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Format for ANSWERING REVIEWERS



January 04, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6704-review.doc).

Title: Cirrhosis and Hepatopulmonary Syndrome

Author: Gokhan Tumgor

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6704

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

COMMENTS TO AUTHORS

First of all, this paper is well constructed review of HPS with new insight of molecular mechanism. However several points should be revised and clarified. Major: Although the authors discussed pathogenesis of HPS in several parts of the paper, no description regarding the pathology of HPS, namely histological character of the lung of the cases with HPS. Pathological analysis should have been done elsewhere in the medline and be cited as a morphological investigation relating the classification of two types of HPS as mentioned in the paper. Furthermore reversibility of HPS by liver transplantation should also be pathologically discussed as in minor revision. Minor: 1) Page 5, in Clinical features, asymptomatic should be asymptomatic. 2) Middle of page 6, orthodexia is explained but the relationship between HPS and orthodexia was not shown. 3) If LT could reverse the HPS to normal pulmonary function, the pathological changes would be reversible by the resolution of hepatic dysfunction. This points should also be precisely discussed and clarified the pathological reversibility. Usually chronic organic damage could not be reversed in a short period like liver cirrhosis treated by interferon resulting viral disappearance. 4) Small character in Figure 1 and 2 should be enlarged for easy reading. 5) Figure 3 and legends need arrow or arrow head to understand the figure legends. 6) Figure 4 needs normal or control angiography without HPS to understand the difference of HPS and without HPS.



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Major:

In the literature it was stated that certain changes occur in lungs of the animals with HPS. In the studies of Silva et al. on rat models, it is indicated that the tidal volume, minute ventilation and mean inspiratory flow were significantly reduced, chest wall pressure dissipation against the resistive and viscoelastic components and elastic elastance were increased, and the lung resistive pressure dissipation was lower but the viscoelastic pressure was higher in the HPS group. The proportion of collagen volume in the vasculature increased by 29% in the HPS animals.

Furthermore, it is indicated that patients with hepatic cirrhosis have an elevated plasma level of lipopolysacchride. As extra LPS was given to the rats with cirrhosis, it is shown that the alveoli wall further widened with decreased density of cells and narrowed alveoli space and integrity of type I cell membrane destructed with infiltration of polymorphs and fibrinous exudates, indicating interstitial pulmonary edema and inflammatory reaction. There was severe stasis of blood in alveolar walls and numerous red cells extravasated the airspace, resulting in the widespread dilatation of alveolar capillaries and the augmentation of permeability of microvasculature.

it was added to article

Minor

1- it was corrected

2- While the PaO₂ was normal in horizontal position, it decreases in the upright position depending on the increase of blood flow velocity in arteriovenous anastomosis in the basal segments of the lungs with the effect of the gravity. This increases the ventilation- perfusion mismatch and the hypoxia becomes apparent. The orthodeoxy have been reported to be present in 20% to 80% of patients with HPS.

it was added to article

3- After liver transplantation and after all the factors that led to HPS disappeared, HPS is recovered. In a single post mortem study, it is indicated that the changes after the transplantation in lungs in HPS could be related to collagen tissue deposition in pulmonary capillary and venule walls. However, the recovery of HPS after transplantation shows that the pathological changes in the lungs in Type I HPS are



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reversible.

4- it was corrected

5- it was corrected

6- Figure 5 was added (Normal pulmonary angiography)



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6704

Title: -CIRRHOSIS AND HEPATOPULMONARY SYNDROME

Reviewer code: 02462032

Science editor: Wen, Ling-Ling

Date sent for review: 2013-10-28 13:49

Date reviewed: 2013-12-03 19:33

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Interesting review. Comments: 1. Contrast echocardiography (CEE) is accepted as sensitive test. You suggest diagnosis if microbubbles appear in left atrium after 3 heart beats after initial appearance in the right side of heart. However other authors (Lenci I, et al) have reported the cut-off of 5 beats. Please, if you think that 3 is better a reference must be necessary. 2. What about diffusion capacity in pulmonary function tests?. Is it important?. 3. As bacterial translocation seems to play an important role in physiopathology, it would be interesting to test selective intestinal decontamination to treat HPS. You write that this does not work, but in your reference (Rabiller A) in a experimental study in rats it seems to decrease some indicators of HPS. Can you clarify this point? 4. You write in discussion that survival after LT was not dependent of PaO₂, but some authors consider that PaO₂ < 50 mmHg is a contraindication to LT because postoperative mortality is too high. Do you think that exists a cut-off of paO₂ that precludes LT?

1- References was shown in article.

2- Unless there is an accompanying pulmonary disease, the spirometric tests in HPS are not impaired. However, abnormal diffusion capacity for carbon monoxide (DLCO) is frequently observed in the patients with HPS. In a study, it is demonstrated that DLCO was decreased in the 80% of the cases. But since its specificity is minor, it is not used in practice. **(it was added to article)**

3- Several ideas were set forth and several studies were conducted for the treatment of HPS. One of them is the experimental study of Rabiller et al. on rats. However, none of the treatments methods in that article yielded concrete results for the treatment of HPS, furthermore there were conflicting results in various studies in which these drugs were used. Rabiller et al. also indicated that when Norfloxacin is given, the activity and expression of lung iNOS were reduced to normal but the level of eNOS did not change. In the article, it was not meant to state that "it does not work" but it was meant that the effects in humans on long term follow ups are not known. Therefore, the role of these drugs for long-term HPS treatment has not been demonstrated. Currently, the most effective treatment is LT.

4- Although there is no information in the literature, according to my own experience; our 5 year old cirrhotic (Child A, PaO₂ <50mmHg) case who had transplantation, was followed up with no problem after transplantation. As a matter of fact, it is thought in recent years that decreased PAO₂ is not a contraindication for liver transplantation and does not affect the survey after the transplantation.

This article was edited and proofread by an academician from English department in our university and also by two academicians from Medical Faculty who had lived in America for long years.

3 References and typesetting were corrected

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



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Thank you for kindly interest

Sincerely yours,

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