

ANSWERING REVIEWERS



March 19, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8561-review.doc).

Title: Exercise Training in Hypertension: role of microRNAs

Author: Vander José das Neves, Tiago Fernandes, Fernanda Roberta Roque Redondo, Ursula Paula Renó Soci, Stéphano Freitas Soares Melo, Edilamar Menezes de Oliveira

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 8561

We appreciated your attention in evaluating our article **Exercise Training in Hypertension: role of microRNAs**.

We corrected the article and submit it again, considering the reviewer suggestions and comments. Reviewers wrote relevant suggestions and constructive analysis which will, certainly, improve the manuscript's quality. You will find corrections highlighted in yellow in the updated vision (ESPS Manuscript NO: 8561-edited). The editor's suggestions were added and all information requested were updated. All corrections were realized according to the reviewer's and editor's suggestions and "BPG's Revision Policies for Topic Highlight".

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) **Reviewer No. 506252**

General Comments: This review paper reports the effect and mechanism of exercise training on high blood pressure. They focus on recently studied biochemical factor microRNAs in heart, vessels, and skeletal muscles, including their own studies.

Specific Comments: 1) There are no figures and tables. It is very convenient for readers when some specific miRNAs are shown how they work in controlling blood pressure. The referee recommends the authors to show some schemes regarding miRNA.

Answers: We added figure and tables in accordance with the referee suggestions. The figures and tables are put at the end of paper and mentioned clearly in the main text.

Minor Comments 1) microRNA is described as "miRNA", "microRNA", "MiRNA" and mir (mir- or Mir-126). Usually, the abbreviation is spelled put when it appears first, then the abbreviation is used after that. When miRNA is the first word in a sentence, "miRNA" is

better than “MiRNA”.

Answers: We thanks the reviewer’s commentary. We have changed the manuscript text according with the commentaries. The corrections were highlighted in yellow in the updated vision (ESPS Manuscript NO: 8561-edited).

(2) Reviewer No. 506276

This is a comprehensive review article focused on the role of miRNA in the effects of exercise training on blood vessels, heart and skeletal muscles in experimental and clinical hypertension. The mechanisms of vascular and cardiac complications of hypertension are discussed, followed by review of the literature in which effect of exercise training on miRNA is covered. The manuscript is in general well-written and provides a lot of information for those interested in hypertension research. However, some issues should be addressed to further improve this manuscript:

1) It would be reasonable to include the table in which role of miRNA mentioned in this paper would be summarized; that is different miRNAs should be listed and genes/proteins whose expression is targeted by them should be presented.

Answer: The suggested table was added in the paper in accordance with the reviewer.

2) In the other table effect of exercise on different miRNAs, changes in the expression of proteins whose mRNA are targeted by these miRNAs and physiological consequences of these changes (for example decrease in arterial stiffness) should be presented.

Answer: The suggested table was added in the paper in accordance with the reviewer.

3) In each section (heart, vessels and skeletal muscles) experimental (animal) and clinical (human) studies should be clearly separated.

Answer: We revised the manuscript and it was reorganized in accordance with reviewer.

4) Due to possible diagnostic/monitoring implications, studies in which circulating miRNAs (potentially available for more routine diagnosis) were measured should be clearly highlighted in each section.

Answer: We discussed about some circulating miRNAs in the “Discussion section” and in the “Future Perspectives”.

(3) Reviewer No. 214274

I have read this review on "Exercise training in hypertension role of microRNAs".

General comments: The subject is interesting and the review extensive with recent data. I have only some minors remarks. You use the denomination pathological cardiac hypertrophy, physiological cardiac hypertrophy, maladaptative cardiac hypertrophy, cardiac hypertrophy, ET-induced CH or hypertension-induced CH. It would be more clear if you

add a short definition the first time they appear in the text, or even add a figure on the different type of cardiac hypertrophy and use always the same denomination for the same type. You have to check all the acronyms. Some of them were correctly defined but used only once like SNS, SBP. Some of them were not described the first time they were used, some of them were described but not always used later in the text, and others were not described at all. You should limit the acronyms to the strict necessary.

Answer: Thanks for this observation. We revised the manuscript text and corrected the mistakes related with cardiac hypertrophy and acronyms in accordance with reviewer.

(4) Reviewer No. 31349

The manuscript reviews the roles of microRNA in the pathogenesis of hypertension-associated cardiac muscle, smooth muscle, and skeletal muscle remodeling. The present review is both novel and important. The following suggestions would be potentially helpful for the better understanding of the landscape of micro-RNA signaling in hypertensive muscles.

1. This is a comprehensive view of micro-RNA-associated hypertensive muscle change, including molecular, cellular, and muscle events. To increase the readership, please summarize and categorized the main points in a table.

Answer: We revised the paper and summarized the main points in tables and figures.

2. Information on miR-34a is lacking in the current version. Please add the relevant reports on the three muscle system since miR-34a plays an important role in the dysfunction of cardiovascular system.

Answer: Thank You for this observation. We added the information about miRNA-34a in the "Discussion section".

3. Please reorganize the contents of heart muscles based on cardiac myocytes and non-myocytes (fibroblasts).

Answer: We've reorganized the contents according to this suggestion.

4. Please further explain the following statement in the abstract: "...on the other hand, exercise training may be able to exert the opposite effect on the mechanisms that lead to hypertension in the main text." Otherwise, please delete it.

Answer: The statement in the abstract was revised and then deleted as suggested by reviewer.

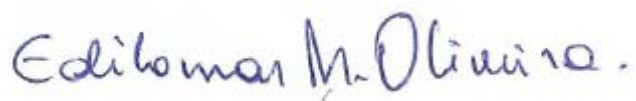
(5) Reviewer No. 69693

The reviewer 5 did no required changes. But their observations were: "Classification" Grade A (Excellent); "Language evaluation: Grade A: priority publishing, and "Conclusion" was Accept.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Cardiology*.

Sincerely yours,

A handwritten signature in blue ink that reads "Edilamar M. Oliveira." The signature is written in a cursive, flowing style.

Edilamar Menezes de Oliveira, PhD

School of Physical Education and Sport

Laboratory of Biochemistry and Molecular Biology of the Exercise

University of São Paulo

Av. Professor Mello Moraes, 65

Cidade Universitária, São Paulo, SP, Brazil

Fax: +55-11-3813-5921

edilamar@usp.br