

COPD as a Small Airways Disease, Do we have a new Pharmacotherapy Target?

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by a persistent airflow limitation. A small airways dysfunction (SAD) is used to define a small airways involvement, defined by an internal diameter ≤ 2 millimeters. In the context of different methods to assess a SAD, the impulse oscillometry system (IOS), a type of forced oscillation technique, may be useful because it is effort independent, has a robust range of values and has a clinically validated methodology. In this editorial we emphasize the role of small airways as a target for a pharmacotherapy. In fact, the presence of SAD in COPD patients and the methodology of IOS for the evaluation of the treatment efficacy may open new scenarios for the pharmacotherapy. In COPD patients SAD drives symptoms and impact of disease; an

inhaled medication that reaches deeper the airways and that has a probable effect on the SAD may have a reasonable role to exist.

Key words: Chronic obstructive pulmonary disease; Small airways; Impulse oscillometry system; Pharmacotherapy; COPD assessment test

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EDITORIAL

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic airflow limitation caused by both small airways disease and parenchymal destruction^[1]. The involvement of small airways is related to the progression of disease, with the accumulation of inflammatory mucous exudates in the lumen and infiltration of the wall as an innate and adaptive response^[2,3]; these changes are coupled to a remodeling process causing a thickness of the walls of airways^[2,3]. Structural changes affecting the terminal bronchioles precede emphysematous destruction^[3]. The small airways, defined by an internal diameter ≤ 2 millimeters^[1-4], represent in COPD patients the functional major site of airflow obstruction^[1,2]; for this reason the term of small airways dysfunction (SAD) is often used to characterize it^[1,2]. Due to discrepancy between the extensive damage of SAD and the occurrence of any symptom, the small airways are defined as a “*silent zone*”^[1,2,5].

In the context of different methods to assess a SAD the impulse oscillometry system (IOS), a type of forced oscillation technique, has been recently proposed^[6]. This technique offers some advantages, such as to be effort independent, to have a robust range of values and to be a clinically validated methodology due to many studies that support her usefulness^[7]. According to the international recommendations^[8], IOS implies the application of a pressure fluctuation to the airways using sound waves. The patients are asked to wear a nose clip and to seat during tidal breathing with their neck slightly

extended and their lips sealed tightly around the mouthpiece. During the exam at least 3 trials are performed, each lasting 30 seconds; the mean values are chosen. The results are expressed by the resistance and reactance of the airways^[8]. Usually, by the IOS is possible to calculate the resistance at both 5 Hz (R5) and 20 Hz (R20) that are considered measures of total and proximal airway resistance, respectively^[9]. The fall in resistance between R5 and R20 (R5-R20) is considered an index for the resistance of peripheral airways, together the value of reactance at 5 Hz (X5) and resonant frequency (F_{Res}). Providing measures of both proximal and distal airway resistance^[9], in COPD patients IOS is a better method to detect a SAD than standard spirometry, due to forced expiratory volume in the first second (FEV₁) that is mainly able to measure expiratory flow at high and mid volume^[10]. Two cut-offs of $R5-R20 \geq 0.03 \text{ kPa} \cdot \text{s} \cdot \text{L}^{-1}$ ^[11,12] and $\geq 0.07 \text{ kPa} \cdot \text{s} \cdot \text{L}^{-1}$ ^[13] have been proposed from literature to define a small airways impairment. However in COPD patients, in comparison to asthmatics^[14], the possibility to use the cut-off $\geq 0.07 \text{ kPa} \cdot \text{s} \cdot \text{L}^{-1}$ may have conceptually the advantage of a reasonable certainty of a SAD, representing a conservative upper limit of normality for R5-R20^[15].

In COPD, IOS is useful to define different subgroups of patients according to the airflow obstruction^[16], to detect an early phase of disease^[17], to monitor the annual change especially during the acute exacerbation^[18] and to have a specific measure of symptom-reported and quality of life^[19]. Related to the response to inhaled medications, IOS by X5 and F_{Res} is able better than FEV₁ and forced vital capacity (FVC) to measure the effect of incremental doses of salbutamol^[20] identifying COPD patients with a bronchodilator responsiveness phenotype^[11] and in particular patients volume-responders^[11]. In this context, the assessment of a SAD may be considered as a functional marker useful to evaluate drug-related improvements in COPD patients with a specific phenotype of volume responsiveness, and this despite no changes in FEV₁^[21]. In fact, a recent study comparing the effect of indacaterol/glycopyrronium *versus* tiotropium in COPD patients has shown an increase at 52 weeks of R5, R20 and X5 in the indacaterol/glycopyrronium group only^[22], although FEV₁ was not able to detect this improvement^[22].

COPD is a heterogeneous disease requiring multifaceted approach^[23]; a targeted drug then is frequently needed for a personalized pharmacotherapy also in COPD patients^[23]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee in the 2011^[24] proposed different risk categories to have a look of a complex disease, that is not FEV₁ only driven. In addition, in the recent GOLD update^[25] the evaluation of dyspnea (with the modified Medical Research Council scale-mMRC) and impact of disease (with the COPD assessment test score-CAT) are requisites to prescribe or change a therapy based on bronchodilators and/or inhaled corticosteroids^[25]. Based on the evaluation of the relationship between a peripheral airway dysfunction and the GOLD categories a prospective study on more than two hundred moderate-to-severe COPD outpatients demonstrated a prevalence of SAD in 74% of patients^[13] that had specific clinical and functional characteristics^[13]. In general, was evident a progressive and increasing peripheral airway dysfunction among GOLD classes of risk^[13], with a strong correlation between the value of R5-R20 and the CAT score ($r = 0.527$; $p < 0.001$). Finally, in a multivariate regression model predicting the probability to have a CAT score ≥ 10 the presence of SAD was able to identify patients with higher impact (Odds ratio 11.96, confidence interval 4.53 to 31.58, $p < 0.001$)^[13].

Now, starting from the concepts that COPD patients have a SAD and that it drives mMRC^[19], SGRQ^[19] and CAT^[13], an inhaled medication having the possibility to reach deeper the airways, having a

probable effect on the SAD with the aim to change symptoms and impact of disease may have a reasonable role to exist. However, while in patients with asthma the role of SAD as a therapeutic target for bronchodilators plus inhaled corticosteroids with extra-fine formulations is consolidated^[26], in COPD this role is not yet fully established, although improvements in air trapping, in dyspnoea perception^[27] and in other patient-related outcomes^[28] have been demonstrated. Moreover, the possibility to have a methodology such as IOS that is able to provide evaluation of the treatment efficacy in COPD patients^[20,21,29,30] may open new scenarios in an accurate evaluation of pharmacotherapy. Finally, by identifying in COPD patients a bronchodilator responsiveness phenotype^[11,31] with a worse SAD^[11] it is possible to assume that in selected patients with higher impact of disease (CAT score ≥ 10) an extra-fine formulation may find an effective use. In COPD patients with SAD further studies are needed to explore other outcomes related to a pharmacotherapy target such as the effect on static and dynamic lung hyperinflation, on exercise capacity, on exacerbation rate, and finally on survival.

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