Author’s response to reviews

Title: Assessment of intrahepatic blood flow by Doppler ultrasonography: relationship between the hepatic vein, portal vein, hepatic artery and portal pressure measured intraoperatively in patients with portal hypertension

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Author’s response to reviews: see over
Dear editor:

This is the second revised version of the submitted article “Assessment of intrahepatic blood flow by Doppler ultrasonography: relationship between the hepatic vein, portal vein, hepatic artery and portal pressure measured intraoperatively in patients with portal hypertension”. The article was further revised according to the opinions of the three reviewers especially the opinion of Annalisa Berzigotti. The authors attached great importance to the reviews’ opinions and discussed deeply. We consulted some related articles to refresh knowledge about portal hypertension. Supplementary data and figures were added to improve the whole article. All the revisions were highlighted with red characters. We sincerely hope this article is well-organized and could be accepted by your journal. The point-to-point response was attached as followed.

Thank you very much!

Yours sincerely,

Li Zhang

Reviewer: Annalisa Berzigotti

Reviewer's report:
The authors answered only partially to most criticisms; consequently unfortunately the content of the article did not improve significantly.

1) A main flaw of the study is the lack of data about inferior vena cava pressure and other parameters related to systemic hemodynamics. Absolute portal pressure is obviously an indicator of the severity of portal hypertension, but from a pathophysiological point of view the consequences of portal hypertension depend on the portal pressure gradient, which is calculated as the difference between portal pressure and inferior vena cava pressure (Bosch et al. Seminars Liver Diseases 2006). Therefore, the lack of IVC pressure measurement decreases the reliability of the results.

----- First of all, we agree that the lack of data about inferior vena cava pressure is the main flaw in our article. However, from previous studies, we can find that there is a good correlation between the HVPG and portal venous pressure either with a wedge catheter or a balloon catheter measured, especially in patients with alcoholic cirrhosis and hepatitis B virus (HBV) cirrhosis [1-8]. In the study, another reason that we did not acquire the related data of either the inferior vena cava pressure, or subsequently
the portal pressure gradient was according to the patients’ conditions and the operation methods we used. If HVPG can be confirmed in further studies, indicative value of HV waveform and its cause can be illustrated adequately. We discussed this part in Discussion Section (see par. 2 in Discussion Section).


2) As the authors acknowledge, right heart catheterization or at least echocardiography should have been performed to rule-out heart valvular diseases or other conditions which can directly affect HV Doppler pattern. Moreover, the assessment of cardiac output, systemic arterial pressure and systemic vascular resistance would have given data on the presence of hyperdynamic syndrome, which could also be a determinant of abnormality of HV Doppler flow.
Firstly, we should declaim that every inpatient in our hospital would take ultrasound examinations for heart and ECG routinely. The patients we choose in this study had been ruled out heart valvular disease or right heart disfunction which can directly affect HV Doppler pattern. Furthermore, we also ruled out the patients with hypertension. The systemic vascular resistance we did not evaluated in this study. We still think that portal pressure is a kind of perfusion pressure and little evidence showed that the portal pressure can affected by systemic pressure or higher systemic vascular resistance significantly. We illustrated this part in the Method Section and Discussion Section. (see par. 1 in Method Section and the last par in Discussion Section). We believe that if systemic vascular resistance can be determined in the future studies, whole study could be illustrated perfectly.

3) The study population is poorly described (see table 1): data on etiology of cirrhosis, prevalence and size of gastroesophageal varices, previous episodes of bleeding from varices, ascites, … should be added to support the hypothesis that abnormalities in HV Doppler pattern depend principally from portal pressure increase. Indeed, ascites increases intrabdominal pressure which could flatten HV Doppler pattern. ---- Some data on etiology of cirrhosis we had collected were added in Table 1.

4) Design of the study: the study lacks a clear hypothesis, which should be better defined. ---- The proper hypothesis will be added in the introduction section. (see par. 2 in Background Section)

