Author's response to reviews

Title: Dynamic cardiac dyssynchrony is strongly associated with 2-year dialysis adequacy in continuous ambulatory peritoneal dialysis patients

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Author's response to reviews: see over
Dear Dr. Hayley Henderson,

We are most grateful for the opportunity to re-submit our revised manuscript entitled, “Dynamic cardiac dyssynchrony is strongly associated with 2-year dialysis adequacy in continuous ambulatory peritoneal dialysis patients”. We have substantially revised the manuscript and responded to the comments point-by-point. The major changes have been highlighted (deleted sentence with gray color and adding sentence with red color) in the revised manuscript. We hope the responses to the comments and the revisions to the manuscript have fully addressed your and the Reviewers’ concerns.

Thank you again for consideration of this manuscript.

Sincerely Yours

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Responses to Reviewer 1

Point-to-point

We wish to thank you for all your comments, which we have tried to incorporate into the manuscript. We hope that our responses that follow and the revisions made to the manuscript adequately address your comments, and that you will approve our manuscript for publication in *BMC Nephrology*.

Reviewer's report:

**Major Compulsory Revision:**

The manuscript, entitled "'Cardiac dyssynchrony is strongly correlated with 2-year dialysis adequacy and N-terminal prohormone of brain natriuretic peptide levels in continuous ambulatory peritoneal dialysis patients'" was reviewed.

It is an interesting paper investigating the relation between cardiac dyssynchrony and dialysis adequacy in continuous ambulatory peritoneal dialysis patients.

The comments are as follows;

1) The title of manuscript should be changed because it is not good enough for identify the study and it is too long. “NT-proBNP” section may be removed. For example: 'Cardiac dyssynchrony is strongly correlated with 2-year dialysis adequacy.

**Response:** In response to this comment, we have revised the title to:

“Dynamic cardiac dyssynchrony is strongly associated with 2-year dialysis adequacy in continuous ambulatory peritoneal dialysis patients”

2) Introduction section;

First paragraph in introduction section should be re-written because it is too long.

**Response:** We have substantially rewritten and shortened the Introduction.
3) Method section;

The last paragraph in eighth page should be transported to the part of subject in method section.

**Response:** In response to this comment, we have rewritten and transported the following sentence to the Methods (Page 6, lines 118–120). We hope this is the content the reviewer is referring to: “Dialysis adequacy was calculated as Kt/V, where K = dialyzer clearance of urea, t = dialysis time, and V = volume distribution of urea.”

4) Result section;

The last sentence of the second paragraph in result section should be re-written because it has not been expressed clearly enough.

**Response:** In response to this comment, as well as comments from the Editor and Reviewer 2, we have substantially rewritten the Results, having revised the statistical analyses.

5) Discussion section should be re-written. The other factors that affect cardiac dyssynchrony in CAPD patients should also discussed. In addition to the relationship between troponin-I and cardiac dyssynchrony should be mentioned and compared with similar information in the literature.

**Response:** In response to this comment, we have extensively rewritten the Discussion by describing the factors that may affect cardiac dyssynchrony in CAPD patients. Regarding the second part of the comment, we actually found no correlation in this study between troponin-I and cardiac dyssynchrony, as there was no difference in troponin-I concentrations between patients with low (≤1.1%) or high (>1.1%) SDI (0.025 [0.09–0.05] vs. 0.035 [0.009–0.05] mg/mL, P = 0.247). However, there are very few reports describing the correlation between troponin-I levels and cardiac dyssynchrony in populations other than acute myocardial infarction. We have discussed this issue on Page 15, Lines 334–336).
Responses to Reviewer 2

Point-to-point

We wish to thank you for all your comments, which we have tried to incorporate into the manuscript. We hope that our responses that follow and the revisions made to the manuscript adequately address your comments, and that you will approve our manuscript for publication in BMC Nephrology.

Reviewer's report:

Huang et al report a 2-year follow-up study of continuous peritoneal dialysis patients. The main aim of the study was to link left ventricular dyssynchrony assessed by 3D echocardiography and peritoneal solute clearance at 2 years.

The question raised by the author seems relevant and the methodology is novel and appropriate. However, several issues need to be fixed before considering the present manuscript for publication.

Major Compulsory Revisions

1. The authors should identify clearly a main endpoint and several secondary endpoints. This could help them to present the methods and the results and to organize the discussion. In the present form, the manuscript is difficult to read and it’s also difficult for the reader to catch the information.

