

Comments to the Author

In this manuscript the authors aim to characterize the effects of glycopyrrolate (a LAMA) and formoterol fumarate (a LABA) both administered via a metered dose inhaler on airway volume and resistance measured using Functional respiratory imaging (FRI) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

They report that both therapies significantly improved airway volume and airway resistance at Day 15 versus baseline and that these improvements were greater with Formoterol compared to glycopyrrolate although some individuals displayed greater responses with each of the two treatments. They conclude that FRI endpoints demonstrated increased sensitivity and that inpatient differences in treatment response between the LAMA and the LABA provide further support for the benefit of dual bronchodilator therapies.

The manuscript is very well written and provides information on the action of two bronchodilators, belonging in different drug classes, on the bronchial tree in COPD patients. The results provide information on airway function beyond spirometry. My comments are the following

1. The authors provide information on alterations on airway resistance and airway volume. It is the fact that these alterations are not very well represented by spirometric data, with the exception of IC, which leads to the conclusion that both therapies are effective in ameliorating air trapping. However, it is a fact that all patients included in the study were symptomatic and it would be interesting to see whether these differences are related with symptomatic improvement in their group of patients (mainly dyspnea but also CAT score)
2. The authors state that there were inpatient differences in treatment response between the LAMA and the LABA. This fact in combination with the observation that Formoterol seems to be more potent in the small airways raises some questions. Is it possible to provide data on the differences between patients which are more responsive to LAMA and those more responsive to LABA? Is this difference in response related to disease severity, air trapping or the presence of emphysema? If the authors have data they should provide them.
3. Table 1 is very poor since it shows only baseline characteristics. I believe that it should be expanded showing results at the end of treatment with formoterol and at the end of treatment with glycopyrronate.
4. Figure 4 is very confusing. The authors should find another way of reporting the differences of the two types of drugs in the different airway generations.
5. What is the clinical impact of these findings? The authors report the necessity for dual bronchodilation but do not provide data on patients receiving both drugs so it is unclear if there will be a benefit in such an occasion regarding the primary and secondary outcomes of the current study.