Reviewer's report

Title: Inhaled beta-agonist does not modify sympathetic activity in patients with COPD

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Reviewer: Arnoldus J.R. van Gestel

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Manuscript Number:
Title: INHALED #-AGONIST DOES NOT MODIFY SYMPATHETIC ACTIVITY IN PATIENTS WITH COPD
Authors: Helge Haarmann, Cordula Mohrlang, Uta Tschiesner, David B. Rubin, Thore Bornemann, Karin Rüter, Slavtcho Bonev, Tobias Raupach, Gerd Hasenfuss, Stefan Andreas

The authors of this study investigated the effects of salmeterol therapy, a long-acting #2-agonists (LABA), on sympathetic activation and lung function in patients with COPD. The evaluation of the effect of inhaled therapy with salmeterol on muscle sympathetic nerve activity (MSNA) in COPD patients was conducted at baseline and after a follow up period of 4 weeks. While #2-agonists improve lung function, quality of life and exacerbations in COPD patients, its effect on sympathetic activity have never been investigated. This manuscript is of importance to detect a potentially link between pulmonary and systemic effects in patients with COPD. However, the manuscript has to be improved on following issues:

Abstract:
1- Information about the variables (HRV, BRS) and the methods used (Finapres) are missing. Also the duration of the assessment is missing.
2- The results should include the #2-agonists induced changes/ differences of all the main variables (HR, HRV, BRS).

Background
3- The authors formulated their aim of the study as followed: « We aimed to investigate... » I would recommend writing it in a more neutral form like: This study investigates the effect....
4- The association between sympathetic tone and chemoreflexes, baroreflexes and lung hyperinflation needs to be more elucidated. The abnormality of autonomic function in patients with COPD may affect stimulus reception, afferent nerve conduction, central processing, efferent nerve conduction, and neuromuscular response. The sensory receptors that might play a significant role in autonomic dysfunction in patients with COPD are arterial and cardiac baroreceptors, metabolic and pulmonary stretch receptors, bronchopulmonary
C-fibres and arterial chemoreceptors. Large intrathoracic pressure changes, as occurring in chronic obstructive pulmonary disease due to hyperinflation, are transmitted to the heart and great vessels and can influence both peripheral baroreceptors and cardiac performance. Large pressure changes may cause fluctuations in cardiac performance, and therefore, in systemic blood pressure provoking finely modulated compensatory changes of the heart rate mediated by separate outputs of intrathoracic baroreceptors.

Methods

5- The authors included subjects with COPD GOLD stage II or III. Why were COPD GOLD stage IV exclude from the study?

6- Measurement and data analysis:

« The 2-hour measurement period comprised the continuous recording of MSNA, respiration and other measurements as explained below (...) » (122). Please describe all measurements because it is very uncommon to refer to paragraphs who are yet to come.

In addition « MSNA and the other following parameters were only assessed (...) » (132) Here it is not clear which following parameters are meant to be assessed. Please explain more precisely what is meant.

7- „Under the assumption that adequate microneurographic recordings can only be obtained in 75% of all subjects studied (...)”. Where does this assumption come from? Please underline this statement with literature.

Results

8- In the result part there is a good division of the individual parameter assessed. It would be helpful to see this division already in the method section (cardiovascular, respiratory and autonomic nervous system). Further a graphical overview of the assessed parameters would be helpful.

Results

9- Baseline MSNA was elevated in all patients. Please include normal values incl. references to the literature.

10- A valid signal for visit 1 was obtained in 18 patients, while in 14 patients a valid signal could not be obtained. How do the authors explain this fact?

11- The layout/ format of the tables is inadequate. It is unable to get a clear overview of the data. Furthermore there are a lot small errors (p=>0.01, P= 0.01, p= 0.01). It looks like there are p-values missing for lung function parameters.

Discussion

12- The discussion is poorly structured. I would suggest that the second paragraph (effects on heart rate) underlines the short term effects of B2 agonist on heart rate en heart rate variability. There is clear evidence that B2 agonist increases sympathetic tone and decreases parasympathetic tone. In addition the long term effects can be discussed.

13- “The fact that salmeterol......autonomic nervous system”. Is this really true?

14- I would suggest that the third paragraph (sympathetic activation) underlines
the short term effects of B2 agonist on MSNA. In addition the long term effects can be discussed.

15- In an additional paragraph the contradictorily results of HR/ HRV versus MSNA can be discussed.

Other details

16- Please make sure that the unnecessary line numbers are deleted in the whole manuscript. Just write line numbers where there is some text. Further it would be nice to shorten the whole manuscript.

17- Please make sure there are no blank pages in the manuscript (page 19)

18- Table 1 is not placed in the centre of the page. Please make sure to put the legends on the same page as the table itself. Table 2 and 3 should be placed on one page rather than split off two pages. Further the first column is very confusing in all tables. It would be good to put some extra work in the layouts of the tables to get them look more attractive.

19- Table 2,3 and 4 are very confusing because there are different n postulated between baseline and endpoint measure. Change between different n is not meaningful. Please include just participants which completed measurements at baseline and after salmeterol.

In Table 4 there are problems in data presentation:
- Inconsistent decimal places (column 1)
- Layout Mean/ SD not appropriate
- Title of table 4 is not appropriate

20- The graphs on Page 28 and 29 are unsharp printed and don't look attractive at all. See comment 16. Make sure to put the Figure legends from page 27 to the figures appropriate.

Figure 1: Why did you use bar chart to illustrate this result? I would recommend a trend figure.

21- The layout of the graphs a not attractive... They need further styling. Do we need figure 2 as there are only 12 dots?

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

In the context of peer review, there is no competing interest....