Author’s response to reviews

Title: Relationship of 24-hour ambulatory blood pressure and heart rate with markers of hepatic function in cirrhotic patients

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Author's response to reviews: see over
Dear Sirs,
Please find the revised manuscript entitled “Relationship of 24-hour ambulatory blood pressure and heart rate with markers of hepatic function in cirrhotic patients”, manuscript id 1958283917334431, which we would like to be considered for publication in BMC Gastroenterology. This manuscript has been revised in light of the editor’s and the reviewers’ comments. Following you will find a point-by-point response to the concerns of all reviewers. Changes made in the revised manuscript are highlighted yellow. References to the manuscript text in the cover letter are in italics.

RESPONSE TO REVIEWERS

EDITOR

We strongly encourage you to include an Acknowledgements section between the Authors’ contributions section and Reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements. Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section. Authors must describe the role of the funding body, if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns. As substantial points were raised, we will need to seek further advice on the revised manuscript. Please also highlight (with ‘tracked changes’/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.
Please refer to the revised Authors’ contributions section. An Acknowledgement section is added between Authors’ contributions and Reference list, where it is clarified that the study was funded by the Hypertension Center, Third University Department of Medicine, Sotiria Hospital, Athens, Greece.

REVIEWER 1 (Luis Olmedilla)
Changes made in the revised manuscript are highlighted yellow

1. I am not clear on the practicality of a 24 hours ambulatory BP and HR measuring to evaluate a poor liver function. It’s easier to measure classical biochemical markers in a blood sample.

The following text was added in the Discussion:
We hypothesized that because hemodynamic parameters such as low office BP and increased HR are related to the severity of liver damage, a detailed evaluation of the BP profile, as provided by 24-hour ambulatory BP measurement, would be proved a more reliable index of liver dysfunction than the conventional office assessment.

2. All the correlation factors are low. The best is 0.56 (office HR-renin). This can be translated in a coefficient of determination $r^2$ of 0.3136: 31% of the variation in HR can be explained by the renin variation. The correlation can be statistically significant but showing a weak association between the two variables. (Pace NL. Research design and statistics. In Clinical Anesthesia, Edited by Barash PG, Cullen BF and Stoelting RK. Philadelphia : Lippincott Company. Philadelphia, 1989: 45-68).

We agree with this comment and added the following text in the Discussion:
The correlation factors are relatively low and according to the $r^2$ value for the association between HR of office visit 2 and serum rennin, only 31% of the variation of HR could be explained by the renin variation (Table 4).

3. The differences between the groups A and B, even significant, are very small (DBP office visit 1: 81 vs. 73, office visit 2: 79 vs. 72, asleep ambulatory 66 vs. 61). Why do the authors think there is not a significant difference in the HR?

The following text was added in the Discussion:
Because the sample size is relatively small, the main analysis was performed by treating the data as continuous rather than categorical variables, which allows the assessment of associations.

4. With the showed results, do the authors consider useful to measure the BP and HR to evaluate liver function? If a clear relation was showed, would the authors recommend to evaluate BP and HR ambulatory measurement in cirrhotic patients?

The following text was added in the Conclusions:
In conclusion, these data do not support the use of 24-hour ambulatory BP and HR as a more accurate method than office measurements for the evaluation of the severity of liver insufficiency.
5. Methods: It’s difficult to conclude something in Child C patients with only 4 cases. You must exclude them or include more cases.

The main inclusion criterion was fully ambulatory cirrhotic patients and only 4 of them marginally fulfilled the Child stage C criteria. Although this subgroup is too small to allow definite conclusions, its inclusion resulted in a wider range of liver insufficiency severity, which allowed a clearer demonstration of the investigated associations. In an interim analysis, where these subjects were excluded, the findings were almost the same, yet with weaker associations. Moreover, during the two-year recruitment of the study we found it difficult to find patients at this stage who were fully ambulatory and willing to participate. Therefore, we prefer to keep these marginal stage C patients in the analysis.

6. Minor revisions
References:
15: Tripathi
25: …… Heagerty AM, Kjeldsen ……
Tables
Table 2 error in edition: SBP in office visit 1
Table 3, 4 and 5: Correlation factors

Corrected names in references 15 and 23, corrected table 2 and added correlation factors to tables’ 3 and 4 legends (table 5 has been omitted and findings added in text).

