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Clinical Report

Fixed Airflow Limitation in Severe Asthma: Rethinking the Role of Small Airway Disease

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ABSTRACT

Small airway disease (SAD) remains a challenging and underrecognized driver of fixed airflow obstruction in severe asthma. Impulse oscillometry (IOS) provides valuable insight into peripheral airway dysfunction and allows characterization of different bronchodilator response patterns. We describe two cases of late-onset severe asthma with confirmed SAD by spirometry and IOS, unresponsive to systemic corticosteroids and to biologics, despite optimized high-dose extrafine triple inhaled therapy and adherence. Both patients exhibited persistent airflow obstruction and abnormal IOS parameters, suggesting a resistant SAD phenotype. Importantly, the role of corticosteroid challenge in this subgroup remains unclear, as it failed to predict subsequent biologic response. These observations highlight the clinical utility of IOS in diagnosing and monitoring SAD and reinforce the need for personalized therapeutic approaches to address this treatment-resistant endotype of severe asthma.

Obstrucción fija al flujo aéreo en el asma grave: repensando el papel de la enfermedad de la pequeña vía aérea

Palabras clave:
Enfermedad de pequeña vía aérea
Oscilometría de impulsos
Asma grave

RESUMEN

La enfermedad de la vía aérea pequeña constituye un componente difícil de diagnosticar en el asma grave con obstrucción grave. La oscilometría de impulsos (IOS) permite caracterizar la disfunción periférica y describir distintos patrones de respuesta broncodilatadora, aportando un fenotipado más preciso. Presentamos dos casos de asma grave de inicio tardío con afectación de vía pequeña confirmada por espirometría e IOS, refractarios a corticoides sistémicos y a biológicos, a pesar de tratamiento inhalado triple optimizado y buena adherencia. Ambos mostraron obstrucción persistente y parámetros oscilométricos alterados, sugiriendo un fenotipo resistente. Destacamos que el papel del reto con corticoides en este subgrupo de pacientes sigue siendo incierto, pues no predijo la respuesta posterior a biológicos. Estos hallazgos refuerzan el valor de la IOS en el diagnóstico y seguimiento de la afectación de vía aérea pequeña, y subrayan la necesidad de estrategias terapéuticas personalizadas.

Small airway disease (SAD) remains a silent driver of fixed airflow obstruction in severe asthma—underdiagnosed,[1] undertreated, and often unresponsive to biologics. In patients with persistent obstruction despite treatment, a systemic corticosteroid trial may help identify the diagnosis and assess reversibility.[2] The ATLANTIS study[3] highlighted a strong association between spirometry-defined airflow limitation, SAD, and type 2 inflammation biomarkers. Notably, SAD has been independently associated with increased mortality, particularly from respiratory causes.[4]

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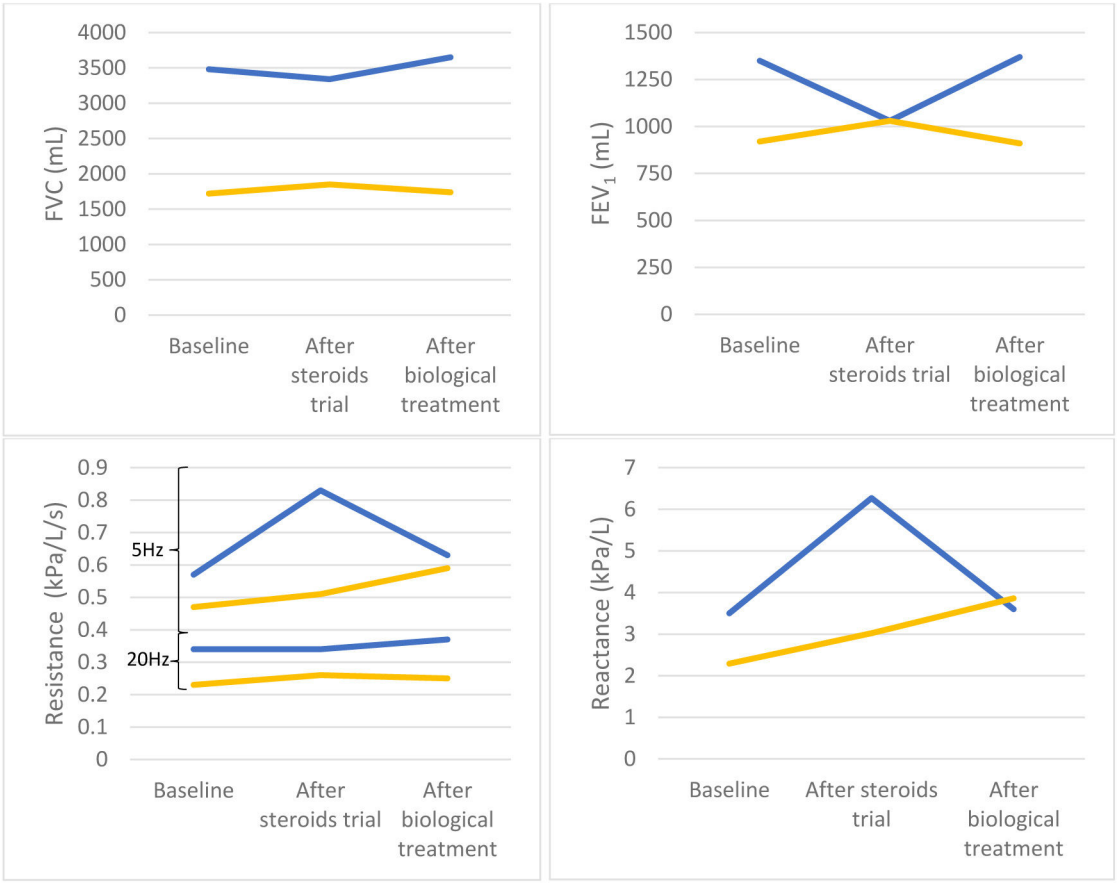

