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Lian-Sheng Ma, President and Company Editor-in-Chief
Baishideng Publishing Group Inc
World Journal of Cardiology
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Re. Number ID: 00227594; Publication Name: World Journal of Cardiology

Dear Editor:

Please find attached the revised Brief Report: Basic Study (**Manuscript Number 25460**) for consideration for publication in the World Journal of Cardiology, entitled “Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in heart failure”.

We thank the reviewers for their constructive comments. We have addressed the reviewer comments to the best of our abilities and as logistically possible as described below:

Reviewer 02745062

New data to address the changed levels of different adrenoreceptor subtype expression in the isolated monocytes for CHF compared to healthy subjects.

Response: We agree with the reviewer that the next step would be to demonstrate similar changes in adrenoreceptor expression in monocytes isolated from human subjects. This was considered in the original work, however, the yield from monocyte isolation was deemed too low to allow replication of the THP-1 cell experiments. In addition, we would also want to demonstrate this in myocytes themselves, however, we did not have access to actual human myocardial biopsy samples. Have added a sentence stating this limitation to the discussion. “Unfortunately we did not have an adequate number of human monocytes to evaluate adrenoreceptor expression between HF and healthy subjects which would strengthen these preliminary findings.”

Statistical symbol missing from figure.

Response: The significant differences have been indicated on the human monocyte data (Figure 1). Formal statistical comparisons of the dose-response experiments was not conducted for these preliminary studies.

Reviewer 00227677

Provide additional citations for certain sentences.

Response: Thank you for pointing that out. We had removed many references to submit this as a brief report but have re-inserted them.

“Visual inspection” of concentration-response curves.

Response: Due to the preliminary nature of the dose-response experiments, determination of plausible effect was gained by visual inspection of the curves. An exact comparative analysis was not planned for these preliminary experiments, hence this manuscript is being submitted as a brief report.

How are values expressed. Mean \pm SD or SE.

Response: Values are mean \pm standard deviation. This has been added to the figure legends. Thank you.

Add table with patient demographics.

Response: Done. Thank you for pointing out this obvious deficiency.

Add inclusion and exclusion criteria.

Response: Added to methods section. Thank you.

Improve figures.

Response: The figures are limited by what Excel allows. They appear to be clear enough to allow for determination of the results.

Reference formatting.

Response: References have been added and reformatted to the journal style.

Reviewer 00258135

Specify limitation of small sample size in Discussion.

Response: A section for limitations has been added to the Discussion.

Show baseline characteristics of patient populations.

Response: A table has been added as pointed out by multiple reviewers. Thank you.

Inclusion and exclusion criteria should be better clarified.

Response: As above, this was pointed out by multiple reviewers and was an obvious oversight on our part. Has been added to the Methods section. Thank you.

Better clarify mechanisms for the reduced responsiveness to norepinephrine observed in monocytes of chronic heart failure patients. Clarify the lack of interaction with beta-blocker therapy.

Response: A brief section was added that discusses the altered beta1- and beta2 receptor expression and function in the failing heart. In addition, two sentences were added to mention the equivocal nature of the lack of interaction with beta-blocker therapy.

Reference formatting.

Response: References have been updated and formatting adjusted for the journal requirements.

Minor comments.

Minor comments have been addressed. References were added throughout the introduction. Thank you for pointing that out. We had removed many references to submit this as a brief report but have re-inserted them.

Reviewer 00259343

Differential effect of Beta2-adrenergic receptor subtype on inflammatory cytokines.

Response: Thank you for your comments. We agree that the beta2 receptor is the receptor responsible for the anti-inflammatory effects of catecholamines. In fact, in designing the THP-1 experiments, we felt it was already well established that this was the case, and hence we did not examine specifically the relative effect of beta2 vs beta1. In addition, although NE is relatively weaker for the beta2 receptor, the maximal magnitude of effect seen with isoproterenol was similar to NE suggesting (although we agree indirectly) the effects of NE were mediated through beta2. Unfortunately we do not have the ability to continue/repeat these experiments at this time so we have added commentary to the Discussion pointing this out. We have also throughout the manuscript attempted to send the message that our findings are preliminary and need to be interpreted as such.

Reviewer 02638028

Patient characteristics should be presented.

Response: A table has been added as pointed out by multiple reviewers. Thank you.

THP-1 cells are not identical with isolated monocytes in heart failure.

Response: We agree with the reviewer and have added a sentence to the limitations section. It was not possible to perform these experiments with isolated human monocytes as the yield from isolation experiments was inadequate (another sentence has been added to mention this).

More detail to discussion of beta-receptors on attenuation of TNF production.

Response: Additional commentary has been added to discuss the issue of beta2 vs beta1 contribution. Additional referencing has been added to the Introduction as well as it relates to this.

Are there any effects of TNF production by the addition of PROP, YOH, PRAZ.

Response: Unfortunately we do not have the ability to continue/repeat these experiments at this time, and we did not include experiments to confirm these antagonists have no direct effect on inflammatory cytokine production, although there is no data to suggest there would be. A sentence has been added to the limitations section.

Thank you for your time and consideration we hope that you will find this work suitable for publication.

Sincerely,

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