Author’s response to reviews

Title: Autonomic nervous system response to remote ischemic conditioning: heart rate variability assessment

Authors:
Daniel Osório (d.osorio@fct.unl.pt)
Ricardo Viana-Soares (ricardo.soares@nms.unl.pt)
João Marto (joao.pedro.seabra.marto@gmail.com)
Marcelo Mendonça (marcelomendoncasousa@gmail.com)
Hugo. Silva (hsilva@plux.info)
Cláudia Quaresma (q.claudia@fct.unl.pt)
Miguel Viana-Baptista (mvianabaptista@nms.unl.pt)
Hugo Gamboa (hgamboa@fct.unl.pt)
Helena L.A. Vieira (helena.vieira@nms.unl.pt)

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Lisbon, 31st July 2019

Dear Editor,

We are herein re-submitting our manuscript BCAR-D-19-00328, entitled “Autonomic nervous system response to remote ischemic conditioning: heart rate variability assessment” by Osório et al., which was submitted to BMC Physiology on the 12th October 2018, then re-submitted to BMC Physiology on the 19th March and required to be transferred to BMC Cardiovascular Disorders on the 15th April.

On the 17th July we received some more recommendations from a reviewer (Eduardo Migliaro) of BMC Cardiovascular Disorders, and although the manuscript was already accepted, we considered important to incorporate those suggestions in order to improve the manuscript.
The authors are grateful for the final suggestions and please find below point-by-point responses to the reviewer suggestions. All changes in the manuscript are highlighted in yellow.

Looking forward to hearing your opinion on the manuscript.

Yours sincerely,

Helena L. A. Vieira

MAIN CONCERNS

1) Page 6 line 55-58. The authors wrote "Response time of parasympathetic activity is much shorter than sympathetic. Thus parasympathetic activity is associated with changes in HF spectral more than LFs"

It is difficult to me understand how a shorter response time, could be associated with the HF band of frequency domain analysis. Perhaps "shorter" could be understand as "faster". Even in this case the phrase it is not so accurate. Actually, the HF band reflects faster changes of heart rate, that are related with parasympathetic activity. The "Response time" could be confused with the delay after a parasympathetic (or sympathetic) stimulation. Please clarify.

The referee is right and the sentence was re-phrased in order not to lead to any misunderstanding.

2) At page 9 line 36, the manuscript stated: "Changes in SD2 were significantly and positively correlated with changes in pNN50 and rMSSD. These results reinforce the RIC involvement of parasympathetic system via vagal response, since SD2 positively correlates with pNN50 (r=0.45 with p=0.03) and with rMSSD (r=0.54 with p=0.01), which are both associated with parasympathetic system."

This point deserves a deeper explanation. One can accept that the results of this work show a positive correlation between SD2 and pNN50 and rMSSD. However, the SD2 axis of the Poincaré plot, is related with SDNN and long term variability associated with both branches of
autonomic system (as the authors stated this concept in the same page at line 17). Therefore, it is difficult to accept that SD2 can be "associated with parasympathetic system" Such association has been proved for SD1 axis.

The authors thank the referee’s comment. Indeed, the way it was stated could lead to misunderstandings. In fact, SD2 is also associated with sympathetic activity and we have now added one more sentence to clearly state the final message.

3) At page 10 line 29 "Thus, the more pronounced difference in SD2 parameter found in senior group could be due to both effects: a lower basal autonomic nervous activity and/or a better response to RIC" The last statement claims for a stronger support. It is difficult to accept that "senior" population have a better response to RIC.

This was a speculative statement. The authors agree that it is difficult to envisage a scenario where senior subgroup would have a more efficient autonomic response to RIC. In the manuscript’s Discussion it is now written: “Thus, the more pronounced difference in SD2 parameter found in senior group could be due to a lower basal autonomic nervous activity”.

4) At page 10 line 39. The phrase "In addition, the risk of cardiovascular diseases increases with age, which might also modulate autonomic nervous system" has to be explained. It is true the first part (risk increases with age), but the "modulation" of Autonomic Nervous System with age includes a reduction of this response capacity, then it cannot accomplish for the observed higher increase of SD2 in senior subjects.

The word “modulation” has been exchanged by “decrease”. In addition, the potential explanation for SD2 difference being higher in senior subset is now only based on the fact that this group presents lower basal levels of HRV features.

5) The two diabetic subjects must be excluded.

It was not excluded from the senior subset because the main rational is to evaluate the effect of RIC on aged people with all their associated co-morbidities. Moreover, these two subjects had a
proper glycemic control, and also had no clinical evidence of neurological dysfunction. Thus, it is not expectable these two subjects to significantly disrupt the final findings.

Anyway, we have recalculated all features for the senior subset without the 2 diabetic subjects, and the non-linear feature SD2 continues to be the single parameter that significantly increases after RIC procedure in senior subset. Please see supplementary table for reviewer only.

6) At page 11 line 3 "SDNN (or SD1)

SD1 was eliminated from the sentence.

MINOR CONCERNS

At page 6 line 39. The authors stated "Since R-R interval is not a perfectly sampled event..."
Perhaps they like to say that the tachogram constructed using the R-R intervals it is not an equally sampled signal end then must be resampled.

The sentence was rephrased to “Since R-R interval is not a perfectly sampled event, the tachogram must be resampled to be an equally sampled signal. This can be achieved by interpolating the signal to a higher frequency.”

At page 7 line 5. "Nevertheless, there is no consensus about LF and slow sympathetic response"
It means that there is no consensus about the contribution of sympathetic branch to LF band? I believe that the phrase could be improved.

Sentence was rephrased for: “there is no consensus about the contribution of the sympathetic and parasympathetic branch in the LF band.”

At page 7 line 10. "The resulting plot is usually an ellipsis" I understand that "ellipse" instead "ellipsis" would be better.
Besides, the "resulting plot" it is not exactly an ellipse. Actually, it could be fitted into an ellipse (as the authors stated in the next phrase).

It is now written: “The resulting plot can be usually fitted into an ellipse, thus this method is used to describe the Poincaré plot.”

At page 7 line 47 "SD1 is similarly calculated as root mean square of successive differences (rMSSD)." It is true that SD1 and rMSSD have equivalent signification, but calculations procedures are different.

Indeed, SD1 is associated with the width of the ellipse axis, which is a linear scaling of the standard deviation of successive differences. Thus, the sentence was eliminated.

At page 9, the first paragraph that begins with: "During aging, there is a decrease of endogenous response..." should be considered to be included in the Introduction section instead in the Results one.

This sentence was added into the Introduction Section. Nevertheless, it was not eliminated from Results Section since it helps to understand the rational of having two subsets of subjects.