7. Discretionary revisions: I think diabetes patients must be excluded because they can have an autonomic dysfunction that can alter the hemodynamic results.

Because diabetic patients were equally distributed between the two groups (Child A and B) and in order to avoid having a too small sample size, we preferred to keep the 5 diabetic subjects in the analysis. Moreover, these patients had no diagnosis of autonomic dysfunction, yet subtle changes cannot be excluded.

REVIEWER 2 (Matthias J. Bahr)
Changes made in the revised manuscript are highlighted yellow

1. In the introduction, the authors focus on the improvement of clinical patient care by their study. In detail, they want to answer the question whether 24-hour blood pressure recording provides more relevant information than single office BP measurements.

The following text was added in the Discussion:
We hypothesized that because hemodynamic parameters such as low office BP and increased HR are related to the severity of liver damage, a detailed evaluation of the BP profile, as provided by 24-hour ambulatory BP measurement, would be proved a more reliable index of liver dysfunction than the conventional office assessment.

2. First, the most endangered patients, namely those who are at highest risk for deterioration of their situation were excluded from the study (serum creatinine >133 µmol/l, serum sodium <130 mmol/l). In addition, also patients with hepatic encephalopathy were excluded. The reason to do this remains unclear.
The following text was added in the Discussion:

This study intended to investigate the relationship of the 24-hour ambulatory BP and HR with markers of liver dysfunction. Therefore, only fully ambulatory patients were included in whom a few days withdrawal of drug treatment (diuretics and b-blockers) was acceptable. On the other hand, severely diseased patients in whom the diurnal variation of these hemodynamic parameters was distorted due to limited physical activity, which is outside the standards of ABP monitoring [25] and in whom drug treatment could not be withdrawn, were excluded.

3. It is also unclear whether any stage of HE was excluded (even subclinical?). There were Child C patients in the study group. No sign of HE in these patients?

Please see previous comment. No patients with clinical signs of hepatic encephalopathy were included (this is clarified in text, please refer to Methods).

4. Looking at the results, one gets the impression that nonexistent correlations between liver function and circulatory parameters may be, at least in part, due to the protocol restrictions of the study group. Another reason for the worse results in 24-hour monitoring appears to be the differences in daytime activity in ambulatory patients.

Please see response to comment 2.

Also the following text was added in the Discussion:

Indeed, the effect of differences in daytime activity during 24h ambulatory monitoring is offset by the larger number of readings and the fact that these are taken in routine daily conditions, resulting thereby to superior reproducibility of ambulatory compared to office BP measurements.

5. Second, the patients were taken off cardio-vascular medication for at least 7 days prior to the measurement of circulatory parameters. In clinical practice we would not want to establish a test that leaves our patients for such long periods without protection from b-blockers, especially as rebound effects of b-blocker withdrawal are well known. Therefore, the study conditions do not reflect clinical practice. We cannot conclude from the data delivered by the study that patients taking cardio-vascular drugs should be controlled by office-based BP measurement.

The reason for withdrawing BP-lowering drugs was to have an unbiased picture of the 24-hour BP and HR profile. Otherwise, any findings regarding BP and HR would be criticized as being largely affected by drug treatment.

6. Third, to show correlations between circulatory parameters and tests / scores of liver function does not establish these tests as useful means in the monitoring of patients with liver cirrhosis. In fact, it is the part of information that is outside of the correlations which is additional. A new test is especially worthy if it provides additional data. Therefore, a correlation to other endpoints should be sought: survival, development of complications, deterioration of liver function. The recruitment of patients stopped in 2006. As the number of patients is not very high, it appears possible to acquire the above mentioned data, which would strengthen the current study enormously.

The following text was added in the Discussion:
This was a cross-sectional study investigating associations and was not designed to assess hard end-points. Moreover, the study sample is too small to allow conclusions in relation to outcome. Further research is needed, in order to investigate the association between hemodynamic parameters and hard endpoints such as survival and hospitalization.

