April 22, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17269-review.docx).

Title: Peripheral reflex feedbacks in chronic heart failure: is it time for a direct treatment?

Authors: Alberto Giannoni, GianlucaMirizzi, Alberto Aimo, Michele Emdin, Claudio Passino

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 21192

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

Reviewer 1:

General comments: This mini-review article is nicely summarized the peripheral reflex feedbacks in chronic heart failure using upmost literatures included. The presentation style is well-organized and will provide useful information to the subscribers of this journal. Specific comments: 1. In the section describing "BAROREFLEX", it would be helpful to insert precise description of the central, afferent- and efferent nervous systems conveying peripheral reflex feedback. 2. In the section describing "BAROREFLEX", it would be appropriate to add one or more figures/drawings showing the method of baroreceptor stimulation. 3. In the reference section, references No. 5 and 14 are identical. Please delete reference No. 14 and re-arrange the cited references in the text.

Answer: We thank the Reviewer for his/her helpful criticisms. We added the following paragraph better describing the baroreflex pathways: "The baroceptors are mechanoreceptors located in the sinus caroticus and in the aortic arch, where terminal nerve endings are endowed in the wall of these vessels and activated by blood pressure-induced wall stretch. Information deriving from these sites travel along a path constituted by the nerve of Hering, that merges with the fibres of the glossopharingeal nerve; those travelling from the aortic arch take the path of the afferent fibres of the *vagus* nerve. Inputs hence travel towards the principal centre of integration of information regarding the cardiovascular system, that is the *nucleus tractus solitarii* (NTS) in the dorsal area of its medial and lateral divisions. Here signal are processed and integrated with information ascending from the periphery and descending from central nervous system and given back to the heart and peripheral arterial vessels *via* the vagus nerve."
In addition, we prepared a new figure summarizing the reflex feedbacks involved in heart failure and the potential therapeutical interventions.
Finally, we corrected the reference list.

Reviewer 2:
This is a timely, pertinent and well written editorial. Very clear and easy to read. My only comment is a typo in "neurohormonal" in the first sentence of the Future Perspectives section.

Answer: Thanks for your comments and acknowledgment of the value of the paper. The typo has been corrected in the revised manuscript

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

Sincerely yours,

Claudio Passino, MD,
Division of Cardiology and Cardiovascular Medicine
Fondazione Toscana Gabriele Monasterio
via Giuseppe Moruzzi 1, 56124,
Pisa, Italy
passino@ftgm.it