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 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. I sought language edition from a professional copyediting service. I also found some related articles to refresh my knowledge and further discussed the results. 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

The paper explores an interesting issue, which has been previously evaluated by other authors but that is still poorly understood. However, the study has some major limitations, which are listed below:

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.

----- Portal pressure gradient is considered as the gold standard for assessing the degree of portal hypertension, but there still existed some limitations we mentioned in the discussion section. In our studies, the research subjects we chose were the patients with portal hypertension who would undertake surgery. It is a conventional procedure to measure the PP from the right gastroepiploic vein during surgery and also a good chance to get the directly measured PP in one hand. In the other hand, objectively speaking, it will take a great risk to take another measurement of PP via the portal
pressure gradient assessment for these patients.

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.

---- Portal pressure is a kind of perfusion pressure. Little evidence showed that the portal pressure can be affected by systemic pressure significantly. The patients we enrolled in the study did not have the history of hypertension. The drugs and pattern used in general anesthesia were the same in all subjects. After discussion, we think that assessment of cardiac output, systemic arterial pressure and systemic vascular resistance could not be the determined factors.

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.

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 ultrasound scan was performed during inspiration suspended the day before the surgery. Portal pressure is perfusion pressure. The patients we enrolled in the study did not have the history of hypertension and the drugs and pattern used in general anesthesia were the same in all subjects. Portal pressure was measured when the right gastroepiploic vein was isolated under the condition that the blood pressure was maintained at a stable level. The related details used will be illustrated in the method section.

6) 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?

---Child-Pugh scores is one of the indexes for grading the severity of portal hypertension. In our studies, we investigated Child-Pugh scores of patients, although the directive correlations between the HV Doppler pattern and Child-Pugh scores was not found, we found a significant correlation between Child-Pugh scores and PP, the latter was also correlated with the HV flow pattern, which can reflect the relationship between HV waveforms and severity of portal hypertension indirectly. This 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.

Many studies suggested that an abnormal hepatic vein Doppler curve, believed to reflect an increased stiffness of the liver parenchyma around the hepatic veins, may be a non-specific indicator of liver abnormality, also in individuals with normal liver biochemistry. 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, the relationship between PP and histological changes was consistent with the findings of Nagula et al., but histological changes did not seem to be responsible for the changes in HV waveforms.

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.

-----This will be rewrite.

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)

Reviewer: soon koo Baik

Reviewer's report:

The main conclusion of the study is that hepatic vein (HV) waveform changes in patients with portal hypertension can indicate severity of portal pressure: There are
some limitations as following;

1. Accuracy and Reproducibility: Accurate measurement with being reproducible is the most crucial in the study of Doppler ultrasonography. Authors did not state the intra-and inter-observer variability. Authors should show up the coefficient of variation (calculated by dividing the standard deviation by mean and multiplying by 100) in terms of reproducibility. For instance, to evaluate the intraindividual reproducibility, one must measure the day-to-day variability for at least 5 consecutive days in about 10 subjects. Acceptable coefficient of variation would be approximately 10% in HV and 5% in PVV according to previous study.

--- We mentioned the assessment of Accuracy and Reproducibility.

2. Why were HV waveforms measured not in right hepatic vein but in middle hepatic vein? : Most of previous studies for hepatic vein abnormalities showed that HV waveform were measured at right HV because of advantage in terms of accuracy and reproducibility, rather than middle HV. Authors should clarify this point.

------ We selected the middle HV as the measuring object as results of the most consistent triphasic flow in healthy people and the most favorable Doppler angle. We had clarified the reasons in the method section.

Reviewer: Seyed-Mohammad Fereshtehnejad

Reviewer's report:

19 December 2010

Abstract

• In addition to the patients, the presence of a control group must be also mentioned in the "Methods" section of the abstract.

---- It will be added in the abstract section.

Introduction

• In regard to the focused subject of BMC Gastroenterology journal, it is better to mention some evidences in relation with hepatic diseases as well as radiologic aspects
of this subject in the "Introduction" section of the manuscript.
---- We will add related information in the Introduction section.

Methods

• More detailed information of patients and control groups should be stated in the "Patients" section of "Methods". This could be included patients diagnosis and selection, full eligible criteria of both case and control groups, source of control selection, sample size calculation, etc.
---- We will add related information in this section.

• Evaluating the factors which are considerably related to baseline characteristics like age, gender, etc need to be matched between patient and control groups regarding these potential confounding factors. Was it considered in this study? If yes, please mention the details in the "Patients" section of "Methods".
---- During the study, we tried to match the baseline characteristics to avoiding the statistical error. We will mention the details in the Method section.

• As some measurements are not performed in controls, it is recommended to more clearly declare which indexes are measured in each groups of the study.
---- The parameter we didn’t measured in the control group is the portal pressure, Child-Pugh scores. In the corresponding part we will declare more details.

Results

• Please add the baseline characteristics of the control group to Table 1, and compare the differences of these factors between two groups of the study.
---- In Table 1, the baseline characteristics we can added were the ages and gender, we had mentioned that we make a reasonable match between study group and control group to minimize the bias.

• Please mention the measurement units wherever it is needed (e.g. line 13 of
"Results" section).

----These will be added.

- How did the authors evaluate the confounding effects of some baseline characteristics (e.g. patients' age) in the relationship found between HV waveforms and PP? Or HAPI and HV waveforms? Are these variables considered in linear regression models?

----In our studies, we didn't evaluate the baseline characteristics in the relationship fund between HV waveform and PP. Because we tried to match the baseline characteristics to avoiding the statistical error.

- It is recommended to add the boxplots for PVVel and HAPI of control group in Figures 2 and 3, respectively; and state the P-value of comparisons with control data as well.

----Because only one person in control group exhibited monophasic. The statistical software can not conduct the comparison.

- Although it is previously studied in other manuscripts, it is recommended to evaluate the relationship between histopathological findings (e.g. severity of cirrhosis and grade of fibrosis) and these radiologic indexes in the "Results" section of the manuscript, too. It will help to better understanding of the association between severity of liver disease and hepatic hemodynamic and make it more useful for gastroenterologists.

----Some information will be added.

Discussion

- How did the authors conclude that "Of these parameters, HAPI seemed more sensitive to reflect abnormal HV waveforms."? Considering the statistical approaches, receiver operating characteristics curve (ROC) analysis must be performed to evaluated the diagnostic values (e.g. sensitivity) of different continuous variables to predict a dichotomous outcome (e.g. normal vs. abnormal HV waveform). However,
it is recommended to perform ROC statistical procedure in order to estimate and compare the diagnostic values of these indexes to predict abnormal HV waveform or even high grade versus low grade fibrosis. It is also of interest to derive the appropriate cutoff points for each measurement as well.

"Of these parameters, HAPI seemed more sensitive to reflect abnormal HV waveforms."---This sentence will be deleted in the revised article. We discussed the meaning of this sentence and we think whether HAPI is the suitable parameter to reflect abnormal HV waveform or not doesn’t make any sense.

* As it is declared within the limitations of current study, it is not ethical to rule out possible liver abnormalities in control group by biopsy. Since it is known, normal liver function test is not acceptable enough to evaluate some common conditions like NAFLD. Therefore, was fatty infiltration evaluated in control group using non-invasive methods such as ultrasonography of liver parenchyma?

---- No. To our knowledge, until now none of the non-invasive methods can diagnose fatty infiltration in liver.