Reviewer's report

Title: High Prevalence of Altered Cardiac Repolarization in Patients with COPD

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Reviewer: Kyndaron Reinier

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In this study, the authors have compared 91 patients with COPD (enrolled over 2+ years at a hospital clinic) to 2 control groups: (1) 32 age, cardiovascular-risk, and medication-matched controls, and (2) 41 healthy controls. This study examines a clinically relevant question; determining potential mechanisms by which COPD increases risk of arrhythmias may lead to new opportunities for prevention in this population. However, the study design and statistical analysis are problematic, and therefore, the results are difficult to interpret. The age-matched control group is possibly over-matched (see below), and has relatively low oxygen saturation, while the healthy control group is so much younger than the COPD group that comparisons are problematic. Improved description of the age-matched control group, with additional analyses excluding the healthy control group (or restricting to an older age range), may help to address these concerns.

Major compulsory revisions:

1. Methods, para 1: Is it not clear how the original 157 patients with COPD were identified – were these all of the patients with COPD who met initial criteria in the study time period?

2. Methods, para 2: For the matched control subjects, please provide more detail regarding how the matching was done and which cardiovascular risk factors and medications were used in the matching. If medications to treat COPD were included in the matching (e.g., anticholinergics, beta-adrenergic and steroids) there seems to be a possibility of over-matching (i.e., making controls so similar to cases that relevant differences could be missed). Also, please provide an explanation regarding why only 32 matched controls were available.

3. Methods, para 3: Why were the healthy control subjects so much younger than the other 2 groups? Because the mean age is so much lower than that of the COPD patients (30 ± 8.7 years vs. 62 ± 7.1 years) there is very little overlap between the groups in age, and the risk profile is extremely different. The analysis could be restricted to the COPD and age-matched control group instead – this could make the results more easily interpretable; alternatively, a healthy control group more similar in age to the COPD patients would be preferable.

4. Methods, Data analysis and statistics: As mentioned above, the very large age difference between the healthy control group and the other two groups makes statistical analysis between the groups problematic. In addition, the regression of QTc after combining the groups is problematic, since there is a strong correlation
between cardiovascular profile, lung function, and use of medications by group status. It is likely that unmeasured differences (confounders) between the healthy group and the other groups may also help to drive the multivariate findings for QTc. Because of this, it would be helpful to see the regression analysis restricted to the COPD group and the age-matched group to see if SaO2 and other lung function measures remain associated with QTc in univariate models, and to see whether the results remain consistent in the multivariate model.

5. Results, para 2: For QT dispersion, it looks like results are presented as median, IQR? Please clarify in statistical methods how the comparison was done.

6. Results, para 4& 5: For univariate and multivariate regression results, please see comment above regarding the correlation of most potential predictors of QTc and control group membership. Please present, if possible, univariate and multivariate regression including only the age-matched control group to demonstrate whether the findings are consistent, or perhaps driven mostly by the young, healthy control group.

7. Results, para 5: It is perplexing that there are so many highly significant predictors of QTc in univariate analyses, yet only one remains significant in multivariate analysis. This suggests, possibly, that the predictors are highly correlated. Did authors examine possible collinearity between variables (e.g., diagnosis of COPD and use of beta-adrenergics or anti-cholinergics; or smoking and FEV; or FEV and SaO2).

8. Table 1: What explains the relatively low oxygen saturation among matched controls (95.1%) if they do not have lung disease? If they are being seen for an acute pulmonary illness, is it possible that ECG parameters would be temporarily abnormal as well?

9. Table 2: The 95% CI appears to be around the point estimate (beta coefficient) but for some, the point estimate is not contained in the confidence intervals (E.g., SaO2, beta-adrenergic medications, statins.) Can the authors please clarify this?

10. Figure 3: This figure does not include information on QT dispersion; please edit figure legend to clarify.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.