

May 30, 2021

World Journal of Cardiology
Editorial Office

Re: World Journal of Cardiology Manuscript NO 66341

Dear Editors-in-Chief,

Thank you for your response concerning our manuscript entitled "**Exercise-mediated adaptations in vascular function and structure: beneficial effects in coronary artery disease**".

The Reviewers' comments were very helpful and we have made the appropriate revisions to our manuscript. Please find below the Reviewers' comments in bold and our responses in regular fonts. We also include below our responses to the issues raised by the Science Editor.

We are grateful for the opportunity to revise our manuscript. We think it has been improved by the Reviewers' suggestions and comments, and it is now much clearer.

We hope that our manuscript is now suitable for publication in the *World Journal of Cardiology*.

Sincerely,

Michail I. Papafaklis, MD, PhD, FESC

Corresponding author

Response to Reviewer #1

The authors discussed exercise-medicated adaptations in vascular function and structure. They focused on the beneficial effects in coronary artery disease. This article is well-written. But some issues need to be addressed.

1. Exercise improves endothelial function by endothelial shear stress (ESS). You may add more discussion about the improved endothelial function has beneficial effects in secondary prevention of coronary artery disease.

Following the Reviewer's suggestion, we have enriched our discussion regarding the beneficial effects of improved endothelial function on secondary prevention of coronary artery disease. Exercise improves endothelial function in patients with both stable and acute coronary artery disease. Since endothelial function has a pivotal role in myocardial ischemia, and NO bioavailability is disturbed in patients with coronary artery disease, exercise reduces paradoxical vasoconstriction and myocardial ischemia by improving the detrimental effect of endothelial dysfunction. Ultimately, improved endothelial function is associated with a lower rate of adverse cardiac events in patients with known coronary artery disease.

We have revised the manuscript including recent references, and the additional text now reads as follows:

“Patients with CAD following a 6-month aerobic exercise training program had higher peak response to acetylcholine when they performed high-frequency exercise compared with low frequency cardiac rehabilitation programs^[130]. In addition, a 2-week twice daily aquatic endurance plus calisthenics exercise training program in patients with a recent myocardial infarction or revascularization intervention improved both aerobic exercise capacity and vascular endothelial function^[131]. Kollet, et al. conducted a randomized pilot study and enrolled post-myocardial infarction patients undergoing PCI who performed a 30-minute moderate-intensity aerobic training program. This group of patients demonstrated enhanced endothelial function as determined by improved FMD of the brachial artery after each exercise period^[132].” (p. 19, para. 2, lines 12-22)

and

“Patients with newly diagnosed CAD and improved FMD after 6 months of optimized therapy for reducing cardiovascular risk factors had a lower rate of adverse cardiac events (10 vs. 26%, $p < 0.01$) during 3 years of follow-up, while persistent impairment of endothelial vasomotor function was an independent predictor of adverse outcomes^[134].” (p. 20, para. 1, lines 1-5)

2. Acute exercise may activate renin activity which causing blood pressure elevation and left ventricular hypertrophy such as athlete's heart. This issue may have detrimental effect on vascular structure.

The Reviewer raises an important issue and we agree that acute exercise may activate renin activity leading to increased angiotensin II levels and subsequently to deterioration of vascular function and elevated blood pressure. In addition, exercise-induced hypertension has been associated with increased rates of coronary artery plaques and may constitute a novel risk factor for plaque formation.

In the revised text, we have highlighted these issues and added new latest references as follows:

“Kim, et al. enrolled middle-aged marathoners with exercise-induced hypertension and reported increased angiotensin II with a reduction in NO levels. These findings may explain the deterioration of arteries vasodilator capacity and elevated blood pressure during exercise in this group of long-distance runners as well as the therapeutic effect of angiotensin II inhibitors in patients with exercise-induced hypertension^[42]. Experimental data also support the hypothesis that physical exercise combined with the administration of renin-angiotensin-aldosterone system blockers could have beneficial effects in order to prevent hypertensive cardiac alterations (e.g., left ventricular hypertrophy)^[43].” (p. 7, para. 3, lines 10-12 and p.8, para. 1, lines 1-7)

And later in the text,

“In addition, Kim, et al. studied veteran marathon runners and reported increased prevalence of coronary artery plaques among those with exercise-induced hypertension, thereby suggesting that exercise-induced hypertension could be a novel risk factor for coronary artery plaque formation^[96].” (p. 14, para. 2, lines 6-9)

Response to Science Editor

- References: A total of 128 references are cited, including 9 references published in the last 3 years;

In the revised manuscript, a total of 135 references are cited, including 16 references published in the last 3 years (2018-2021).

- Self-cited references: There are 2 self-cited references. The self-referencing rates should be less than 10%.

In the revised manuscript, there are 2 self-cited references, i.e., self-referencing rate of only 1.5%.

- The title is too long, and it should be no more than 18 words

The title of the article "*Exercise-mediated adaptations in vascular function and structure: beneficial effects in coronary artery disease*" is 13 words.

- The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

We now provide the figure in a PowerPoint file. We have adapted the figure from previous publication.

- Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights.

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We have also indicated the reference source and copyrights in the legend of the article, and the reference source is included in the References list.

The legend of the Figure includes the following:

"Adapted from Newcomer SC, et al.^[14] with permission from the American Physiological Society. Citation: Newcomer SC, Thijssen DH, Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics. J Appl Physiol (1985) 2011; 111(1): 311-20. Copyright ©The American Physiological Society (APS)."