5) Study protocol: both portal pressure and central venous pressure can be affected by drugs used in general anesthesia; the authors should carefully comment on the protocol of anesthesia used, specifying if this was the same in all patients, and in which moment PP and Doppler were performed. Were the patients ventilated? How was respiration suspended? ---- Doppler HV waveforms were recorded for at least 5 s with end-expiration breath holding the day before the surgery. The drugs used in general anesthesia were the same in all subjects. The details of drugs used in anesthesia as followed: anesthesia induction used intravenous injection of dexamethasone 10mg, diazepam 0.2-0.3mg/kg, thiopental 2-4mg/kg, fentanyl 2ug/kg, scoline 1-2mg/kg, anesthesia maintained with intravenous injection of 1% procaine and 0.06% succinycholine, fentanyl was used if necessary. HR, ECG, Spo2, PETCO2, blood pressure and temperature were continuously monitored. Portal pressure was measured when the right gastroepiploic vein was isolated under the condition that the blood pressure was maintained at a
The results show that flattened HV Doppler flow pattern indicated more severe portal hypertension; however, all patients had severe portal hypertension since this was an inclusion criteria, and differences in PP between patients with normal and abnormal flow were very small (2-3 mmHg); how do the authors suggest to interpret the finding of abnormal HV Doppler pattern in a patients with known clinically significant portal hypertension? Did the patients with more flattened HV Doppler pattern show a different outcome on follow-up (decompensation, death, bleeding...), so supporting a clinical usefulness of the Doppler finding?

---In our study, we used Child-Pugh scores as one of the indexes for grading the severity of portal hypertension. In our studies, we investigated the relationship between Child-Pugh scores and some hemodynamic parameters of patients. Although the direct correlations between the HV Doppler pattern and Child-Pugh scores was not found, a significant correlation between Child-Pugh scores and PP was found, the latter was correlated with the HV flow pattern. We’d thought that it could reflect the relationship between HV waveforms and severity of portal hypertension indirectly. Furthermore, the quantitative index----damping index was introduced in the article and results showed that DI was an indicator of higher PP and more severe liver function. Some misunderstanding-caused illustration will be revised.

7) Discussion: a referral to “liver stiffness” is made in some sentences. In the methods and results no mention on direct liver stiffness measurement is made; was liver stiffness evaluated (transient elastography? ARFI? Other methods?) or is HAPI used as the only surrogate of liver stiffness? If it is so, the authors should better clarify the background for the use of Doppler impedance of hepatic artery as an indicator of liver stiffness.

--- Nagula et al. showed that small nodule size in the liver is also indicative of greater damage and architectural distortion of liver tissue, and further increases intrahepatic resistance. Patients with small nodules have higher PP. In the article, we introduced this suggestion. In the present study, we did not evaluate the stiffness through transient elastography or ARFI. We did not use HAPI as the only surrogate of liver stiffness. We just assessed the pathological damage by nodule size of liver parenchyma. The relationship between PP and histological changes (small nodules with higher portal pressure) was consistent with the findings of Nagula et al. We introduced HAPI and PVVel combined with HV waveform in order to discuss the hypothesis that liver parenchyma changes not intrahepatic fistula would be the cause...
of abnormal HV waveform from the hemodynamic angle. We should admit that the histological evidence was not sufficient enough to support our hypothesis that abnormal HV waveform was caused by pathological abnormality. The illustration about evaluation on liver stiffness was added in Discussion Section. (see par. 6 and 7 In Discussion Section)

8) Conclusions: Since no correlation was observed between HV Doppler flow pattern and histological findings it is difficult to accept the conclusion (see last lines of the abstract), which should be changed. Minor comments Histological findings might be better explained in the results section and not only in table 1; moreover, the lack of correlation between portal pressure and histological findings should be described in the results section and not in the discussion.

----- Histological findings and its correlation with portal pressure was illustrated in Results Section. (see last par. In Result Section)

The paper would improve if the authors transform the semi-quantitative data of HV Doppler flow pattern into a more objective and numerical index, such as the damping index (Kim et al. Liver International 2007)

-----Damping index (DI) was calculated and the correlation between DI and portal pressure and severity of portal hypertension was also assessed in the article. Some data and graphs were added in the new revised version.

Reviewer: Seyed-Mohammad Fereshtehnejad

Reviewer's report:

Dear editor of BMC Gastroenterology journal;
I reviewed the revised version of the manuscript titled: "Assessment of intrahepatic blood flow by Doppler ultrasonography: relationship between the hepatic vein, portal vein, hepatic artery and portal pressure measured intraoperatively in patients with portal". The manuscript is well revised; however, some minor points remained including:

1. As it was previously mentioned, it is better to give some data about sample size calculation in the "Methods" section of the article.

-----see Patients and control subjects in Method Section.

2. Although the authors answered that the two groups of study were matched regarding some baseline characteristics, nothing is mentioned about the details of matching process in the text of the revised manuscript.

---- see Patients and control subjects in Method Section.
3. No data on baseline characteristics of the control group are presented neither in the text of the results nor in the Table 1. Finally, I think it is necessary to consider these comments in this manuscript.

------ See Table 3