Format for ANSWERING REVIEWERS

August 28, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **20691-Review 28 8 2015.doc**).

Title: Regression of cardiovascular remodeling in hypertension: novel relevant mechanisms

Author: Jorge E Jalil, María P Ocaranza

Name of Journal: *World Journal of Hypertension*

ESPS Manuscript NO: 20691

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

We thank both reviewers for their comments in order to improve our manuscript.

RESPONSES TO REVIEWER 1
Reviewer's code: 00253523

REVIEWER COMMENT: This review article seems to be well-written; however, major revisions are need **to clarify the purpose of this review** and to be easily understandable for the readers.

RESPONSE TO THE REVIEWER: We appreciate the reviewer comment and in order to clarify the purpose of this review we modified the second paragraph accordingly
PREVIOUS VERSION:

Thus, in hypertension, it is relevant to develop new therapeutic perspectives, beyond reducing blood pressure to further prevent/reduce target organ damage by acting on pathways that trigger and maintain cardiovascular and renal remodeling[2]. We will review here some novel mechanisms of target organ damage in hypertension, their role and evidence in prevention/regression of cardiovascular remodeling and their possible clinical impact as well. Specifically, we will focus at this time on the signaling pathway RhoA/Rho kinase, on the impact of the vasodilatory peptides from the renin angiotensin system and some insights on the role of estrogens and myocardial chymase in cardiovascular hypertensive remodeling.

CURRENT VERSION

Thus, in hypertension, it is most relevant to develop new therapeutic

perspectives, beyond reducing blood pressure to further prevent/reduce target organ damage by acting on pathways that trigger and maintain cardiovascular and renal remodeling[2]. Our purpose is to review here three novel mechanisms of target organ damage in hypertension, their role and evidence of regression of cardiovascular remodeling and their possible clinical impact as well. Specifically, we will focus on the signaling pathway RhoA/Rho kinase, on the impact of the vasodilatory peptides from the renin angiotensin system and on the role of estrogens and the myocardial chymase-angiotensin II pathway in cardiovascular hypertensive remodeling. Interestingly, the 3 aforementioned mechanisms interact strongly with the renin angiotensin system at the cardiovascular level.

REVIEWER COMMENT: 1.The topic of this article suggested by the current title is too broad. Therefore, this reviewer suggests that the title would be changed concretely.

RESPONSE TO THE REVIEWER: According to the reviewer comment we modified the title to a more focused one:
PREVIOUS VERSION: Clinical impact of cardiovascular remodeling regression in hypertension: novel relevant mechanisms
CURRENT VERSION: Regression of cardiovascular remodeling in hypertension: novel relevant mechanisms

REVIEWER COMMENT: 2. In this article, the authors focused on Rho kinase, RAS-related vasodilatory peptides, and estrogen. However, relationship among these topics is poorly described. At least, the relationship between Rho kinase and RAS-related vasodilatory peptides should be described. In addition, this reviewer feels that the estrogen section is not needed and should be deleted.

RESPONSE TO THE REVIEWER: We sincerely appreciate the reviewer comment in order to clarify the message of this review. In view of that we did modifications to better describe the relationships among the topics by establishing the purpose of the review: "*Our purpose is to review here three novel mechanisms of target organ damage in hypertension, their role and evidence of regression of cardiovascular remodeling and their possible clinical impact as well*". **The mechanisms covered in our review (the signaling pathway RhoA/Rho kinase, the vasodilatory peptides from the renin angiotensin system and the estrogens and the myocardial chymase-angiotensin II pathway) interact strongly with the renin angiotensin system at the cardiovascular level and that is the main reason to keep the third mechanism (the estrogens and the myocardial chymase-angiotensin II pathway) within the scope of this review.**

REVIEWER COMMENT: 3. To better understand the role of Rho kinase, it would be better to add a figure schematically describing this pathway involved in hypertension and cardiovascular remodeling.
RESPONSE TO THE REVIEWER: According to this excellent suggestion, in this modified version a new Figure 1 was adde: Figure 1. **ROCK activation and downstream effects on cardiovascular remodeling in hypertension**

REVIEWER COMMENT: 4. Figure 3: This figure doesn't reflect the text. The key peptides described in the subtitle should be covered and included.
RESPONSE TO THE REVIEWER:
According to the reviewer, in the current modified version the key peptides in the new and modified Figure 4 (Figure 3 in the previous version) are covered and included in the text

REVIEWER COMMENT: 5. The conclusion or summary section should be added
RESPONSE TO THE REVIEWER: According to the reviewer, in the current modified version we added a last paragraph:
In **Conclusion**, the evidence about the three novel mechanisms of target organ damage in hypertension in this review: the RhoA/Rho kinase pathway, the vasodilatory peptides from the RAS and the estrogens-myocardial chymase interaction, open new therapeutic opportunities to effectively improve quality of life, reduce/prevent hypertensive cardiovascular remodeling and residual risk due to hypertension.

RESPONSES TO REVIEWER 2

Reviewer's code: 00503204

REVIEWER COMMENT: This is a comprehensive review article. I would like to ask the authors to present limitations and drawbacks of each agent they describe.

RESPONSE TO THE REVIEWER: According to the reviewer, in the current modified version we added the following paragraph before the conclusions:

Current **limitations and challenges**: more potent ROCK inhibiton is a main challenge at this time although there is preclinical evidence of newer inhibitors in this regard[15,19]. As a consequence, clinical studies with ROCK inhibitors in hypertension will follow. In the field of the vasodilatory peptides from the RAS, Ang 1-9 is effective as antihypertensive and anti remodeling. However, human data are necessary as well as pharmacodynamic information and means for appropriate delivery. With relationship to the role of the estrogens-myocardial chymase interaction, from our point of view, more preclinical data are required since the number of studies is small.

Thank you again for publishing our manuscript in the *World Journal of Medical Genetics*

Sincerely yours,

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