

Point-by-point Response to Reviewers` comments for manuscript originally submitted to “World Journal of Cardiology” as #53295:

Reviewer #1:

1) Would you please kindly correct all your typos and grammar errors throughout the manuscript.

Author response: We thank this reviewer for the overall kind and positive comments about the quality of our work. We apologize for any typos or grammatical errors made in the original manuscript, which we have now corrected.

2) Please, reduce the length of your Introduction to one page with strong justification of the objective which must be provided at the end of the Introduction.

Author response: We thank this reviewer for the suggestion but we respectfully disagree. All the necessary background information needs to be provided in “Introduction”, so that even readers that are non-experts in the tobacco research field can comprehend and follow the present study appropriately. Therefore, we do not feel that the “Introduction” needs to be shortened to only one page necessarily. As for the objective/hypothesis, it is clearly stated in the last paragraph of the “Introduction”, as per the reviewer`s wish.

3) Please, clarify your Limitations and Future Perspective in the Discussion.

Author response: We thank this reviewer for this excellent suggestion. We have included a paragraph at the end of “Discussion” clearly listing the limitations of the present study. The future perspectives are outlined in the “Conclusions” paragraph of “Discussion”. We hope this now satisfies this reviewer.

4) Your Methods are quite short. Please elaborate it with all the necessary and relevant details. For instance, the animals are not described at all.

Author response: Done.

5) Please justify your statistical power in Methods.

Author response: Done.

6) There must be a scheme of your hypothesis and/ or study.

Author response: We are not sure what the reviewer means by “scheme” here. The hypothesis for the present study and the rationale behind it are clearly and fully explained in both the “Abstract” and the “Introduction” of the revised manuscript. We hope this satisfies this reviewer.

Reviewer #2:

1) In the clinical setting, the chronic smokers and/or patients with primary aldosteronism have usually normal cardiac function, while patients with heart failure sometimes show hyperaldosteronism, which is not defined as the cause or result of heart failure. As for me, I can not believe these results easier. Was the dose of nicotine with 1mg/kg/day for rats proper? The authors should comment on these results and their interpretation in detail.

Author response: We thank this reviewer for the overall kind and positive comments about the quality of our work. The dosage of nicotine (1 mg/kg/day) was the proper one, as documented by several similar studies performing chronic i.p. nicotine administration in experimental rats (e.g. see: Front Pharmacol. 2019;10:1493; Niger J Physiol Sci. 2019;34:83-90; Brain Res.

2019;1706:41-47; to cite a few recent ones). Furthermore, this dose is expected to produce plasma nicotine levels comparable to those of chronic tobacco smokers (see Ref. 9 of our manuscript). We have added a sentence in the “Results” of the revised manuscript to that effect, as follows: “*Of note, the daily dose of nicotine administered (1 mg/kg/day) is known to lead to blood circulating levels of nicotine comparable to those of chronic human smokers [9].*”, p. 10, par. 2, of the revised manuscript. We hope this now satisfies this reviewer.

2) The authors should show the numbers of cells and rats in the "Method" section, while these numbers were shown only in figures legends.

Author response: Done. Thank you for the suggestion.

3) "Introduction" section seems to be too lengthy. The authors had better shorten them appropriately.

Author response: We respectfully disagree. All the necessary background information needs to be provided in “Introduction”, so that even readers that are non-experts in the tobacco research field can comprehend and follow the present study appropriately. Therefore, we do not feel that “Introduction” needs to be shortened. We hope the reviewer understands.

4) The authors should revise "Abstract" section in the structured format, such as Method, Result, etc.

Author response: Done. Thank you for the suggestion.