ESPS Manuscript No. 20109
World Journal of Respirology

Title: β2-Adrenoceptor in Obstructive Airway Diseases: Agonism, Antagonism or Both?

Reviewer 1:

C1:
Only thing that I was missing was the statistics on the use of beta blockers as well as the frequencies of diagnosed 'pure' obstructive airway disease, airway disease + cardiovascular disease and 'pure' cardiovascular disease, in order to understand how common these are issues now.

R1:
We have added this paragraph, "According to the 2015 reports from Global initiative for Asthma (GINA) and Global initiative for chronic obstructive lung disease (GOLD), the prevalence of asthma ranges from 1 to 18% worldwide, while prevalence of COPD is about 6%[1,2]." to page 3 under "Introduction".

We have also added this paragraph, "A recently published study by Bellocchia et al.[30], which recruited 229 patients, showed that 51% COPD and 30% asthmatic patients had cardiovascular disease. Congestive heart failure (CHF) in COPD patients range from 8 to 27% while coronary artery disease (CAD) in COPD patients range from 15 to 25%[31]. In a recent RHYTHMOS study, in a population of 280 CAD with COPD patients, only 52.8% were treated with β-blockers, where most were treated with suboptimal dosages[32]. In another study by Puente-Maestu et al.[31], only 58% of COPD patients with indication for CHF/CAD were prescribed with β-blockers, while 97% of non-COPD patients with indications were treated with β-blockers." to page 9 under the heading "β_2-Blocker or inverse agonist and their role in obstructive airway disease".

1. **Global initiative for asthma.** Global strategy asthma management and prevention. 2015. http://www.ginasthma.org.
2. **Global initiative for chronic obstructive lung disease.** Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2015. http://www.goldcopd.org.
30. **Bellocchia M**, Masoero M, Ciuffreda A, Croce S, Vaudano A, Torchio R, Boita M, Bucca C. Predictors of cardiovascular disease in asthma and chronic obstructive pulmonary disease. *Multidiscip respir med* 2013; **8**: 58. [PMID: 24004921 DOI: 10.1186/2049-6958-8-58]
31. **Puente-Maestu L**, Calle M, Ortega-González A, Fuster A, González C, Márquez-Martín E, Marcos-Rodriguez PJ, Calero C, Rodríguez-Hermosa JL, Malo de Molina R, Aburto M, Sobradillo P, Alcázar B, Tirado-Conde G, GEMEPOC Group. Multicentric study on the β-blocker use and relation with exacerbations in COPD. *Respir Med* 2014; **108**: 737-744. [PMID: 24635914 DOI: 10.1016/j.rmed.2014.02.009]
32. **Andrikopoulos G**, Pastromas S, Kartalis A, Toli K, Mantas I, Tzeis S, Kyrpizidis C, Olympios C, Manolis AJ, Foussas S, Kranidis A, Pras A, Pipilis A, Chryssos D, Gotsis A, Trikas A, Richter D, Alexopoulos D, Parthenakis F, Theodorakis G, Konstantinides S, Vardas P. Inadequate heart rate control is associated with worse quality of life in patients with coronary artery disease and chronic obstructive pulmonary disease. The RYTHMOS study. *Hellenic J Cardiol* 2012; **53**: 118-26. [PMID: 22484777]

Reviewer 2:

C1:
Two points are relevant for checking before to consider your manuscript in WJR:
1. Please check the use of english language and the meaning of intended sentences. (An example, I suggest: Obstructive airway disease is a complex entity including several maladies characterized by bronchoconstriction and abnormal airway inflammation.)

R1:
We have made all necessary changes and improved the English language throughout the manuscript. As suggested, we have revised the statement to “Obstructive airway disease is a complex disease entity including several maladies characterized by bronchoconstriction and abnormal airway inflammation.” on page 2 under “Abstract”.

C2:
I suggest you the inclusion of some mechanisms probably involved in the 'beneficial-action' of beta-blockers (as is mentioned in your references 37, 58 and 59). Please read the following documents and analyze the last sections of your manuscript as well as your conclusions (and probably some of your figures).

1. Recent structural advances of β1 and β2 adrenoceptors yield keys for ligand recognition and drug design. Soriano-Ursúa MA, Trujillo-Ferrara JG, Correa-Basurto J, Vilar S. J Med Chem. 2013 Nov 14;56(21):8207-23.
2. β-Adrenoceptor blockers and pulmonary function in the general population: the Rotterdam Study. Loth DW, Brusselle GG, Lahousse L, Hofman A, Leufkens HG, Stricker BH. Br J Clin Pharmacol. 2014 Jan;77(1):190-200.
3. Clinical implications of recent insights into the structural biology of beta2 adrenoceptors. Amezcua-Gutierrez MA, Cipres-Flores FJ, Trujillo-Ferrara JG, Soriano-Ursua MA. Curr Drug Targets. 2012 Sep 1;13(10):1336-46. Best regards, Reviewer

R2:
Based on your recommended papers 1 and 3, We have added, “β_2-AR have been studied intensively, and depending on the ligand binding site, it can induce differential stabilized conformation which in turn elicits a variety of selectivity toward G-protein-dependent and β-arrestin-dependent signaling[44,45] It was further proposed that a secondary binding site may be exposed upon adequate conformational state, leading to a different signaling cascade[44].” as reference no. 44 and 45, to page 10 under the heading “β_2-Blocker or inverse agonist and their role in obstructive airway disease”.

We have cited your recommended paper 2 as reference no. 35 for “β-Adrenoceptor blockers and pulmonary function in the general population: the Rotterdam Study. Loth DW, Brusselle GG, Lahousse L, Hofman A, Leufkens HG, Stricker BH. Br J Clin Pharmacol. 2014 Jan;77(1):190-200” in this statement “Studies of using β-blockers in asthma and COPD have demonstrated decreased airway reversibility[33] and reduction in FEV_1[34,35].”on page 9 under the heading “β_2-Blocker or inverse agonist and their role in obstructive airway disease”.

We have also revised the legend for Figure 3, adding this statement, “The differential response could be due to the binding of ligand to a shallower secondary binding site exposed only when an adequate conformational state is obtained as proposed by Soriano-Ursúa *et al.*, however more work need to be done to validate the mechanism[44].”