Author’s response to reviews

Title: Impact of Hypertension with or without Diabetes on Left Ventricular Remodeling in Rural Chinese Population: a Cross-Sectional Study

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Author’s response to reviews:

Dear Nassos Manginas:

Thank you for your letter and giving us a chance to revise our manuscript entitled “Impact of Hypertension with or without Diabetes on Left Ventricular Hypertrophy and Geometrical Changes in Rural Chinese Population: a Cross-Sectional Study” (ID: BCAR-D-17-00317). We also thank the reviewers for his/her constructive suggestions which are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion have been marked in red in the revised manuscript. The main corrections in the paper and the responds to the reviewers’ comments are attached below.

We would be grateful if this revised paper could be accepted for publication in BMC Cardiovascular Disorders and look forward to hearing from you soon.

Best regards,
Response to reviewers:

Reviewer 1:

1. The authors have information of levels of glycated hemoglobin (HBA1c) and its correlation with LVH? For subgroup with hypertension are available information's regarding the type of hypertensive durugs, dose, and compliance?

Answer: First of all, we’d like to express our heartfelt thanks to you for your comments, which we highly value, and we have studied the related references carefully. However, unfortunately, we did lack the test results of glycated hemoglobin (HBA1c) and feel deeply sorry that we could not provide information of its correlation with LVH. Moreover, the detailed and complete records regarding the type of hypertensive drugs, dose, and compliance were not available, which was one of the limitations of our study. Thank you for your constructive reminding. We have added these limitations into limitation part of our manuscript, as shown in Line 269. In our future research and follow-up work, we will make up for above missing information.

Reviewer 2:

1. Firstly, the authors should be commended for the high response rate of 83.5% in the study as well as the strict training and standards they set for investigators and implementation of committees and subcommittees to monitor the quality of the study.

Answer: Thank you for your high evaluation and we really appreciate it.
2. Missing data: demographic characteristics from the questionnaire/interview including lifestyle risk factors, dietary habits, family income, evaluation of psychological status, and quality of life. This information either needs to be provided or these variables must be removed from analysis.

Answer: Thank you very much for your valuable suggestion. We have removed demographic characteristics from the questionnaire/interview including lifestyle risk factors, dietary habits, family income, evaluation of psychological status, and quality of life, and corresponding statement from our manuscript.

3. Age is associated with diastolic decline and with increases in LV structural measurements. The study would be strengthened if the authors confirmed that their data set exhibited these same normal associations (as it would increase confidence that results obtained from their sample population are relevant to the wider population).

Answer: We totally agree with your point of view, and thank you very much for your guidance. According to your suggestion, we compared the echocardiographic parameters of all the participants based on age groups (35-45 year group, 45-55 year group, 55-65 year group, >65 year group), the results of which confirmed that age was associated with diastolic decline and with increases in LV structural measurements. Moreover, corresponding results have been described in “Results-Echocardiographic parameters comparison” part, as shown in Line 193.

4. Please specify if parasternal short or long axis was measured and if the measurements listed were taken during diastole in the methodology section.

Answer: Thank you for your suggestions. With your guidance, we have specified the corresponding methodology section, as shown in Line 142.

5. Hypertension was characterised as SBP \( \geq 140 \) mmHg and (or) a DBP \( \geq 90 \) mmHg. Can the authors please provide data that shows how many subjects within each group presented with both systolic and diastolic hypertension, systolic hypertension only with normal diastolic blood pressure and diastolic hypertension only with normal systolic blood pressure. And can the authors comment on why they chose to include subjects with diastolic hypertension with normal
systolic blood pressure? As systolic hypertension is considered the main driver of hypertension induced LVH and dysfunction.

Answer: Thank you for your questions. Hypertension was diagnosed as having a SBP ≥140 mmHg and (or) a DBP ≥90 mmHg and (or) being under antihypertensive treatment [1]. There are 2090 subjects with both systolic and diastolic hypertension, 2568 subjects with systolic hypertension only and 173 subjects with diastolic hypertension only. In our study, subjects who met the diagnostic criteria for hypertension were all included. However, we did not divide hypertension into systolic and diastolic hypertension, and did not choose to include subjects with diastolic hypertension only.

6. Variables such as fasting blood glucose, cholesterol and pulse pressure have previously been reported to associate with or to predict alterations in LV geometry and function. Did the authors perform statistics to determine whether any of the basic clinical data (Table 1) associated with the observed alterations in LV geometry, structure and function? This analysis may be beneficial to tease out the influence of these variables with the observed alterations. Particularly as the basic clinical data listed in Table 1 varied between groups.

