Author’s response to reviews

Title: Factors associated with parasympathetic activation following exercise in patients with Rheumatoid Arthritis: a cross-sectional study

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Author’s response to reviews:

Dr Timothy Shipley

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Title: Factors associated with parasympathetic activation following exercise in patients with Rheumatoid Arthritis: a cross-sectional study
Dear Dr Shipley,

We would like to thank you and the reviewers for your positive responses to our manuscript entitled ‘Factors associated with parasympathetic activation following exercise in patients with Rheumatoid Arthritis: a cross-sectional study’, which we submitted to BMC Cardiovascular Disorders.

Please see below the responses to the comments made by the reviewers. The changes in the manuscript in response to these comments have been underlined and highlighted in the manuscript.

We sincerely hope that the responses below answer the comments of the reviewers and the editor, and that the revised manuscript is suitable for publication in BMC Cardiovascular Disorders.

I look forward to hearing from you.

Kindest regards,

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REVIEWER 1

Comment 1: Osailan and colleagues conducted a cross-sectional study regarding factors associated with parasympathetic activation following exercise in patients with Rheumatoid Arthritis in UK. The paper was well written, but there was some minor points needed to be addressed.

Response: Thank you for the positive comments.

Minor points

Comment 2. In the methods, the authors did not mention whether atrial fibrillation is excluded from the study population.

Response: Apologies for this oversight, as well as excluding patients who had any comorbidity incompatible with exercise as per American College of Sports Medicine guidelines, we also excluded patients with atrial fibrillation. We have now added this for clarification (please see page 4, Methods, Study Population)

Comment 3: As we know, resting heart rate may reflect the ANS status. In the analyses, did the authors test the correlation of resting HR with HRR1 and HRR2? Or did the authors analysis the correlation of other independent variables with resting HR?

Response: As the reviewer suggests, resting HR is correlated with HRR1 and HRR2. This was expected given that HR peak, a measure used to calculate HRR, is strongly correlated with
resting HR. We have considered including this in the model. Following advice from a statistician, we have excluded HR from the model to avoid collinearity.

Comment 4: Antihypertensive medications such as beta-blocker and calcium-channel blockers may affect the HR response post exercise, did antihypertensive medications were discontinued before the exercise test in the protocol?

Response: The participants in our study were not asked to discontinue their medication for ethical reasons. We have mentioned this in the Results (see page 7), which also states the only 24% of participants were taking anti-hypertensive medication. We did consider exploring the effects of the different kind of medications on HRR. However, as the patients are often on a mix of medications, we ended up with too many different medication groups and did not achieve appropriate statistical power to do these analyses. With regards to antihypertensive medication, it is also worth noting that Cole et al (1999) did explore the effects of anti-hypertensive medication on HRR and found no association. This suggests that it is unlikely that anti-hypertensive medication would have influenced our findings. However, we have now acknowledged in the limitations section (please see page 11, Discussion) that we did not explore the potential influence of medication on the findings, and that this would be an interesting area for future research.

Comment 5. In line 42, on page 10:....."HRR1" has been suggested to be a better predictor of mortality, whereas HRR2 is a better predictor of coronary artery disease (CAD)

Response: We apologize for this somewhat ambiguous statement. We have extended the statement to clarify this (please see page 10, Discussion)

Comment 6: Although the authors declared that the study aimed to investigate the factors associated with parasympathetic activation following exercise in patients with Rheumatoid Arthritis, the HRR1 and HRR2 were close to the results the middle aged healthy subjects in many studies. These findings may imply that the parasympathetic function in RA may not be impaired very much in reference to the healthy populations. The authors should make a soft conclusion regarding the issue of parasympathetic dysfunction in RA since there was no healthy subjects as a control group in this study.
Response: The reviewer is correct that the levels of HRR in this study are comparable to the levels reported in other studies. However, we need to be cautious in comparing the findings of different studies as variations in the procedures and methods might influence the findings. We have now added a comment about this in the limitations paragraph in the Discussion to acknowledge that the levels of HRR were comparable to those in healthy populations (please see page 11, Discussion)

REVIEWER 2

Comment 1: This is a well conducted study addressing the parasympathetic impairment in patients with rheumatoid arthritis related to CV risk. Authors conclude that parasympathetic activation was associated with overall CVD risk, arthritis-related burden and wellbeing in patients with RA. The study is interesting, methodology is sound and conclusions are supported by results. There are some issues that should be discussed.

Response: Thank you for your kind comments.

Comment 2 Please provide more data on the sample under investigation: duration of disease, type of therapy at time of testing.

Response: The duration of the disease has now been added to results section (please see page 7, Results, Patient characteristics), apologies for not having included this before. The medication therapy used by the participants is also mentioned the same paragraph.

Comment 3: The study design should be reported as well as study hypothesis.

Response: Thank you for this suggestion. We have emphasized the study design when we state the aim of the study at the end of the Introduction, just before the statement of the study hypothesis (please see page 4, Introduction)
Comment 4: Please separate the analysis of CVD risk and wellbeing. CVD risk is objective whereas the data on wellbeing reflect the subjective opinion of patients. It adds something to the type of sample under investigation but make the results a little confusing. A secondary aim of the study should be included in order to give a clearer message.

Response: We agree that the methods of assessment for the CVD risk factors and measures of wellbeing are different. In an initial draft, the results for these objective and subjective measures were reported in separate paragraphs. However, that made the results unnecessarily lengthy. To make a clearer distinction between the different measures used, we have now added sentences to the results paragraph (page 7, Results, correlation). This will make it clearer to the reader which measures are reported in the section. In addition, we have changed the phrasing of the hypothesis (page 4, Introduction) to clarify that different groups of outcome measures are used.

Comment 5: Please clarify the reasons why heart rate recovery was chosen respect to HRV. Give advantages and disadvantages and limitations.

Response: Both are validated measures of autonomic nervous system and reflect different aspects of the autonomous nervous system. The advantage of heart rate recovery over heart rate variability is the ease of incorporating this assessment in clinical practice. Apart from the more sophisticated equipment and analyses software, the protocol to measure HRV is also more demanding compared to the protocol for measuring HRR. For example, a minimum period of 5 minutes resting ECG is required to apply frequency domain method to measure HRV. In contrast, heart rate recovery is easy to measure and can be applied in a clinical setting by professionals without previous experience. We do agree that it would be interesting to explore the factors associated with other measures of the autonomic nervous system. We have added a suggestion for future research to explore the association between CVD risk, inflammation and wellbeing with other measures of ANS (page 12, Discussion).

Comment 6: There are several studies addressing the sympathetic impairment in RA and should be cited, even though they did use HRR.

Response: We agree with the reviewer that several studies have explored the autonomic nervous system in people with RA, which has been recently reviewed by Adlan et al, which is used as a reference in the Introduction. We have now emphasized that this reference is a review paper (see
page 3, Introduction). Of course, we do agree with the reviewer that we cannot base the manuscript on a review paper, and we have therefore mentioned the individual studies throughout the Discussion, where appropriate. This does include studies which use other measures of the autonomic nervous system. We have now clarified the methods which were used in these individual studies (please see page 9 and 10, Discussion).

Comment 7: The discussion is very long and is not focused on the novelty of these results and their clinical implications.

Response: To make the Discussion briefer, we have deleted one paragraph, but have also made other paragraphs more concise.