Format for ANSWERING REVIEWERS

October 17, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: The Splanchnic-Aortic Inflammatory Axis in Experimental Portal Hypertension

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3847

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 reviewers:

To the Reviewer 1

Firstly we would like to acknowledge the Reviewer for considering that our manuscript *"is an interesting review on the systemic and hepatic inflammatory effects of experimental portal hypertension"* In relationship with the issues that should be addressed, we've made the corresponding changes in our manuscript, which we describe point-by-point below and have highlighted in yellow in the text::

1. The reason for using the triple stenosis for TPVL although the surgical technique most frequently used in the rat was described by Chojkier and Groszmann in 1981 is why, If it is taken into account that the intensity of the portal hypertension is determined by the resistance to the inflow produced by the constriction of the portal vein conditioning its posterior evolution, this experimental model of prehepatic portal hypertension could be improved by increasing the initial resistance to the blood flow. With this objective in mind, we have modified the surgical technique by increasing the length of the stenosed portal tract with three equidistant stenosing ligations since,

according to the Poiseuille equation (R = 8 μL/πr4), the resistance (R) to the flow of a vessel

depends of the length (L) on the radius (r), and the coefficient of viscosity of the blood (μ). In brief, three partial ligations were performed in the superior, medial and inferior portion of the portal vein, respectively and maintained in position by the
previous fixation of the ligatures to a sylastic guide. The stenoses were calibrated by a simultaneous ligation (3-0 silk) around the portal vein and a 20-G needle.

Of course, before we choosed this modified technique prehepatic portal hypertension in the rat, we compared both techniques (Diéguez B, Aller MA, Nava MP, Palma MD, Arias JL, López L, Arias J. Chronic portal hypertension in the rat by triple-portal stenosing ligation. *J Invest Surg.* 2002;15(6):329-36.). In this study, we showed that the development of a triple stenosing ligation worsens the complications inherent to the prehepatic chronic portal hypertension obtained in rats with a single-portal stenosing ligation. In particular, the incidence of portosystemic and portohepatic collateral circulation and of the mesenteric venous vasculopathy increases in the animals with triple-portal stenosing ligation.

In addition, Abraldes et al. (World J Gastroenterol 2006; 12 (41): 6577-6584) also agree in which the stenoses degree condition the evolution of portal hypertension in the rat.

2. We have studied animals with very long-term PVL evolution (22 months) since in our experience, this postoperative time is the maximum obtained with the rats lowest mortality.

3. Although we´ve carefully revised this interesting subject , we didn´t found any evidences that relate portal hypertension without cirrhosis to increased cardiovascular risk in humans. However, we suspect that prehepatic portal hypertension is one of the causes of the "systemic endothelial sick" condition and, therefore probably it also produces cardiovascular pathology

4. The paper has been critically revised by Elizabeth Mascola, a professional linguistic reviewer, which has studied an American Master in Spanish language and literature, as well as a native English speaker. The mistakes found by the Reviewer and the changes made by

her are highlighted in the text in yellow.

Finally, the authors acknowledge the excellent revision as well as the vital suggestions the Reviewer.

(2)
3 References and typesetting were corrected

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

Sincerely yours,

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