Reviewer's report

Title: Patterns of heart rate variability and cardiac autonomic modulations in controlled and uncontrolled asthmatic patients

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Reviewer: Harikrishnan Parameswaran

Reviewer's report:

In this study, Dr. Lutfi examines heart rate variability (HRV) in healthy (N =40) and asthmatic subjects. The asthmatic population is subdivided into controlled asthmatics (N=37) and uncontrolled asthmatics (N=43) based on the test scores from the asthma control test questionnaire. Standard frequency domain indices of HRV are measured in these subjects along with FEV1 as well as peak/forced expiratory flow measurements. Compared to healthy subjects, the study finds that the mean heart rate was significantly higher in asthmatic subjects. Analysis of the low frequency (interpreted here as a surrogate of the sympathetic tone) and high frequency (interpreted here as a surrogate of the parasympathetic tone) components of HRV suggests augmented parasympathetic and depressed sympathetic autonomic modulations in controlled asthmatics compared to uncontrolled asthmatic patients. However, there were no statistical differences between uncontrolled asthmatics patients compared to healthy subjects for any of the measured HRV parameters.

Major Comments:

1. It is unclear to me how you adjust for the effect of medications in your subject population. For instance, the increased heart rate you observe in asthmatics (P7 L20) could be the result of beta-adrenoceptor agonist medication rather than the effect of the disease itself. You appear to do this using a general linear model (P7 L13-14), but how do you quantify anti-asthma therapy (AAT)? The statistical adjustment for AAT appears to be critical to your overall conclusions, but the description of how AAT is quantified and normalized for differences in drug/dosage is missing from the methods.
2. The frequency domain indices of heart rate variability can be influenced by respiratory rates and deep breaths. This can confound your interpretation of the HRV indices, esp. the HF component. If you have considered this in your study design and have already made any measurements that can eliminate differences in respiratory rates/deep breaths in your interpretation of HRV parameters, please include them in a revision. If not, please add this as a discussion point.

3. Table 3: Why is the numerator of the LF/HF ratio expressed in log, while the denominator is not? Please use the more standard LF/HF.

4. I find it very difficult to reconcile your finding that the controlled asthmatics can have an augmented parasympathetic and depressed sympathetic autonomic modulations compared to uncontrolled asthmatics while at the same time, none of the HRV parameters measured in the uncontrolled asthmatics differ from the healthy subjects! The studies you bring up in the Discussion section to explain this incongruity did not help. Many of them are irrelevant and/or cannot be compared to your study. The Kazuma study (P9- L13), for instance, involves circadian rhythms—something which you tried to avoid in your study design (P6, L11) because of its confounding effects. Similarly the findings from the Cabiddu study which examines sleeping subjects cannot be compared to yours. The results from the Dominik study results only apply during the antigen challenge, whereas your data is measured at baseline.

5. Figure captions are missing for Figures 1 and 2.

6. Units for the HRV parameters are inconsistent and incorrect. On Page 8, L1 and 2 the LF, HF and total power is expressed in milliseconds (ms). In Table 3, the units become ms²/Hz. Please use the correct units.

7. Please include mean heart rate in Table 2.

Minor:

1. Please check the manuscript for errors in spelling and grammar.
2. The present finding that parasympathetic activity may be
enhanced in controlled asthmatics compared to uncontrolled asthmatics is very interesting and novel. Additional measurements such as baseline resistance may help to confirm your finding. Please consider functional measurements in future studies.

3. P6, L16. BMI formula should be weight/height^2

4. P7 L5: please rephrase this to avoid the term “abnormally distributed variables”. There is no such thing.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests