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 evolution, and treatment, especially in severe asthma. However, little is known about functional abnormalities and their correlation with the inflammatory subtypes, especially in non-severe disease.

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

The MEGA study is the largest prospective cohort of Spanish asthmatic patients with varying degrees of severity recruited from eight Spanish university hospitals to evaluate the natural history and pathobiological mechanisms underlying the disease [7,8]. Previously from this cohort, Rial MJ 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 greater symptoms and exacerbations, lower asthma control, severe rhinitis, and bronchiectasis [7,8].

The present study aimed to describe the characteristics of asthmatic patients with different lung function patterns, including spirometric and plethysmographic data. As a secondary objective, we examined the agreement between air trapping diagnosed by spirometry criteria and plethysmography.

A retrospective observational study was conducted by reviewing the MEGA cohort electronic database. A total of 445 asthmatic patients with complete data were selected and divided according to their functional pattern as defined by Sorkness et al. [4] and Stocks et al. [9]; More description in *Supplementary I*

Among the 445 study subjects, the mean age was 48.5 years and 66.2% were women. 56.8% had a normal lung function pattern, followed by obstructive (23.6%) and air trapping as determined by spirometry (22.5%) and based on plethysmography (19.5%).

Higher age and increased frequency of bronchiectasis and nasal polyps within the obstructive group were observed. Atopy and higher education level were

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significantly associated with air trapping. No other characteristics had significant effects on spirometry-based classification. Details are given in Table I.a *(Supplementary II).*

The number of patients on long-term oral corticosteroids, biological treatment and ICS/LABA was significantly higher in the obstructive group (all *P<0.05*). Severe asthma was significantly associated with air trapping and obstructive groups, while moderate asthma was associated with normal and obstructive functional status. Asthma Control Test (ACT) scores showed that non-controlled asthma was associated with the obstructive pattern. In addition, a significant association was found between more frequent exacerbations and emergency room visits and obstructive pattern.

There was no significant difference in diffusing capacity or bronchial hyperresponsiveness to methacholine among functional patterns (P<0.05). Lung function patterns are described in Table I.b (Supplementary II).

Higher FeNO value was found among the normal pattern, while higher total IgE in obstructive. No other inflammatory biomarkers demonstrated any statistically significant changes. Table I.c (Supplementary II).

Air trapping was diagnosed in 100 patients (22.5%) using spirometric criteria and in 75 in accordance with plethysmography (18.5%). No significant correlation was found between the two tests. Kappa was 0.056 (95% CI, 0.004 to 0.108), indicating slight agreement. Spirometry overestimated 4% of diagnoses compared to plethysmography. Significant differences were obtained between the two 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 in severe disease has been found when measured by 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 ED 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, mucosa thickening and fibrosis [3,6]. This remodeling has been demonstrated to be irreversible in many cases [6]. In our study, the lack of association between air trapping and other clinical parameters of severe asthma could be explained by a potential

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type II error, since only 20% of the patients studied had air trapping. Gelb et al. [10] reported the presence of mild emphysema as a cause of loss of lung 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 spirometric pattern.

We demonstrated the overestimation of the air-trapping diagnosis through spirometry when compared to plethysmography, the gold standard. The absence of correlation between the two tests contrasts with some studies [3] but supports the findings of other research [11].

Clinical characteristics such as age, CRSwNP, and bronchiectasis have been closely related to severe and non-controlled asthma [3,4,7,12], as in our results. No relation was found between asthma severity and sex or atopy, which is consistent with our previous findings [7] and those of other studies [5], though it contrasts with other reports [13]. Tobacco use has been previously associated with severe asthma [12,13], increased exacerbation rate, and hospital admission. Of note, this study showed that both are independent factors of asthma severity.

Higher FeNO and sputum eosinophilia are present in poorly controlled and severe asthma [14,15]. Ten Brinke et al. related sputum eosinophilia to persistent airflow limitation [5]. Despite including different degrees of asthma severity in the present study, only FeNO and IgE levels showed a significant association with asthma 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 the inflammatory profile.

In conclusion, our study suggests that some abnormalities in lung function, such as airway obstruction, are a good predictor 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 air trapping diagnosis compared to plethysmography. This finding highlights the need to perform complete lung function tests in all asthmatics when possible.

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REFERENCES

1. 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.
2. 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.
3. 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 ApplPhysiol (1985). 2008;104(2):394-403.
4. 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. Journal of Allergy and Clinical Immunology. 2018;142:1090-9.e4.
5. 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;1;164(5):744-8.
6. 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.
7. 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. ClinTransl Allergy. 2021;11(1):e12001.
8. 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:S0300-2896(18)30009-7.
9. 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.
10. Gelb AF, Yamamoto A, Verbeken 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.
11. Sorkness RL, Kienert C, O'Brien MJ, Fain SB, Jarjour NN. Compressive air trapping in asthma: effects of age, sex, and severity. Journal of Applied Physiology. 2019;126:1265-71.

doi: 10.18176/jiaci.0866

12. 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.
13. 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.
14. 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.
15. 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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