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Jerzy Tadeusz Chudek, MD

Editor-in-Chief

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Dear Prof. Jerzy Tadeusz Chudek:

We are re-submitting our revised manuscript entitled “**Altered Heart Rate Variability and Pulse-wave Velocity after Spinal Cord Injury**” for publication as an original research article in *World Journal of Clinical Cases*.

We appreciate the reviewers’ thoughtful comments and we have revised our report accordingly. Briefly, study variables have been described in more detail. The participants in the non-SCI group were patients admitted to the study hospital for causes other than neurological injury. The limitations of this single-institution cross-sectional pilot study have been fully discussed. The conclusion was thoroughly revised to avoid overstatement.

Changes to the manuscript have been recorded with the track changes. Below please find our point-by-point response to the comments, which includes corresponding changes made to the manuscript.

We are most grateful for this opportunity to revise our paper and to have it reconsidered for possible publication in *World Journal of Clinical Cases*.

Sincerely,

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## Responses to reviewer comments

### Reviewer #1

#### SPECIFIC COMMENTS TO AUTHORS

I read with interest the article "Alterations in Both Heart Rate Variability and Pulse Wave Velocity in People with and without Spinal Cord Injury". The article has serious methodological shortcomings that need to be corrected before ev. acceptance for publication.

1. Namely, a number of factors can affect heart rate variability (HRV) such as gender, age, associated diseases (hypertension, coronary heart disease, diabetes, etc.), use of various medications, time elapsed since SCI, etc.

**Response:** Thank you for your insightful comment. We compared comorbidities and medication use between patients with and without spinal cord injury, and present the results in new Table 1. The results section was revised accordingly (Page 10, Lines 4-11).

2. The control group is very sparingly described. It needs to be described in detail, and it should be sex / age matched with the SCI group! and complementary to all other criteria listed above. Currently, there are two very heterogeneous groups, which can lead to bias, so the results are dubious and less valuable.

**Response:** Thank you for your comments. The participants in the non-SCI group were patients admitted to the study hospital for causes other than neurological injury. This information was added to the Methods section (Page 7, Lines 10, 11).

Because the study was closed, we were not able to conduct sex-matched sampling. The unmatched sex ratio is a limitation of this pilot study, which is now addressed in the 'limitations' paragraph of the Discussion section (Page 15, Line 25; Page 16, Lines 1, 2).

Furthermore, the mean age did not differ significantly between the SCI and the non-SCI groups (new Table 1). This information was added to the Results section (Page 9, Lines 23, 24).

3. There is a large standard deviation of the time elapsed since the appearance of SCI

which can affect the results

**Response:** Thank you for your comment. However, the extent to which the results of this study were affected by the large standard deviation in the time elapsed is unclear. This shortcoming is a limitation of this pilot study, which is now addressed in the 'limitations' paragraph of the Discussion section (Page 16, Lines 3, 4).

4. In addition to the short term measurement of HRV, it would be good if its 24-hour measurement was done, because the results related to mean RR and SDNN would be more representative.

**Response:** Thank you for your insightful comment. We strongly agree with the reviewer that continuous monitoring of dynamic HRV and PWV would be of greater clinical significance than the assessments employed in this pilot study. Continuous monitoring will be one of our future research directions, as stated in our revised conclusion. This study limitation is now addressed in the limitations paragraph in the Discussion section (Page 16, Lines 4-7).

5. It is necessary to describe in a few sentences in more detail the concept of HRV with appropriate references (Eur Heart J 1996. Task force, etc.)

**Response:** Thank you for this valuable feedback. A more detailed description of heart rate variability and its related parameters has been added to the Introduction section (Page 5, Lines 11-25; Page 6, Lines 1-3).

## **Reviewer #2**

### **SPECIFIC COMMENTS TO AUTHORS**

Dear authors Thank you for your work. Although it does not have new results, is interesting and valuable, and is well-written. It can be considered for publication after revision.

1. The authors should explain the unfamiliar variables (parameters of heart rate variability and pulse wave velocity, 7-level scale vascular age, and so on) in a separate section.

**Response:** Thank you for this valuable feedback. More detailed descriptions of heart rate variability and its related parameters and pulse-wave velocity has been added to the Introduction section (Page 5, Lines 11-25; Page 6, Lines 1-3).

In addition, the vascular age scale is now described in more detail in the Methods section (Page 9, Lines 4-8).

2. Considering the sympathetic and parasympathetic activity, are there any differences between healthy males and females? Two groups are not matched according to sex. Did this mismatch affect the results?

**Response:** The participants in the non-SCI group were patients admitted to the study hospital for causes other than neurological injury. This information was added to the Methods section (Page 7, Lines 10, 11).

Because the study was closed, we were not able to conduct sex-matched sampling. The unmatched sex ratio is a limitation of this study, which is now addressed in the 'limitations' paragraph of the Discussion section (Page 15, Line 25; Page 16, Lines 1-2).

3. As we know, the outcome after SCI in different spine levels significantly differed, especially between the cervical and other levels, and between cord injury and cauda equina injury. Why did not the authors analyze the results between subgroups (as they mentioned in the limitation section)? If it was not possible, why did they include SCI at the whole spine level? The mechanism and outcome of traumatic and nontraumatic SCI are deferred, the authors should separate and analyze the results between these two entities.

**Response:** Thank you for your comments. However, due to the small sample size of subgroups after stratification (Table 2), we did not perform additional subgroup analysis. A heterogeneous group of SCI patients was recruited in this single-institution pilot study; therefore, further large-scale multi-center studies are warranted to evaluate differences in HRV and PWV between subgroups of SCI patients. The lack of further subgroup analysis to distinguish outcome differences according to spinal injury level is a limitation in this pilot study. The above information was added to the limitations paragraph in the Discussion section (Page 16, Lines 2, 3; Lines 7, 8).

4. Few grammatical errors need English editing.

**Response:** The entire manuscript was edited by a biomedical scientist whose native language is English.

### **Reviewer #3**

#### **SPECIFIC COMMENTS TO AUTHORS**

Dear editors and authors, the manuscript “Alterations in Both Heart Rate Variability and Pulse Wave Velocity in People with and without Spinal Cord Injury” requires a revision of the basic concept of the study.

1. The data are heterogeneous and variable.

**Response:** The patient cohort in this study is heterogeneous in part because the participants in the non-SCI group were patients admitted to the study hospital for causes other than neurological injury (Page 7, Lines 10, 11).

To address the concern of cohort heterogeneity, we compared comorbidities and medication use between patients with and without spinal cord injury and present the results in new Table 1. The results section was revised accordingly (Page 10, Lines 4-11).

The unmatched sex ratio is a limitation of this study, which is now addressed in the ‘limitations’ paragraph of the Discussion section (Page 15, Line 25; Page 16, Lines 1, 2). Further large-scale multi-center studies are warranted to evaluate differences in HRV and PWV between subgroups of SCI patients (Page 16, Lines 7, 8).

2. The authors try to interpret the obtained data cross-section on heart rate variability and pulse wave velocity, and the general state of the cardiovascular system as a long-term course of traumatic spinal cord disease that has already taken place, which is incorrect in the absence of dynamic observation of the studied patients. In this case, the publication of the manuscript seems impossible. In addition, the correlations and dependencies found without comprehensive consideration of

individual constitutional parameters and somatic status do not bear significant scientific novelty.

**Response:** Thank you for your thoughtful comments. These concerns have been included as limitations of this cross-sectional pilot study in the 'limitations' paragraph of the Discussion section, and the Conclusion was revised accordingly (Page 15, Lines 23-25; Page 16, Lines 1-18).