7. The most interesting point for me was that the highest correlations between circulatory and liver function parameters were found for albumin. This points to the role of plasma oncotic pressure for the development of circulatory disturbances in cirrhosis which obviously needs to be mentioned at the side with peripheral vasodilation.

The following text was added in the Discussion:
*It is noteworthy that serum albumin is related with all hemodynamic parameters studied (Tables 3 and 4) suggesting that, apart from peripheral vasodilatation, plasma oncotic pressure reduction remains an important determinant of hyperdynamic circulation in cirrhosis.*

8. The biggest shortcoming of the current study with regard to the understanding of pathophysiology is the small set of circulatory parameters. Especially with regard to the ongoing discussion on the role of cirrhotic cardiomyopathy it would have been interesting to have echocardiographic data or at least ECG or 24-hour ECG. For practical reasons, these data will probably not be available. However, it should be possible to provide a set of age and sex-matches healthy controls for the BP and heart rate data.

This study has focused on the association of the 24-hour profile of ambulatory BP and HR, with markers of liver dysfunction. Some of these associations might also be present in healthy subjects, yet it is difficult to recruit healthy people for 24-hour ambulatory monitoring and blood samples. On the other hand, we do not believe that such data would largely enhance the validity of the present study.

9. Minor comments
   Methods, subjects, exclusion criteria: As heart failure might develop secondary to cirrhosis, how was heart failure defined?

   Only on the basis of patients records in the Liver Clinic plus symptoms and clinical examination.

   What about other significant heart diseases, e.g. CHD?

   Patients with known history of CHD were not excluded. There were 2 patients with diagnosed CHD (one with old inferior MI and another with positive thallium scan) who had no echocardiographic or clinical evidence of heart failure.

   Methods, BP measurements: Have left-right arm differences been excluded?

   Unfortunately we did not check left-right arm BP differences.

   Methods, statistics: What kind of correlation coefficient was calculated?
Pearson correlation coefficient, corrected in Statistical Analysis.

**Table 2:** Headings, change “Group BC” in “Group B”. Table: formatting errors.

Appropriate corrections made.

**Table 5:** Table can be omitted. Results can be presented as non-significant in the text.
The low number of significant results in this table will disappear if corrections for multiple testing are used”.

Corrected appropriately.

The following text was added in the Results:

Awake-asleep differences in ABP (dipping) revealed a few correlations with laboratory parameters. Correlations were negative between SBP dipping, renin and aldosterone concentration (-0.33 and -0.35, p<0.05 respectively), negative between DBP dipping and aldosterone concentration (-0.32, p<0.05), positive between HR dipping and albumin concentration (0.35, p<0.05) and negative between HR dipping and Child score (-0.22, p<0.05).

Additional figure: Correlations between serum albumin and BP / HR should be presented as scatter plots.

The following text was added in the Results:

*Correlations between serum albumin and BP and HR measurements in the office (visit 1) and with 24-hour ambulatory monitoring are presented as scatter plots in Figure 1.*

Please refer to Legend to figure 1 in text and Figure 1 itself.

**REVIEWER 3 (Flemming Bendsten)**

Changes made in the revised manuscript are highlighted yellow

1. The two groups are not matched according to etiology of cirrhosis, since only 30% of CHILD A patients have alcohol as etiology, while patients with more severe disease in 60% have alcohol as etiology. Since alcohol by itself may affect cardiac function, patients need to be stratified according to cause of liver disease.

We agree with this comment and added the following text in the Discussion:

*A limitation of the present study concerning this point is that alcoholic cirrhosis was significantly more frequent among group B patients* (**Table 1**).

2. I wonder how patients were selected. Were they consecutively recruited (51 patients recruited out of 60 in 30 months?)

Yes. This is clarified in Results – Patients’ characteristics.
3. Minor essential revisions
Blood samples page 6, line 5, drawn and not drown.
Corrected.

Page 8 top. It is not surprising, that there is a difference between the two groups with respect to CHILD and MELD score, since the two groups were defined by this. Can be deleted from the text.

We agree, yet prefer to keep these data as important descriptive characteristics of the patients. We removed p values.

Table 2. Top should be identical with table 1, dividing patients in Group A and not in group a and BC. There is problems with the right margin in print.

Corrected.

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Yours sincerely
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