

February 1, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 15475-review.docx).

Title: Cardiac Autonomic Dysfunction in Patients with Gastroesophageal Reflux Disease.

Author: Branislav Milovanovic, Branka Filipovic, Slavica Mutavdzin, Marija Zdravkovic, Tatjana Gligorijevic, Jovana Paunovic, Marina Arsic

Name of Journal: World Journal of Gastroenterology

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SUMMARY OF CHANGES

First, we would like to say thank you to the reviewers for the useful comments to improve the paper. Revision has been made according to the suggestions of the reviewers. We have addressed all the comments as explained below.

1. REVIEWER 1:

1) *"It may be better to increase the number of patients in comparison with healthy volunteers"*
These are our first results obtained from testing the small group of patients, but we plan to continue study including more patients.

2) *"How about the cardiac prognosis of patients with GERD in this report?"*
With prolonged duration of GERD, cardiovascular diseases are more common, particularly supraventricular arrhythmias. In our further research the cardiac prognosis will be analyzed especially related to the presence of supraventricular arrhythmias.

3) *"How about the clinical characteristics of patients with GERD and healthy volunteers?"*
We performed this investigation on healthy volunteers and patients with diagnosis of GERD without other diseases. Exclusion criteria for all subjects were the anamnestic data about: coronary artery disease, atrial fibrillation, secondary arterial hypertension, renal failure (serum creatinine >1.2 mg/dL), autoimmune disease, or previous treatment with antipsychotics, anidepressants, mood stabilizers, antiarrhythmics, or cimetidine (mentioned on page 5).

4) *"What is the mechanism of impairment of parasympathetic function of the patients with GERD in this report?"*

The mechanism of impairment of parasympathetic function of the patients with GERD is not completely clear, but in all autonomic neuropathies the first stage of dysfunction is damage of parasympathetic neuron, possibly because the general function of autonomic nervous system depends of vagal activity (added on page 13).

5) *"Did Helicobacter pylori infection affect the ANS of patients with GERD in this report?"*

Chronic inflammation including also Helicobacter pylori inflammation is the cause of autonomic dysfunction. According to the previous, in our further research we plan to treat patients with commercially used GERD medications and to analyze their autonomic function (added on page 13).

6) *"Did medication to GERD improve the ANS of patients with GERD in this report?"*

In this report we did not test the influence of medication to GERD on the ANS function. These studies will be part of our further research, where we will treat patients with commercially used GERD medications and after the treatment we will assess their autonomic function. Also, our further research will include design of the study using medications for autonomic function modulation and assessment of this medication on GERD and cardiac symptoms (added on page 13).

2. REVIEWER 2:

1) *"There are several diagnostic codes that need clear definition:*

- early and definitive parasympathetic dysfunction,*
- positive cardiovascular reflex test,*
- severe autonomic dysfunction,*
- abnormal vagal function,*
- abnormal response to Valsalva maneuver*

and so on..... "

"Results of all cardiovascular reflex tests were expressed as normal, borderline or abnormal, according to cut-off values given by Ewing. Based on the results of the tests, a scoring system was applied and autonomic dysfunction in each patient was qualified as: vagal denervation, vagal and sympathetic damage or severe autonomic neuropathy." This explanation and reference that indicates the paper which contains definitions and detailed explanations of the cardiovascular reflex tests are added in "Material and methods" section on page 7.

2) *"Clarify which were the 5 standard Ewing tests performed, as stated in the methods section. Later in this section it seems that only 3 tests were performed. Also, handgrip test is not mentioned in the summary of the tests at the beginning of this methods section (page 5)"*

Materials and methods section is re-organized differently, so that it is clearer that we used all five Ewing's test. Study protocol section as well as Clinical Autonomic Function Tests section are changed now (page 5 and 6). Evaluation of autonomic

function and hemodynamic status section is contained in Study protocol section and therefore it is not given in a separate paragraph anymore.

3) *"There is information about the tables in the middle of the text (?) which belongs to the Tables section."*

Information about the tables in the middle of the text are removed and written in the Tables section.

4) *"The paper is too long and difficult to follow. There is repeated information everywhere. It should be shortened by 40%. The abstract is also too long"*

Manuscript text and abstract are shortened.

5) *"Information of the tables should not be repeated in the text"*

Results are shortened and information of the tables is not anymore repeated in the text.

6) *"Which are the clinical implications of the study, if any? Or what further research may be derived from this study?"*

The main clinical implication of our study is to treat patients according to the type of autonomic pattern (added on page 3). We plan to continue our study including more patients. The further research will include design of the study by using medications for autonomic function modulation and assessment of the medication effects on GERD and cardiac symptoms. Since chronic inflammation including also *Helicobacter pylori* inflammation is the cause of autonomic dysfunction, we plan to treat the patients with commercially used GERD medications and to analyze their autonomic function (added on page 13).

7) *"Abbreviations should be provided in the Tables, as well as the p values for intergroup comparisons."*

Abbreviations as well as the p values are provided in the Tables now.

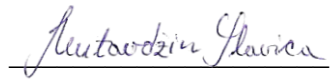
8) *"The use of the English language needs adequate revision. The authors write as if other investigators did the research, instead of themselves."*

Sentence constructions are changed according this suggestion.

3. The following requirements are added as footnotes in the manuscript: Author contributions, Ethics approval, Informed consent, Conflict of interest and Data sharing statement, Core tip, Comments Footnotes.

Thank you very much for your suggestions.

Sincerely yours,

A handwritten signature in cursive script, reading "Mutavdzin Slavica", is positioned above a horizontal line.

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