Answer: We totally agree with your point of view, and thank you for your questions. Table 3 showed the associations of HT, HT+DM with abnormal geometrical patterns using multiple logistic regression analyses. Considering these associations of basic clinical data with alterations in LV geometry, we have performed statistics and adjusted for variables (Table 1) when we were doing logistics regression.

7. Following on from above, in Table 3. Multiple logistic regression analysis was preformed however established cardiovascular risk factors HDL-C, LDL-C, FBG, SBP were not included in analysis. Do statistical differences remain when these variables are accounted for?

Answer: Thank you very much for your valuable questions. In our study, after adjustment for age, gender, race, height, weight, WC, heart rate, smoking, drinking, TC, TG, LDL-C, HDL-C, PC, hemoglobin, UA, antihypertensive and antidiabetic medication, multiple logistic regression analysis was performed to observe the associations between hypertension with or without diabetes and abnormal geometrical patterns, as shown in Table 3. As independent variables, the established cardiovascular risk factors HDL-C, LDL-C, FBG, SBP have been included in analysis and adjusted.
8. Line 57 the authors state "As a result of adaptation of left ventricle to neurohormonal activation and chronically increased hemodynamic load, there are three abnormal LV geometrical patterns including concentric remodelling, concentric hypertrophy and eccentric hypertrophy". The authors are reminded that neurohormonal signalling and increased hemodynamic load may be contributing factors to alterations in LV geometry and may not be requirement. As such the authors statement is misleading. Alterations in cardiac metabolism for example are of particular interest in the diabetic heart, where an increased reliance on fatty acid oxidation and uncoupling between glucose oxidation and glycolysis are suggested to promote LVH. Please see the following paper for more information Can J Cardiol. 2017 Mar 19. pii: S0828-282X(17)30114-9. doi: 10.1016/j.cjca.2017.03.009.

Answer: Thanks for your valuable suggestions and sorry for our misleading statement. We have deleted the first half sentence-“As a result of adaptation of left ventricle to neurohormonal activation and chronically increased hemodynamic load”, as shown in Line 57. Moreover, we have carefully read the helpful article you offered and applied it to our manuscript. We added the statement-“Alterations in cardiac metabolism for example are of particular interest in diabetes, where an increased reliance on fatty acid oxidation and uncoupling between glucose oxidation and glycolysis are suggested to promote LVH” in background part, as shown in Line 61.

9. Line 155, reference 14 is specific to a study that assessed LV geometry in children and adolescents. This reference is inappropriate for the subject demographics in the current study. Please provide a more appropriate reference.

Answer: Thanks sincerely for your reminding. We have revised the error and provided an appropriate reference [2].

10. Line 213 the authors state "It indicated that the synergistic effects of hypertension and diabetes with both stress damage and interstitial deposition of advanced glycation end products in cardiac tissue can induce more serious LV hypertrophy and remodelling". I have two comments for this statement, first, the study did not include a normotensive DM group. Normotensive patients with DM have previously been reported to exhibit alterations in LV geometry, structure and function that are comparable to hypertensive patients (Cardiovasc Diabetol. 2017 Apr 20;16(1):53. doi: 10.1186/s12933-017-0535-5). Can the authors please comment on how they are confident that the alterations observed in the study are a synergistic effect between HT and DM, when they do have a DM only group? And secondly, the authors
may consider re-wording this statement, they have no evidence from their current study that interstitial deposition and advanced glycation end products in cardiac tissue were present in their populations.

Answer: We appreciate it very much that you have given us too many valuable suggestions and guidance, and we totally agree with your point of view. We have carefully read the article you offered, being very helpful. Our current study did not include a normotensive DM group, but we will discuss the association of normotensive diabetes with alterations in LV geometry, structure and function in the future study. Our current statement was indeed inappropriate. The results of echocardiographic parameters comparison indicated that hypertension with diabetes could induce more obvious LV hypertrophy and remodeling compared with hypertension only. It was inadequate to explain a synergistic effect between HT and DM, and suggested no evidence that interstitial deposition and advanced glycation end products in cardiac tissue were present in our populations. We have reworded this statement, as shown in Line 215.

11. Only 8% of subjects were hypertensive with DM. Can the authors please comment on this limitation?

Answer: Thank you for your questions. Our team's previous study has reported that the prevalence of diabetes among adults in our population was 10.6% (10.0% in men and 11.1% in women) and discussed its associated characteristics in detail [3]. So it's not surprising that the prevalence of hypertension with diabetes in our population is 8% but with 818 subjects, which is relatively big in the field included into statistical analysis. However, diagnosis of diabetes in our study relied on FPG level and/or being on treatment for diabetes without integrating HbA1c into the diagnostic criteria, which means that the prevalence of hypertension with diabetes may have been underestimated. This limitation has been added into our limitations part.

References

