Author's response to reviews

Title: Cardioprotection afforded by exercise training prior to myocardial infarction is associated with autonomic function improvement

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Version: 3 Date: 3 July 2014

Author's response to reviews: see over
Dear Executive Editor of BMC Cardiovascular Disorders

Dr Timothy Shipley

Thank you for your consideration of our manuscript entitled “Cardioprotection afforded by exercise training prior to myocardial infarction is associated with autonomic function improvement”. We have reviewed the comments of the reviewers and have thoroughly revised the manuscript. We found the comments helpful, and we believe that our revised manuscript represents a significant improvement over our initial submission.

We hope that now our manuscript is suitable for publication as a Research Article in in BMC Cardiovascular Disorders.

Below are the Reviewers response.

Best regards,

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Reviewer 1#

General comments:

The paper is in general well written and the message is easily gleaned. Results appear to be supported by an appropriate methodological approach. My main concern is about statistics, which somehow flaws (see my specific comments).

Moreover, the paper can be improved by adding some recent reviews dealing with the effect of exercise training and hemodynamics in chronic heart failure. Moreover, the fact that the present study is on rats and that findings cannot be applied straightforwardly on humans should be clearly stated.

Specific points:

- Introduction, page 4, lines 6-10: please refer to the recent review by Piepoli et al. (Int. J. Cardiol. 2008) which is more recent than papers you cite; page 4, lines 13-15: similar as the previous point: please refer to the very recent review by Piepoli and Crisafulli (Exp. Physiol. 2014) on the effects of exercise training in CHF hemodynamics.

We thank the Reviewer suggestion and the papers were added.

- Statistical analyses, page 9: please specify which main factors have been used in the two way ANOVA and spell out ANOVA (analysis of variance). Why did you use repeated measure ANOVA to find out differences between data measured over time?

According to the definition, we can analysis data using a repeated measure ANOVA for two types of study design: “studies that investigate either (1) changes in mean scores over three or more time points, or (2) differences in mean scores under three or more different conditions”. In the present study, the analyzed
variable was velocity obtained in maximal treadmill exercise test, at the beginning of the protocol (initial evaluation), after exercise training or following protocols (final evaluation), and 2 days after Sham/MI surgeries. This information was added in the methods of the manuscript.

- From figures it seems that you have also assessed differences between groups. Thus, this approach is misleading. Please explain.

Statistical differences between the groups in all evaluations (except in maximal treadmill exercise test) were obtained by two-way (exercise training and myocardial infarction) analysis of variance (ANOVA) followed by the Bonferroni post-test. Thus, the differences between the experimental groups at the final evaluation were obtained in this way, being better described in the methods and added in Figure legends.

- You sowed results of correlation, but nowhere in the statistical analysis paragraph the statistic approach has been specified.

We added the description of this statistical analyze on the methods.

Reviewer 2#

In the present manuscript, Rodrigues and collaborators have investigated the effects of a 4-week exercise training program (performed prior to MI induction) on LV remodeling/function, baroreflex sensitivity and cardiac autonomic modulation, in a rat model of surgically induced myocardial infarction. The manuscript is clear and well written, the method section and the paragraph on statistical analysis are well described.

I have few suggestions/concerns:
1) The authors state that their exercise program is able to decrease mortality rate. In the opinion of the present reviewer, it is not possible to draw conclusion on mortality from the present study. First of all, a higher number of animals is required for studies on survival; second, acute mortality (within few days after MI induction) is largely dependent on surgical procedures (i.e. bleeding, lung injury). Thus, I believe that the authors can describe this result but they have to remove from the text any conclusions on the effect of exercise training on mortality rates.

- We thank the Reviewer suggestion and conclusions about effect of exercise training on mortality rates were removed.

2) Capisco che gli autori hanno già dimostrato una correlazione tra la dimensione dell'infarto valutata mediante ecocardiografia con la dimensione infartuale misurata dal istologia; tuttavia, la mancanza di dati sulla dimensione dell'infarto misurati da istologia dovrebbe essere riconosciere in un paragrafo sui limiti dello studio.

- We appreciate the suggestion of the Reviewer and a paragraph with the study limitations was added to the end of the discussion.

3) The authors have mentioned several beneficial effects/mechanisms by which exercise training is known to influence cardiac structure and function. However, they did not mention the relevant effect of exercise training on MI-dependent neurohormonal hyperactivation. In particular after MI, it is well known that catecholamine production and release from adrenal glands and from cardiac SNS nerve endings are enhanced. Increased NE and Epi levels have relevant effects on cardiac beta-adrenergic receptor signaling/function influencing cardiac autonomic modulation. Can the authors measure cardiac or circulating catecholamine levels in their study groups? These results would be of great interest. In any case, SNS hyperactivity, its effects on cardiac beta-adrenergic receptor signaling and the effects of exercise training on SNS hyperactivity should be discussed in the text (quoting relevant recent literature on this argument).

- We agree with the Reviewer that measurements of cardiac or circulating catecholamine levels would be of great interest and could enrich the present study. However, taking into consideration the impossibility to perform such analysis, we
added information about this important point in the discussion. Possibly, these evaluations will be part of our future studies.

4) Additional histological data on cardiac fibrosis and angiogenesis, as well as, biochemical analysis for molecular markers of hypertrophy/remodeling and beta-adrenergic receptor signaling status would add significance to the present study. If the authors cannot produce these data, they have to acknowledge the lack of these data.

- We agree with Reviewer that additional histological data and molecular analyzes would add significance to the present study, and are limitations of this study (described at the final of the discussion). However, the lack of such data does not invalidate the importance of our results. To our knowledge, this is the first study to demonstrate that the attenuation of cardiac autonomic modulation changes may be an important mechanism associated with the cardioprotection conferred by exercise training. We believe these results can support new clinical or experimental research in preventive cardiology.