Author’s response to reviews

Title: Anticholinergics aggravate the imbalance of the autonomic nervous system in stable chronic obstructive pulmonary disease

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There are our point-by-point responses to the comments raised by the reviewers. The comments are reproduced in quotes and our responses are given directly afterward.

Reviewer 2 (Reviewer 1): PEER REVIEWER ASSESSMENTS:

1. 'The MS is largely well written with clear goals (there are some minor grammatical issues in the Introduction and part of the Discussion). The results are of interest and may instruct on how to address this potential parasympathetic imbalance and monitor more closely the patients on anti-cholinergics.'

   Thanks for these comments. In order to improve the English language within our manuscript, we asked a colleague who is a native English speaker to review our manuscript. We amended some words and sentences according to his suggestions. For his personal reasons, we cannot mention his name in Acknowledgements section. Here are the details of language improvement.

   1) Introduction section, line 12, page 3:  … and the meta-analyses.

   Modified:  … and the meta-analyses of these trials. (Introduction section, line 20, page 3)

   2) Introduction section, line 13, page 3:  … risk was unknown.

   Modified:  … risk remains unknown. (Introduction section, line 21, page 3)
3) Introduction section, line 23-25, page 3: there were fewer studies to investigate if an abnormal HRR is related to anticholinergics which were used widely in patients with COPD. (Introduction section, line 24-25, page 4 & line 1, page 5)

Modified: only a few studies have investigated whether an abnormal HRR is related to use of anticholinergics in patients with COPD. (Introduction section, line 3-4, page 5)

4) Introduction section, line 1-3, page 4: we performed the present study to compare the HRR between COPD patients with and without inhaled anticholinergic.

Modified: we determined whether inhaled anticholinergic bronchodilators alter HRR in COPD patients. (Introduction section, line 2-3, page 5)

5) Discussion section, line 3-6, page 9: The present study mainly found HRR was significantly lower in subjects with Tiotropium than in the controls, further extends this notion by showing that the Tiotropium could be used as an independent influencing factor of HRR in the stable COPD patients.

Modified: The key finding of the present study is that HRR was significantly lower in COPD patients taking tiotropium than those on no bronchodilator therapy. Further tiotropium use was shown to be an independent influencing factor for prediction of HRR in the stable COPD patients. (Discussion section, line 8-11, page 10)

6) Discussion section, line 10-11, page 9: By decreasing parasympathetic input to the heart, it can increase the incidence of tachyarrhythmia and ischemia.

Modified: A decreased parasympathetic input to the heart is known to increase the potential for tachyarrhythmia and ischemia (Discussion section, line 16-17, page 10)

7) Discussion section, line 17, page 9: The study showed that abnormal HRR was associated with all-cause mortality in COPD.

Modified: Their study showed that abnormal HRR was associated with higher all-cause mortality in COPD. (Discussion section, line 1-2, page 11)

8) Discussion section, line 18, page 9: Though → However (Discussion section, line 3, page 11)

9) Discussion section, line 1-2, page 10: It has been reported in many types of research that cardiovascular disease is …

Modified: It is an important and frequently-reported finding that cardiovascular disease is … (Discussion section, line 5-6, page 11)
10) Discussion section, line 12, page 10: From a clinical standpoint, → Therefore, there is considerable evidence that (Discussion section, line 19, page 11)

11) Discussion section, line 7, page 11: hypothesized that was related to → hypothesized that this risk was related to (Discussion section, line 17, page 12)

12) Discussion section, line 12, page 11: high-frequency components after 1 month…
Modified: high-frequency components of heart rate variability (HRV) (also a correlate of autonomic imbalance) after 1 month… (Discussion section, line 22, page 12 & line 1, page 13)

13) Discussion section, line 14, page 11: These changes reflected at early treatment decreased …
Modified: These findings are consistent with early in treatment decreased … (Discussion section, line 3, page 13)

14) Discussion section, line 4, page 12: records → responses (Discussion section, line 13, page 13)

15) Conclusion section, line 11-12, page 12: Tiotropium could reduce HRR in stable COPD patients, which in turn affects cardiac autonomic function,
Modified: stable COPD patients using tiotropium demonstrate reduced HRR, which may indicate alterations in cardiac autonomic function, (Conclusion section, line 22, page 13 & line 1, page 14)

16) Conclusion section, line 14, page 12: monitored for → considered for monitoring of (Conclusion section, line 4, page 14)

17) Conclusion section, line 15, page 12: alert to → prescribers should be alert for (Conclusion section, line 5, page 14)

2. 'My main recommendation is to move several parts of the discussion to the Introduction, notably on summarizing the overall concept of parasympathetic imbalance, its frequency in patients on Tiotropium, and the value of HRR as an measure of this imbalance.'