Response: In response to this comment, we have clearly stated the primary and secondary objectives, and the corresponding parameters, in the Abstract and Introduction, as follows:

Abstract

“Our primary objective was to determine the association between LV dynamic dyssynchrony and CAPD clearance at 2 years. Secondary objectives were to identify the factors influencing dynamic dyssynchrony, and to examine the association between dialysis adequacy and echocardiography-assessed LV outcomes.” (Page 2, Lines 22–26)

“The main endpoint was systolic dyssynchrony index. Secondary endpoints, including NT-proBNP, troponin-I, Kt/V, and biochemical parameters were measured before stress echocardiography, and Kt/V was measured again 2 years later” (Page 2, Lines 28–32)
Introduction

“From this context, the main objective of this study was to investigate the association between LV dynamic dyssynchrony and CAPD clearance 2 years later. Our secondary objectives were to identify which factors influence dynamic dyssynchrony and to determine the association between dialysis adequacy and echocardiography-determined LV outcomes.”

(Page 5, Lines 95–99)

2. The discussion needs to be deeply revised. Indeed, the authors rather than discuss give results that’s were not previously reported in the Results section.

**Response:** In response to this comment, we have substantially rewritten the Discussion sections.

3. The statistical analyses need to be improved.
   - Because the sample size is small and because it seems very unlikely that the continuous variables were normally distributed, it seems adequate to use non-linear model. Then, rather than using generalized linear model, the authors should use non-linear model or prove that the effect of the studied variables is linear.
   - There is no sample size calculation. Why the authors choose to include 13 controls?
   - The authors didn’t describe the selection process of the variables included in the multivariate models. Was it based on the p value in the univariate analysis or based only on the clinical relevance?
   - In the Table 5, the authors should use the same approach than for the previous models and give regression coefficients rather than correlation coefficient. There is no reason for using a different approach and it make the results difficult to read.
Response: In response to these comments, we have reviewed and revised our statistical analyses. In brief, we have replaced the analyses with non-parametric procedures and shown data as medians with interquartile ranges.

Regarding the sample size of the control group, because infusion of dobutamine may induce arrhythmia, palpitation, and tachycardia, we did wish to enroll many subjects to avoid unwanted harms. Furthermore, for economic efficiency, we used a ratio of experimental subjects to control subjects of about 4:1. To limit bias, the subjects in both groups were matched by age and sex.

The variables included in multivariate models were selected based on the $P$ values in univariate analyses and considering their clinical importance, which we have specified on Page 9, Lines 190–192.

Finally, we have repeated and reviewed our statistical analyses to ensure our results are concise and easy to read.

Minor Essential Revisions

1. The term “correlated” in the Title should be replaced by “associated” which is more appropriate in the statistical point of view.

Response: Thank you for this suggestion. We have included this term in the title.

2. In the abstract:
   - In the methods section, the authors should clearly identify a main endpoint
   - In the results section, the sentence “Difference in SI (…) control group” needs to be clarified.
   - The conclusion needs to give a “take home message” eventually usable in the clinical practice which is not the case in its present form.

Response: We have rewritten the Abstract in accordance with these comments.
3. The authors didn’t perform a reproducibility study. There is some evidence in the literature concerning this aspect. The authors need to discuss this point.

**Response:** In response to this comment, we have assessed reproducibility both within and between observers, and added the following text to the manuscript under the subheading Intraobserver and interobserver variability:

**Methods**

“Intraobserver variability was determined by repeating the offline 3DE measurements of SDI at 2 weeks after baseline in all subjects. Interobserver variability was determined by comparison of all offline measurements by two cardiologists who were blinded to each other’s interpretations. Variability values were calculated as the absolute difference between the corresponding measurements in terms of the mean percentage.” (Page 9, Line 199–Page 10, Line 205)

**Results:**

“The interobserver variability for SDI was 6.3%, while intraobserver variability was 5.7%.” (Page 12, Lines 263–265)

4. The numerical results must be presented as median [interquartile range] and not as mean +/- SD as the continuous variables are not normally distributed (as stated by the authors)

**Response:** We have replaced all values with median and interquartile range in the Text and Tables.

5. The Table 2 is useless and the corresponding results should simply be inserted in the text of the Results section.
Response: In accordance with this comment, we have deleted the previous Table 2 and inserted the data into the text as appropriate. The remaining tables have been renumbered as appropriate.

6. The references 8 and 20 are the same.

Response: Thank you for spotting this error, which we have revised.