Dear editor-in-chief,

Respectfully, I'm grateful for allocating your valuable time to manage the review process. Regarding the respected reviewers' comments, we revised whole the manuscript NO. 24318 entitled "*Contribution of mammalian target of rapamycin (mTOR) in pathophysiology of cirrhotic cardiomyopathy*" topic by topic. All the alterations are highlighted by yellow color in the main text.

Response to reviewers:

Reviewer #1

Thank you very much for the important and productive comments. As the respected reviewer made these questions, I have revised the manuscript based on the comments.

2. On figure 2 it is better to show us if there is a statistical significant difference, regarding the QTc, between the cirrhotic/rapa rats and cirrhotic/NS rats. 3. According to first paragraph, page 11, the figure 3 is absolutely wrong. Fig 3B must take the place of Fig 3A and 3A must take the place of 3B. Additionally, on figure 3D you mention that there is no statistical significant difference among the 4 groups. This is not true. Please correct. 4. You found that cirrhotic rats have blunted cardiac contractility and increased phosphorylated mTOR on the endothelial cells but not on cardiomyocytes of left ventricles. After the administration of rapamycin the cardiac dysfunction improved. In addition, p-mTOR on the cardiomyocytes increased comparing to p-mTOR of endothelial cells. Please explain why and how this change leads to improvement of cardiac dysfunction. 5. On the field of discussion, please give some information about the potential contingency between mTOR and TNF-α. 6. Please update your references.

1. As the reviewer requested, I have deleted the repeated statistical method on the figure legends.
2. On figure 2, it is mentioned at the legend that there is a statistical significant difference, regarding the QTc, between the cirrhotic/rapa rats and cirrhotic/NS rats ($^{++}P<0.01$). This sentence is highlighted in figure 2 legend.
3. Figure 3B is taken the place of Figure 3A and vice versa.

   Additionally, we have mentioned that there is no statistical significant difference among the EC_{50} of the 4 groups, but there is a significant difference between R_{max} of the studied groups.
4. To explain the relationship between change of p-mTOR translocation in cardiomyocytes rather than endothelial cells in cirrhotic rats treated with rapamycin and improvement of cardiac dysfunction is described.

   Endothelial cells are the first group of cells, which are exposed to circulatory pro-inflammatory and immunomodulatory factors and there is a cross-talk between endothelium and myocardium (1. Adler A, Huang H, Wang Z, et al. Endocardial endothelium in the avascular frog heart: role for diffusion of NO in control of cardiac O_2 consumption. Am J Physiol Heart Circ Physiol 2004; 287: H14 – 21. 2. Jazaeri F, Tavangar SM, Ghazi-Khansari M, Khorramizadeh MR, Mani AR, Dehpour AR. Cirrhosis is associated with development of tolerance to cardiac chronotropic effect of endotoxin in rats. Liver International 2013; 33: 368-374. [PMID: 23311391]). Therefore, in cirrhosis, we observed mTOR activation in endothelial cells rather than cardiomyocytes. On the other hand, we showed a significant decrease of phosphorylated mTOR in myocardium of cirrhotic rats, while p-mTOR in cardiomyocytes rather than endothelial cells was higher. The finding, for first time, is resulted and, actually, future studies can reveal the reason for the cross-talk between

endothelium and myocardium in the improvement of contractile force in cirrhotic cardiomyopathy.

5. The potential contingency between mTOR and TNF-α is described and highlighted in the field of Discussion.

   Otherwise, decreased tissue levels of TNF-α after treatment with rapamycin confirmed the hypothesis that reduction in overproduced cytokines, such as TNF-α and IL-1β, from hepatic and systemic reticuloendothelial cells can reverse their negative inotropic effects[16, 45, 46]. Evidences have shown that rapamycin acts as an effective agent, like isoproterenol, to raise intracellular cyclic adenosine monophosphate (cAMP) by reducing the expression and release of pro-inflammatory cytokine TNF-α from human heart tissue[47]. Also, rapamycin may inhibit nuclear factor-kappa B (NFκB) activation and TNF-α, as a potent inducer of in vascular smooth muscles[48].

6. The references have been rechecked and their PMID are updated.

Reviewer #2

Thank you very much for the valuable and productive comments. I have revised the manuscript based on the respected reviewer's comments and tried to improve the scientific level of this manuscript.

1. As the reviewer requested, I have tried to describe more clearly the clinical significance of our findings.

   This assumption is strongly amplified since a common etiology is considered for cardiac and liver diseases[6]. Although experimental and clinical investigations on cirrhotic patients revealed the latent heart failure with impaired response to

provocations and subsequent mortality, no effective treatment is still found to recommend to the patients with cirrhotic cardiomyopathy and evident ventricular failure for improvement of cardiac contractility[6]. As the prolongation in QT interval is considered as an important life-threatening element in the patients with cirrhotic cardiomyopathy, early identifying and treatment of the patients are necessary.Therefore, due to the anti-cytokine and beneficial role of rapamycin in correcting the abnormal cardiac contractile force and QT interval, rapamycin is expected to be the subject for further clinical investigations in the patients with cirrhotic cardiomyopathy.

2. The suggested minor language polishing is performed and highlighted in the manuscript.

Thank you very much for your precise and important suggestions for improvement of the manuscript. Based on your productive comments, the language, grammar, format and spelling of this manuscript has been corrected. In addition, whole the manuscript has been arranged according to the instructions for authors.

Ultimately, I think that the results of the present study would be useful for scientists and professional readers.I hope the revised manuscript would be acceptable for publication in World Journal of Gastroenterology.

Sincerely,

Prof. Ahmad Reza Dehpour