

## **Responses to Reviewers' Comments**

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We sincerely appreciate the valuable comments and suggestions from the reviewers. The thorough review helped immensely in the shaping of the manuscript. The suggestions and comments have been closely followed and revisions have been made accordingly. The following are the questions extracted from the reviewers' comments along with our summarized responses. For the reviewers' convenience, the revisions have been underlined in the manuscript.

### **Responses to the comments from Reviewer 01955969**

#### Comments:

Cardiac remodeling, which is featured by hypertrophy and fibrosis, is the main pathological alteration in myocardium post heart injury, which consequently impairs heart contractile function. Correspondingly, inhibition of cardiac remodeling can enhance cardiac function and subsequently improve viability post myocardial infarction. This review manuscript presents the main cellular and molecular mechanisms of cardiac remodeling, and summarizes the beneficial effects of physical training on cardiac remodeling inhibition. Finally, a conclusion is made that physical training-based cardiac rehabilitation is an effective therapy to prevent or protect against cardiac remodeling post myocardial infarction. Overall, this is a well-organized manuscript to highlights the import role of physical training post myocardial infarction, but there are some points to be addressed before acceptance and publication.

1. The title of this submission did not convey ideas precisely. "Exercise Training" is seldom used in native English, and "Physical training" is suggested to replace it. In addition, I suggest author to replace current title with "Cardiac Remodeling and Physical Training Post Myocardial Infarction".

Response: As suggested, both the title of and short title have been revised in order to more effectively convey the central idea of the manuscript.

2. Different physical training protocols may produce diverse results on cardiac remodeling, as well as the recovery of cardiac function. Therefore, it is necessary

to retrospect and summarize current physical training protocols post myocardial infarction. Specifically, what is the kind of physical training that used in recovery? What is the duration and intensity in physical training post myocardial infarction?

Response: Training protocols from these post-MI physical training studies have been summarized as suggested in Table 1.

3. Some descriptions are not rigorous in current manuscript, which have been list below:

1) In the last sentence of Abstract, it is described that “exercise-based cardiac rehabilitation is one of the most effective.....”. How do you know it is the most effective? Is there any clinical evidence to support it?

Response: The reviewer makes a great point: there is no evidence suggesting that exercised based intervention is the *most* effective means of rehabilitation; therefore, the following revision was made:

“Additionally, meta-analyses revealed that exercise-based cardiac rehabilitation has proven to be effective, and remains one of the least expensive therapies for both the prevention and treatment of cardiovascular disease, and prevents re-infarction.” Please see page 2.

2) As is described shown in page4, paragrah2, 3rd line, the phrase “the abrupt increase in loading conditions”. What is kind of loading condition? Is it pressure overload or volume overload? The same problem appears in the last paragraph in the same page.

Response: In response to the reviewer’s question regarding the specificity of loading condition, the document was revised accordingly, as volume overload is the primary mechanism responsible for the increase in blood volume after myocardial infarction. Please see page 4.

3) In the 1<sup>st</sup> line in page 9, “thus, suggesting a relationship between exercise intensity and time after infarction. What is the kind of relationship? Is there a positive or negative correlation between them?

Response: The reviewer raised a good question. The sentence in question was vague. We changed the sentence to “During the first week after induction of MI, recovering mice slowly titrated up their daily running activity, reaching distances similar to their sham-operated counterparts towards the end of the study, thus, suggesting that early post-MI

exercise training may have positive effect in post-MI recovery and myocardial remodeling.”. Please see page 9.

4) In the 3<sup>rd</sup> line in page 9, the units of LV fractional shortening have not been shown. The units should be shown with “%”.

Response: The units were revised to reflect percentage. Please see page 9.

4. A section of “Conclusion” or “Future prospect” is suggested to be added at the end of this review.

Response: A conclusion section has been added. Please see page 17.

### **Responses to the comments from Reviewer 00233953**

Interesting Review Comment #1: please add a few illustrative figure.

Response: Due to copy right issues and time constrain, we would ask your permission for not to include figures.

Comment #2: Please add a summary/Conclusion

In this review, the authors nicely summarize the effect of exercise training post-MI with respect to cardiac remodeling and function. It is a very well written review; however, I have a couple of suggestions to improve your submission. 1. The authors review results obtained from experimental animal models as well as outcomes in humans. Can the authors present a summarized version of the results including the potential mechanism of exercise training post-MI using tables. It would be nice to include a table using results obtained from human subjects (clinical results) and a separate table for results in animal models.

Response: Thanks for the suggestions. We have provided summary tables for both human and animal studies as suggested (please see page 19-20) and a conclusion section as suggested (page 17).