Reviewer’s report

Title: Heart Rate n-Variability (HRnV) and Its Application to Risk Stratification of Chest Pain Patients in the Emergency Department

Version: 0 Date: 05 Feb 2020

Reviewer: Han-Kuei Wu

Reviewer's report:

This study aimed to build up a novel representation of heart rate n-variability (HRnV) by conducting a retrospective analysis of data collected from the emergency department. In the manuscript, the measurement of HRnV and its application for cardiac risk was described. The results showed that several HRV parameters and HRnV parameters were significantly associated with 30-day MACE. The predication model for MACE, which consisted of one HRV, seven HRnV parameters, troponin, ST segment changes, and several other factors, performed well in the ROC analysis (area under the ROC curve of 0.917).

Here are some comments and questions to the article.

1. Since there was no HRnV model before, a ROC curve analysis with cross validation (divided groups in the current database) would be still recommended and be more rigorous to build up a brand new and outperformed risk prediction model. Because the generalization error should be considered in a self-consistency test evaluation.

2. Age and sex were well known and important factors of HRV. Since there was significant differences on age and sex between MACE and non-MACE groups, a table of multivariate analysis with adjustment would be better to show the evaluation of all the HRV parameter under the consideration of the confounding factors. The information in the table of logistic regression was limited.

3. The physiology of HRnV was unknown, since the calculation was different from the conventional HRV. Past study has showed the relationship between the frequency domain parameters and ANS. However, the definition of high or low frequency should be modified and further confirmed. When the mean NN was 2 or 3 times of the conventional parameters, the parameters in the frequency domain should be recalculated, or the VLF and LF would be more and HF would be less according to the conventional cut line. The meaning may be quite different.

4. The HRV is an objective tool to assess the activities of the ANS. However, ANS is very sensitive to several factors, whether physical activity, day/night, emotion, pain... may influence the HRV parameter. Was the HRV measurement in this study performed in a fixed position after 5-10 minutes rest? Was there any interaction between pain score and HRV/HRnVm parameters?

5. More discussion about the relationship between the novel parameters and cardiac disorder would be recommended rather than the black-box theory to support the result that the HRnV model was better than other well-established model in ROC analysis, especially for the parameters included in the logistic regression. Furthermore, what was the difference/interaction between HR2V ApEn and HR2V1 ApEn, or the difference/interaction between HR2V skewness and HR3V skewness? They were similar parameters in different HRnV analysis, but seemed to be independent factors in logistic regression.
6. In this study, patients were excluded if they had ST-elevation myocardial infarction (STEMI). However, ST elevation was one factor that was included in the logistic model. The criteria and definition in this study need to be further described.

7. In P. 15 line 15, . This HRnV could be a signal smoother. However, unexpected spikes and sudden changes should be filtered by the amplitude when counting normal-to-normal [NN] intervals. What was the difference to deal with the the spikes and sudden change when n=1 or n>1 in this novel HRnV analysis? Was there any spike in the HRV analysis (n=1) in this study? Were the spikes taken randomly in HRnV analysis?

8. There were several items in the medical history in Table 1. However, in table 5, the "cardiac history" should be defined.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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