Fig. 1. Spirometric and oscillometric evolution in two patients with severe asthma and confirmed small airway disease. Despite optimized therapy, both cases (case 1: blue, case 2: yellow) showed persistent airflow obstruction and abnormal IOS parameters. No meaningful functional response was observed following systemic corticosteroids or biologic treatment.

Impulse oscillometry (IOS) has emerged as a valuable method for detecting SAD,[1] especially spirometry fails to capture peripheral airway dysfunction. IOS is particularly suited for functional phenotyping in asthma, though its routine clinical application remains limited. SAD can be identified by IOS parameters such as elevated resistance (R) difference between 5 and 20 Hz (R5-20), reduced reactance at 5 Hz (X5), or an increased area under the reactance curve (AX).[5] Although standardized thresholds for bronchodilator response in IOS are not yet universally established, commonly used criteria include a ≥40% decrease in R 5 Hz, ≥50% increase in X 5 Hz and ≥80% decrease in AX relative to baseline.[6] Current therapeutic strategies for SAD include triple inhaled therapy.[7] Biologics have shown encouraging results,[1] particularly when initiated early.[7] However, the value of corticosteroid challenge in predicting response remains unclear.

We present two cases of late-onset severe asthma with confirmed SAD and persistent functional impairment, despite confirmed adherence to optimized triple inhaled therapy with extrafine high-dose beclometasone/formoterol/glycopyrronium. Asthma-related comorbidities – including chronic rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnea, vocal cord dysfunction, obesity, and anxiety – were systematically assessed and appropriately managed. Microbiological and autoimmune tests were negative. Neither patient showed evidence of allergic sensitization or allergic bronchopulmonary aspergillosis.

Case one, was a 58-year-old man, former smoker (10 pack-years in early adulthood), with asthma control test (ACT) score of 10. Case two was a 57-year-old woman, never smoker, with ACT of 22. Asthma diagnosis was supported in both cases by prior bronchodilator positive test, and clinical response to appropriate therapy.

Case 1 had peripheral eosinophila (700/μL), FeNO of 16 ppb. Case 2 showed undetectable eosinophils and FeNO 25 ppb.

High-resolution CT scan excluded mucus plugging, mosaic attenuation or other parenchymal abnormalities in both cases.

Functional evaluation, including both spirometry and IOS, confirmed baseline SAD in both cases. Case 1 (post-bronchodilator) had a forced vital capacity (FVC) of 3480 mL (90% predicted), forced expiratory volume in one second (FEV_1) of 1350 mL (44%) and FEV_1/FVC ratio of 39%, indicating severe airway obstruction. Mid-expiratory flow ($MEF_{25–75\%}$) was markedly reduced at 370 mL/s (14%) and FEV_3/FVC 59%. IOS revealed increased R5-20 (0.23 kPa/L/s), increased R5 (0.57 kPa/L/s; 190% of predicted) with preserved R20 (0.34 kPa/L/s; 131%), markedly reduced X5 (−0.29 kPa/L/s) and elevated AX (3.50 kPa/L), supporting the presence of SAD. Despite a significant bronchodilator response in FEV_1 (+22%, +240 mL), IOS abnormalities persisted. Case 2 had an FVC of 1720 mL (64%), FEV_1 920 mL (43%), FEV_1/FVC 53%, $MEF_{25–75\%}$ 250 mL/s (12%) and FEV_3/FVC 74%. IOS revealed abnormal peripheral airway metrics: R5-20 0.24 kPa/L/s, R5 0.47 kPa/L/s (120%), R20 0.23 kPa/L/s (69%), X5 −0.28 kPa/L/s and AX 2.29 kPa/L. No bronchodilator response was observed, and IOS values remained essentially unchanged, further confirming lack of reversibility.[1]

A two-week course of oral prednisone (40 mg daily) was administered to both patients. However, neither showed significant clinical (ACT score), spirometry, or IOS improvement. In case 1, lung function even deteriorated slightly: FVC increased to 3650 mL (95%) but FEV_1 remained low at 1370 mL (45%), FEV_1/FVC at 38%, and

R5Hz increased to 0.63 kPa/L/s. In case 2, lung function remained essentially unchanged, indicating no significant response to a corticosteroid trial.

Both patients were initiated on biologic therapy according to their phenotypes, case one with mepolizumab and case two with Tezepelumab.[7] After three months, a comprehensive re-evaluation showed no meaningful improvement in clinical, spirometric, or IOS parameters (Fig. 1). In case 1, FEV_1 remained at 1370 mL (45%) and $MEF_{25-75\%}$ at 370 mL/s (14%), while R5 Hz and R20 Hz slightly worsened. Due to lack of clinical and functional improvement after six months of treatment with Mepolizumab, biologic therapy was switched to Benralizumab. However, no significant improvement was observed after three additional months. In case 2, FEV_1 was stable at 910 mL (41%), FVC at 1740 mL (65%), and FEV_1/FVC at 52%, with persistent negative bronchodilator response. Tezepelumab was maintained as it improved asthma control. Our observations are consistent with Carpagnano et al., [8] who found limited IOS and spirometric improvement after Tezepelumab in a subgroup of patients with established SAD, despite improvements in symptom control and exacerbations.

These cases underscore a clinically significant subgroup of severe asthma with persistent SAD that appears refractory to corticosteroids and biologics. Lung function remains a crucial parameter for assessing clinical remission, alongside symptom and exacerbation control.[9] These observations suggest a potential SAD phenotype defined by fixed airflow obstruction and limited reversibility. Even with optimized inhaled and biologic therapy, some patients demonstrate minimal functional response, highlighting a treatment-resistant endotype. A potential strategy in these patients could be switching to a biologic with a different mechanism of action. In a recent study, switching biologic therapy led to improved lung function and asthma control in patients not responding to initial treatment.[10] While IOS provides a sensitive tool for diagnosis and monitoring SAD, its findings in these cases indicate structural or non-type 2 inflammatory changes may underlie resistance. Further studies are urgently needed to elucidate the mechanisms underlying corticosteroid and biologic resistance in SAD, and to inform the development of more effective, personalized therapies for this potentially distinct SAD endotype.

These cases call for a paradigm shift: lung function—and especially small airway evaluation through IOS—must regain prominence in defining asthma control and in guiding therapeutic and prognostic decisions.

Artificial intelligence involvement

During the preparation of this worth the authors used CHAT GPT 4 solely to assist with language editing under the authors' supervision. After using this tool/authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Informed consent

Each patient provided written informed consent for the publication.

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Authors' contributions

MJG and RMDC contributed to data acquisition, writing and manuscript review. IGM contributed to clinical management, data interpretation and manuscript review. All authors approved the final version of the article.

Conflicts of interest

The following authors declare having received fees for lectures and congress participation from the listed companies (alphabetic order): MJG (Chiesi, FAES, GSK, Sanofi), RMDC (AstraZeneca, GEBRO, GSK, Sanofi), IGM has been on Advisory boards of: AstraZeneca, GSK, Novartis, Sanofi Genzyme, Stallergenes, and received speaker's honoraria from: Allergy therapeutics, ALK-Abelló, AstraZeneca, Chiesi, GSK, Leti, Mundipharma, Novartis, Orion Pharma, Pfizer, Sanofi Genzyme, Stallergenes, and Teva.

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