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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The letter is 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):"REVISION ASSESSMENT FROM THE ACADEMIC PEER REVIEWER:

‘My only recommendation is to possibly include a ROC curve with those with vs. without anti-cholinergics to set up the cutoff level to dichotomize low and high HRR. Despite the finding of significantly reduced HRM in the anti-cholinergic group, there were no differences in the % of anti-cholinergic treated patients in the low vs. high HRR with the used cutoff of 12 beats. I wonder whether a different cutoff might provide significance in the comparison.’

Thanks for this recommendation. To our knowledge, Cole et al. [1] firstly proposed 12 beats as the cutoff value for abnormal HRR. In this research, for six years, Cole et al. followed 2428 consecutive adults without a history of heart failure or coronary revascularization and without pacemakers. The primary end point was death from all causes. A cutoff value of 12 beats per minute was found to maximize the log-rank test statistic. This cutoff value has been widely used by other studies [2-4]. Therefore, we also used this cutoff level to define the abnormally low HRR in our study. In order to demonstrate the definition of this cutoff level more clearly, we have added some brief descriptions as follows:

Several studies have demonstrated that HRR was delayed in patients with abnormal spirometry, most of whom had COPD; and an abnormal HRR (≤12 beats) was a powerful predictor of overall mortality. (Introduction section, line 22-24, page 4)
Differences in the proportion of patients with an abnormal value for HRR (≤12 beats) were compared with use of the chi-square test for trend. (Methods section, line 17-19, page 7)

In another study, the threshold used to dichotomize abnormal from normal HRR was based on the lower limit of the 95% confidence interval of HRR in healthy subjects. As the 95% confidence interval of HRR in healthy subjects was 15–24 beats, the threshold for abnormal HRR was then established at 14 beats; thus a HRR ≤14 beats was considered abnormal.

According to the comment, we created a ROC curve with those with vs. without anticholinergics (shown in Supplemental Figure.) and found that the new cutoff point maybe at 23 beats. The area under the curve (AUC) at this new cutoff point is the largest, which is 0.708. The new cutoff point provided significance in the comparison. The percent of abnormal HRR in using tiotropium group is higher than those in the control group (91.7% vs 38.9%), P= 0.000.

However, we think this ROC curve is not reasonable. Because there is no ‘gold standard’ or ‘true condition’ in these data. This ROC curve would be established only if all patients in tiotropium group had cardiac autonomic dysfunction or cardiovascular events. We hypothesized that anticholinergics reduced vagal nervous activity. But it was inconclusive that all patients in tiotropium group had this nervous dysfunction or had higher incidence of cardiovascular events. These are the limitations of our study. We intend to follow up the incidence rate of cardiovascular events and cardiac death in subsequent study. And then, we would create a conclusive ROC curve and find out the optimal cutoff level to dichotomize low and high HRR.

Due to the modification of the manuscript, we renewal the abbreviations list and the order of references conforming to the journal style.

References in this letter


