Author’s response to reviews

Title: Angiotensin II Receptor Blockade is Associated with Preserved Muscle Strength in Chronic Hemodialysis Patients

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BNEP-D-18-00441

Angiotensin II Receptor Blockade is Associated with Preserved Muscle Strength in Chronic Hemodialysis Patients

Dear Editor,

We would like to thank the reviewers for their extensive assessment of our manuscript, and for important and helpful comments and suggestions. These comments are really helpful to the improvement of the manuscript. We are sending you the revised version of the manuscript (BNEP-D-18-00441 R1). We have provided a point-to-point response to the comment from the reviewers. We sincerely hope that these changes in our manuscript will make it more suitable for considering of further process.
Responses to technical Comments:

1. Rename the heading Matethods to “Methods”

Answer: Thanks you very much. We have corrected this typing error.

2. Author’s Contribution - Please include a statement in the Authors’ contributions section to the effect that “all authors have read and approved the manuscript”, and ensure that this is the case

Answer: Thank you for your suggestion. We have ensured that all authors have read and approved the manuscript and added the statement in the Authors’ contributions Section.

Responses to editor comments:

This manuscript needs major revision, just like reviewer said, the authors should make the results more believable, i.e., increasing KT/V decreased the strength of muscles.

Anyhow, we look forward to seeing the revised version, thank you.

Answer: We thank the editor to remind us for further explanation about our unexpected observation between Kt/V and handgrip strength. Our finding can be partially explained by an enhanced skeletal muscle protein catabolism and loss during hemodialysis session. This finding was also reported in the other studies which were summarized in Table 3.

(Journal of the American Society of Nephrology 2005, 16(4):862-868)

We described this issue in the Discussion Section and added 3 articles, marked as Reference 37-39, to support our viewpoint.

Meanwhile, patients with malnutrition and small body size, who had a low “V”, can contribute to an overestimation of Kt/V other than dialysis exposure per se. We re-analyzed our data and found a significant inverse association between Kt/V and BMI (r=-0.552, P<0.001) (as shown in
the figure below). Therefore, we believe high Kt/V in the study might actually imply the small body size or malnutrition status of our patients. Indeed, extremely high Kt/V was observed to be associated with increased mortality in dialysis patients. We added our finding in the Discussion Section and extend two articles as Reference 40 & 41.

Responses to reviewers’ comments:

We appreciate all the comments from the reviewers, and make efforts to improve our manuscript.

Hussein Alhawari, M.D. (Reviewer 1):

Yu-Li Lin et al., presented a study that indicates a potentially protective effect of ARB on muscle strength in chronic HD patients. The result of the study is very interesting and definitely further and larger studies on this topic are needed. Methodology is excellent. The authors conducted an excellent literature review. It needs some language correction before being published.

Answer: Thank you for your encouragement and suggestions. We have corrected several language errors to make this article more fluent.

H. Argani (Reviewer 2):

1) In the abstract section: The resulted numbers and their accompanied p values should be mentioned.

Answer: Thank you for your suggestions. We already added the effective size, 95% confidence interval and p values into the Abstract Section.

2) In the result section and also in the Tables: By increasing KT/V the strength of muscles decreased; it is unbelievable and unpredictable result, as by increasing efficacy of HD, general condition including HGS should be increased.

Answer: We thank the editor to remind us for further explanation about our unexpected observation between Kt/V and handgrip strength. Our finding can be partially explained by an enhanced skeletal muscle protein catabolism and loss during hemodialysis session. This finding was also reported in the other studies which were summarized in Table 3.
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3) The sample size is not enough to rely on the results.

Answer: Thank you for your comments. Though the limited sample size is obviously a flaw, as we described in the Limitation Section; however, in our multiple logistic regression analysis for ARB effect, the key variable concerned is still revealed its significance ($OR = 0.25$, $95\% CI = 0.07-0.93$, $P= 0.039$).

4) ARBs were using for control of Blood pressure. The degree of poor or well controlled BP did not noted. It may be suggested that ARB by better controlled BP causes increased HGS, not by a direct mechanism.

Answer: We fully agree with the reviewer’s viewpoint. We had added the information of pre-HD systolic and diastolic blood pressure in Table 1, which showed no difference between normal and low HGS group (SBP $142.6 \pm 26.1$ versus $142.6 \pm 27.8$mmHg, $P=0.990$; DBP $80.2 \pm 16.2$ versus $76.0 \pm 16.8$mmHg, $P=0.192$).

5) As this study is a cross sectional trial it imposed a lot of biases.

Answer: As the reviewer mentioned, the cross sectional study is prone to bias and does not provide definitive proofs about the cause-and-effect relationship. We regard our work as a pre-test to evaluate our etiological hypotheses before a development of interventions. However, our results that consistent with the findings from previous animal studies made longitudinal cohort studies are worthwhile to be conducted. We also remind the readers in our Limitation Section that our result should be only regarded as hypothesis generating and over-interpretation should be avoided.