights the need to perform complete lung function tests in all asthma patients when possible.

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Conflicts of Interest

Dr. Betancor is supported by a Rio Hortega Research Contract from Instituto Carlos III, Ministry of Science. Dr. Valverde has received fees for lectures from GSK and is part of the advisory board for Organon. Dr. Rial reports personal fees from GSK, Allergy Therapeutics, and AstraZeneca outside the submitted work. Dr. González Barcala reports personal fees from ALK, AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Gebro Pharma, GlaxoSmithKline, Laboratorios Esteve, Menarini, Mundipharma, Novartis, Rovi, Roxall, Stallergenes-Greer, and Teva and grants from Mundipharma outside the submitted work. Dr. Quirce reports personal fees from AstraZeneca, Novartis, Sanofi, Boehringer Ingelheim, Teva, ALK, Mundipharma, GSK, Chiesi, and Leti outside the submitted work. Dr. Soto-Retes reports nonfinancial support from CIBER de Enfermedades Respiratorias (CIBERES) during the the study. She also reports personal fees from Stallergenes-Greer, Menarini, Novartis, GSK, Hal Allergy, Allergy Therapeutics, and AstraZeneca and grants from Sociedad Española de Alergología e Inmunología Clínica (SEAIC) and Sociedad Española de Neumología y Cirugía Torácica (SEPAR) outside the submitted work. Dr. Martínez Rivera reports grants and personal fees from AstraZeneca, Teva, GSK, Novartis, and Mundipharma, outside the submitted work. Dr. Muñoz reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Mundifarma, Chiesi, and Faes outside the submitted work. Dr. Sastre reports grants and personal fees from Sanofi, GSK, Novartis, AstraZeneca, Mundipharma, and Faes Farma outside the submitted work. Dr. Olaguibel reports grants from Sanofi and/or personal fees from AstraZeneca and Mundipharma outside the submitted work. Dr. Plaza reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Merck, Chiesi, Novartis, Menarini, and Sanofi outside the submitted work. Dr. Mullol reports personal and other fees from Sanofi-Genzyme and Regeneron, Novartis, Viatrix (Mylan Pharma), Uriach Group, Mitsubishi-Tanabe, Menarini, UCB, AstraZeneca, GSK, and MSD outside the submitted work. Dr. Del Pozo reports personal and other fees from Sanofi, AstraZeneca, and GSK outside the submitted work. The remaining authors declare that they have no conflicts of interest.

References

- Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004;59(5):469-78.
- Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med*. 1999;160(3):1001-8.
- Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, et al; National Heart, Lung, and Blood Institute Severe Asthma Research Program. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* (1985). 2008;104(2):394-403.
- Sorkness RL, Zoratti EM, Kattan M, Gergen PJ, Evans MD, Visness CM, et al. Obstruction phenotype as a predictor of asthma severity and instability in children. *J Allergy Clin Immunol*. 2018;142:1090-9.e4.
- ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med*. 2001;164(5):744-8.
- Ito R, Yokoyama A, Hamada H, Yasuhara Y, Kohno N, Higaki J. Effect of inhaled bronchodilators on air trapping in patients with stable asthma. *J Asthma*. 2006;43(2):125-9.
- Rial MJ, Álvarez-Puebla MJ, Arismendi E, Caballero ML, Cañas JA, Cruz MJ, et al. Clinical and inflammatory characteristics of patients with asthma in the Spanish MEGA project cohort. *Clin Transl Allergy*. 2021;11(1):e12001.
- Muñoz X, Álvarez-Puebla MJ, Arismendi E, Arochena L, Ausín MDP, Barranco P, et al. The MEGA Project: A Study of the Mechanisms Involved in the Genesis and Disease Course of Asthma. *Asthma Cohort Creation and Long-Term Follow-Up*. *Arch Bronconeumol (Engl Ed)*. 2018;19:50300-2896(18)30009-7.
- Stocks J, Quanjer PhH. Reference values for residual volume, functional residual capacity and total lung capacity. *ATS Workshop on lung volume measurements. Official statement of the European Respiratory Society*. *Eur Respir J*. 1995;8:492-506.
- Gelb AF, Yamamoto A, Verbeke EK, Schein MJ, Moridzadeh R, Tran D, et al. Further Studies of Unsuspected Emphysema in Nonsmoking Patients With Asthma With Persistent Expiratory Airflow Obstruction. *Chest*. 2018;153(3):618-29.
- Sorkness RL, Kienert C, O'Brien MJ, Fain SB, Jarjour NN. Compressive air trapping in asthma: effects of age, sex, and severity. *J Appl Physiol* (1985). 2019;126:1265-71.
- Ain VV, Abejie B, Bashir MH, Tyner T, Vempilly J. Lung volume abnormalities and its correlation to spirometric and demographic variables in adult asthma. *J Asthma*. 2013;50(6):600-5.
- Hylkema MN, Sterk PJ, de Boer WI, Postma DS. Tobacco use in relation to COPD and asthma. *Eur Respir J*. 2007;29(3):438-45.
- Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. *Chest*. 2020;157(4):790-804.
- Demarche SF, Schleich FN, Paulus VA, Henket MA, Van Hees TJ, Louis RE. Asthma Control and Sputum Eosinophils: A Longitudinal Study in Daily Practice. *J Allergy Clin Immunol Pract*. 2017;5(5):1335-43.

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