We are grateful for the suggestion. According to the comment, we modified several parts as follows:

1) We have added the overall concept of parasympathetic imbalance as follows: Parasympathetic nerve fibers serve as a component of the efferent limb of the baroreceptor, chemoreceptor, and of other cardiovascular and respiratory reflexes involved in the regulation of cardiac automaticity and contractility. Parasympathetic tone and
parasympathetically mediated reflexes are profoundly depressed in heart failure and in various forms of heart disease.” (Introduction section, line 4-8, page 4)

2) The frequency of parasympathetic imbalance in patients on tiotropium has been described in Introduction section as follows: LAMAs can affect cardiac function in two opposing ways. For one thing, by relaxing the bronchiolar smooth muscle and increasing oxygenation, anticholinergics indirectly decrease pulmonary artery pressure and compensatory sympathetic stimulation of the heart, which could lessen the incidence of tachyarrhythmia and ischemia. For another, anticholinergics suppress parasympathetic control of heart rate which is associated with an increased incidence of tachyarrhythmia and myocardial ischaemia. Once the imbalance of the indirect and direct cardiac activity occurs, it may aggravate the autonomic nervous disorder. (Introduction section, line 9-17, page 4)

3) The part about the value of HRR has been moved to Introduction section as follows: Heart rate recovery (HRR) after exercise reflects parasympathetic reactivity and has been used as a marker of cardiac autonomic function. Decreased HRR reflects a lower parasympathetic activity. A decreased parasympathetic input to the heart is known to increase the potential for tachyarrhythmia and ischemia.” (Introduction section, line 18-22, page 4)

3. ‘I would suggest that the authors emphasize the importance of their findings and the potential implications on patient management.’

We are grateful for the suggestion. According to the guideline of COPD, LAMAs are currently recommended as first-line maintenance treatment for patients with moderate-to-severe COPD. Tiotropium bromide is commonly used in COPD patients, especially in China. So, how to identify and prevent potential drug side effects is important for patient management.

Regarding this suggestion, in Introduction section, we have emphasized the importance of LAMAs in COPD treatment as follows: Bronchodilators are a mainstay of COPD management. Long-acting antimuscarinic antagonists (LAMAs, of which tiotropium bromide monohydrate was the first available) have shown benefit and improved quality of life in COPD patients in large randomized clinical trials (RCTs), and are currently recommended as first-line maintenance treatment for patients with moderate-to-severe COPD. (Introduction section, line 9-14, page 3) the higher cardiovascular risk with inhaled anticholinergics has also been demonstrated in several randomized controlled trials and the meta-analyses of these trials. But the mechanism linking anticholinergics to cardiovascular risk remains unknown. (Introduction section, line 18-21, page 3)

Then, we have described the importance of our findings on patient management in previous manuscript: The results of our study showed that HRR was lower in patients who had been used
for more than one year than in the control group. That may provide evidence that the longer-term usage of tiotropium could also affect autonomic balance, which could increase the risk of adverse cardiac events. (Discussion section, line 4-8, page 13)

Finally, the potential implications of our findings on patient management have been emphasized as follows: 'Therefore, we recommend that COPD patients taking anticholinergic bronchodilators should be considered for monitoring of cardiac function and prescribers should be alert for potential cardiovascular events that may arise from autonomic nervous imbalance.(Conclusion section, line 3-6, page 14)

4. 'As the study did not involve a follow up, it is unclear whether these patients are/were at increased risk of adverse CV events. Though one prior study is mentioned, it may be worthwhile mentioning how a subsequent study can be organized and the hypothesis to be tested (to further expand the reported data).' Thank the reviewer for underlining this deficiency. Regarding the subsequent study, we have added a brief description as follows: We intend to follow up the frequency of cardiovascular (CV) events and cardiac death within three years. These CV events include heart failure, tachyarrhythmia, myocardial infarction and angina pectoris. This subsequent study would show whether these patients using tiotropium are at increased risk of adverse CV events. (Discussion section, line 16-20, page 13)

5. In addition, due to the modification of the manuscript, we renewal the abbreviations list and the order of references conforming to the journal style.